Alfred Bader

Articles

[Articles about Alfred Bader]

[3001-]

1924 – Ein guter Jahrgang

Alfred Bader
Franz Ferdinand Cap
Michael J. Higatsberger
Otto Hittmair
Karl Schlögl
Hans Tuppy

Eine Ausstellung der Österreichischen Zentralbibliothek für Physik

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PHYSIKALISCHES INSTITUT
DER UNIVERSITÄT WIEN
Nº
5

Jahrgang 1924

„Wissenschaft ist eine sich nur in Kommunikation abspielende Entwicklung. Sie ist von und für Menschen da und muss sich im Kontakt mit anderen Menschen bewähren, und Einzelgänger müssen sich auch erst im Kontakt mit den übrigen Wissenschaftlern bewähren. Wissenschaft ist ein permanenter Korrekturprozess und das zeichnet sie aus." Hans Tuppy

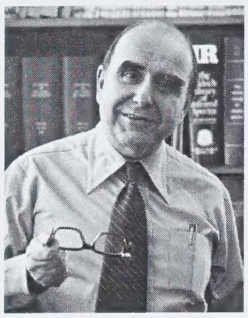
Sechs 1924 in Österreich geborene Naturwissenschaftler, drei Chemiker und drei Physiker, haben heuer ihren achtzigsten Geburtstag.

Alfred Bader
Franz Ferdinand Cap
Michael J. Higatsberger
Otto Hittmair
Karl Schlögl
Hans Tuppy

Die sechs Personen eint nicht nur ihre Geburt im Jahr 1924, sondern auch, dass sie sich unter schwierigsten Bedingungen und Lebensumständen – sie waren bei Ausbruch des Zweiten Weltkrieges gerade erst 14 Jahre alt – entschieden haben, ein Leben für die Wissenschaft bzw. Wirtschaft zu führen. Sie haben sich der Verantwortung, die Ihnen als Forscher auferlegt war, nicht entzogen und haben auch zu strittigen Themen wie Kernenergie oder Gentechnik Stellung genommen. Sie gehörten in ihren Bereichen zur Weltspitze und wurden oft an berühmte Universitäten eingeladen, um über ihre Arbeiten zu berichten.
Die Bereiche, in denen sie tätig waren (und zum Teil noch immer sind), erstrecken sich vom Weltraum bis zu den allerkleinsten „Bauteilen" des Lebens, von der friedlichen Nutzung der Kernenergie bis hin zur Stereochemie. Sie haben viel geleistet für Forschung und Lehre, haben tausende Studenten ausgebildet und gefördert und zahlreiche wissenschaftliche Publikationen veröffentlicht. Und doch sind sie außerhalb der Fachwelt nur wenigen bekannt.

Grund genug, sie einer breiteren Öffentlichkeit vorzustellen ...

Wolfgang Kerber



Alfred Bader

Dr. phil., mult. Dr. h. c.
President & Chairman Emeritus, Sigma-Aldrich Corporation

Werdegang:

28. 4. 1924	Geboren in Wien, Eltern: Alfred und Elisabeth Bader
	Verheiratet in zweiter Ehe mit Isabel Bader, geb. Overton;
	2 Kinder aus erster Ehe
	Volksschule und Gymnasium in Wien
10. 12. 1938	Emigration nach England
1941	Als *„enemy alien"* im Internierungslager in Kanada
1945	BSc (Engineering Chemistry) an der Queen's University , Kingston, Ontario
1946	BA (History) an der Queen's University
1947	MSc (Chemistry) an der Queen's University
1949	MA (Chemistry) an der Harvard University
1950	PhD (Chemistry) an der Harvard University
1950–1953	Research Chemist, Pittsburgh Plate Glass Co.
1951	Gründer der Aldrich Chemical Company in Milwaukee, Wisconsin
1953–1954	Group Leader, Pittsburgh Plate Glass Co.
1954–1955	Chief Chemist, Aldrich Chemical Co.
1955–1981	President, Aldrich Chemical Co.
1981–1991	Chairman, Aldrich Chemical Co.
1975–1980	President, Sigma-Aldrich Corporation
1980–1991	Chairman, Sigma-Aldrich Corporation
1991–1992	Chairman Emeritus, Sigma-Aldrich Corporation

Publikationen:
Bader veröffentlichte in einschlägigen Fachzeitschriften
1995 erschien seine Autobiografie „Adventures of a Chemist Collector".

Ehrungen (Auswahl):
9 Ehrendoktorate von Universitäten in den USA, Schottland und Tschechien
Winthrop-Sears-Medal (1980)
The J. E. Purkyne-Medal of the Czech Akademy of Sciences (1994)
Charles Lathrop Parsons-Award, American Chemical Society (1995)
Gold Medal, American Institute of Chemists (1997)
American Chemical Society Award: „One of the Top 75 Distinguished Contributors to the Chemical Enterprise in the Last 75 Years" (1998)
Commander of the British Empire (1998)

Mitgliedschaften (Auswahl):
Guest Curator, Milwaukee Art Museum (1976 and 1989)
Honorary Fellow, Royal Society of Chemistry (1990)
Fellow of the Royal Society of Arts
Ehrenbürger der Universität Wien (1995)
Honorary Fellow, Chemical Institute of Canada
Ehrenmitgliedschaft der Gesellschaft Österreichischer Chemiker (2003)

„Life is full of ‚what ifs'."

Kindheit in Wien

Bader wurde am 24. April 1924 in Wien geboren. Sein Vater, der zwei Wochen nach seiner Geburt verstarb, stammte aus Mähren, seine Mutter Elisabeth stammte aus Ungarn. Nach dem Tod des Vaters wurde er von seiner Tante Gisela adoptiert.

Praterstraße um 1934

Emigration – England, Internierung – Kanada

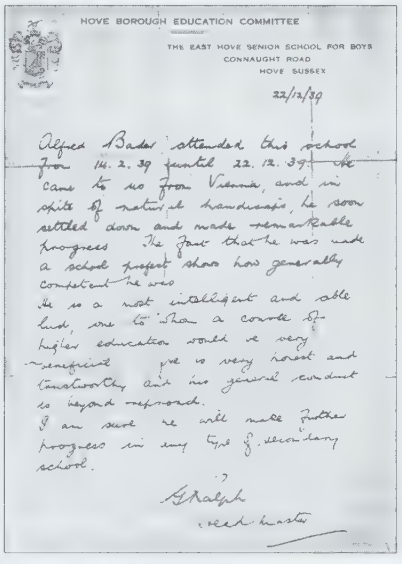
1938 stellte England für jüdische Kinder vom Kontinent 10 000 Visa zur Verfügung. Bader konnte/musste/durfte als 14-jähriger in einem Kindertransport emigrieren. Er sollte die meisten seiner Familienangehörigen nie wieder sehen. Seine Tante Gisela wurde in Theresienstadt ermordet, seine Mutter starb 1948 an den Folgen eines Schlaganfalles.

Er lebte in England bei einer Gastfamilie, durfte wieder eine Schule besuchen und lernte die englische Sprache. Aufgrund der guten schulischen Leistungen wurde er im Brighton Technical College aufgenommen. 1940 kam er als *„enemy alien"* in ein Internierungslager. Es folgte der Transport nach Kanada, wo Bader in einem aufgelassenen Fort an der amerikanischen Grenze interniert war und eine intern organisierte Schule besuchte.

Jüdisches Neujahr im Internierungslager, 1941

Portrait von Bader im Internierungslager, 1941

Schule im Internierungslager, 1941



HOVE BOROUGH EDUCATION COMMITTEE

THE EAST HOVE SENIOR SCHOOL FOR BOYS
CONNAUGHT ROAD
HOVE SUSSEX

22/12/39

Alfred Bader attended this school from 14. 2. 39 until 22. 12. 39. He came to us from Vienna, and in spite of natural handicaps, he soon settled down and made remarkable progress. The fact that he was made a school prefect shows how generally competent he was.
He is a most intelligent and able lad, and to whom a course of higher education would be very beneficial. He is very honest and trustworthy and his general conduct is beyond reproach.
I am sure he will make further progress in any type of secondary school.

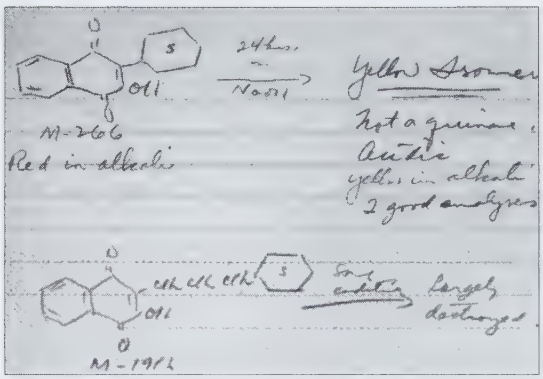
G. Ralph
Head Master

Schulbesuchsbestätigung, 1939

Studium

1945, nach dem Krieg, suchte Bader in den USA einen Studienplatz, um Chemie zu studieren. Von der McGill University sowie der Universität in Toronto wurde er abgelehnt, erst die Queens University in Kingston, Ontario akzeptierte ihn. Das Studium des Chemie-Ingenieurwesens finanzierte er sich durch die Arbeit bei der Murphy Paint Co (Lacke, Beschichtungen und Farben) in Montreal. Später ermöglichte ihm das Unternehmen das Doktorratsstudium an der Harvard University. Pittsburgh Plate Glass Co (PPG) übernahm die Firma, und mit Baders Hilfe spezialisierte sich das Labor auf neue Monomere, die aus billigen Ausgangsstoffen hergestellt wurden. Die wissenschaftliche Literatur beschrieb zu diesem Zeitpunkt, dass diese Methode nicht erfolgreich sei, Bader fand aber heraus, dass spezifische Vorgangsweisen doch zum Erfolg führen. Die Verfahren wurden patentiert, und die Firma Johnson Wax zeigte Interesse, das Patent zu kaufen. Eine betriebswirtschaftlich korrekte Amortisation des Aufwandes wäre bei einem Verkaufspreis von 10.000 Dollar gegeben gewesen. Bader empfahl jedoch, den Marktwert auszutesten und eine Million zu verlangen. Johnson Wax rechnete seine geschäftlichen Chancen durch und kaufte zu diesem Preis.

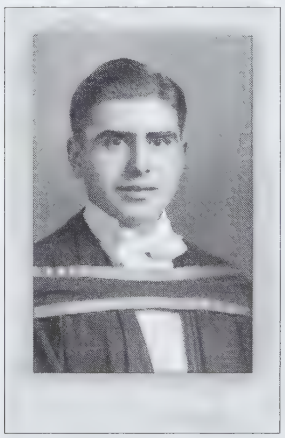
Mit Studienkollegen Martin Ettlinger an der Harvard University, 1948



Erstes PhD-Problem an der Harvard University, 1947

Das Wort Chemie ist ein hässliches Wort geworden. Wenn man um 1947 Leute gefragt hat, was ihnen als erstes zu Chemie einfällt, haben sie gesagt: „Vitamine, Plastik und neue Medikamente". Stellt man heute diese Frage, sagen sie: „Umweltverschmutzung und krebserregende Stoffe". Wir haben den Menschen nicht deutlich genug gezeigt, wieviel Gutes sie der Chemie verdanken.

Hillel Foundation executive in der Queen's University, 1945

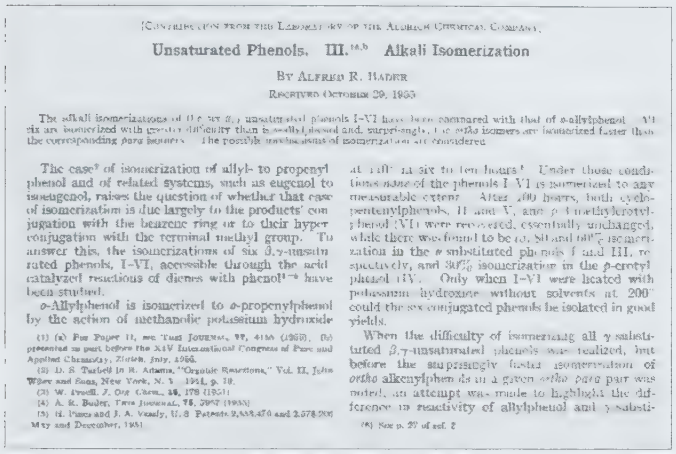


Studienabschluss an der Queen's University, 1945

Aldrich – 1. Gebäude, 1958

Aldrich – 3. Gebäude, 1967

70. Geburtstag, mit Marvin Klitsner, 1994



[Contribution from the Laboratory of the Aldrich Chemical Company]

Unsaturated Phenols. III.[1a,b] Alkali Isomerization

By Alfred R. Bader

Received October 29, 1955

The alkali isomerizations of (1) o- or p-unsaturated phenols I–VI have been compared with that of o-allylphenol. VII to six are isomerized with greater difficulty than o-methallylphenol and, surprisingly, the ortho isomers are isomerized faster than the corresponding para isomers. The possible mechanisms of isomerization are considered.

The case[2] of isomerization of allyl- to propenyl phenol and of related systems, such as eugenol to isoeugenol, raises the question of whether that ease of isomerization is due largely to the products' conjugation with the benzene ring or to their hyperconjugation with the terminal methyl group. To answer this, the isomerizations of six β,γ-unsaturated phenols, I–VI, accessible through the acid catalyzed reactions of dienes with phenol[3-5] have been studied.

o-Allylphenol is isomerized to o-propenylphenol by the action of methanolic potassium hydroxide at 175° in six to ten hours.[6] Under these conditions none of the phenols I–VI is isomerized to any measurable extent. After 200 hours, both cyclopentenylphenols, II and V, and p-(1-methylcrotyl)-phenol (VI) were recovered, essentially unchanged, while there was found to be 50 and 60% isomerization in the α substituted phenols I and III, respectively, and 30% isomerization in the p-crotylphenol IV. Only when I–VI were heated with potassium hydroxide without solvents at 200° could the six conjugated phenols be isolated in good yields.

When the difficulty of isomerizing all γ substituted β,γ-unsaturated phenols was realized, but before the surprisingly faster isomerization of *ortho* alkenylphenols in a given *ortho para* pair was noted, an attempt was made to highlight the difference in reactivity of allylphenol and γ-substi-

(1) (a) For Paper II, see This Journal, 77, 4185 (1955). (b) presented in part before the XIV International Congress of Pure and Applied Chemistry, Zürich, July, 1955.

(2) D. S. Tarbell in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 19.

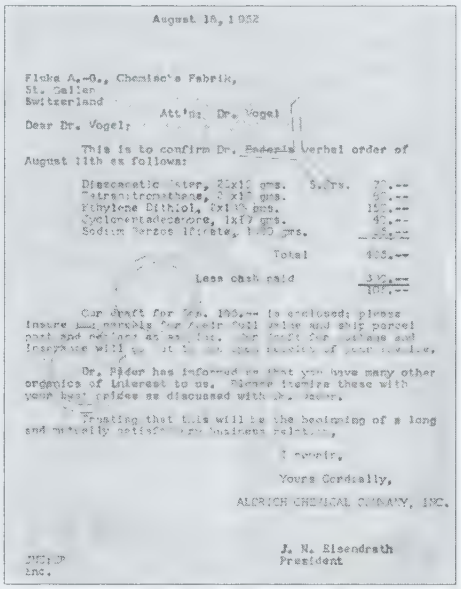
(3) W. Ipatieff, *J. Org. Chem.*, **16**, 178 (1951).

(4) A. R. Bader, This Journal, **75**, 5967 (1953).

(5) H. Pines and J. A. Vesely, U. S. Patents 2,553,470 and 2,578,200 (May and December, 1951).

(6) See p. 27 of ref. 2

Publikation von Bader, 1955



August 18, 1952

Fluka A.-G., Chemische Fabrik,
St. Gallen
Switzerland

Att'n: Dr. Vogel

Dear Dr. Vogel:

This is to confirm Dr. Sadegh's verbal order of August 11th as follows:

Diazomethane ether, 22x10 gms.	5.Trs.	30.--
Nitrosotrimethene, 2 x1 gms.		6.--
Ethylene Dithiol, 9x1 gms.		18.--
Cyclopentadecanone, 1x17 gms.		42.--
Sodium Perzos Iodate, 1x50 gms.		50.--
Total		146.--
Less cash paid		3 %.--
		141.--

Our draft for Sw. 146.-- is enclosed; please insure [illegible] parcels for their full value and ship parcel post and express as ex. [illegible]. Our draft for postage and insurance will be at [illegible] when receipt of [illegible].

Dr. Bader has informed me that you have many other products of interest to us. Please itemize these with your best prices as discussed with Dr. Bader.

Trusting that this will be the beginning of a long and mutually satisfactory business relation,

I remain,

Yours Cordially,

ALDRICH CHEMICAL COMPANY, INC.

J. N. Eisendrath
President

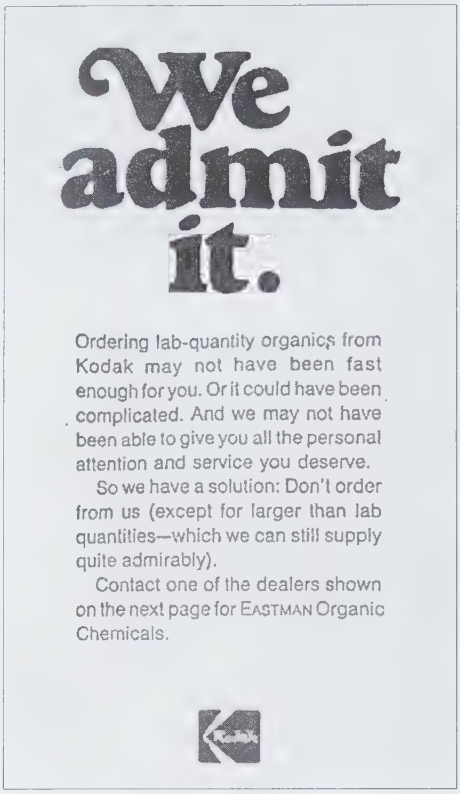
JNE:jf
Enc.

Bestätigung einer Bestellung von Fluka, 1952

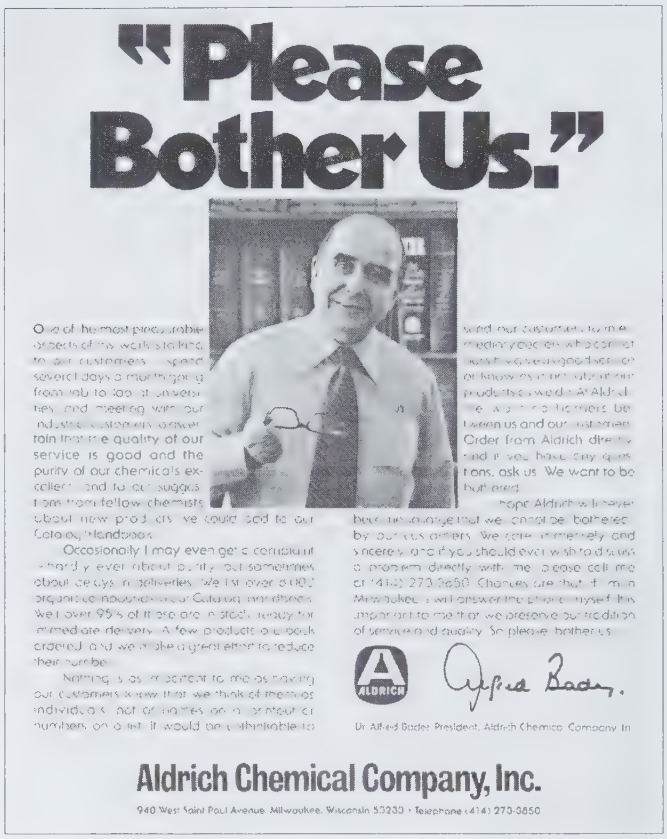
Ich bin sehr stolz, Aldrich gegründet zu haben. Wir haben Forschung sehr erleichtert und Chemikern viele Stunden erspart, die sie nun ihren Forschungen widmen konnten, ohne selbst erst ihre Forschungsmaterialien produzieren zu müssen.

Aldrich Chemical Co., Sigma-Aldrich

1951 hatte Bader die Idee, mit Forschungschemikalien in Kleinmengen Geld zu verdienen. Dies wurde von der Firmenleitung zwar zurückgewiesen, es wurde ihm jedoch die Erlaubnis erteilt, es auf eigenes Risiko zu versuchen. 250 Dollar waren der Einsatz, den Bader und Jack N. Eisendrath, ein befreundeter Rechtsanwalt, aufwendeten, um eine Firma zu gründen. Sie gaben ihr den Namen Aldrich Chemical Company. 1952 hatte der Betrieb 12 Produkte im Angebot. 1955 verkaufte Eisendrath um $ 15 000,– seine Anteile an Bader, der damit alleiniger Eigentümer wurde. Bader erkannte, dass er, um erfolgreich zu werden, nicht nur Chemikalien selbst produzieren, sondern auch als Wiederverkäufer auftreten musste. Er begab sich in Europa auf die Suche nach Zulieferfirmen und knüpfte viele gute Geschäftskontakte. 1955 umfasste der 7. Katalog der Firma Aldrich bereits eine Produktpalette von 1600 Chemikalien. Im selben Jahr traf Bader Marvin E. Klitsner, mit dessen Hilfe Aldrich größer und größer und schließlich zu einem weltumspannendem Unternehmen wurde.
Kodak, der einzige Konkurrent, war teuer und gestand sogar in einem Inserat ein, dass das Service nicht gut war. Aldrich antwortete mit folgendem Inserat: „Belästigen Sie uns! Wir hoffen, dass wir nie so groß werden, dass Sie mit uns nicht mehr sprechen können!“



Kodak-Werbung



Aldrich-Antwort auf die Kodak-Werbung

Sigma-Aldrich-Executive: Tom Cori, Bader, David Harvey, Peter Gleich, Kirk Richter, 1986

Mit Dan Broida, Gründer von Sigma, 1976

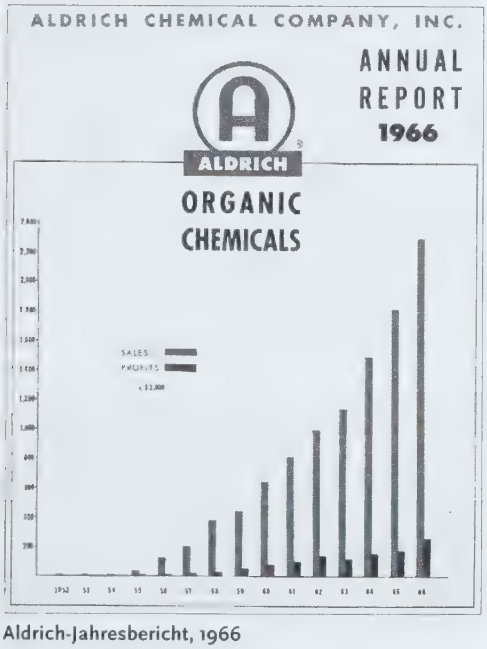
Es gab kein einziges Jahr, in dem der Umsatz der Firma Aldrich unter dem des Vorjahres lag. 1965 ging Aldrich Chemical Company an die Börse.
Ende 1960 erkannte Bader, dass Wachstum zukünftig hauptsächlich in der Biochemie zu erwarten war, und Aldrich begann, eine Abteilung für Biochemie einzurichten. Nebenbei interessierte man sich für einen Zusammenschluss mit einem biochemischen Betrieb. Die Biochemikalienfirma Sigma erschien als der geeignetste Partner, und 1975 wurde die Vereinigung mit Sigma realisiert. Durch diese Fusion war es Sigma-Aldrich nun möglich, eine Produktpalette von 30 000 Chemikalien anzubieten. Dan Broida, der Präsident von Sigma zum Zeitpunkt des Zusammenschlusses, wurde der erste Vorstandsvorsitzende und Bader der erste Präsident von Sigma-Aldrich. Bader hat mit vielen bedeutenden Chemikern des vergangenen Jahrhunderts zusammengearbeitet, darunter die Chemie-Nobelpreisträger Herbert C. Brown, E. J. Corey und Vladimir Prelog.

Ein wichtiges Ergebnis der Arbeit von Bader und Aldrich ist der Aufbau einer Bibliothek von Chemikalien. Derzeit beinhaltet diese Sammlunng Proben und Informationen über rund 100 000 Chemikalien und chemische Verbindungen.

Mit Vladimir Prelog (Nobelpreis 1975) und Albert Eschenmoser in Zürich, 1995

Herbert Brown (Nobelpreis 1979), Isabel und Alfred Bader, Sarah Brown, 1992

Nobelpreis für E. J. Corey, Feier in Harvard mit Corey und Eschenmoser, 1990

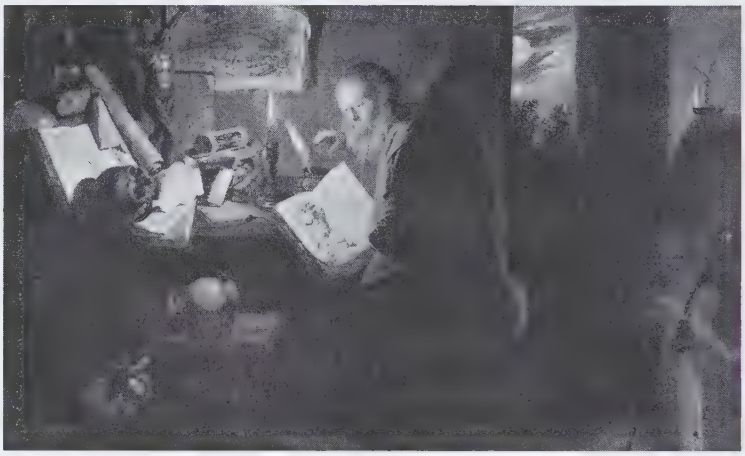


Aldrich-Jahresbericht, 1966


A Letter To Chemists

Alfred Bader

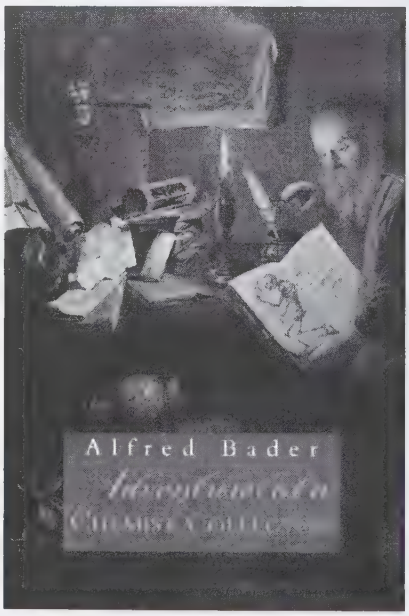
Abschied von Sigma-Aldrich, 1992



Werke aus der Sammlung Bader

Der Kunstsammler

Neben seinen Tätigkeiten als Chemiker und Geschäftsmann hat sich Bader zeit seines Lebens auch immer für Kunst und Kunstgeschichte interessiert und eine der weltweit bedeutendsten privaten Sammlungen von Arbeiten holländischer Meister aus dem 17. Jahrhundert zusammengetragen. Er verstand es auch immer wieder, außergewöhnliche Kunstwerke an Museen – die derartige Summen nicht auf einmal auslegen konnten – weiterzugeben.



Autobiographie von Bader, 1995

Der Kunstsammler, 2000

Der Mäzen

Bader ist Initiator vieler Preise und Stipendien für seine beiden Hauptinteressen Chemie und Kunst. Die Royal Society of Chemistry vergibt einen Alfred Bader- und einen Josef Loschmidt-Preis.
Darüber hinaus zeigt sich die stete Verbundenheit mit den europäischen Wurzeln durch Förderung aller Aktivitäten, die ihm wissenschaftlich wertvoll erscheinen.
Die spektakulärste Aktion Baders stellt wohl der Kauf des Schlosses von Herstmonceux für die Queen's University dar. Das Schloss, bis in die späten 1980er Jahre Sitz des königlichen Greenwich Observatoriums, soll nach dem Willen Baders als europäischer Sitz der kanadischen Universität dienen. Im Rahmen eines großen mittelalterlichen Festes zur Eröffnung übergab er der Universität, die ihm seinerzeit das Tor zu einer wissenschaftlichen Ausbildung geöffnet hatte, das Schloss als Zeichen seiner außerordentlichen Dankbarkeit.

Isabell und Alfred Bader vor Schloss Herstmonceux, 1992

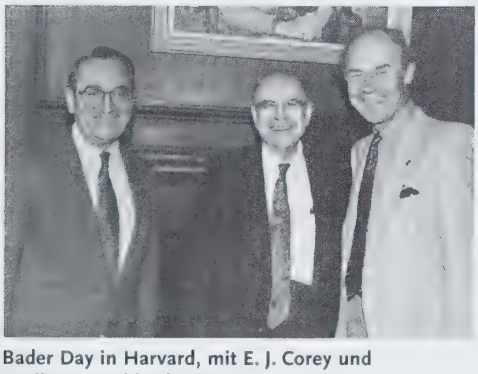
Ausschreibung des Ignaz Lieben-Preises 2004

„Ich schenkte das Schloß Herstmonceux der Queen's Universität, weil ich dort das erste Mal in meinem Leben nicht als Jude sondern als Mensch behandelt wurde."

Ehrungen

Bader wurde vielfach ausgezeichnet und geehrt. Er erhielt unter anderem neun Ehrendoktorate von Universitäten in den USA, Schottland und Tschechien. Die American Chemical Society zeichnete ihn 1998 als „One of the Top 75 Distinguished Contributors to the Chemical Enterprise in the Last 75 Years" aus.

Ehrendoktorat der Glasgow University, 1999



Bader Day in Harvard, mit E. J. Corey und Dudley Herschbach, 1993

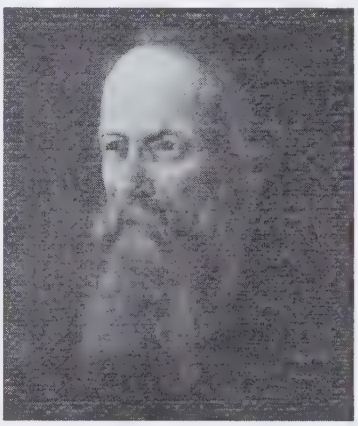
Ehrendoktorat der Queen's University, 1986

Verbundenheit mit Wien

Die großzügige finanzielle Unterstützung von Isabel und Alfred Bader ermöglicht es der ÖAW, den Ignaz L. Lieben-Preis zu reaktivieren und heuer zum ersten Mal neu auszuschreiben. Der älteste Preis der ÖAW, 1863 gestiftet, musste 1937 wegen Verfolgung der Stifterfamilie Lieben eingestellt werden. Renommierte Wissenschaftlerinnen und Wissenschaftler, wie die Physikerinnen Marietta Blau und Lise Meitner sowie die beiden Nobelpreisträger Viktor Hess und Otto Loewy wurden mit diesem Preis ausgezeichnet. Der Preis soll auf Wunsch der Stifter an junge Forscherinnen und Forscher aus Bosnien-Herzegowina, Kroatien, Slowakei, Slowenien, Tschechien, Ungarn und Österreich für herausragende Arbeiten auf den Gebieten der Molekularbiologie, Chemie und Physik verliehen werden.

Bader hat sich auch zum Ziel gesetzt, das Leben und Wirken Josef Loschmidts als Naturwissenschafter bekannt zu machen und veröffentlichte gemeinsam mit Christian R. Noe einige Arbeiten über Loschmidt. Wien verdankt ihm das Loschmidt-Symposium, das 1995 stattfand. Die Universität Wien machte Bader zu ihrem Ehrenbürger. Die Gesellschaft Österreichischer Chemiker verlieh ihm auf Grund seiner Verdienste um die Chemie die Ehrenmitgliedschaft. Obwohl ihm und seiner Familie in Wien so übel mitgespielt wurde, hat Bader immer Kontakt zu Wien gehalten. Er fand hier nicht nur Geschäftspartner, sondern auch gute Freunde.

Mit Franz Sobek, lange der beste Freund in Wien, 1970



Joseph Loschmidt

Mit Robert Rosner in Wien, 1995

Abschied von Wiener Freunden, Bader, Dr. Peter Schuster, Isabel Bader, Familie Noe, Ehepaar Löw-Beer (v. li.)

Ferdinand Franz Cap

Emer. Univ.-Prof., Mag. phil. Dr. rer. nat.
Institut für theoretische Physik an der Universität Innsbruck

Werdegang:

25. 6. 1924	Geboren in Payerbach (Niederösterreich), Eltern: Dr. Franz Cap und Marianne Cap Verheiratet mit Dr. Theresia Cap; ein Sohn
1930–1934	Volksschule in Wien XIII
1934–1942	Hietzinger Gymnasium; 1130 Wien, Fichtnergasse 15
1942–1945	Studium der Mathematik, Physik und Chemie an der Universität Wien, Sponsion zum Mag. Phil.
1946	Promotion zum Dr. rer. nat. sub ausp. pres. Dissertation: „Über zwei Verfahren zur Lösung eindimensionaler instationärer gasdynamischer Probleme“
1944–1949	Assistent an der Universität Wien
1948	Gastforscher an der ETH Zürich
1949–1958	Dozent für theoretische und technische Physik an der Universität Innsbruck
1958–1960	Ao. Univ.-Prof. Universität Innsbruck
1960–1988	O. Univ.-Prof. für theoretische Physik an der Universität Innsbruck
1951–1980	Gastprofessuren und Gastvorlesungen an über 20 Universitäten weltweit
seit 1988	Emer. Univ.-Prof. der Universität Innsbruck

Publikationen:
Über 400 wissenschaftliche Arbeiten in einschlägigen wissenschaftlichen Zeitschriften
Lehrbücher u. a.: „Physik und Technik der Atomreaktoren“
„Einführung in die Plasmaphysik“
„Handbook on Plasma Instabilities“

Ehrungen (Auswahl):
Rutherford Medal of the UDSSR Academy of Sciences (1974)
Award of VIP Encyclopedia USA (1985)
Ehrenmitglied der Indischen Akademie der Wissenschaften Raiastan
Ehrenzeichen des Landes Tirol (1990)
Goldenes Doktor-Diplom der Universität Wien (1996)

Mitgliedschaften (Auswahl):
Österreichische Physikalische Gesellschaft
Physikalisch-Mathematische Gesellschaft Innsbruck
Mitglied der Kommission zur Koordination von Kernforschung in der Österreichischen Akademie der Wissenschaften
International Academy of Astronautics
EU-INTAS Commission for the Evaluation of Research Proposals

„Wissenschaftler zu sein ist etwas, was das ganze Leben, die ganze Persönlichkeit erfordert.“

Kindheit, Schulzeit

Franz Ferdinand Cap wurde am 25. Juni 1924 in Payerbach, Niederösterreich, geboren. Seine Eltern waren Dr. jur. Franz Cap und Marianne Cap, geb. Grill. Nach Besuch der Volksschule in Wien XIII musste er auf Wunsch des Vaters das humanistische Gymnasium mit Latein und Griechisch in der Fichtnergasse in Hietzing besuchen, obwohl er lieber in eine Realschule gegangen wäre.
Cap hat sich schon als Kind mit ca. zehn Jahren viel mit Technik beschäftigt, hat Radios gebastelt und ist durch gute Mathematik- und Physiklehrer weiter für die Physik begeistert worden.

Studium, Krieg

1942 bis 1945 studierte Cap als Werkstudent (Übersetzer) an der Universität Wien Mathematik, Physik und Chemie. 1943 wurde er zum Militärdienst in die Roßauer Kaserne eingezogen und arbeitete in der Freizeit an Übungsarbeiten für theoretische Physik. Wegen seiner guten Studienleistungen wurde Cap durch Fürsprache von Erwin Fues vom Militärdienst befreit und schon während des Studiums 1944 als wissenschaftliche Hilfskraft am Institut für Theoretische Physik eingestellt.

Bundespräsident Waldheim bei der Promotion von Ferdinand und Clemens Cap, 1989

Das Studium konnte Cap mit sub auspiciis praesidentis-Bedingungen abschließen.
„Bei der Promotion war die Aula der Uni oben offen und es hat hereingeschneit; an der Tür stand ein russischer Soldat mit einer Kalaschnikow; alle hatten einen Wintermantel an, so dass man nicht einmal den Talar des Rektors sehen konnte."
Da es zur damaligen Zeit keine sub auspiciis-Ehrung gab, wurde Cap nachträglich im Jahr 1989 gemeinsam mit seinem Sohn Clemens sub auspiciis praesidentis promoviert.

Akademische Laufbahn – Innsbruck

Als nach dem Krieg Erwin Fues die Universität Wien verlassen musste und Hans Thirring wieder die Leitung des Institutes für Theoretische Physik übernahm, wurde Cap bis 1949 Assistent bei Thirring. Thirring förderte Cap sehr, unter anderem, weil dieser sich zusammen mit dem damaligen Leiter der Bibliothek, Robert Chorherr, bei der Rettung der Zentralbibliothek, die von den Nazis nach Deutschland verlegt werden sollte, verdient gemacht hatte. Thirring verschaffte Cap im Jahr 1948 eine Stelle als Gastforscher an der ETH Zürich. 1949 erkrankte Professor Arthur March vom Institut für theoretische Physik in Innsbruck schwer und Cap übernahm – durch die Vermittlung von Hans Thirring – dessen Vertretung.

Über eine Erweiterung der Strömungs- und der Kontinuitätsgleichung der instationären Gasdynamik für den Fall des Vorhandenseins von Gasquellen und des Mitgerissenwerdens fester oder flüssiger Partikel.

Von

Ferdinand Cap.

Institut für theoretische Physik, Universität Wien.

(Eingelangt am 16. Dezember 1946.)

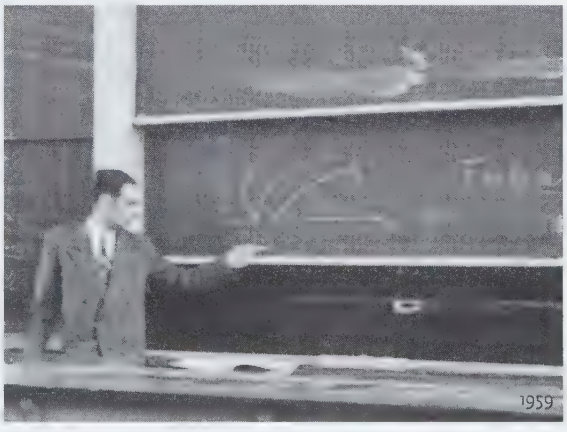
Einleitung und Problemstellung.

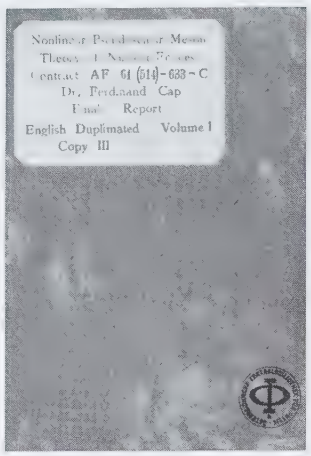
Die Lösung zweidimensionaler stationärer und eindimensionaler instationärer gasdynamischer Probleme, die mathematisch infolge des komplizierten Baues der aus der Kontinuitätsgleichung folgenden Potentialgleichung[1]) große Schwierigkeiten bietet, ist mit Hilfe graphischer Näherungsmethoden leicht zu erhalten[1]) [2]) [3]).

Molenbrock[4]) hat folgenden — in den Grundzügen auch für instationäre Probleme gültigen — Weg zur Lösung der zweidimensionalen stationären Probleme angegeben: Man überführt die Potentialgleichung (die quasilinear ist) mit Hilfe der *Legendre*-Transformation in eine lineare Differentialgleichung. Die Charakteristiken dieser linearisierten Potentialgleichung liegen nun ein für allemal fest[5]) [6]) [7]); die Charakteristiken der quasilinearen Potentialgleichung sind jedoch von den Randbedingungen des jeweiligen Problems abhängig, so daß sie sich nicht für ein graphisches Verfahren eignen. Man zeichnet sich daher die Charakteristiken der linearisierten Potentialgleichung (Charakteristikendiagramm) und nimmt dann graphisch auf Grund bekannter geometrischer Beziehungen zwischen den beiden Charakteristikenscharen derart die Rücktransformation vor, daß man

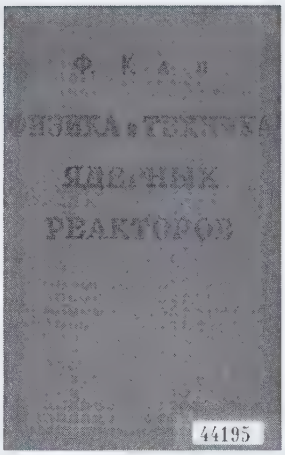
[1]) *Cap*, Dissertation Universität Wien 1945.
[2]) *Prandtl-Busemann*, Stodola-Festschrift, Zürich 1929
[3]) *Schultz-Grunow*, Forsch. Ing. Wesen 1942—13, Nr. 3.
[4]) *Molenbrock*, Arch. Math. Phys., Grunert-Hoppe, Reihe 2, Bd. 9, 1890, S. 157.
[5]) *B. Baule*, Partielle Differentialgleichungen.
[6]) *Goursat*, Cours d'Analyse.
[7]) *Forsyth*, Diff. Equ

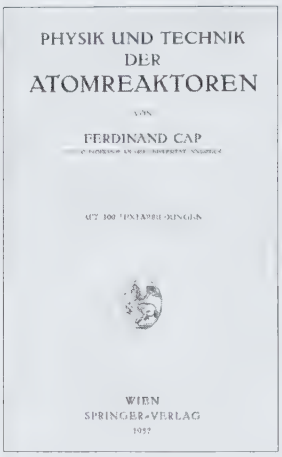
Acta Physica Austriaca. Bd. I 1





Meson Theorie of Nuclear Forces, 1. Forschungsauftrag der US-Regierung, 1954





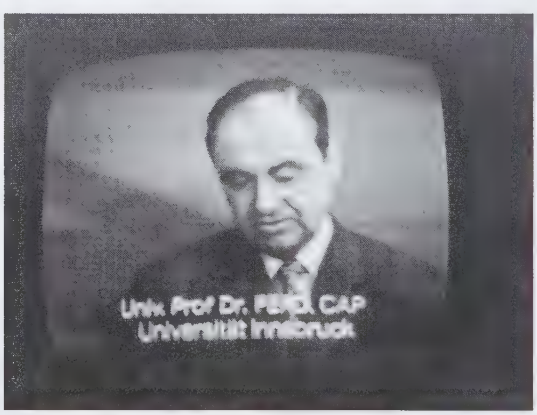
Lehrbuch „Physik und Technik der Atomreaktoren", deutsch und russisch

Cap habilitierte sich in theoretischer und technischer Physik und betreute damals bis zu 25 Dissertant-Innen gleichzeitig. 1951 wurde Cap als Assistent Erwin Schrödinger zugeteilt, der in Innsbruck eine Gastprofessur hatte. Mit ihm unternahm er Bergtouren und konnte viel von ihm lernen.
Nach dem Tod von Prof. March im Jahr 1958 wurde Cap a.o. Professor und 1960 Ordinarius für theoretische Physik an der Universität Innsbruck.
In den Jahren 1946 bis 1949 arbeitete Cap auf dem Gebiet der Gasdynamik, der Elementarteilchen, der Relativitäts- und Feldtheorie sowie der Kernkräfte und erhielt 1954 seinen ersten bezahlten Forschungsauftrag der amerikanischen Regierung. Basierend auf den neuen Methoden des Innsbrucker Mathematikers Grübner berechnete Cap mit diesem 1957 im Auftrag der NASA Bahnen zum Mond.

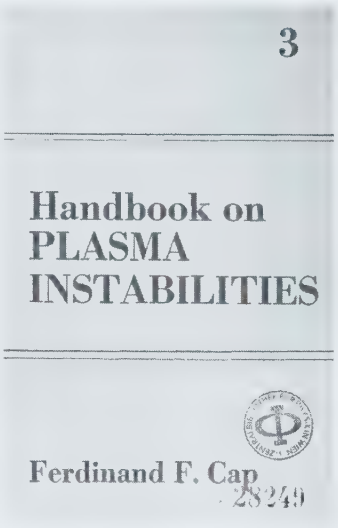
Von der Regierung wurde Cap in den Jahren 1966 bis 1975 als österreichischer Vertreter in den wissenschaftlichen Weltraumausschuss der Vereinten Nationen entsandt.
1957 erschien im Springer-Verlag das Lehrbuch „Physik und Technik der Atomreaktoren", welches 1960 auch ins Russische übersetzt wurde.
Cap machte aus der Not der Studierenden sein Hauptforschungsgebiet: Angeregt durch den Wunsch der Studierenden, Lehrinhalte angeboten zu bekommen, die ihnen den Einstieg ins Berufsleben erleichtern sollten, begann Cap sich in dieser Zeit mit dem eigentlichen Forschungsschwerpunkt seines wissenschaftlichen Lebens zu beschäftigen: mit der Plasma- und Energiephysik.

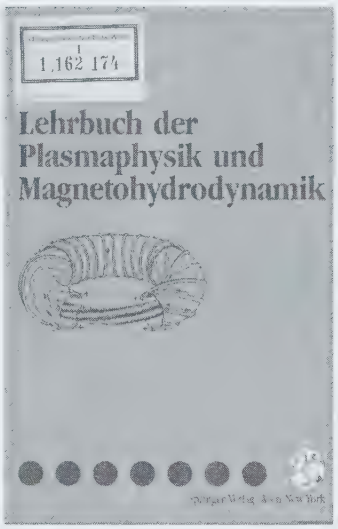
Das Wissen über Radioaktivität ist in Österreich total schlecht. Es handelt sich um ein komplexes Wissensgebiet, wo viele (auch Wissenschaftler) sich nicht die Arbeit antun, es zu erlernen.

Internationaler Weltraumkongress in Innsbruck, 1986



Cap als Experte zur Mondlandung im ORF, 1969





Wie begründen wir die Annahme, dass Dinge verursacht werden müssen? Warum können wir nicht annehmen, dass Dinge einfach von selbst entstehen?

Instabilitätenkongress in New Delhi – Noriyoshi Sato, Cap, Frau Cap, Siegbert Kuhn, 1989

Plasmakongress Innsbruck 1992

Plasma- und Energiephysik

Seit 1958 ist Caps Hauptforschungsgebiet die Plasma- und Energiephysik. Er organisierte zweimal in Innsbruck internationale Kongresse über Plasmaphysik und verfasste auch mehrere Lehrbücher über dieses Spezialgebiet:
1970 erschien im Verlag Vieweg, BRD, das dreibändige Lehrbuch „Einführung in die Plasmaphysik".
Im Verlag Academic Press, New York, erschienen die drei Bände des „Handbook on Plasma Instabilities".

Bei Springer in Wien erschien 1994 das Lehrbuch „Plasmaphysik und Magnetohydrodynamik".
Aus der von Cap begründeten Innsbrucker Schule der Plasma- und Energiephysik gingen mehrere derzeit in Deutschland und in den USA als Hochschulprofessoren tätige Schüler hervor.

Cap als Forschungsunternehmen

Von 1963 bis 1981 gelingt es Cap, Forschungsaufträge von der amerikanischen Regierung auf dem Gebiet der Plasma- und Energiephysik im Wert von einigen Millionen Dollar zu bekommen und er schaffte so wohl den Beweis, dass man mit guter wissenschaftlicher Forschung auch in Österreich viel Geld lukrieren kann.
Auch der FWF förderte den Forschungsschwerpunkt Plasmaphysik über zehn Jahre lang.
Zwischen 1957 und 1973 leitete Cap für die Kongressbibliothek Washington und für mehrere deutsche und amerikanische Verlage ein wissenschaftliches Übersetzungs- und Abstracting-Programm, bei dem zeitweilig bis zu 80 MitarbeiterInnen beschäftigt waren.
Die US-Subventionen und viele ausländische Kontakte ermöglichten es Cap, zahlreichen Studierenden Dissertationsstipendien zu gewähren und auch viele seiner Schüler an ausländischen Universitäten unterzubringen.

William P. Allis vom MIT (Massachusetts Institute of Technology) bei Cap, 1975

THE LIBRARY OF CONGRESS
WASHINGTON 25, D. C.

REFERENCE DEPARTMENT
AIR INFORMATION DIVISION

June 16, 1961

My dear Professor Cap:

I have your letter of June 13th and hasten to respond to your question concerning the signing of a new contract.

Since it seems unlikely that there will be any change in the arrangements in the very immediate future, I fear there is very little choice but for you to sign the contract for the new fiscal year beginning July 1. I will, of course, discuss with you the full state of affairs when you are here in July.

In connection with your visit, I will call you at your friend's home in Bel Air on July 4th. We can then arrange for our meeting on the following day. If you are not obliged to leave on the evening of the 5th, I hope you will be able to spend that evening at our home.

Since you are not leaving Innsbruck until June 23rd, I trust this letter will reach you several days in advance of your departure.

I am certainly looking forward to seeing you on July 5th.

Sincerely yours,

George A. Pughes, Jr.,
Chief
Air Information Division

Professor Ferdinand Cap
Institute of Theoretical Physics
Innsbruck University
Innsbruck, Austria
Innrain 52

THE FOREIGN SERVICE
OF THE
UNITED STATES OF AMERICA

12 February 1962

Herrn
Professor Dr. F. Cap
Institut fuer Theoretische Physik
der Universitaet Innsbruck
Innsbruck

Dear Professor Cap!

As you are aware, the funds dispersed by the United States Government within the Universities of Austria are solely to support Austrian Research and enlarge collaboration between Austrian and scientific institutions in the United States. This support, which incidentely is virtually world wide, has, as you know, the approval of your Government.

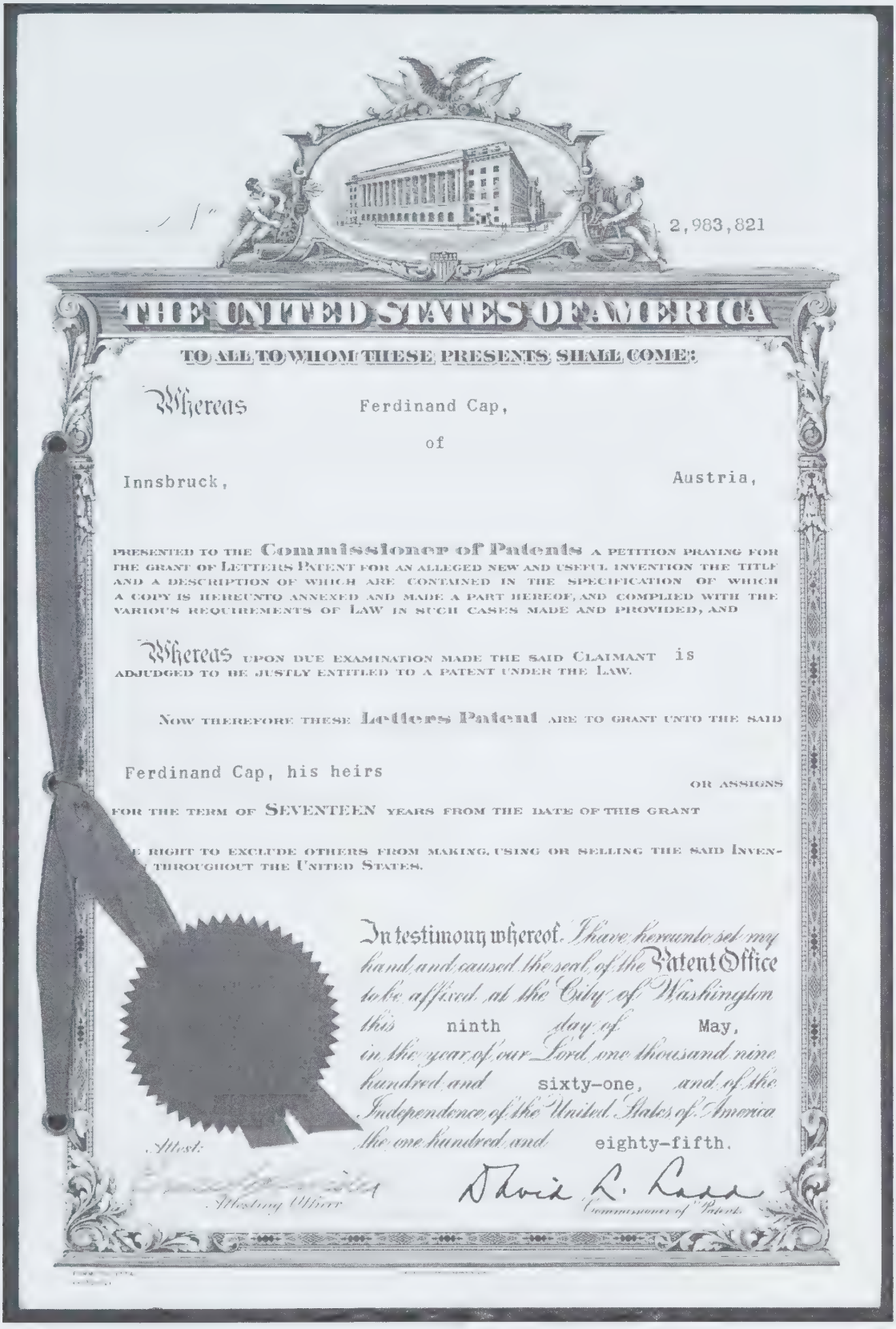
These funds are, of course, funds of the United States Government appropriated strictly for the support of scientific research and can never be used for the support of a commercial enterprise. Funds for Austria are usually administered by the United States Embassy in Vienna although, occasionally, other United States Government administrative offices within western Europe may administer certain scientific contracts.

Because of the wide range of interests of your Institute as are extremely happy to support several of your research projects. We feel that this support not only furthers scientific research within Austria but also that it contributes to the advancement of World science because of your involvement with many of the very frontiers of nuclear and space research.

Please be assured of our continuing esteem and the hope that you will continue your already recognized research in these very important areas of scientific effort.

Very truly yours,

EMERSON W. CURTIS
Assistant Attache



2,983,821

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

Whereas Ferdinand Cap,

of

Innsbruck, Austria,

PRESENTED TO THE **Commissioner of Patents** A PETITION PRAYING FOR THE GRANT OF LETTERS PATENT FOR AN ALLEGED NEW AND USEFUL INVENTION THE TITLE AND A DESCRIPTION OF WHICH ARE CONTAINED IN THE SPECIFICATION OF WHICH A COPY IS HEREUNTO ANNEXED AND MADE A PART HEREOF, AND COMPLIED WITH THE VARIOUS REQUIREMENTS OF LAW IN SUCH CASES MADE AND PROVIDED, AND

Whereas UPON DUE EXAMINATION MADE THE SAID CLAIMANT is ADJUDGED TO BE JUSTLY ENTITLED TO A PATENT UNDER THE LAW.

NOW THEREFORE THESE **Letters Patent** ARE TO GRANT UNTO THE SAID

Ferdinand Cap, his heirs OR ASSIGNS

FOR THE TERM OF SEVENTEEN YEARS FROM THE DATE OF THIS GRANT

E RIGHT TO EXCLUDE OTHERS FROM MAKING, USING OR SELLING THE SAID INVEN- THROUGHOUT THE UNITED STATES.

In testimony whereof I have hereunto set my hand and caused the seal of the Patent Office to be affixed at the City of Washington this ninth day of May, in the year of our Lord one thousand nine hundred and sixty-one, and of the Independence of the United States of America the one hundred and eighty-fifth.

Attest:

Attesting Officer

David L. Ladd

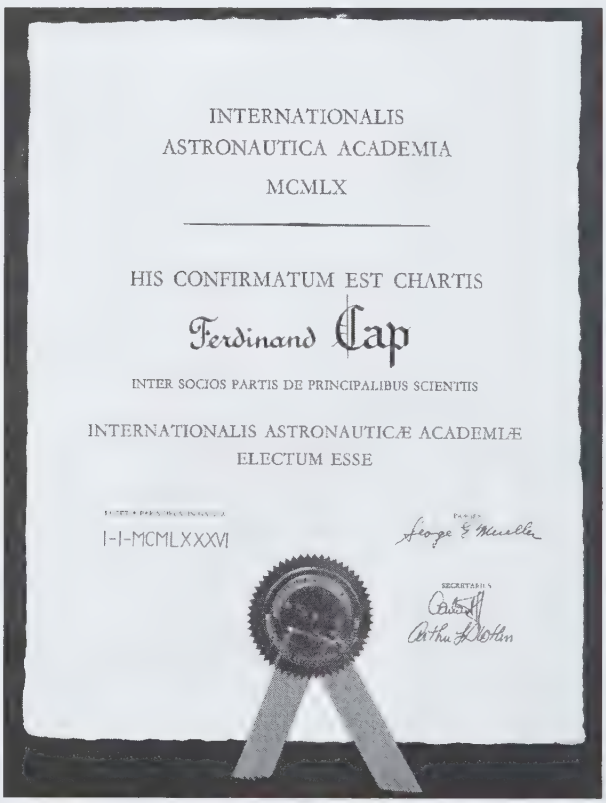
Commissioner of Patents.

Nobelpreisträger Peter Kapitza überbringt Cap die Rutherford-Medaille, 1974

Nicht die Natur wurde so geschaffen, dass sie für Lebewesen geeignet war, sondern die Lebewesen entwickelten sich so, dass sie an die Umwelt bestens angepasst waren.

Arbeiten, Auslandskontakte

Cap publizierte insgesamt über 400 Arbeiten in einschlägigen wissenschaftlichen Zeitschriften und ist Inhaber von mehr als 60 internationalen Patenten, u. a. für einen Atomschutzanzug, ein Gerät zur Umwandlung mechanischer in elektrische Energie (parametrischer Generator) und ein Atomstrahlenmessgerät.
Sechzehnmal wurde Cap an ausländische Universitäten berufen, lehnte aber alle Berufungen ab und blieb der Universität Innsbruck treu. Er nahm jedoch öfter kurze Gastprofessuren an und lehrte u. a. in Deutschland, der Sowjetunion, Japan, Indien, Südafrika, Italien, Bulgarien, Rumänien, den USA, Belgien, Frankreich, Norwegen und Polen.
Zahlreiche internationale Ehrungen wurden an den Physiker vergeben, so die Ehrenmitgliedschaft der Akademie der Wissenschaften von Rajastan und die Mitgliedschaft der International Academy of Astronautics. Von der sowjetischen Akademie der Wissenschaften erhielt er deren Rutherford-Medaille „Ehre dem wissenschaftlichen Lehrer und Forscher".



Mitglied der International Astronautic Academie

Voruntersuchung

über die Berechnung des Reflexionskoeffizienten in dünnen Schichten.

Problem: Ist es prinzipiell möglich, das Minimum des Reflexionskoeffizienten von Radarwellen an Radar Black Layers für einen größeren Wellenlängenbereich zu verbreitern?

Zwischenbericht

über die Zeit 15. Februar - 7.April 1955.

von

F. Cap und W. Gröbner

Research Center Innsbruck , 2.April 1955.

Contents

Prof. Lindg M.I.T.

§1. Introduction
§2. Physical Description, Differential Equation
§3. Mathematical Explanation and Solution

Daraus entstand der Tarnkappenbomber (Stealth-Flieger)

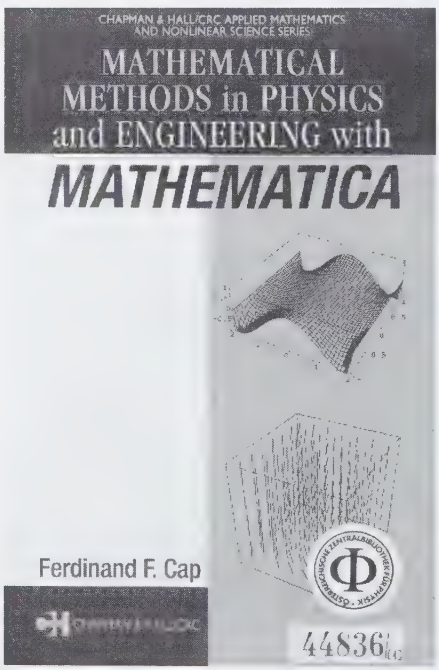
Cap und Todor Karman in Paris

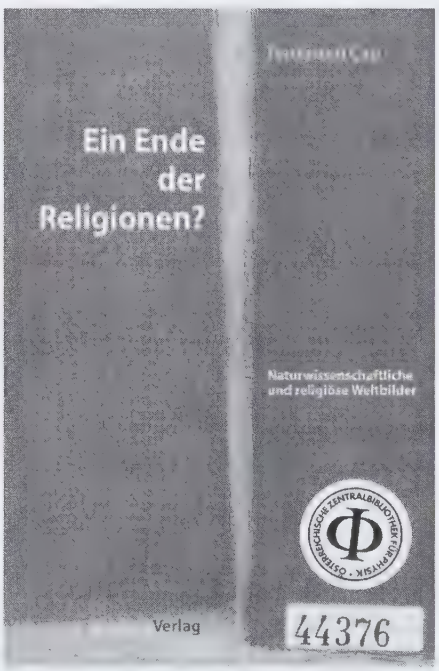
Österreichischer Delegierter bei einem Energiekongress in Rom, 1985

NOS RECTOR UNIVERSITATIS
LITTERARUM VINDOBONENSIS
LUDOVICUS ADAMOVICH
IURIS DOCTOR
PROFESSOR IURIS AC RERUM POLITICARUM PUBLICUS ORDINARIUS
GUILELMUS CZERMAK
PHILOSOPHIAE DOCTOR
PROFESSOR AEGYPTOLOGIAE ET AFRICANISTICAE PUBLICUS ORDINARIUS
H.T. DECANUS
JOSEPHUS KEIL
PHILOSOPHIAE DOCTOR
PROFESSOR HISTORIAE ET EPIGRAPHIAE GRAECAE PUBLICUS ORDINARIUS
PROMOTOR RITE CONSTITUTUS
IN VIRUM CLARISSIMUM
FERDINANDUM CAP
E PAYERBACH IN AUSTRIA INFERIORE ORTUM
POSTQUAM ET DISSERTATIONE CUI INSCRIBITUR
"ÜBER ZWEI VERFAHREN ZUR LÖSUNG EINDIMENSIONALER INSTATIONÄRER GASDYNAMISCHER PROBLEME"
ET EXAMINIBUS LEGITIMIS LAUDABILEM IN PHYSICA DOCTRINAM PROBAVIT
DOCTORIS PHILOSOPHIAE
NOMEN ET HONORES IURA ET PRIVILEGIA
CONTULIMUS IN EIUSQUE REI FIDEM HASCE LITTERAS
UNIVERSITATIS SIGILLO SANCIENDAS CURAVIMUS
VINDOBONAE DIE XIX MENSIS DECEMBRIS MCMXLV
J. KEIL M.P. L. ADAMOVICH M.P. G. CZERMAK M.P.

TITULUM HOC DIPLOMATE CONLATUM DOCTORI SUO
FERDINANDO CAP
QUI DE PHYSICA PLASMARI INVESTIGANDA ET
DE PHYSICA THEORETICA DOCENDA OPTIME MERITUS EST
PLUS QUINQUAGINTA ANNIS POST DIEM
XIX MENSIS DECEMBRIS MCMXLV
FELICITER PERACTIS
COLLEGIO FACULTATIS
ORDINIS RERUM NATURALIUM PERITORUM
UNIVERSITATIS VINDOBONENSIS
RENOVARI PLACUIT
VINDOBONAE DIE XXII MENSIS IANUARII MDCCCCXCVI
RECTOR UNIVERSITATIS
DECANUS FACULTATIS

Ferdinand Cap ist zwar seit 1988 emeritiert, aber nach wie vor nicht im Ruhestand.
Im Jahr 2003 erschienen zwei Bücher von Cap, welche die ganze Bandbreite seiner Interessen widerspiegeln:
Bei Chapman & Hall/CRC ein Buch über die Anwendung des Programmpaketes Mathematica auf Physik und technische Probleme: „Mathematical methods in physics and engineering with Mathematica", und im Innsbrucker Studienverlag ein Buch über naturwissenschaftliche und religiöse Weltbilder: „Ein Ende der Religionen?"





Michael J. Higatsberger

Emer. Univ.-Prof., Dr. Dr. h. c.
Institut für Experimentalphysik der Universität Wien

Werdegang:

8. 6. 1924	Geboren in Unterbergern (Niederösterreich), Eltern: Michael und Berta Higatsberger, Verheiratet mit Dr. Lucia Higatsberger, geb. Sartori; ein Sohn
1943	Humanistisches Gymnasium Krems, Matura mit Auszeichnung Studium der Mathematik, Physik, Chemie und Philosophie an der Universität Wien
1949	Promotion zum Dr. phil. mit Auszeichnung Dissertation: „Elektronenoptische Zylinderlinsenwirkung des realen Plattenkondensators“
1949–1952	Universitätsassistent am 1. Physikalischen Institut der Universität Wien
1952–1953	University of Minnesota
1954–1955	Konsulent des Forschungslaboratoriums Fort Belvoir, Virginia und Lehrtätigkeit an der Catholic University of Washington
1956–1971	Technisch-wissenschaftlicher Geschäftsführer der Österreichischen Studiengesellschaft für Atomenergie und des Reaktorzentrums Seibersdorf
1958	Habilitation an der Universität Wien; Habilitationsschrift: „Neuere Apparate in der Massenspektroskopie“
1965	Honorarprofessor für Reaktorphysik an der TH-Graz
1969	Ao. Univ.-Prof. an der Universität Wien
1971	O. Univ.-Prof. an der Universität Wien
1992	Dr. h. c. der Universität Tel Aviv, Israel
ab 1994	Emer. Univ.-Prof. für Experimentalphysik und Industriekonsulent
ab 1965	Im Aufsichtsrat von verschiedenen österreichischen Firmen
7. 1. 2004	Professor Higatsberger verstirbt in Wien

Publikationen:
70 wissenschaftliche Publikationen (inklusive fünf Bücher)
128 populärwissenschaftliche Publikationen (inklusive ein Buch)
73 österreichische und ausländische Patente

Ehrungen (Auswahl):
Kulturpreis des Landes Niederösterreich (1967)
Ehrenbürger der Gemeinde Bergern (1968)
Großes Goldenes Ehrenzeichen des Landes Steiermark (1984)
Wilhelm Exner-Medaille des Österreichischen Gewerbevereines (1991)
Ehrenmedaille der Bundeshauptstadt Wien in Gold (1994)
Österreichisches Ehrenkreuz für Wissenschaft und Kunst I. Klasse (2001)

Mitgliedschaften (Auswahl):
American and British Nuclear Society
European Atomic Energy Society (1970–1971 Executive Vice-President)
Europäisches Komitee des Weizmann Institute of Science
European Physical Society
Max-Auwärter-Stiftung in Liechtenstein (Wissenschaftlicher Beirat)
Chemisch-Physikalische Gesellschaft (Präsident 1976/1977 und 1993/1994)
Forschungsgesellschaft Joanneum Graz (Kuratoriumsmitglied)
Österreichische Physikalische Gesellschaft – Gründungsmitglied (1972–1974
Österreichisches IIASA Komitee
Österreichische Biophysikalische Gesellschaft
Österreichische Gesellschaft für Vakuumtechnik
Präsident der Gesellschaft Österreichischer Chemiker (1985–1991)
Member New York Academy of Sciences (1987)
Sekretär der mathematisch-naturwissenschaftlichen Klasse der ÖAW (1987–1991)
Generalsekretär der Österreichischen Akademie der Wissenschaften (1991–1995)
Korrespondierendes Mitglied der Nordrhein-Westf. Akademie der Wissenschaften (1996)
Vizepräsident der Österreichischen Akademie der Wissenschaften (1997–2000)

„Wir leben in einem Zeitalter, das durch ein Element, Uran, geprägt wird; unsere Zivilisation sollte aber nicht durch Uran begrenzt oder gar beendet werden.“

Kindheit, Gymnasium

Michael J. Higatsberger wurde am 8. Juni 1924 in Unterbergern bei Krems/NÖ als Sohn von Michael und Berta Higatsberger geboren. Er maturierte 1943 am Humanistischen Gymnasium in Krems mit Auszeichnung.

Studium, Auslandserfahrungen

Higatsberger promovierte 1949 nach einem Studium der Physik, Chemie, Mathematik und Philosophie mit Auszeichnung an der Universität Wien zum Dr. phil. Dissertation: „Elektronenoptische Zylinderlinsenwirkung des realen Plattenkondensators".
Es folgte eine Tätigkeit als Assistent am Ersten Physikalischen Institut der Universität Wien, begleitet von mehreren Auslandsaufenthalten, insbesondere an der University of Minnesota, am Research Laboratory Corps of Engineers in Fort Belvoir und an der Catholic University in Washington, USA.
Higatsberger hat bei diesen Tätigkeiten gelernt, sein enormes experimentalphysikalisches Wissen direkt in realistischen Anwendungen bis hin zu technischen Produkten praktisch umzusetzen. Davon zeugt insbesondere auch der Titel seiner Habilitationsschrift: „Neuere Apparate in der Massenspektroskopie".
Er erlebte in den USA den Aufschwung der friedlichen Nutzung der Atomenergie und lernte dort auch die dafür notwendigen Großforschungseinrichtungen kennen.

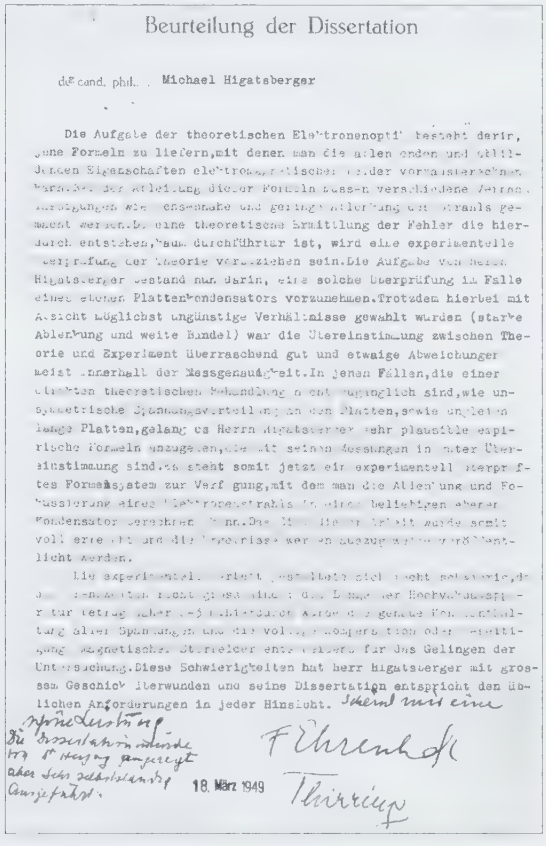

Lichtbild des Inhabers

Reichs-Nr. | Hochschul-Nr.

Studienbuch

des ordentlichen Hörers

Higatsberger Michael


Beurteilung der Dissertation

Michael Higatsberger

Die Aufgabe der theoretischen Elektronenopti[k] besteht darin, Formeln zu liefern, mit denen man die [...] Eigenschaften elektronischer [...] der vorausberechnen kann. Bei der Ableitung dieser Formeln müssen verschiedene Vereinfachungen wie [...] und geringe Ablenkung des Strahls gemacht werden. Bei einer theoretischen Ermittlung der Fehler die hierdurch entstehen, muß durchführbar ist, wird eine experimentelle Überprüfung der Theorie vorzuziehen sein. Die Aufgabe von Herrn Higatsberger bestand nun darin, eine solche Überprüfung im Falle eines ebenen Plattenkondensators vorzunehmen. Trotzdem hierbei mit Absicht möglichst ungünstige Verhältnisse gewählt wurden (starke Ablenkung und weite Bündel) war die Übereinstimmung zwischen Theorie und Experiment überraschend gut und etwaige Abweichungen meist innerhalb der Messgenauigkeit. In jenen Fällen, die einer direkten theoretischen Behandlung nicht zugänglich sind, wie unsymmetrische Spannungsverteilungen an den Platten, sowie ungleich lange Platten, gelang es Herrn Higatsberger sehr plausible empirische Formeln anzugeben, die mit seinen Messungen in guter Übereinstimmung sind. Es steht somit jetzt ein experimentell überprüftes Formelsystem zur Verfügung, mit dem man die Ablenkung und Fokussierung eines Elektronenstrahls in einem beliebigen ebenen Kondensator berechnen kann. Die [...] ist somit voll erreicht und die Ergebnisse werden [...] wertvoll werden.

Die experimentelle [...] gestellte sich recht schwierig, da [...] recht gross sind: Der Krümmungsradius betrug [...] Hierdurch [...] gewisse Konstruktion [...] Spannungen und die volle Kompensation oder Ausschaltung magnetischer Störfelder erforderlich für das Gelingen der Untersuchung. Diese Schwierigkeiten hat Herr Higatsberger mit grossem Geschick überwunden und seine Dissertation entspricht den üblichen Anforderungen in jeder Hinsicht. Schade muss eine [...] Die Dissertation wurde [...] Herzog empfiehlt aber sehr selbständig [...] angefertigt.

18. März 1949

Ehrenhaft

Thirring

Erster wissenschaftlicher Vortrag, 1948

Seibersdorf

Die Kombination von naturwissenschaftlichem Wissen und Kenntnis der Notwendigkeiten der praktischen Umsetzung führten dazu, dass sich Michael J. Higatsberger, heimgekehrt nach Österreich, im Jahr 1955 voll für die Errichtung eines Kernforschungszentrums in Österreich einsetzte.
Er konnte alsbald die österreichische Bundesregierung – der Staatsvertrag war gerade unterzeichnet worden und Österreich ein freies Land – von der Idee überzeugen.
So kam es bereits 1956 zur Gründung der „Österreichischen Studiengesellschaft für Atomenergie", deren erster wissenschaftlich-technischer Geschäftsführer er ab der Gründung bis zum Jahre 1971 war.
Die Gesellschaft begann sofort mit der Planung der Großforschungsanlage und bestimmte als deren Standort Seibersdorf. Im Jahr 1961 konnten der Forschungsreaktor und die Institute für Physik, Elektronik, Chemie, Metallurgie und Strahlenschutz eröffnet werden.

Durch seine 15-jährige Aufbautätigkeit hat er den Grundstein zur Etablierung von Seibersdorf als international anerkanntes Forschungsunternehmen gelegt. Die Ausrichtung hat sich seither zwar gewandelt – vom primär auf Nuklearforschung ausgerichteten Kernforschungszentrum zum auf Kernkompetenzen aufgebauten Forschungsunternehmen. Die Grundidee – durch Spitzenqualität der geleisteten Arbeit auf speziell ausgewählten Gebieten auch mit den Möglichkeiten und Mitteln eines kleineren Landes international anerkannte Leistungen zu erbringen – ist jedoch geblieben.

Eröffnung mit Bundespräsident Schärf, 1960

Seibersdorf Reactor and Research Centre

by
MICHAEL J. HIGATSBERGER
Österreichische Studiengesellschaft
für Atomenergie
Ges m b.H

For twelve years, industry and the universities have jointly been running the national atomic energy organization.

TWELVE years ago almost to the day, on May 15, 1956, representatives of the Austrian Government, university professors and leading industrialists joined in an effort to create a national atomic energy organization. The flexible form of a limited liability company was chosen as being optimal under Austrian law, and the organization was named the Österreichische Studiengesellschaft für Atomenergie Ges.m.b.H. (SGAE). In the years which followed, the planning and the building of the country's biggest research institute took place at Seibersdorf, which is located some 35 kilometres south of Vienna.

During this time nearly 300 million Austrian schillings (£4·8 million) have been invested in modern research facilities, ranging from a 5 MW research and test reactor, over laboratories for reactor components development, industrial isotope application, metallurgy, chemistry, solid state physics, nuclear physics, health physics, mathematics and electronics to agricultural and biological facilities of international standard. Fig. 1 shows graphically the investment trend over the years up to the end of 1967.

The running costs of the centre amounted to more than 70 million Austrian schillings (nearly £1 million) in 1967. The staff numbers about 500; in Fig. 2 the growth of the staff over the years is given. In 1967 the total of 494 staff members included 102 graduate students working on their diplomas and PhD theses. The staff structure, divided into scientific personnel, technicians, workers and administrative employees, is shown in Fig. 3.

Initial Research Programme and Policy

The capital investments in and the operating costs of the Seibersdorf reactor centre have been defrayed since its foundation by the Republic of Austria and some fifty of the most important Austrian industrial firms and utilities. It was therefore necessary to define a programme acceptable to the representatives of both science and industry. In the initial planning stage, working teams comprising representatives of the Austrian universities and experts from industrial circles co-operated to make recommendations. Today, scientific and industrial advisory committees formulate the guide lines of the short term and the long range programmes of the reactor centre's various institutes.

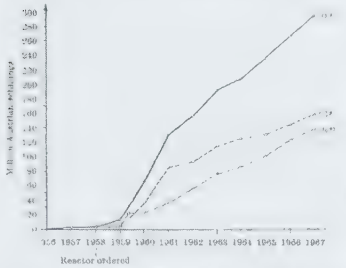


Fig. 1. Growth of capital assets, ... total of capital assets, ... (excluding nuclear equipment).

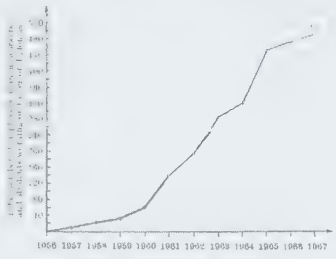


Fig. 2. Growth of staff from 1956–1967.

The basis of the programme is defined in paragraph 3 of the statute of the SGAE, which reads:

"(1) The objective of the organization is the pursuit of basic studies in nuclear energy, their peaceful application, the acquisition of relevant patents and their application, in particular through the granting of licences, the utilization of the products resulting from work undertaken by the organization, especially of isotopes, as well as the carrying out of special tasks in the field of nuclear energy with which the organization is entrusted by the Austrian Federal Government.

(2) The objective of the organization is to be reached in co-operation with government, industry and science."

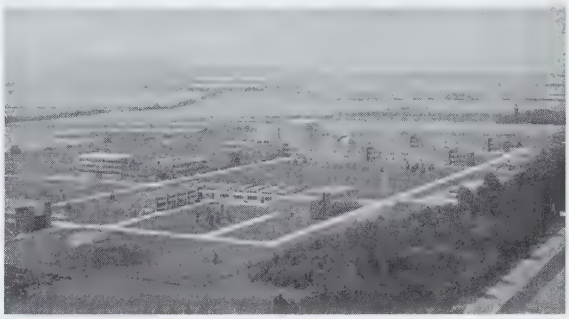
Despite the fact that activities in the atomic energy field are the major responsibility of the reactor centre, it was always recognized that the research equipment and the personnel must be chosen to cope with a research and development programme as broad and universal as possible. Through the participation of important industrial firms and many institutes of the Austrian universities, diversification took place from the very beginning. This may be one of the reasons why the Austrian centre does not today face problems similar to those found with atomic energy organizations in other countries.

Originally, roughly one-third of the SGAE's scientific activity was devoted to basic research in connexion and co-operation with the Austrian universities. The other

Veröffentlichung
in „Nature",
1968

Das Grundkonzept von Seibersdorf basiert auf einer Zusammenarbeit von Staat, Wirtschaft und Wissenschaft.

Reaktorzentrum Seibersdorf

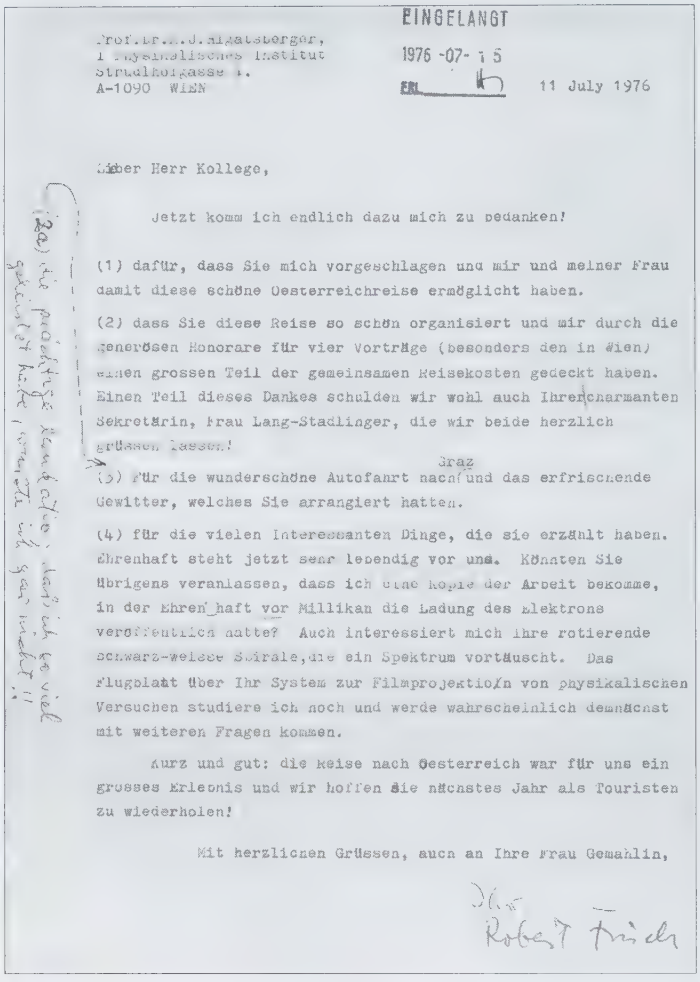


10 Jahre
Österreichische Studiengesellschaft
für Atomenergie Gesellschaft m. b. H.
1956-1966

Goldenes Doktordiplom an Robert Otto Frisch, 1976

Vakuum- & Oberflächen-Kongress Hofburg, 1977 (Kirchschläger, Firnberg)

Mit Nobelpreisträger Peter Kapitza in Wien, 1972



EINGELANGT
1976 -07- 15

Prof.Dr. M.J.Higatsberger,
I.Physikalisches Institut
Strudlhofgasse 4.
A-1090 WIEN

11 July 1976

Lieber Herr Kollege,

Jetzt komm ich endlich dazu mich zu bedanken!

(1) dafür, dass Sie mich vorgeschlagen und mir und meiner Frau damit diese schöne Oesterreichreise ermöglicht haben.

(2) dass Sie diese Reise so schön organisiert und mir durch die generösen Honorare für vier Vorträge (besonders den in Wien) einen grossen Teil der gemeinsamen Reisekosten gedeckt haben. Einen Teil dieses Dankes schulden wir wohl auch Ihrer charmanten Sekretärin, Frau Lang-Stadlinger, die wir beide herzlich grüssen lassen!

(3) für die wunderschöne Autofahrt nach Graz und das erfrischende Gewitter, welches Sie arrangiert hatten.

(4) für die vielen interessanten Dinge, die sie erzählt haben. Ehrenhaft steht jetzt sehr lebendig vor uns. Könnten Sie übrigens veranlassen, dass ich eine Kopie der Arbeit bekomme, in der Ehrenhaft vor Millikan die Ladung des Elektrons veröffentlicht hatte? Auch interessiert mich Ihre rotierende schwarz-weisse Spirale, die ein Spektrum vortäuscht. Das Flugblatt über Ihr System zur Filmprojektion von physikalischen Versuchen studiere ich noch und werde wahrscheinlich demnächst mit weiteren Fragen kommen.

Kurz und gut: die Reise nach Oesterreich war für uns ein grosses Erlebnis und wir hoffen sie nächstes Jahr als Touristen zu wiederholen!

Mit herzlichen Grüssen, auch an Ihre Frau Gemahlin,

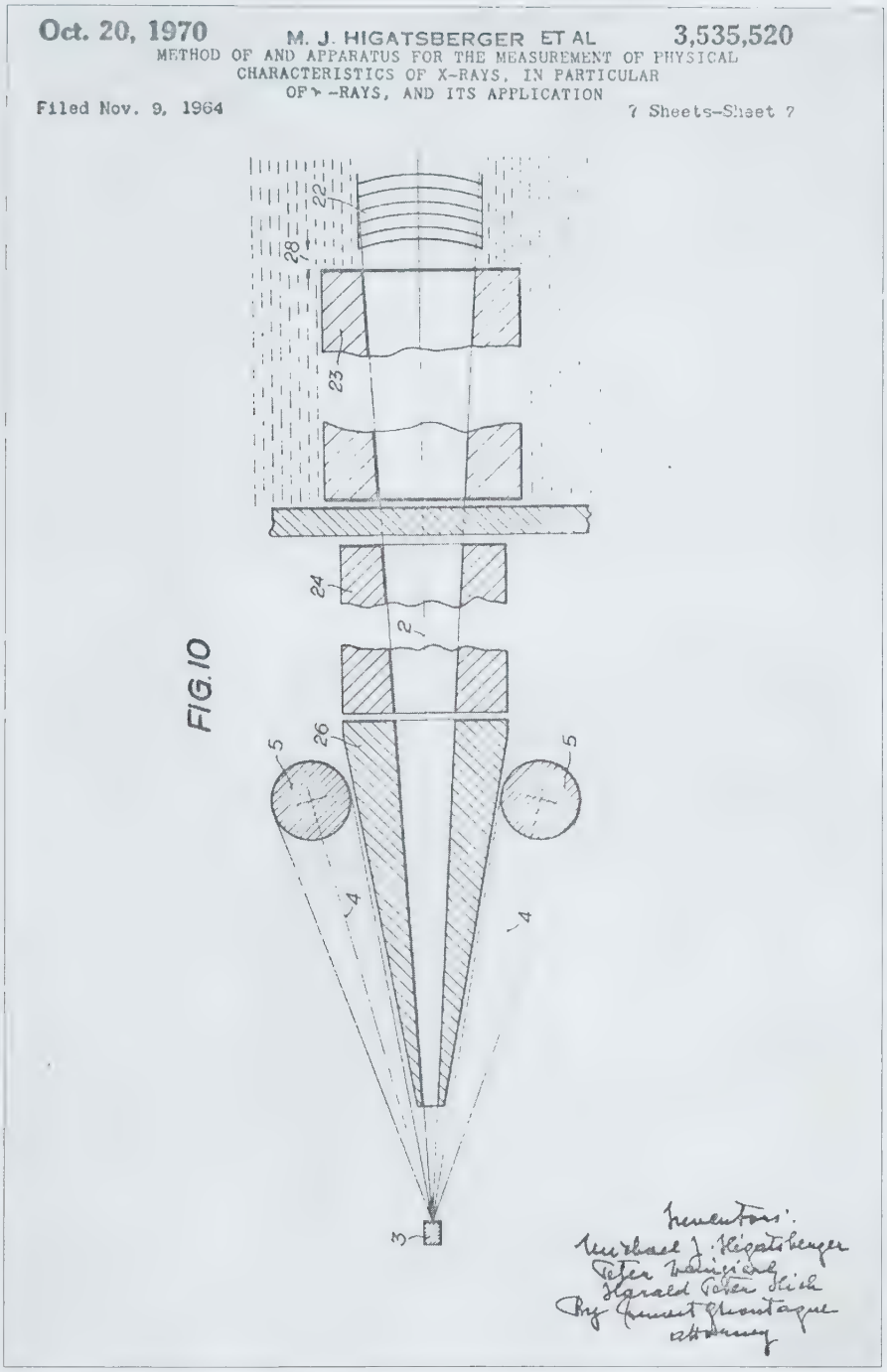
Ihr
Robert Frisch

Brief von Robert Otto Frisch an Higatsberger, 1976

Lehre, Universität

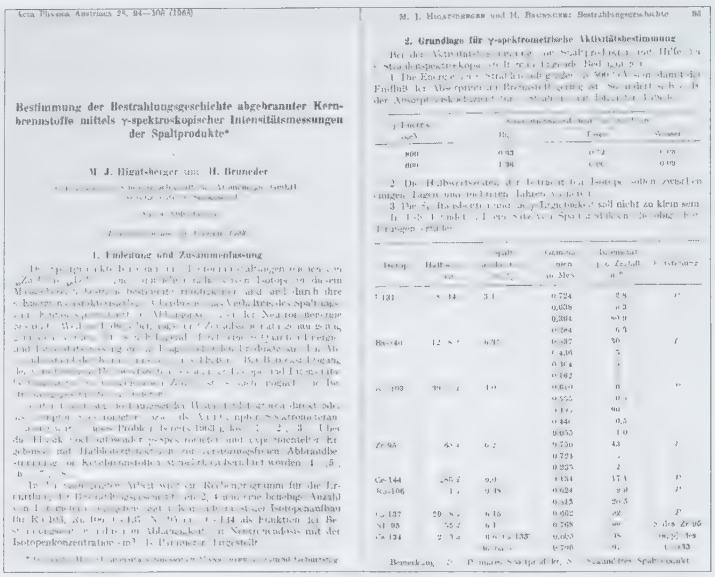
Parallel zu seiner Tätigkeit als Leiter des Forschungszentrums Seibersdorf hat sich Michael J. Higatsberger immer intensiv der Lehre gewidmet. So wurde er 1965 Honorarprofessor für Reaktorphysik an der Technischen Hochschule Graz und 1969 ao. Univ. Prof. an der Universität Wien. Dem folgte 1971 die Berufung als ordentlicher Universitätsprofessor für Experimentalphysik und Vorstand des Ersten Physikalischen Instituts der Universität Wien. In seiner langjährigen Tätigkeit als Universitätslehrer hat Michael J. Higatsberger viele Generationen an Studierenden, darunter auch viele Nichtphysiker, in die Grundkonzepte der Physik eingeführt.

Legendär ist seine Betonung der Bedeutung des physikalischen Experiments in der Lehre. Gemeinsam mit MitarbeiterInnen – insbesondere Norbert Klaus, Vassiliki Berner und Christl Langstadlinger – hat Michael J. Higatsberger eine umfassende Sammlung von Experimenten der Physik auf Bildplatten geschaffen, die heute noch in den Vorlesungen an der Universität Wien eingesetzt werden. 1977 erschien das Lehrbuch „Physik in 700 Experimenten" im Blick in die Welt-Verlag.
Seine Verbindung zu Industrie und Wirtschaft kommt durch seine Tätigkeit als Aufsichtsratsmitglied in zahlreichen Institutionen, darunter die Metallwerk


Oct. 20, 1970 M. J. HIGATSBERGER ET AL 3,535,520
METHOD OF AND APPARATUS FOR THE MEASUREMENT OF PHYSICAL CHARACTERISTICS OF X-RAYS, IN PARTICULAR OF γ-RAYS, AND ITS APPLICATION
Filed Nov. 9, 1964 7 Sheets-Sheet 7
FIG. 10
Inventors:
Michael J. Higatsberger
Peter Weissel
Harald Peter Reich
By Fleit, Gipple & Jacobson
Attorneys

US-Patent für einen „Atomspion", 1970

Plansee AG, die Jungbunzlauer AG sowie die Bank Gutmann AG ebenso zum Ausdruck, wie in der Tatsache, dass er neben seinen zahlreichen wissenschaftlichen Publikationen 73 in- und ausländische Patente und Patentanmeldungen vorweisen kann. Zu seinen Arbeitsgebieten gehörten neben der Massenspektroskopie und ihren Hilfstechniken wie Elektronenoptik und Hochvakuumtechnik die Physik von Kernreaktoren und die dazugehörigen Technologien, ferner in jüngerer Zeit verschiedene Verfahren der Festkörperphysik und Festkörpertechnologien, bis hin zur Nanotechnologie.
Michael J. Higatsberger war seit 1989 auch Vorsitzender der Postgradualen Universitätslehrgänge für Medizinische Physik an der Universität Wien.

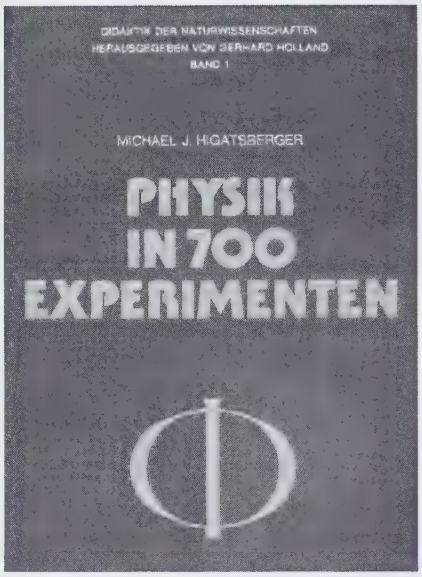


Bestimmung der Bestrahlungsgeschichte abgebrannter Kernbrennstoffe mittels γ-spektroskopischer Intensitätsmessungen der Spaltprodukte*

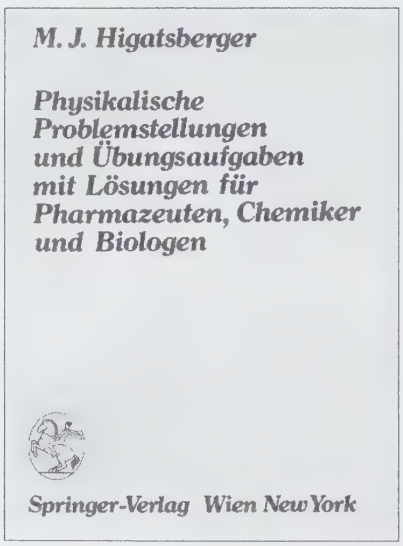
M. J. Higatsberger und H. Brunedet

1. Einleitung und Zusammenfassung

2. Grundlage für γ-spektrometrische Aktivitätsbestimmung



Das Experiment ist immer wieder ein Prüfstein des naturwissenschaftlichen Wahrheitsgehalts und liefert außerdem die Tatsachen, deren genaue Kenntnis verbunden mit kritischem Denken und logischer Folgerung erst ermöglicht, die Physik besser zu begreifen.



80. Geburtstag von Franziska Seidl, 1972

Mit Edmund Hlawka, 1999

Berta Karlik wird Ehrenmitglied der Chemisch-Physikalischen Gesellschaft, 1978

Mit Alfred Ebenbauer anläßlich der Emeritierung, 1994

Mit Hans Bethe in Rehovot, 1978

Mit Hermann Mark bei der 50 Jahr-Feier des Weizmann Institutes, 1984

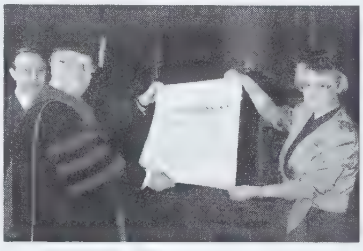
Mit dem israelischen Präsidenten Weizmann, 1984

Israel

Nach seiner Emeritierung im Jahre 1994 hat sich Michael J. Higatsberger um die wissenschaftlichen Beziehungen zwischen Österreich und Israel sehr verdient gemacht. Er wurde 1996 verantwortlicher Koordinator seitens der Universität Wien für die Zusammenarbeit mit der Universität Tel Aviv, deren Ehrendoktorat ihm 1992 verliehen worden war.

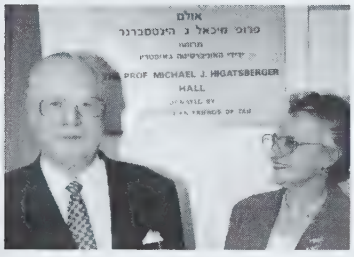
In Anerkennung dieser Verdienste wurde 2000 ein Hörsaal der Universität Tel Aviv in „The Prof. Michael J. Higatsberger-Hall" umbenannt. Higatsberger war auch Mitglied des Board of Governors der Universität Tel Aviv und des International Board of Governors des Weizmann Institute of Science.

Treffen der Freunde der Universität Tel Aviv; Bundeskanzler Sinowatz, BM Vranitzky, Leo Wallner, 1985



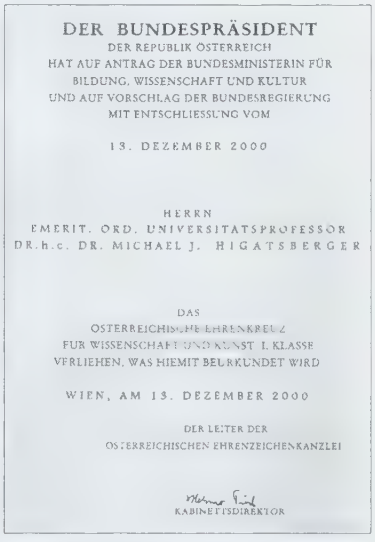
Ehrendoktorat der Tel Aviv University, 1990

Als Mittler zwischen den Konfessionen (mit Kardinal König und Chaim Eisenberg), 1995



Eröffnung der Higatsberger Hall an der Uni Tel Aviv mit Christl Langstadlinger, 2000

Biografie über Higatsberger, 2002



DER BUNDESPRÄSIDENT
DER REPUBLIK ÖSTERREICH
HAT AUF ANTRAG DER BUNDESMINISTERIN FÜR
BILDUNG, WISSENSCHAFT UND KULTUR
UND AUF VORSCHLAG DER BUNDESREGIERUNG
MIT ENTSCHLIESSUNG VOM

13. DEZEMBER 2000

HERRN
EMERIT. ORD. UNIVERSITÄTSPROFESSOR
DR.h.c. DR. MICHAEL J. HIGATSBERGER

DAS
ÖSTERREICHISCHE EHRENKREUZ
FÜR WISSENSCHAFT UND KUNST I. KLASSE
VERLIEHEN, WAS HIEMIT BEURKUNDET WIRD

WIEN, AM 13. DEZEMBER 2000

DER LEITER DER
ÖSTERREICHISCHEN EHRENZEICHENKANZLEI

KABINETTSDIREKTOR

Österreichisches Ehrenkreuz für Wissenschaft und Kunst I. Klasse

Nachruf

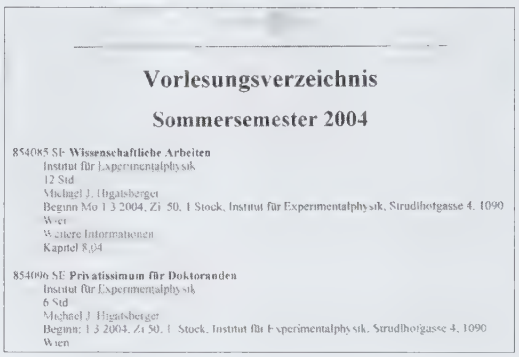
Michael J. Higatsberger war Träger zahlreicher Ehrungen und Auszeichnungen wie z. B. der Wilhelm-Exner-Medaille des Österreichischen Gewerbevereins oder des österreichischen Ehrenkreuzes für Wissenschaft und Kunst 1. Klasse.

Seine wissenschaftlich-technischen Leistungen, seine Beiträge zur Ausbildung und Erziehung junger Menschen der Wissenschaft, sowie sein unermüdlicher Einsatz für internationale Kooperationen und gegenseitiges Verstehen werden weit in die Zukunft wirken.

Wir leben in einer Zeit, wo mit alten Überlieferungen und traditionellen Handlungen gebrochen werden muß, um einen Grad an Flexibilität zu erreichen, der neuen Zielen und neuen Erfindungen den Weg ebnet.

Er war immer gerne bereit, Funktionen im Dienst der Allgemeinheit wahrzunehmen und war Mitglied zahlreicher wissenschaftlicher und technischer Vereinigungen weltweit. Hier sollen nur die British Nuclear Energy Society, die Chemisch-Physikalische Gesellschaft, deren Präsident er zweimal war, und das Europäische Komitee des Weizmann Institute of Science erwähnt werden.
Auch nach seiner Emeritierung war Michael J. Higatsberger jederzeit bereit, sich als Kollege für Anliegen des Institutes für Experimentalphysik in Forschung und Lehre einzusetzen und seine Erfahrung zur Verfügung zu stellen.

Neben seinem wissenschaftlichen Tätigkeiten war Higatsberger ein begeisterter Jäger und vielgelobter Hobbyweinbauer!
Michael J. Higatsberger hat bis zuletzt an der Universität Wien Vorlesungen über Experimentalphysik gehalten. Im Vorlesungsverzeichnis für das Sommersemester 2004 ist er noch als Vortragender mit eigener Vorlesung angeführt. Dieser Verpflichtung kann er zum großen Bedauern aller nun nicht mehr nachkommen.



Vorlesungsverzeichnis

Sommersemester 2004

854085 SE **Wissenschaftliche Arbeiten**
Institut für Experimentalphysik
12 Std
Michael J. Higatsberger
Beginn Mo 1.3.2004, Zi 50, 1 Stock, Institut für Experimentalphysik, Strudlhofgasse 4, 1090 Wien
Weitere Informationen
Kapitel 8.04

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Michael J. Higatsberger
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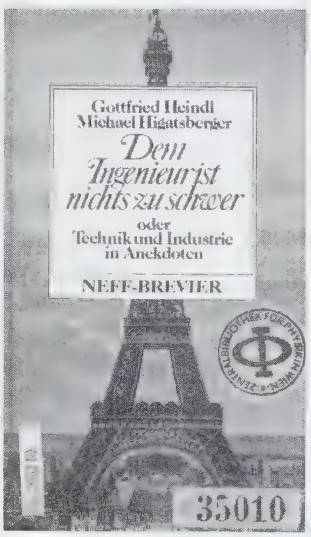


Der Jäger, Reutte 1989

Der Hobbyweinbauer

Otto Hittmair

Emer. Univ.-Prof., Dr. phil. Dr. h. c.
Institut für Theoretische Physik an der TU Wien

Werdegang:

16. 3. 1924	Geboren in Innsbruck, Eltern: Dr. Rudolf und Margarethe Hittmair Verheiratet mit Anni Hittmair, geb. Rauch; 4 Kinder Volksschule und Gymnasium in Innsbruck Studium in Innsbruck und Basel
1942–1945	Militärdienst
1949	Promotion zum Dr. phil. sub auspiciis; Dissertation: „Relativistisch invariante Darstellung der Wechselwirkung zwischen Strahlung und Materie mit Berücksichtigung der fundamentalen Länge“
1950	Auslandsaufenthalt bei Markus Fierz, Universität Basel
1951	Stipendium des Dublin Institutes for Advanced Studies bei Erwin Schrödinger
1951–1952	Stipendium am Massachusetts Institut of Technologie
1952–1954	Anstellung am Institut Henri Poincaré der Sorbonne
1953	Habilitation in Innsbruck; Arbeit über Kern-Winkelkorrelationen
1954–1956	Senior Fellow an der Universität Sydney
1957	Berater und Dozent an der Argentinischen Atomkommission
1958–1960	Mitarbeiter am Atominstitut der Österreichischen Hochschulen in Wien
1960	Ao. Univ.-Prof. für theoretische Physik und Institutsvorstand an der TU Wien
1963	O. Univ.-Prof. an der TU Wien
1968–1969	Dekan der TU Wien
1977–1979	Rektor der TU Wien
1987–1991	Präsident der Österreichischen Akademie der Wissenschaften
1991–1997	Vizepräsident der Österreichischen Akademie der Wissenschaften
1992	Emer. Univ.-Prof. der TU Wien
5. 9. 2003	Professor Hittmair verunglückt bei einer Bergtour auf der Nordkette tödlich.

Publikationen:
114 wissenschaftliche Veröffentlichungen und 5 Bücher

Ehrungen (Auswahl):
Jubiläumsmedaille der Universität Innsbruck (1970)
Erwin Schrödinger-Preis der Österreichischen Akademie der Wissenschaften (1974)
Wilhelm Exner-Medaille (1980)
Grosses Goldenes Ehrenzeichen der Republik Österreich (1980)
Preis der Stadt Wien (1982)
Dr. h. c. der TU Budapest (1982)
Ehrenzeichen des Landes Tirol (1988)
Prechtl-Medaille der TU Wien 1996
Goldmedaille der Internationalen Gesellschaft für Ingenieurpädagogik (1997)
Ein Kleinplanet wird nach Hittmair benannt (2001)

Mitgliedschaften (Auswahl):
Wirkliches Mitglied der Österreichischen Akademie der Wissenschaften (1970)
Österreichische Physikalische Gesellschaft
Mitglied der Königlichen Sozietät der Wissenschaften zu Uppsala (1978)
Internationale Gesellschaft für Ingenieurpädagogik (1973–97 Vizepräsident)

„Was über das Beobachtbare hinausgeht, ist Meinung.“

Kindheit, Schulzeit, Studium

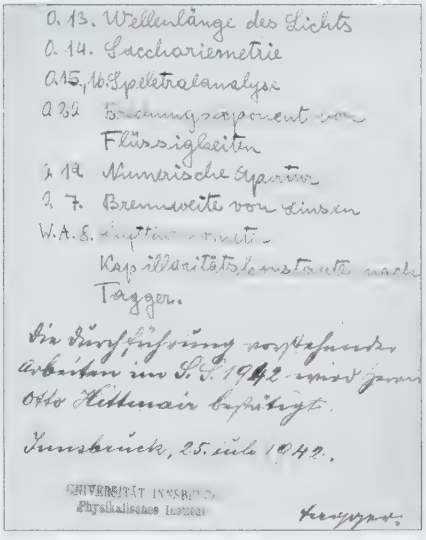
Otto Hittmair (2. v. r.), mit Geschwistern

Otto Hittmair wurde am 16. März 1924 als zweites von fünf Kindern einer Innsbrucker Gelehrtenfamilie geboren. Sein Vater war Universitätsprofessor für Anglistik, seine Mutter Besitzerin der Innsbrucker Universitätsbuchhandlung. Alle fünf Kinder erwarben akademische Grade. Hittmair verbrachte seine Kindheit, Schul- und Studienzeit in Innsbruck. Er besuchte das Humanistische Gymnasium mit Latein und Griechisch. In dieser Zeit bildete sich seine Vorliebe für Physik, Mathematik, Geschichte und Sprachen heraus. Zur Physik,

die ihn gleich sehr faszinierte, kam Hittmair durch den Mittelschullehrer Professor Margreiter.
Die damals (um 1940) neue und sehr moderne Quantenphysik und der damit verbundene Umsturz im Weltbild der Physik hat bei Hittmair nachhaltigen Eindruck hinterlassen. Theoretische Physik war von allem Anfang an für ihn interessanter als Experimente. Hittmair maturierte 1942 mit Auszeichnung und wurde nach einem Semester Physikstudium zur Wehrmacht eingezogen, wo er bis 1945 in einer Funkkompanie Dienst versah. Nach 1945 kehrte er an die Uni Innsbruck zurück.

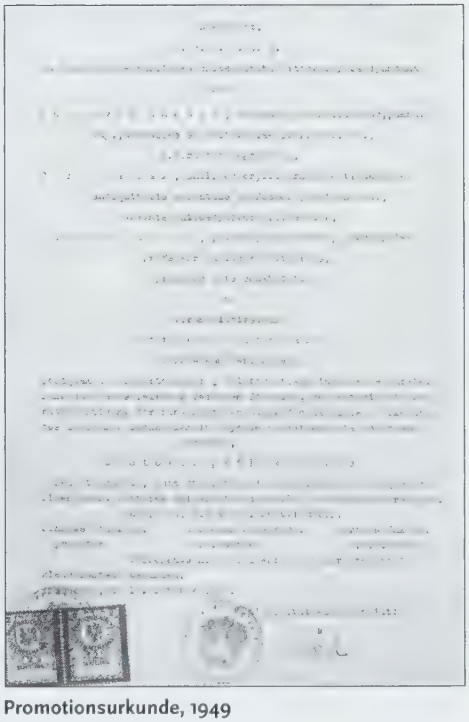
Maturaklasse, 1942

„Alle waren damals hungrig nach dem Wissenschaftsbetrieb."
March, sein Professor an der Uni Innsbruck, war ein guter Lehrer und ein früher Kenner der Quantentheorie, dem auch die Philosophie sehr wichtig war. Zu Hause diskutierte Hittmair oft mit Professor Strohal, einem Freund der Familie, über Quantenphysik und Philosophie. Seine Vorbilder in der modernen Quantenphysik waren Schrödinger, Dirac und Heisenberg.



Erstes physikalisches Praktikum, 1942

Promotion, 1949



Promotionsurkunde, 1949

Basel

Nach der Promotion unter sub auspiciis-Bedingungen ging Hittmair 1950 als unbezahlter Gast zu Markus Fierz an die Universität Basel, um seine Kenntnisse in der Quantenfeldtheorie zu vertiefen. In seiner Freizeit konnte der passionierte Bergsteiger hier seinem Hobby nachgehen und bestieg unter anderem das Matterhorn.

Separatum
EXPERIENTIA
Vol. III/8, 1947

Über die Möglichkeiten und die Grenzen der heutigen Theorie der Atomkerne

Von M. FIERZ, Basel[1]

Wie Sie wohl wissen, vermögen wir heute keine Theorie der Atomkerne aufzubauen, die Entsprechendes leistet wie die Wellenmechanik für die Physik der Atomhüllen. Es fehlen uns hiezu noch die Grundlagen. Das hängt zum Teil damit zusammen, daß die Wellenmechanik des Spinelektrons und die Quantenelektrodynamik, die das Vorbild für die Theorie der Atomkerne bilden, selber nicht logisch befriedigend aufgebaut sind.

Die DIRACsche Theorie führt bekanntlich zu Zuständen negativer Energie des Elektrons. DIRAC hat allerdings mit Hilfe des Pauli-Prinzips und einer passenden Definition dessen, was man unter dem Vakuum verstehen solle, diese Schwierigkeit überwunden und ist so zu einer Theorie der positiv geladenen Elektronen gelangt. Dieser große Erfolg wurde aber dadurch erkauft, daß der ursprüngliche Standpunkt eines wellenmechanischen Einkörperproblems verlassen werden mußte; denn im aufgefüllten «See» negativer Zustände sitzen ja stets unendlich viele Elektronen. Das führt dann zu neuen, eigenartigen Schwierigkeiten. Die

[1] Vortrag, gehalten vor der Physikalischen Gesellschaft in Zürich am 27. Februar 1947

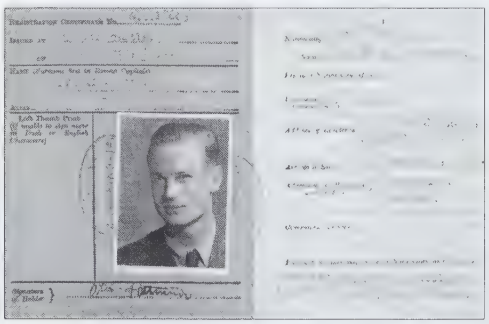
Arbeit von Markus Fierz, Basel 1950

Es ist eine Ordnung in der Natur, die oft überrascht, und die Mathematik erlaubt es, die vorgefundenen Ordnungen zu erfassen.

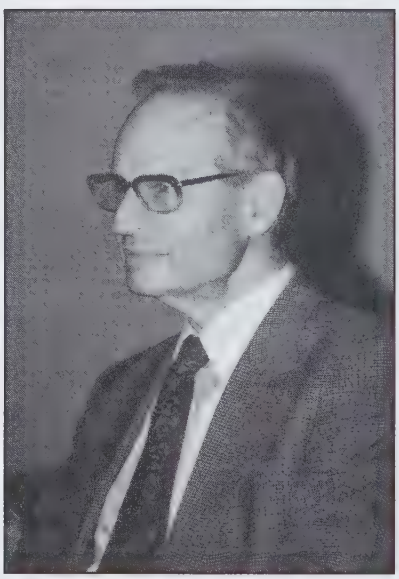
Dublin

Otto Hittmair hatte das Glück, schon zu Beginn seiner Karriere mit Erwin Schrödinger in Irland zusammenarbeiten zu können. Schrödinger machte ihm das Angebot, mit ihm das elektromagnetische Feld zusammen mit dem Gravitationsfeld aus einer verallgemeinerten Raummetrik her zu beschreiben (unified field theory). Der endgültige Erfolg blieb ihnen zwar versagt, aber es gelang ihnen, mathematische Teilerfolge zu veröffentlichen.

Dr. Otto Bergmann – Kollege in Irland, 1950



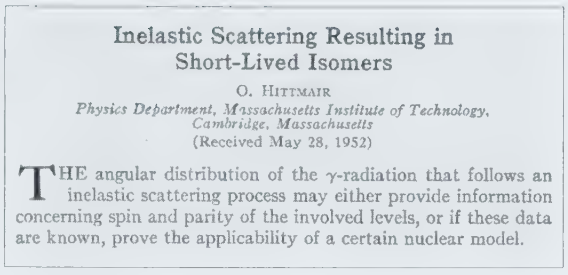
Registration Card Irland, 1951



Arbeit mit Schrödinger, 1951

MIT, USA

An diesen vielversprechenden Anfang schlossen sich dann Hittmairs kernphysikalische Arbeiten an. Noch im Sommer 1951 beendete Hittmair seinen Aufenthalt in Dublin und besuchte als Fulbright Stipendiat das Massachusetts Institute of Technology in Cambridge, USA. Hier traf er den Experimentalphysiker Martin Deutsch, der Kern-Winkelkorrelationen untersuchte und an einer Analyse seiner Ergebnisse interessiert war. Hittmair konnte nun die mathematisch abstrakte Gruppentheorie auf die Richtungskorrelationen zweier aufeinander folgender Strahlungen eines Kerns anwenden, die sich insbesondere auf die Entwicklung der Theorie der Richtungsverteilungen von Kernreaktionen bezogen. Diese Theorie erwies sich als ein sehr wertvolles Instrument, um wichtige Eigenschaften der betreffenden Atomkerne zu ermitteln.



Inelastic Scattering Resulting in Short-Lived Isomers

O. Hittmair

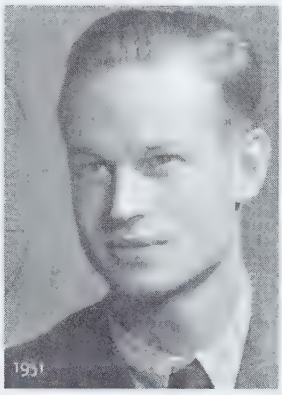
Physics Department, Massachusetts Institute of Technology, Cambridge, Massachusetts

(Received May 28, 1952)

THE angular distribution of the γ-radiation that follows an inelastic scattering process may either provide information concerning spin and parity of the involved levels, or if these data are known, prove the applicability of a certain nuclear model.

Veröffentlichung in Physical Review, 1952

Hittmair traf am MIT Hermann Mark und Gattin, 1951/52



Die Wahrheit ist pluriform und nur annäherungsweise erreichbar.

Massachusetts Institute of Technology

LE JOURNAL DE PHYSIQUE ET LE RADIUM. TOME 14, AVRIL 1953, PAGE 270.

LETTRES A LA RÉDACTION

LE MODÈLE STATISTIQUE ET LES DISTRIBUTIONS ANGULAIRES

Par Otto HITTMAIR,
Institut Henri Poincaré, Paris.

Le modèle statistique [1] donne de premiers renseignements sur les sections efficaces de la diffusion élastique ou inélastique. Mais l'accord avec l'expérience n'est qu'approché [2], car on fait des hypothèses trop spécifiques et trop simplifiées sur la dépendance radiale de la fonction d'onde de la particule à l'intérieur du noyau composé. Il est cependant probable que l'hypothèse fondamentale du modèle statistique, l'existence d'un continuum des niveaux nucléaires est, en général, réalisée pour les noyaux et les énergies dont on s'occupe.

Une méthode d'examen de ce problème est fournie par l'étude des distributions angulaires des particules diffusées ou des rayons γ qui suivent la diffusion inélastique. Considérons le cas où l'hypothèse statistique est valable non seulement pour le noyau composé, mais aussi pour le noyau cible et le noyau résiduel [3]. Dans ce cas, la section efficace différentielle de la diffusion inélastique des particules de spin $\frac{1}{2}$ est donnée par :

$$\sigma(\vartheta, E, E') = \frac{\left(\frac{\lambda}{2\pi}\right)^2}{(2i_1+1)} \sum_{ajm\nu} (2l_3+1)$$
$$\cdot T_{i_1}(E)\, T_{j_3}(E') \, |(l_3 j_3 m_3 - m_3 | j_3 m_3)|^2$$
$$\sum_{\ldots} T \ldots$$
$$\times (l_2 j_2 M_2 m_2 | i_2 m_2)^2 \, |V^{j_2}_{M_2}|^2 \frac{2j_2+1}{D(E-E')},$$

E est l'énergie de la particule incidente, λ est la longueur d'onde de de Broglie. E' est l'énergie de la particule émise. Les moments cinétiques orbitaux respectifs sont l_1 et l_2, leurs composantes sur l'axe des z. M_1 et M_2 i représente les spins des niveaux et j les canaux correspondants. Leurs nombres quantiques magnétiques sont désignés par m. Les $T_l(E)$ sont les coefficients de transmission. La somme du dénominateur est à effectuer par rapport à tous les niveaux qui peuvent être atteints à partir de i_2. $D(E-E')$ est la distance entre les niveaux du noyau résiduel pour une énergie d'excitation de $E-E'$. L'axe des z coïncide avec le rayon incident.

On peut effectuer la somme par rapport à j_3, m et M et l'on obtient

$$\sum_{j_3 m_3 M_2} (2j_3+1)(l_1 j_1 0 m_1 | i_2 m_1)^2 (l_2 j_2 M_2 m_2 - M_2 | i_2 m_1)^2 \, |V^{j_2}_{M_2}|^2$$
$$= \frac{\ldots 2l_2+1)(2i_2+1)}{(2i_1+1)} \ldots;$$

dans ce cas, la distribution angulaire des particules diffusées est donc isotrope. Cependant, ce résultat n'est valable pour les noyaux intermédiaires que si l'excitation du noyau résiduel est suffisamment grande. Si tel n'est pas le cas et si l'hypothèse statistique n'est valable que pour le noyau composé, tandis que le noyau cible et le noyau résiduel ont des résonances discrètes, la distribution angulaire sera généralement anisotrope et dépendra des coefficients de transmission. Néanmoins, il existe aussi dans ce cas des méthodes pour éprouver la validité de l'hypothèse statistique pour le noyau composé sans avoir recours à des hypothèses trop spécifiques pour les fonctions d'onde du noyau.

Si le noyau résiduel retombe à son état fondamental uniquement par émission γ [4], la distribution angulaire de cette radiation sans observation des particules diffusées est donnée par

$$\sigma(\vartheta, E) = \frac{\pi \left(\frac{\lambda}{2\pi}\right)^2}{\ldots} \frac{1}{\ldots} \sum_{\ldots} (-)^{\ldots} \frac{T_{i_1}(E)\, T_{\ldots}(E)}{\sum_{\ldots} T_{\ldots} T_{\ldots}}$$
$$\times (2I_1+1)(2I_2+1)(2i_2+1)^2(2i_3+1)$$
$$\cdot (I_1 \ldots I_1 \ldots | I_2 \ldots)$$
$$\times W(I_1 i_2 I_2 i_2, j_1 \nu)\, W(i_2 j_3 i_2 j_3, I_2 \nu)$$
$$\times W(I_3 i_3 I_3 i_3, i_1 \nu) \frac{1}{1+\alpha} P_\nu(\cos\vartheta),$$

où α est le coefficient total de conversion interne; les W sont les coefficients de Racah [5] introduits dans la sommation des coefficients de Clebsch-Gordan; L_3 est l'ordre multipolaire du rayon γ.

Supposons que le spin de l'état fondamental soit zéro, ce qui est réalisé pour tous les noyaux pairs-pairs, et que seul son premier niveau soit excité par la diffusion inélastique. Si nous choisissons maintenant l'énergie de la particule incidente de façon que l_2 soit égal à zéro, $\sigma(\vartheta, E)$ ne dépend plus des coefficients de transmission et, par conséquent, seule l'hypothèse du continuum des niveaux du noyau composé entre dans le calcul.

L'efficacité de cette méthode se fonde sur le fait

Le Journal de Physique, 1953

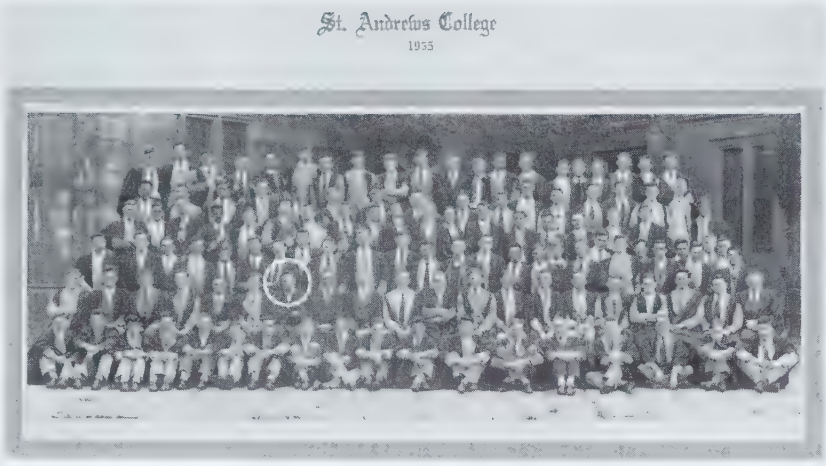
Paris

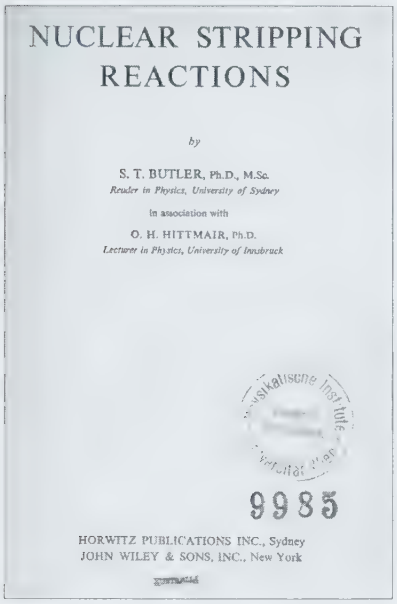
Auf Vermittlung des späteren Nobelpreisträgers Alfred Kastler konnte Hittmair 1952 bis 1954 am Institut Henri Poincaré in Paris arbeiten. Dieses Institut war in erster Linie eine Hochburg der Mathematiker. Hier konnte Hittmair die Linie der Winkelkorrelationen bei Kernreaktionen unter Heranziehung des statistischen Kernmodells (Kontinuumstheorie) weiterverfolgen. Während seiner Pariser Zeit habilitierte sich Hittmair an der Innsbrucker Universität für theoretische Physik.

Studentenausweis Paris, 1953/54

Sydney

1954 bis 1956 bekam Hittmair Gelegenheit, mit dem australischen Kernphysiker Steward Butler in Sydney über Deuteron-Stripping-Reaktionen zu arbeiten. In Zusammenarbeit mit Butler verfasste er ein Buch über diese Art von Kernreaktionen:
Nuclear Stripping Reactions, New York, 1957.
In Sydney war Hittmair auch Tutor am St. Andrews College der Universität.




NUCLEAR STRIPPING REACTIONS

by

S. T. BUTLER, Ph.D., M.Sc.
Reader in Physics, University of Sydney

in association with

O. H. HITTMAIR, Ph.D.
Lecturer in Physics, University of Innsbruck

9985

HORWITZ PUBLICATIONS INC., Sydney
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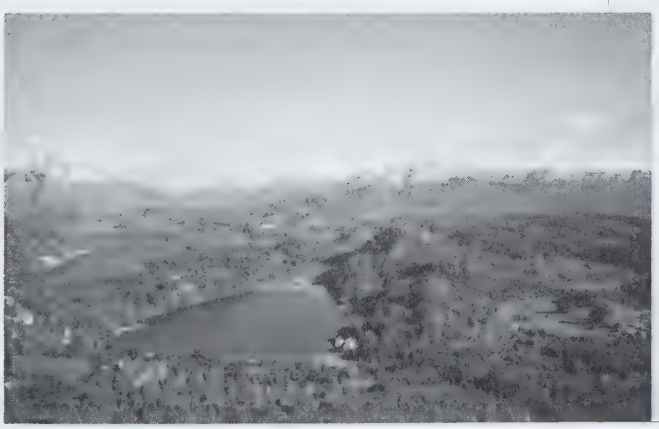
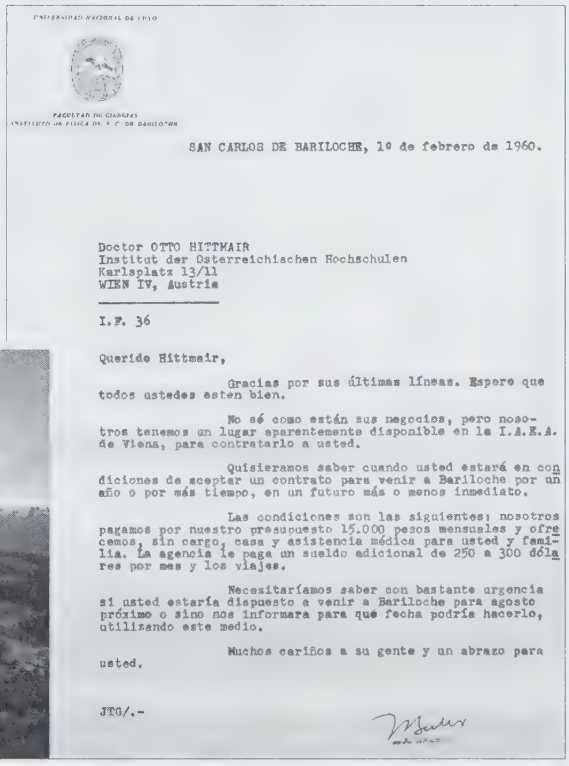
Argentinien

Die Jahre 1956 und 1957 verbrachte Hittmair großteils in Argentinien, wo seine Aufgabe neben Vortragstätigkeit in Buenos Aires und in San Carlos de Bariloche hauptsächlich darin bestand, in einem Zyklotron gemessene deuteroninduzierte Kernreaktionen zu analysieren.


Ansicht von Bariloche


SAN CARLOS DE BARILOCHE, 1º de febrero de 1960.

Doctor OTTO HITTMAIR
Institut der Österreichischen Hochschulen
Karlsplatz 13/11
WIEN IV, Austria

I.F. 36

Querido Hittmair,

Gracias por sus últimas líneas. Espero que todos ustedes esten bien.

No sé como están sus negocios, pero nosotros tenemos un lugar aparentemente disponible en la I.A.E.A. de Viena, para contratarlo a usted.

Quisieramos saber cuando usted estará en condiciones de aceptar un contrato para venir a Bariloche por un año o por más tiempo, en un futuro más o menos inmediato.

Las condiciones son las siguientes: nosotros pagamos por nuestro presupuesto 15.000 pesos mensuales y ofrecemos, sin cargo, casa y asistencia médica para usted y familia. La agencia le paga un sueldo adicional de 250 a 300 dólares por mes y los viajes.

Necesitaríamos saber con bastante urgencia si usted estaría dispuesto a venir a Bariloche para agosto próximo o sino nos informara para qué fecha podría hacerlo, utilizando este medio.

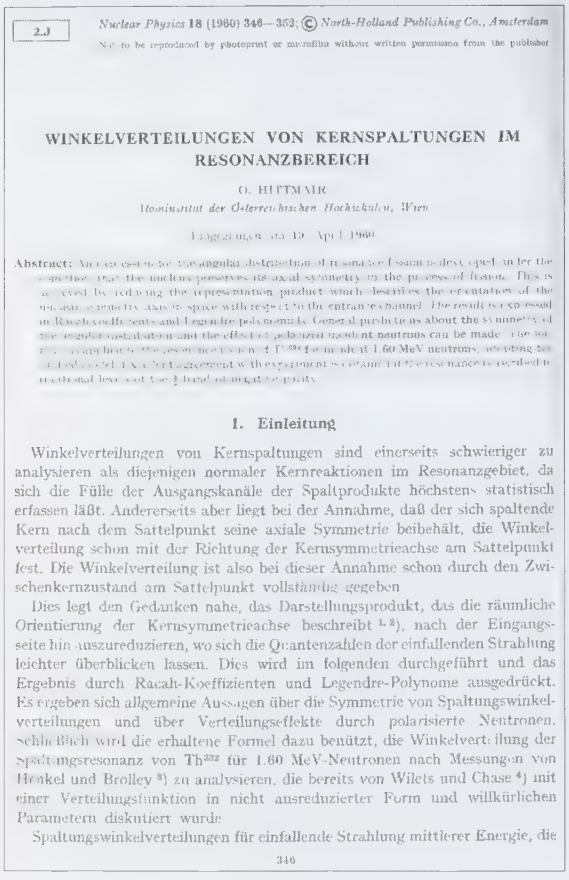
Muchos cariños a su gente y un abrazo para usted.

JTG/.-

Einladung nach Bariloche, 1960

Grundsteinlegung für den Forschungsreaktor mit Gustav Ortner (weißer Hut), 1959

Mit Guido Beck und Anni Hittmair, 1968



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Nuclear Physics 18 (1960) 346—352; © *North-Holland Publishing Co., Amsterdam*

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WINKELVERTEILUNGEN VON KERNSPALTUNGEN IM RESONANZBEREICH

O. HITTMAIR

Atominstitut der Österreichischen Hochschulen, Wien

Eingegangen am 19 April 1960

Abstract: An expression for the angular distribution of resonance fissions is developed under the assumption that the nucleus preserves its axial symmetry in the process of fission. This is achieved by reducing the representation product which describes the orientation of the nuclear symmetry axis in space with respect to the entrance channel. The result is expressed in Racah coefficients and Legendre polynomials. General predictions about the symmetry of the angular distribution and the effect of polarized incident neutrons can be made. The formalism is applied to the fission resonance of Th^{232} at 1.60 MeV neutrons, adopting the R-matrix level formula. Agreement with experiment is obtained if three resonances are added in a destructive interference with the 3 broad resonances given by Wilets.

1. Einleitung

Winkelverteilungen von Kernspaltungen sind einerseits schwieriger zu analysieren als diejenigen normaler Kernreaktionen im Resonanzgebiet, da sich die Fülle der Ausgangskanäle der Spaltprodukte höchstens statistisch erfassen läßt. Andererseits aber liegt bei der Annahme, daß der sich spaltende Kern nach dem Sattelpunkt seine axiale Symmetrie beibehält, die Winkelverteilung schon mit der Richtung der Kernsymmetrieachse am Sattelpunkt fest. Die Winkelverteilung ist also bei dieser Annahme schon durch den Zwischenkernzustand am Sattelpunkt vollständig gegeben.

Dies legt den Gedanken nahe, das Darstellungsprodukt, das die räumliche Orientierung der Kernsymmetrieachse beschreibt [1,2], nach der Eingangsseite hin auszureduzieren, wo sich die Quantenzahlen der einfallenden Strahlung leichter überblicken lassen. Dies wird im folgenden durchgeführt und das Ergebnis durch Racah-Koeffizienten und Legendre-Polynome ausgedrückt. Es ergeben sich allgemeine Aussagen über die Symmetrie von Spaltungswinkelverteilungen und über Verteilungseffekte durch polarisierte Neutronen. Schließlich wird die erhaltene Formel dazu benützt, die Winkelverteilung der Spaltungsresonanz von Th^{232} für 1.60 MeV-Neutronen nach Messungen von Henkel und Brolley [3] zu analysieren, die bereits von Wilets und Chase [4] mit einer Verteilungsfunktion in nicht ausreduzierter Form und willkürlichen Parametern diskutiert wurde.

Spaltungswinkelverteilungen für einfallende Strahlung mittlerer Energie, die

346

Nuclear Physics, 1960

Gerhard Adam
Otto Hittmair

Wärmetheorie

3., verbesserte Auflage

Mit 86 Bildern

vieweg

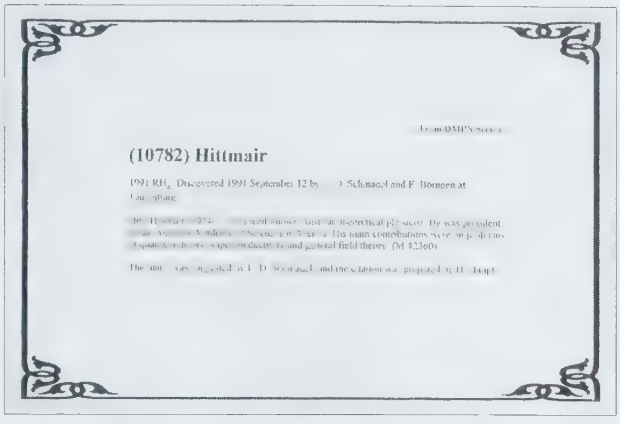
Wärmetheorie, 1970

Österreich, Atominstitut, TU Wien

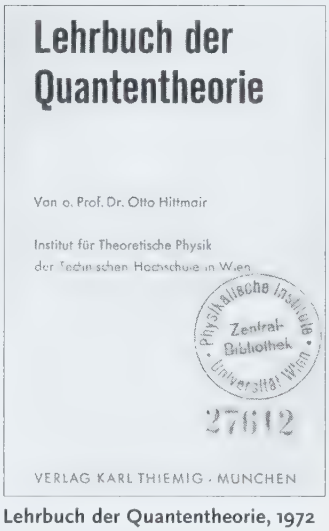
Im Mai 1958 kehrte Hittmair nach acht Jahren Forschungstätigkeit auf drei Kontinenten nach Österreich zurück, wo er zuerst unter Gustav Ortner am neugeschaffenen Atominstitut in Wien arbeitete. Aber schon im Studienjahr 1959/60 übernahm er die Leitung des Institutes für Theoretische Physik der TH Wien. 1960 erfolgte die Ernennung zum Extraordinarius und Institutsvorstand, 1963 wurde Hittmair zum Ordinarius ernannt.
Fragen der theoretischen Kernphysik, vor allem Kernreaktionen, standen auch nach seiner Rückkehr nach Österreich im Mittelpunkt seiner Arbeit. Weitere Schwerpunkte in Hittmairs wissenschaftlicher Tätigkeit betrafen die Beschäftigung mit der Quantentheorie und der Supraleitung. Vor allem das Problem der stark gekoppelten Supraleiter, des kritischen Feldes und der spezifischen Wärme dieser Supraleiter waren Themen in einer Reihe viel beachteter Publikationen. Hier konnte er mit grundlegenden neuen Ansätzen große Erfolge erzielen.
Hittmair verfasste über 100 wissenschaftliche Arbeiten und einige Lehrbücher, wie z. B.:

Institutsfeier, 1973

Feier 25 Jahre Reaktor, 1987



Planet Hittmair, 2001



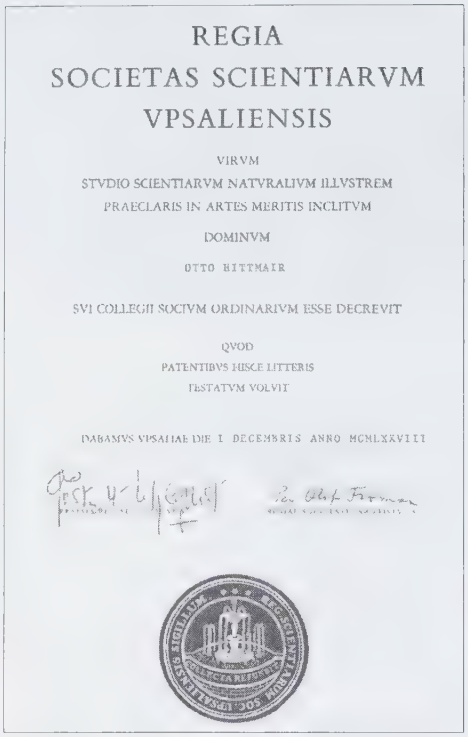
Lehrbuch der Quantentheorie, 1972

BM Hertha Firnberg überreicht Hittmair das Große Goldene Ehrenzeichen der Republik Österreich, 1980

Nicht nachgebeteter Konformismus, sondern Originalität des Denkens bringt Fortschritt.

- Lehrbuch der Quantentheorie, 1972
- Supraleitung zusammen mit H. W. Weber, 1979
- Wärmetheorie, zusammen mit G. Adam, 1988

Im Zuge seiner wissenschaftlichen Karriere war Hittmair 1968/1969 Dekan der Technisch-Naturwissenschaftlichen Fakultät der TH Wien und 1977 bis 1979 Rektor der nunmehrigen TU Wien.
1970 wurde er zum wirklichen Mitglied der Österreichischen Akademie der Wissenschaften bestellt, 1983 bis 1987 war er Generalsekretär und ab 1987 bis 1992 als Nachfolger Hans Tuppys Präsident der ÖAW.
Hittmair war als Nachfolger von Werner Heisenberg seit 1977 auch Mitglied der Königlichen Sozietät der Wissenschaften zu Uppsala.
Hittmair erhielt für seine Verdienste die höchste Auszeichnung der TU Wien, die Prechtl-Medaille. 1980 wurde ihm das Große Goldene Ehrenzeichen der Republik Österreich zuerkannt. 2001 benannte die internationale astronomische Union einen Kleinplaneten nach Hittmair.



REGIA
SOCIETAS SCIENTIARVM
VPSALIENSIS

VIRVM
STVDIO SCIENTIARVM NATVRALIVM ILLVSTREM
PRAECLARIS IN ARTES MERITIS INCLITVM

DOMINVM

OTTO HITTMAIR

SVI COLLEGII SOCIVM ORDINARIVM ESSE DECREVIT

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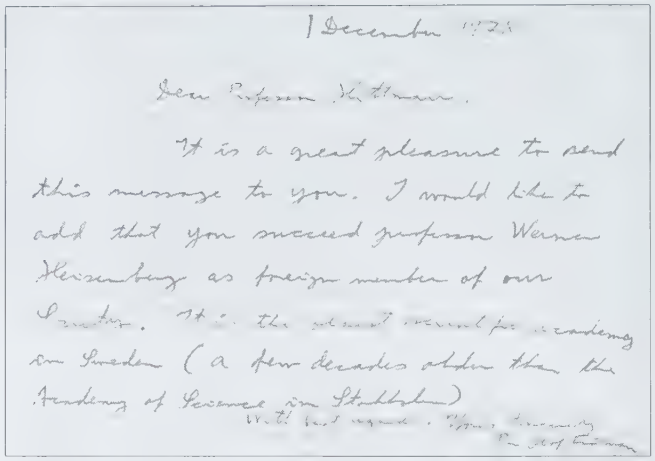
DABAMVS VPSALIAE DIE I DECEMBRIS ANNO MCMLXXVIII

Mitglied der königlichen Sozietät Uppsala, 1978



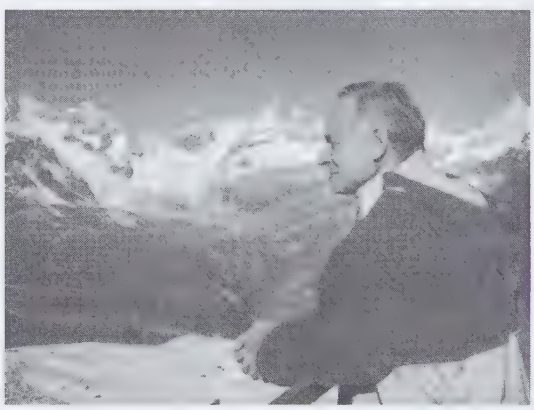
1 December 1978

Dear Professor Hittmair,

It is a great pleasure to send this message to you. I would like to add that you succeed professor Werner Heisenberg as foreign member of our Society. It is the highest honour for a scientist in Sweden (a few decades older than the Academy of Sciences in Stockholm)

Mitglied der königlichen Sozietät Uppsala, Brief, 1978

Mit Kardinal König, 1977



Am Jungfrauenjoch, um 1995

„Man muß kein Tiroler sein, um ein ambitionierter Bergsteiger zu sein."
Ein passionierter Bergsteiger war Hittmair zeit seines Lebens. Im September 2003 verunglückt er auf einer Bergtour tödlich. Österreich hat mit ihm einen Wissenschaftler von Weltgeltung verloren.

Karl Schlögl

Emer. Univ.-Prof., Dr. phil.
Institut für Organische Chemie an der Universität Wien

Werdegang:

5. 10. 1924	Geboren in Wien, Eltern: Karl und Katharina Schlögl Verheiratet mit Rosemarie Schlögl, geb. Storteczky Gymnasium in Wien
1943	Matura mit Auszeichnung
1945–1950	Studium der Chemie in Wien, Promotion zum Dr. phil., Chemie
1950–1958	Assistent an der Universität Wien
1954–1955	Postdoc, University of Manchester (British Council Scholar)
1959	Habilitation für organische Chemie an der Universität Wien
1970	Ao. Univ.-Prof. für Organische Chemie an der Universität Wien
1971	O. Univ.-Prof. für Organische Chemie an der Universität Wien
1974–1990	Vorstand des Institutes für Organische Chemie der Universität Wien
1977–1979	Dekan der Formal- und Naturwissenschaftlichen Fakultät der Universität Wien
1990	Emer. Univ.-Prof. der Universität Wien
1991–1995	Generalsekretär der Österreichischen Akademie der Wissenschaften
1997–2000	Vizepräsident der Österreichischen Akademie der Wissenschaften

Publikationen:
Über 220 Arbeiten auf dem Gebiet der organischen Chemie
Mehrere Handbuchartikel
Einige Patente auf dem Gebiet der Heilmittelsynthese

Ehrungen (Auswahl):
Rudolf Wegscheider-Preis der Österreichischen Akademie der Wissenschaften (1959)
Universitätspreis der Wiener Wirtschaft (1983)
Erwin Schrödinger-Preis der Österreichischen Akademie der Wissenschaften (1985)
Preis für Naturwissenschaften der Stadt Wien (1989)
Ehrenpräsident der Gesellschaft Österreichischer Chemiker (1991)
Wilhelm Exner-Medaille des Österreichischen Gewerbevereins (1991)
Loschmidt-Medaille der Gesellschaft Österreichischer Chemiker (1993)

Mitgliedschaften, Funktionen (Auswahl):
Mitglied der Gesellschaft Österreichischer Chemiker (1950)
Korrespondierendes Mitglied der Österreichischen Akademie der Wissenschaften (1978)
Mitglied, Internationaler Fachbeirat das Max Plank-Instituts für Biochemie (1980–1989)
Wirkliches Mitglied der Österreichischen Akademie der Wissenschaften (1982)
Präsident der Gesellschaft Österreichischer Chemiker (1985–1991)
Member New York Academy of Sciences (1987)
Sekretär der mathematisch-naturwissenschaftlichen Klasse der ÖAW (1987–1991)
Generalsekretär der Österreichischen Akademie der Wissenschaften (1991–1995)
Korrespondierendes Mitglied der Nordrhein-Westf. Akademie der Wissenschaften (1996)
Vizepräsident der Österreichischen Akademie der Wissenschaften (1997–2000)

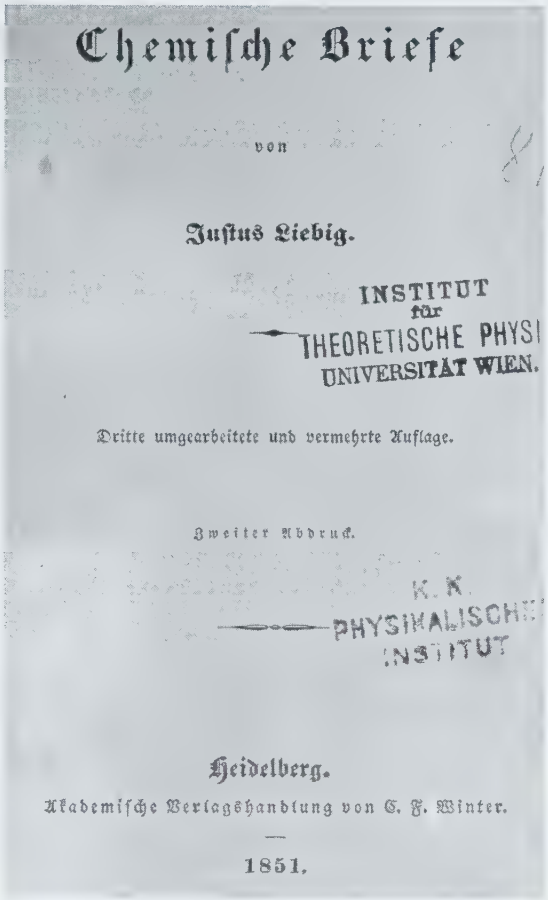
„Alles Leben ist Stereochemie. Chiralität ist also eine conditio sine qua non für Leben, wie wir es kennen."

Kindheit, Gymnasium

Karl Schlögl wurde am 5. Oktober 1924 in Wien geboren. Sein Vater war Hauptschuldirektor und unterrichtete Mathematik, Physik und Chemie. Schlögl las Romane von Schenzinger und Dominik. Justus Liebig war eines seiner Vorbilder. Den ersten Kontakt mit der Chemie hatte Schlögl im Alter von 12 bis 15 Jahren. Manchmal nahm ihn sein Vater mit in die Schule und machte dort für ihn Versuche.
Viele Lehrer, so auch die Physik- und Chemielehrer, waren im Krieg, und die Ersatzlehrer hatten von den Fächern, die sie unterrichteten, wenig Ahnung. Er beschäftigte sich aber zu Hause mit Chemie (mit Hilfe von Chemiebaukästen). Schlögl maturierte 1943.

Studium, Krieg

Schlögl war aus gesundheitlichen Gründen (Asthma) nicht bei der Wehrmacht. Er begann noch im Krieg mit dem Studium der Chemie. Sein erstes Studiensemester absolvierte er von April bis Juni 1944. Es gab oft Fliegeralarm, und die Studierenden mussten immer wieder in den Luftschutzkeller. Unter diesen Bedingungen war kein regulärer Studienbetrieb möglich.
Die Vorlesungen waren laut Schlögl trotzdem sehr gut. Vor allem Ernst Späth hat Schlögl sehr imponiert. Er bot Schlögl schon bald die Mitarbeit am Institut an. Auch nach dem Krieg waren die Studienbedingungen sehr schlecht. Die technische Ausstattung der Labors war sehr mangelhaft, und die Studierenden mussten selbst für Werkstoffe bezahlen.
Schlögls wichtigste Lehrer waren Ernst Späth, Wilhelm Gruber und Friedrich Wessely. Bei Gruber dissertierte er über Schierlingsinhaltsstoffe (Synthese des Pseudoconhydrins). Danach wurde er von Friedrich Wessely als Assistent übernommen. Das Hauptinteresse Schlögls galt seit jeher der organischen Chemie.
Nach der Promotion 1950 schlug Schlögl die akademische Laufbahn ein, obwohl es für ihn kein Problem gewesen wäre, in der damals boomenden Privatwirtschaft Arbeit zu finden. Doch ihn interessierten Forschung und Lehre. Diese beiden Arbeitsbereiche lassen sich laut Schlögl gut vereinbaren, da man in die Lehre immer neue Forschungsergebnisse einbauen muss und Studierende oft unbequeme Fragen stellen, die den Lehrer immer wieder fordern. Administrative Tätigkeiten waren damals noch nicht so wichtig.



Chemiſche Briefe

von

Juſtus Liebig.

INSTITUT für THEORETISCHE PHYSI UNIVERSITÄT WIEN.

Dritte umgearbeitete und vermehrte Auflage.

Zweiter Abdruck.

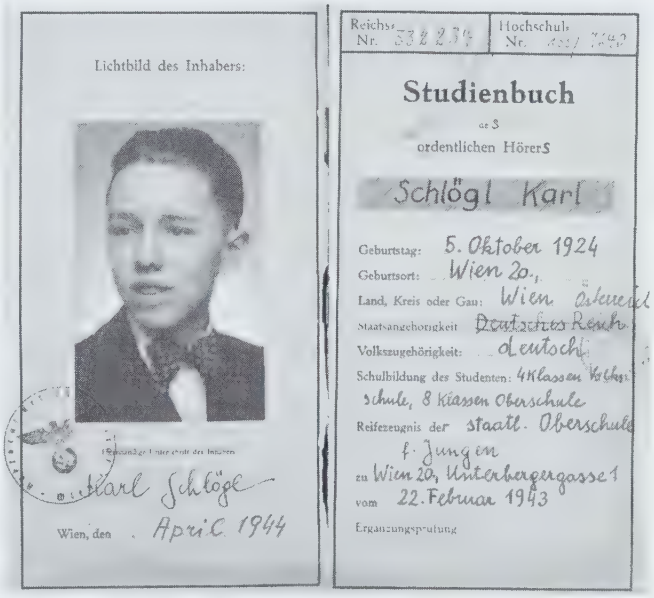
K. K. PHYSIKALISCHES INSTITUT

Heidelberg.

Akademiſche Verlagshandlung von C. F. Winter.

1851.

Ein Buch, das bleibenden Eindruck hinterlassen hat



Lichtbild des Inhabers:

Karl Schlögl

Wien, den April 1944

Reichs-Nr. 533234 Hochschul-Nr. 7949

Studienbuch

ordentlichen Hörers

Schlögl Karl

Geburtstag: 5. Oktober 1924
Geburtsort: Wien 20.,
Land, Kreis oder Gau: Wien Österreich
Staatsangehörigkeit: Deutsches Reich
Volkszugehörigkeit: deutsch
Schulbildung des Studenten: 4 Klassen Volks-schule, 8 Klassen Oberschule
Reifezeugnis der staatl. Oberschule f. Jungen zu Wien 20, Unterbergergasse 1 vom 22. Februar 1943
Ergänzungsprüfung

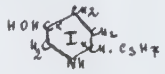
Es ist mir ein aufrichtiges Bedürfnis, an dieser Stelle Herrn Universitäts-Assistenten Dr. Wilhelm G r u b e r , unter dessen Anleitung diese Arbeit entstanden ist, für seine immerwährende und tatkräftige ideelle und materielle Unterstützung ergebenst zu danken.

L. 278

Beurteilung der Dissertation

descand. phil. Karl S c h l ö g l

Dem Kandidaten war die Aufgabe gestellt, das Schierlings-Nebenalkaloid Pseudoconhydrin I zu synthetisieren. Es waren theore-



tisch drei Wege möglich. Von diesen führten zwei zum Ziel.

Der erste geht vom 2-Chlor-5-Nitropyridin aus, in dem das Chloratom mit Hilfe von Aethylmalonsäureester gegen den Propylrest ausgetauscht wurde. Reduktion der Nitro- zur Aminogruppe und deren Ueberführung in die OH-Gruppe führten zum 2-n-Propyl-5-oxypyridin, das bei der Reduktion mit Natrium und Alkohol ein Gemisch der zwei möglichen Racemate von I ergab. Die Spaltung eines dieser mit Hilfe von Dinitrodiphensäure lieferte das natürliche Alkaloid.

Im Laufe dieser Arbeit wurden eine Reihe wertvoller Beobachtungen über die Chemie der x-halogen-5-Nitropyridine gemacht und brauchbare Wege zur Synthese sonst schwer zugänglicher Verbindungen aufgezeigt, z.B. des x-Amino-5-Nitropyridins und des 5-Nitro-2-propyl pyridins und der Pyridyl-2-essigsäure, von welchen die beiden zuletzt genannten mit Hilfe von Lithium-Verbindungen dargestellt wurden.

Der zweite Weg sollte von der 2-Propyl-pyridin-5-sulfosäure durch Ersatz der Sulfogruppe gegen OH zum Alkaloid führen. Die entsprechenden Versuche hatten aber keinen Erfolg.

Beim dritten Weg wurde die Kondensation von Cyanessigsäureamid mit dem gesuchten 1,5-Dicarbonyl-Körper aus Oxymethylen-methyl-n-propylketon und über mehrere Zwischenstufen das 2-Propyl-3-aminopyridin dargestellt, von dem aus das Alkaloid wie auf dem ersten Weg hergestellt wurde.

Die Arbeit ist sowohl theoretisch als auch experimentell sehr selbständig ausgeführt worden. Es traten beträchtliche experimentelle Schwierigkeiten auf, die soweit als möglich durch gründliche systematische Versuche überwunden wurden. Die Ergebnisse sind wertvoll und die Arbeit entspricht sehr gut den Anforderungen, die an eine Dissertation zu stellen sind.

Wien, 13.10.49.

L. Ehrenst.

417 43 ÖSTERR. STAATSDRUCKEREI

Manchester

Von 1954 bis 1955 war Schlögl im Rahmen eines British Council Scholarship an der University of Manchester. Dort beschäftigte er sich erstmals mit metallorganischen Verbindungen. Die Arbeit mit Ferrocen, die damals in England begann, sollte für Schlögls weiteres wissenschaftliches Leben prägend sein.

University of Manchester

Wien, Professur

Ab 1955 arbeitete Schlögl wieder als Assistent an der Universität Wien, am Institut für Organische Chemie. Er etablierte neue Forschungsgebiete, wie metallorganische Verbindungen (Beziehung zwischen anorganischer und organischer Chemie) und Stereochemie (Beschäftigung mit dem räumlichen Bau der Moleküle), die er

Ferrocen-Arbeitsgruppe 1968 (v. l.):
hinten: Peter Reich Rohrwig, Othmar Hofer, Manfred Walser, Gilbrecht Haller, Klaus Bauer
Mitte: Heike Gowal, Ulrike Haslinger, Christine Krasa
vorne: Helmut Egger, Karl Schlögl, Heinz Falk

in England kennen gelernt hatte, und richtete eine eigene Forschungsgruppe zu diesem Thema ein. In dieser Zeit gab es auch eine sehr fruchtbare Zusammenarbeit mit dem Nobelpreisträger Vladimir Prelog.
Schlögl habilitierte sich 1959, wurde 1970 außerordentlicher Professor und 1971 Ordinarius für Organische Chemie an der Universität Wien.
1974 wurde er zum Vorstand des Institutes ernannt und 1978 zum Institutsvorstand gewählt.
1977 wurde Schlögl der erste gewählte Dekan der Formal- und Naturwissenschaftlichen Fakultät der Universität Wien.

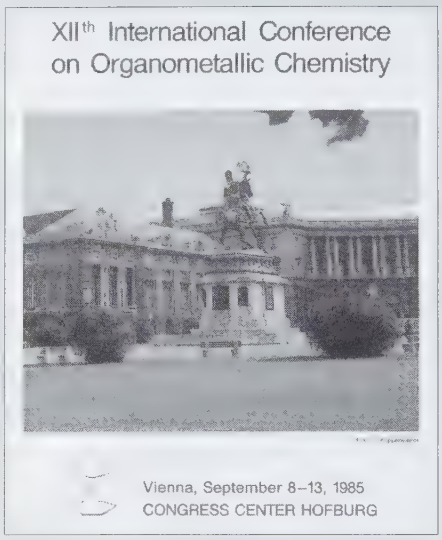
Mit Wissenschaftsministerin Firnberg bei der Eröffnung des 400 Megaherz-Kernresonanzspektrometers, 1970

Vladimir Prelog wird Ehrenmitglied der Gesellschaft Österreichischer Chemiker (GÖCH)

Schlögl als Dekan, 1978

Kongress 1985

1985 gelang es Schlögl, einen großen Kongress, die XII. Internationale Konferenz über Metallorganische Verbindungen, nach Wien zu bringen.

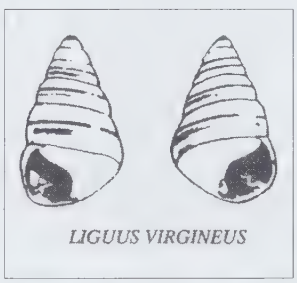


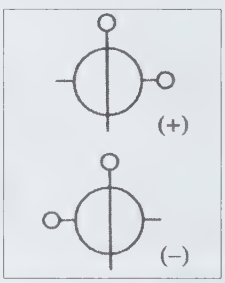
Schlögl mit Wissenschaftsminister Fischer und Nobelpreisträger Ernst Otto Fischer

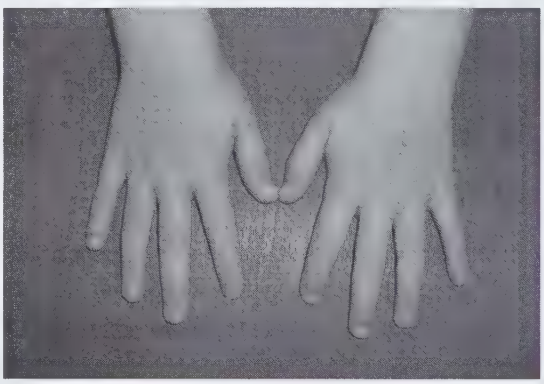
Schlögl mit dem aus Wien stammenden weltbekannten Chemiker Otto Vogl (links)

Das Werk

Das wissenschaftliche Lebenswerk von Karl Schlögl ist von zwei wesentlichen Aspekten der organischen Chemie geprägt: von der Stereochemie, also dem räumlichen Bau von Kohlenstoffverbindungen, sowie dem Gebiet der Organometallverbindungen, im speziellen der Übergangsmetall-Komplexe von Aromaten mit Eisen, Chrom, Mangan oder Ruthenium. Von diesen sind besonders jene mit dreidimensionaler „Sandwichstruktur", die sogenannten Metallocene, wegen ihres räumlichen Baues und der hohen Aromatizität von Interesse. Ferrocen (Bicyclopentadienyl-Eisen) als ihr bekanntester Vertreter spielt eine zentrale Rolle in den Arbeiten von Karl Schlögl und machte ihn zu einem weltweit anerkannten Repräsentanten der „Ferrocenchemie".
Schlögl hat ab 1963 die Stereochemie (bzw. ab 1970 die Chiralität) organischer Verbindungen in zahlreichen theoretischen und vor allem experimentellen Arbeiten eingehend studiert. Heute sind die Ausdrücke „Chiralität" und „chiral" in der Chemie allgemein verbreitet. Chiralität (Händigkeit, griech. *chiros* = Hand) ist die Erscheinung, dass sich zwei Strukturen wie Bild und Spiegelbild verhalten und im Raum nicht zur Deckung gebracht werden können; ein Ausdruck, der vom Nobelpreisträger Vladimir Prelog in die Chemie eingeführt wurde. Solche Spiegelbilder werden als Enantiomere







Das Prinzip Chiralität anhand einfacher Beispiele

Pergamon

Prog. Polym. Sci., Vol. 19, 1031–1044, 1994

0079-6700/94 $26.00

0079-6700(94)00015-8

TORSIONAL CHIRAL STRUCTURES – KEYSTONES IN STEREOCHEMICAL RESEARCH*

KARL SCHLÖGL
Institute of Organic Chemistry, University of Vienna, A-1090 Vienna, Austria

CONTENTS

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1. INTRODUCTION

Rotation represents a fundamental movement both in the macroscopic and the microscopic world as well as in daily life. Think of the rotation of galaxies, of planets and the spin of electrons, and even of the Viennese waltz.

Torsion can be defined as a rotation around an axis with a torsional angle smaller than 360°. If torsion of any structure occurs in opposite directions, and with a sufficiently high torsional barrier leading to mirror images which are not superimposable, then torsion represents a special element of chirality, namely torsional (or axial) chirality (Fig. 1).[1]

A wide variety of torsional chirality is encountered in art, in living organisms (Fig. 2), or in structures relevant to life – such as the α-helix in proteins or nucleic acids – and in an increasing number of torsional chiral molecules which have attracted much interest in the field of structural and stereochemistry. The arc spans from the so-called atropisomeric, i.e., torsional isomeric biaryls (extensively studied by Mislow and his group[2]) to more elaborate structures which have been investigated in our laboratory. A few of these will be briefly presented in this paper. Torsional chirality also includes chiral macromolecules, such as helical polymers, an aspect closely related to some of Otto Vogl's pioneering work in this field,[3] justifying the choice of the topic of my paper for this special occasion.

One of the most important features in stereochemical research is the need to separate enantiomers, i.e., the problem of optical resolution. Classical methods, namely separation via diastereomers are very often rather tedious procedures and are sometimes more of an art than science. Within the last few years, enantioselective chromatography has gained increasing importance, making use of chiral, mainly helical polymers as stationary phases. The advantages are obvious: Almost no loss of substance, and immediate knowledge of enantiomeric purity if a baseline separation can be achieved. We have obtained excellent results even for preparative amounts – employing microcrystalline cellulose triacetate (CTA).[4] A few examples of the many types of racemates separated thus far are shown in Fig. 3.

Rotational (axial) chirality in a more simple molecular representation is shown in

*Presented at the symposium entitled *Polymer Science and Technology in the 21st Century*, New York, November 8–10, 1992

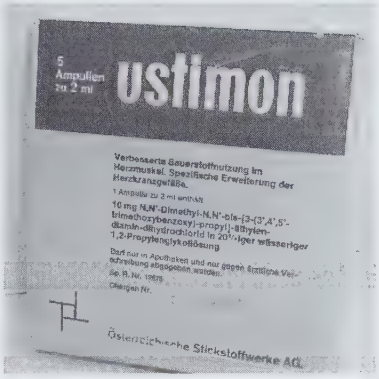
bezeichnet. Sie unterscheiden sich bei sonst identischen Eigenschaften nur in der Drehung der Ebene des linear polarisierten Lichtes, also ihrer optischen Aktivität – als (+)- und (–)-Form – und allenfalls auch in ihrer biologischen Wirkung. Beispiele sind Aminosäuren, Zucker, Proteine oder Nucleinsäuren. Chiralität ist also eine conditio sine qua non für Leben, wie wir es kennen.

In zahlreichen Untersuchungen wurde von der Schule Schlögl gezeigt, dass Metallocene oder entsprechend überbrückte aromatische Verbindungen (Cyclophane) bei geeigneter Substitution chiral sind und dann optisch aktiv erhalten werden können. Diese neuen Typen der Chiralität wurden von ihm als „Metallocen"- bzw. „Planarchiralität" bezeichnet. Wird durch geeignete Substitution die Rotationsbarriere von Biarylen (im einfachsten Fall Bi-phenyl) entsprechend erhöht, tritt gleichfalls Chiralität, die Axialchiralität, auf. Auch dafür lieferte die Arbeitsgruppe Schlögl zahlreiche, sehr wesentliche Bespiele. Da bei vielen dieser chiralen Strukturen eine klassische Trennung der Enantiomere (etwa durch Kristallisation) versagt, wurde als effiziente Methode die chromatographische Trennung an optisch aktiven Trägern (etwa Triacetylcellulose, „enantioselektive Chromatographie") entwickelt, die sich auch bei anderen Strukturen bestens bewährte.

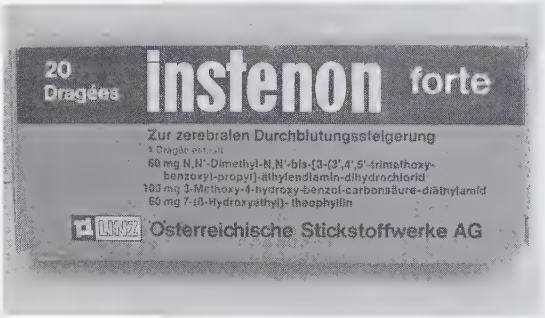
Die Biologie hat einen unerhört chemischen Touch bekommen.

Optisch aktive Biaryle und Metallocene, vor allem Ferrocen, werden heute als wertvolle Katalysatoren zur gezielten Synthese optisch aktiver Wirkstoffe –

besonders in der Pharmaindustrie – herangezogen. Schlögl entwickelte gemeinsam mit dem pharmakologischen Institut und seinem Vorstand Prof. Otto Kraupp für die Österreichischen Stickstoffwerke auch zwei pharmazeutische Wirkstoffe zur Durchblutungssteigerung in Herz und Gehirn (Ustimon und Instenon), mit denen in ganz Europa gute Heilerfolge erzielt werden konnten.
Die hier genannten sowie einige weitere Untersuchungen, vor allem zur Aminosäure- und Peptidchemie, wurden in über 200 Publikationen und vier Patenten niedergelegt, welche u. a. die Ergebnisse von 51 Dissertationen und zehn Diplomarbeiten zusammenfassen.
Nach seiner Emeritierung engagiert sich Karl Schlögl in der Österreichischen Akademie der Wissenschaften, deren Generalsekretär er von 1991 bis 1995 war; von 1997 bis 2000 war er Vizepräsident der ÖAW.

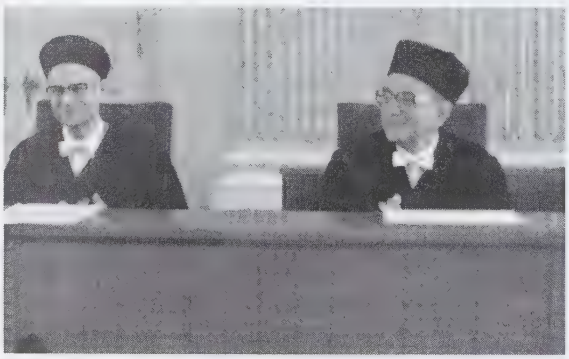


Ustimon: Österr. Patent Nr. 231.432 gemeinsam mit Otto Kraupp



Instenon: Österr. Patent Nr. 234.701 gemeinsam mit Otto Kraupp

Die Chemie soll das Leben der Menschheit verbessern und erleichtern. Wenn es gelingt, schwere Geißeln der Menschheit in den Griff zu bekommen, dann wird die Chemie sicherlich federführend dabeisein.



Mit Otto Hittmair bei einer Sitzung der ÖAW, Anfang der 90-er Jahre

China-Besuch der ÖAW mit Otto Hittmair, 1989

U R K U N D E

Das Präsidium und der Vorstand der Gesellschaft Österreichischer Chemiker haben einstimmig beschlossen,

Herrn
Univ.Prof.Dr.Karl Schlögl

in dankbarer Anerkennung seines großen und überaus erfolgreichen persönlichen Einsatzes als GÖCH - Präsident von 1985 bis 1990 zum

EHRENPRÄSIDENTEN
DER
GESELLSCHAFT ÖSTERREICHISCHER
CHEMIKER
AUF
LEBENSZEIT

zu wählen.

Wien, am 7.November 1991

Das Präsidium der
Gesellschaft Österreichischer Chemiker

Verleihungsurkunde

Der Vorstand der Gesellschaft Österreichischer Chemiker hat einstimmig beschlossen, die zum ehrenden Andenken an Josef Loschmidt gestiftete

Josef Loschmidt-Medaille

Herrn Univ.-Prof. Dr. phil.

Karl Schlögl

für hervorragende wissenschaftliche Leistungen auf dem Gebiet der organischen Stereochemie zu verleihen.
Sein wissenschaftliches Werk umspannt einen weiten Bogen über bahnbrechende Arbeiten an Chemie und Stereochemie von Metallocenen, insbesondere an Ferrocen, über die Chemie und Stereochemie einer Vielfalt von axial- und planarchiralen Molekülen, bis zur enantioselektiven Chromatographie an mikrokristalliner Triacetylcellulose, der Ermittlung absoluter Konformationen mit chiroptischen Methoden und der Kinetik von Torsionsisomeren mittels dynamischer NMR-Spektroskopie.

Wien, am 23. November 1993

Das Präsidium der
Gesellschaft Österreichischer Chemiker

Ehrungen, Preise

Schlögl wurde für sein Werk mehrfach geehrt. Unter anderem erhielt er 1985 den Erwin Schrödinger-Preis der Österreichischen Akademie der Wissenschaften, 1989 den Preis für Naturwissenschaften der Stadt Wien und 1991 die Wilhelm Exner-Medaille des Österreichischen Gewerbevereins. Schlögl ist auch Ehrenpräsident der Gesellschaft Österreichischer Chemiker auf Lebenszeit.

ÖSTERREICHISCHER GEWERBEVEREIN

ögv

Der Österreichische Gewerbeverein hat in der Hauptversammlung vom 27. November 1991
Herrn
o.Univ.Prof.Dr.Karl Schlögl,
Universität Wien
für seine ausgezeichneten Beiträge zur Chemie und Stereochemie chiraler Verbindungen und zur Zusammenarbeit von akademischer Wissenschaft und gewerblicher Wirtschaft
die
WILHELM-EXNER-MEDAILLE
verliehen.

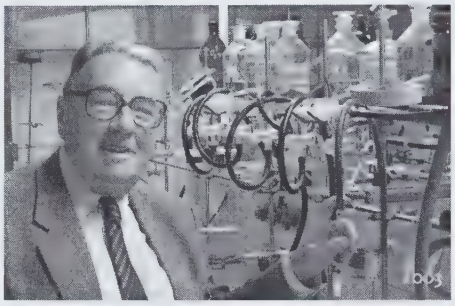
Helmut Zilk überreicht Schlögl den Preis für Naturwissenschaften der Stadt Wien, 1989

Karl Schlögl und Hans Tuppy als Gäste bei der Vergabe des Novartis-Preises, 2001

Mit Bundespräsident Klestil und Otto Hittmair bei der jährlichen Verleihung der Exner-Medaille, 2002


1948


um 1970


2003

Ich war immer glücklich mit meiner Entscheidung, Chemiker zu werden. Ich würde es noch einmal machen. Und wieder die organische Chemie.

Hans Tuppy

Emer. Univ.-Prof., Dr. phil. DDr. h. c.
Institut für medizinische Biochemie an der Universität Wien

Werdegang:

22. 7. 1924	Geboren in Wien, Vater: Dr. Karl Tuppy; führte als Staatsanwalt 1934 die Anklage gegen die nationalsozialistischen Dollfuß-Mörder und wurde 1939 von den Nazis im KZ ermordet. Verheiratet mit Erika Tuppy, geb. Höbartner, 3 Kinder aus erster Ehe Schottengymnasium und Staatsgymnasium I in Wien
1942–1948	Studium der Chemie an der Universität Wien
1948	Promotion zum Dr. phil. mit einer Dissertation aus der Alkaloidchemie bei Späth
1949–1950	Stipendium des British Councils, Forschungsaufenthalt bei Fred Sanger am Biochemischen Institut in Chambridge
1950–1951	Forschungsaufenthalt am Carlsberg-Laboratorium in Kopenhagen
1951–1956	Assistent am II. Chemischen Institut der Universität Wien
1956–1958	Habilitation an der naturwissenschaftlichen Fakultät der Universität Wien
1958–1963	A.o. Univ.-Prof. für Biochemie an der Medizinischen Fakultät der Universität Wien
1960	Gastprofessor an der Yale University, USA
ab 1963	O. Univ.-Prof. für Biochemie an der Medizinischen Fakultät der Universität Wien
ab 1967	Mitglied der Österreichischen Akademie der Wissenschaften
1970–1972	Dekan der Medizinischen Fakultät der Universität Wien
1974–1982	Präsident des Fonds zur Förderung der wissenschaftlichen Forschung
1983–1985	Rektor der Universität Wien
1985–1987	Präsident der Österreichischen Akademie der Wissenschaften
1987–1989	Bundesminister für Wissenschaft und Forschung
1994	Emer. Univ.-Prof. der Universität Wien
ab 2003	Vorsitzender des Universitätsrates der Universität für Bodenkultur

Publikationen:
Mehr als 100 wissenschaftliche Veröffentlichungen vor allem auf dem Gebiet der Chemie und Biochemie

Ehrungen (Auswahl):
Rudolf Wegscheider-Preis der Österreichischen Akademie der Wissenschaften (1955)
Ehrendoktor der Veterinärmedizinischen Universität Wien (1968)
Erwin Schrödinger-Preis der Österreichischen Akademie der Wissenschaften (1973)
Österreichisches Ehrenzeichen für Wissenschaft und Kunst (1975)
Ehrendoktor der Universität für Bodenkultur Wien (1990)
Ludwig Wittgenstein-Preis (2002)

Mitgliedschaften (Auswahl):
Wirkliches Mitglied der Deutschen Akademie der Naturforscher Leopoldina Halle (1965)
Wirkliches Mitglied der Österreichische Akademie der Wissenschaften (1967)
Päpstliche Akademie der Wissenschaften (1970)
Akademia Europaea (1989)

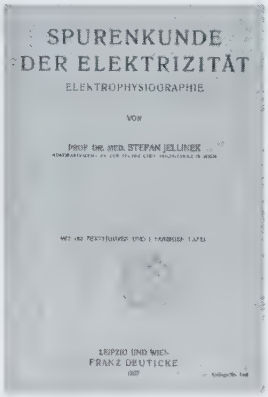
„Die Wissenschaft ist eines der wesentlichen Elemente, die Menschen zusammenbringen. Sie ist eine wesentliche Stütze des Weltgedankens der Menschheit."

Kindheit, Gymnasium

Hans Tuppy wurde am 22. Juli 1924 in Wien geboren. Tuppys Eltern kamen aus dem heutigen Tschechien; der Vater aus Brünn, die Mutter aus Prag. Mit der Machtübernahme der Nationalsozialisten fand seine glückliche Kindheit ein jähes Ende. Sein Vater Karl Tuppy, er war als 1. Staatsanwalt Ankläger im Prozess gegen die Dollfußmörder, wurde am 18. März 1938 verhaftet und am 14. November 1939 von den Nazis im KZ Sachsenhausen ermordet. Tuppy: *„Ich war ab 14 Jahren gewohnt, auf jedes Wort zu achten!"*

Karl Tuppy

Tuppys Eltern förderten sein Interesse an der Natur mit viel Verständnis, z. B. mit Büchern von Römpp oder von Karl von Frisch.

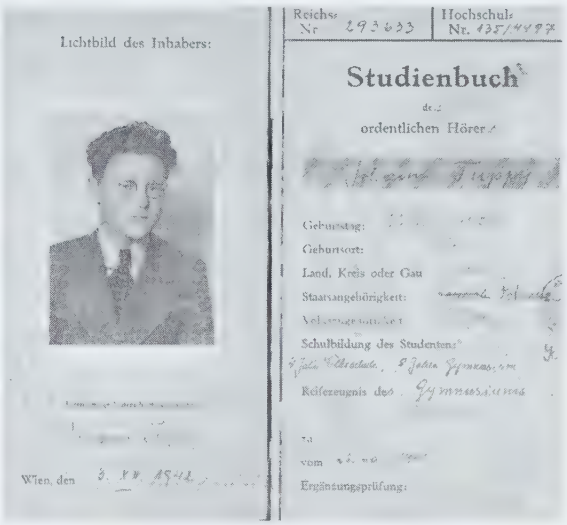

SPURENKUNDE
DER ELEKTRIZITÄT
ELEKTROPHYSIOGRAPHIE
VON
PROF. DR. MED. STEFAN JELLINEK
LEIPZIG UND WIEN
FRANZ DEUTICKE

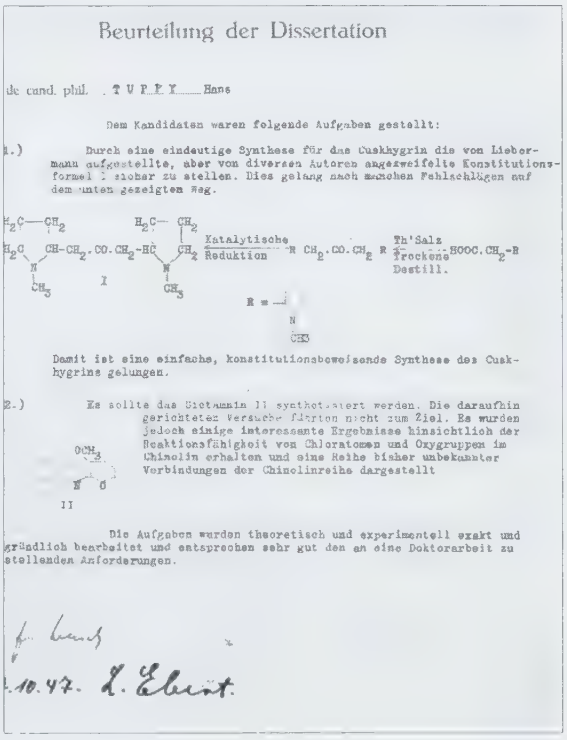
Stefan Jellinek und Hans Thirring waren „Vorbildgestalten" für Hans Tuppy.

Tuppy hat schon früh mit Gerüchen experimentiert, hat Pflanzenfarbstoffe extrahiert, mikroskopiert und Sprengstoffe hergestellt. Sein Laboratorium war die Küche. Hans Thirring und der Elektropathologe Stefan Jellinek waren Freunde der Familie und „Vorbildgestalten".
Schon als Mittelschüler besuchte Tuppy Vorlesungen für medizinische Chemie.
Er maturierte 1942.

Studium, Krieg

Im Krieg kam Tuppy zum Arbeitsdienst, wo er bald schwer verletzt wurde und nicht mehr kriegsverwendungsfähig war. Er konnte daher schon früh in Wien mit dem Studium der Chemie beginnen und hatte bis 1945 bereits fünf Semester absolviert und das Vordiplom gemacht. Seine wichtigsten Lehrer damals waren Ernst Späth, dessen ausgezeichnete Experimentalvorlesung auf Tuppy bleibenden Eindruck hinterlassen hat, und später Friedrich Wessely.
Die wissenschaftlichen Höhepunkte im Studium waren Alkaloidsynthesen bei Späth.


Lichtbild des Inhabers:
Reichs-Nr. 293633
Hochschul-Nr. 135/4497
Studienbuch
ordentlichen Hörer
Geburtstag:
Geburtsort:
Land, Kreis oder Gau
Staatsangehörigkeit:
Schulbildung des Studenten:
Reifezeugnis des Gymnasiums
Wien, den
Ergänzungsprüfung:


Beurteilung der Dissertation

de cand. phil. TUPPY Hans

Dem Kandidaten waren folgende Aufgaben gestellt:

1.) Durch eine eindeutige Synthese für das Cuskhygrin die von Liebermann aufgestellte, aber von diversen Autoren angezweifelte Konstitutionsformel I sicher zu stellen. Dies gelang nach manchen Fehlschlägen auf dem unten gezeigten Weg.

Katalytische Reduktion
Th'Salz trockene Destill.
R =

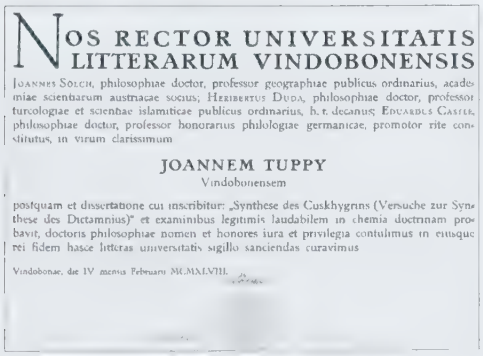
Damit ist eine einfache, konstitutionsbeweisende Synthese des Cuskhygrins gelungen.

2.) Es sollte das Dictamnin II synthetisiert werden. Die daraufhin gerichteten Versuche führten nicht zum Ziel. Es wurden jedoch einige interessante Ergebnisse hinsichtlich der Reaktionsfähigkeit von Chloratomen und Oxygruppen im Chinolin erhalten und eine Reihe bisher unbekannter Verbindungen der Chinolinreihe dargestellt

II

Die Aufgaben wurden theoretisch und experimentell exakt und gründlich bearbeitet und entsprechen sehr gut den an eine Doktorarbeit zu stellenden Anforderungen.

.10.47. L. Ebert


NOS RECTOR UNIVERSITATIS LITTERARUM VINDOBONENSIS

JOANNEM TUPPY
Vindobonensem

Vindobonae, die IV mensis Februarii MCMXLVIII.

Cambridge – Insulin

Friedrich Wessely hat den Auslandswunsch von Tuppy sehr gefördert. Er korrespondierte mit Max Perutz, welcher dem erst 25-jährigen Tuppy eine Stelle bei Frederick Sanger in Cambridge vermittelte. Perutz wurde ein guter „väterlicher Freund" von Tuppy. In Cambridge arbeitete Tuppy an der Insulinsynthese. Das Insulinmolekül konnte gemeinsam mit Sanger aufgebrochen und seine Struktur erforscht werden. Für diesen Erfolg erhielt Sanger 1958 den Nobelpreis. Tuppy war als Sangers Mitarbeiter mit 26 als „Tappy" in Wissenschaftskreisen weltbekannt geworden.

FREDERICK SANGER

The chemistry of insulin

Nobel Lecture, December 11, 1958

Sanger beschreibt die Arbeit von Tuppy:

At this point (1949) I was joined by Dr. Hans Tuppy who came to work in Cambridge for a year. Although we did not seriously envisage the possibility of being able to determine the whole sequence of one of the chains within a year, it was considered worth while to investigate the small peptides from an acid hydrolysate using essentially the methods that had been applied to "gramicidin-S". Studies were initiated on both the chains at the same time but it soon became clear that there would be more difficulties with fraction A although it was the shorter chain and the work on fraction B progressed so favourably and Tuppy worked so hard that by the end of the year we were virtually able to deduce the whole of the sequence of its 30 residues*.

Ausschnitt aus: Sanger, Nobel Lecture, 1958

Frederick Sanger, 1950

Hans Tuppy, 1948

The Amino-acid Sequence in the Phenylalanyl Chain of Insulin

1. THE IDENTIFICATION OF LOWER PEPTIDES FROM PARTIAL HYDROLYSATES

BY F. SANGER (Beit Memorial Fellow) AND H. TUPPY*
Biochemical Laboratory, University of Cambridge

(*Received* 17 *January* 1951)

When insulin is oxidized with performic acid, the —S—S— bridges of the cystine residues are broken by conversion to —SO_3H groups (Sanger, 1949*a*) and the molecule is split into its separate polypeptide chains. From the oxidized insulin two fractions could be isolated: an acidic fraction *A*, which contained only glycyl *N*-terminal residues (see below) and no basic amino-acids, and a basic fraction *B*, having phenylalanyl *N*-terminal residues. These appeared to be the only significant fractions present.

From a study of the partial hydrolysis products of the dinitrophenyl (DNP) derivatives of the two fractions it was possible to determine the sequence of the amino-acids adjoining the *N*-terminal residues and adjoining the lysine residues (Sanger, 1949*b*). In the case of fraction *B* the terminal sequence was shown to be Phe.Val.Asp.Glu and the lysine residues were present in the sequence Thr.Pro.Lys.Ala (abbreviations for amino-acids are given in Table 1 below). No DNP-peptides were present which did not fit into these sequences, and from an estimation of the yields of the DNP-peptides produced on partial hydrolysis of DNP-insulin it was concluded that all the *N*-terminal phenylalanyl residues of insulin and all the lysine residues were present in the above two sequences respectively, and hence that there was only one type of phenylalanyl polypeptide chain in insulin. Similar though rather less clear-cut results were obtained for fraction *A*. Assuming a molecular weight of 12,000, it was concluded from these experiments that insulin is built up of two identical phenylalanyl polypeptide chains and two identical glycyl chains, these four chains being joined together by six —S—S— bridges. Various possible structures for the molecule were suggested (Sanger, 1949*c*).

The results with the terminal peptides gave a preliminary indication that the fractions *A* and *B* are both relatively homogeneous preparations of molecules having a single polypeptide chain and containing approximately 20 and 30 amino-acid residues respectively. It thus seemed that an investigation of the smaller peptides produced on partial hydrolysis might yield considerable information about the overall amino-acid sequence in these fractions. Consden, Gordon & Martin (1947) have described a method for the fractionation of lower peptides using paper chromatography which was successfully used to determine the pentapeptide sequence of 'gramicidin S' (Consden, Gordon, Martin & Synge, 1947). The present paper describes the application of this technique to partial acid hydrolysates of fraction *B* and the determination of a number of amino-acid sequences.

Throughout this paper the abbreviations for the amino-acid residues suggested by Brand & Edsall (1947) are used. These are listed in Table 1. In referring to peptides of known structure, the abbreviations for the residues are joined by a full stop (e.g. glycylalanine is written Gly.Ala). When two or more residues are included in square brackets the order is unknown. Thus, for instance, Gly.[Ala, Leu] refers to a peptide or peptides containing glycine, alanine and leucine, in which the free amino group is on the glycine residue, but the relative order of the alanine and leucine residues is unknown. The residues having the free α-amino groups in peptides will be referred to as *N*-terminal residues, those with free α-carboxyl groups as *C*-terminal residues.

Table 1. *Abbreviations for amino-acid residues*

Amino-acid	Abbreviation
Cysteic acid	$CySO_3H$
Aspartic acid	Asp
Glutamic acid	Glu
Serine	Ser
Glycine	Gly
Threonine	Thr
Alanine	Ala
Tyrosine	Tyr
Valine	Val
Leucine	Leu
Phenylalanine	Phe
Proline	Pro
Histidine	His
Lysine	Lys
Arginine	Arg
Ornithine	Orn

* Present address: II. Chemisches Universitätslaboratorium, Vienna, Austria.

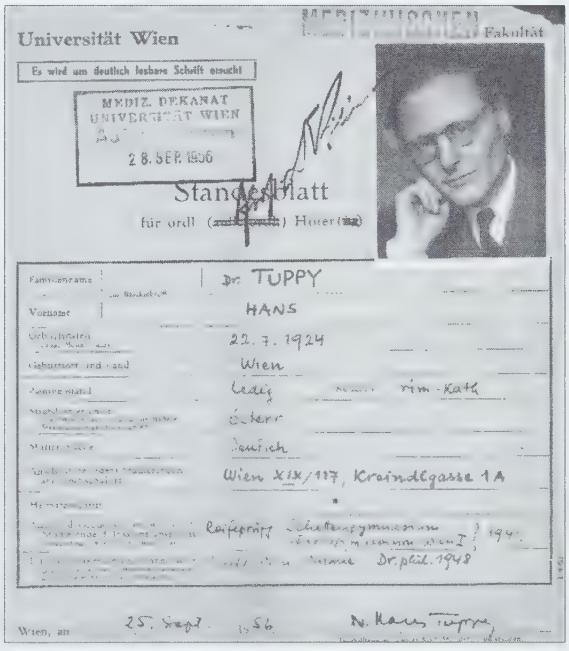
Veröffentlichung von Tuppy und Sanger über ihre Insulinforschungen, 1951

Cambridge 1950, Hans Tuppy (vorne) und Frederick Sanger

Man sollte davon wegkommen, dass die Natur, so wie wir sie empfinden, die Natur ist. Denn die Natur ist ja schon übersetzt. Unser ganzer sinnlicher Eindruck ist ja schon übersetzt. Wir nehmen ja nur unter gewissen Gesichtspunkten alles wahr.

Wien-Professur

Von Cambridge ging Tuppy nach Dänemark ans Karlsberg-Laboratorium und kehrte 1951 nach Wien zurück. Er wurde Assistent am II. Chemischen Institut der Universität Wien, habilitierte sich 1956, wurde 1958 außerordentlicher Professor und 1963 Ordinarius am Institut für Biochemie an der medizinischen Fakultät der Universität Wien.
Tuppy spezialisierte sich wissenschaftlich nie auf ein Thema, sondern bearbeitete immer mehrere Themen gleichzeitig, z. B. Nukleinsäuren, Kohlehydrate, Viren. In seinen Forschungsarbeiten beschäftigte sich Tuppy vor allem mit der Zusammensetzung und Funktion von Eiweißstoffen und Peptiden, mit den Organellen der Zellatmung und mit Molekülen (Antigenen) an Zelloberflächen, welche die Blutgruppenzugehörigkeit und die Infektion durch Viren bestimmen.
In Zusammenarbeit mit Heribert Michl klärte Tuppy die Aminosäuresequenz des Oxytocins auf. Darauf folgten Untersuchungen über das Enzym Oxytocinase und andere Aminopeptidasen. Zusammen mit


Universität Wien

Fakultät

Es wird um deutlich lesbare Schrift ersucht

MEDIZ. DEKANAT UNIVERSITÄT WIEN
28. SEP. 1956

Standesblatt

für ordl. (außerordl.) Hörer(in)

Familienname: Dr. TUPPY

Vorname: HANS

22. 7. 1924

Wien

Lezig

Österr.

Israelitisch

Wien XIX/117, Krottenbachgasse 1A

Reifeprüft

Dr. phil. 1948

Wien, am 25. Sept. 1956

N. Hans Tuppy

Gerhard Bodo und Günther Kreil bearbeitete er die Primärstruktur und Artspezifität des Elektronenüberträgers Cytochrom c.
Ein weiteres wichtiges Forschungsgebiet war die Biochemie der Mitochondrien; gemeinsam mit Gottfried Schatz und Ellen Haslbrunner gelang Tuppy der Nachweis von DNA in Mitochondrien.
Die enzymatische Umwandlung von Blutgruppensubstanzen des ABO-Systems war ein Resultat gemeinsamer Arbeit mit Helmut Schenkel-Brunner, die Entdeckung einer Gruppe von Neuraminsäurederivaten mit antiviraler Wirksamkeit ein Erfolg der Zusammenarbeit mit Peter Meindl.

Tuppy bei einer Promotion, 1984

Vol. 15, No. 2, 1964 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS

DEOXYRIBONUCLEIC ACID ASSOCIATED WITH YEAST MITOCHONDRIA

G. SCHATZ, E. HASLBRUNNER and H. TUPPY
Institut für Biochemie, University of Vienna, Austria.

Received January 27, 1964

DNA is generally considered to be confined to the nucleus. Small amounts of DNA sometimes found in other cell fractions are usually attributed to contamination by nuclear material (Allfrey 1959). The presence of significant amounts of extranuclear DNA occurring in the cytoplasm of the amphibian oöcyte (Stich 1962), the kinetosomes (Clark and Wallace 1960), and in the chloroplasts of plant cells (Chun et al. 1963) is well documented but is regarded rather as an exception than as a rule, because in these cases DNA is associated with cellular components absent from higher cells.

This paper presents evidence that preparations of mitochondria from baker's yeast, purified by flotation in density gradients, contain a significant quantity of DNA. The amount found is far in excess of that accounted for by the polydeoxyribonucleotide component (Appleby and Morton, 1960) of mitochondrial cytochrome b_2.

Since the mitochondrion represents an organelle present in most cells, including those of mammals, the occurrence of DNA in yeast mitochondria suggests the possibility, that extranuclear DNA is much more common that hitherto suspected

Mitochondrial function in the yeast cell is in part controlled by extrachromosomal genetic factors (Ephrussi and Hottinguer 1951), whose exact chemical nature is unknown. The presence of DNA in yeast mitochondria is thus of special interest.

Experimental: The wild type strain W of Saccharomyces cerevisiae was grown as described previously (Schatz 1963). The concentration of glucose in the growth medium was 0.8 %. The preparation of the yeast homogenates and of the crude mitochondrial fractions was the same as in earlier work (Schatz et al. 1963), except that the medium employed for the homogenization and washing procedures contained 0.25 M mannitol, 20 mM tris-buffer pH 7.4 and 1 mM EDTA. For density gradient flotation, a linear continuous sucrose gradient (volume 25 ml; 0.98-1.66 M sucrose; additions as above)

Über die chemische Struktur des Oxytocins.

Von
H. Tuppy und **H. Michl.**

Aus dem II. Chemischen Laboratorium der Universität Wien.

(Eingelangt am 23. Juli 1953. Vorgelegt in der Sitzung am 8. Oktober 1953.)

Mit 3 Abbildungen.

Mit Perameisensäure oxydiertes Oxytocin wurde sowohl durch Säurehydrolyse als auch mit Hilfe eines bakteriellen Enzyms abgebaut. Die dabei entstehenden Peptide wurden nach chromatographischer Trennung chemisch charakterisiert. Aus ihrer Natur läßt sich die Struktur des Hormons erschließen:

Cys-Tyr-Ileu-Glu(NH_2)-Asp(NH_2)-Cys-Pro-Leu-Gly(NH_2).

Oxytocin, das uterusstimulierende Prinzip des Hirnanhanges, ist seiner chemischen Natur nach ein Peptid. Es wurde, ebenso wie auch das zweite Hormon des Hypophysenhinterlappens, Vasopressin, welches sowohl blutdrucksteigernde als auch antidiuretische Eigenschaften besitzt, in den letzten Jahren vor allem von *du Vigneaud* und seinen Mitarbeitern intensiv bearbeitet[1–8]. Beide Hormone enthalten, wie die Untersuchung

[1] *A. H. Livermore* und *V. du Vigneaud*, J. Biol. Chem. **180**, 365 (1949).
[2] *J. G. Pierce* und *V. du Vigneaud*, J. Biol. Chem. **182**, 359 (1950).
[3] *J. M. Mueller, J. G. Pierce, H. Davoll* und *V. du Vigneaud*, J. Biol. Chem. **191**, 309 (1951).
[4] *E. A. Turner, J. G. Pierce* und *V. du Vigneaud*, J. Biol. Chem. **193**, 359 (1951).
[5] *H. Davoll, R. A. Turner, J. G. Pierce* und *V. du Vigneaud*, J. Biol. Chem. **193**, 363 (1951).
[6] *J. G. Pierce, S. Gordon* und *V. du Vigneaud*, J. Biol. Chem. **199**, 929 (1952).
[7] *H. G. Kunkel, S. P. Taylor* und *V. du Vigneaud*, J. Biol. Chem. **200**, 559 (1953).
[8] *R. A. Turner, J. G. Pierce* und *V. du Vigneaud*, J. Biol. Chem. **191**, 21 (1951).


WIENER UNIVERSITÄTSREDEN

Neue Folge 1

Kurt Schubert

Die Wiedereröffnung der Universität Wien im Mai 1945

hatten. In dieser Funktion befand sich die heutige Ordinaria für Zeitgeschichte Erika Weinzierl, die damals als Erika Fischer noch Medizin studierte.

Der Kreis, dem ich selbst angehörte, nannte sich „Katholische Studentenseelsorge". Das Zentrum und der unbestrittene Mittelpunkt war der Studentenseelsorger Dr. Karl Strobl. Dort trafen wir uns. Außer der schon genannten Erika Weinzierl-Fischer waren es noch einige Dutzend Kolleginnen und Kollegen. Von den noch jetzt an der Universität Wien wirkenden Professoren sei besonders der vielseitig tätige Hans Tuppy genannt. Auch Heribert Berger, der derzeitige Ordinarius für Kinderheilkunde an der Universität Innsbruck, gehörte unserer Gruppe an. Damit nannte ich nur Aktivisten der ehemaligen „Katholischen Studentenseelsorge", die heute Vorstände von Instituten österreichischer Universitäten sind. Unser Raum, in dem wir uns halblegal trafen, war die Sakristei von St. Peter in Wien. Ich sagte halblegal, weil wir uns zu religiösen Zusammenkünften treffen durften, wir aber auch andere Problemkreise besprachen als nur religiöse. Ein weiterer Treffpunkt für gemeinsame Eucharistiefeiern war die Kirche St. Ruprecht. Es war für uns immer ein besonderes Hochgefühl, so nahe dem Sitz der Geheimen Staatspolizei am Morzinplatz ein christliches Leben zu führen, das wir als unverzichtbaren Bestandteil unseres Widerstandswillens gegen den Nationalsozialismus betrachteten. Wir alle hofften auf den Tag und die Stunde, da der Nationalsozialismus zusammenbrechen werde. Und als es so weit war, konnten wir beim Wiederaufbau Österreichs all das realisieren, von dem wir bisher nur geträumt hatten.

Kurt Schubert über die Wiedereröffnung der Universität Wien 1945

Vereinigung. Die Richtlinien der Gruppe kristallisierten sich in langen Sitzungen bei Strobl heraus, man war kulturell-religiös orientiert, doch nicht klerikal, und politisch engagiert, doch kein "Ableger der ÖVP". Und schon in der ersten Maiwoche 1945 begründeten Czerny, Kurzel-Runtscheiner, Lewandowski, Schubert, Tuppy und andere die *Freie österreichische Studentenschaft (FÖST)*. Anschließend

"trat man jeden 2. Tag unter dem Vorsitz von Proksch zusammen. Lewandowski und Aschböck widmeten sich vor allem Hochschulfragen, Beroldinger und (Kurzel-Runtscheiner) übernahmen die innere Organisation; Erika Fischer hatte die Büroleitung über und die Hauptarbeit erledigte Tuppy als Sekretär."[1]

Scheiber, Barbara; Freud und Leid der österreichischen Studenten in der Nachkriegszeit Diplomarbeit, Innsbruck, 1993

Wissenschaftspolitische Karriere

Nach dem Krieg war Tuppy neben Erika Fischer (verehelichte Weinzierl), Kurt Schubert und einigen anderen am Wiederaufbau der Uni beteiligt und an führender Stelle Mitbegründer der Studentenliste „Freie Österreichische Studentenschaft", die 1946 die erste ÖH-Wahl gewann.

„Die Tätigkeit im Widerstand und der Wiederaufbau der Uni waren kein persönlicher Verdienst, sondern eher ein Verdienst der Umstände!"

Von Bundeskanzler Klaus wird Tuppy im Rahmen der 1965 ins Leben gerufenen „Aktion 20", die eine enge Zusammenarbeit zwischen Politik und Wissenschaft zum Ziel hat, zum Leiter des Arbeitskreises Bildung und Forschung bestimmt.

Ende der 1960-er Jahre wird Tuppy Mitglied der Hochschulreformkommision von Unterrichtsminister Piffl-Percevic. In dieser Zeit erarbeitete er gemeinsam mit Raoul Kneucker und Rudolf Strasser ein Hochschulreformpapier („Die Universität als autonomes Lehr- und Forschungsunternehmen"), in welchem erstmals der unternehmerische Charakter der Universitäten herausgestrichen wurde.

Später war Tuppy an der Formulierung des Forschungsförderungsgesetzes 1981 beteiligt, durch das der Fonds zur Förderung der wissenschaftlichen Forschung (FWF) entstanden ist. Damit wurde erstmals in Österreich eine reelle Möglichkeit geschaffen, Forschungsgelder durch korrekte Begutachtung und nicht über Beziehungen und politische Kanäle bewilligt zu bekommen. 1974 bis 1982 war Tuppy Präsident des FWF.Tuppy wurde 1970 Dekan der medizinischen Fakultät und 1983 Rektor der Universität Wien.

1967 wurde er Mitglied der Österreichischen Akademie der Wissenschaften, 1985 wählte die ÖAW Tuppy zu ihrem Präsidenten.

Tuppy unterstützte die konkrete Förderung von interaktiven Projekten zwischen Wissenschaft und industrieller Praxis. Konkret wurde 1986 ein Joint Venture zwischen Genentech Inc. und Boehringer Ingelheim vom Bund und dem Land Wien gefördert. Der Grundstein für das Biocenter Wien war gelegt.

Zwischen 1987 und 1989 war Tuppy Bundesminister für Wissenschaft und Forschung in der Regierung

1967: Tuppy leitet einen Arbeitskreis im Rahmen der „Aktion 20"

Mein Ziel war es immer, in der Forschung organisatorisch, strukturell und infrastrukturell etwas auf die Beine zu bringen.

Vranitzky. Dies war die Krönung und die logische Konsequenz von Tuppys Laufbahn. Tuppy war der erste ÖVP-Minister in dem 1970 geschaffenen Ministerium. Politische Gründe, nicht sachliche, kosteten ihn nach nur zwei Jahren den Regierungsjob. Er entzog sich Verlockungen der Politik, er benötigte keine Umstiegshilfe und konnte ohne Abstriche in seinen wissenschaftlichen Beruf zurückkehren. Der Universitätslehrer an der Spitze des Wissenschaftsministeriums war eine Ausnahme in diesem Ressort.
Alle diese Tätigkeiten waren für Tuppy Tätigkeiten mit ähnlichem Ziel: nämlich in der Forschung organisatorisch, strukturell und infrastrukturell etwas auf die Beine zu stellen.


KNEUCKER · STRASSER · TUPPY

Die Universität
als autonomes Lehr- und
Forschungsunternehmen

Ein Modellentwurf

Manzsche Verlags- und Universitätsbuchhandlung · Wien

VIROLOGY 58, 457-463 (1974)

Inhibition of Neuraminidase Activity by Derivatives of 2-Deoxy-2,3-dehydro-N-acetylneuraminic Acid

P. MEINDL,* G. BODO,* P. PALESE,† J. SCHULMAN,† AND H. TUPPY‡

Arzneimittelforschung GmbH, Vienna A-1121, Austria; †Department of Microbiology, Mt. Sinai School of Medicine of CUNY, New York, New York 10029; ‡Institut für Biochemie University of Vienna, Vienna, Austria

Accepted December 10, 1973

Eighteen derivatives of 2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid were assayed for inhibitory activity against neuraminidases from viral and bacterial sources. Twelve of these compounds were active against neuraminidases of *Vibrio cholerae*, influenza A/Mel, B/Lee, and Newcastle disease virus, causing 50% enzyme inhibition in concentrations ranging from 10^{-3} *M* to 10^{-4} *M*. The most active of them and the most potent neuraminidase inhibitor described so far is 2-deoxy-2,3-dehydro-*N*-trifluoroacetylneuraminic acid. This compound has an inhibitor constant (K_i) of $7,9 \times 10^{-7}$ *M* for influenza A/Mel virus neuraminidase whereas the K_m of the virus enzyme for the substrate is 1000 times weaker ($K_m = 6,9 \times 10^{-4}$ *M*). The mechanism of inhibition is competitive, and enzyme inhibition is independent of enzyme concentration. 2-Deoxy-2,3-dehydro-*N*-trifluoroacetylneuraminic acid inhibits hemagglutination by NDV and SV5 but does not inhibit agglutination of red cells by Sendai virus or influenza A and B viruses.

INTRODUCTION

Neuraminidases have been isolated from bacteria, protozoa, and a variety of animal tissues. Among the viruses, myxoviruses and some paramyxoviruses are unique in their possession of a virus-coded neuraminidase which is incorporated into the virion envelope. Two groups of synthetic inhibitors of this enzyme have been described. One diverse group consists of high molecular weight substances like Congo red and trypan blue (Becht and Drzeniek, 1967) and low molecular weight compounds, such as derivatives of oxamic acid (Edmond *et al.*, 1966), substituted β-aryl-α-mercaptoacrylic acids and other more complicated heterocyclic substances such as benzimidazoles (Haskell *et al.*, 1970). These substances, belonging to different chemical classes show varying *in vitro* inhibitory activity against neuraminidases but are nonspecific enzyme inhibitors; they also have been shown to inhibit many other enzyme reactions not related to the metabolism of sialic acids. In contrast to these nonspecific inhibitors a second group of neuraminidase inhibitors has been described, which consists of analogues and derivatives of neuraminic acid with a high degree of specificity for neuraminidases. Among this second group, small *N*-glycosides and small S-glycosides of *N*-acetylneuraminic acid have been shown to be very effective neuraminidase inhibitors, having inhibitor constants ranging from 2×10^{-5} to 4×10^{-6} *M* (Khorlin *et al.*, 1970).

Another synthetic neuraminic acid derivative, 2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid which differs from naturally occurring *N*-acetylneuraminic acid by one double bond between carbon atom 2 and carbon atom 3 has been shown previously to inhibit bacterial, viral and mammalian neuraminidases (Meindl and Tuppy, 1969b; Meindl *et al.*, 1971; Tuppy and Palese, unpublished results).

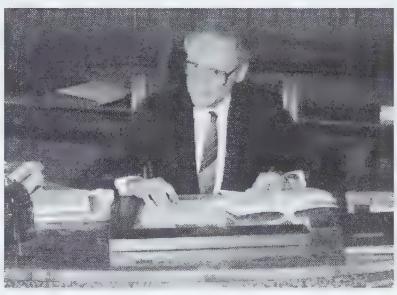
In this communication we describe and compare some *in vitro* properties of neuraminidase inhibitors derived from 2-deoxy-2,3-

Hans Tuppy kann persönlich auf nicht zu unterschätzende Erfolge zurückblicken. Die größte Leistung für Tuppy selbst war seine acht Jahre währende Tätigkeit als Präsident des Fonds zur Förderung der wissenschaftlichen Forschung und aus wissenschaftlicher Sicht die Beteiligung am Aufbrechen der Struktur des Insulins.

Für sein Werk wurde Tuppy vielfach geehrt: Er erhielt Ehrendoktorate der Universität für Bodenkultur und der Veterinärmedizinischen Universität Wien. 1975 wurde er mit dem Österreichischen Ehrenzeichen für Wissenschaft und Kunst ausgezeichnet, 2002 erhielt er für sein Lebenswerk den Ludwig Wittgenstein-Preis der Österreichischen Forschungsgemeinschaft, etc ...

Der „Fast-Nobelpreisträger" und ehemalige Präsident des Fonds zur Förderung der wissenschaftlichen Forschung, Rektor der Universität Wien und Bundesminister, ist Biochemiker und Forscher geblieben.

Biozentrum Bohrgasse – Tuppy unterstützte die Förderung von interaktiven Projekten zwischen Wissenschaft und Industrie.



Tuppy als Rektor, 1984

Tuppy als Wissenschaftsminister, 1987

Wissenschaftsminister Tuppy und Altbundespräsident Kirchschläger, 1989

Tuppy bei einem Treffen der päpstlichen Akademie der Wissenschaften, Mitte der 1980-er Jahre

LH Krainer überreicht Tuppy das Ehrenzeichen des Landes Steiermark, 1992.

Verleihung des Ehrendoktortitels der Hochschule für Bodenkultur an Tuppy, 1990

Wissenschaft ist für Menschen da, sie hat kulturelle Bedeutung, sie hat wirtschaftliche Bedeutung, sie hat politische Bedeutung.

Leben und Wissen

Symposium zu Ehren von Hans Tuppy

anläßlich der

Verleihung des
Ludwig Wittgenstein-Preises 2002

Beiträge von Ernst Bruck, Max Birnstiel,
Adolf Portmann
und Hans Tuppy

Herausgegeben von der
Österreichischen Forschungsgemeinschaft

ÖSTERREICHISCHE ZENTRALBIBLIOTHEK FÜR PHYSIK

44607

Tuppy erhält den Ludwig Wittgenstein-Preis der Österreichischen Forschungsgemeinschaft für sein Lebenswerk, 2002.

5.06. Biochemie

1. Hauptvorlesung

506 485 Biochemie für Mediziner (Hauptvorlesung gem. SIG); (beschränkte Teilnehmerzahl, max. 100); Blocklehrveranstaltung , 1.3.-14.5.2004 Mo-Fr 15:00-17:00 Hörsaalzentrum Medizinisch Theoretische Institute, 9 Schwarzspanierstr. 17, HP, Kleiner HörsaalVO 1st. lt. Aushang am Institut f. Med. Chemie Blockveranstaltung, Beginn am 1. März 2004

Hans Tuppy

Termine für Rigorosen WS 2003/04

Prüfer Biochemie: Tuppy, Küchler, Barta, Skern

Termine für das Rigorosum "Biochemie für Mediziner" WS 2003/04

Anmeldung: 03.09. - 09.09.2003
Prüfung in der Zeit von: 06.10. - 11.10.2003

Anmeldung: 05.11. - 11.11.2003
Prüfung in der Zeit von: 09.12. - 13.12.2003

Anmeldung: 26.11. - 02.12.2003
Prüfung in der Zeit von: 12.01. - 17.01.2004
Anmeldeschluß jeweils 12.00 Uhr

Erläuterungen zu den Rigorosenprüfungen:

Prüfungen halten ab: Rig. "Biochemie für Mediziner"

Prof. Dr. Hans Tuppy
Prof. Dr. Ernst Kuchler
Ao. Prof. Dr. Andrea Barta
Ao. Prof. Dr. Timothy Skern

Und ... er hält immer noch Vorlesungen!

Anhang

Das Physikstudium an der Universität Wien; Ordinarien

Das Chemiestudium an der Universität Wien; Ordinarien

Einige der wichtigsten Universitätslehrer und Vorbilder der sechs Professoren

Emigration und Entlassungen an der Universität Wien nach 1938

Aussagen der Professoren Cap, Schlögl und Tuppy zu Wissenschaft und Wissenschaftsvermittlung in Österreich

Das Physikstudium an der Universität Wien

„Was man prinzipiell nicht nachweisen kann, das existiert für den Physiker nicht. So hält er in gut positivistischer Art seine Werkstatt von metaphysischen Gespenstern rein."

Otto Hittmair

Die erste feste Lehrkanzel für Physik wurde 1554 an der Philosophischen Fakultät der Universität Wien durch Kaiser Ferdinand I. im Zuge der „neuen Reformation" geschaffen. Das 1715 gegründete Physikalische Cabinet, eine Art Museum über Werkzeuge und Maschinen für das Fach Physik, sollte der Erläuterung des Experimentalunterrichts dienen.
Zusätzlich zu diesen der Lehre verpflichteten Institutionen wurde 1850 das k.k. Physikalische Institut unter der Leitung von Christian Doppler errichtet. Dieses hatte einerseits die Heranbildung von praktisch geschulten Physiklehrern, andererseits zeitgemäße physikalische Forschung zum Ziel. Es war zuerst an der (Alten) Universität, später in Wien-Erdberg untergebracht und erlangte besonders unter der Leitung von Josef Stefan großes Ansehen. 1875 übersiedelten sowohl das k.k. Physikalische Institut als auch das Physikalische Cabinet in das Haus Türkenstraße 3 im 9. Wiener Gemeindebezirk. Hier wurde 1875 auch das Physikalisch-Chemische Laboratorium gegründet, als dessen erster Vorstand Josef Loschmidt fungierte.
Anfang des 20. Jahrhunderts gab es Bestrebungen, die Kompetenzen der drei zu dieser Zeit an der Wiener Universität mit Physik befassten Institutionen neu zu ordnen. So kam es 1902 zu einer Institutsneueinteilung, nach welcher das k.k. Physikalische Institut in das Institut für Theoretische Physik umgewandelt und als sein Leiter Ludwig Boltzmann eingesetzt wurde. Das Physikalische Cabinet wurde zum I. Physikalischen Institut, das Physikalisch-Chemische Laboratorium zum II. Physikalischen Institut.
Baubeginn für die neuen Gebäude der Institute für Mathematik, Physik und Chemie der Universität Wien und für das Institut für Radiumforschung der Akademie der Wissenschaften war 1909. Sie entstanden auf den „Bäckenhäusel-Gründen", dem Areal zwischen Währinger Straße, Boltzmanngasse und Strudlhofgasse. Die Bezeichnung bezieht sich auf das Haus eines Bäckers, das seit dem 15. Jahrhundert an der Abzweigung der heutigen Boltzmanngasse von der Währinger Straße gestanden war. Die neuen Institutsgebäude wurden im Zeitraum 1909 bis 1915 errichtet. Das Institut für Radiumforschung der Akademie der Wissenschaften wurde 1910 fertiggestellt, das Gebäude der Physikalischen Institute 1912.
1913 wurde das neuerrichtete Institutsgebäude an der Ecke Boltzmanngasse/Strudlhofgasse im 9. Wiener Gemeindebezirk bezogen.
1920 erfolgte eine weitere Neuordnung der Physikalischen Institute. Sie war unter anderem durch die Schaffung einer allen physikalischen Instituten gemeinsamen Bibliothek gekennzeichnet, aus der sich in der Folge die heutige Zentralbibliothek für Physik in Wien entwickelte.
Ende der siebziger Jahre erfolgte eine partielle Neudefinition der Institutsziele unter gleichzeitiger Namensänderung: das I. Physikalische Institut wurde zum Institut für Experimentalphysik und das II. Physikalische Institut zum Institut für Festkörperphysik.
Abschließend sei noch auf das bis vor kurzem der Österreichischen Akademie der Wissenschaften unterstellte Institut für Radiumforschung (heute: Institut für Isotopenforschung und Kernphysik) hingewiesen. Es wurde 1908 aufgrund einer Stiftung von Karl Kupelwieser gegründet und 1910 eröffnet. Hier nahm die Entdeckung der kosmischen Höhenstrahlung durch Viktor F. Hess sowie die Entwicklung der radioaktiven Indikatorenmethode durch Fritz Paneth und Georg von Hevesy ihren Ausgang.
Im folgenden Überblick werden alle Ordinarien der Physikinstitute an der Universität Wien seit 1850 aufgelistet.

Landstraße 104

Physik an der Universität Wien seit 1850, Ordinarien

1850–1875: Wien-Erdberg, Landstraße 104
1875–1913: Wien 9., Türkenstraße 3
ab 1913: Wien 9., Boltzmanngasse 5/Strudlhofgasse 4

1850 Physikalisches Cabinet

Kunzek August 1850–1865
Lang Viktor von 1865–1902

1875 Physik.-Chem. Laboratorium

Loschmidt Josef 1875–1891
Exner Franz Serafin 1891–1902

1850 k.k. Physikalisches Institut

Doppler Christian 1850–1852
Ettingshausen Andreas von 1852–1866
Stefan Josef 1866–1893
Boltzmann Ludwig 1894–1900

1902 I. Physikalisches Institut

Lang Viktor von 1902–1909
Lecher Ernst 1909–1925
Schweidler Egon von 1926–1940
Kirsch Gerhard 1941–1945
Ehrenhaft Felix 1946–1952
Stetter Georg 1953–1967
Weinzierl Peter 1967–1993
Reeger Ernst 1971–1972
Higatsberger Michael J. 1971–1994
Preining Othmar 1971–1995
Warhanek Hans 1971–1995

1977 Institut für Experimentalpysik

Weinzierl Peter 1967–1993
Higatsberger Michael J. 1971–1994
Preining Othmar 1971–1995
Warhanek Hans 1971–1995
Rupp Romano ab 1997
Zeilinger Anton ab 1999
Dellago Christoph ab 2003

1902 II. Physikalisches Institut

Exner Franz S. 1902–1920
Jäger Gustav 1920–1934
Schweidler Egon von 1936–1939
Stetter Georg 1939–1945
Przibram Karl 1947–1951
Schmid Erich 1951–1967
Lintner Karl 1968–1983
Seeger Karl-Heinz 1971–1995
Schöck Gunther 1971–1996
Stangler Ferdinand 1971–1996

1977 Institut für Festkörperphysik

Lintner Karl 1968–1983
Seeger Karl-Heinz 1971–1995
Schöck Gunther 1971–1996
Stangler Ferdinand 1971–1996
Vogl Gero ab 1985

1996 Inst. für Materialphysik

Vogl Gero ab 1985
Höpfel Ralph 1996–1997
Hafner Jürgen ab 1998

1902 Institut für Theoretische Physik

Boltzmann Ludwig 1902–1906
Hasenöhrl Friedrich 1907–1915
Jäger Gustav 1918–1920
Thirring Hans 1927–1938
Thirring Hans 1946–1958
Thirring Walter 1959–1995
Sexl Roman 1971–1986
Pietschmann Herbert 1971–2004
Bartl Alfred ab 1973
Yngvason Jakob ab 1996

1920 III. Physikalisches Institut

Ehrenhaft Felix 1920–1938

1910 Radiuminstitut

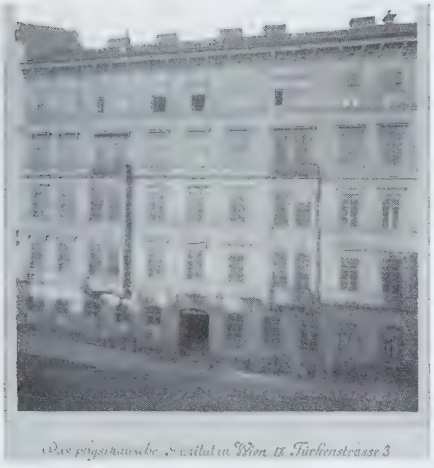
Exner Franz S. 1910–1920
Meyer Stefan 1920–1938
Ortner Gustav 1939–1945
Meyer Stefan 1945–1949

1955 Institut für Radiumforschung und Kernphysik

Karlik Berta 1956–1974
Vonach Herbert 1974–1992
Kutschera Walter ab 1993

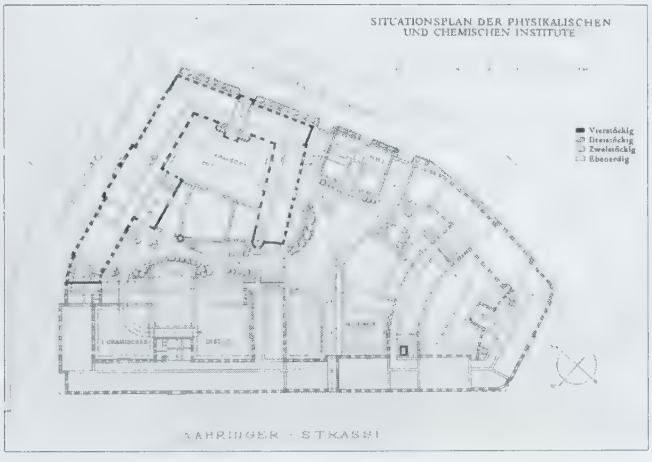
2000 Institut für Isotopenforschung und Kernphysik

Kutschera Walter ab 1993



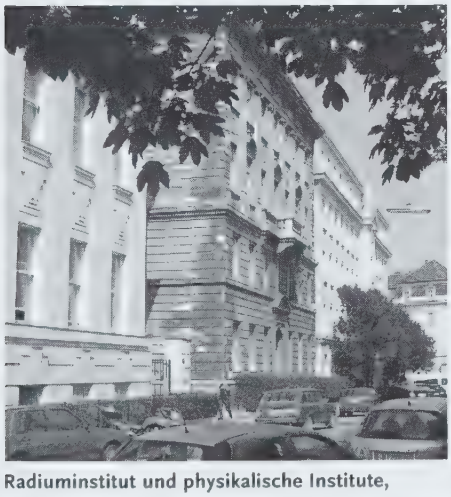
Türkenstraße 3, 1902

Türkenstraße 3, 2004

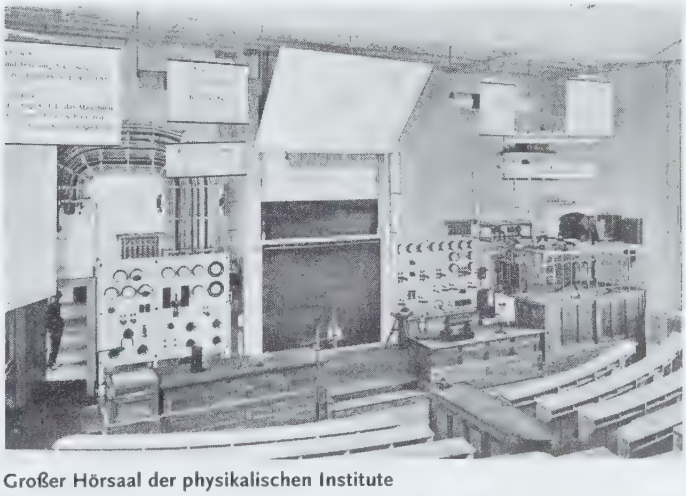


Währinger Straße/Boltzmanngasse, Plan

Radiuminstitut und physikalische Institute, Boltzmanngasse, Zeichnung



Radiuminstitut und physikalische Institute, Boltzmanngasse, 2004



Großer Hörsaal der physikalischen Institute

Das Chemiestudium an der Universität Wien

„Physik und Chemie dringen sehr tief in die Biologie ein. Sie werden das noch weiter tun. Die Biologie ist die Leitwissenschaft geworden. Innerhalb der Biologie liegen große Chancen für Physik und Chemie."

Hans Tuppy

Ab 1749 gab es eine Professur für Botanik und Chemie im Rahmen der medizinischen Fakultät. Nikolaus Joseph Jacquin übernahm diesen Lehrstuhl 1769.
Im Jahr 1838 wurden im Gebäude der Alten Universität selbständige Lehrstühle für Chemie bzw. für Botanik geschaffen. Auch damals betrachtete man die Chemie noch als Hilfswissenschaft der Medizin und forschte daher hauptsächlich über Fragen, bei denen ein unmittelbarer Nutzen für die menschliche Gesundheit möglich erschien.
Im Oktober 1849 wurde vom k. k. Ministerium für Cultus und Unterricht angeordnet, die Studienfächer Naturgeschichte und Chemie aus der medizinischen Fakultät auszuscheiden und der philosophischen Fakultät zuzuordnen. Gleichzeitig wurde der Übertritt Redtenbachers an die philosophische Fakultät verordnet. Redtenbacher ging schnell daran, ein Laboratorium im Theresianium einzurichten.
Die 1870 geschaffene Organisationsstruktur der Chemie an der Universität Wien, mit einem I. und II. Chemischen Laboratorium und dementsprechend zwei Lehrstühlen, blieb bis Ende der 50-er Jahre des 20. Jahrhunderts aufrecht. Die beiden Laboratorien waren zunächst im Gebäude Währinger Straße 10 untergebracht. Von 1871 bis 1909 bestand ein III. Chemisches Laboratorium, das aber eine kleine Einrichtung blieb.
1909 wurde auf den „Bäckenhäusel-Gründen" mit dem Neubau von Institutsgebäuden der Institute für Mathematik, Physik und Chemie der Universität Wien und für das Institut für Radiumforschung der Akademie der Wissenschaften begonnen. Wegen des Ersten Weltkrieges konnte bis 1914/15 nur der Rohbau der chemischen Institute errichtet werden. Der Innenausbau und die Einrichtung erfolgten erst in den Nachkriegsjahren. 1920 stand ein Teil der Einrichtungen zur Verfügung, und am 15. Jänner 1921 wurde der Große Hörsaal I (am II. Chemischen Institut) feierlich eröffnet. Die Übersiedlung aller Abteilungen der chemischen Institute wurde im Herbst 1924 abgeschlossen.
1957 wurde eine Neuorganisation der chemischen Institute beschlossen. Es sollte die an der Wiener Universität bestehende Doppelgleisigkeit – mit Abteilungen für analytische, anorganische und organische Chemie an beiden chemischen Instituten – aufgehoben und sechs „selbständige" Chemieinstitute gegründet werden.
Die Neuorganisation erfolgte in Schritten: 1959 wurden die Bezeichnungen I. und II. Chemisches Institut aufgelassen und drei Institute gebildet: Analytisches Institut, Organisch-chemisches Institut und Anorganisch- und Physikalisch-chemisches Institut. Mit Wirksamkeit vom 1. Oktober 1960 wurde dann das Anorganisch- und Physikalisch-chemische Institut aufgelassen und gleichzeitig wurden zwei neue Institute gebildet: Das Institut für Physikalische Chemie und das Institut für Anorganische Chemie.
Aus Abteilungen des Organisch-chemischen Instituts entstanden zwei weitere selbständige Institute: das Institut für Theoretische Chemie (1968; spätere Bezeichnung: Institut für Theoretische Chemie und Strahlenchemie) und das Institut für Allgemeine Biochemie (1972; spätere Bezeichnung: Institut für Biochemie und Molekulare Zellbiologie).
Im folgenden Überblick werden alle Ordinarien der Chemieinstitute an der Universität Wien seit 1849 aufgelistet.

Theresianum, Ingenieurakademie

Währinger Straße/Boltzmanngasse, um 1930

„Bäckenhäusel" um 1900

Chemie an der Universität Wien seit 1850, Ordinarien

1849–1870: Wien 4., Theresianum
1870–1924: Währinger Straße 10
ab 1924: Währinger Straße/Ecke Boltzmanngasse

1849 Lehrkanzel für Chemie im Rahmen der Philosophischen Fakultät

Redtenbacher Josef 1849–1870

1870 I. Chemisches Laboratorium

Schneider F. C. 1870–1876
Barth Ludwig 1877–1890
Weidel Hugo 1891–1899
Herzig Josef 1899–1902
Wegscheider Rudolf 1902–1931
Mark Hermann 1932–1938
Ebert Ludwig 1939–1956
Novotny Hans 1958–1971

1870 II. Chemisches Laboratorium

Rochleder Friedrich 1870–1875
Lieben Adolf 1875–1906
Skraup Z. H. 1906–1910
Goldschmiedt Guido 1911–1915
Schlenk Wilhelm 1916–1921
Franke Adolf 1921–1924
Späth Ernst 1924–1946
Wessely Friedrich 1948–1967

1871 III. Chemisches Laboratorium

Ludwig Ernst 1871–1874
Lippmann Eduard 1874–1909

1959 drei Institute für Chemie

Anorganische und Physikalische Chemie

Novotny Hans 1958–1977

Organische Chemie

Wessely Friedrich 1948–1967

Analytische Chemie

Hecht Friedrich 1959–1974

1960 vier Institute für Chemie

Physikalische Chemie

Novotny Hans 1958–1977
Breitenbach J. W. 1965–1978

Anorganische Chemie

Brukl Alfred 1960–1965
Komarek Kurt 1966–1994

Organische Chemie

Wessely Friedrich 1948–1967
Schmidt Ulrich 1967–1977

Analytische Chemie

Hecht Friedrich 1959–1974

Im II. Chemischen Laboratorium 1935: Max Perutz (li.), Friedrich Wessely (re.)

1968 sechs Institute für Chemie

Physikalische Chemie

Novotny Hans 1958–1977
Breitenbach J.W. 1965–1978
Broda Engelbert 1968–1980
Kohler Friedrich 1971–1975
Stickler Roland 1971–1998
Neckel Adolf 1979–1996
Olaj Oskar Friedrich 1978–2001
Fringeli Urs Peter ab 1984

Organische Chemie

Schmidt Ulrich 1967–1977
Schlögl Karl 1971–1990
Kratzl Karl 1971–1986
Zbiral Erich 1974–1991
Mulzer Johann ab 1996
Brinker Udo ab 1996

Analytische Chemie

Hecht Friedrich 1959–1974
Kainz Gerald 1971–1991
Huber J. F. K. 1974–1995
Dickert Franz ab 1994
Lindner W. ab 1996

Anorganische Chemie

Komarek Kurt 1966–1994
Schönfeld Thomas 1972–1993
Keppler Bernhard ab 1996
Ipser Herbert ab 1998

Biochemie und molekulare Zellbiologie

Hoffmann-Ostenhof Otto 1971–1985
Ruis Helmuth 1986–2001
Wiche Gerhard ab 1991

Theoretische Chemie und molekulare Strukturbiologie

Polansky Oskar E. 1968–1972
Getoff Nikola 1973–1993
Schuster Peter ab 1973
Lischka Hans ab 1997
Steinhauser Othmar ab 1997

Theresianum heute

Währinger Straße 10, Bau von Ferstel

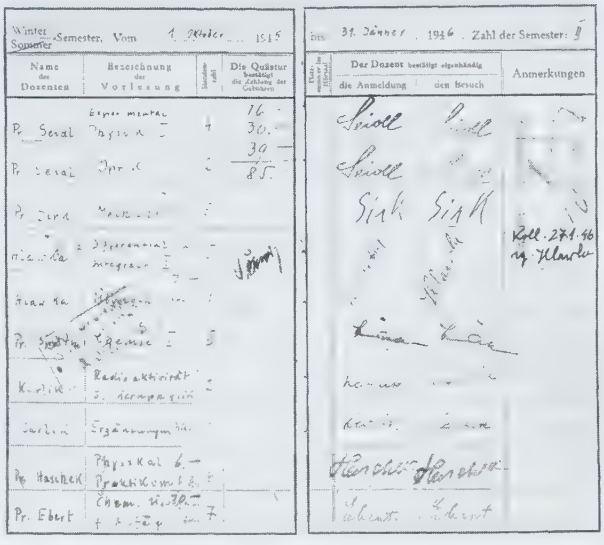
Währinger Straße/Boltzmanngasse, 2004

Währinger Straße/Boltzmanngasse, Entwurf

Die Lehrer

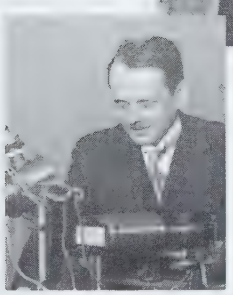
„Lehrer können die Lebensläufe ihrer Schüler beeinflussen."
Ferdinand Cap

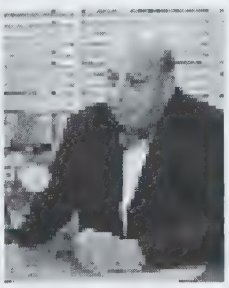
Als die Gewürdigten zu studieren begannen, waren die Universitäten längst von Juden und Systemkritikern „gesäubert". Mit der Machtübernahme der Nazis 1938 wurden an den Physik- und Chemieinstituten der Universität Wien rund 40% der Professoren und Dozenten entlassen. Die meisten von ihnen mussten emigrieren. Da gab es z. B. die Physiker Felix Ehrenhaft und Hans Thirring, oder die Chemiker Hermann Mark und Max Perutz, die von den Nationalsozialisten ihrer Arbeit und all ihrer Habe beraubt wurden.
Die verbliebenen Universitätslehrer entstammten ganz unterschiedlichen Lagern. Sie waren entweder überzeugte Nationalsozialisten oder sie hielten sich aus der Politik heraus, so weit es ihnen möglich war.


Winter- / Sommer-Semester. Vom 1. Oktober 1915 bis 31. Jänner 1916. Zahl der Semester: 9

Name des Dozenten	Bezeichnung der Vorlesung	Stunden-zahl	Die Quästur bestätigt die Zahlung der Gebühren	Der Dozent bestätigt eigenhändig die Anmeldung	Der Dozent bestätigt eigenhändig den Besuch	Anmerkungen
Pr. Seral	Experimentalphysik	4	16.– 30.–	Seidl	Seidl	
Pr. Seral	Spr. [illegible]	2	30.– 85.–	Seidl	Seidl	
Pr. Sigmund	Mechanik	3		Sigk	Sigk	Kell. 27.1.16 m. Klarke
[illegible]	Differential- und Integralrechnung	3				
[illegible]	[illegible]	1				
Pr. [illegible]	[illegible]	2				
[illegible]	Radioaktivität	2				
[illegible]	[illegible]	1				
[illegible]	Ergänzungsstunden					
Pr. Hasenöhrl	Physikalisches Praktikum für Anfänger	6.– 5				
Pr. Ebert	Chemisches Praktikum für Anfänger	7.–				

Studienbuch Higatsberger





Ludwig Ebert, Chemie

Geboren am 19. 6. 1894 in Würzburg, gestorben am 2. 11. 1956 in Wien
1934 Ordinarius an der Technischen Hochschule in Karlsruhe
1939 Nachfolger von Prof. Dr. Hermann Mark in Wien
1939–1956 Leitung des I. Chemischen Laboratoriums

Felix Ehrenhaft, Physik

Geboren am 24. 6. 1879 in Wien, gestorben am 4. 3. 1952 in Wien
1920–1938 Ordinarius am III. Physikalischen Institut
1938 Emigration über Paris, Brasilien und London in die USA
1946 Vorstand des I. Physikalischen Institutes an der Universität Wien, das mit dem III. Physikalischen Institut vereinigt worden war.

Louis F. Fieser, Chemie

Geboren am 7. 4. 1889 in Columbus (Ohio), gestorben am 25. 7. 1977
1937–1967 Professor an der Harvard Universität in Cambridge (Mass.)
1939 Entdecker des Vitamins K1
An der Entwicklung von Napalm beteiligt

Berta Karlik, Physik

Geboren am 24.1.1904 in Wien, gestorben am 4.2.1990 in Wien
1942 mit Traute Bernert-Cless gelang Karlik der Nachweis des Elements 85 (Astatin) in der Natur
1947–1974 Leitung des Radiuminstitutes
1956 Ernennung zur o. Prof.

Gerhard Kirsch, Physik

Geboren 21.6.1890 in Wien, gestorben am 15.9.1956
1932 ao. Prof., 1938 kommissarische Leitung des III. Physikalischen Institutes
1939 außerplanmäßiger Professor
1941–1945 Vorstand des I. Physikalischen Institutes
1945 enthoben, 1947 als Assistent pensioniert

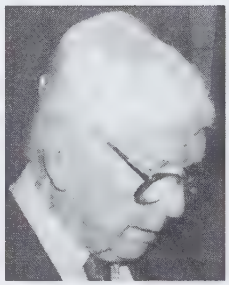
Kirsch diffamierte nach 1938 öffentlich Einsteins Relativitätstheorie als „jüdisches Machwerk".

Arthur March, Physik

Geboren am 23.2.1891 in Brixen (Südtirol), gestorben am 17.4.1957 in Bern
1926 ao. Prof. an der Universität Innsbruck
1934–36 Gastprofessor in Oxford
1936 o. Prof. an der Universität Innsbruck
Während des 2. Weltkriegs in der Widerstandsbewegung

„March war ein früher Kenner der Quantentheorie und ein sehr guter Pädagoge, dem auch die Philosophie sehr wichtig war. Man hatte wärend seiner Vorlesungen das Gefühl, alles zu verstehen." Otto Hittmair

Hermann Mark, Chemie



Geboren am 3.5.1895 in Wien, gestorben am 6.4.1992 Austin (USA)
1932–1938 o. Prof. am I. Chemischen Laboratorium der Universität Wien
1938 Emigration

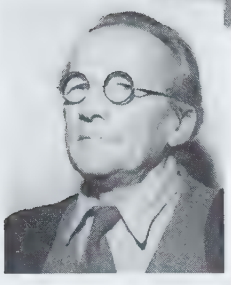
Begründete in New York das Polymer-Institut und war ein Pionier der Polymerisation.
Mark war nicht nur wissenschaftliches Vorbild für viele Studenten, er war in Amerika auch gerne Anlaufstelle für junge österreichische WissenschaftlerInnen.

Hans Nowotny, Chemie

Geboren am 27.9.1911 in Linz, gestorben am 5.10.1996 in Steinbach (Niederösterreich)
1941–45 Mitarbeiter am Kaiser-Wilhelm-Institut für Metallforschung in Stuttgart
1947–1952 ao. Prof. in Wien
1958–77 Vorstand des I. Chemischen Instituts der Universität Wien sowie an der TH Wien
nach 1977 Forschungstätigkeit an der University of Connecticut

Max Perutz, Chemie

Geboren am 19. 5. 1914 in Wien, gestorben am 6. 2. 2002 in Cambridge
1936 Emigration nach Cambridge, 1941 in Kanada interniert
1947–1979 Universitätsprofessor in Cambridge
1962 Nobelpreis für Chemie



Erwin Schrödinger, Physik

Geboren am 12. 8. 1887 Wien, gestorben am 4. 1. 1961 in Wien
1927 o. Prof. an der Friedrich Wilhelms-Universität Berlin (heute Humboldt-Universität)
1933 Wechsel an die Universität Oxford
1933 Nobelpreis für Physik gemeinsam mit Paul Dirac
1936 Ruf an die Universität Graz
1938 Flucht aus Österreich
1940 Direktor am Dublin Institute for Advanced Studies
1950/51 Gastprofessor in Innsbruck (Cap und Hittmair arbeiten mit Schrödinger)
1956 Rückkehr an die Universität Wien

Franziska Seidl, Physik

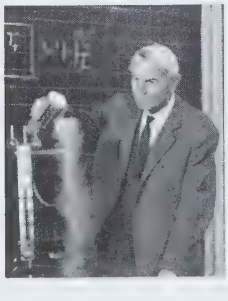
Geboren am 1. 7. 1892 in Wien, gestorben am 14. 6. 1983 in Wien
1934 Privatdozentin an der Universität Wien
1942 außerplanmäßige Professorin und Abteilungsvorstand am I. Physikalischen Institut der Universität Wien
1945–1947 provisorischer Vorstand des I. Physikalischen Institutes
1946 tit. ao. Prof., 1958 ao. Prof., 1963 tit. o. Prof. und Emeritierung
Forschungen über Ultraschall, Röntgenstrukturuntersuchungen und mit Dielektrika

Ernst Späth, Chemie

Geboren am 14. 5. 1886 in Bärn (Beroun, Tschechien), gestorben am 30. 9. 1946 in Zürich
1924–1946 Vorstand des II. Chemischen Laboratoriums der Universität Wien
1938–45 Generalsekretär, 1945/46 Präsident der ÖAW

„Späth war ein Fanatiker, aber ein fanatischer Chemiker."
Karl Schlögl

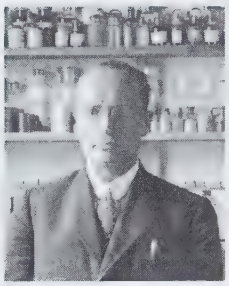
„Ernst Späth war bedeutender Naturstoffchemiker, ein Mann der klassischen organischen Chemie. Späth war Sohn eines Schmieds und hielt eine ausgezeichnete Experimentalvorlesung. Er war kein Nazi." Hans Tuppy



Georg Stetter, Physik

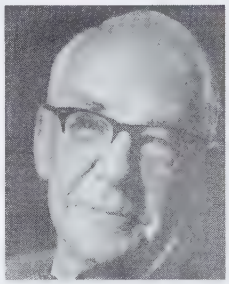
Geboren am 23. 12. 1895 in Wien, gestorben am 14. 7. 1988
1934 ao. Prof. an der Universität Wien
1939–1945 Vorstand des II. Physikalischen Institutes der Universität Wien
1953–1967 Vorstand des I. Physikalischen Institutes der Universität Wien

Hans Thirring, Physik

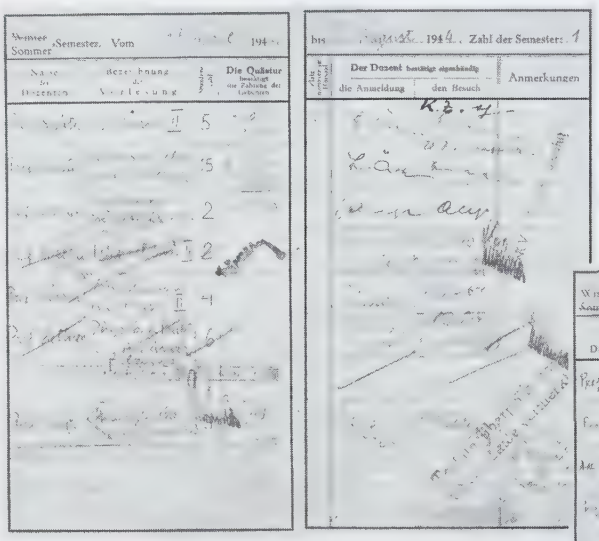


Geboren am 23. 3. 1888 Wien, gestorben am 22. 3. 1976 in Wien
1921–38 Vorstand des Institutes für Theoretische Physik in Wien,
1938 zwangspensioniert
1945 Wiedereinsetzung in seiner alten Stellung
1946/1947 Dekan der Philosophischen Fakultät der Universität Wien
1957–63 Abgeordneter zum Bundesrat (SPÖ)
Aktivist der Friedensbewegung, Mitbegründer der PUGWASH-Bewegung, Idee einer einseitigen Abrüstung Österreichs („Thirring-Plan")

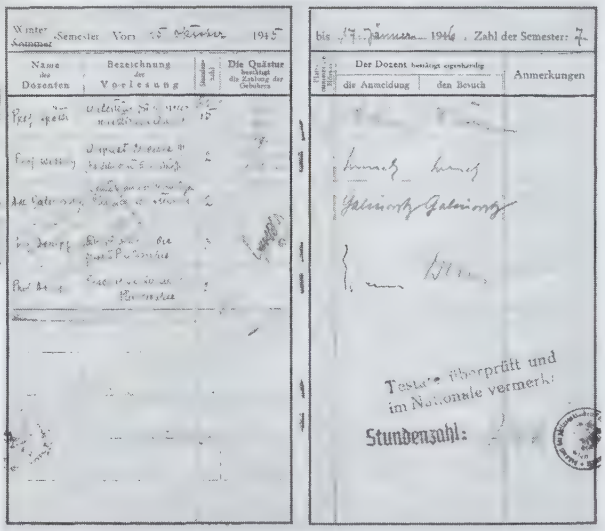
Friedrich Wessely, Chemie



Geboren am 3. 8. 1897 in Kirchberg am Wagram, gestorben am 17. 12. 1967
1945–1948 Leiter des Institutes für Medizinische Chemie, 1946 o. Prof.
1948–1959 Vorstand des II. Chemischen Laboratoriums
1959–1967 Vorstand des Institutes für Organische Chemie



Studienbuch Schlögl



Studienbuch Tuppy

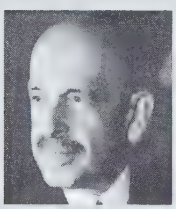
Emigration

„Den dauernden Verlust an geistiger Potenz zu betonen, den Österreich durch die Vertreibung der Vernunft erlitten hat, ist sehr wohl nach wie vor notwendig, weil ihn vermutlich viele Österreicher in seiner ganzen Bedeutung bis heute nicht erfaßt haben."

Erika Weinzierl

Fast die Hälfte aller Universitätslehrer verloren nach der Machtübernahme durch die Nationalsozialisten aus rassistischen oder politischen Gründen ihre Positionen. Viele haben Österreich für immer verlassen, andere wurden verhaftet, schikaniert und deportiert. Manche von ihnen wurden in Konzentrationslagern ermordet.

Allein am 22. April 1938 wurden über Antrag der Universität Wien 252 Universitätslehrer von ihren Positionen entfernt.
Nachfolgende Professoren und Dozenten der physikalischen und chemischen Institute der Universität Wien wurden zwischen 1938 und 1945 von der Universität Wien vertrieben:

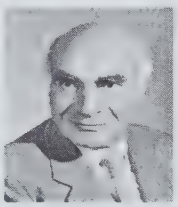


Emil ABEL (1875 Wien–1958 London)
Privatdozent, Physikalische Chemie; 1938 pensioniert, von der Gestapo verfolgt, 1939 Flucht nach England, Arbeit am University College in London, 1949 Goldenes Diplom der TH Wien

Jean BILLITER (1877 Paris–1965 Salzburg)
Privatdozent (ao. Prof.), Physikalische Chemie; 1938 entlassen, emigriert nach Frankreich

Felix EHRENHAFT (1879 Wien–1952 Wien)
O. Prof., Physik; 1938 beurlaubt, verhaftet, emigriert nach Rio de Janeiro, dann in die USA, 1947 wieder eingestellt (Gastprofessur)

Friedrich FEIGL (1891 Wien–1971 Rio de Janeiro)
Privatdozent (ao. Prof.), Anorganische Experimental- und Analytische Chemie; 1938 emigriert in die Schweiz, dann nach England und Belgien, von da in ein südfranzösisches Internierungslager verschleppt, 1940 Flucht nach Rio de Janeiro, 1967 Ehrendoktorat der Philosophischen Fakultät



Philipp GROSS (1899 Wien–1974 London)
Privatdozent (ao. Prof.), Theoretische und Physikalische Chemie; 1938 enthoben, emigriert nach England, 1968 Honorarprofessor für Thermochemie

Fritz HAUER (1889 Wien–1961 Wien)
Privatdozent, Physik; 1939 Venia legendi entzogen, 1945 wieder eingestellt

Alfons KLEMENC (1885 Ljubljana–1960 Wien)
Privatdozent, Anorganische und Physikalische Chemie; 1938 beurlaubt, 1942 zum Dozenten neuer Ordnung ernannt, konnte an der Universität nicht arbeiten, Forschungen im Privatlabor, 1945 wieder eingestellt

Moritz KOHN (1878 Teschen–1955 New York)
Privatdozent (ao. Prof.), Organische Chemie; 1938 enthoben, emigriert nach Havanna (Kuba), dann nach New York

David Kurt KONSTANTINOWSKY (geboren 1892 in Wien)
Privatdozent, Physik; 1938 auf die Dozentur verzichtet, emigriert nach London

Friedrich KOTTLER (1886 Wien–1965 Rochester/New York)

Ao. Prof., Mathematische Physik; 1938 zwangspensioniert, emigriert nach Rochester/New York (USA), 1955 Honorarprofessur

Fritz LIEBEN (1890 Wien–1966 Wien)

Privatdozent (ao. Prof.), Physiologische Chemie; 1938 Venia legendi entzogen, emigriert nach New York (USA), 1953 wieder eingestellt

Johann Friedrich LUDLOFF (1899 Königsberg–1965 Wien)

Privatdozent, Theoretische Physik; 1938 Venia legendi entzogen, emigriert 1940 nach New York (USA)

Hermann MARK (1895 Wien–1992 Austin/Texas)

O. Prof., Chemie; 1938 entlassen, emigriert in die Schweiz, dann nach Kanada, 1940 nach New York, 1955 Gastprofessur, Ehrenzeichen der Universität Wien, 1980 Ehrendoktorat der Philosophie

Stefan MEYER (1872 Wien–1949 Bad Ischl)

O. Prof., Physik; 1938 zurückgetreten, pensioniert, 1945 Honorarprofessur, wieder eingestellt

Jaques POLLAK (1872 Budapest–1942 KZ Theresienstadt)

Ao. Prof., Chemie; 1938 Lehrtätigkeit untersagt, 1942 deportiert ins KZ Theresienstadt

Karl PRZIBRAM (1878 Wien–1973 Wien)

Ao. Prof., Physik; 1938 entlassen, 1940 emigriert nach Belgien, 1946 wieder eingestellt

Erwin SCHRÖDINGER (1887 Wien–1961 Alpbach in Tirol)

Hon.-Prof., Theoretische Physik; 1938 (als Honorarprofessor) entlassen, Flucht nach Rom, Gent, Dublin, 1956 wieder eingestellt

Hans THIRRING (1888 Wien–1976 Wien)

O. Prof., Physik; 1938 zwangspensioniert, 1945 wieder eingestellt

Ernst ZERNER (geboren 1884 in Ebenschütz)

Privatdozent (ao. Prof.), Organische und Anorganische Chemie; 1938 Venia legendi entzogen, emigriert nach London

	Physik	Chemie
Anzahl der Professoren und Dozenten 1938	28	20
Anzahl der Entlassenen	9	10
Entlassene in %	32 %	50 %
Anzahl der Emigranten	6	8
Anzahl der Emigranten in %	22 %	40 %
Anzahl der Remigranten	3	0
Anzahl der Remigranten in %	50 %	0 %

Forschung und Lehre

Aussagen der Professoren Cap, Schlögl und Tuppy zu Wissenschaft und Wissenschaftsvermittlung in Österreich

Franz Ferdinand Cap

Ich würde heute nicht mehr studieren wollen. Man hat damals völlige Freiheit gehabt, das zu hören, was man wollte. Man musste nur eine bestimmte Anzahl von Stunden vorweisen und die Prüfungen bestehen. Heute ist das Studium viel zu stark verschult, und die Studierenden werden mit Pflichtvorlesungen eingedeckt.

Ferdinand Cap

Karl Schlögl

Die Nachkriegszeit war schwer. Man musste improvisieren lernen, weil es an allem fehlte. 1946/1947 ist es langsam wieder normal geworden: Aufbruchstimmung war da, und Spaß war wieder da. Jetzt geht alles nach bestimmten Regeln. Wenig Vorteile, viele Nachteile!

Karl Schlögl

Der Stellenwert der Wissenschaft in Österreich ist derzeit sehr schlecht. Weil die Gesamtkosten in vielen Bereichen steigen, müssten auch die Förderungen im universitären Bereich steigen, um Forschung und Lehre auf hohem Niveau zu halten.

Karl Schlögl

Hans Tuppy

Manchmal bedauere ich, dass ich nicht doch im Ausland geblieben bin. Ich hätte vielleicht doch mehr leisten können und nicht so viel G'wirks und Murks mit Verwaltung und Projekten gehabt wie in Österreich.

Ferdinand Cap

Franz Ferdinand Cap

Es gibt heute keine Entschuldigung materieller Art mehr, wenn die Forschung in Österreich nicht so gut ist wie in anderen Ländern.

Hans Tuppy

Es ist viel besser geworden. Man kann jetzt beim FWF Projekte einreichen und hat 50% Förderquote. Niemand kann heute sagen, dass es am Geld liegt. Die Universitäten haben wenig Geld, aber der Fonds hat Geld.

Hans Tuppy

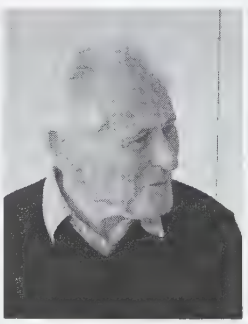
Karl Schlögl

Um dieser Angst vor der Wissenschaft entgegenzutreten, wäre in Österreich die Schule gefordert. Die Lehrer müssen besser werden. Schuld ist letztlich die romantische Wissenschaftsgeschichte bzw. ein verklärtes Wissenschaftsbild.

Hans Tuppy

Wissenschaftsvermittlung ist ein großes Problem. Ich fürchte mich nur vor Dingen, die ich nicht kenne. Es ist bei uns oft fast elegant geworden, etwas nicht zu wissen.

Karl Schlögl



Hans Tuppy

Wir dürfen nicht sagen, Wissenschaft ist gut oder Wissenschaft ist schlecht, sondern wir müssen fragen: Was ist verantwortbar, und was ist nicht verantwortbar?

Hans Tuppy

Sechs 1924 in Österreich geborene Naturwissenschaftler, drei Chemiker und drei Physiker, haben heuer ihren achtzigsten Geburtstag:
Sie haben viel geleistet für Forschung und Lehre, haben Tausende Studierende ausgebildet und zahlreiche wissenschaftliche Publikationen veröffentlicht.
Und doch sind sie außerhalb der Fachwelt nur wenigen bekannt.
Grund genug, sie im Rahmen einer Ausstellung einer breiteren Öffentlichkeit vorzustellen!

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THE GLOBE AND MAIL
WEDNESDAY, OCTOBER 26, 2005

Former PoW gives to his alma mater, Queen's, in spades

BY OMAR EL AKKAD

In 1941, after more than a year in a Montreal prisoner-of-war camp, Alfred Bader tried to go to university. The 17-year-old had already passed his junior and senior matriculation exams, earning exceptional grades.

But when he applied to study at McGill University, the response was blunt and final: The school's Jewish quota is full, apply next year.

Over the next half-century, the decision to turn Mr. Bader away would cost McGill about $50-million. That's how much the chemical company founder and art collector has donated to the school that did accept him, Queen's University.

Mr. Bader earned his chemistry PhD at Harvard after studying at Queen's, and went on to amass a multimillion-dollar fortune as the head of a global chemical business.

He offered his Canadian alma mater another helping hand this week. Mr. Bader will put up the money to build a waterfront arts centre at the Kingston school.

Mr. Bader's gift is the latest in a series of donations he has made to Queen's, in part to give back to the institution he credits for changing his negative perception of Canada.

"It was just absolutely terrible," he said in an interview yesterday, speaking of his first year in Canada after he arrived in 1940. "I thought Canadians were dishonest."

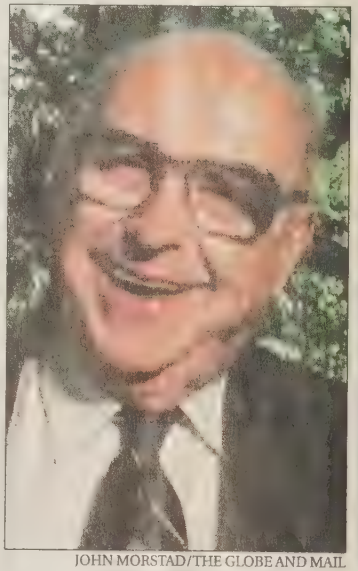
It was hard for the Vienna-born Jew to find evidence to the contrary, as he and the other 270 camp residents watched soldiers cut open their luggage upon arrival. He still remembers an immigration officer telling him one Jew in Canada is one Jew too many.

At Queen's, he saw Canada in a different light. "I learned that most Canadians are honest, and that Christians are capable of being good people," he said. "In Vienna, all I saw of Christianity was hypocrisy."

Today, it's impossible for a student to earn a degree at Queen's without coming across something donated by the Bader family.

A $10-million Rembrandt painting hanging in the University's art gallery is a gift from Mr. Bader. The residence at the school's international study centre — Herstmonceux Castle in East Sussex, England — is also named after the Baders, who bought the castle and donated it to Queen's in the early 1990s.

"He has given so many gifts to Queen's," school principal Karen Hitchcock said. "He brought something very special to the university: his own experiences. Sometimes that gets lost because he donated a castle or he donated a Rembrandt."



JOHN MORSTAD/THE GLOBE AND MAIL

Alfred Bader, shown in this 1999 photo, went to Queen's University after McGill rejected him because its Jewish quota was full.

John Barber

Caps for all a solution to tax mess

How is it that politicians can bawl ceaselessly for months every new year before deciding on a barely noticeable tax hike of a few per cent in April, yet sit by without a peep of protest or debate while whole neighbourhoods experience automatic tax increases up to 10 times greater as a result of ballooning, bubble-economy assessments?

This mystery survives in spite of the recent populist outcry against the Municipal Property Assessment Corporation and its nefarious ways. My theory as to why, is that

Rights activist Rosa Parks dies at 92

See page 9

Will the Astros be allowed to raise the roof?

See page 17

Hockey's back. So is Murphy's Challenge

See page 18

THE KINGSTON WHIG-STANDARD

PROUDLY SERVING THE KINGSTON COMMUNITY SINCE 1834 | KINGSTON, ONTARIO • TUESDAY, OCTOBER 25, 2005 • 79¢+GST

Raging dog kills woman's little pet

Rottweiler wasn't wearing a muzzle

By Jennifer Pritchett
Whig-Standard Staff Writer

A KINGSTON WOMAN whose Lhasa apso was killed by a rottweiler outside a Kingston coffee shop fears the aggressive dog with a violent history will attack again.

Ann Marie McCann could only scream when a 34-kilogram rottweiler, tied to a post outside Tim Hortons in Portsmouth, broke from its leash and lunged at her lap dog.

The little Lhasa apso, named Bilbo, tried to run underneath a nearby car, but it was too late.

"I've never seen anything so violent from out of nowhere in my life," said McCann. "Here's this rottweiler and my poor little dog is in its jaws and he's shaking the life out of him."

It took two men to wrestle the raging rottweiler to the ground and pull the badly injured little Lhasa apso out of its mouth.

By the time the owner of the large dog came out of the coffee shop, the damage was done.

The attack occurred Oct. 8.

McCann scooped up Bilbo. A passerby, Bill Matthews, drove them to the veterinary clinic where she discovered the extent of her dog's injuries.

"We laid him on his back and as his legs separated, you could see how his whole chest was ripped open," she said, weeping. "You could see where the dog had ripped the tissue underneath and it was so deep, I could see his heart beating."

It's an image that haunts her still.

"I'm a little traumatized by this myself," said McCann. "I wake up in the middle of the night and I say, 'Where's Bilbo?' and then I realize he's not here anymore."

Bilbo, a Christmas present from a couple of friends, had to be euthanized because of the seriousness of his injuries.

"I'm on a disability now and that's why Bilbo was such a godsend to me," McCann said. But what upsets her most is that the attack on her dog wasn't the first time the aggressive rottweiler named Poncho hurt another dog.

Please see VIOLENT, Page 8

MORE INSIDE:

Second site to save lives

Hotel Dieu opens the doors to the city's second breast screening Program site, at which women over 50 can be screened without a doctor's [illegible]

Please see Page

Multiplex still dry

Private companies in the running to build a multiplex recreation centre in the city didn't include a pool in their proposals to the city. Pool enthusiasts [illegible]

Please see Page

IT'S HIP TO BE CUBED

Michael Lea/The Whig-Standard

Four months after he first picked up a Rubik's Cube, Kingston teen Craig Bouchard could solve the puzzle in under 27 seconds. Next month he'll vie to become world champion. For story, please see Page 4

Meet the architect behind health-care reform in Ontario

'Frank, unvarnished' book tells juicy tale of frustration

By Ann Lukits
Whig-Standard Staff Writer

For 'Thirty Minutes With ... Duncan Sinclair,' please see Page 2.

THERE WAS A TIME NOT SO LONG AGO THAT THE name Duncan Sinclair evoked a visceral response among the elite group of doctors, lawyers and administrators who comprise the inner circle of Kingston's hospitals and health-care institutions.

For four tumultuous years, Sinclair headed a powerful commission appointed by former Conservative premier Mike Harris – another person who evoked visceral responses, though of a different type – to reform the province's chaotic health system, particularly the hospital sector.

When the commission turned its attention to Kingston, where its order to close Hotel Dieu Hospital triggered community backlash and three lawsuits, Sinclair did the honourable thing. He declared a conflict of interest and extricated himself from the nasty debate over the realignment of Kingston's health services.

But in hospital boardrooms and corridors around the city, the question was often asked. What does Duncan Sinclair, a highly respected former dean of the Queen's University medical school and one of our own, think of the mess his commission created?

Five years after the commission's sunset, Sinclair, now 72, still isn't prepared to discuss Kingston or, for that matter, the dozens of communities visited by the commission. He maintains that silence in a new book entitled *Riding the Third Rail*, the "frank and unvarnished" story of the Health Services Restructuring Commission, which he wrote with commission colleagues Mark Rochon and Peggy Leatt.

The term "third rail" refers to an issue that, when touched, can cause mortal damage to a political party – the issue in this case being health care.

"The major criticism I've had of the book, from people I know pretty well, is that there's not enough dirt in it," Sinclair said in an interview.

Please see COMMISSION, Page 2

Grad offers Queen's $10M

Alumnus hopes to build arts centre on King Street

The Whig-Standard

QUEEN'S UNIVERSITY IS ACTIVELY pursuing [illegible] waterfront land to build a performing arts centre, thanks to an offer from a wealthy alumnus of more than $10 million to bankroll the project.

"It's my way of saying thank you to a wonderful university," Alfred Bader told *The Whig-Standard* in a telephone interview from his office in Milwaukee, Wis.

BADER

Bader, 81, is a multi-millionaire who graduated from Queen's in 1945 with a degree in engineering chemistry. He made his fortune in the chemical business.

He has contributed millions of dollars to Queen's over decades, [illegible] through donations of valuable art work and through the funding of positions and programs. He and his wife, Isabel, paid to build a beautiful performing arts hall at University of Toronto and they'd like to see something similar in Kingston.

The Isabel Bader Theatre in Toronto sits 500 and sports a 60-ft.-wide stage.

It was built, he said, without difficulty because the university had land available. Queen's, a growing school already packed into a dense urban core, is starved for real estate for expansion.

Bader would like to see a Queen's performing arts centre built on land on King Street, such as the property that now houses the J.K. Tett complex at 370 King St. West. Nine community arts and cultural groups currently rent space from the city in the Tett complex.

Please see QUEEN'S, Page 8

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Mutual Fund Listings will not appear in today's newspaper

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THE WHIG-STANDARD
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TODAY'S WEATHER

6/2

Rain with northeasterly winds

Details on page 5

Q AND A WITH...

Duncan Sinclair

How did a veterinarian come to lead Ontario's health-care reform? And does he mind that his son is more famous than he is?

Duncan Sinclair is one of Canada's most sought-after health policy experts. He's also the proud father of Gordon Sinclair, the bass guitarist for Kingston's Tragically Hip. At 72, Sinclair is in steady demand as a speaker, consultant and teacher.

He started his career as a veterinarian, went on to earn a doctorate in human physiology but found his niche in administration. During a 30-year career at Queen's University, he served as dean of medicine, vice-principal of two departments and dean of arts and science.

In 1995, on the verge of retirement, Sinclair was asked to chair a Health Services Restructuring Commission to carry out the Ontario Conservative government's health-reform agenda. The "inside story" of the commission's four tumultuous years is the subject of a new book, *Riding the Third Rail*, written by Sinclair with input from his commission colleagues Peggy Leatt and Mark Rochon. Sinclair discussed the book and other issues recently with *The Whig-Standard*'s Ann Lukits

Q How did a veterinarian end up chairing a provincial health commission – much less leading a medical school?

A. My father was a very distinguished biochemist who died when I was a teenager. He had been brought to Canada to start the department of biochemistry at Queen's. And with the wisdom of an 18-year-old leaving high school, I thought that if I were to follow in my father's footsteps, a veterinarian education would be a firmer foundation than a medical education. I never did practise [as a vet]. I filled in for people now and again and paid off a few debts.

Q. *Riding the Third Rail* is riddled with references to foot-dragging, inaction and the "eerie silence" of bureaucrats, not to mention commissioners' efforts to penetrate the "deep dark hole of the [health] ministry." Have you had any nasty feedback from the ministry?

A. No. You don't have to scratch very deeply to find that people in the ministry of health know that about themselves. In fact, most parts of government know that they operate as a very ponderous and closed shop. It's a source of frustration to bureaucrats, interestingly, and yet they are the source of the problem.

Q. What did you do with the $4 you earned during the four years you were a commissioner?

A. I think they're stuck somewhere on a plaque. They're either somewhere in a cupboard or maybe on the wall.

Q. What happens when a famous health-care expert like you goes to the doctor? Do you get special attention? Do you get your ears talked off?

A. No. Happily, there's not much wrong with me. I've been seen by a resident who hasn't a clue who I am or what I did, or care.

Q. Who is better known in your family, you or Gordon?

A. Oh, Gordon. My favourite introduction was given many years ago by the-then dean of medicine at Dalhousie. He was introducing me – I was speaking to a large group of physicians – and he said, if you want to know who this guy really is, this is Gordon Sinclair's father. Everybody clapped. They knew Gordon Sinclair but they didn't have a clue who I was.

Q. What's your favourite Tragically Hip song?

A. My favourite is one that has never appeared on a CD. It was one of their very early pieces and I still think it's one of the best they've done. It's called the Low-Down Baptist Blues. They haven't played it in many, many years but we have a somewhat bootlegged copy of it. But Ahead By A Century, I like. Small Town Bringdown, I like that one, too. Boots or Hearts.

Q. Are you allowed to have other musical tastes? What other music do you like?

A. My wife and I attend the Kingston Symphony regularly and have done for many, many years.

Q. If you were God and could make one change to the health system, what would it be?

A. I would never aspire to be God, but I often say if I were the czar...

Q. OK, if you were the czar...

A. Well, there are two choices. One involves an attitude change on the part of a lot of people. So you'd have to be a very powerful czar to do that. In fact, that would probably have to be done by God alone. But if I were the czar, I would put a ton of money, time and effort into the development of a genuine capacity for health information management. We spent last year $130 billion in Canada on what we refer to as health-care services, and we really don't have a clue what we bought.

Q. How do you sell health information management to people who just want a doctor?

A. That's where political leadership comes in. Politics is often described as the art of the possible. Politics ought to be the art of making possible that which needs to be done. And political leaders and our political culture are not attuned to that.

Q. Is medicine still a good profession for young people to pursue?

A. It's a wonderful thing for people to do, not only medicine, but nursing and occupational therapy and physical therapy and dentistry and pharmacy – all the health professions. It's an area the most idealistic of young people should go into because they then have an opportunity to really help other people. Sadly, I've seen far too many medical students converted from very idealistic young people into very materialistic young people. One of the things medical schools do very well, to our discredit, is that we cure young people of their aversion to money. It's not nice, not nice, but it's true.

Michael Lea/The Whig-Standard

Commission should have replaced more boards, Sinclair says

Continued from Page 1

"And there isn't. We promised those who submitted stuff to us that it would remain confidential so we kept that promise.

"As I told my colleagues and friends who complained about the lack of dirt, that's where the dirt is."

The commission established by the Harris government in 1996 was different from other bodies appointed to fix the health system. It had unprecedented authority to do whatever was deemed necessary to make the health system more efficient, both financially and operationally. If that meant shutting down hospitals, closing beds, or consolidating programs and boards, the commission had a free hand to do so – and did.

During its brief mandate, the commission reduced the number of hospital corporations in Ontario by 85 – from 225 to 160 – and closed 10 sites. It also pushed the government to spend $2-billion on more long-term care beds and home-care services. Kingston was one of a number of communities that attempted to fight the commission's directions, specifically the closure of Hotel Dieu, in court. The commission won all but one of the legal challenges – it lost a bid to close Ottawa's francophone Montfort Hospital – but, in many communities, the anger and resentment generated by the orders linger to this day.

If Riding the Third Rail fails to offer a juicy "blow-by-blow account" of the commission's dealings with individual hospitals, it gives a surprisingly juicy account of the commission's dealings with stonewalling bureaucrats and a government that "lost its nerve" before restructuring was completed.

Sinclair writes that the commissioners quickly learned a fundamental truth about their world: "that the survival instincts of organizations are as strong as those of individuals."

The 200-page book is riddled with references to frustrated commissioners in a passage that echoes the experience of many in the local hospital community. Sinclair writes that the ministry's initial reaction to notices and directions issued by the commission was "dead silence."

Commissioners felt "as if their recommendations had been dropped into a deep, dark hole," he writes. "Frequently, the ministry's response would come to the commission only after it had been requested formally, sometimes repeatedly, in letters from the chair to the minister. Everybody came to appreciate the deep frustration of 'working with the government.'"

Sinclair and his colleagues found the Canadian public much more open to its reforms than politicians and hospital boards. The irony was that the very government that created the commission proved to be its biggest stumbling block.

The book blames the "mixed results" of the commission's reform efforts on three things: the government's failure to talk up the vision of a genuine health-services system to the public; the lack of investment in community care (specifically long-term care facilities and nursing homes); and the refusal to provide the necessary capital to rebuild and maintain the hospital system.

In fact, the government's preoccupation with saving money undercut the commission's mission at every step, the book claims.

"The Harris government pulled off a clever trick – retaining all the power while creating the illusion of relinquishing a substantial amount of it," the book states.

Although the commissioners' "collective conscience is clear," there were notable failures on their part as well. One was their inability to persuade the government to proceed past hospital restructuring, to develop a health information management system and make other fundamental organizational changes.

The commissioners also erred in opting not to use their considerable powers to replace some hospital boards. In hindsight, the commissioners should have selectively ordered more takeovers and fewer mergers, Sinclair writes.

"These new consolidated hospitals would have been far better served had the commission been less patient and less tolerant of some of their predecessors' obstructive shenanigans."

> *'These new consolidated hospitals would have been far better served had the commission been less patient and less tolerant of some of their predecessors' obstructive shenanigans'*
>
> **– Duncan Sinclair**

"The commissioners were not naive," Sinclair writes. "But all were distressed at the depth and ferocity of the resistance to change among so many health-care participants, not only providers but also the owners/governors and managers of health care's many institutions and organizations, including the government bureaucracy."

If he had his druthers, Sinclair told *The Whig*, he would create a new health services commission, give it a 10-year mandate and finish the job started by the 1996 commission. "Politically, it would take an enormous amount of courage, but frankly I think that's perhaps the only thing that would work," he said.

One of the titles initially considered for the book was "Moving Health's Mountain – A Little."

"There's no question it's moved," Sinclair said, "but I can't say how far because it's not done yet."

Riding the Third Rail mentions Kingston's experience with hospital restructuring twice. The first is in a section describing the court challenges launched by Ontario hospitals – what the commission's CEO Mark Rochon referred to as the commission's "busy legal practice."

The second mention is included in a section describing the commission's success in changing hospital roles and governance structures. The book notes that all the governance changes ordered by the commission "have been completed, with the notable exception of Kingston."

Sinclair told *The Whig* that he believes the current premier will give his blessing, possibly soon, to a longstanding request on the part of local hospitals to rescind the commission's directions and allow Hotel Dieu to retain its separate identity.

In the 1998 final directions issued by the commission, Hotel Dieu was ordered to close its Brock Street site and forfeit its separate governance. Kingston General Hospital was to assume responsibility for the Dieu's programs and services. Despite repeated efforts to overturn those directions over the past two years and enthusiastic support from Kingston's MPP John Gerretsen, the hospitals have yet to receive a response from Queen's Park.

In Toronto, however, the premier recently rescinded commission orders merging Women's College Hospital, Orthopaedic and Arthritic Hospital and Sunnybrook Hospital. Women's College will be reborn as an independent, ambulatory outpatient centre, what Sinclair calls "the hospital of the future."

"I was asked my opinion on that, as a matter of fact at the book launch, as it was announced the very same day," Sinclair said. "I said it seemed to me a good example of the first rule of the hole: when you're in a hole, stop digging."

alukits@thewhig.com

Riding the Third Rail: The Story of Ontario's Health Services Restructuring Commission, 1996-2000, is published by the Institute for Research on Public Policy in Montreal. To order a copy, visit www.irpp.org or contact Jeremy Leonard at jleonard@irpp.org or Jasmine Sharma at jsharma@irpp.org.

Correction

A Kingston woman is seeking a court order to overturn the city's decision to attach the name of the Springer family to Market Square. A headline Saturday was incorrect.

LETTERS TO THE EDITOR are welcome at: Our mailing address by fax (613) 530-4118; or by e-mail, cwhiged@thewhig.com – text only please, no attachments. Letters must contain the author's name, address and a daytime telephone number. *The Whig-Standard* reserves the right to edit, condense or reject any letter.

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FORUM

Three remembrances

St. Lawrence nurtured Clay McIntosh, and eventually it claimed him

COLUMN

'Twas last spring, deep in the heart of the Thousand Islands near the village of Ivy Lea, a small green-and-yellow tugboat was winding its way carefully and unobtrusively through one of the many hidden coves near Champagne Island. Even its chugging engine blended in harmony with several red-wing blackbirds chirping out their territories among the tall marsh reeds.

BRIAN JOHNSON

I watched from my vantage point on the gravel road beside the canal as the Blue Quail swung gently to starboard, lining itself up to join with its barge. In the wheelhouse, skipper Jay McIntosh spun the steering wheel and moved gently ahead, nudging the bow of the tug perfectly into the notch as deckhand Willie Sauer took a line, making it fast to the bits. In a minute, Jay was down on the deck, helping Willie with another line.

"Great job, skipper," I said after introducing myself and telling him why I was there.

"Well, I learned from the best," replied McIntosh with the same grin as his older brother. "Hopefully something rubbed off."

These were river men at work, carrying on their business in spite of tragedy because they have to. The Boss would have wanted it that way.

You would see him upon the decks of the Blue Quail, soaring from Kingston to Brockville and building seawalls, docks and more. Clay McIntosh, The Boss, grew up on the river. Tall and curly haired, his quick smile and affable demeanour were genuine. "He always found time for other people and their needs," said his best friend, Ron Huck of Rockport. "He was the ultimate people person."

Indeed, Clay McIntosh was the guy smiling an impish grin and hiding a secret that only he understood but couldn't wait to share with someone, anyone, before he burst at the seams. "He was a devil with that mischievous grin," Huck added.

He was the guy who drove up, got out and teased the dog just to hear him bark," remembered sister-in-law Nancy McIntosh. He was the guy who walked up to you and said, "Hey. How're ya doin?" and really meant it.

Clay McIntosh truly was Huckleberry Finn all grown up, as only Mark Twain could have imagined him.

Born and raised in this quiet bay just west of Ivy Lea, the third-eldest son of Roly and Eleanor McIntosh was a genuine "river rat," hunting along the shoreline, fishing secret bays and guiding his tug through the many channels and bays he knew so well to the next job.

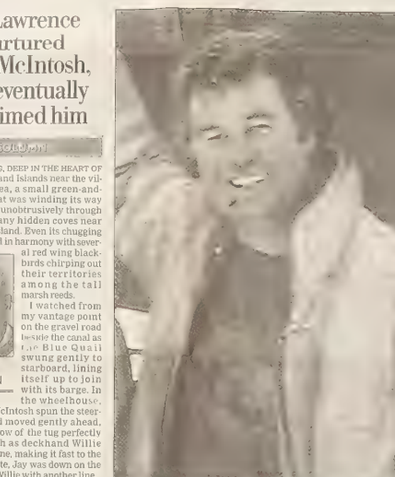


Photo courtesy of Brian Johnson

'River rat' Clay McIntosh died in an accident on the St. Lawrence River in April.

The St. Lawrence River had a magnetic effect on him, especially in spring. Springtime allowed him back on his river to earn his living.

This past spring, the river claimed him as its own. Returning home late on the night of April 22, Clay nursed the throttle of his Sea-Doo along the north side of Tar Island, just east of the village of Rockport, probably watching the tree line carefully through the mist and shadows of the narrow channel, relying heavily on his experience and river instinct for direction. What he didn't know was that directly ahead of him, coming fast, was another speedboat.

The body of Clay McIntosh, once a loving husband, proud father, beloved friend and "river rat," was found in his partially submerged boat around 5:10 a.m., after an extensive search.

Clay's wife Kathy was devastated when she heard the news of her husband's sudden death – on the river, of all places. How would she tell their children, Nicole and Kristen, and son-in-law Bret Rose, and especially at that time, for Bret and Nicole were expecting their first baby any day?

"He was born on the river, the river nurtured him, and in the end, the river took him," said Ron Huck. He paused for a minute, then added: "I'm going to see his truck pulling into my driveway for a long time to come."

About six years ago, Clay McIntosh started his own company, St. Lawrence Marine and Dredging. He had worked for marine contractor John Bishop for most of his life and finally decided to strike out on his own.

"From a work boat and a welding machine he built one of the most formidable marine construction businesses on the St. Lawrence River," said friend Dan Morrow.

The Blue Quail, home from another job, is tied alongside its barge sheltered from the northwest wind stirring up the river just outside the bay. A few leaves stick to its decks as they fall from the nearby trees.

It's been a busy summer. The red-wing blackbirds are gone now and it is quiet. Even the autumn colours are starting to fade on this dull, rainy October day.

Oh, and Nicole and Bret had a baby boy. They named him Clayton River Rose.

Grandpa River Rat would be very proud.

□ Brian Johnson is a Kingston freelance writer and skipper of the Wolfe Islander III.

Bassoonist brought artistry and humour to orchestra

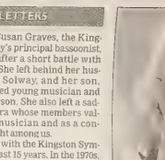
LETTERS

On Sept. 26, Susan Graves, the Kingston Symphony's principal bassoonist, passed away after a short battle with brain cancer. She left behind her husband, Kenny Solway, and her son, Jesse, a talented young musician and fine young person. She also left a saddened orchestra whose members valued her as a musician and as a constant bright light among us.

Susie played with the Kingston Symphony for the last 15 years. In the 1970s, she and her husband were founding members of the Tafelmusik Orchestra in Toronto.

Her dedication to our orchestra in Kingston was incredible. Consider this: Susie and her family lived near Cobourg. This meant she commuted to Kingston at least 800 times over 15 years, through all the sometimes treacherous driving conditions Highway 401 has to offer. I cannot remember a rehearsal or concert that she missed.

Susie's artistry came to full light on *March 20 as she performed, with the Kingston Symphony,* an accomplished and beautiful Mozart bassoon concerto. That concerto is representative of Susie's life, as it offers profound beauty, high spirit and a particular humour. Susie was full of. We were so proud of her. My memories of this performance and countless other performances she gave will always give me a smile and deep sense of gratitude for her time among us.



Susan Graves: 'Constant bright light'

The Kingston Symphony will be dedicating a performance of Verdi's *Requiem to the memory of Susie on Nov. 27.*

Glen Fast
Music Director
Kingston Symphony Association

Dedicated music teacher always had time to help

We recently lost one of the greatest musical talents I have ever known. Jim "The General" Preston could play almost any instrument with ease and skill, and he was probably the humblest man I ever met.

Although I had never seen him play hockey, I heard he was quite good at it. He never talked about how many goals he scored.

Most people knew him as "Jimmy" or "The General." I knew him as "Mr. P," and I am one of the lucky teachers at St. Joseph's School in Gananoque who had the pleasure of working with him for the past 16 years.

At Jim's memorial service on Sept. 9, I heard other wonderful stories from his family, friends and hockey buddies. I was especially proud that in each story his love of teaching, his colleagues and his students were mentioned.

I can only imagine the stories Jim told his hockey buddies in that smelly change room. I wish I had the strength that day to get up and tell some of my own stories about Mr. P.

Mr. Preston was a great teacher and colleague. He was probably the most unselfish and easy-going teacher we had at our school.

I cannot remember many days during the last 16 years when I didn't see Jim in his room at lunch time with a handful of students. He was either giving a music lesson, supervising the chess club, helping with the choir or just letting students stay and chat.

It didn't matter whether it was a Christmas concert, track-and-field day or kindergarten celebration. All we had to do was ask and Jim was there. He was loved and respected by each and every teacher.

Jim Preston 'a special person'

I am going to miss his humour and our hockey chats, though I could never convince him to cheer for the Boston Bruins. I am especially going to miss him for his musical talent. I enjoy playing guitar myself and on a moment's notice, I could run down the hall with guitar in hand and ask Jim to write out the chords for a particular song I needed that day.

It didn't matter what he had on his plate at the time. Mr. Preston always made time to help.

We lost a special and unique person in Jim "The General" Preston.

Chris Shannon
Gananoque

SPORTS

COLUMN

Hockey visors are – or should be – a no-brainer

The National Hockey League has returned to the ice. A bitter battle between the owners of the 30 NHL teams and their players over a salary cap has ended, and pro hockey has returned. Opening night was Oct. 5 and every team was back on the ice that night.

Revised rules and a renewed vow to penalize obstruction fouls had this fan, and many other fans, hoping for a return to wide-open, end-to-end hockey as we settled in that night for the first series in this season's "Battle of Ontario" between Mats Sundin's Toronto Maple Leafs and their provincial rivals, the Ottawa Senators.

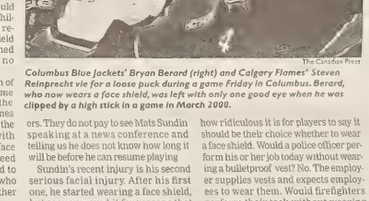
CRAIG LEWIS

Sundin, the $6-million-dollar man (literally, and in U.S. dollars), was on the ice for his third shift of the game when an errant puck deflected and caught him near the left eye. The result: the first of what will be many serious eye injuries in the "new" NHL, and one that will see the Leafs' most-expensive player sidelined for a month to six weeks. It was an instant flashback to 55 years ago when then Leafs defenceman Bryan Berard was hit in the eye during a game against the Sens. Berard lost most of the vision in that eye.

Fast forward two weeks after Sundin's injury. Detroit Red Wings veteran Kris Draper is hit in the face by a puck. The result: another player out of the lineup for an undetermined period with an eye injury.

And so the debate continues. Should hockey players, whether they are children or professional athletes, be required to wear a protective face shield while playing in league-sanctioned games? The answer, to me, is a no brainer. Yes.

At the risk of enduring the wrath of hockey analyst Don Cherry, the time has come for the owners to take the next step to ensure pro hockey games that will feature the best players in the world. That step is to negotiate with the players' association to make face shields mandatory. We do not need any more studies. Nor do we need to hear more rhetoric from players who say it should be their choice whether to wear a visor.



The Canadian Press

Columbus Blue Jackets' Bryan Berard (right) and Calgary Flames' Steven Reinprecht vie for a loose puck during a game Friday in Columbus. Berard, who now wears a face shield, was left with only one good eye when he was clipped by a high stick in a game in March 2000.

The owners are paying these players a lot of money to play hockey. The fans are paying top dollar to attend games, and they deserve to see the best players. They do not pay to see Mats Sundin speaking at a news conference and telling us he does not know how long it will be before he can resume playing.

Sundin's recent injury is his second serious facial injury. After his first one, he started wearing a face shield, but soon removed it for reasons that make no sense to me.

Playing hockey is Sundin's job and he is well paid to do it. If I can make a few comparisons, surely others can see how ridiculous it is for players to say it should be their choice whether to wear a face shield. Would a police officer perform his or her job today without wearing a bulletproof vest? No. The employer supplies vests and expects employees to wear them. Would firefighters perform their task without wearing the protective clothing supplied to them? No. The employer provides it and, again, expects it to be worn.

Our government has made many rules when it comes to safety equipment. If you ride in a motor-vehicle, you must wear a seatbelt. If you drive or ride a motorcycle, you must wear an approved helmet. The reasons for these rules are crystal clear: they save lives and prevent serious injuries.

We all pay for health care and it is a proven fact that if safety equipment was not used, our health-care costs would go up. Would you like to venture a guess as to how much the health-related costs are for Sundin? I would suspect they are thousands of dollars for his latest injury. The cost to the players in the three major junior leagues that make up the Canadian Hockey League. The professional players are role models for so many youngsters and some are sending the wrong message to these potential hockey stars of the future by not wearing visors.

□ Craig Lewis is a Kingston freelance writer and a former member of The Whig-Standard's Community Editorial Board.

Q AND A WITH...

Duncan Sinclair

How did a veterinarian come to lead Ontario's health-care reform? And does he mind that his son is more famous than he is?

Duncan Sinclair is e[illegible] sought-after health p[illegible] the Tragically Hip's [illegible] and then they are the source of [illegible] ten say if I were the czar

[illegible] earned a doctorate in human physiology but found his niche in administration. During a 30-year career at Queen's University, he has been dean of medicine, vice-principal of two departments and dean of arts and science.

In 1986, on the verge of retirement, Sinclair was tapped to chair a Health Services Restructuring Commission to carry out the Ontario Conservative government's health-reform agenda. The "inside story" of the commission's four tumultuous years is the subject of a new book, *Riding the Third Rail*, written by Sinclair with input from his commission colleagues Peggy Leatt and Mark Rochon. Sinclair discussed the book and other issues recently with *The Whig-Standard*'s Ann Lukits.

Q. How did a veterinarian end up chairing a provincial health commission – much less leading a medical school?

A. We [illegible] chemist who died when I was a teenager. He had been brought to Canada to start the department of biochemistry at Queen's. And with the wisdom of an 18-year-old leaving high school, I thought that if I were to follow in my father's footsteps, a veterinarian education would be a firmer foundation than a medical education. I never did practise [as a vet]. I filled in for people now and again and paid off a few debts.

Q. *Riding the Third Rail* is riddled with references to foot-dragging, inaction and the "eerie silence" of bureaucrats, not to mention commissioners' efforts to penetrate the "deep dark hole of the [health] ministry." Have you had any nasty feedback from the ministry?

A. No. You don't have to scratch very deeply to find that people in the ministry of health know that about themselves. In fact, most parts of government know that they operate as a very ponderous and closed shop. It's a source of frustration to bureaucrats

Q. What did you do with the $4 you earned [illegible] four years you were a commis[illegible]

A. I think they're stuck somewhere on a plaque. They're either somewhere in a cup board or maybe on the wall.

Q. What happens when a famous health care expert like you goes to the doctor? Do you get special attention? Do you get your ears talked off?

A. No. Happily, there's not much wrong with me. I've been seen by a resident who hasn't a clue who I am or what I did, or care.

Q. Who is better known in your family, you or Gordon?

A. Oh, Gordon. My favourite introduction was given many years ago by the-then dean of medicine at Dalhousie. He was introducing me – I was speaking to a large group of physicians – and he said, if you want to know who this guy really is, this is Gordon Sinclair's father. Everybody clapped. They knew Gordon Sinclair but they didn't have a clue who I was.

Q. What's your favourite Tragically Hip song?

A. My favourite is one that has never appeared on a CD. It was one of their very early pieces and I still think it's one of the best they've done. It's called the Low-Down Baptist Blues. They haven't played it in many, many years but we have a somewhat bootlegged copy of it. But Ahead By A Century, I like. Small Town Bringdown, I like that one, too. Boots or Hearts.

Q. Are you allowed to have other musical tastes? What other music do you like?

A. My wife and I attend the Kingston Symphony regularly and have done for many, many years.

Q. If you were God and could make one change to the health system, what would it be?

A. I would never aspire to be God, but I of[illegible]

Q. OK, if you were the czar.

A. Well, there are two choices. One involves an attitude change on the part of a lot of people. So you'd have to be a very powerful czar to do that. In fact, that would probably have to be done by God alone. But if I were the czar, I would put a ton of money, time and effort into the development of a genuine capacity for health information management. We spent last year $130 billion in Canada on what we refer to as health-care services, and we really don't have a clue what we bought.

Q. How do you sell health information management to people who just want a doctor?

A. That's where political leadership comes in. Politics is often described as the art of the possible. Politics ought to be the art of making possible [illegible] which needs to be done. [illegible] political leaders and [illegible] political culture are not [illegible] to that.

Q. Is medicine still a good profession for young people to pursue?

A. It's a wonderful thing for people to do, not only medicine, but nursing and occupational therapy and physical therapy and dentistry and pharmacy – all the health professions. It's an area the most idealistic of young people should go into because they then have an opportunity to really help other people. Sadly I've seen far too many medical students converted from very idealistic young people into very materialistic young people. One of the things medical schools do very well, to our discredit, is that we cure young people of their aversion to money. It's not nice, not nice, but it's true.

Michael Lea/The Whig-Standard

Commission should have replaced more boards, Sinclair says

Continued from Page 1

[illegible] "And there isn't. We promised those who submitted stuff to us that it would remain confidential so we kept that promise.

"As I told my colleagues and friends who complained about the lack of dirt, that's where the dirt is."

The commission established by the Harris government in 1996 was different from other bodies appointed to fix the health system. It had unprecedented authority to do whatever was deemed necessary to make the health system more efficient, both financially and operationally. If that meant shutting down hospitals, closing beds, or consolidating programs and boards, the commission had a free hand to do so – and did.

During its brief mandate, the commission reduced the number of hospital corporations in Ontario by 65 – from 225 to 160 – and closed 10 sites. It also pushed the government to spend $2-billion on more long-term care beds and home-care services.

Kingston was one of a number of communities that attempted to fight the commission's directions, specifically the closure of Hotel Dieu, in court. The commission won all but one of the legal challenges – it lost a bid to close Ottawa's francophone Montfort Hospital – but, in many communities, the anger and resentment generated by the orders linger to this day.

If *Riding the Third Rail* fails to offer a juicy "blow-by-blow account" of the commission's dealings with individual hospitals, it gives a surprisingly juicy account of the commission's dealings with stonewalling bureaucrats and a government that "lost its nerve" before restructuring was completed.

Sinclair writes that the commissioners quickly learned a fundamental truth about their world – "that the survival instincts of organizations are as strong as those of individuals."

The 290-page book is riddled with references to frustrated commissioners. In a passage that echoes the experience of many in the local hospital community, Sinclair writes that the ministry's initial reaction to notices and directions issued by the commission was "dead silence."

Commissioners felt "as if their recommendations had been dropped into a deep, dark hole," he writes. "Frequently, the ministry's response would come to the commission only after it had been requested formally, sometimes repeatedly, in letters from the chair to the minister. Everybody came to appreciate the deep frustration of working with the government."

Sinclair and his colleagues found the Canadian public much more open to its reforms than politicians and hospital boards. The irony was that the very government that created the commission proved to be its biggest stumbling block.

The book blames the "mixed results" of the commission's reform efforts on three things: the government's failure to talk up the vision of a genuine health-services system to the public; the lack of investment in community care (specifically long-term care facilities and nursing homes); and the refusal to provide the necessary capital to rebuild and maintain the hospital system.

In fact, the government's preoccupation with saving money undercut the commission's mission at every step, the book claims.

"The Harris government pulled off a clever trick – retaining all the power while creating the illusion of relinquishing a substantial amount of it," the book states.

Although the commissioners' "collective conscience is clear," there were notable failures on their part as well. One was their inability to persuade the government to proceed past hospital restructuring, to develop a health information management system and make other fundamental organizational changes.

The commissioners also erred in opting not to use their considerable powers to replace some hospital boards. In hindsight, the commissioners should have selectively ordered more takeovers and fewer mergers, Sinclair writes.

"These new consolidated hospitals would have been far better served had the commission been less patient and less tolerant of some of their predecessors' obstructive shenanigans.'

"The commissioners were not naive,' Sinclair writes. "But all were distressed at the depth and ferocity of the resistance to change among so many health-care participants, not only providers but also the owners/governors and managers of health care's many institutions and organizations, including the government bureaucracy."

If he had his druthers, Sinclair told *The Whig*, he would create a new health services commission, give it a 10-year mandate and finish the job started by the 1996 commission. "Politically, it would take an enormous amount of courage, but frankly I think that's perhaps the only thing that would work," he said.

One of the titles initially considered for the book was "Moving Health's Mountain – A Little."

"There's no question it's moved," Sinclair said, "but I can't say how far because it's not done yet."

Riding the Third Rail mentions Kingston's experience with hospital restructuring twice. The first is in a section describing the court challenges launched by Ontario hospitals – what the commission's CEO Mark Rochon referred to as the commission's "busy legal practice."

The second mention is included in a section describing the commission's success in changing hospital roles and governance structures. The book notes that all the governance changes ordered by the commission "have been completed, with the notable exception of Kingston."

Sinclair told *The Whig* that he believes the current premier will give his blessing, possibly soon, to a longstanding request on the part of local hospitals to rescind the commission's directions and allow Hotel Dieu to retain its separate identity.

In the 1998 final directions issued by the commission, Hotel Dieu was ordered to close its Brock Street site and forfeit its separate governance, Kingston General Hospital was to assume responsibility for the Dieu's programs and services. Despite repeated efforts to overturn those directions over the past two years and enthusiastic support from Kingston's MPP John Gerretsen, the hospitals have yet to receive a response from Queen's Park.

In Toronto, however, the premier recently rescinded commission orders merging Women's College Hospital, Orthopaedic and Arthritic Hospital and Sunnybrook Hospital. Women's College will be reborn as an independent, ambulatory outpatient centre, what Sinclair calls "the hospital of the future."

"I was asked my opinion on that, as a matter of fact at the book launch, as it was announced the very same day," Sinclair said. "I said it seemed to me a good example of the first rule of the hole: when you're in a hole, stop digging."

alukits@thewhig.com

'These new consolidated hospitals would have been far better served had the commission been less patient and less tolerant of some of their predecessors' obstructive shenanigans'

– Duncan Sinclair

Riding the Third Rail: The Story of Ontario's Health Services Restructuring Commission, 1996-2000, is published by the Institute for Research on Public Policy in Montreal. To order a copy, visit www.irpp.org or contact Jeremy Leonard at jleonard@irpp.org or Jasmine Sharma at jsharma@irpp.org.

Correction

A Kingston woman is seeking a court order to overturn the city's decision to attach the name of the Springer family to Market Square. A headline Saturday was incorrect

LETTERS TO THE EDITOR are welcome at. Our mailing address; by fax (613) 530-4118, or by e-mail [illegible]khured > thewhig.com>, text only, please, no attachments. Letter[illegible] must contain the author's name address and a daytime telephone number. *The Whig-Standard* reserves the right to edit, condense or reject any letter.

FORUM

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Three remembrances

St. Lawrence nurtured Clay McIntosh, and eventually it claimed him

BRIAN JOHNSON

Just upstream, deep in the heart of the Thousand Islands near the village of Ivy Lea, a small green-and-yellow tugboat was winding its way carefully and unobtrusively through one of the many hidden coves near Chippewa Island. Even its chugging engine blended in harmony with several red wing black birds chirping out their territories among the tall marsh reeds.

I watched from my vantage point on the gravel road beside the canal as the Blue Quail swung gently to starboard, lining itself up to join with its barge. In the wheelhouse, skipper Jay McIntosh spun the steering wheel and moved gently ahead, nudging the bow of the tug perfectly into the notch as deckhand Willie Sayer took a line, making it fast to the bits. In a minute, Jay was down on the deck, helping Willie with another line.

"Great job, skipper," I said after introducing myself and telling him why I was there.

"Well, I learned from the best," replied McIntosh with the same grin as his older brother. "Hopefully something rubbed off."

These were river men at work, carrying on their business in spite of tragedy because they have to. The Boss would have wanted it that way.

You would see him upon the decks of the Blue Quail, soaring from Kingston to Brockville and building seawalls, docks and more. Clay McIntosh, The Boss, grew up on the river. Tall and curly haired, his quick smile and affable demeanour were genuine. "He always found time for other people and their needs," said his best friend, Ron Huck of Rockport. "He was the ultimate people person."

Indeed, Clay McIntosh was the guy smiling an impish grin and hiding a secret that only he understood but couldn't wait to share with someone, anyone, before he burst at the seams. "He was a devil with that mischievous grin," Huck added.

He was the guy who drove up, got out and teased the dog just to hear him bark," remembered sister-in-law Nancy McIntosh. He was the guy who walked up to you and said, "Hey, How're ya doin?" and really meant it.

Clay McIntosh truly was Huckleberry Finn all grown up, as only Mark Twain could have imagined him.

Born and raised in this quiet bay just west of Ivy Lea, the third-eldest son of Roly and Eleanor McIntosh was a genuine "river rat," hunting along the shoreline, fishing secret bays and guiding his tug through the many channels and bays he knew so well to the next job.

The St. Lawrence River had a magnetic effect on him, especially in spring. Springtime allowed him back on his river to earn his living.

This past spring, the river claimed him as its own. Returning home late on the night of April 22, Clay nursed the throttle of his Sea-Doo along the north side of Tar Island, just east of the village of Rockport, probably watching the tree line carefully through the mist and shadows of the narrow channel, relying heavily on his experience and river instinct for direction. What he didn't know was that directly ahead of him, coming fast, was another speedboat.

The body of Clay McIntosh, once a loving husband, proud father, beloved friend and "river rat," was found in his partially submerged boat around 5:10 a.m., after an extensive search.

Clay's wife Kathy was devastated when she heard the news of her husband's sudden death – on the river, of all places. How would she tell their children, Nicole and Kristen, and son-in-law Bret Rose, and especially at that time, for Bret and Nicole were expecting their first baby any day?

"He was born on the river, the river nurtured him, and in the end, the river took him," said Ron Huck. He paused for a minute, then added: "I'm going to see his truck pulling into my driveway for a long time to come."

About six years ago, Clay McIntosh started his own company, St. Lawrence Marine and Dredging. He had worked for marine contractor John Bishop for most of his life and finally decided to strike out on his own.

"From a work boat and a welding machine he built one of the most formidable marine construction businesses on the St. Lawrence River," said friend Dan Morrow.

The Blue Quail, home from another job, is tied alongside its barge, sheltered from the northwest wind stirring up the river just outside the bay. A few leaves stick to its decks as they fall from the nearby trees.

It's been a busy summer. The redwing blackbirds are gone now and it is quiet. Even the autumn colours are starting to fade on this dull, rainy October day.

Oh, and Nicole and Bret had a baby boy. They named him Clayton River Rose.

Grandpa River Rat would be very proud.

□ Brian Johnson is a Kingston freelance writer and skipper of the Wolfe Islander III

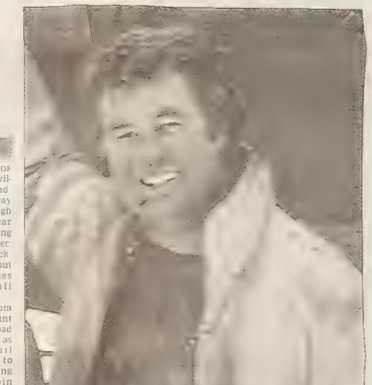


Photo courtesy of Brian Johnson

'River rat' Clay McIntosh died in an accident on the St. Lawrence River in April.

Bassoonist brought artistry and humour to orchestra

LETTERS

On Sept. 26, Susan Graves, the Kingston Symphony's principal bassoonist, passed away after a short battle with brain cancer. She left behind her husband, Kenny Solway, and her son, Jesse, a talented young musician and fine young person. She also left a saddened orchestra whose members valued her as a musician and as a constant bright light among us.

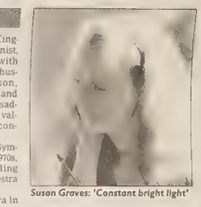
Susie played with the Kingston Symphony for the last 15 years. In the 1970s, she and her husband were founding members of the Tafelmusik Orchestra in Toronto.

Her dedication to our orchestra in Kingston was incredible. Consider this: Susie and her family lived near Cobourg. This meant she commuted to Kingston at least 800 times over 15 years, through all the sometimes treacherous driving conditions Highway 401 has to offer. I cannot remember a rehearsal or concert that she missed.

Susie's artistry came to full light on March 20 as she performed, with the Kingston Symphony, an accomplished and beautiful Mozart bassoon concerto. That concerto is representative of Susie's life, as it offers profound beauty, high spirit and a particular humour. Susie was full of. We were so proud of her. My memories of this performance and countless other performances she gave will always give me a smile and deep sense of gratitude for her time among us.

The Kingston Symphony will be dedicating a performance of Verdi's Requiem to the memory of Susie on Nov. 27.

Glen Fast
Music Director
Kingston Symphony Association



Susan Graves: 'Constant bright light'

Dedicated music teacher always had time to help

We recently lost one of the greatest musical talents I have ever known, Jim "The General" Preston could play almost any instrument with ease and skill, and he was probably the humblest man I ever met.

Although I had never seen him play hockey, I heard he was quite good at it. He never talked about how many goals he scored.

Most people knew him as "Jimmy" or "The General." I knew him as "Mr P." and I am one of the lucky teachers at St. Joseph's School in Gananoque who had the pleasure of working with him for the past 16 years.

At Jim's memorial service on Sept. 9, I heard some wonderful stories from his family, friends and hockey buddies. I was especially proud that in each story his love of teaching, his colleagues and his students were mentioned.

I can only imagine the stories Jim told his hockey buddies in that smoky change room. I wish I had the strength that day to get up and tell some of my own stories about Mr. P.

Mr. Preston was a great teacher and colleague. He was probably the most unselfish and easy-going teacher we had at our school.

I cannot remember many days during the last 16 years when I didn't see Jim in his room at lunch time with a handful of students. He was either giving a music lesson, supervising the chess club, helping with the choir or just letting students stay and chat.

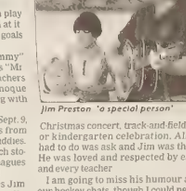
It didn't matter whether it was a Christmas concert, track-and-field day or kindergarten celebration. All we had to do was ask and Jim was there. He was loved and respected by each and every teacher.

I am going to miss his humour and our hockey chats, though I could never convince him to cheer for the Boston Bruins. I am especially going to miss him for his musical talent. I enjoy playing guitar myself and on a moment's notice, I could run down the hall with guitar in hand and ask Jim to write out the chords for a particular song I needed that day.

It didn't matter what he had on his plate at the time. Mr. Preston always made time to help.

We lost a special and unique person in Jim "The General" Preston.

Chris Shannon
Gananoque



Jim Preston 'a special person'

SPORTS COLUMN

Hockey visors are – or should be – a no-brainer

The National Hockey League has returned to the ice. A bitter battle between the owners of the 30 NHL teams and their players over a salary cap has ended, and pro hockey has returned. Opening night was Oct. 5 and every team was back on the ice that night.

Revised rules and a renewed vow to penalize obstruc[illegible]gon fouls had [illegible]is fan, and many other fans, [illegible]oping for a return to wide-open, end-to-end hockey as we settled in that night for the first sor[illegible]tis in this season's "Battle of Ontario" be[illegible]tween Mats Sundin's Toronto Maple Leafs and their provincial rivals, the Ottawa Senators.

Sundin, the $6-million-dollar man (literally, and in U.S. dollars), was on the ice for his third shift of the game when an errant puck deflected and caught him near the left eye. The result: the first of what will be many serious eye injuries in the "new" NHL, and one that will see the Leafs' most expensive player sidelined for a month to six weeks. It was an instant flashback to 5½ years ago when then-Leafs defenceman Bryan Berard was hit in the eye during a game against the Sens. Berard lost most of the vision in that eye.

Fast forward two weeks after Sundin's injury. Detroit Red Wings veteran Kris Draper is hit in the face by a puck. The result: another player out of the lineup for an undetermined period with an eye injury.

And so the debate continues. Should hockey players, whether they are children or professional athletes, be required to wear a protective face shield while playing in league-sanctioned games? The answer, to me, is a no brainer. Yes.

At the risk of enduring the wrath of hockey analyst Don Cherry, the time has come for the owners to take the next step to ensure pro hockey games that will feature the best players in the world. That step is to negotiate with the players' association to make face shields mandatory. We do not need any more studies. Nor do we need to hear more rhetoric from players who say it should be their choice whether to wear a visor.

The owners are paying these players a lot of money to play hockey. The fans are paying top dollar to attend games and they deserve to see the best players. They do not pay to see Mats Sundin speaking at a news conference and telling us he does not know how long it will be before he can resume playing.

Sundin's recent injury is his second serious facial injury. After his first one, he started wearing a face shield, but soon removed it for reasons that make no sense to me.

Playing hockey is Sundin's job and he is well paid to do it. If I can make a few comparisons, surely others can see how ridiculous it is for players to say it should be their choice whether to wear a face shield. Would a police officer perform his or her job today without wearing a bulletproof vest? No. The employer supplies vests and expects employees to wear them. Would firefighters perform their task without wearing the protective clothing supplied to them? No. The employer provides it and, again, expects it to be worn.

Our government has made many rules when it comes to safety equipment. If you ride in a motor-vehicle, you must wear a seatbelt. If you drive or ride a motorcycle, you must wear an approved helmet. The reasons for these rules are crystal clear: they save lives and prevent serious injuries.

We all pay for health care and it is a proven fact that if safety equipment was not used, our health-care costs would go up. Would you like to venture a guess as to how much the health-related costs are for Sundin? I would suspect they are thousands of dollars for his latest injury. The cost to his employer of having to pay him while he is injured amounts to an even larger amount.

The time has come to require that all hockey players wear protective visors. They have to from the time they start playing our national game and are mandatory right up to and including the players in the three major junior leagues that make up the Canadian Hockey League. The professional players are role models for so many youngsters and some are sending the wrong message to these potential hockey stars of the future by not wearing visors.

□ Craig Lewis is a Kingston freelance writer and a former member of The Whig-Standard's Community Editorial Board.

CRAIG LEWIS

The Canadian Press

Columbus Blue Jackets' Bryan Berard (right) and Calgary Flames' Steven Reinprecht vie for a loose puck during a game Friday in Columbus. Berard, who now wears a face shield, was left with only one good eye when he was clipped by a high stick in a game in March 2000.

LOCAL NEWS

Violent dog's owner defends his pooch's right to life

Continued from Page 1

Poncho attacked a dog earlier this year, an incident that resulted in a complaint being laid with the city's animal control department. At that time, animal control issued a muzzle order on Poncho under the city's animal control bylaw.

When McCann's Lhasa apso was attacked, Poncho wasn't wearing a muzzle. McCann said the rottweiler is a danger to the public and should be put down.

If he doesn't get put down, this is going to happen again and it could be a kid that gets killed, not somebody's pet like my Bilbo," she said.

"I'm just so upset because I could still have a dog if this guy had got a muzzle. You would think that the owner of a rottweiler would have his dog on a metal chain. No, no. He wasn't on a super duper rope or a chain or anything.

McCANN

"I just don't want to see anyone else hurt by this dog."

She reported the incident to both Kingston Police and the city's animal control.

Her brother, David McCann, is so upset about what happened that he wrote letters to a slew of officials, including Ontario Premier Dalton McGuinty and Attorney General Michael Bryant, Kingston and the Islands MP Peter Milliken, Kingston city councillors and Kingston Police Chief Bill Closs.

"I hope that you will move swiftly and decisively to protect the citizens of Ontario from this vicious dog and others like him," his letter stated.

The owner of the rottweiler, Vanja Andrin, disagrees. Despite the two attacks, he doesn't believe Poncho should be euthanized.

"She doesn't attack people," he said. "She doesn't always attack other dogs. She's just violent. I knew that she was an aggressive dog, but there are dogs that are much worse that Poncho is.

"I don't feel that it's my right to say whether a dog loses its life."

He said he feels awful about what happened to McCann's dog.

"I mean, I cried," he said. "I talked to the lady. It's not like I'm some sort of savage beast that owns aggressive dogs. If people could see Poncho and if they knew what she was like 90 per cent of the time [illegible]."

Andrin, a music student at St. Lawrence College, said Poncho wasn't wearing a muzzle at the time of the attack because he hadn't been able to find one that was big enough for the dog.

He confirmed there had been an attack earlier this year against another dog, when Poncho got out of the house and bit a dog across the street.

Andrin said that dog wasn't seriously injured, but it did have to go to the vet for treatment. He said he paid the bill.

"She didn't kill it or anything because I got out there pretty quick and I stopped it," he said.

He told *The Whig-Standard* that he has since been able to find a muzzle for Poncho and he has given her away to a family that lives on a farm.

She's gone and she's fully muzzled," he said.

He declined to say who has the dog now.

Kim Leonard, the city's supervisor of licensing and bylaw enforcement, was unaware of the specifics of the attack against McCann's Lhasa apso.

Typically in cases like these, she said, the city's animal control office starts an investigation after it gets a report from Kingston Police.

Before a dog is ordered put down, the case goes to court and a justice of the peace makes that decision under the Dog Owners Liability Act.

Leonard knows of only one case of a dog attack that has resulted in a judge ordering that the pet be euthanized.

The Dog Owners Liability Act was amended at the end of August to keep communities safer from dangerous dogs. The new legislation increased fines to a maximum to $10,000 and allows for jail sentences of up to six months for individuals who own dangerous dogs that bite, attack or pose a threat.

jprutchett@thewhig.com

Queen's hopes to partner with community groups

Continued from Page 1

If we get the land, it would be very nice to have a performing arts centre there, at a beautiful spot," Bader said.

"There is that very long [stone] building where there are a number of groups operating and they, of course, want to continue operating and that's the way I think it should be. They're very good groups."

Bader is anxious to write a cheque to Queen's. He said it would be simpler for him to pay for the project if it gets done while he's alive.

"About a year ago, we met with the mayor, Mayor Rosen, who seemed very supportive and a very likeable guy but of course he's got bureaucracy behind him, he can't just say, 'Yep, we'll sell you the land' ... but if he did, I would immediately give Queen's the money to buy that land.

Rosen has declined comment about the Queen's proposal.

"We're looking into a number of ways of having access to that property," said Queen's vice-principal Patrick Deane. "The university wants to develop a centre for the arts."

Deane couldn't say how negotiations are proceeding.

"They're quite sensitive so I can't say," he said. "We're at the beginning of the process here."

The university and city have discussed a sale price for the Tett land in the neighbourhood of $2 million, *The Whig-Standard* has learned. The 1.4-hectare site is valued according to tax records, at $1.279 million.

It includes several old stone build[illegible]s and several newer additions. One part of the site, the Stella Buck complex, was declared unsafe two years ago and was closed. The entrance to that building is ringed by a razed fence.

Deane said Queen's isn't necessarily wedded to any one site, but is committed to building a much-needed performing arts facility.

Bob Silverman, deans of arts and science at Queen's, said he hasn't seen any drawings or concept plans for a performing arts centre.

"We're in very preliminary stages," he said.

Silverman said many visions are being considered, including the idea that the school of music and other related disciplines, including drama and film studies, could move to such a facility.

The university hopes that community groups operating there could stay, but no commitment has been made.

"This should be seen as a partnership," Silverman said.

Corrections Canada says it has been approached by Queen's about purchasing the federal agency's property immediately east of the Tett site.

"We have not decided that we wish to dispose of this property at this time," said Holly Knowles, a Corrections representative at the regional headquarters in Kingston.

The federal prison service owns a 2.6 hectare tract of waterfront property at 440 King St. W. that is home to St. Helen's, a 168-year-old stone and stucco villa built for then-mayor Thomas Kirkpatrick. The striking two-storey building overlooks a terraced lot that slopes away to Lake Ontario.

It houses the senior officials who work in the prison service's regional headquarters.

Corrections also owns the adjoining property, 462 King St. W., where Stone Gables stands. It's a limestone mansion built in 1924 for a wealthy Kingston engineer.

The Queen's plan to acquire water front properties was a secret until about two weeks ago, when Principal Karen Hitchcock invited a number of officials and citizens to a private luncheon.

She explained at the luncheon that Queen's wants to partner with community groups on the project.

"She's a nice lady but her background is strictly business," said Valerie Robertson, of Theatre 5, who attended the luncheon.

Theatre 5 operates at the Tett complex.

Robertson is cautious given that plans are very preliminary.

"I would like to see an informed plan from Queen's," she said. "I'd like to see the nuts and bolts.

Bader has a long history of making substantial donations to the university's stock of artistic and cultural resources.

Two years ago, he gave the school a painting valued at $10 million by Dutch master Rembrandt Harmenszoon van Rijn. It brought to roughly 120 the number of paintings donated to Queen's by Bader.

He made a substantial donation that helped the university pay for a $7.2-million makeover of the Agnes Etherington Art Gallery. A wing is named in honour of the Baders.

He has also funded the creation of several research chairs.

This is the second time in just over a year that news has leaked out that Queen's will build a performing arts venue.

The January 2004 issue of Queen's alumni magazine, mailed to 24,000 grads, revealed that the school was about to build a 500-seat concert hall using money from a donor who was not named.

At the time, Alfred Bader told *The Whig* that he was not the donor.

That plan, to build the hall next to the university's school of music, fell through after the estimates of the cost of the project came in higher than expected.

Queen's vice-principal Andrew Simpson said at the time that the idea was put on hold.

Kingston also will soon have a new look civic performing arts centre.

The city-owned Grand Theatre is undergoing a $9-million renovation that will restore the lustre to a tired, historic facility.

The properties

Queen's University has approached the city and federal Correctional Service about acquiring waterfront properties on King Street West.

Stone Gables

LOCATION: 462 King St. W.
DESCRIPTION: A 2½-storey limestone mansion built in 1924 as a home for prosperous city construction engineer Tom A. Alexander McGinnis.
CURRENTLY: Office space owned by Corrections Canada.
DEAL: No decision about disposal.

J. K. Tett Creativity Complex

LOCATION: 370 King St. W.
DESCRIPTION: Several waterfront, stone and sided buildings including the Stella Buck building, which was [illegible] years ago after it was deemed unsafe.
SIZE: 1.4 hectares.
CURRENTLY: Home to community groups including theatre companies, visual arts and arts groups, leased space from the city.
DEAL: The city is considering selling the site to Queen's University.

St. Helen's

LOCATION: 440 King St. W.
DESCRIPTION: Large, two-storey stone villa built in 1847 as the new [illegible] for the then mayor of Kingston, describes architecturally as "an elegant country villa built on an irregular plan."
SIZE: 2.6 hectares.
CURRENTLY: Houses regional headquarters of Correctional Service of Canada, owner of the site.
DEAL: Two options under discussion.

BRIEF

Mideast peace lecture tonight

Hanan Ashrawi, a scholar and activist in the struggle for a Palestinian homeland, will deliver the Queen's 2005 Dunning Trust Lecture tonight. He'll discuss the global context and human imperative of peace in the Middle East. Ashrawi, founder and secretary general of the Palestinian Initiative for the Promotion of Global Dialogue and Democracy, has helped develop and create awareness of Palestinian culture. The 7:30 p.m. free lecture at Grant Hall is open to the public.

Missing girl returns home

A 14-year-old girl who was reported missing Oct. 20 has been located and is now back home. Kaitlyn Preston left her home at 7:30 a.m. that day to go to school at Holy [illegible]. She wasn't seen or heard from for three days until she was found Sunday. Police wouldn't divulge any further details about where she went or who found her.

Men in custody after robbery

Three men are in custody after the Erinsville General Store was robbed Sunday night. Police patrolling the area caught the fleeing suspects on County Road 41. Maurice Cleroux, 35, Henri Cleroux, 40, and Jeffery Jones, 34, have been charged with break and enter, possession of stolen property under $5,000 and possession of break-in tools.

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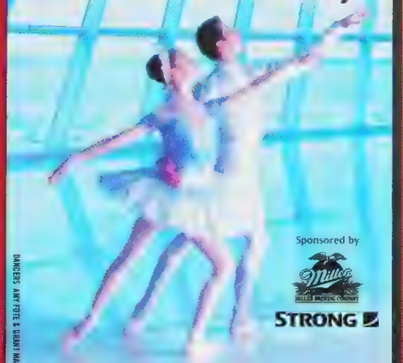

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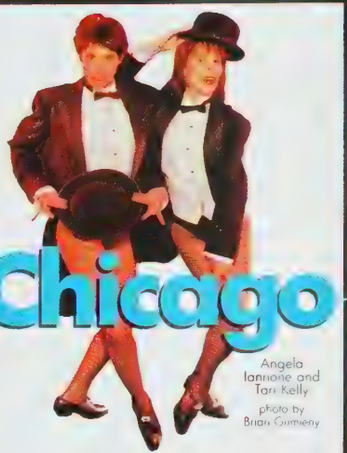

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Angela Iannone and Tari Kelly

photo by Brian Gurmeny

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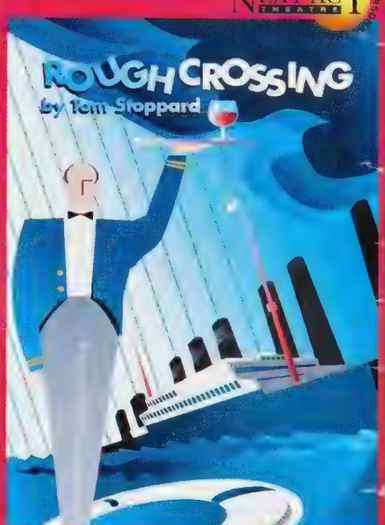

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2002-2003 SEASON

CORPORATE PROFILE

The family's culture

Story by Jordan Fox · Photography by Lila Aryan

When Helen Bader died in 1989, the former businesswoman and Milwaukee social worker left the bulk of her $100 million estate to charity. To her children she left her personal belongings — and most significantly — her legacy of dedicated social work.

"Throughout her life, she always strived to help people," says her son Dan Bader. "So when she died, we decided to create a charitable foundation in her name." The Helen Bader Foundation, now located in Milwaukee's Third Ward, opened its doors and its wallet in 1992 with Bader as president and CEO, positions that he still holds. Since it was established the foundation has awarded more than $102 million in grants.

Bader says the foundation annually awards $12 million to organizations representing their six special areas of interest, which include Alzheimer's Disease and dementia in Wisconsin; economic development and job creation in Milwaukee's inner city; education reform in Milwaukee; Jewish education in Milwaukee; early childhood development, primarily in Jewish and Arab communities in Israel; and the Sankofa-Youth Development Program, which creates a Milwaukee inner city environment that helps children develop "strong, caring hearts and minds."

"The quality of life in our hometown has been a central concern and we've supported over time innovative efforts to help less-privileged residents succeed in the face of the difficulties of life," he says.

"We try to be more than an organization that just gives money away," says Bader. "We try to be a catalyst, to be active in the community and find ways to further progress in our respective fields of interest."

"Milwaukee's past, present and future excite me," says Daniel Bader. "There are so many great ideas and projects here, so many energized people, so much talent devoted to improving things."

Raised in South Dakota, Helen Bader attended Downer College in Milwaukee and earned a degree in botany. She later met Alfred Bader, a chemist from Austria, and together they married, started a family and created the Aldrich Chemical Co.

"Later my mom went back to school, earned a master of social work degree at UWM and at age 40 became a social worker," Bader says. "Her field work with the Legal Aid Society involved helping many people in need, including single mothers and adults with mental illness. She also worked at the Milwaukee Jewish Home, where she became acquainted with the issues of aging. She specialized in the area of Alzheimer's Disease and had a great interest in working with older adults who were afflicted with some types of dementia.

"Our 18 staff members (compared to five when the foundation was created ten years ago) devote only about a third of their time reviewing grant applications," he explains. "The bulk of their time is spent on organizing the community, building coalitions, researching various topics and trying to develop special projects that will further the community."

Bader, who graduated from Hillel Academy and Riverside High School, holds a bachelor's degree in business administration from the Rochester Institute of Technology (in New York state) and has worked in high tech fields, including a position with a software development company in Madison. He's currently a partner in Granite Microsystems in Mequon, a company that manufactures custom-integrated computers and computer-related products.

A Milwaukee native, he and his brother David were raised by parents who, along with being astute business people, had "very giving" natures.

"They influenced us to be the same types of person. When I started working full time, Mom sat me down and encouraged me to give some of my salary to charity. She would suggest organizations for me to donate money or my time to

"My dad, who is 78, is no longer active in the chemical company. He now runs a local art gallery and continues to start and fund small businesses. He had been doing that from our living room when I was growing up and does that now from his office. We were always surrounded by people coming in and wanting to start new companies. That's been part of our culture. As a family, we are involved today in many small start-up companies."

Milwaukee? "It's a fabulous place to live. I've been lucky to have had the opportunity to travel around the country and the world and have seen many great cities. But I always truly love returning here. Milwaukee is a large city, with many wonderful cultural activities, but it's not too big. We've got the best of all possible worlds; it's a very manageable city."

The 41-year-old foundation executive is married to wife Linda and lives on the city's East Side with their two sons. "We're festival fans and go to as many as we can during our summers in Milwaukee. Every weekend we find something new to do, including the concerts in the parks."

rsvp

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Stephan Balkenhol, Two Male Heads, 1998. Two sculptures; painted wawa wood.

Eighth Benefit Art Auction

The Contemporary Art Society, a support group of the Milwaukee Art Museum, will sponsor the Eighth Benefit Art Auction on Saturday, Nov. 2. The auction is the primary fund-raising event for the museum's purchase of contemporary artworks. The auction includes work by Marsden Hartley, Roy Lichtenstein, Andy Warhol, Chuck Close, Jennifer Bartlet, Tony Ourseler, Tom Otterness and many more. The art is on exhibition through Nov. 2. The Live Auction takes place in the Lubar Auditorium. A silent auction and reception precede the event at 6:30 p.m., and dinner and dancing follow. Call in bids are accepted during the auction. Tickets are $250. For reservations call (414) 224-3815.

Baskets of Hope

Eisenhower Center Inc.'s 65th Annual Baskets of Hope Dinner and Auction will take place at Gu: International Deli on Thursday, Nov. 7 beginning at 5:30 p.m. A variety of exciting events include a Mexican buffet, dessert table, Restaurant Raffle, Midwest Express Raffle, a live auction hosted by Steve "The Homer" True and a silent auction. Proceeds will help support the Eisenhower Center, a non-profit organization for adults with cerebral palsy and other developmental disabilities. For tickets or further information contact Roselyn Smolej-Hill at (414) 353-8480.

Designer Fashion Show

The Vera Wang Collection will be presented in the Grand Ballroom at the Pfister Hotel on Monday, Nov. 18. All proceeds benefit the Milwaukee Symphony Orchestra. To receive an invitation call the League office at (414) 291-6010. Tickets run from $60 to $100 for the luncheon; $70 to $125 for dinner. Seating is first-come, first-served, with preference given to full patron tables.

Planning the show are (l-r) Carla Meyst, Heidi Martin, Bonny Hauser and Cynthia Dietz.

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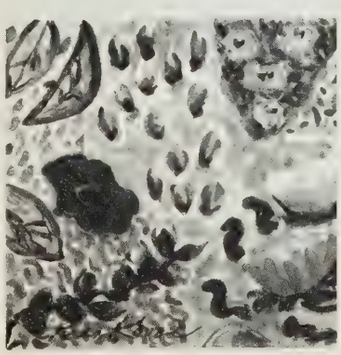

Artwork by Thea Kovac will appear in the fund-raiser.

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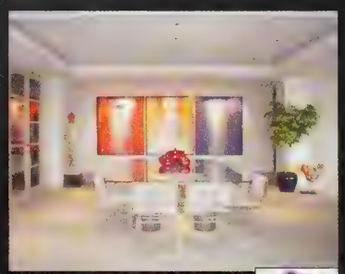

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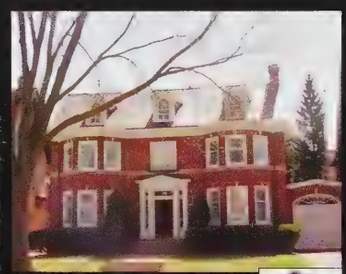

East Side: Center entrance red brick Classic. Oak floors, leaded glass, generous room sizes, stainless steel commercial style kitchen with butler's pantry. Lake views from the 2nd floor sitting room. Charming 3rd floor. 5 BR. #8460

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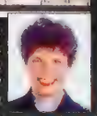

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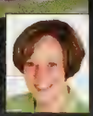

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CLIK

Photographer Tom MacDonald snapped the chic and lived to tell about it.

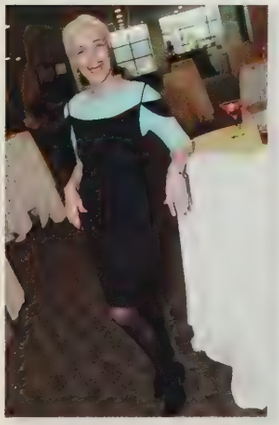
@ WAMI SHOW Potowatomi Northern lights Theater.

Stephanie Dosen
of Milwaukee

Stephanie designed the lace fabric black top she wears. Her jeans are Guess; shoes from New York. Her jewelry is handmade.

Terry T. Robinson
of Milwaukee

Terry dresses in a lilac suit from the House of Threads in Milwaukee. His shoes, also from the House of Threads, are by Torrence Ethel.



Mary Manion
of Milwaukee

Mary wears a French cut dress from Saks Fifth Ave. Her top — and jewels — are from Three Graces on Brady Street.

COVER STORY

Story by Judy Steininger
Photography by Doug Edmunds

Portrait of the Chemist as an Art Man

Renowned chemist, art collector and benefactor, his story fascinates.

Multi-millionaire Alfred Bader, Ph.D. shrugs, "I haven't bought a tie since Filene's (the Boston discount store) stopped selling them for 99 cents. I do keep one in the office closet, just in case."

He rummages in the closet for a moment then emerges with a grin. "Here it is."

"It" is a white tie emblazoned with the periodic table of the elements. That tie is the key to Bader and the company he co-founded.

MILWAUKEE LIFE Style MAGAZINES

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CITY LifeStyle
June 2003
Volume 3 • Number 7

Photo by Doug Edmunds

On the cover...

Judy Steininger broadly sketches the troubles and triumphs of Alfred Bader.

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62 **LEGACY**
A last look at lifestyles gone by.

Bader has a lot of money. Don't be impressed; he's not. As the co-founder of Aldrich Chemical, he is still the largest individual shareholder (about 5 percent ownership) in the merged company known as Sigma-Aldrich, NASDAQ symbol SIAL, market capitalization $3.2 billion dollars and revenues in excess of $1.1 billion.

With operations in 33 countries and 6,500 employees (3,600 of them in the U.S.), Sigma-Aldrich bills itself as the "world's leading supplier of high quality research chemicals and products for use in life science and high technology applications."

Bader is old, born in 1924, but he is not elderly. The black hair of his youth is partially gone and turned gray; never a tall man, he's even shorter now. His academic's posture and deliberateness make it easy to picture him puttering around a lab bench checking a stopcock here, looking for a pipette there. "I was very good in the lab, but by the 1960s the business was growing so large I had to leave it."

His doctorate is in organic chemistry from Harvard University. Where did he study business? "I think I took half a course in business one time, but I don't remember it."

How Bader came to Milwaukee and founded a company listed on the benchmark NASDAQ 100 Index is a history about war, refugees, prison camps, higher education, Horatio Alger and love. But Bader isn't ready to be a history lesson, yet.

Bader is obsessed with art; he fusses over it and shows it to clients like the curator of the London National Gallery. His latest office, occupied since 1992, is in the Alfred Bader Fine Arts Gallery, a former apartment in the Astor Hotel.

Bader's office, a former bedroom, contains a huge desk stacked with papers, bookshelves, and file cabinets; the walls are covered with letters and photos from Nobel Prize winning chemists like Robert Burns Woodward and Linus Pauling. One framed certificate is his Commander of the British Empire awarded by Queen Elizabeth in October of 1997. The dollar receipt for an early patent is yellowing in a black frame. A couple of Old Masters are propped on chairs.

In the other rooms, faded damask covered sofas and chairs, tired 1950s style formal draperies, and ubiquitous worn beige carpet can't diminish the tumble of Old Masters (large and small) hung on walls, propped against chairs, each other and stashed in cubicles.

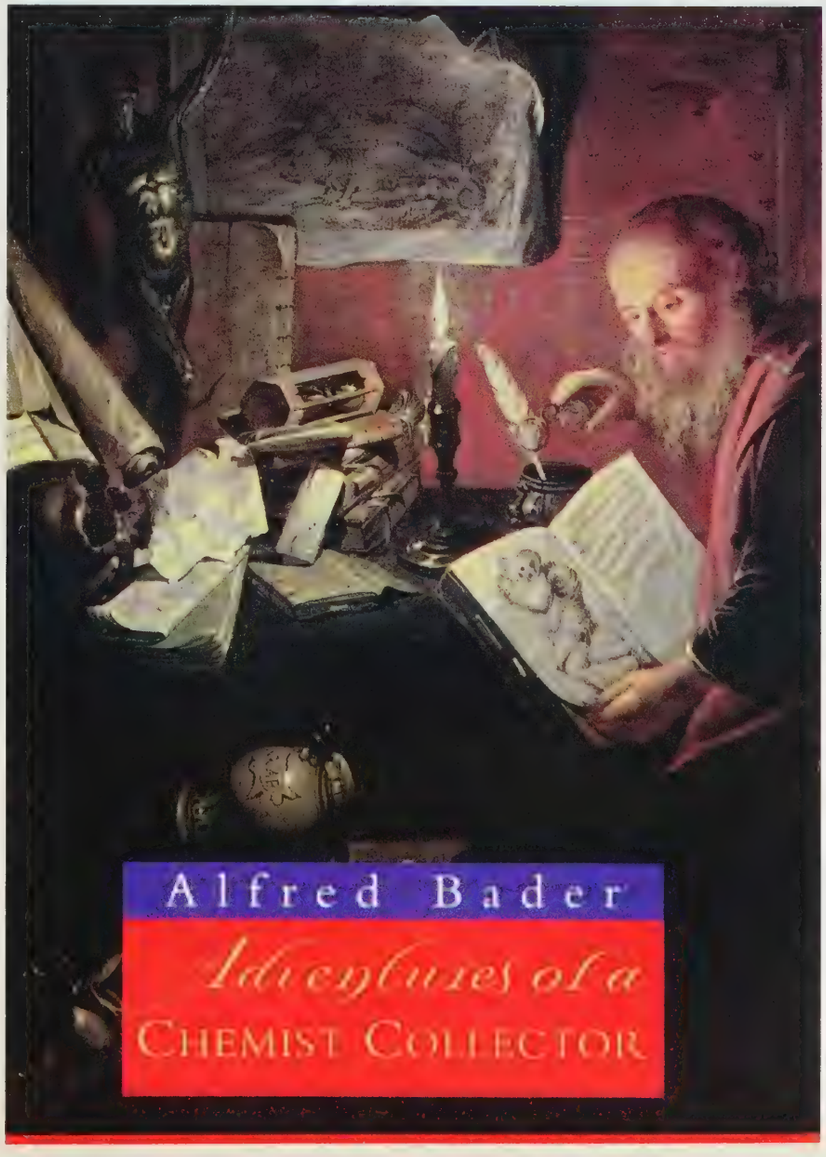
"I have some very important art here," Bader says softly and precisely with only a hint of an accent. "Every year I sell two or three hundred paintings."

He points out one small painting from the 1500s of Christ tortured by a crown of thorns and says with just a touch of sensitive humor, "I sold that to a stock broker; it's not been a good year for him." While many pieces sell in the high six figures, Bader points out he also has paintings from $100 and up; no one should feel intimidated to drop by.

That said, this disclaimer follows: if you're in the market for a Jackson Pollock, don't look here. His Web site (www.alfredbader.com) states, "We do not carry modern art, frankly, we don't understand it."

Since he left Sigma-Aldrich in 1992, the gallery has been Bader's full-time job. In the states and abroad he has a reputation as an Old Masters expert. He and his wife, Isabel, have been guest curators and written the introduction to catalogs for shows like the Milwaukee Art Museum's exhibit in 1989 titled "The Detective's Eye: Investigating the Old Masters." Bader frequents Europe for auctions and to practice his favorite of pastimes, rummaging old buildings looking at cobweb-coated, grime-encrusted paintings hoping to uncover yet another lost masterpiece. His personal collection is significant, with an emphasis on Rembrandt and his students. One piece, Rembrandt's "Old Man Wearing A Cap" is currently on loan to a museum in Frankfurt, Germany.

One of **Bader's** contributions to industry is his **introduction** of Old **Master paintings** as **covers** of **Aldrich's** chemical **catalogs and** annual **reports.**



Bader's autobiography, "Adventures of a Chemist Collector," features on its cover "The Alchemist" painted by David Ryckaert in 1648.

"The Alchemist" painting is symbolic of Bader, the man. An alchemist was a medieval scientist who attempted to change lead into gold. Bader has worked some alchemy in his own life and has, after some time, mobilized his fortune to do good. His childhood would not have been a predictor of wealth or happiness.

Bader was born in Vienna, Austria on April 28, 1924, to a Jewish father, Alfred Bader, and a Catholic mother, Elisabeth Serenyi. Bader's paternal grandfather, Moritz Ritter von Bader, a Viennese civil engineer, worked with Ferdinand de Lesseps to build the Suez Canal. His maternal grandparents were aristocracy: Count Johann Nepomuk Serenyi and Irma, Countess Dessewffy.

In 1912, after his mother's family tried to have her committed to an asylum rather than see her marry a Jew, Bader's parents eloped.

In 1924, two weeks after Bader was born, his father committed suicide or was murdered;

the historical details are murky. Shortly thereafter, an Aunt Gisela whom he refers to as "Mother" adopted him; Elisabeth remained his "Mama." Bader writes and talks lovingly about both of them. He places Elisabeth in the historical context of a young woman raised to be a lady, forced to be a widow with two small children and no way to care for them, facing the approaching storm of W.W.II, the economic maelstrom in Europe at the time, and what became known as the Jewish Problem.

Living with Mother in Vienna on Praterstrasse in a house he describes as "crammed with paintings, French rococo antique furniture and carpets" plus a villa in Baden sounds like something out of the movies. It all evaporated.

From the balcony of the apartment, the little boy Bader watched parades, including Adolf Hitler's in 1938. Bad investments, rampant inflation, and war soon forced the family to sell off its possessions and live in one room. Mother, prisoner #821, died in Theresienstdt concentration camp near Prague. Mama died of a stroke in 1948.

After the Nazi rampage, Kristallnacht, in November of 1938, the British granted 10,000 visas for Jewish children; Bader was one of the lucky ones. But in 1940, at the age of 16, he and all refugees between 16 and 65 living in England were put in detention centers. Months after living in tents surrounded by barbed wire, Bader, prisoner #156, and hundreds of others were put on the ship Dunera to be sent as POWs to camps in Canada.

And that is how Bader arrived in the New World. He was released from the Ft. Lennox prison on St. Helen's Island in the St. Lawrence River near Montreal into the care of a family. The boy who had pieced together an education in POW camps was denied entrance to McGill and the University of Toronto for lack of proper credentials. However, Queen's University, Kingston, Ontario did accept him and he began his studies, handicapped by starting halfway through the term. A B.Sc. in engineering chemistry, a B.A. in history and an M.Sc. in chemistry later, his gratitude to the university for admitting him is still being expressed in gifts: numerous works of art, a $6 million dollar 500-seat theater donated to Victoria University to "show his love and admiration for his wife Isabel" and $10 million to purchase and maintain a 140-room, 15th century castle in Sussex, England, home of the Astronomer Royal. Read and weep, McGill and Toronto.

From Queens, he was off to Harvard University where he earned an M.A. and Ph.D. in Chemistry.

He came to Milwaukee in 1950, as a chemist with Pittsburgh Plate Glass (PPG). Some of Bader's early work produced patents worth millions of dollars. PPG eventually left the city, but by then Bader and Jack Eisendrath had started a company selling research chemicals. "We incorporated on Aug. 17, 1951, each putting in $250. We tossed up (a coin) for the name; I lost the toss. Jack was engaged to a charming girl, Betty Aldrich, and the company was named the Aldrich Chemical Company."

Bader is candid about his personal life in his autobiography. Milwaukeeans are familiar with his first wife Helen, in large part through the Helen Bader Foundation, a very generous benefactress to the city and throughout the world. Bader and Helen have two sons, Daniel, the director of the foundation which grants on average $10 million a year, and David, an architect living in Pennsylvania.

He has five grandchildren.

Bader and Helen were divorced in 1981; she died in 1986.

After the divorce, Bader married Isabel Overton, a Canadian living in England whom he had known decades earlier.

Of all **my** jobs **giving** away **money** **is** the **hardest.**

Isabel and he are inseparable: traveling, writing art catalogs, and translating German articles into English. Along with their modest East Side home, they retain the small house in England where she used to live.

In his gallery at the Astor, Bader is content. From this control central he gives away millions of dollars a year, deals in art, corresponds with scientists and friends around the world, and plans his next art buying adventure, accompanied by Isabel, of course. "Of all my jobs giving away money is the hardest. Every year Isabel and I sit down at tax time and figure out our income, then we give away half of it. I like to give to the American Joint Distribution Committee, a Jewish group that helps people all over the world. Right now I'm helping them help the Romas or gypsies in Eastern Europe. I think the Quakers are wonderful people and I help with their work in Africa. One of Isabel's ancestors started the Salvation Army and every year I live I add a thousand dollars to my contribution to them."

He muses on his unusual life: "In the beginning I was too frugal;" or "The key to business is always treat your people, customers and suppliers well," and "Politically, I am a Socialist at heart, but I know it doesn't work — people need the money incentive."

What does the future hold? "I love what I do and as long as the good Lord gives me strength and my wonderful wife Isabel, I will keep doing it."

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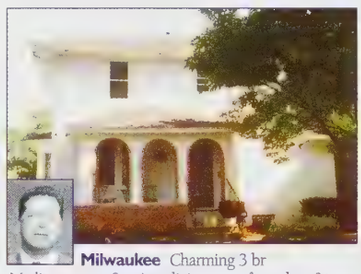

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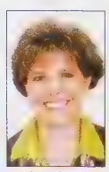

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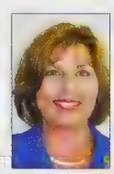

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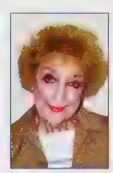

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provides work, promotes tolerance
From: <dan@hbf.org>
Date: Thu, 14 Oct 2004 16:26:40 -0400
To: <baderfa@execpc.com>

Ann, Please print this out for Dad. Thanks Daniel Bader

Following is an article from JTA — The Global News Service of the Jewish People. For in-depth coverage of the latest developments affecting Jews all over the world, click: www.jta.org

In Bosnia, a philanthropist's gift
provides work, promotes tolerance
By: Ruth Ellen Gruber

BANJA LUKA, Bosnia and Herzegovina, Oct. 13 (JTA) — Bojana Vukotic looks up from her computer and for the first time in her 28 years has a conversation in English, a language she learned from watching movies.

A bright woman with short hair, Vukotic describes her life at a unique print shop operation designed to help disabled people like herself conduct their lives in dignity.

Vukotic and about 50 co-workers live and work at the Distroficara Institution printing works, believed to be the only facility of its kind in a country struggling to rebuild in the wake of a devastating war.

Like most of the employees, Vukotic suffers from muscular dystrophy; her muscles are atrophied and her arms are semi-paralyzed. She shares a rent-free room with another worker and earns the equivalent of $100 a month, out of which she must pay utilities and other expenses.

"It was difficult to get into this place, but it is the best we can get," she tells Yechiel Bar Chaim, the American Jewish Joint Distribution Committee's country director for Bosnia.

If it weren't for this print shop, she says, she doubts she would have a job.

No one at the plant is Jewish. But now, thanks to a grant from a Jewish Holocaust survivor that was channeled through the JDC, the facility will replace a 40-year-old print machine, upgrade at least some of its computers and make it easier for its workers to live productive lives.

"Meeting Bojana and hearing about her struggle ripped me up inside," said Bar Chaim, who visited the facility in September to inspect conditions and formalize the grant.

Her wages are modest, but in a country where many able-bodied persons have no work whatsoever, "Bojana's ability to cover many of her expenses by the fruit of her own labor should be seen, it seems to me, as a true source of pride and satisfaction," Bar Chaim told JTA.

"The whole point of the project is to help Bojana and her fellow workers to use their abilities and remain as self-reliant as possible."

During the Bosnian War in the early 1990s, the Jewish community emerged as one of the key conduits of nonsectarian aid to society at large, regardless of religion or ethnicity.

Nonsectarian grants such as the one at the printing facility continue that tradition and underscore core civic values of integration and tolerance.

"What the Jewish community says is that we live in a reality in which we are integrated into the general population," Bar Chaim said. "There is no way in a crisis that we can just help ourselves."

Banja Luka's 70-member Jewish community will benefit too: Its leaders identified the print shop as an appropriate target for a grant and will receive a small part of the allocation both for its work in setting up the project and for helping to oversee its implementation on behalf of the JDC.

The only condition is that the print shop will publish an ecumenical calendar taking note of the symbols and primary institutions of Catholics, Orthodox Christians, Muslims and Jews in the Banja Luka area.

"That won't be easy where the Jews are concerned," Bar Chaim said. "There is no synagogue left standing in Banja Luka and the old Jewish cemetery was turned into tennis courts under the former communist regime."

Historic mosques, too, were destroyed by Serb forces during the Bosnian War.

The grant to the Banja Luka print shop and a number of other nonsectarian, JDC-coordinated projects in Bosnia and elsewhere have been made possible by generous donations from Alfred Bader, 80, a successful chemist and art collector and dealer in Milwaukee.

Through the JDC and other channels, Bader has donated millions of dollars to institutions and individuals in Israel, the United States and Europe. Much of the funding is earmarked for Jewish communal projects or institutions, but a significant part is directed to individuals or projects in society at large.

"To put it into a nutshell," Bader told JTA in an e-mail, "my wife and I try to help the neediest and the ablest."

For example, he said, "Year after year we have given substantial funds to help the Roma," or Gypsies, "this through the JDC. You must know how miserably the Roma were treated by the Nazis but haven't been compensated as we have been, because few people have spoken up for them."

Bader's life story influenced his decision to use philanthropy to fight injustice.

Born in Vienna, he escaped the Nazis on a Kindertransport to England at age 14. Two years later, he was imprisoned by the British government as an "enemy alien" and deported to an internment camp in Canada.

After the war, he did a doctorate in chemistry at Harvard and founded the Aldrich Chemical Company, which eventually became Sigma-Aldrich, the 50th largest chemical company in the United States. He also has developed a "second career" as an art collector, gallery owner, curator and lecturer.

Bader, whose son Daniel is on the JDC board of directors, said a "good deal" of his donations, both for Jewish communal and nonsectarian projects, are channeled through the JDC. The funds include a roughly $1 million general endowment, as well as targeted grants.

He said he likes giving through the JDC because he trusts the judgment of field staff such as Bar Chaim in locating worthy projects.

Other projects Bader has financed in Bosnia include home care for 670 elderly Serbs, Croats, Muslims and Jews in Sarajevo and five provincial cities, and a

country-wide breast cancer support and awareness initiative.

He also backs the manufacture of so-called "Bader Vests" — sweaters knitted by paraplegics and other handicapped persons in Sarajevo and then distributed to the home care recipients.

His funds also are used to buy ceramic-making equipment to provide light employment for severely retarded youth and young adults in Mortar. Like the calendar in Banja Luka, the ceramic artifacts are to feature the symbols of the four religions.

Bader likes to say that his professional life falls into four categories — art, Bible, chemistry and philanthropy.

"Of these, the fourth, giving money away sensibly, is the hardest," he told JTA. "Luckily, we have very good people to help us."

Dear Ms. Gruber,

Thank you for that wonderful write-up! I only have one very minor correction: Sigma-Aldrich is the 50th largest chemical company in the US, not the 80th.

With many thanks and best wishes,
Alfred Bader

Ruth Ellen Gruber wrote:

> Dear Dr.Bader --
>
> Here, FYI, is my story for JTA. It is being sent with a photo of the young woman, Bojana Vukotic, speaking with Yechiel. FYI I've also sent it to Yechiel.
>
> All the best
>
> Ruth Gruber

Yechiel --

Please check this. If it looks OK I'll send a copy to Dr. Bader.

ruth

Banja luka 10-10
From Ruth Ellen Gruber
BANJA LUKA, BOSNIA AND HERZEGOVINA
(JTA) -- Bojana Vukotic looks up from her computer and for the first time in her 28 years has a conversation in English, a language she learned from watching movies.

A bright woman with short-cut hair, Vukotic describes her life at a unique print shop operation designed to help handicapped people like herself conduct their lives in dignity.

Vukotic and about 50 co-workers both live and work at the Distroficara Institution printing works, believed to be the only facility of its kind in a country struggling to rebuild in the wake of the devastating Bosnia War.

Like most of the other employees, Vukjotic suffers from muscular dystrophy. Her muscles are atrophied and her arms are semi-paralyzed. She shares a rent-free room with another worker and earns the equivalent of $100 a month, out of which she must pay all utilities and other expenses.

"It was difficult to get into this place, but it is the best we can get," she tells Yechiel Bar Chaim, the American Jewish Joint Distribution Committee's country director for Bosnia.

If it weren't for this print shop, she says, she doubts if she would have a job.

No-one at the plant is Jewish.

But now, thanks to a grant from a Jewish Holocaust survivor and channeled through the JDC, the facility will replace a 40-year-old print machine, upgrade at least some of its computers, and make it easier for its workers to live productive lives.

"Meeting Bojana and hearing about her struggle ripped me up inside," said Bar Chaim, who visited the facility in September to inspect conditions and formalize the

grant.

"Although her wage is very modest (in a country where many able-bodied persons have no work whatsoever), Bojana's ability to cover many of her expenses by the fruit of her own labor should be seen it seems to me as a true source of pride and satisfaction," Bar Chaim told JTA. "The whole point of the project is to help Bojana and her fellow workers to use their abilities and remain as self-reliant as possible."

During the Bosnian War in the early 1990s, the Jewish community emerged as one of the key conduits of non-sectarian aid to society at large, regardless of religion or ethnicity.

Non-sectarian grants such as the one in Banja Luka continue this tradition and underscore core civic values of integration and tolerance.

"What the Jewish community says is that we live in a reality in which we are integrated into the general population," Bar Chaim said. "There is no way in a crisis that we can just help ourselves. What JDC is affirming actually comes from Hillel. To put it in modern terms, 'If we can look after our own, we should be able to assist others in need as well.'"

Banja Luka's 70-member Jewish community will benefit too. Its leaders identified the print shop as an appropriate target for a grant and will receive a small part of the allocation both for its work in setting up the project and to enable it to oversee its

implementation on behalf of the JDC.

The only condition is that the print shop will publish an ecumenical calendar taking note of the symbols and primary institutions of Catholics, Orthodox Christians, Muslims, and Jews in the Banja Luka area.

"That won't be easy where the Jews are concerned," said Bar Chaim. "There is no synagogue left standing in Banja Luka and the old Jewish cemetery was turned into tennis courts by the former communist regime." Historic mosques, too, were destroyed by Serb forces during the Bosnian War.

The grant to the Banja Luka print shop and a number of other non-sectarian JDC-coordinated projects in Bosnia and elsewhere have been make possible by generous donations from Dr. Alfred Bader, 80, a successful chemist and art collector and dealer based in Milwaukee.

Through the JDC and other channels, Bader has donated millions of dollars to institutions and individuals in Israel, the United States and Europe. Much of this funding is earmarked for Jewish communal projects or institutions, but a significant part is directed to individuals or projects in society at large.

"To put it into a nutshell," Bader told JTA in an email, "my wife and I try to help the neediest and the ablest."

For example, he said, "Year after year we have given substantial funds to help the Roma, this through the JDC. You must know

how miserably the Roma (Gypsies) were treated by the Nazis but haven't been compensated as we have been, because few people have spoken up for them."

Bader's life story has influenced his decision to use philanthropy to fight injustice.

Born in Vienna, he escaped the Nazis on a *Kindertransport* to England at the age of 14. Two years later, he was imprisoned by the British government as an "enemy alien" and deported to an internment camp in Canada.

After the war, he went on to take a doctorate in chemisty at Harvard and later found the Aldrich Chemical Company, which eventually became Sigma-Aldrich, the 80th largest chemical company in the United States. He has also developed a "second career" as an art collector, gallery owner, curator, and lecturer.

Bader, whose son Daniel is on the JDC board of directors, said a "good deal" of his donations, both for Jewish communal and non-sectarian projects, are channeled through the JDC. These funds include a roughly $1 million general to endowment as well as targeted grants.

He said he likes giving through the JDC because he trusts the judgement of field staff such as Bar Chaim in targeting worthy projects.

Other projects in Bosnia financed by Bader, for example, include homecare for 670 elderly Serbs, Croats, Muslims, and Jews in Sarajevo and five provincial cities and a

country-wide breast cancer support and awareness initiative.

He also backs the manufacture of so-called "Bader Vests" -- sweaters knitted by paraplegics and other handicapped persons in Sarajevo and then distributed to the homecare recipients.

His funds also go to an investment in equipment for making ceramics to provide light employment to severely retarded youth and young adults in Mostar. Like the calendar in Banja Luka, the ceramic artifacts are to feature the symbols of the four religions.

Bader said that sometimes he did not know whether to call a contribution "sectarian" or not.

"We have given hundreds of thousands of dollars to a wonderful woman in Jerusalem, Adina Shapiro, to help MECA, the Middle East Children's Association, which brings together Israeli and Palestinian teachers to talk to each other," he said. "Is that sectarian? Those funds have not gone through the JDC, but through the Foundation for the Jewish Community."

And, he added, "Are our gifts of $36,000 a year through the JDC to the Quakers sectarian or not? I came to England on a Kindertransport and of the 10,000 or so children that arrived in England as Kinder, almost half were looked after by Quakers without their in any way trying to convert these children. At the time there were 18,000 Quakers in Britain and 300,000 Jews. Need I say more?"

Bader likes to say that his professional life falls into four categories -- art, Bible, chemistry and philanthropy.

"Of these the fourth, giving money away sensibly, is the hardest," he told JTA. "Luckily, we have very good people to help us."

endit

--

Ruth Ellen Gruber
author of:
Virtually Jewish: Reinventing Jewish Culture in Europe
University of California Press

National Research Council Canada

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Canadian Journal of Chemistry

Revue canadienne de chimie

Volume 84, Number 10, October 2006

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Special Issue
Dedicated to Dr. Alfred Bader

Numéro spécial
Dédié à Alfred Bader

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Page couverture : Tête d'un vieil homme par Rembrandt Harmensz. van Rijn, vers 1630, huile sur panneau. Collection de l'Agnes Etherington Art Centre, Université Queen's, Kingston, Canada. Don d'Alfred et Isabel Bader, 2003. 46-031.

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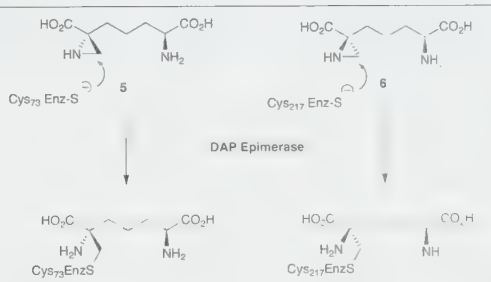

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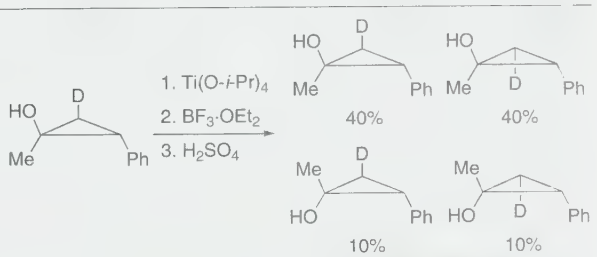

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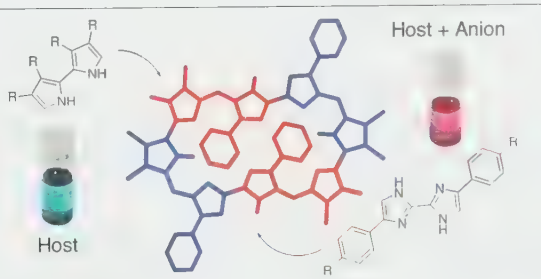

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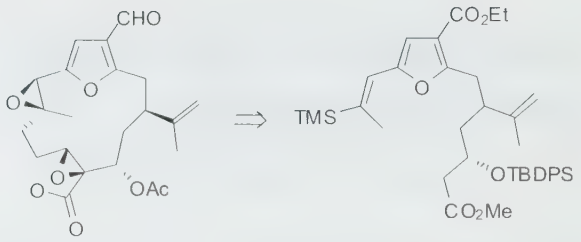

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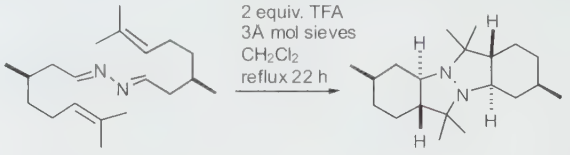

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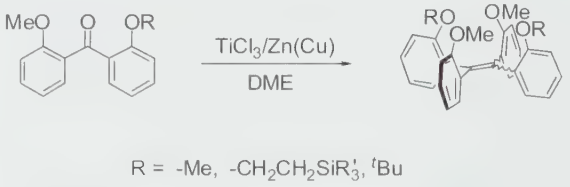

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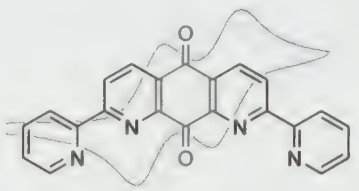

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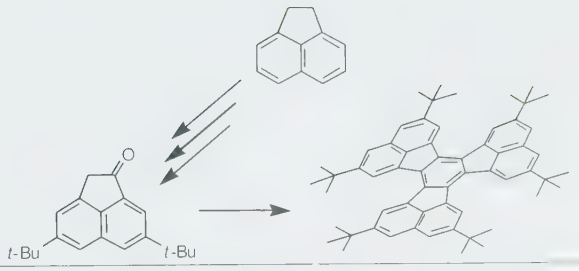

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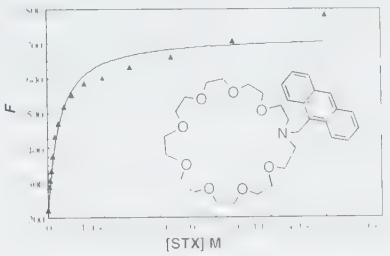

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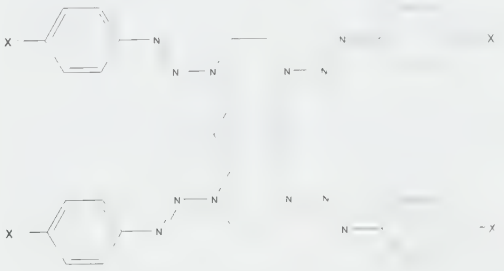

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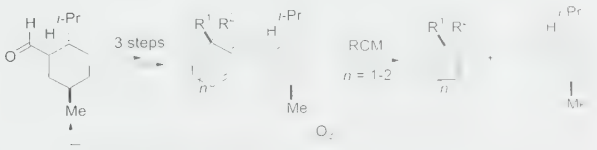

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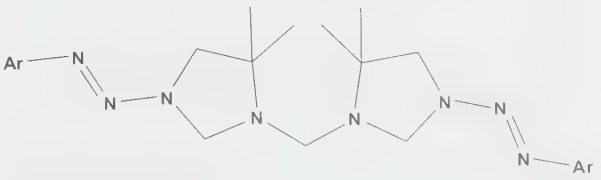

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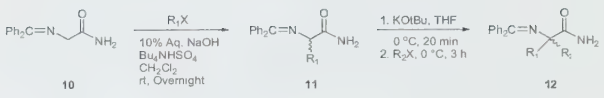

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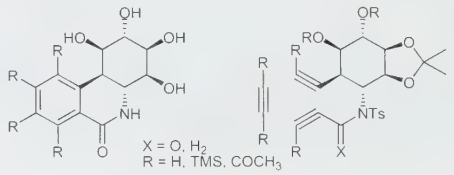

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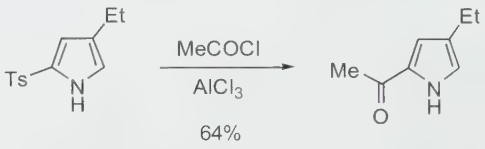

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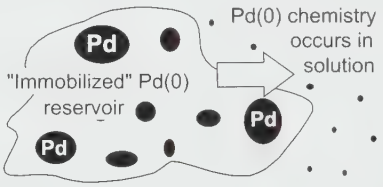
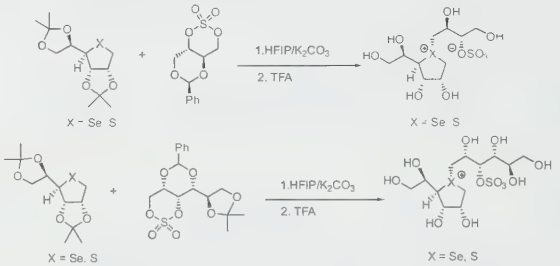


Design and synthesis of selenonium and sulfonium ions related to the naturally occurring glucosidase inhibitor salacinol

Hui Liu and B. Mario Pinto

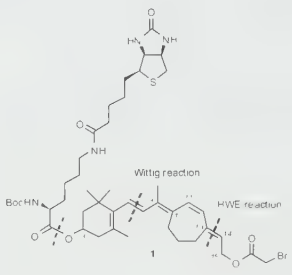
1351–1362



Synthesis of an 11-*cis*-locked biotinylated retinoid for sequestering 11-*cis*-retinoid binding proteins

Hiroko Matsuda, Shenglong Zhang, Andrea E. Holmes, Sonja Krane, Yasuhiro Itagaki, Koji Nakanishi, and Nasri Nesnas

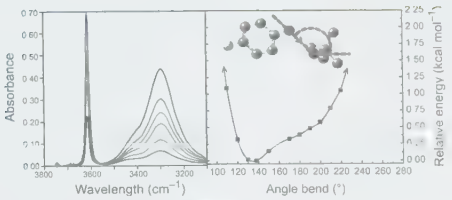
1363–1370



A theoretical and experimental investigation of some unusual intermolecular hydrogen-bond IR bands — Appearances can be deceptive

Grzegorz Litwinienko, Gino A. DiLabio, and K.U. Ingold

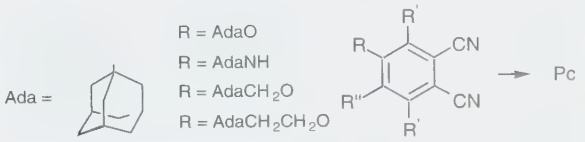
1371–1379



Syntheses and characterization of phthalonitriles and phthalocyanines substituted with adamantane moieties

Patrick W. Causey, Igor Dubovyk, and Clifford C. Leznoff

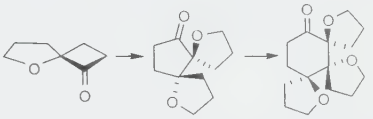
1380–1387



Synthesis and Lewis acid induced isomerization of mono-, di-, and tri-spiro α-keto tetrahydro-furans and -pyrans

David G. Hilmey, Peter R. Selvaraj, and Leo A. Paquette

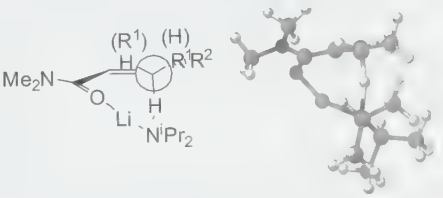
1388–1396



Deprotonation of β,β-disubstituted α,β-unsaturated amides — Mechanism and stereochemical consequences

James R. Green, Marek Majewski, and Victor Snieckus

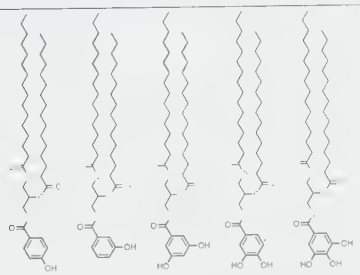
1397–1410



Synthesis and characterization of a series of novel phenol- and polyphenol-based glycerolipids

Rolf Schmidt, Joseph G. Carrigan, and Christine E. DeWolf

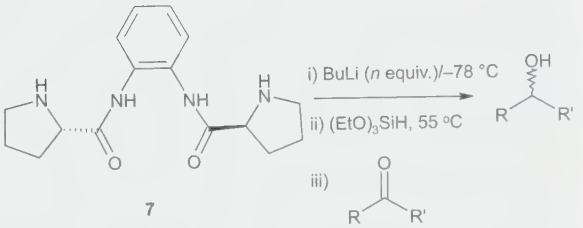
1411–1415



Hydrosilylation of ketones catalyzed by C_2-symmetric proline-derived complexes

Li Gan and Michael A. Brook

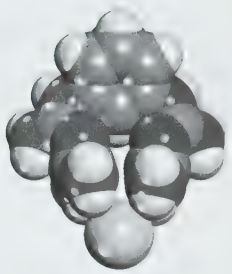
1416–1425



Hydrogen-bonded networks in crystals built from bis(biguanides) and their salts

Olivier Lebel, Thierry Maris, and James D. Wuest

1426–1433



Triazene derivatives of (1,*x*)-diazacycloalkanes. Part VII. Synthesis of a series of 1-aryl-2-[3-(3-[2-aryl-1-diazenyl]-1,3-diazepan-1-ylmethyl)-1,3-diazepan-1-yl]-1-diazenes from the reaction of diazonium salts with mixtures of formaldehyde and 1,4-diaminobutane

Reid Tingley and Keith Vaughan

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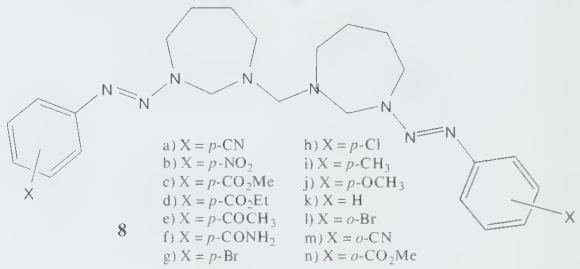

In situ nitrosonium ion generation — α-Oximinylation of enol ethers from steroidal spiroketals: Introduction of C23 (*R*)-OH in cephalostatin intermediates

Seongmin Lee and Philip L. Fuchs

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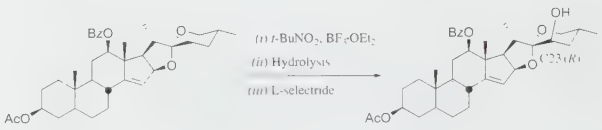
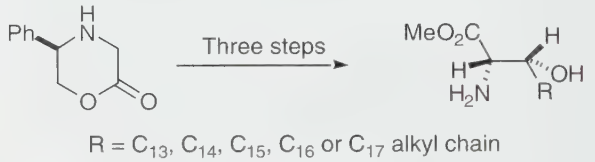


Preparation of enantiopure long chain *threo*-2-amino-3-hydroxyesters via chiral morpholinone-derived azomethine ylids

Victoria A. Brome, Laurence M. Harwood, and Helen M.I. Osborn

1448–1455



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Michael Harmata, Paitoon Rashatasakhon, and Charles L. Barnes

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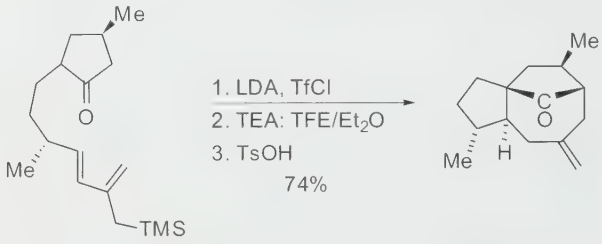
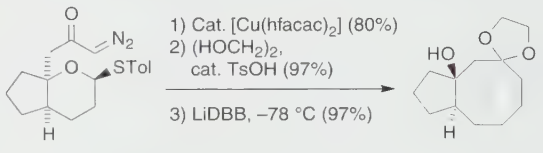


Polycyclic oxonium ylides — Use of cyclic acetals as convenient scaffolds in the construction of fused bicyclic compounds containing a medium ring

Graham K. Murphy, Fredrik P. Marmsäter, and F.G. West

1470–1486



An examination of VANOL, VAPOL, and VAPOL derivatives as ligands for asymmetric catalytic Diels–Alder reactions

Douglas P. Heller, Daniel R. Goldberg, Hongqiao Wu, and William D. Wulff

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This special issue is dedicated to

Dr. Alfred Bader

on the occasion of his 80th birthday

Associate Editor: Victor A. Snieckus

Le présent numéro est dédié à

Alfred Bader

à l'occasion de son 80e anniversaire de naissance

Directeur scientifique associé : Victor A. Snieckus

Dr. Alfred Bader

BIOGRAPHY / BIOGRAPHIE

Born in Vienna, Alfred Bader fled to England at the age of fourteen, ten months before the outbreak of World War II. Although a Jewish refugee from the Nazis, he was interned in 1940 along with other 'enemy aliens', and sent to a Canadian prisoner of war camp.

Today, Dr. Bader is one of the most respected men in his field. In this heartwarming book, he tell the fascinating story of how he made good in the land of opportunity, the United States.

It was a case of hard study and hard work. Obtaining release in 1941, he was accepted at Queen's University in Kingston, Ontario, where he studied engineering chemistry. There followed a fellowship in organic chemistry at Harvard. He worked in Milwaukee as a research chemist for the Pittsburgh Plate Glass Company and in 1951 co-founded Aldrich, which today, as Sigma-Aldrich, is the world's largest supplier of research chemicals.

He spent forty years building Aldrich's distinctive reputation and the extraordinary story of how he was eventually thrown off the board of Sigma-Aldrich will be of key interest to people in the chemical industry worldwide, as well as to students of business.

After leaving Sigma-Aldrich, he continued a fruitful career as an art collector and dealer, and he has some very pertinent and amusing things to say about his experiences in the art world.

Alfred Bader and his family have earned a reputation as generous benefactors, notably in the fields of chemistry, education, and Jewish interests. Dr. Bader's personal philanthropy has been particularly directed towards helping students of chemistry and art history. He recently gave £6,000,000 to Queen's University to purchase and renovate Herstmonceux Castle in Sussex (the home of the old Royal Greenwich Observatory) – one more 'thank you' to the Canadian institution that had enabled him to take the first step on the road to success, so entertainly described in this book.

(Alfred Bader, Adventures of a Chemist Collector. Weidenfeld & Nicolson, London, 1995)

Né à Vienne, Alfred Bader s'enfuit en Angleterre à l'âge de 14 ans, dix mois avant qu'éclate la Seconde Guerre mondiale. Réfugié juif des nazis, il est quand même interné en 1940 avec d'autres « ressortissants de pays ennemis » et déporté au Canada dans un camp de prisonniers de guerre.

Aujourd'hui, Bader figure parmi les plus respectés de son domaine. Dans ce récit attachant et émouvant, il retrace les événements qui lui ont permis de faire sa marque dans un pays d'avenir, les États-Unis.

C'est l'histoire d'un solide engagement envers les études et de persévérance. Libéré en 1941, il étudie le génie chimique à l'Université Queen's. Il fait un stage postdoctoral en chimie organique à Harvard. Il travaille à Milwaukee à titre de chimiste de recherche pour la *Pittsburgh Plate Glass Company*. En 1951, il cofonde l'*Aldrich Chemical Company*, aujourd'hui la *Sigma-Aldrich Corporation*, le plus important fournisseur de substances chimiques employées dans la recherche du monde entier.

Malgré le fait qu'il consacre quarante ans de sa vie à cultiver la réputation d'excellence d'Aldrich, il se fait exclure du conseil de Sigma-Aldrich, une histoire qui est sfre d'intéresser tous les intervenants de l'industrie, sans compter les étudiants en administration.

Il quitte donc Sigma-Aldrich pour poursuivre une carrière fructueuse en tant que collectionneur et marchand d'Éuvres d'art. Il a d'ailleurs des anecdotes fort amusantes et très pertinentes à raconter à propos de ses expériences dans l'univers des arts.

La très grande réputation de bienfaisance et de bonté d'Alfred Bader et de sa famille, notamment au profit de la chimie, de la pédagogie et de la culture juive, n'est plus à démontrer. Parmi les plus importants bénéficiaires de leur générosité figurent les étudiants en chimie et en histoire de l'art. Un autre grand bénéficiaire de la philanthropie des Bader est l'Université Queen's, qui s'est vu remettre la somme de 6 000 000 £ pour acquérir et rénover le château Herstmonceux, B Sussex (le site de l'Observatoire royal de Greenwich) – une autre façon de « remercier » l'établissement canadien qui lui a permis de faire un premier pas vers la réussite, tel que décrit de manière si divertissante dans cet ouvrage.

(Alfred Bader, Adventures of a Chemist Collector. Weidenfeld & Nicolson, Londres, 1995)

TRIBUTE / HOMMAGE

It is a great privilege and honour for us to write the dedication for this Special Issue honouring Alfred Bader. Alfred Bader, a true visionary, has had a profound effect on the way chemists do research. But Alfred Bader's influence is much broader than chemistry as he is an entrepreneur, businessman, art collector, Rembrandt expert, and philanthropist.

Throughout his childhood and teenage years Alfred faced great adversity. He was born in Vienna in 1924 and two weeks after his birth, his father died. In November 1938 following the anti-Jewish demonstrations on Kristallnacht, Alfred's mother sent him to the U.K. He lived in Sussex and entered Brighton Technical College in 1939. In May 1940, the British government, given the escalating conflict with Germany, arrested German and Austrian males including Alfred and put them in internment camps. The Canadian government agreed to accept custody of some of the interned individuals comprising prisoners of war and strongly anti-Nazi refugees as well as German civilians. Alfred Bader was one of those interned in Canada and was sent to a fortress on an island on the Richelieu River near Lake Champlain. While there, he and some others were determined to continue their education and Alfred passed both the Junior and Senior Matriculation exams before being released in 1941. Bader applied to several universities and was accepted by Queen's University in Kingston. Alfred enjoyed his studies at Queen's and to earn money to continue university and go on dates, he worked at Murphy Paint Company in Montreal on the formulation of enamels and lacquers. There, he also learned to appreciate industry and entrepreneurship.

Bader recognized the need for a research chemicals business while he was a graduate student at Harvard working with Louis Fieser, a leading organic chemist. At that time nearly all chemicals came from Eastman Kodak, which had a product list of 4000 chemicals. Although others tried to discourage him, Alfred persevered and together with a friend, Milwaukee attorney Jack Eisendrath, incorporated Aldrich Chemical Company on August 17, 1951, each putting up $250. The first home of Aldrich was a garage they rented for $25 per month. They were two part-time employees, their catalogue was a mimeographed sheet with one offering, and sales in the first year was $1705.

The company moved to 1000 square feet of rented space where Bader single handedly carried out all the syntheses. In 1955 Aldrich expanded into medicinal chemistry, which gave Alfred tremendous satisfaction. Alfred's hard work and determination paid off and by 1958 they had a staff of 12 and purchased a three-story building. What was so impressive was the commitment by Alfred to deliver chemicals in a highly efficient manner. It was clear by then that Bader's vision and integrity coupled with his determination and dedication would lead to a highly successful career.

The company continued to grow at a tremendous rate and by 1962 had sales of one million dollars, up from $5,400 a decade earlier. In 1990, Aldrich merged with Sigma to become Sigma-Aldrich, the 80th largest corporation in the US, employing over 4,000 people with subsidiaries in many European countries, Israel, and Japan. After serving as Chair of the Board from 1980 to 1991 he "officially retired" but became chairman emeritus.

One of Bader's key recommendations to those building a business is "listen carefully to your customers". This personal approach was the cornerstone of Alfred's success. The trademark Aldrich advertisement had a picture of Alfred with the heading "Please Bother Us". He and his wife Isabel travelled tirelessly to laboratories throughout North America and around the world where he listened attentively to problems chemists were having with syntheses and offering advice and proposing solutions. Bader comments in his book *Adventures of a Chemist Collector* "Although all of our visits to universities begin in the hope of getting to know our customers and perhaps finding exciting new compounds, they often become pure personal pleasure for Isabel and me". My (Anne's) first encounter with Alfred Bader was in 1966, discussing with him over breakfast in the Windsor Hotel in Montreal, the possibility of making a diazo compound in larger quantities than the few mg I had amassed after a lengthy process. The research went in another direction and Aldrich did not make the compound but I will never forget my first meeting with Alfred and Howard's and my good fortune in getting to know Alfred and Isabel in the years following.

Bader's vision and accomplishments go far beyond chemistry and the chemicals business. Bader calls himself an "inveterate collector" beginning with stamps at 8, drawings at 10, and paintings at 20. When Alfred was a child in Vienna his mother's apartment was filled with paintings, 19th and 20th century Viennese works. He knew he did not like these but became very interested in painting. Bader has been buying selling, trading, and giving away paintings for many years. When Aldrich was on a firm footing and he could give a little more time to what he calls an enjoyable pastime, he established Alfred Bader Fine Arts and since 1992 has devoted more and more of his time to it. Although he now trades in very expensive art including works by Rembrandt and Rubens, he always considered it much more fun to pay a few thousand dollars for a work that might prove great and valuable after cleaning. He loves discoveries not only of material value but also of great beauty. Bader has shared his love of paintings with others. On his visits to universities and at every Aldrich exhibit booth, he distributed prints of some of the paintings in his vast collection Chemists will remember the Alchemist well and each year a painting appeared on the cover of the Aldrich catalog. He thus served a very important role in art appreciation for the chemical community

In addition to Bader's impact on chemistry and his contributions to art collecting, art history, and art conservation, his generosity of spirit will leave a lasting impact. He gives back to the discipline of chemistry, to Queen's University that accepted him when other universities did not, and to other institutions and foundations. It started with small no strings attached grants to chemists in need of funding around the world. Many of these have become internationally recognized scientists. He has established prizes, scholarships, and awards for students in Canada, the United States, Britain, and the Czech Republic recalling the benefit such awards provided him when he was a student. He established the Alfred Bader Award in Organic Chemistry for the American Chemical Society (now known as the Aldrich award) and the Canadian Society for Chemistry and the Royal Society of Chemistry in the UK. More recently he endowed the ACS Alfred Bader Award in Bioinorganic or Bioorganic Chemistry and supported the ACS Project Seed to enable undergraduate chemistry students to experience laboratory work.

Bader's donations to Queen's have included: Chairs in Organic Chemistry and Art History, outstanding paintings from his collection for the Agnes Etherington Art Centre, and seed money for a new museum. Bader Lane at Queen's connects the Chemistry Building with the Agnes Etherington Art Centre. Perhaps the most unusual gift to Queen's has been Herstmonceux Castle, a moated castle in Sussex England parts of which date from the 15th century. In addition, Bader has supported many Jewish educational projects and set up charitable foundations in Milwaukee.

Alfred Bader has been recognized for his work by a number of Honorary Doctorates from different universities including Simon Fraser University and the University of Ottawa, an honorary Fellowship in the Royal Society of Chemistry, and the ACS Charles Lathrop Parsons Award, given in recognition of outstanding public service by a member of the ACS. He is also a Honorary Fellow of the Chemical Institute of Canada.

Another facet of Alfred, and Isabel, is their remarkably intense romantic relationship. Several years ago, a new book was published by Isabel entitled "A Canadian in Love". It contains some beautifully composed letters by Isabel to Alfred and at the end of the book, a letter from Alfred to Isabel dated April 18, 1975. One paragraph in the letter states:

"You had not written to me from September 11, 1950 until August 11, 1951, your last letter to me for 24 years. I have read that letter so often that I know it by heart and it has torn me apart these many years. What power you have over me! Your last words to me were "God bless you, Alf" and of course you meant this with all your heart. And God has indeed blessed me by giving me you as a beacon in my life. Whatever important I have done, I have thought of you, and done the right thing. As David said-"Whither shall I go from your spirit, or whither shall I flee from your presence? If I ascend into heaven, you are there, and if I make my bed in hell, behold, you are there". All of us have part of God in us, and the great goodness in you is so plain to me".

Following his retirement from Aldrich, Alfred was able to devote nearly all his time and energy to his activities as an art collector, lecturer, and philanthropist. Alfred says that getting to know people involved in art has enriched his life. Those of us who have been fortunate to know Alfred have had our lives enriched by him.

Anne Alper
Howard Alper

TRIBUTE / HOMMAGE

Nous sommes extrêmement privilégiés et honorés de rédiger la dédicace du présent numéro spécial de la Revue, qui rend hommage à Alfred Bader. Véritable visionnaire, Alfred Bader a certes profondément transformé la façon dont les chimistes réalisent aujourd'hui leurs recherches, mais son influence s'étend beaucoup plus loin puisqu'il est aussi un entrepreneur, un homme d'affaires, un collectionneur d'œuvres d'art, un spécialiste de Rembrandt et un philanthrope.

L'enfance et l'adolescence d'Alfred ont été marquées par l'adversité. Alfred est né à Vienne, en 1924; deux semaines après sa naissance, son père est décédé. En novembre 1938, dans le sillage de la campagne antisémite « Nuit de Cristal », la mère d'Alfred a envoyé son fils au Royaume-Uni. Là-bas, il a vécu au Sussex et est entré au Brighton Technical College en 1939. En mai 1940, aux prises avec un conflit grandissant avec l'Allemagne, le gouvernement britannique a fait arrêter tous les hommes allemands et autrichiens, y compris Alfred, et les a fait placer dans des camps d'internement. Le gouvernement du Canada a accepté de prendre à sa charge quelques-uns de ces détenus, principalement des prisonniers de guerre, des réfugiés antinazis et des civils allemands : c'est ainsi qu'Alfred Bader a été envoyé au Canada, plus précisément dans une forteresse sur une île de la rivière Richelieu, près du lac Champlain. Malgré cet internement, Alfred et quelques autres détenus étaient déterminés à poursuivre leurs études et Alfred est arrivé à obtenir son immatriculation junior et son immatriculation senior avant sa libération, en 1941. Alfred a frappé à la porte de plusieurs universités avant d'être accepté à l'Université Queen's, à Kingston, où il a vécu des jours heureux. Pour financer la poursuite de ses études et ses rendez-vous galants, il a travaillé pour la Murphy Paint Company, à Montréal, où il planchait sur la formulation de peintures-émail et de peintures-laque. C'est auprès de cette société qu'il a nourri un intérêt pour l'industrie et l'entrepreneuriat.

Tandis qu'il était étudiant de troisième cycle à l'Université Harvard, sous la direction de Louis Fieser, chimiste organicien réputé, Alfred a pris conscience de la nécessité de fonder une entreprise de production de produits chimiques spécialisée en recherche. À l'époque, presque tous les produits chimiques provenaient de la société Eastman Kodak, dont le catalogue recensait quelque 4 000 substances. Bien que plusieurs de ses pairs aient tenté de l'en dissuader, Alfred a constitué l'Aldrich Chemical Company le 17 août 1951, avec son ami Jack Eisendrath, un avocat du Milwaukee, chacun ayant investi 250 $ dans le projet. À ses débuts, Aldrich occupait un garage loué à 25 $ par mois; la société comptait deux employés à temps partiel et son catalogue se bornait à une page polycopiée. Ses ventes se sont chiffrées à 1 705 $ la première année.

La société a subséquemment déménagé dans des locaux loués de 1 000 pieds carrés, où Alfred réalisait à lui seul toutes les synthèses. En 1955, Aldrich a étendu ses activités aux produits chimiques médicinaux, ce qui a particulièrement ravi Alfred. L'ardeur et la détermination d'Alfred ont porté fruit et, en 1958, sa société, qui employait 12 personnes, s'est enfin installée dans son propre édifice de trois étages. Une qualité particulièrement admirable chez Alfred était son engagement à fournir des produits chimiques dans la plus grande efficacité. On voyait déjà dans son acuité et son intégrité, conjuguées à sa détermination et à son dévouement, les signes annonciateurs d'une carrière remarquable.

La société a poursuivi son ascension et, en 1962, ses ventes ont atteint le million de dollars, bien loin des 5 400 $ de dix ans auparavant. En 1990, Aldrich a fusionné avec Sigma et est devenue Sigma-Aldrich, la 80^{e} plus importante société américaine, forte de 4 000 effectifs et de filiales dans de nombreux pays d'Europe, en Israël et au Japon. Après avoir occupé la présidence du conseil d'administration de la société de 1980 à 1991, Alfred a « officiellement pris sa retraite », mais est toutefois demeuré président émérite.

Un des principaux conseils qu'Alfred se plaisait à donner aux nouveaux entrepreneurs était le suivant : « Écoutez attentivement vos clients. » Cette attitude était la clé de voûte de son succès. D'ailleurs, toute la publicité d'Aldrich arborait une photo d'Alfred au-dessus de laquelle figurait la phrase « Prière de déranger ». Lui et sa conjointe, Isabel, voyageaient sans relâche d'un laboratoire à l'autre, en Amérique du Nord et partout dans le monde, et Alfred écoutait attentivement les difficultés qu'éprouvaient les chimistes en matière de synthèse, puis leur livrait des conseils ou leur proposait des solutions. Dans son autobiographie *Adventures of a Chemist Collector*, il déclarait : « Bien que toutes nos visites dans les universités soient mues par le désir de mieux connaître nos clients et peut-être, de découvrir de nouveaux composés prometteurs, elles aboutissent souvent à une délicieuse expérience personnelle pour Isabel et pour moi. » Mon premier contact avec Alfred Bader [c'est Anne qui parle] remonte à 1966, à l'hôtel Windsor de Montréal. À l'occasion d'un petit déjeuner, je m'entretenais avec lui de la possibilité d'accroître ma production actuelle d'un composé diazoïque – à peine quelques milligrammes à la suite d'un long procédé. Les recherches ont pris un autre cours et Aldrich n'est jamais revenu sur la question, mais je n'oublierai jamais notre première rencontre avec Alfred, à Howard et à moi, et la chance qui m'a été donnée de côtoyer ultérieurement Alfred et Isabel au cours des années qui ont suivi.

Le talent et les réalisations d'Alfred vont bien au-delà de la chimie et du commerce des produits chimiques. Alfred se [illegible] un « collectionneur invétéré » : son parcours a commence avec les timbres, à l'âge de 8 ans, puis s'est poursuivi avec les étampes, à l'âge de 10 ans, et enfin avec les tableaux, a l'âge de 20 ans. Lorsqu'Alfred était enfant, à Vienne, l'appartement de sa mère regorgeait de tableaux, principalement d'œuvres viennoises des XIX^{e} et XX^{e} siècles. Bien que ces écoles ne l'aient pas particulièrement séduit, la peinture a fait vibrer une corde sensible chez lui. Alfred fait le commerce et le don de tableaux depuis nombre d'années. Une fois qu'Aldrich eut été bien établie et qu'il eut davantage de temps à consacrer à ce qu'il estime être un joli passe-temps, Alfred a fondé Alfred Bader Fine Arts et, depuis 1992, il s'emploie de plus en plus à cette activité. Bien qu'il gravite dans les hautes sphères du commerce des œuvres d'art, notamment celui des tableaux de grands maîtres, tels que Rembrandt et Rubens, Alfred tire énormément de plaisir à ne payer que quelques milliers de dollars pour une œuvre d'art qui, au prix de quelques efforts de restauration, est appelée à devenir un objet de grande valeur. C'est non seulement le caractère monnayable des œuvres d'art qui l'anime, mais aussi leur caractère esthétique. Alfred n'hésite jamais à partager son amour de la peinture. Lors de ses visites dans les universités et à tous les

kiosques aménagés par Aldrich, il distribuait des représentations de tableaux tirés de sa vaste collection. Les chimistes ne sauront oublier l'*Alchimiste* et, chaque année, un tableau faisait la page couverture du catalogue d'Aldrich. Alfred a de ce fait beaucoup contribué à l'« éducation artistique » de la collectivité de la chimie.

En plus de ses contributions à la chimie, à la collection et la conservation d'œuvres d'art et à l'enrichissement de l'histoire de l'art, Alfred a fait preuve d'une vaste générosité qui laissera une empreinte indélébile. En effet, il est prodigue avec les membres de la collectivité de la chimie, avec l'Université Queen's, qui lui a ouvert ses portes alors que les autres universités l'avaient repoussé, ainsi qu'avec d'autres institutions et fondations. Tout a commencé par de petites subventions sans condition destinées aux chimistes du monde entier en manque de financement; plusieurs de ces chimistes sont devenus des scientifiques réputés à l'échelle internationale. Alfred a impulsé la création de primes, de bourses et de prix pour les étudiants du Canada, des États-Unis, de la Grande-Bretagne et de la République tchèque, étant reconnaissant de l'aide que de tels appuis financiers lui avaient procurée quand il était lui-même étudiant. Il est le père du prix de chimie organique Alfred Bader de la American Chemical Society (aussi connu sous le nom « Prix Aldrich ») de même que d'autres prix éponymes de la Société canadienne de chimie et de la Royal Society of Chemistry du Royaume-Uni. Plus récemment, il a fondé le prix de chimie bio-inorganique et bio-organique Alfred Bader de l'ACS et financé la fondation de démarrage de l'ACS, qui permet aux étudiants de chimie de premier cycle de se familiariser avec le travail de laboratoire.

Alfred a fait de nombreux dons à l'Université Queen's, dont une chaire en chimie organique, une chaire en histoire de l'art, de superbes tableaux de sa collection privée destinés à l'Agnes Etherington Art Centre et du financement de lancement d'un nouveau musée. (Au fait, la voie Bader, sur le campus de l'Université Queen's, relie la faculté de chimie et l'Agnes Etherington Art Centre). Le don le plus original fait par Alfred à l'Université Queen's est sans contredit le château de Herstmonceux, dans le comté de Sussex, en Angleterre, dont certaines sections datent du XV^{e} siècle. Par ailleurs, Alfred a appuyé plusieurs projets éducatifs pour la communauté juive et a mis sur pied des organisations caritatives à Milwaukee.

Les contributions d'Alfred Bader ont été soulignées par des doctorats honorifiques de plusieurs universités, y compris l'Université Simon Fraser et l'Université d'Ottawa; par un honorariat de la Royal Society of Chemistry de même que par le prix Charles Lathrop Parsons de l'ACS, soulignant l'indéfectible engagement d'un membre de l'ACS au bien public. Alfred est également membre honoraire de l'Institut de chimie du Canada.

Un autre admirable trait d'Alfred et de sa conjointe est leur profonde tendresse l'un pour l'autre. Il y a quelques années, Isabel a publié l'ouvrage, *A Canadian in Love*, dans lequel elle citait de magnifiques lettres qu'elle avait adressées à Alfred. On y retrouvait aussi, en toute fin, une lettre qu'Alfred lui avait écrite le 18 avril 1975. Nous nous permettons d'en traduire un paragraphe :

« Tu ne m'as pas écrit du 11 septembre 1950 au 11 août 1951, ta dernière lettre depuis 24 ans. J'ai tant lu et relu ce mot que je le connais par cœur et cela me bouleverse depuis tout ce temps. Quelle emprise tu as sur moi! Les derniers mots que tu m'as adressés étaient "Que Dieu te bénisse, Alf". Cette imploration, je le savais, venait du creux de ton âme. Et Dieu m'a certes béni en faisant de toi la lumière de ma vie. Tous mes accomplissements, je les sais justes, car continuellement inspirés de toi. Comme l'a dit David "Où irais-je loin de ton esprit; et où fuirais-je loin de ta face? Si je monte aux cieux, tu y es; si je me couche au séjour des morts, t'y voilà." Dieu est présent en chacun de nous et, chez toi, Sa Bonté m'apparaît flagrante. »

Après avoir tiré sa révérence à Aldrich, Alfred a pu consacrer presque tout son temps et son énergie à la collection d'œuvres d'art, à la présentation de conférences et à des activités philanthropiques. Il estime que le fait d'avoir forgé des rapports avec la communauté des arts a enrichi sa vie. Ceux d'entre nous qui ont eu la chance de forger des rapports avec Alfred peuvent aussi affirmer que leur vie en a été enrichie.

Anne Alper
Howard Alper

Unwrapped

for Alfred Bader and a city

by Roald Hoffmann

I didn't expect
to receive it
watching "The Third

Man," to hear it
in Anna's schmal-
tzy lines, in her

black and white walk
down the allée. No,
it would have made

more sense for it
to surface in
the angle of cut

of the vines still
strapped to wires.
Or at night. But

if one is in-
clined to sadness,
it plain takes over --

like an arch, all
of-a-sudden
perceived as off-

center, like the
leaping buck in
my lights. Until...

you realize you
have been granted
a gift, the salty,

loosening gift
of the road in
to the father -

no chance, then,
to mourn; the
time rending

gift, Vienna, her;
The gift I wish
would pass from me.

AWARD LECTURE / CONFÉRENCE D'HONNEUR

2005 Alfred Bader Award Lecture Diaminopimelate and lysine biosynthesis — An antimicrobial target in bacteria[1,2]

John C. Vederas

Abstract: The development of bacterial resistance to current antibiotic therapy has stimulated the search for novel antimicrobial agents. The essential peptidoglycan cell wall layer in bacteria is the site of action of many current drugs, such as β-lactams and vancomycin. It is also a target for a number of very potent bacterially produced antibiotic peptides, such as nisin A and lacticin 3147, both of which are highly posttranslationally modified lantibiotics that act by binding to lipid II, the peptidoglycan precursor. Another set of potential targets for antibiotic development are the bacterial enzymes that make precursors for lipid II and peptidoglycan, for example, those in the pathway to diaminopimelic acid (DAP) and its metabolic product, L-lysine. Among these, DAP epimerase is a unique nonpyridoxal phosphate (PLP) dependent enzyme that appears to use two active site thiols (Cys73 and Cys217) as a base and an acid to deprotonate the α-hydrogen of LL-DAP or meso-DAP from one side and reprotonate from the other. This process cannot be easily duplicated in the absence of the enzyme. A primary goal of our work was to generate inhibitors of DAP epimerase that would accurately mimic the natural substrates (meso-DAP and LL-DAP) in the enzyme active site and, through crystallographic analysis, provide insight into mechanism and substrate specificity. A series of aziridine-containing DAP analogs were chemically synthesized and tested as inhibitors of DAP epimerase from *Haemophilus influenzae*. Two diastereomers of 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylic acid (AziDAP) act as rapid irreversible inactivators of DAP epimerase; the AziDAP analog of LL-DAP reacts selectively with the sulfhydryl of Cys73, whereas the corresponding analog of meso-DAP reacts with Cys217. AziDAP isomers are too unstable to be useful antibiotics. However, mass spectral and X-ray crystallographic analyses of the inactivated enzymes confirm that the thiol attacks the methylene group of the aziridine with concomitant ring opening to give a DAP analog bound in the active site. Further crystallographic analyses should yield useful mechanistic insights.

Key words: enzyme mechanism, enzyme inhibition, antibiotics, aziridines, amino acids.

Résumé : Le fait que les bactéries aient développé de la résistance aux antibiotiques actuels a stimulé la recherche de nouveaux agents antimicrobiens. La paroi cellulaire essentielle des bactéries qui est formée de peptidoglycane est le site d'action de plusieurs médicaments actuels, y compris les β-lactames et la vancomycine. C'est aussi la cible d'un certain nombre de peptides antibiotiques très puissant produits par des bactéries, telles la nisine A et la lacticine 3147 qui sont toutes les deux des antibiotiques fortement modifiés d'une façon post-translationnelle qui agissent en se liant au lipide II, le précurseur du peptidoglycane. Un autre ensemble de cibles potentielles pour le développement d'antibiotiques sont les enzymes bactériens qui fabriquent des précurseurs du lipide II ou du peptidoglycane, dont ceux qui se retrouvent dans la voie conduisant à l'acide diaminopimélique (ADP) et à son produit de métabolisme, la L-lysine. Dans cette catégorie, l'épimérase de l'ADP est un enzyme unique qui ne dépend pas du phosphate de pyridoxyal (PLP) et qui semble utiliser les deux sites thiols actifs (Cys73 et Cys217) comme acide et base pour déprotoner l'hydrogène α des LL-ADP et méso-ADP à partir d'un côté pour le reprotoner de l'autre. Il n'est pas possible de réaliser ce processus en l'absence d'un enzyme. Un des objectifs primaires de notre travail a été de générer des inhibiteurs de l'épimérase d'ADP qui pourraient imiter correctement les substrats naturels (méso-ADP et LL-ADP) dans le site enzymatique actif et, par le biais d'études cristallographiques, pourraient nous donner une idée sur le mécanisme et sur la spécificité du substrat. On a réalisé la synthèse d'une série d'analogues de l'ADP contenant une aziridine et on les a

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[1]This article is part of a Special Issue dedicated to Dr. Alfred Bader.
[2]Presented at the Canadian Society for Chemistry Conference, Saskatoon, Sask. May 2005.

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testés comme inhibiteurs de l'épimérase d'ADP provenant du *Haemophilus influenzae*. Deux diastéréoisomères de l'acide 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylique (AziADP) agissent comme inactivateurs irréversibles rapides de l'épimérase d'ADP; l'analogue AziADP du LL-ADP réagit d'une façon sélective avec le groupe sulfhydryle du site Cys73 alors que l'analogue correspondant du méso-ADP réagit avec celui du site Cys217. Les isomères du AziADP sont trop instables pour être utiles comme antibiotiques. Toutefois, les spectres de masse et les analyses par diffraction des rayons X des enzymes inactivés confirment que le thiol attaque le groupe méthylène de l'aziridine avec une ouverture de cycle concomitante qui conduit à la formation d'un analogue ADP lié au site actif. Des études cristallographiques ultérieures devraient permettre d'obtenir un nouvel éclairage sur le mécanisme.

Mots clés : mécanisme enzymatique, inhibition enzymatique, antibiotiques, aziridines, acides aminés.

[Traduit par la Rédaction]

Introduction

Resistance to common antibiotics was observed shortly after their introduction into clinical practice in the late 1940s and early 1950s, and has become a serious and costly problem in health care. Although it is well-understood that overuse of antibiotics produces resistance, it is estimated that currently about half of the 100 million prescriptions per year written by office-based physicians in the United States are unnecessary because they are prescribed for the common cold and other viral infections, against which antibiotics are not active (1). The approximate direct cost of antibiotic resistance may be more than $3 billion annually with an associated indirect cost of perhaps 10 times that amount (2). Another concern that exacerbates this problem is that the market for antibiotics is a fragile one. Unlike medicines for chronic conditions, such as high cholesterol or high blood pressure, that are taken daily for long periods of time, antibiotics are only taken for a short time and only when a patient suffers particular diseases. Thus, the profitability of this class of medications is limited and it has become even more limited because the costs and standards for regulatory approval match those for the more profitable drugs that see daily use.

Formation of peptidoglycan, the netlike cell wall layer in bacteria, is a primary target for many antibiotics, including the β-lactams (e.g., penicillins, cephalosporins) as well as vancomycin and related glycopeptides (3). Interestingly, lipid II, the monomer unit that is polymerized to form peptidoglycan, is also a target for antimicrobial agents (Fig. 1). The topical peptide antibiotic bacitracin inhibits utilization and processing of its lipid portion (4), whereas a number of lantibiotics (lanthionine-containing peptides), such as nisin A, bind to it (5). Nisin A (Fig. 2), which is approved for use as a food preservative, uses lipid II as a docking molecule not only to inhibit peptidoglycan formation, but also to create pores in bacterial cell membranes. Although nisin A is many orders of magnitude more potent than conventional antibiotics, its instability at neutral pH and its tendency to be inactivated by Michael addition of ubiquitous thiols, such as glutathione, to its dehydroamino acid residues precludes its therapeutic use in mammals (6). Fortunately, lacticin 3147, a very potent two-peptide lantibiotic consisting of A1 and A2 peptides and certain other lantibiotics, appears to be much more stable and may be useful in such applications (7, 8).

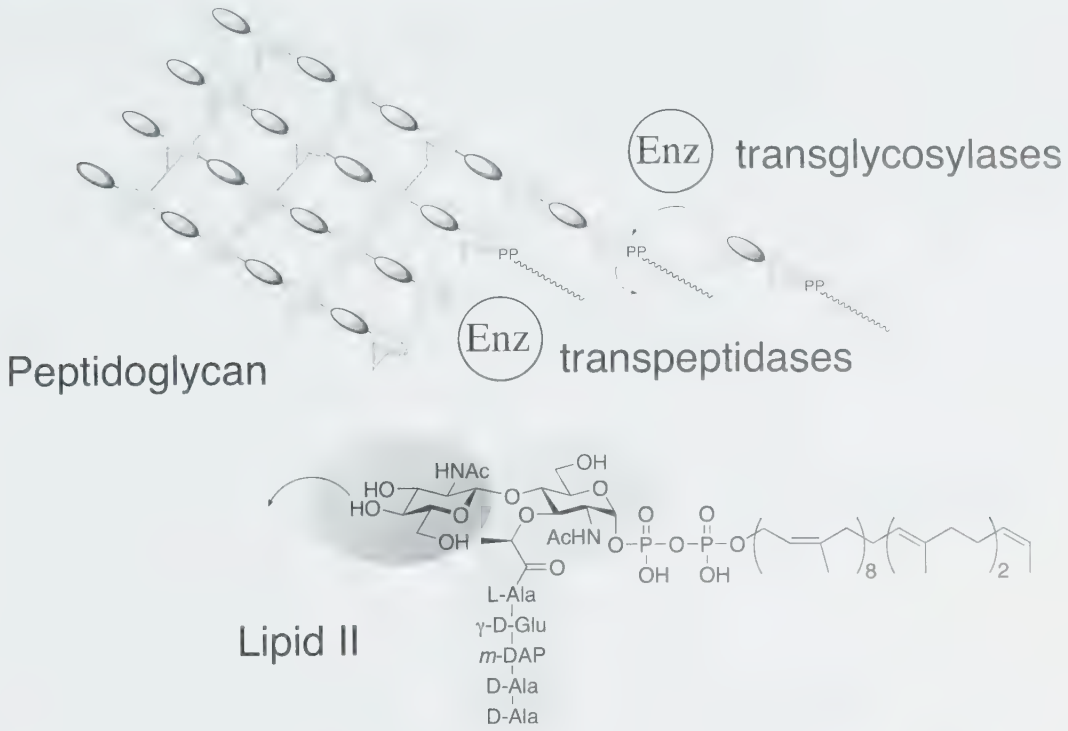
Lipid II in Gram-negative bacteria contains a *meso*-diaminopimelic acid (meso-DAP) residue that acts as a cross-linking amino acid in peptidoglycan via attack at the penultimate D-alanine amide bond of a nearby pentapeptide moiety (Fig. 3) (9). In most Gram-positive bacteria, the DAP moiety is replaced by its metabolic product, L-lysine, which serves the analogous function. For some time, we and others have been interested in targeting the DAP pathway to L-lysine (Fig. 4), which occurs in bacteria and higher plants, for possible development of new antibiotics (10). The DAP pathway is absent in mammals, which require L-lysine in their diet as an essential amino acid. Hence, it is likely that specific inhibitors of the bacterial enzymes in this metabolic route could be potent antimicrobial agents against bacteria resistant to conventional antibiotics and would be nontoxic to humans and animals. Limited antibiotic activity has already been demonstrated for an heterocyclic analog of DAP that inhibits DAP dehydrogenase (11).

DAP epimerase and its properties

DAP epimerase is an enzyme of particular interest because of its unusual mechanism, although it may not be the best target for antibiotic development as it appears late in the pathway and its function may be circumvented (12). The enzyme reversibly interconverts LL-DAP and meso-DAP without the use of cofactors, metals, or keto or imine intermediates (13). Although a number of enzymes racemize amino acids using pyridoxal phosphate (PLP) (14, 15), DAP epimerase belongs to the class of PLP-independent racemases, which includes aspartate racemase (16), glutamate racemase (17, 18), and proline racemase (19). Based on early work by Albery and Knowles (19), Wiseman and Nichols (13) proposed that DAP epimerase uses two cysteines in the active site (Fig. 5) as an acid and a base to remove the α-proton and reprotonate from the opposite side. During this process, a primary kinetic isotope effect is observed and the α-hydrogen exchanges with solvent via the thiol (13, 20). DAP epimerase is highly specific and does not transform the DD-isomer of DAP or any isomer of lanthionine (the 3-thia analog of DAP). All substrate carboxyl and amino groups of DAP must be present for successful binding and neither the D- or L-isomers of lysine or α-aminopimelic acid are substrates or effective inhibitors (21).

This type of epimerization is not a trivial process and the half-life for such a transformation in the absence of enzyme is estimated to be in excess of 1500 years (22). Several major obstacles block this reaction in the absence of enzyme. The most important is the inherent lack of acidity of the α-hydrogen in a free α-amino acid compared with the much

Fig. 1. Simplified schematic of the formation of peptidoglycan from lipid II. In Gram-positive bacteria, *m*-DAP is usually replaced by L-lysine.



more acidic hydrogens on the carboxyl oxygen in a fully protonated amino acid or on the ammonium group in the zwitterionic form. The pK_a of the α-hydrogen has been estimated to be 34 for the deprotonated anionic amino acid, about 29 for the zwitterionic form, and 21 for the corresponding fully protonated version (23). Thus, a free base in solution will rapidly take a proton first from the carboxyl oxygen and then from the ammonium group, at which point removal of the α-hydrogen requires an extremely strong base. A second major problem is that the free thiol of a cysteine residue typically has a pK_a of ca. 10 and, as a result, the corresponding thiolate is a poor base for deprotonation at the α-carbon.

Nevertheless, the formation of an α-anion in the epimerization process could be confirmed by elimination of hydrogen fluoride from pure β-fluoro-DAP stereoisomers (24). Interestingly, the loss of HF proceeds very rapidly from isomers **1** and **3**, but diasteromers **2** and **4** epimerize reversibly and only slowly undergo elimination of hydrogen fluoride (Fig. 6).

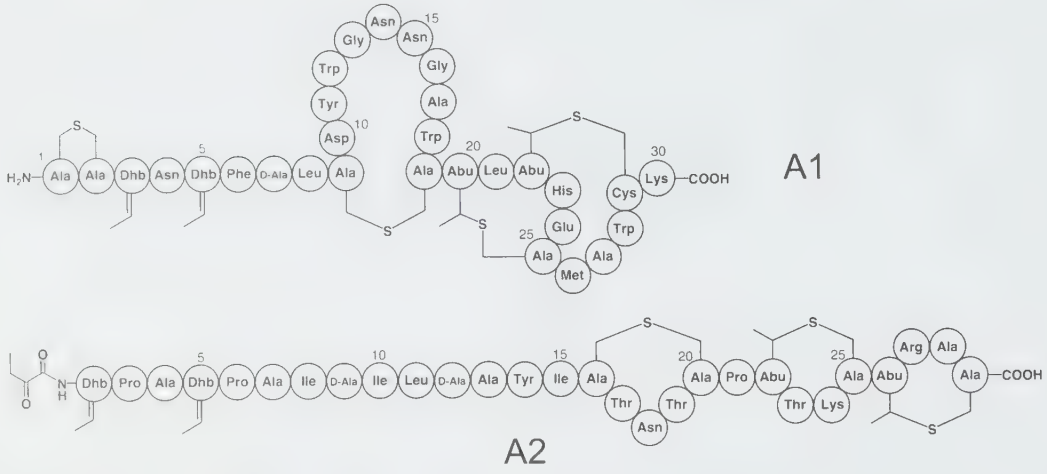
These results indicate not only that anionic character forms at the α-carbon, but also that the substrate, which is normally conformationally mobile, is rigidly held in the enzyme active site so as to orient the cleaving bonds at the α- and β-carbons synperiplanar or antiperiplanar in the rapidly eliminating isomers. Subsequent experiments with β-fluoro-DAP stereoisomers **1** and **2**, using site-specific mutants Cys73Ala and Cys217Ala, demonstrate that Cys73 is the base that removes the α-proton from LL-DAP, whereas Cys217 performs the analogous function on meso-DAP (25).

A major breakthrough in the understanding of this unusual enzyme was the elucidation by Blanchard and co-workers (26) of the crystal structure (2.7 Å) of an inactive form of DAP epimerase from *Haemophilus influenzae* in which Cys73 and Cys217 formed a disulfide. This was subsequently refined by Roper and co-workers (27) to 1.75 Å. The monomeric enzyme (274 amino acid residues) displays an unusual pseudo twofold symmetry axis around the central cleft that forms the putative active site. Unfortunately, unambiguous modeling of DAP isomers as substrates in the active site is not readily accomplished using this inactive disulfide structure. Subsequent crystallographic structures of related PLP-independent racemases such as aspartate racemase (16) and glutamate racemase (17, 28), also do not permit definitive placement of substrate (29) in the active sites in such a way as to elucidate the catalytic mechanism. Thus, a primary goal of our work was to generate inhibitors of DAP epimerase that would accurately mimic the natural substrates (meso-DAP and LL-DAP) in the enzyme active site and provide mechanistic insight through crystallographic analysis.

Synthesis of AziDAP isomers

In 1990, Higgins and co-workers (30) reported that a crude mixture of all possible diastereomers of 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylic acid (AziDAP), generated by heating a mixture of α-halomethyl DAP isomers, caused irreversible inactivation of DAP epimerase (Fig. 7). Enzymatic digestion of the inactivated enzyme indicated that Cys73 had been alkylated by the inhibitor through an attack

Fig. 2. Structures of nisin A and lacticin 3147 (a two-component antibiotic consisting of A1 and A2 peptides).



by the thiol on the methylene of the aziridine ring in AziDAP. Subsequently, an elegant study by Tanner and Miao (31) employed an aziridino analog of glutamic acid to inactivate the PLP-independent glutamate racemase. A diastereomeric mixture of oxa analogues of AziDAP was also found to irreversibly inactivate DAP epimerase, probably by thiol opening of the epoxide moiety (32). We reasoned that the synthesis of pure AziDAP isomers **5** and **6**, corresponding to the natural substrates LL-DAP and meso-DAP, respectively, would provide probes that could give crystallographic pictures of the DAP epimerase active site with a bound substrate analog. These would have a stereochemically locked DAP skeleton. Although the AziDAP isomers **5** and **6** are quite small molecules, their synthesis provides a considerable challenge because of high reactivity of the aziridine ring under acidic conditions. This sensitivity is exacerbated by the presence of five internal nucelophiles (four carboxyl oxygens and the distal amino group). In addition, complete stereochemical purity at well-separated centers is required. We also embarked on the synthesis of the DAP derivatives **7** and **8**, having an internal aziridine moiety, to test their ability to analogously inactivate DAP epimerase.

Analog **8** could be prepared by aziridination of an α,β-unsaturated amide bearing a chiral auxiliary. We had earlier reported (33) the diastereoselective aziridination of *N*-enoylbornane[10,2]sultams by *N*-aminophthalimide mediated by lead tetraacetate. This reaction subsequently proved feasible with oxoalkenyloxazolidinone (34) and camphor auxilliaries (35). Hence, we targeted an analogous route with the use of 3-amino-2-ethyl-3,4-dihydroquinazolin-4-one (**15**) to provide the stereoselective synthesis of the internal aziridine moiety to be followed by deprotection using N—N bond reduction with metal in ammonia. As shown (Fig. 8), reaction of the chiral phosphonate ester with *N*,*N*-di-Boc glutamate semialdehyde (**9**) gives exclusively the *trans*-alkene. One Boc protecting group could then be cleaved with TFA to generate the desired precursor **10** for aziridination. Lead tetraacetate aziridination with quinazolin-4-one at –40 °C gives a diastereomeric ratio of 9:1. The major isomer **11** is readily isolated by recrystallization. Although the absolute stereochemistry of this aziridine could not be directly confirmed by X-ray crystallography, it is known that addition to *N*-enoylbornane[10,2]sultams occurs by syn attack from the re face of the α-carbon (33). Removal of the Boc group, base hydrolysis, and reductive cleavage of the N—N bond with Li and ammonia affords the target **8**. With stereochemically pure **8** available, we also synthesized a 1:1 mixture of **8** and its diastereomer **7** to test for irreversible in-

Fig. 3. Expanded view of a pentapeptide chain of peptidoglycan showing DAP and sites that form cross-links to adjacent pentapeptide moieties.

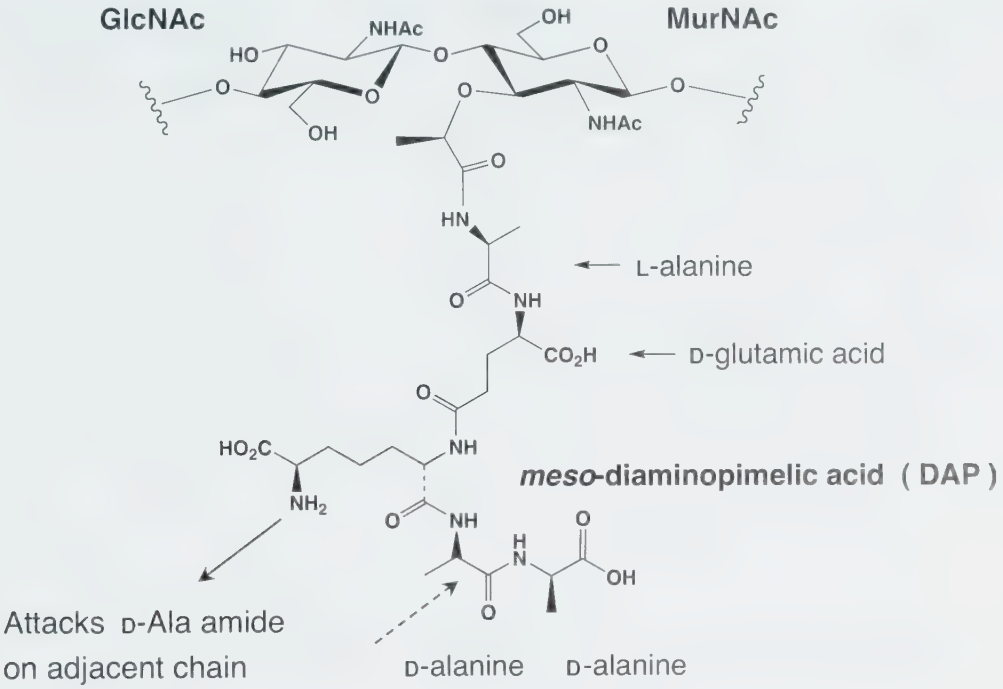
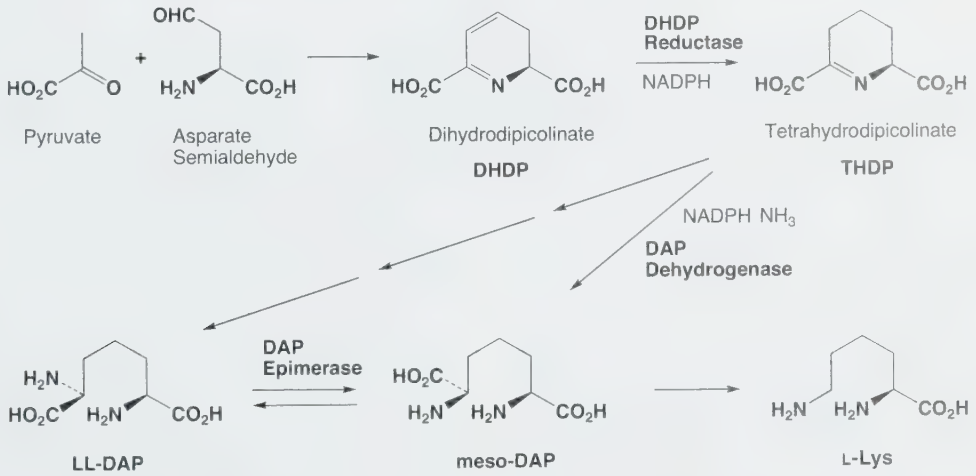


Fig. 4. Diaminopimelate pathway to L-lysine in bacteria. Most bacteria use the route via LL-DAP, but some Gram-positive bacteria employ a shortcut to meso-DAP via DAP dehydrogenase.



activation of DAP epimerase. This mixture was made by by nonstereospecific aziridination of the dimethyl ester **12** followed by analogous deprotection (Fig. 8).

Numerous approaches for synthesis of stereochemically pure **5** and **6** were tried, and the most successful method involved the tethering of a chiral aziridinating moiety via an ester linkage (36, 37) to the unsaturated amino acid framework to allow intramolecular reaction. The required unsaturated α-aminopimelic ester **16** was constructed by photolysis of the Barton ester of *N*-Cbz-L-glutamic acid α-methyl ester with methyl α-thiophenol methylacrylate to give a 68% yield over three steps (Fig. 9) (38). The chiral aziridinating portion, (*R*)-aminoquinazolin-4(3*H*)-one (**18**), was then coupled to the monoacid **17**, which was made by saponification of **16** and selective monoesterification using methanol and polymer-bound PTSA (39). Although the tethering of the aziridinating agent to form **20** works reasonably well using DCC–DMAP, several cycles of flash chromatography are re-

Fig. 5. Proposed mechanism for DAP epimerase.

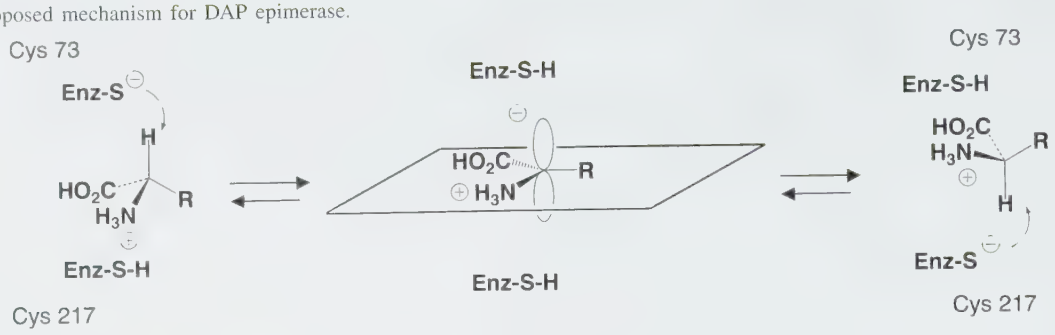
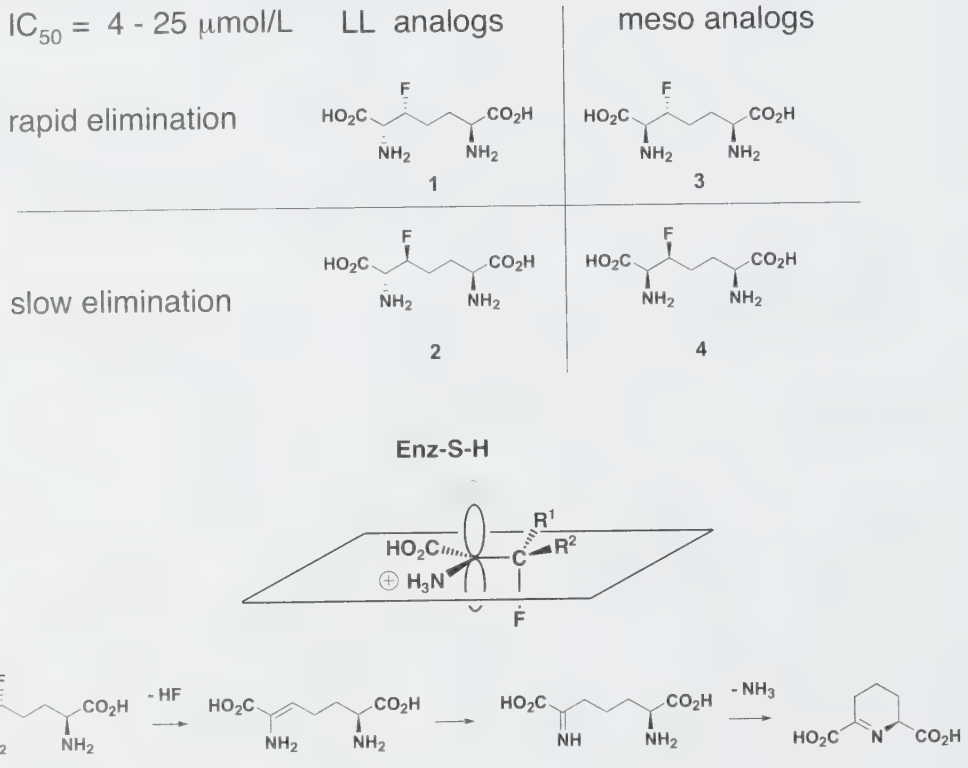
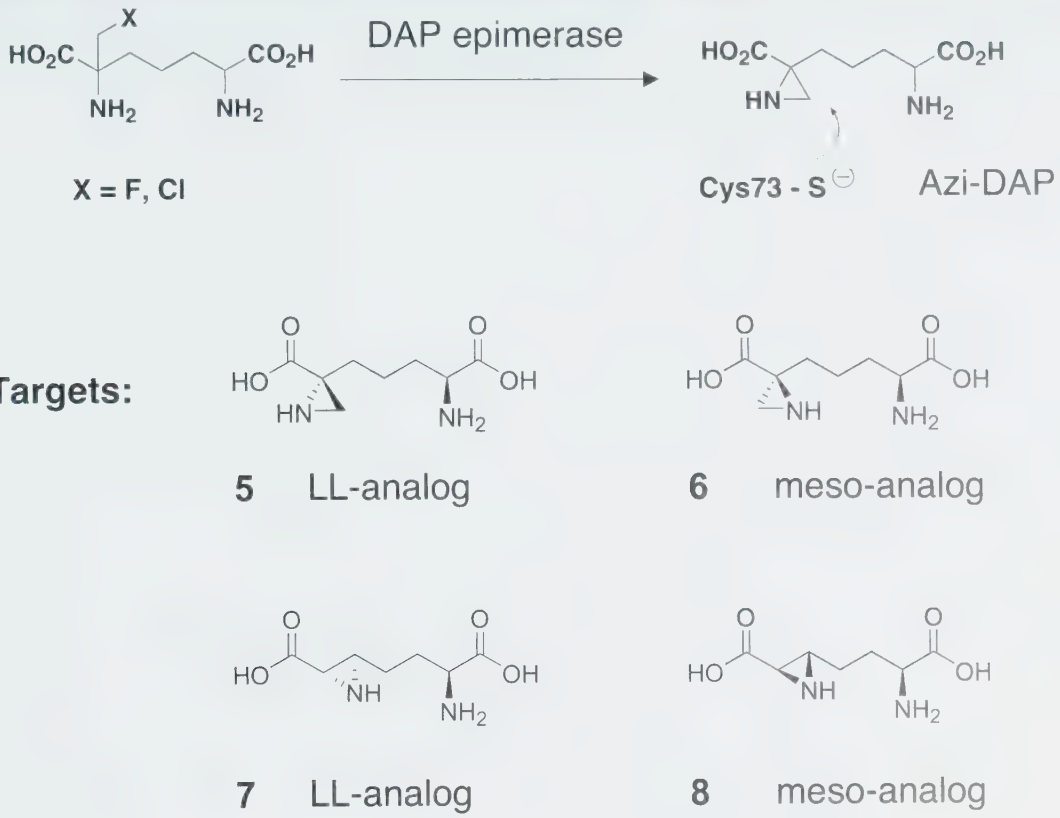


Fig. 6. Interaction of β-fluoro analogs of DAP with DAP epimerase.



quired to remove the unwanted urea by-product. In contrast, resin-bound *N*-benzyl-*N*-cyclohexylcarbodiimide reagent (PS-DCC) (40) permits facile purification after coupling of acid **17** to the (*S*)-aminoquinazolin-4(3*H*)-one (**19**) to give **22** in 51% yield. Intramolecular aziridination of **22** progresses rapidly upon treatment with lead tetraacetate at 0 °C to give the target **23** with complete diastereoselectivity (>99:1 dr). NOE studies confirm the stereochemical outcome of this reaction. In particular, there is a strong (3%) NOE interaction of the hydrogen on the stereogenic centre bearing the methyl group across the face of the 10-membered ring with the methylene hydrogens of the side chain (Fig. 10). Preparation of the diastereomeric aziridine **21** under analogous conditions is slightly less selective (98:2 dr), but the minor diastereomer can be removed by careful column chromatography to give a >99:1 dr. Interestingly, the diastereomeric compounds **21** and **23** can be distinguished by ^{13}C NMR spectroscopy despite the relatively wide separation of the stereogenic centres. Hydrolysis of the fully protected AziDAP **23**, using lithium hydroxide or sodium hydroxide, results in decomposition. Fortunately, sodium carbonate (41) in methanol–water allows quantitative generation of the salt of the diacid. Subsequent deprotection with sodium or lithium in ammonia at –78 °C gives AziDAP isomer **6** as the major product along with ε-methyl-α-aminopimelic acid in a 5.6:1 ratio. This undesired product is formed as a 1:1 mixture of diastereomers at the carbon bearing the methyl. It may result from reductive aziridine ring cleavage to generate an anion α to the carboxylate followed by elimination of nitrogen and further reduction of the resulting conjugated olefin. Separation of the crude reaction mixture using preparative TLC under basic conditions gives

Fig. 7. Inactivation of DAP epimerase by a mixture of AziDAP isomers and synthetic targets.



a low isolated yield (23% for AziDAP **6**). Pure AziDAP **5** could be prepared in improved yield (30%) by direct reduction, without preliminary HPLC purification of the diacid salt. AziDAP isomers **5** and **6** are extremely sensitive compounds that are stable in a strong base, but decompose quickly under acidic or neutral conditions. The multiple internal nucleophiles (four carboxylate oxygens and the distal amino group) promote rapid intramolecular aziridine ring opening. As solid carboxylate salts, **5** and **6** decompose somewhat more slowly at room temperature, with half-lives of about 2 weeks. They are stable for longer periods only under cryogenic (–80 °C) conditions, but this propensity to decompose in aqueous media precludes evaluation of their antimicrobial activity in bacterial cultures.

Interaction of DAP epimerase from *H. influenzae* with AziDAP isomers

As mentioned previously, Higgins and co-workers (30) reported that a crude mixture of all possible diastereomers of AziDAP caused irreversible inactivation of DAP epimerase with covalent modification of Cys73 in the enzyme active site. Exposure of cloned and overexpressed (*Eschrichia coli*) DAP epimerase from *H. influenzae* (25) to **5**, **6**, **7**, and **8** demonstrates that the compounds with the internal aziridine ring (**7** and **8**) are weak reversible inhibitors (IC_{50} for **8** is 2.88 mmol/L) that do not bind permanently in the active site. In contrast, the AziDAP isomers **5** and **6** rapidly and irreversibly inactivate the enzyme at low concentration and show both time and concentration dependence. The covalent attachment of both isomers to the enzyme can be demonstrated by electrospray mass spectroscopy. Because of the instability of these compounds in aqueous media, it is not possible to obtain accurate kinetic constants, an observation already reported by the Higgins group with the isomeric mixture (30). Earlier studies (25) suggested that pure LL-AziDAP **5** should result in selective attachment to Cys73 of DAP epimerase, whereas DL-AziDAP **6** would react with Cys217. Inactivation of DAP epimerase with individual AziDAP isomers, followed by treatment with thermolysin and trypsin, generates fragments that afford excellent sequence coverage (89%) by MS–MS and allow separate examination of both active site cysteines. The reaction of **5** with Cys73 of the enzyme is readily demonstrated by this approach. In contrast, analysis of DAP epimerase inhibited with a large excess (10- to 100-fold) of AziDAP **6** reveals that in addition to the expected alkylation of Cys217, attack also occurs at Cys73 to a certain extent. In principle, it is possible that a single diasteroisomer of AziDAP (i.e., 29) reacts with both cysteines. However, the excess of inhibitor **6** could possibly be contaminated by very small amounts (<1.0%) of the other AziDAP diastereomer **5**, which is not easily detectable and could act on the DAP epimerase. The use of such a large excess of inhibitor was initially prompted

Fig. 8. Synthesis of **7** and **8**. See ref. 37. Reagents: (*i*) **Xc**-$COCH_2PO(OEt)_2$, DBU, LiCl (85%); (*ii*) TFA (94%); (*iii*) **15**, $Pb(OAc)_4$, HMDS (72%); (*iv*) TFA (99%); (*v*) LiOH, MeOH–H_2O (85%); (*vi*) Li, NH_3 (48%); (*vii*) $MeO_2CCH{=}PPh_3$ (88%); (*viii*) TFA (88%); (*ix*) **15**, $Pb(OAc)_4$, HMDS (83%); (*x*) TFA (quant.); (*xi*) LiOH, MeOH–H_2O, (84%); (*xii*) Li, NH_3 (48%).

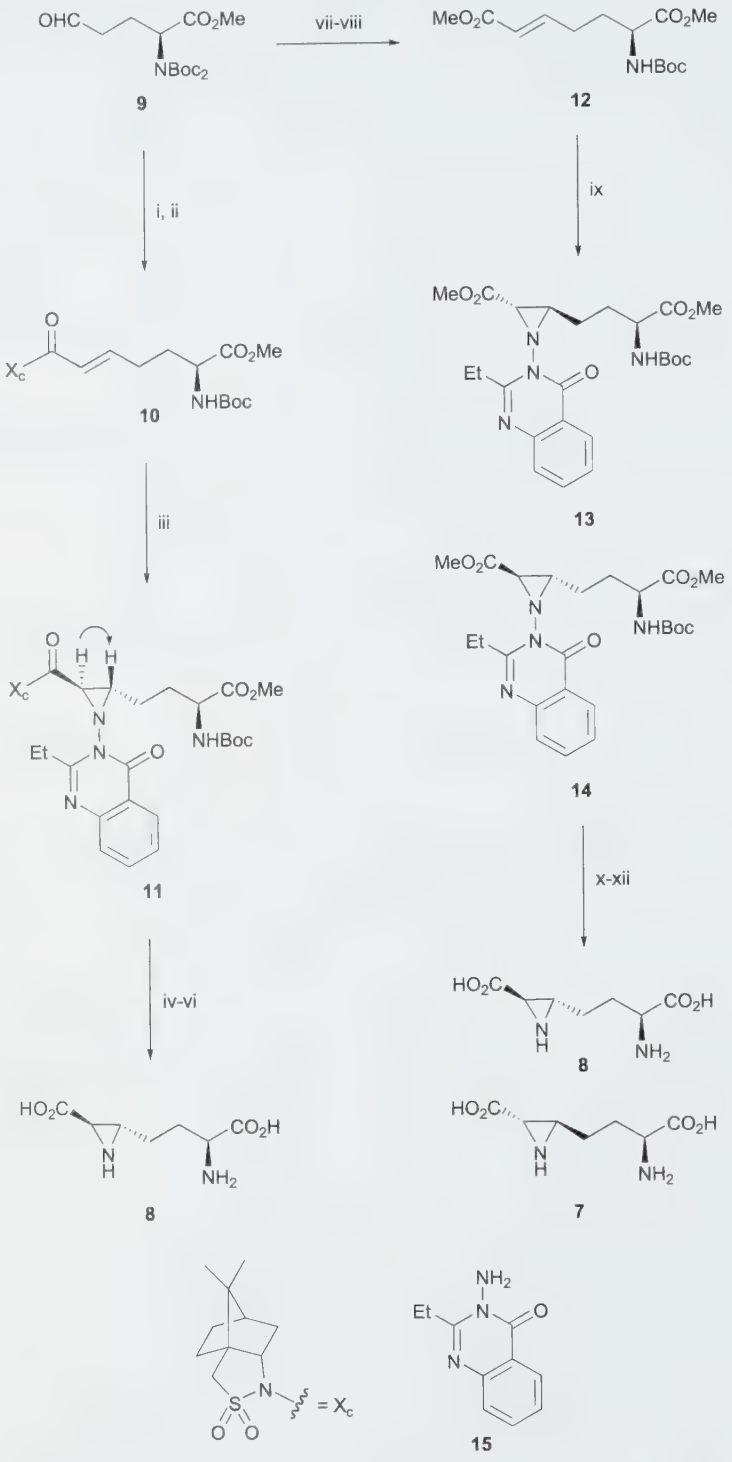


Fig. 9. Synthesis of **5** and **6**. See ref. 37. Reagents: (*i*) LiOH, MeOH–H_2O (82%); (*ii*) PS-PTSA, MeOH (95%); (*iii*) **18**, DCC, DMAP (62%); (*iv*) **19**, PS-DCC, DMAP (51%); (*v*) $Pb(OAc)_4$, HMDS (**21**, 55%; **23**, 87%); (*vi*) Na_2CO_3, MeOH–H_2O (from **23**, 69%); (*vii*) Li, NH_3 (**5**, 30% over two steps; **6**, 23%).

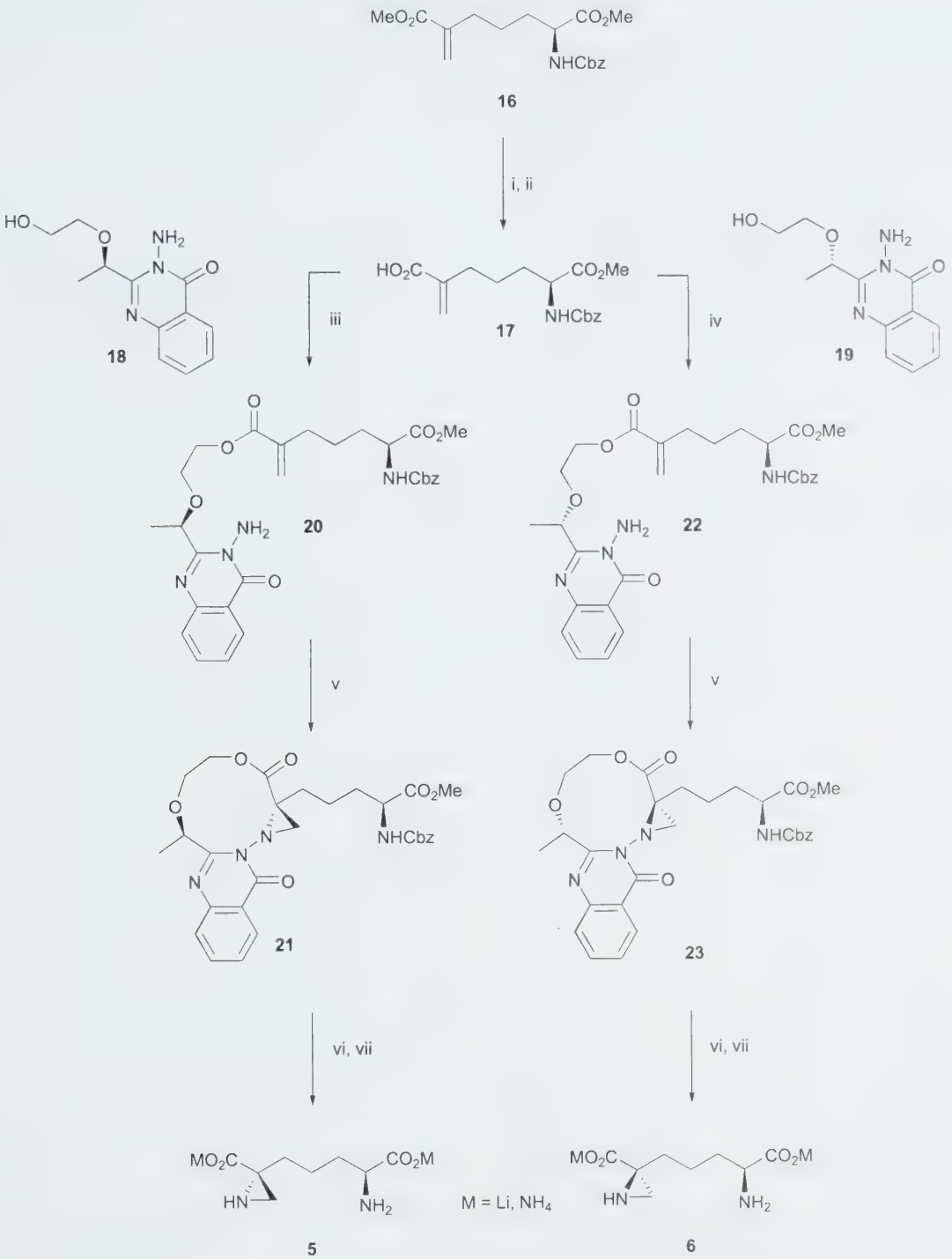
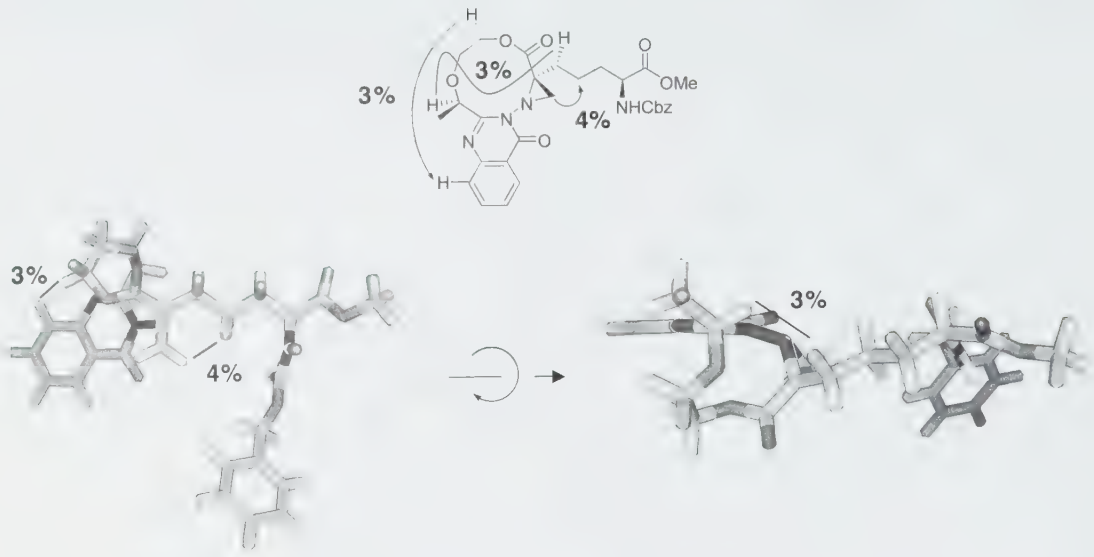


Fig. 10. Determination of aziridination stereochemistry by NOE effects. Selected NOE enhancements for **21** are shown with its calculated preferred conformation (two views).



by the desire to completely and rapidly inactivate the enzyme for crystallographic studies prior to its facile aerobic oxidation to form the internal disulfide between Cys73 and Cys217.

Fortunately, X-ray crystallography studies by our collaborators, Professor Michael James and Dr. Bindu Pillai (Department of Biochemistry, University of Alberta), on DAP epimerase separately inhibited with the individual AziDAP isomers showed that LL-AziDAP **5** bound exclusively to Cys73 and that DL-AziDAP **6** attached only to Cys217. In both cases, inactivation proceeds as predicted by attack of the thiolate on the aziridine methylene. Although these three-dimensional structures will be the subject of a separate report (submitted for publication), the key features essential for the unusual catalysis are readily evident. As one of the active site thiols in DAP epimerase has a considerably reduced pK_a (6 to 7) (20), the two cysteines are likely to exist as a thiolate–thiol pair prior to substrate binding. Binding of AziDAP and ring opening by the thiolate gives an analog of the substrate–enzyme complex in which the α-hydrogen of the corresponding DAP substrate is replaced by a methylene group. The enzyme–inactivator complex shows a significant domain shift, compared with the inactive disulfide version of the enzyme (26, 27), to enclose the DAP analog, similar to what has been very recently reported for glutamate racemase with D-glutamate in the active site (42). This creates a very tight-fitting pocket for binding the substrate, which is lined with hydrophobic side chains and also has a series of hydrogen bond donors and acceptors to recognize and interact with the substrate–inhibitor carboxyl and amino functionalities. As expected, the carboxylate attached to the α-carbon that undergoes epimerization is fully hydrogen bonded to allow electron delocalization. The amino group at the α-carbon is also protonated and α-helices near the carboxylate assist dispersion of negative charge. Finally, relatively rigid binding of substrate–inhibitor with exclusion of solvent, and location of the thiolate base close to the α-hydrogen with separation from the carboxyl and amino groups, enables catalysis with minimal movement. The crystallographic details will be reported in a forthcoming publication (43).

Acknowledgements

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Mechanism of cyclopropanol to cyclopropanol isomerization mediated by Ti(IV) and a Lewis acid[1]

Charles P. Casey and Neil A. Strotman

Abstract: Isomerization of *trans*-3-deutero-*r*-1-methyl-*cis*-2-phenylcyclopropan-1-ol (**1-trans-d**) to three isomeric cyclopropanols was facilitated by reaction with a mixture of Ti(O-*i*-Pr)$_4$ and $BF_3{\cdot}OEt_2$. The more Lewis acidic Cl_2Ti(O-*i*-Pr)$_2$ catalyzed this reaction in the absence of $BF_3{\cdot}OEt_2$. This cyclopropanol to cyclopropanol rearrangement involves reversible ring opening to a β-titanaketone. When the major species in solution prior to quenching was a titanium cyclopropoxide, a 40:40:10:10 mixture of cyclopropanols **1-trans-d**:**1-cis-d**:**2-trans-d**:**2-cis-d** was obtained; this is close to the equilibrium ratio of the titanium cyclopropoxides. When a catalytic quantity of Ti(O-*i*-Pr)$_4$ and a large excess of cyclopropanol was used, quenching gave a 29:29:21:21 mixture; this is closer to the equilibrium ratio of the cyclopropanols than the cyclopropoxides. Extrapolation to 0% and to 100% cyclopropoxide gave equilibrium constants for both cyclopropanols (K_{eq} = [**2**]/[**1**] = 1.3) and cyclopropoxides (K_{eq} = [**2-Ti**]/[**1-Ti**] = 0.18). A mechanism for these isomerization processes that involves ring opening and (or) ring closing with both retention and inversion of configuration at the carbon bearing phenyl is proposed.

Key words: cyclopropanol, titanium isopropoxide, Kulinkovich hydroxycyclopropanation.

Résumé : L'isomérisation du *trans*-3-deutéro-*r*-1-méthyl-2-phénylcyclopropan-1-ol (**1-trans-d**) en trois cyclopropanols isomères est facilitée par une réaction avec un mélange de Ti(O-*i*-Pr)$_4$ et de $BF_3{\cdot}OEt_2$. Le Cl_2Ti(O-*i*-Pr)$_2$, un acide de Lewis plus acide, catalyse cette réaction sans $BF_3{\cdot}OEt_2$. Ce réarrangement d'un cyclopropanol en un autre implique une ouverture de cycle réversible en β-titanacétone. Quand l'espèce principale en solution avant le captage le cyclopropylate de titane, on obtient un mélange 40 : 40 : 10 : 10 des cyclopropanols **1-trans-d** : **1-cis-d** : **2-trans-d** : **2-cis-d**, une proportion qui se rapproche du rapport à l'équilibre des cyclopropylates de titane. Quand on utilise une quantité catalytique de Ti(O-*i*-Pr)$_4$ avec un large excès de cyclopropanol, le piégeage conduit à un mélange 29 : 29 : 21 : 21 qui est plus près du rapport d'équilibre des cyclopropanols que de celui des cyclopropylates. Une extrapolation à des quantités égales à 0 % et à 100 % de cyclopropylate permet d'obtenir les constantes d'équilibre tant pour les cyclopropanols ($K_{éq}$ = [**2**]/[**1**] = 1,3) que pour les cyclopropanolates ($K_{éq}$ = [**2-Ti**]/[**1-Ti**] = 0,18). On propose un mécanisme pour ces processus d'isomérisation qui impliquent des ouvertures et des fermetures de cycle impliquant des rétentions et des inversions de configuration au niveau du carbone portant le noyau phényle.

Mots clés : cyclopropanol, isopropylate de titane, hydroxycyclopropanation de Kulinkovich.

[Traduit par la Rédaction]

Introduction

The Kulinkovich hydroxycyclopropanation, discovered in 1989, allows for the one-step preparation of polysubstituted cyclopropanols from esters, Grignard reagents, and Ti(O-*i*-Pr)$_4$ (Scheme 1) (1). Advances in this methodology have resulted in the employment of catalytic quantities of titanium (2), highly diastereoselective (3), and enantioselective (4) variants of this reaction and a widely broadened substrate scope.

This reaction is believed to involve a Ti(II)-alkene complex (**B**), formed via alkane loss from an unstable dialkyl-Ti(IV) intermediate (**A**) (Scheme 2). In the presence of an added alkene, exchange occurs, leading to increased product diversity. Reductive coupling of the alkene and the ester carbonyl by Ti(II) leads to metallacycle **C**. This metallacycle fragments with alkoxide loss to give β-titanaketone (**D**). Attack of the nucleophilic carbon bound to titanium on this γ-carbonyl moiety results in ring closure to form cyclopropoxide.

We recently demonstrated that the final step of the Kulinkovich hydroxycyclopropanation reaction involves frontside attack of the carbon–titanium bond on the γ-carbonyl to form a cyclopropoxide (Scheme 3) (5). Deuterium labelling revealed that the carbon bound to titanium retained its configuration throughout this process to give *trans*-3-

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Dedicated to Dr. Alfred Bader on the occasion of his 80th birthday. As a Past President of the American Chemical Society, I want to express the thanks of all our members to Dr. Bader for his generous support of the ACS Project Seed, the Bader Scholars program, and the ACS World Reach Fund and for sponsoring the Alfred Bader Award in Bioinorganic or Bioorganic Chemistry.

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[1]This article is part of a Special Issue dedicated to Dr. Alfred Bader.

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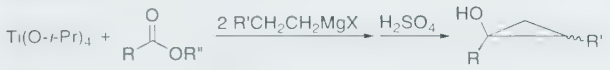
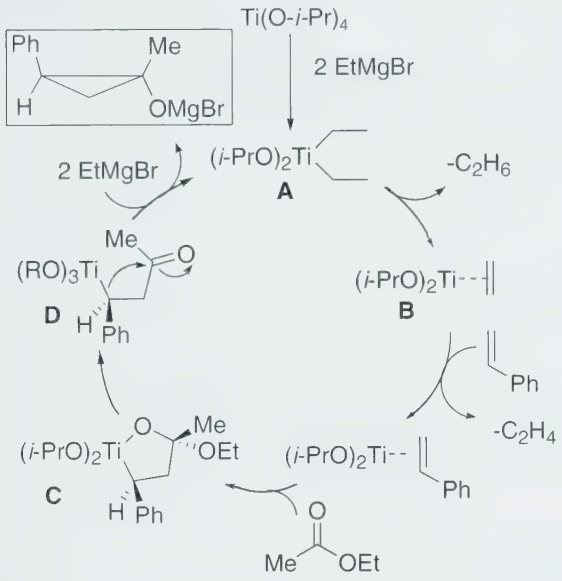
 doi:10.1139/V06-069

Scheme 1.



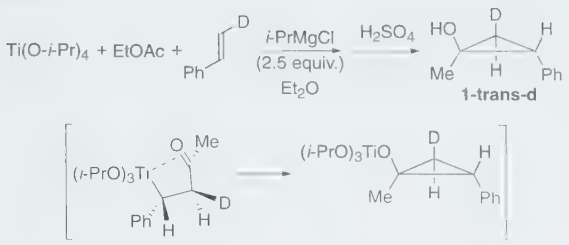
Scheme 2.



deutero-*r*-1-methyl-*cis*-2-phenylcyclopropan-1-ol (**1-trans-d**)[3] as the only observed product (5, 6).

We wondered whether introduction of a Lewis acid into this reaction, prior to cyclopropoxide formation, might result in a different ring closure mechanism. It seemed likely that the carbonyl oxygen would bind more tightly to an electron deficient Lewis acid, such as BF_3, than intramolecularly to the electron rich alkyltitanium triisopropoxide unit (Scheme 4). This would inhibit coordination of the carbonyl oxygen to titanium and would cause the alkyltitanium species to adopt a less sterically demanding transition structure. This opens the possibility that ring closure might occur with inversion of configuration at the carbon bound to titanium. An analogous transition structure, in addition to being involved in iron- (7), tin- (8), and zirconium-mediated (5) cyclopropane formation, was consistent with the inversion of configuration that we observed at the carbon–titanium bond in de Meijere's cyclopropylamine synthesis (5, 9) (Scheme 4). The addition of BF_3 during the Kulinkovich reaction produced additional cyclopropanol isomers. Here, we report an

Scheme 3.



unusual cyclopropanol to cyclopropanol rearrangement, catalyzed by Ti(O-*i*-Pr)$_4$ and BF_3·OEt_2, that is responsible for the observation of additional isomers (10).[4] This isomerization is shown to require reversible ring opening of a cyclopropoxide. Moreover, two different mechanisms for the reversible ring opening are required; one involves retention and the other involves inversion of configuration at the carbon bound to titanium in the ring-opened intermediate.

Results

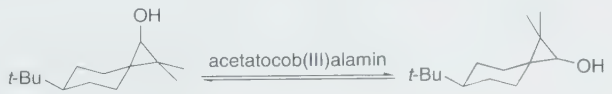
To test our hypothesis that a Lewis acid could affect a different ring closure mechanism in the Kulinkovich hydroxycyclopropanation, we modified the cyclopropanation procedure (*3d*). In the original Kulinkovich procedure, 2.5 equiv. of *i*-PrMgCl were added to a solution of Ti(O-*i*-Pr)$_4$, EtOAc, and *trans*-β-deuterostyrene in refluxing ether over a 1 h period. However, in our variation, the Grignard reagent was added over 5 min at 0 °C, followed by the addition of 2.5 equiv. of BF_3·OEt_2 and stirred for 1 h (Scheme 5).

Formation of two deuterium-scrambled cyclopropanols in the presence of BF_3

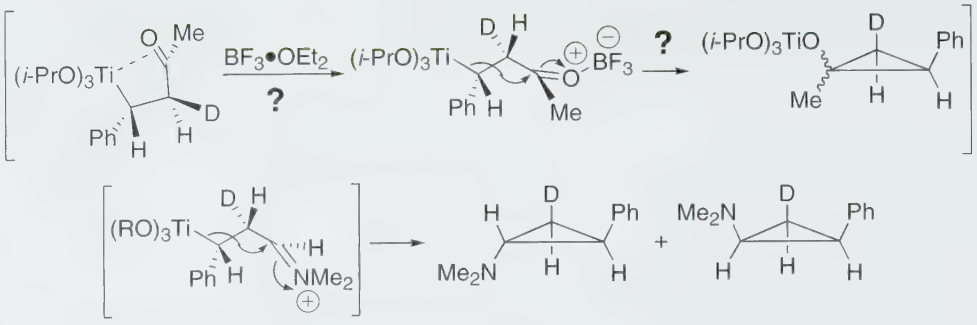
In contrast to the reaction in the absence of BF_3·OEt_2, which produced only a single cyclopropanol (**1-trans-d**), the addition of BF_3·OEt_2 led to the formation of three additional isomeric cyclopropanols: *cis*-3-deutero-*r*-1-methyl-*cis*-2-phenylcyclopropan-1-ol (**1-cis-d**), *trans*-3-deutero-*r*-1-methyl-*trans*-2-phenylcyclopropan-1-ol (**2-trans-d**), and *cis*-3-deutero-*r*-1-methyl-*trans*-2-phenylcyclopropan-1-ol (**2-cis-d**). ^{1}H NMR spectroscopy of the crude product mixture showed the formation of **1-trans-d** and **1-cis-d** (δ 2.31) and **2-trans-d** and **2-cis-d** (δ 1.98) in 37% and 19% yields, respectively. ^{2}H NMR spectroscopy showed a 1:1:0.46:0.46 mixture of **1-trans-d**:**1-cis-d**:**2-trans-d**:**2-cis-d**. A mixture of **1-trans-d** and **1-cis-d** was isolated as a white solid (35%) by

[3] The stereochemistry of cyclopropanes is specified using the IUPAC reference system where *r*- is used to specify the reference substituent.

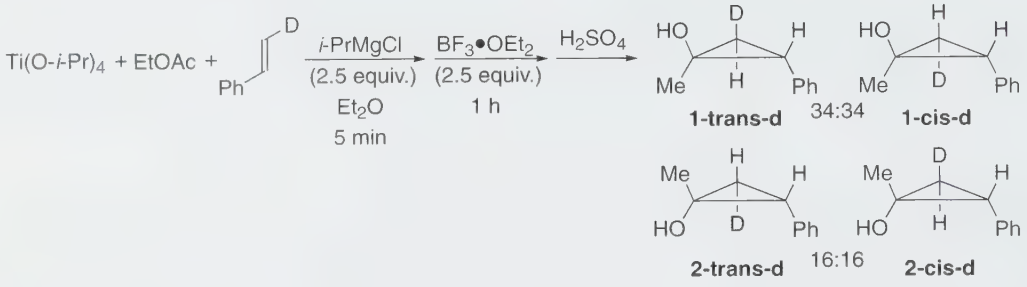
[4] This isomerization from one cyclopropanol to another is very unusual. We found only two other reports containing evidence of a cyclopropanol to cyclopropanol rearrangement. Kasatkin and Sato (*3b*) observed a temperature dependence on the cis/trans product ratio of cyclopropanols generated from homoallyl esters, Ti(O-*i*-Pr)$_4$, and 2 *i*-PrMgBr. When the reaction mixture was allowed to equilibrate at room temperature for 1.5 h before quenching, the trans product was favored greatly with a 95:5 trans:cis ratio, compared with a 41:59 ratio obtained without this equilibration period. In a second example, acetatocob(III)alamin catalyzed the equilibrium isomerization of a spiro-fused cyclopropanol in a maximum of 29% yield (eight other products from oxidation of the cyclopropanol were also seen).



Scheme 4.



Scheme 5.



recrystallization. Since *r*-1-methyl-*trans*-2-phenylcyclopropan-1-ol (**2**) could not be obtained by crystallization, it was eventually isolated by preparative TLC (see the following).

The ^{1}H NMR spectrum of recrystallized **1-trans-d** and **1-cis-d** was similar to that of the undeuterated analog *r*-1-methyl-*cis*-2-phenylcyclopropan-1-ol (**1**) except that the two cyclopropyl protons at C-3 (δ 1.21 and 0.97) each gave integrations of 0.5H and each showed coupling only to the benzylic proton. Proton-decoupled ^{2}H NMR spectroscopy showed peaks at δ 1.21 and δ 0.98 of equal integration corresponding to a 1:1 mixture of **1-trans-d** and **1-cis-d**. ^{13}C NMR spectroscopy showed the cyclopropyl carbon bearing the deuterium at δ 18.9 (J_{CD} = 24 Hz) as a 1:1:1 triplet. The absence of a larger central peak or any overlapping quintet indicated that no d_0 or d_2 analog was present.

In a similar experiment, preparative TLC led to the isolation of **2**, which was free of **1**. However, the 1:1 mixture of **2-trans-d**:**2-cis-d** also contained ~30% decomposition products.[5] The ^{1}H NMR chemical shifts were consistent with those previously reported for compound **2** (11). The proton decoupled ^{2}H NMR spectrum of the impure mixture of **2-trans-d** and **2-cis-d** showed equal integrations for the peaks at δ 1.05 and δ 1.18, corresponding to deuterium on C-3 of the cyclopropane.

While this BF_3 modification of the Kulinkovich procedure is clearly of no synthetic utility, it suggests the interesting possibility that an unusual cyclopropanol to cyclopropanol isomerization might be occurring. The formation of cyclopropanols **1** and **2** and the 1:1 ratio of deuterium on C-3 of each cyclopropanol strongly suggested that some type of equilibration process had occurred. It seemed highly unlikely that a 1:1 ratio of retention:inversion at the carbon–titanium bond had occurred in the formation of each cyclopropanol. We suspected that isomerization might have occurred *after* cyclopropanol formation, possibly by reversible ring opening.

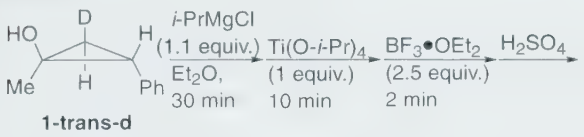
To determine whether the majority of cyclopropane was formed stereospecifically prior to the addition of BF_3, we conducted an analogous experiment in which 2.5 equiv. of *i*-PrMgCl were added to Ti(O-*i*-Pr)$_4$, EtOAc, and *trans*-β-deuterostyrene at 0 °C over 5 min and then quenched with acid and water. In this experiment, with no BF_3·OEt_2 added, a 57% NMR yield of **1-trans-d** was obtained. There was no evidence of other cyclopropanol isomers detected by either ^{1}H or ^{2}H NMR spectroscopy in the crude product mixture. This demonstrated that rapid ring closure (<5 min at 0 °C) to form cyclopropoxide had occurred before Lewis acid addition and that BF_3·OEt_2 was involved in the isomerization of the cyclopropoxide rather than in the initial ring closure step.

Cyclopropanol to cyclopropanol isomerization with *i*-PrMgCl, Ti(O-*i*-Pr)$_4$, and BF_3·OEt_2

We next tested whether pure cyclopropanol **1-trans-d** (5) could undergo cyclopropanol to cyclopropanol rearrangement. Deprotonation of the cyclopropanol **1-trans-d** with 1.1 equiv. of *i*-PrMgCl was followed by the sequential addition of 1.0 equiv. of Ti(O-*i*-Pr)$_4$ and 2.5 equiv. of BF_3·OEt_2 and quenching with H_2SO_4 (Scheme 6). When the reaction was quenched after 2 min, ^{1}H NMR spectroscopy showed both **1** and **2** and integration vs. an internal standard showed quantitative recovery of cyclopropanols. Integration of the ^{2}H NMR peaks for the CHD resonances of **1** and **2** at δ 1.22,

[5] The low recovered yields were due to decomposition on the silica gel as well as incomplete separation of TLC bands.

Scheme 6.



1-trans-d:1-cis-d:2-trans-d:2-cis-d
38:38:12:12

0.98, 1.04, and 1.18 indicated a 38:38:12:12 mixture of **1-trans-d**:**1-cis-d**:**2-trans-d**:**2-cis-d**.[6]

At longer times before H_2SO_4 quenching (>60 min), the ratio of deuterated cyclopropanols remained the same, but the yield of recovered cyclopropanols decreased.

Several recrystallizations from pentane at –78 °C of a mixture obtained from isomerization of **1** led to the isolation of a mixture of pure cyclopropanols greatly enriched in **2**. When this 25:75 mixture of **1**:**2** was subjected to our standard isomerization conditions, a 71:29 mixture of **1**:**2** was obtained (Scheme 7). The observation of the same ratio of isomers of **1**:**2** starting from either **1** or **2** demonstrates that equilibrium between the salts of **1** and **2** was reached.

Attempts to isomerize *cis*-2-butyl-*r*-1-methylcyclopropanol (2), bearing a butyl group in place of the phenyl in **1**, failed under our standard conditions and gave only starting material. This indicates that only a bond to a benzylic carbon can cleave during rearrangement.

Cyclopropanol to cyclopropanol isomerization with *i*-PrMgCl and $Cl_2Ti(O\text{-}i\text{-}Pr)_2$

The isomerization of **1-trans-d** did not occur in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ or BF_3 alone; only the starting cyclopropanol was recovered. Our hypothesis was that both a titanium salt and a Lewis acid were required for isomerization. This hypothesis suggested that the more electron deficient $Cl_2Ti(O\text{-}i\text{-}Pr)_2$ might be used alone to serve this dual purpose.

Deprotonation of **1-trans-d** with *i*-PrMgCl, addition of 2 equiv. $Cl_2Ti(O\text{-}i\text{-}Pr)_2$, and quenching after 30 min led to incomplete equilibration and observation of an 85:8:3:3 ratio of **1-trans-d**:**1-cis-d**:**2-trans-d**:**2-cis-d** (Scheme 8). When the reaction mixture was quenched after 3.5 h, more extensive isomerization to a 46:34:10:10 ratio was seen. This ratio is similar to the equilibrium ratio seen in the $Ti(O\text{-}i\text{-}Pr)_4$–$BF_3$ mediated isomerization. Although $Cl_2Ti(O\text{-}i\text{-}Pr)_2$ proved a competent catalyst for this isomerization, it facilitated rearrangement much more slowly.

Equilibrium formation of titanium cyclopropoxides

We wondered whether irreversible deprotonation of the cyclopropanol by *i*-PrMgCl was necessary for the $Ti(O\text{-}i\text{-}Pr)_4$–$BF_3$ catalyzed isomerization. We first examined the equilibrium for cyclopropanol exchange with $Ti(O\text{-}i\text{-}Pr)_4$. The ^1H NMR spectrum of a solution of equimolar amounts of $Ti(O\text{-}i\text{-}Pr)_4$ and cyclopropanol **1** in $Et_2O\text{-}d_{10}$ showed an equilibrium mixture of titanium alkoxides (Scheme 9). No change in the NMR spectrum of this solution was seen over 80 min, indicating that equilibrium had been rapidly achieved. In addition, no isomerization to the cyclopropoxide of **2** (**2-Ti**) and no ring opening of the cylopropanol was observed. The cyclopropanol **1** and titanium cyclopropoxide **1-Ti** were differentiated by their benzylic proton resonances at δ 2.22 and 2.45, respectively; $Ti(O\text{-}i\text{-}Pr)_4$ and *i*-PrOH were distinguished by their CHO proton resonances at δ 4.52 and 3.87, respectively.[7] At equilibrium, the benzylic protons at δ 2.45 and 2.22 integrated to 89:11 when equimolar amounts of **1** and $Ti(O\text{-}i\text{-}Pr)_4$ were used (K_{eq} = ~65). Apparently, deprotonation of the cyclopropanol by a Grignard reagent is not required to generate titanium cyclopropoxides without deleterious side reactions.

While NMR spectroscopy allowed ready distinction between cyclopropanol and cyclopropoxides, it did not provide a way to distinguish between the various $Ti(O\text{-}i\text{-}Pr)_n(OR)_{4-n}$ species. To determine whether multiple cyclopropoxy units bind to a single titanium center, we studied the equilibrium between cyclopropanol and cyclopropoxides at high ratios of cyclopropanol:titanium by ^1H NMR spectroscopy (Table 1).

In all cases, more cyclopropoxide was seen than predicted by statistics, indicating that **1** is more acidic than isopropanol. Multiple cyclopropoxy groups can clearly bind to titanium. There does not appear to be any significant difference in the selectivity of cyclopropoxide binding to the various $Ti(O\text{-}i\text{-}Pr)_n(OR)_{4-n}$ species.

Cyclopropanol to cyclopropanol isomerization with $Ti(O\text{-}i\text{-}Pr)_4$ and $BF_3{\cdot}OEt_2$

1-trans-d was combined with 1.0 equiv. of $Ti(O\text{-}i\text{-}Pr)_4$ followed by 2.5 equiv. of $BF_3{\cdot}OEt_2$ and the reaction was quenched after 2 min. NMR spectroscopy showed the ratio of **1-trans-d**:**1-cis-d**:**2-trans-d**:**2-cis-d** was 40:40:10:10 (Scheme 10). This shows that $Ti(O\text{-}i\text{-}Pr)_4$ and $BF_3{\cdot}OEt_2$ are sufficient for cyclopropanol to cyclopropanol isomerization and that prior irreversible deprotonation by a Grignard reagent is not necessary.

Both $Ti(O\text{-}i\text{-}Pr)_4$ and $BF_3{\cdot}OEt_2$ are required for isomerization. No isomerization of **1-trans-d** was seen with $Ti(O\text{-}i\text{-}Pr)_4$ alone. Similarly, $BF_3{\cdot}OEt_2$ alone did not catalyze cyclopropanol epimerization although a small amount of decomposition (<10%) of **1-trans-d** was seen.

This equilibrium ratio of products is approximately representative of the relative energies of the cyclopropoxides of **1** and **2** (**1-Ti** and **2-Ti**), since little of the free cyclopropanols exists at equilibrium. This indicates that a $(i\text{-PrO})_3$TiO- unit is more sterically bulky than a methyl group, making the titanium alkoxide **1-Ti** with phenyl cis to methyl slightly more stable than the titanium alkoxide **2-Ti** with phenyl cis to $(i\text{-PrO})_3$TiO-.

Using only a catalytic amount of $Ti(O\text{-}i\text{-}Pr)_4$ should allow direct measurement of the equilibrium ratio of **1**:**2** rather than the equilibrium ratio of the titanium alkoxides **1-Ti**:**2-**

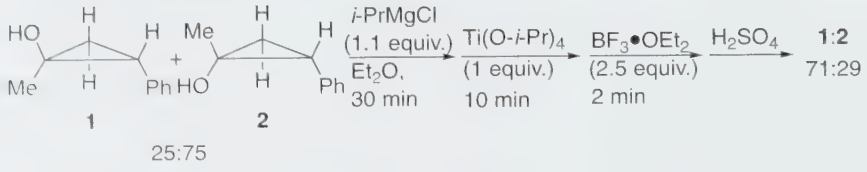
[6] The ratio of cyclopropanols **1** and **2** varied between 83:17 and 72:28 and showed no relationship to reaction time. This variation between runs may be due to the exact ratio of titanium:magnesium employed and the extent of precipitation of magnesium salts. The identity of the metal would affect the relative energies of the cyclopropoxides **1** and **2**.

[7] The resonance at δ 4.52 corresponds to $Ti(O\text{-}i\text{-}Pr)_4$ as well as $(RO)Ti(O\text{-}i\text{-}Pr)_3$ (**1-Ti**).

Table 1. Percent of material present as titanium cyclopropoxide as a function of ratio of **1** : Ti(O-*i*-Pr)4.

1 : $Ti(O\text{-}i\text{-}Pr)_4$	% as **1-Ti**	Expected statistical (% as **1-Ti**)	Theoretical maximum (% as **1-Ti**)
1.0:1	89	80	100
4.0:1	62	50	100
10:1	36	29	40

Scheme 7.

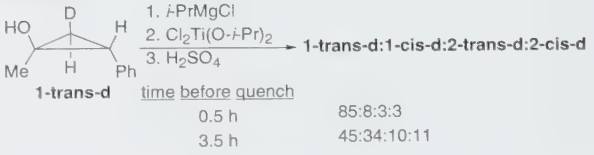


Ti, since most of the material would be in the protonated form. When **1-trans-d** was combined with 0.10 equiv. of $Ti(O\text{-}i\text{-}Pr)_4$ followed by 0.25 equiv. of $BF_3{\cdot}OEt_2$ and quenched after 1 h, the ratio of **1-trans-d**:**1-cis-d**:**2-trans-d**:**2-cis-d** was 30:30:20:20 (Scheme 10). Allowing the same reaction to proceed for 3 h before quenching gave an almost identical ratio 29:29:21:21, demonstrating that equilibrium had been reached after 1 h. To obtain a closer approximation of the equilibrium amounts of cyclopropanols, we attempted to further decrease the amount of $Ti(O\text{-}i\text{-}Pr)_4$. However, catalyst deactivation, indicated by incomplete isomerization of **1-trans-d** to **1-cis-d** even at long reaction times, was seen below 0.1 equiv. of $Ti(O\text{-}i\text{-}Pr)_4$ and 0.25 equiv. of $BF_3{\cdot}OEt_2$.

Equilibrium ratios of cyclopropanols and of cyclopropoxides are both involved in determining the ratios of cyclopropanols upon quenching (Scheme 11). When a 1:1 ratio of cyclopropanol–$Ti(O\text{-}i\text{-}Pr)_4$ was employed (Scheme 10), 89% of the material is present as a titanium cyclopropoxide (Table 1) and the observed 80:20 ratio of **1**:**2** obtained on quenching mainly reflects the equilibrium ratio of cyclopropoxides. When a 10:1 ratio of cyclopropanol:$Ti(O\text{-}i\text{-}Pr)_4$ was employed (Scheme 10), 64% of the material is present as a free cyclopropanol (Table 1) and the observed 58:42 ratio of **1**:**2** obtained on quenching has an increased contribution from the equilibrium ratio of cyclopropanols. The greater equilibrium amount of **2** seen at lower titanium levels indicates that the equilibrium ratio of cyclopropanols **1**:**2** must be substantially less than that of the corresponding cyclopropoxides. The ratio of **1**:**2** obtained upon quenching is the weighted average of the ratios of **1**:**2** and **1-Ti**:**2-Ti** existing in solution. At high titanium concentrations, the equilibrium in Scheme 11 is shifted toward cyclopropoxides **1-Ti** and **2-Ti**, whereas at low titanium concentrations this equilibrium is shifted toward cyclopropanols **1** and **2**.

A linear plot of **1** (in %) in the quench vs. cyclopropoxides **1-Ti** and **2-Ti** (in %) in the solution being quenched was obtained (Fig. 1). [8,9]Extrapolation of the plot to 100% cyclopropoxides gives the percentage of **1-Ti** at equilibrium (**1-Ti**:**2-Ti** = 85:15; K_{eq} = [**2-Ti**]/[**1-Ti**] = 0.18; ΔG = 1.0 kcal mol^{-1} (1 cal = 4.184 J)). Similarly, extrapolation of the plot to 0% cyclopropoxides gives the percentage of free alcohol **1** at equilibrium (**1**:**2** = 43:57; K_{eq} = [**2**]/[**1**] = 1.3, ΔG = –0.17 kcal mol^{-1}).

Scheme 8.



These equilibration studies show that cyclopropoxide **1-Ti** is more stable than **2-Ti**, indicating that an $O\text{-}Ti(OR)_3$ group is more sterically bulky than a methyl group. In contrast, equilibration showed that the free cyclopropanol **2** is more stable than **1**, reaffirming that an OH group has less steric bulk than a methyl group. The order of decreasing steric bulk is : $O\text{-}Ti(OR)_3$ > Me > OH.

Since both cyclopropoxide **2-Ti** and cyclopropanol **2** are present in substantial amounts at equilibrium, the formation of cyclopropanol **1** as the only product of the Kulinkovich hydroxycyclopropanation[9] must be a kinetic phenomenon.

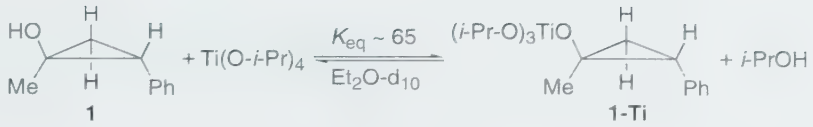
Discussion

Cyclopropanol to cyclopropanol rearrangements, such as the one reported here, are very unusual (10). Normally, cyclopropanols undergo rearrangement to ketones and epimerization is not observed. For example, DePuy (12) observed that **1** undergoes ring-opening isomerization in protic solvents to 4-phenylbutan-2-one by different stereospecific pathways in acidic and basic solution. Ring opening of **1** un-

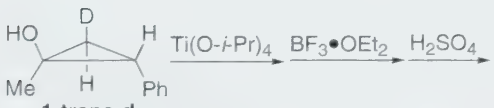
[8] This analysis does not take into account any effect of BF_3 on the cyclopropoxide:cyclopropanol ratio, the cyclopropanol:cyclopropanol ratio, or the cyclopropoxide:cyclopropoxide ratio. ^1H NMR spectroscopy of a mixture of cyclopropanol with $Ti(O\text{-}i\text{-}Pr)_4$ and $BF_3{\cdot}OEt_2$ was unable to resolve any relevant resonances.

[9] Supplementary material provides a derivation of the equation for the plot of the percentage of **1** in quench vs. the percentage of cyclopropoxides **1-Ti** and **2-Ti**. Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5034. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Scheme 9.

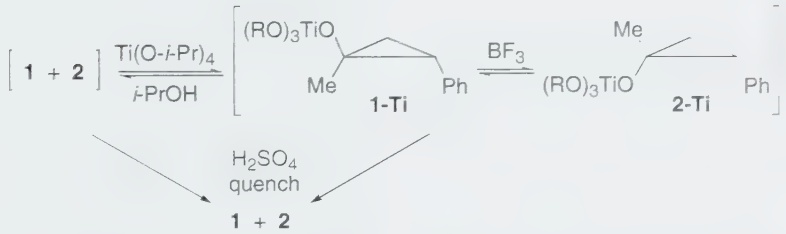


Scheme 10.



Molar ratio			
1.0	1.0	2.5	40:40:10:10
4.0	1.0	2.5	34:34:16:16
10.0	1.0	2.5	29:29:21:21

Scheme 11.



der basic conditions in 1:1 dioxane–D_2O occurred "almost instantaneously" to give 4-phenylbutan-2-one with inversion of configuration, corresponding to corner protonation of the cyclopropane (Scheme 12). Under acidic conditions in 1:1 dioxane:D_2O, slower ring opening of **1** gave a 40:60 mixture of 4-phenylbutan-2-one–3-phenylbutan-2-one; 4-phenylbutan-2-one was formed with exclusive retention of stereochemistry, corresponding to edge protonation of the cyclopropane.

It is interesting that while ring opening of **1** occurs rapidly in the presence of base in 1:1 dioxane–D_2O, we did not observe any ring opening of titanium cyclopropoxide **1-Ti** in the presence of alcohols in Et_2O or CH_2Cl_2. Apparently, titanium alkoxides are more covalent and stable than "free" alkoxide ions. The kinetic stability of titanium cyclopropoxides was confirmed by the calculation of a large barrier (28.8 kcal mol^{-1}) for the ring opening of *cis*-1,2-dimethylcyclopropoxytitanium trimethoxide (6)

Mechanism of cyclopropanol to cyclopropanol isomerization with $Ti(O\text{-}i\text{-}Pr)_4$ and BF_3OEt_2

Any valid mechanism must account for three key observations (13).[10] (*i*) BF_3 is required as a Lewis acid for isomerization; titanium cyclopropoxides are stable in its absence. (*ii*) A 2-phenyl substituent on the cyclopropanol ring is required; *cis*-2-butyl-*r*-1-methylcyclopropanol, bearing a butyl group in place of the phenyl, did not isomerize. This suggests that breaking a bond to the carbon bearing the phenyl group is involved in the isomerization. (*iii*) Since all possible diastereomers of the deuterated cyclopropanol are obtained, at least two of the three ring carbons must undergo epimerization.

[10]At one point we considered the possibility that this apparent scrambling of the deuterium stereochemistry was occurring by deprotonation by an alkoxide α to the carbonyl in the ring-opened intermediate. However, this would lead to d_0 and d_2 products, which is inconsistent with our ^{13}C NMR results showing only d_1 compounds. The possibility of the phenyl substituent being β to titanium and α to the carbonyl has been excluded based on (*i*) computational results (6), (*ii*) analogy with quenching studies of the reaction of ketones (*a*) or imides (*b*) with alkenes, and (*iii*) our quenching experiment with a nitrile and alkene.

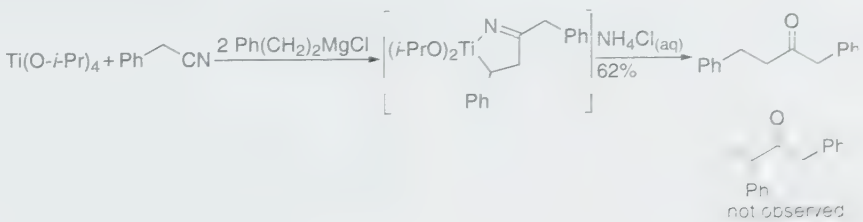
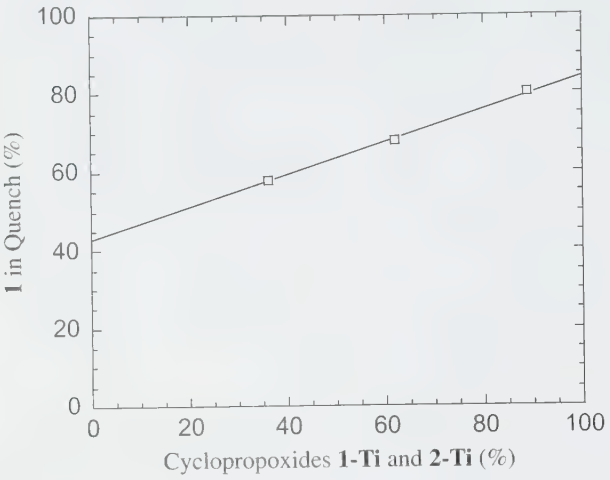


Fig. 1. **1** (in %) in quench vs. cyclopropoxides **1-Ti** and **2-Ti** (in %).

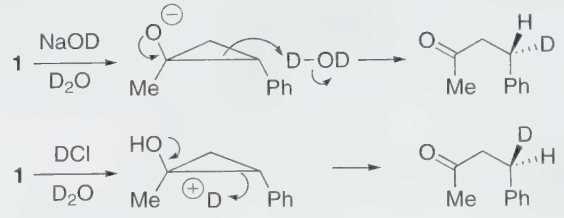


Kasatkin and Sato (*3b*), who observed a temperature dependence on the cis/trans product ratio of cyclopropanols generated from homoallyl esters, $Ti(O\text{-}i\text{-}Pr)_4$, and 2*i*-PrMgBr, attributed this apparent cyclopropoxide isomerization to reversible dissociation of the TiO—C(cyclopropyl) bond. However, the involvement of cyclopropyl cations in our rapid cyclopropanol to cyclopropanol isomerizations can be excluded. While reversible Lewis acid mediated cleavage of the cyclopropyl C—O bond might lead to interconversion of **1** and **2**, this process alone cannot alter the relative stereochemistry of phenyl and deuterium. Although reversible ring opening of the cyclopropyl cation to an allyl cation could, in principle, have isomerized phenyl relative to deuterium, cyclopropyl ring opening is highly exothermic ($\Delta H^{\circ}_{expt} = -30$ kcal mol^{-1}) (14) and is irreversible. Moss and Chu (15) recently generated the 2-phenyl-1-methylcyclopropyl cation in question and found that ring opening to allyl chlorides was competitive with ion pair collapse to a chlorocyclopropane. In addition, we demonstrated that **1-trans-d** is not isomerized by $BF_3{\cdot}OEt_2$ or $Ti(O\text{-}i\text{-}Pr)_4$ alone.

It is possible to directly convert any one of the four cyclopropoxide diastereomers to each of the other three by distinct processes (Scheme 13).

All of the interconversions begin with an electrophilic attack on the cyclopropoxide. The electrophile could be

Scheme 12.

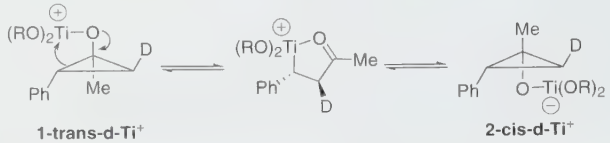


$Ti(OR)_3^+$, generated by the reaction of BF_3 with $Ti(OR)_4$, or another reactive titanium species.[11] Our proposed mechanism for these cyclopropanol isomerization reactions involves two different stereochemistries for the attack of the electrophile on the cyclopropoxide and two different stereochemistries for the microscopic reverse, cyclopropanol ring closing. Electrophilic attack on the cyclopropane bond linking the -OTi and phenyl-bearing carbons leads to retention of configuration at the carbon bearing the phenyl group (Scheme 14); this process is analogous to edge protonation of a cyclopropane. Electrophilic attack on the backside of the same cyclopropane bond leads to inversion of configuration and is analogous to corner protonation of a cyclopropane. The microscopic reverse of this process is responsible for the inversion of configuration at the titanium center in the formation of cyclopropylamines in the de Meijere reaction (5). In both cases, the bond linking the -OTi and phenyl-bearing carbons is attacked and a stabilized benzylic titanium species is generated.

The processes shown in Scheme 14 epimerize the CHPh ring carbon via cyclopropanol ring opening by the backside attack of the electrophile on the phenyl-bearing carbon (inversion of configuration at this carbon), rotation about the C—CHPhTi bond, and frontside ring closure with retention of configuration. Reversing the order of these processes to frontside ring opening with retention, rotation about the C—CHPhTi bond, and backside ring closure with inversion, produces the same result. This corresponds to the processes shown in blue in Scheme 13 that interconverts **1-trans-d** with **2-trans-d** and **1-cis-d** with **2-cis-d**.

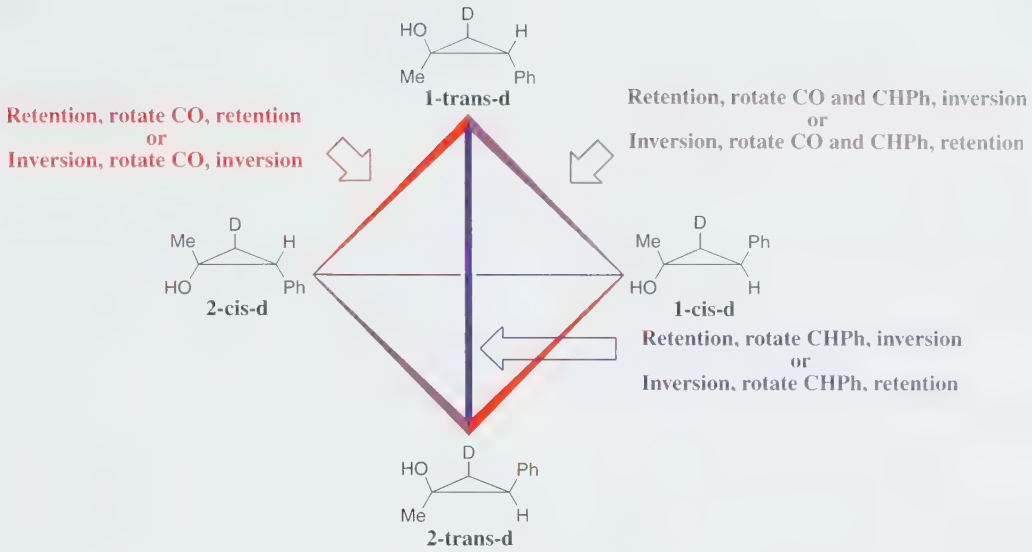
The processes shown in Scheme 15 epimerize the CMeOTi ring carbon by electrophilic cyclopropanol ring opening, rotation about the TiOMeC—C bond, and ring closure with the same stereochemistry as the ring opening. There are two different pathways, one involving ring open-

[11]It is also possible that cationic titanium cyclopropoxide **1-trans-d-Ti$^+$**, generated by BF_3 abstraction of an isopropoxy group from **1-trans-d-Ti**, can ring open in an intramolecular fashion involving only a single titanium. Migration of the benzylic carbon to the highly electrophilic cationic titanium center during cleavage of the carbon–carbon bond should be more favorable than carbon migration to a neutral titanium center. This could explain why isomerization to other cyclopropanols via ring opening is not observed in the Kulinkovich hydroxycyclopropanation, but is made accessible with the addition of BF_3. This suggests that production of only **1-Ti** through the Kulinkovich hydroxycyclopropanation is a kinetic phenomenon, and that when BF_3 is present, ring closure to **1-Ti** is made reversible. Even if only a very small fraction of ring closures lead to **2-Ti**, successive ring closure and ring-opening cycles would eventually lead to a an equilibrium mixture of **1-Ti** and **2-Ti**. Epimerization of the benzylic carbon requires the involvement of two titanium centers.

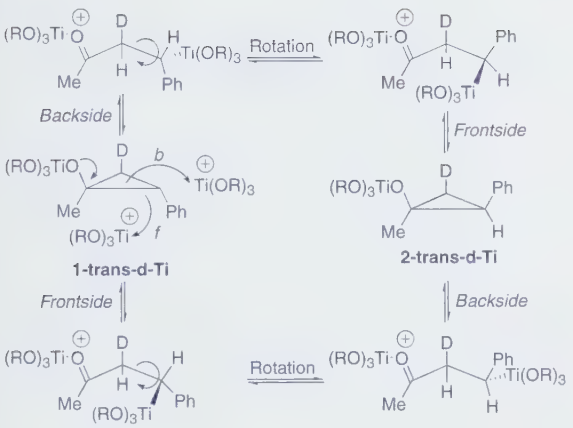


1-trans-d-Ti$^+$ 2-cis-d-Ti$^+$

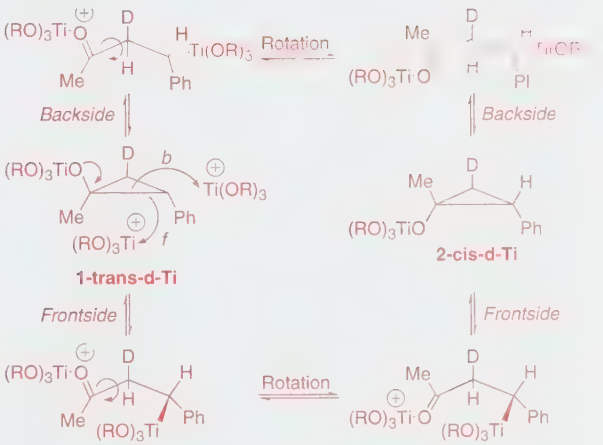
Scheme 13.



Scheme 14.



Scheme 15.



ing and ring closing with inversion of configuration and the other involving ring opening and ring closing with retention. These are the red processes in Scheme 13 that interconvert **1-trans-d** with **2-cis-d** and **1-cis-d** with **2-trans-d**.

The processes shown in Scheme 16 simultaneously epimerize both the CHPh and the CMeOTi ring carbons by electrophilic cyclopropanol ring opening, rotation about both the C—CHPhTi and TiOMeC—C bonds, and ring closure with the opposite stereochemistry. Microscopic reversibility requires equal rates for the processes of retention-double, rotation–inversion, and inversion-double rotation–retention. These are the purple processes in Scheme 13 that interconvert **1-trans-d** with **1-cis-d** and **2-trans-d** with **2-cis-d**.

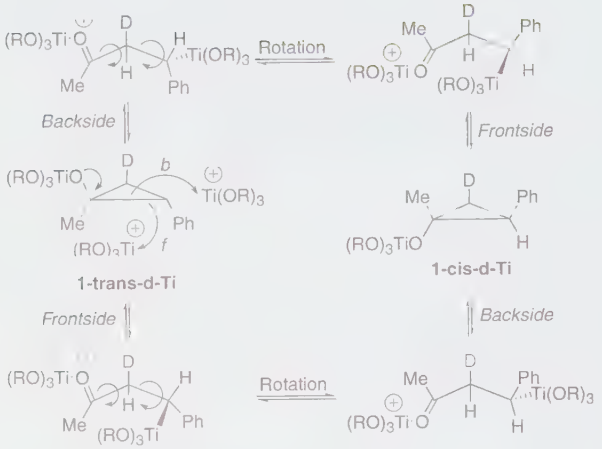
The isomerizations of **1-trans-d** catalyzed by $Ti(O\text{-}i\text{-}Pr)_4$ and $BF_3{\cdot}OEt_2$ occur so rapidly that only fully equilibrated mixtures are seen. Therefore, it is not possible to tell whether any one of the three processes in Scheme 13 occurs more rapidly than another. In the slower isomerization catalyzed by *i*-PrMgCl and $Cl_2Ti(O\text{-}i\text{-}Pr)_2$ (Scheme 8), all three isomerized cyclopropanes formed at rates proportional to their equilibrium distributions. Therefore, it seems likely that the three processes of Scheme 13 all occur at similar rates.

It should be noted that the processes shown in Schemes 14–16 all involve ring opening, rotation, and ring closing. Two of these processes require that ring opening and ring closing occur with opposite stereochemistries. An alternative would be to have the ring opening and closing occur with only a single stereochemistry and to invert the -CHPhTi center by transmetallation. Normally, transmetallation occurs with retention of stereochemistry, but there are examples where inversion has been demonstrated (16).

Conclusions

We have demonstrated a rapid $Ti(O\text{-}i\text{-}Pr)_4$–$BF_3{\cdot}OEt_2$ catalyzed isomerization of cyclopropanols involving epimeriza-

Scheme 16.



tion at two cyclopropyl carbons. This double epimerization requires reversible opening of the cyclopropyl ring to a β-titanaketone and is consistent with two competing stereochemistries for ring closing and opening. Equilibrium constants between epimeric cyclopropoxides and between epimeric cyclopropanols were determined by measuring the effects of catalyst concentration on product ratios.

Experimental section

Kulinkovich hydroxycyclopropanation employing $BF_3{\cdot}OEt_2$

i-PrMgCl (4.2 mL, 2.0 mol/L solution in Et_2O, 8.4 mmol) in Et_2O (5 mL) was added dropwise over 5 min to a 0 °C solution of Ti(O-*i*-Pr)$_4$ (0.99 mL, 3.5 mmol), EtOAc (0.33 mL, 3.4 mmol), and *trans*-β-deuterostyrene (0.71 g, 6.7 mmol) in Et_20 (15 mL). After stirring for 1 min, $BF_3{\cdot}OEt_2$ (1.06 mL, 8.4 mmol) was added and the reaction mixture was allowed to warm to room temperature over 1 h. The reaction mixture was poured into a 10% aq. H_2SO_4 solution (20 mL) and was extracted with Et_2O (3 × 15 mL). The Et_2O extract was washed with a satd. aq. $NaHCO_3$ solution (20 mL) and H_2O (20 mL) and was dried ($MgSO_4$). Solvent was removed by rotary evaporation to give a colorless oil. ^{1}H NMR spectroscopy showed the formation of **1-trans-d** and **1-cis-d** (37%) and of **2-trans-d** and **2-cis-d** (19%), based on integration vs. THF added after workup as an internal standard. Recrystallization from pentane gave a 1:1 mixture of **1-trans-d** and **1-cis-d** (177 mg, 35%).

In a similar experiment, a 1:1 mixture of **1-trans-d** and **1-cis-d** (62 mg, 12%) was obtained by preparative TLC (silica gel, 10:1 pentane–ether, R_f = 0.2) along with a 1:1 mixture of **2-trans-d** and **2-cis-d** (R_f = 0.3) as an impure mixture with decomposition products. The ^{1}H NMR spectrum of this mixture of **2-trans-d** and **2-cis-d** was consistent with the chemical shifts previously reported for unlabelled cyclopropanol **2** (11).

For a 1:1 mixture of **1-trans-d** and **1-cis-d**: ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.28 (t, *J* = 7.5 Hz, 2H), 7.21–7.13 (m, 3H), 2.31 (br d, *J* = 9.3 Hz, 1H, CHPh), 2.13 (br s, 1H, OH), 1.21 (d, *J* = 10.2 Hz, 0.5 H, CHD), 1.16 (s, 3H, Me), 0.97 (d, *J* = 6.6 Hz, 0.5 H, CDH). ^{2}H{^{1}H}NMR (76.7 MHz, CH_2Cl_2) δ: 1.21 (s, 1.00D), 0.98 (s, 1.01D). ^{13}C{^{1}H}NMR (75 MHz, CD_2Cl_2) δ: 139.4, 128.9 (2C), 128.7 (2C), 126.4, 57.8, 31.2, 20.9, 18.9 (t, J_{HD} = 24 Hz). HRMS (EI) calcd. for $C_{10}H_{11}D^{\cdot+}$ ($M^{\cdot+}$): 149.0950; found: 149.0950.

For a 1:1 mixture of **2-trans-d** and **2-cis-d**: ^{2}H {^{1}H} NMR (76.8 MHz, CH_2Cl_2) δ: 1.18 (s, 1.00D), 1.05 (s, 1.02D).

Isomerization of cyclopropanols 1 and 2 *with* deprotonation by a Grignard reagent

A solution of cyclopropanol **1** (25.0 mg, 0.168 mmol) in Et_2O (0.8 mL) was added by syringe over 1 min to a stirred solution of *i*-PrMgCl (92 μL, 2.0 mol/L solution in Et_2O, 0.18 mmol) in Et_2O (1.5 mL). After stirring for 30 min, Ti(O-*i*-Pr)$_4$ (47.8 mg, 0.168 mmol) in Et_2O (0.5 mL) was added. After 10 min, $BF_3{\cdot}OEt_2$ (53 μL, 0.42 mmol) was added and the reaction mixture was stirred for ~2 min before quenching. The mixture was cooled to ~5 °C and cold 10% aq. H_2SO_4 (4 mL) was added. This mixture was extracted with Et_2O (3 × 2 mL) and the combined Et_2O extracts were washed with satd. aq. $NaHCO_3$ (2 mL) and H_2O (3 mL) and dried over 4Å molecular sieves. Evaporation of the solvent gave a 4:1 mixture of cyclopropanols **1** and **2**, which were shown to be >95% pure by ^{1}H and ^{2}H NMR spectroscopy.

When the isomerization of **1** was performed on a 100 mg scale, recrystallization from pentane at –30 °C allowed separation of pure crystalline **1**. Successive crystallizations of the mother liquor at –78 °C gave a mixture of **2** and **1** in a 75:25 ratio that was free of any additional impurities.

For cyclopropanol **2** (11): ^{1}H NMR (500 MHz, CD_2Cl_2) δ: 7.31 (t, *J* = 7.4 Hz, 2H), 7.19–7.26 (m, 3H), 1.98 (dd, *J* = 9.5, 7.0 Hz, 1H, CHPh), 1.72 (br s, 1H, OH), 1.54 (d, *J* = 0.6 Hz, 3H, Me), 1.19 (tq, *J* = 6.6, 0.6 Hz, 1H, CH*H*), 1.05 (dd, *J* = 9.5, 5.9 Hz, 1H, C*H*H). ^{13}C {^{1}H} NMR (126 MHz, CD_2Cl_2) δ: 138.6, 129.0 (2C), 128.6 (2C), 126.4, 57.1, 30.8, 26.2, 20.4. NOESY 1D ^{1}H NMR (500 MHz, CD_2Cl_2): The methyl protons at δ 1.54 were pulsed and integrated for –3.000H, the resonance at δ 1.98 for the benzylic hydrogen cis to the methyl group integrated as +0.035H (3.5%), the resonance at δ 1.05 for the proton on C-3 cis to the methyl group integrated as +0.020H (2.0%), and the resonance at δ 1.18 for the proton on C-3 trans to the methyl group integrated as +0.004H (0.4%).

Isomerization of cyclopropanols 1 and 2 *without* deprotonation by a Grignard reagent

$BF_3{\cdot}OEt_2$ (53 μL, 0.42 mmol) was added to a solution of **1** (25.0 mg, 0.168 mmol) and Ti(O-*i*-Pr)$_4$ (47.8 mg, 0.168 mmol) in Et_2O (2.3 mL). After 2 min, the solution was cooled to 5 °C and quenched by the addition of cold 10% aq. H_2SO_4 (4 mL). This mixture was extracted with Et_2O (3 × 2 mL) and the combined Et_2O extracts were washed with satd. aq. $NaHCO_3$ (2 mL) and H_2O (3 mL) and dried over 4 Å molecular sieves. Evaporation of the solvent gave a quantitative yield of a 4:1 mixture of cyclopropanols **1** and **2**, which were shown to be >97% pure by ^{1}H and ^{2}H NMR spectroscopy.

Reaction of 1-trans-d with $BF_3{\cdot}OEt_2$ in the absence of Ti(O-*i*-Pr)$_4$

$BF_3{\cdot}OEt_2$ (53 μL, 0.42 mmol) was added to a solution of **1** (25.0 mg, 0.168 mmol) in Et_2O (0.8 mL). After 2 min, the

solution was cooled to 5 °C and quenched by the addition of cold 10% aq. H_2SO_4 (4 mL). This mixture was extracted with Et_2O (3 × 2 mL) and the combined Et_2O extracts were washed with satd. aq. $NaHCO_3$ (2 mL) and H_2O (3 mL) and dried over 4 Å molecular sieves. Evaporation of the solvent gave an oily solid that was >90% **1-trans-d** by ^1H and ^2H NMR spectroscopy and contained no other cyclopropanols.

Measurement of cyclopropanol–Titanium cyclopropoxide equilibria

In an NMR tube, cyclopropanol **1** (25 or 50 mg) was combined with Ti(O-*i*-Pr)$_4$ (1.0, 0.25, or 0.10 equiv.) in Et_2O-d_{10} (0.65 mL). Equilibrium was established immediately and spectra of the samples taken directly after the addition or after 20 min showed no differences. Peaks for the methine proton of the isopropanol and titanium isopropoxide were visible at δ 3.9 and 4.5, respectively.[12] The peaks for the benzylic protons of cyclopropanol **1** and the titanium cyclopropoxides of **1** gave resonances at δ 2.22 and 2.5, respectively. The percentage of **1** in the cyclopropanol form relative to the percentage in the titanium cyclopropoxide form was determined from the relative integrations of these two peaks (Table 1).

Acknowledgement

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[12]The peak positions varied slightly for isopropanol and for **1** ($\Delta\delta < 0.02$ ppm) and were dependent on changes in the bulk solvent as catalyst loading increased. The isopropoxides and cyclopropoxides showed more variation ($\Delta\delta < 0.09$ ppm) at different ratios of **1**:Ti(O-*i*-Pr)$_4$. These systematic variations in frequency can be attributed to the changing mix of alkoxides bound to titanium.

Tetraazaoctaphyrin — A biimidazole-containing expanded porphyrin[1]

Jonathan L. Sessler, Bobbi L. Rubin, Marcin Stępień, Thomas Köhler, G. Dan Pantos, and Vladimir Roznyatovskiy

Abstract: A series of expanded porphyrins, incorporating biimidazoles and bipyrroles within their macrocyclic framework, has been synthesized. Insights into the complex conformational characteristics of these systems were obtained from two-dimensional NMR spectroscopic studies. The relative energy values for the various asymmetric structures inferred from these analyses were compared using DFT molecular modeling calculations.

Key words: macrocycles, expanded porphyrins, imidazoles, pyrroles, biimidazoles, supramolecular chemistry, heterocycles.

Résumé : On a réalisé la synthèse d'une série de porphyrines agrandies qui incorporent des biimidazoles et des bipyrroles dans le squelette de leur macrocycle. Sur les bases des études de spectroscopie RMN bidimensionnelle, on a extrait des donnés qui permettent de mieux comprendre les caractéristiques conformationnelles complexes de ces systèmes. On a comparé les valeurs relatives d'énergie de diverses structures asymétriques déduites de ces analyses à celles obtenues par des calculs de modélisation moléculaire sur la base de la théorie de la fonctionnelle de densité.

Mots clés : macrocycles, porphyrines agrandies, imidazoles, pyrroles, biimidazoles chimie macromoléculaire, hétérocycles.

[Traduit par la Rédaction]

Introduction

A new subdiscipline of porphyrin chemistry, involving the synthesis and study of large oligopyrrole macrocycles, so-called expanded porphyrins, was instigated by the serendipitous discovery of sapphyrin by Woodward and co-workers in the mid 1960s (1). In the decades since that time, the field of expanded porphyrin chemistry has grown into a large and vibrant subfield of macrocyclic chemistry (2). Expanded porphyrins have been studied in the context of molecular recognition with anionic, cationic, and neutral substrates (3). Part of what is driving this research is the promise that these systems show in various practical applications, ranging from drug development to anion recognition (4–7). Work in this area has also been inspired by less prosaic motivations, including the synthetic challenge of constructing new oligopyrrolic macrocycles and their inherent aesthetic appeal.

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Most known expanded porphyrins, with the exception of Schiff-base macrocycles, have been constructed from pyrrole and its closely related heterocyclic analogues, furan, thiophene, and selenophene. Recently, efforts have shifted towards incorporating imidazoles and biimidazoles into porphyrin-like structures. Youngs et al. (8) reported the synthesis of a series of cyclophane complexes, or porphyrinoids, which contained imidazoliums incorporated into the skeletal framework of the macrocycle. In 2003, the research groups of Allen (9) and Nonell (10) separately reported the first biimidazole-based porphycene analog, imidacene. There have also been a number of reports that describe the incorporation of imidazole or imidazolium cations into other macrocyclic structures (11–14). These systems show great promise in both anionic and cationic recognition and are made especially interesting because they are potentially capable of recognition both inside and outside the skeletal framework. In spite of this promise, biimidazoles, as opposed to imidazoles, have yet to be incorporated into expanded porphyrin-type frameworks. We report here the first example of such a system, namely 3,6,21,24-tetraaza[32]octaphyrin(1.0.1.0.1.0.1.0).

Results and discussion

The synthesis of tetraazaoctaphyrin target **3** was carried out in a single step via the condensation of biimidazole **1** with bis-α-free bipyrrole **2** under dilute conditions (Scheme 1). Biimidazole **1a** was prepared according to the literature and **1b** was synthesized using an extension of this same basic methodology (10). Bipyrroles **2a**–**2c** were synthesized according to the literature (15, 16).[4] The condensation of biimidazole **1** with bipyrrole **2** was performed in a

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methanol–tetrahydrofuran (THF) mixture using trifluoroacetic acid (TFA) as the acid catalyst. After column chromatographic work-up over silica gel, tetraazaoctaphyrins **3a–3e** were obtained in yields ranging from 26% to 69%, depending on the substrates used. The compounds obtained in this way are unstable when exposed to oxygen and decompose over time. Thus, they were stored in a freezer under a blanket of argon. Under these conditions, little decomposition was seen for a period of 1 week. Elemental analysis was used as a means of characterization and repeatedly resulted in total carbon, hydrogen, and nitrogen counts of 95%–96% of the theoretical values. XPS analysis revealed the presence of silicon and oxygen, which is supported by a singlet near 0 ppm observed in the ^{1}H NMR spectra of **3a–3e**, attributable to a dimethyl siloxane compound. Efforts to remove the impurity included recrystallization, trituration, and extraction, but unfortunately all proved unsuccesful. If, however, the carbon, hydrogen, and nitrogen percentage is normalized to 100% and compared with a theoretical percentage of the same elements, thus accounting for the amount of impurity in these percentages, the experimental results fall within acceptable error values (i.e., $\Delta < 0.20\%$). In an additional experiment, the solvent was passed through a blank column under identical conditions and the siloxane was identified in the eluate by XPS and ^{1}H NMR spectroscopy, thus establishing the silica gel as the likely source of the impurity.

The UV–vis absorption spectrum of **3b**, the prototypical tetraazaoctaphyrin chosen for detailed study, is characterized by a Soret-type band at 299 nm and a Q-type band at 633 nm (Fig. 1). These features, particularly the latter long-wavelength absorption band, are considered diagnostic of an extended conjugated system (17). Dilute solutions of tetraazaoctaphyrin **3** in methylene chloride are blue and fluoresce red (Fig. 2). For the fluorescence emission experiments, excitation was performed at 578 nm, while the emission maximum was observed at 670 nm.

The one-dimensional ^{1}H NMR spectrum of **3b** recorded in dichloromethane-d_2 is shown in Fig. 3. It is apparent from an inspection of this spectrum that the solution structure of **3b** does not exhibit the fourfold symmetry implied by the representation of the macrocycle given in Scheme 1. The actual conformation has only twofold symmetry, which can be inferred from the doubled number of peaks in the aromatic and alkyl regions. The signal at 9.87 ppm integrates to two protons and most likely corresponds to a pyrrole NH proton. When studied as a solution in DMSO-d_6, an additional peak with the same integral intensity can be observed at 10.8 ppm. In dichloromethane-d_2, this signal is broadened by exchange and cannot be observed. Such a solvent dependence is typically found for imidazole NH protons. Based on these findings, the signal is assigned as an imidazole NH; however, its exact placement on the biimidazole unit could not be determined. Chemical shifts of the NH and meso protons indicate an absence of overall macrocyclic aromaticity.

The doubled spectral pattern, indicative of symmetry lowering, is also seen for the other tetraazaoctaphyrin derivatives. It should, however, be noted that the doubled signals assigned to the dominant species present in solution are often accompanied by ones ascribable to an impurity, which gives rise to a single set of peaks. The admixture inferred on this basis cannot be separated by chromatography (all samples yield a single peak on the HPLC chromatogram). While the identity of the additional species could not be ascertained, it is thought that it may correspond to a different symmetrical conformation for each of the different derivatives of **3**.

Fig. 1. Absorbance (—) and fluorescence spectra (----) of **3b** in CH_2Cl_2.

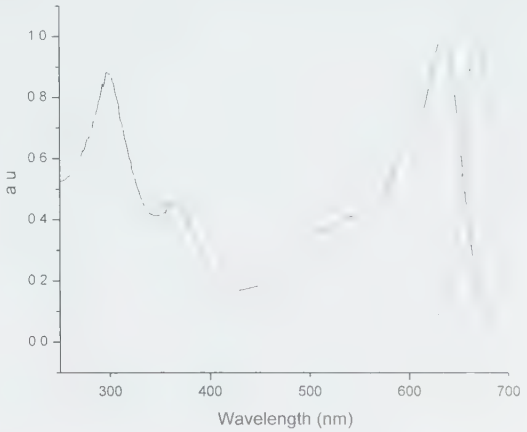
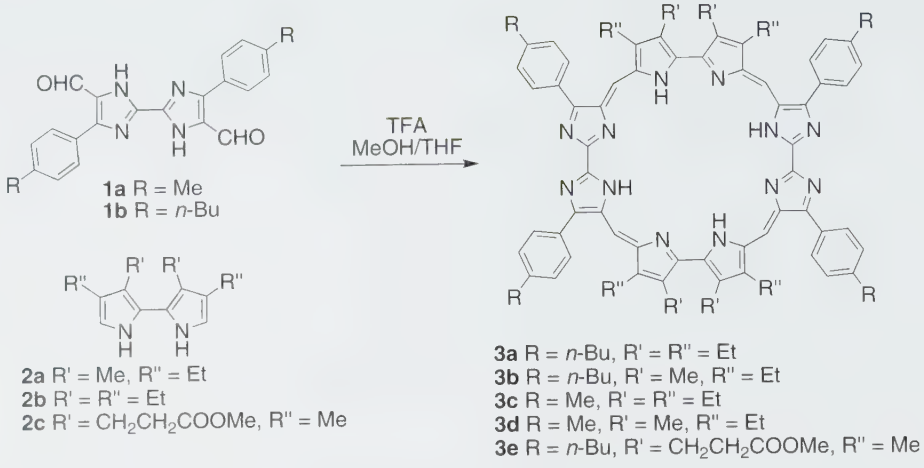


Fig. 2. Dilute solution tetraazaoctaphyrin **3b** in methylene chloride in the absence (left) and presence (right) of an illuminating black light (365 nm).

The assignment of the signals presented in Fig. 3 follows the labeling pattern given in Scheme 2. These assignments were deduced using two-dimensional NMR spectroscopy (COSY and ROESY maps). Figure 4 shows representative expansions of the COSY spectrum, used to establish connectivity within the aryl rings and alkyl chains. There is a significant crowding of signals in the alkyl region, which was resolved on the COSY map. Further insight into the structure and conformation of **3b** was gained from an analysis of the ROESY spectrum (Fig. 5).

Based on selected ROE cross-peaks, it was possible to assign unequivocally each of the signals to one of the two

Scheme 1. Synthesis of tetraazaoctaphyrin **3**.

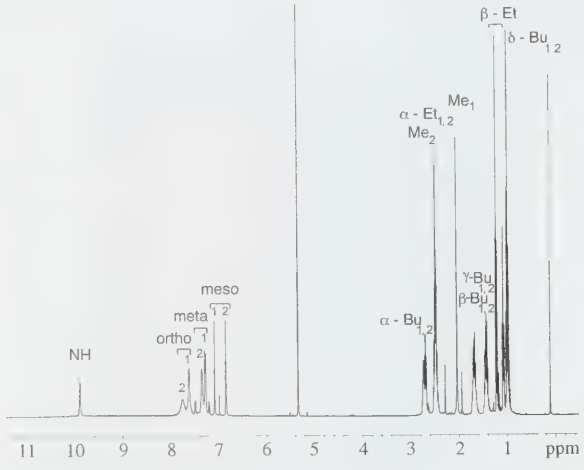


1a R = Me
1b R = *n*-Bu

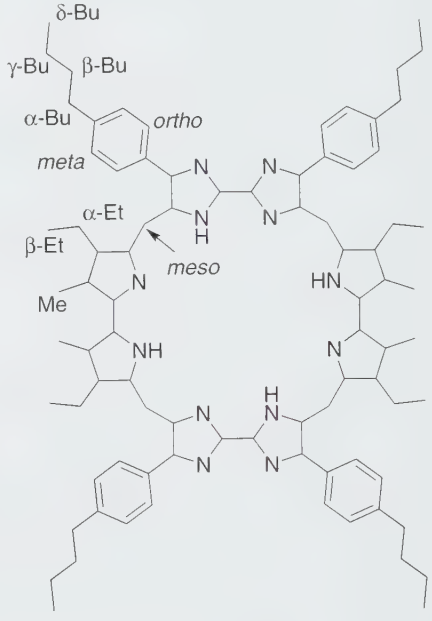
2a R' = Me, R'' = Et
2b R' = R'' = Et
2c R' = CH_2CH_2COOMe, R'' = Me

3a R = *n*-Bu, R' = R'' = Et
3b R = *n*-Bu, R' = Me, R'' = Et
3c R = Me, R' = R'' = Et
3d R = Me, R' = Me, R'' = Et
3e R = *n*-Bu, R' = CH_2CH_2COOMe, R'' = Me

Fig. 3. ^{1}H NMR spectrum of compound **3b** (500 MHz, CD_2Cl_2, 298 K). Labeling of peaks follows that given in Scheme 2.



Scheme 2. Labeling scheme used in the analysis of ^{1}H NMR spectra of **3b**. For simplification, π bonding in the macrocycle is not shown. Placement of pyrrole and imidazole NH protons is arbitrary.



nonequivalent subunits 1 and 2 (Scheme 3). Each of the subunits contains one pyrrole ring and one imidazole ring linked by a meso-bridging carbon atom. In addition, four special ROE correlations provided the information necessary to determine the arrangement of constituent rings in each subunit. The meso signal of subunit 1 ($meso_1$, 7.04 ppm) correlates with the ortho signal of the adjacent aryl ring ($ortho_1$, 7.59 ppm, peak A in Fig. 5), as well as with one of the ethyl CH_3 signals (β-Et1, 1.04 ppm, peak C). In the other subunit, the meso signal ($meso_2$, 6.95 ppm) only correlates with the respective ethyl group (β-Et2, 1.21 ppm, peak D) and shows no cross-peak to the ortho signal ($ortho_2$, 7.72 ppm). However, the latter yields an unexpected correlation with the pyrrolic NH (peak B). This latter correlation can be rationalized by assuming a "kinked" conformation for subunit 2, in which the meso CH fragment is turned away from the aryl ring (Scheme 3).

Macrocycle **3** should contain two subunits of type 1 and two of type 2 combined in such a way that the entire structure exhibits twofold symmetry. The four arrangements that meet the above criterion are shown in Fig. 6. In arrangements A and B, the sequence of subunits in the ring is 1–2–1–2, whereas, in arrangements C and D, the sequence is 1–1–2–2. Furthermore, the aryl rings pointing towards the inside of the macrocycle are positioned on the same side of the macrocyclic plane (in arrangements A and C) or on the opposite sides (B and D). As a result, we obtain four distinct conformers, two of which are chiral (A and D).

Inspection of the molecular models leads to the inference that arrangement B is the least congested of the four conformers and hence the one with the lowest energy. This conclusion is supported by DFT calculations performed at the TZ2p atomic level. Optimized geometries and relative

Fig. 4. ^{1}H COSY spectrum of **3b** (500 MHz, CD_2Cl_2, 298 K). Parts (*A*) and (*B*) show expansions of the aromatic and aliphatic regions, respectively. Peaks corresponding to the symmetrical form are not labeled.

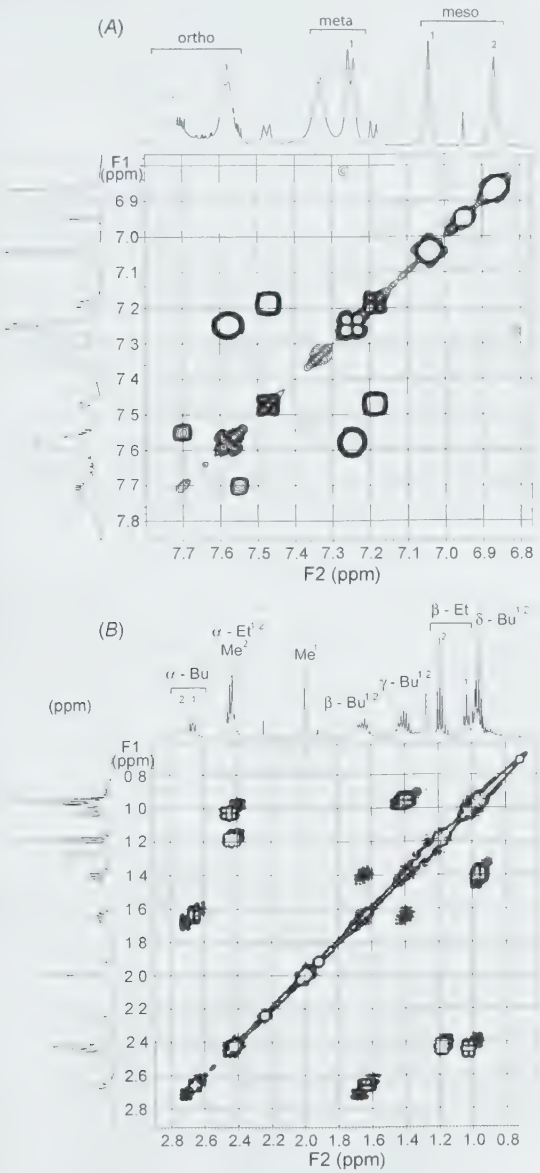
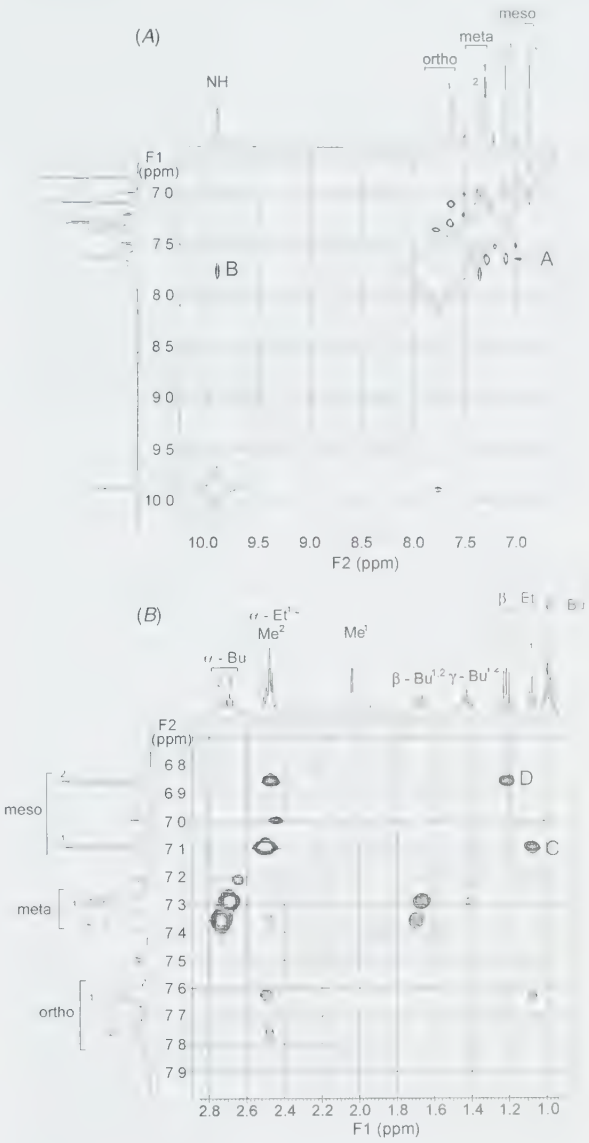


Fig. 5. ^{1}H ROESY spectrum of **3b** (500 MHz, CD_2Cl_2, 298 K). Parts (*A*) and (*B*) show the expansions of aromatic–aromatic and aliphatic–aromatic regions, respectively. The spectrum is phased to give positive ROE crosspeaks.

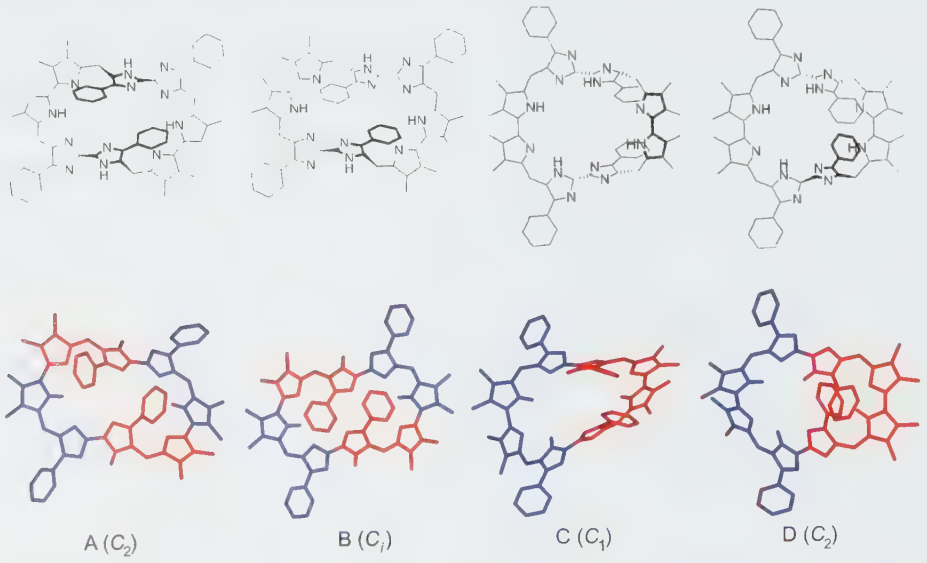


energy values are given in Table 1. Conformer B is the most stable, closely followed in energy by conformer D (Fig. 6); not surprisingly, conformations A and C are higher in energy, likely reflecting the cis arrangement of the phenyl rings within the cavity. Additionally, conformer C, expected to have a symmetry plane (C_s symmetry), collapsed upon optimization into a completely nonsymmetrical geometry.

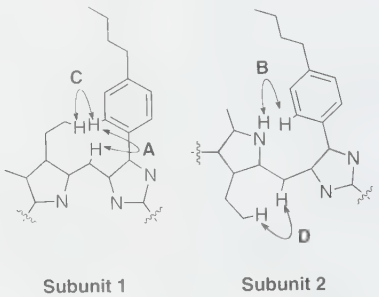
The conformation of **3** observed in solution appears to be rigid. No exchange cross-peaks in the room temperature ROESY and NOESY spectra have been observed between topologically equivalent signals (e.g., meso$_1$ and meso$_2$); nor has any exchange been noted between the major asymmetrical form and the symmetrical admixture mentioned earlier. In point of fact, the lines remain sharp even at 130 °C in DSMO-d_6. However, significant broadening is observed at room temperature for the ortho and meta signals of the aryl rings (Fig. 3). This broadening is most readily interpreted in terms of the aryl moieties being in an unsymmetrical environment and undergoing slow rotation, conclusions that are consistent with the nonplanar conformation noted above.

Interestingly, the conformation proposed for **3** has no apparent precedent among the structures of octaphyrins

Fig. 6. Possible conformers of tetraazaoctaphyrin **3** (top). The bottom part shows the DFT optimized structures and their point symmetries. Within the optimized structures, subunit 1 is highlighted in blue, while subunit 2 is highlighted in red for clarity. With the exception of the NH hydrogen atoms, all the hydrogen atoms have been removed for clarity.



Scheme 3. Illustration of the two subunit structure of **3b**, as determined from the interpretation of the ROESY spectrum. The π electron extended conjugation is removed for clarity.



reported to date. For [32]octaphyrin(1.0.1.0.1.0.1.0), reported by Vogel and co-workers (18), a D_2-symmetrical figure eight conformation with transoid bipyrrole subunits located at the figure eight intersection was observed in the crystal structure. A similar conformation was conjectured for a closely related macrocycle obtained by Setsune et al. (19). Another type of figure eight conformation was observed for [36]octaphyrin(1.1.1.1.1.1.1.1), reported by Furuta, Osuka and co-workers. (20), and for its thiophene analogue obtained by Spruta and Latos-Grażyński (21). However, the presence of four imidazole rings in system **3** and a different substitution pattern (aryl groups at the β-pyrrole positions) may explain why this new macrocycle adopts a conformation different from that of its all-pyrrole analogue (18).

Conclusion

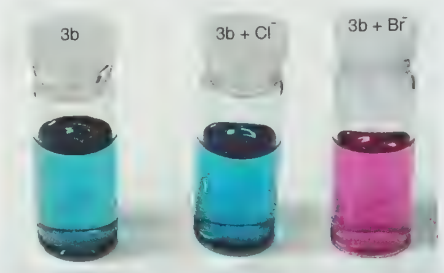
The design and synthesis of a novel expanded porphyrin has been described. The series of tetraazaoctaphyrins **3a–3e** were formed from the condensation of biimidazole dialdehydes **2a** and **2b** with bis-α-free bipyrroles **2a–2c**. The high density of NH functionality makes these systems of potential interest as anion receptors. Initial qualitative tests of this postulate have been performed on tetraazaoctaphyrin **3**. We have found that the neutral host (**3b**) undergoes a naked-eye detectable color change in the presence of fluoride, bromide

Table 1. Minimization energy values for molecular arrangements A–D.

Arrangement	Energy (kcal/mol)	Relative energy
A	–321 084.01	16.76
B	–321 067.25	0
C	–321 053.80	13.45
D	–321 064.63	2.62

Note: 1 cal = 4.184 J.

Fig. 7. Tetraazaoctaphyrin **3b** in acetonitrile in the absence (left) and presence of tetrabutylammonium chloride (middle) and tetrabutylammonium bromide (right).



(Fig. 7), cyanide, hydroxyde, acetate, nitrate, dihydrogenphosphate anions (studied in the form of their respective tetrabutylammonium salts). On the other hand, no change in the spectral properties of **3b** was noted upon addition of chloride, iodide, hypochlorate, nitrite, benzoate, and hydrogensulfate anions. Such observations lead us to propose that this or other neutral biimidazole-incorporated expanded porphyrins may emerge as useful anion sensors.

Experimental

General information

All reagents and solvents were purchased from Sigma-Aldrich Corporation, Fischer Scientific, or Fluka and used without further purification with the following exceptions. Dichloromethane was dried by distillation under argon over calcium hydride. Dimethylformamide was dried by passage through two columns of molecular sieves. Tetrahydrofuran (THF) was dried by passage through two columns of activated alumina. Toluene was dried by passage through two columns of activated alumina. *N*-Bromosuccinimide was recrystallized from boiling water. For column chromatography, silica gel (Scientific Adsorbents Inc., particle size 32–63 μm) was used as the immoble phase.

1-((2-(Trimethylsilyl)ethoxy)methyl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-5-formyl-4-*p*-tolyl-1H-imidazol-2-yl)-4-*p*-tolyl-1H-imidazole-5-carbaldehyde

4,4′-Dibromo-1,1′-bis[(trimethylsilyl)ethoxymethyl]-2,2′-biimidazole-5,5′-dicarbaldehyde (10) (1.68 mmol) and *p*-methylphenyl boronic acid (3.36 mmol) were degassed for 20 min in 9.2 mL of 2 mol/L sodium carbonate and 4 mL of ethanol by purging the solution with argon. Palladium tetrakistriphenylphosphine (10% mol) was added and the reaction was heated to reflux for 7 h using an oil bath. The reaction flask was removed from the oil bath, cooled, and the mixture was diluted with ethyl acetate, dried with sodium sulfate, filtered, and concentrated in vacuo to give an oil. Column chromatography was performed using silica gel as the solid support, eluting initially with hexanes and slowly increasing the polarity to 20% ethyl acetate in hexanes. Desired fractions were combined, concentrated in vacuo, and dried to give an off-white solid in 89% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: –0.13 (m, 9H), –0.08 (m, 9H), 2.02 (s, 3H), 2.42 (s, 3H), 3.58 (m, 4H), 4.10 (m, 4H), 6.31 (s, 2H), 6.37 (s, 2H), 7.30 (d, J = 8.0 Hz, 4H), 7.61 (d, J = 7.6 Hz, 4H), 9.88 (s, 1H), 9.96 (s, 1H). ^{13}C NMR δ: 14.17, 17.86, 21.35, 60.39, 66.41, 127.14, 127.55, 128.75, 128.95, 129.29, 120.49, 129.525, 139.71, 141.16, 154.49, 171.17, 181.00. HR-MS (CI^+) m/z ($M + H^+$) calcd. for $C_{22}H_{18}N_4O_2$: 371.1508; found: 371.1521.

2-(5-Formyl-4-*p*-tolyl-1H-imidazol-2-yl)-4-*p*-tolyl-1H-imidazole-5-carbaldehyde (1a)

The previous compound (0.457 mmol) was dissolved in 10 mL ethanol. Ten milliliters of 10% HCl was added and the reaction was heated to reflux for 1 h using an oil bath. The flask was removed from the oil bath, cooled, and the solution was carefully neutralized with 10% aqueous sodium carbonate. At this juncture, a solid precipitated out of solution. It was filtered and washed with ice-cold water, and dried under vacuum to give the desired compound in the form of a white solid in 78% yield; mp 160–180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.37 (s, 6H), 7.33 (d, J = 7.6 Hz, 4H), 7.79 (d, J = 8.4 Hz, 4H), 9.88 (s, 2H). ^{13}C NMR (500 MHz, DMSO-d_6) δ: 21.00, 125.30, 126.81, 128.73, 128.97, 129.30, 129.58, 129.72, 133.12, 139.25, 140.01, 182.60. HR-MS (CI^+) m/z ($M + H^+$) calcd. for $C_{22}H_{18}N_4O_2$: 371.1508; found: 371.1521.

General procedure for the preparation of tetraazaoctaphyrin derivatives (3)

Biimidazole dialdehyde **1** (0.184 mmol) was dissolved in 200 mL of dry 2:1 methanol–THF containing 1 mL of TFA. Bipyrrole **2** (0.184 mmol) was separately dissolved in 40 mL of the same solvent ratio and placed in an addition funnel. The bipyrrole solution was added dropwise to the biimidazole solution over 30 min and after several hours of stirring at room temperature, an additional 1 mL of TFA was added to the reaction. Stirring was continued overnight with the reaction left open to the atmosphere. After 12 h, the deep blue-black solution was concentrated in vacuo to give a deep purple oil, which was taken to dryness on the vacuum line to remove any residual trifluoroacetic acid. Column chromatography was performed twice over silica gel, eluting initially with methylene chloride before the polarity of the eluent was slowly increased to 3% methanol in methylene chloride. The desired fractions were combined and concentrated in vacuo to give a lustrous blue-black solid. The material was then redissolved in methylene chloride, washed with 5% aqueous sodium bicarbonate, dried over sodium sulfate, filtered, concentrated in vacuo to a blue-black solid, and dried under vacuum. The solid was triturated with distilled pentane to remove any remaining grease. The desired tetraazaoctaphyrin was obtained as a blue-black lustrous solid.

Elemental analysis was pursued as a means of characterization and repeatedly resulted in carbon, hydrogen, and nitrogren counts of 95%–96% of the theoretical values. XPS analysis revealed the presence of 3.14% silicon in the sample of **2.5b**. Taking into account this silicon percentage, the calculated impurity reveals 1.40 equiv. of the siloxane for each equivalent of the host **2.5b**. Anal. calcd. for $C_{84}H_{92}N_{12}\cdot1.4SiO_2(CH_3)_2$: C 74.72, H 7.20, N 12.05; found: C 74.71, H 7.09, N 12.22. Efforts to remove the impurity included recrystallization, trituration, and extraction, but unfortunately all proved unsuccesful.

2,7,20,25-Tetra-*p*-butylphenyl-11,12,15,16,29,30,33,34-octaethyl–3,6,21,24-tetraaza[32]octaphyrin(1.0.1.0.1.0.1.0) (3a)

The compound was obtained from the condensation of biimidazole **1b** (10) with bipyrrole **2b** (16)[4] in 69% yield, following the general procedure given above. UV–vis (CH_3CN, nm (ε)) λ_{max}: 296 (85 800), 534 (41 100), 631 (94 300). ^{1}H NMR (500 MHz, CD_2Cl_2) δ: 0.95–1.09 (comp, 24H, CH_2CH_3, $CH_2CH_2CH_2CH_3$), 1.13–1.21 (comp, 8H, CH_2CH_3), 1.39–1.49 (comp, 8H, $CH_2CH_2CH_2CH_3$), 1.61–1.75 (comp, 8H, $CH_2CH_2CH_2CH_3$), 2.34 (m, 8H, CH_2CH_3), 2.65–2.77 (comp, 12H, CH_2CH_3 & $CH_2CH_2CH_2CH_3$), 2.97 (m, 4H, $CH_2CH_2CH_2CH_3$), 6.94 (s, 2H, *meso-H*), 7.080 (s, 2H, *meso-H*), 7.27 (d, J = 8.0 Hz, 4H), 7.38 (d, J = 8.5 Hz, 4H), 7.53 (d, J = 8.0 Hz, 4H), 7.82 (d, J = 8.0 Hz, 4H), 9.98

(s, 2H, *NH*), 11.70 (br, *NH*). ^{13}C NMR (500 MHz, CD_2Cl_2) δ: 12.95, 13.095, 13.18, 15.12, 16.33, 17.11, 17.21, 18.19, 21.44, 21.59, 32.26, 32.43, 34.59, 34.64, 117.92, 123.68, 126.87, 127.59, 128.09, 128.45, 134.20, 134.86, 136.08, 137.16, 139.27, 141.34, 144.15, 144.29, 148.18, 150.13, 158.59.

2,7,20,25-Tetra*-p-*butylphenyl-11,16,29,34-tetraethyl-12,15,30,33-tetramethyl-3,6,21,24-tetraaza[32]octaphyrin-(1.0.1.0.1.0.1.0) (3b)

The compound was obtained from the condensation of biimidazole **1b** (10) with bipyrrole **2a** (16)[4] in 54% yield, following the general procedure given above. UV–vis (CH_3CN, nm (ε)) λ_{max}: 299 (139 000), 536 (68 500), 633 (142 000). ^{1}H NMR (500 MHz, CD_2Cl_2) δ: 0.93–1.04 (comp, 18H, CH_2CH_3, $CH_2CH_2CH_2CH_3$), 1.16–1.21 (m, 6H, CH_2CH_3), 1.36–1.47 (m, 8H, $CH_2CH_2CH_2CH_3$), 1.59–1.69 (comp, 8H, $CH_2CH_2CH_2CH_3$), 2.00 (s, 6H, CH_3), 2.39–2.47 (comp, 14H, CH_3 and $CH_2CH_2CH_2CH_3$), 2.61–2.72 (comp, 8H, $CH_2CH_2CH_2CH_3$), 6.87 (br, 2H, *meso-H*), 6.95 (s, 1H, *meso-H*), 7.04 (br, 1H, *meso-H*), 7.19 (m, 2H), 7.25 (m, 2H), 7.46 (br, 4H), 7.49 (m, 2H), 7.59 (br, 2H), 7.72 (br, 4H), 9.87 (br, 2H). ^{13}C NMR (500 MHz, CD_2Cl_2) δ: 10.95, 11.67, 14.11, 14.38, 15.64, 18.16, 18.69, 22.81, 33.98, 35.84, 119.71, 121.37, 126.50, 128.68, 129.10, 129.14, 129.42, 137.88, 143.97, 144.85, 147.48, 159.16.

2,7,20,25-Tetra*-p-*methylphenyl-11,12,15,16,29,30,33,34-octaethyl-3,6,21,24-tetraaza[32]octaphyrin(1.0.1.0.1.0.1.0) (3c)

The compound was obtained from the condensation of biimidazole **1a** with bipyrrole **2b** (16)[4] in 62% yield, following the general procedure given above. UV–vis (CH_3CN, nm (ε)) λ_{max}: 299 (78 400), 540 (40 900), 634 (92 400). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 0.90–1.25 (comp, 24H, CH_2CH_3), 2.36–2.99 (comp, 28H, CH_3, CH_2CH_3), 6.89 (s, 1H, *meso-H*), 6.99 (s, 2H, *meso-H*), 7.06 (s, 1H, *meso-H*), 7.22–7.31 (comp, 4H), 7.39 (d, J = 7.6 Hz, 2H), 7.54 (m, 4H), 7.72 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 7.6 Hz, 4H), 10.02 (s, 2H). ^{13}C NMR (500 MHz, CD_2Cl_2) δ: 14.81, 15.22, 15.30, 16.86, 18.17, 18.61, 19.18, 19.54, 21.50, 127.81, 128.92, 129.73, 135.12, 138.73, 147.10, 148.25. HR-MS (FAB$^+$) *m/z* (M + H$^+$) calcd. for $C_{76}H_{77}N_{12}$: 1157.6394; found: 1157.6383.

2,7,20,25-Tetra*-p-*methylphenyl-11,16,29,34-tetraethyl-12,15,30,33-tetramethyl-3,6,21,24-tetraaza[32]octaphyrin-(1.0.1.0.1.0.1.0) (3d)

The compound was obtained from the condensation of biimidazole **1a** with bipyrrole **2a** (16)[4] in 59% yield, following the general procedure given above. UV–vis (CH_3CN, nm (ε)) λ_{max}: 296 (253 000), 531 (140 000), 633 (326 000). ^{1}H NMR (500 MHz, CD_2Cl_2) δ: 1.02 (t, J = 7.5 Hz, 6H), 1.18 (m, 6H), 1.97 (s, 6H), 2.38–2.45 (comp, 6H, CH_3, CH_2CH_3), 6.80 (s, 2H), 7.02 (s, 2H), 7.23 (m, 4H), 7.33 (br, 4H), 7.56 (m, 4H), 7.27 (br, 4H), 9.85 (br, 2H). ^{13}C NMR (500 MHz, CD_2Cl_2) δ: 10.87, 11.55, 14.18, 15.63, 18.17, 18.66, 21.44, 119.89, 121.28, 123.17, 124.99, 126.40, 128.69, 129.44, 129.74, 131.69, 137.54, 138.09, 138.83, 139.80, 147.35, 148.89, 150.94.

2,7,20,25-Tetra*-p-*butylphenyl-11,16,29,34-tetramethyl-12,15,30,33-tetracarboxylate-3,6,21,24-tetraaza[32]octaphyrin(1.0.1.0.1.0.1.0) (3e)

The compound was obtained from the condensation of biimidazole **1b** (10) with bipyrrole **2c** (17) in 26% yield, following the general procedure given above. UV–vis (CH_3CN, nm (ε)) λ_{max}: 275 (34 300), 609 (4790). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 0.98 (m, 12H, $CH_2CH_2CH_2CH_3$), 1.44 (m, 8H, $CH_2CH_2CH_2CH_3$), 1.67 (m, 8H, $CH_2CH_2CH_2CH_3$), 2.05 (s, 12H, CH_3), 2.45 (t, J = 7.4 Hz, 4H, CH_2CH_2), 2.62–2.77 (comp, 12H, CH_2CH_2), 3.02 (t, J = 7.6 Hz, $CH_2CH_2CH_2CH_3$), 3.21 (t, J = 7.2 Hz, 4H, $CH_2CH_2CH_2CH_3$), 3.30 (s, 6H, CO_2CH_3), 3.56 (s, 6H, CO_2CH_3), 7.00 (s, 2H, *meso-H*), 7.13 (s, 2H, *meso-H*), 7.30 (d, J = 7.6 Hz, 4H), 7.41 (d, J = 8.0 Hz, 4H), 7.62 (d, J = 8 Hz, 4H), 7.82 (d, J = 8 Hz, 4H), 10.02 (s, 2H, *NH*).

Molecular modelling studies

Molecular modelling studies were performed using semi-empirical calculations at the PM3 level, using HyperChem® V7.1, for preoptimization. Density functional theory (DFT) calculations were then performed using PRIRODA-04 (22). A PBE functional that includes the electron density gradient was used. The TZ2p atomic basis sets of grouped Gaussian functions were used to solve the Kohn–Sham equations. The criterion for convergence was to reach a difference in energy gradient between two sequential structures below 0.01 kcal/mol/Å (1 cal = 4.184 J). A PDB file for each optimized structure is included in the Supplementary information.[5]

Acknowledgements

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[5] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5038. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

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Toward the total synthesis of lophotoxin — New methodologies and synthetic strategies[1]

Peter Wipf and Michel Grenon

Abstract: Our recent progress toward the synthesis of the furanocembranolide lophotoxin (**1**) is disclosed. Strategies for the stereoselective incorporation of the C_{13} stereocenter by a catalytic desymmetrization of a cyclic *meso*-anhydride, as well as a novel 1,6-addition reaction of organocuprates to unsaturated [1,3]dioxin-4-ones are discussed. Preliminary results on the development of a rhodium-catalyzed asymmetric 1,6-addition reaction are also mentioned. Finally, modifications of a previously reported transition-metal-catalyzed cyclization reaction involving α-propargyl β-keto esters allow furan ring formation either under thermal conditions or by microwave irradiation.

Key words: 1,6-addition, organocuprates, catalytic desymmetrization, furan cyclization, microwave.

Résumé : Nos plus récents progrès concernant la synthèse totale du furanocembranolide lophotoxine (**1**) sont décrits. Des stratégies pour l'incorporation stéréosélective du substituant en C_{13} par la désymétrisation catalytique d'un anhydride cyclique *meso*, ainsi qu'une nouvelle réaction d'addition 1,6-conjuguée d'organocuprates sur des [1,3]dioxin-4-ones insaturées sont discutées. Des résultats préliminaires sur le dévelopement d'une réaction d'addition 1,6-conjugée asymétrique catalysée par le rhodium sont aussi mentionnés. Finalement, la modification d'une réaction de cyclisation catalysée par un métal de transition et mettant en jeu l'α-propargyl β-céto ester permet la formation d'un furane soit sous certaines conditions thermiques ou par irradiation aux micro-ondes.

Mots clés : addition 1,6-, organocuprates, désymétrisation catalytique, cyclisation de furane, microonde.

Introduction

Lophotoxin (**1**) is a member of the furanocembranolides (1), a growing class of natural products that comprise a number of highly functionalized cyclic diterpenes (Fig. 1). This compound is found in a number of marine invertebrates (gorgonian octocorals) located in tropical and subtropical waters (2). Lophotoxin acts as a potent neurotoxin by binding selectively and irreversibly to the Tyr^{190} residue present in the α-subunit of nicotinic acetylcholine receptors, leading to respiratory depression, paralysis, asphyxia, and ultimately death (3). SAR studies have demonstrated that the key structural elements responsible for this unique biological activity can be attributed to the C_7–C_8 epoxide and the lactone oxygens, allowing for a direct structural correlation of the pharmacophore in **1** with acetylcholine (4).

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Dedicated to Dr. Alfred Bader, in recognition of his spirit for entrepreneurship, and his appreciation for the legacy of human accomplishment!

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[1]This article is part of a Special Issue dedicated to Dr. Alfred Bader.

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The presence of a 2,3,5-trisubstituted furan ring adjacent to a trans-trisubstituted epoxide, along with an epoxidized butenolide imbedded in a strained 14-membered macrocycle are the most prominent structural features of this molecule. In addition to the interesting biological activity displayed by this compound, the synthetic challenge offered to organic chemists has prompted a number of research groups to develop strategies aimed at the total synthesis of lophotoxin (5, 6) and other furanocembranolides (7–10).

Our research group has been interested in this class of molecules for a few years and we have recently disclosed a method to construct the 2-alkenyl-3,5-trisubstituted furan (**2**) from the simple acyclic α-propargyl β-keto ester (**3**) (Fig. 1) (11). This method is based on a general strategy for the construction of five-membered heterocycles (12) and features the use of a palladium catalyst and an inorganic base to induce the 5-exo-dig cyclization and concomitant aromatization to the furan ring. High levels of selectivity for the (*Z*)-isomer **2** were obtained as a result of the facial-selective protonation of an allene intermediate. With the furan in hand, the vinylsilane moiety was further elaborated to the C_{19} methyl group attached to the trans-trisubstituted epoxide in lophotoxin.

Some issues that were not addressed in our previous communication concern the installation of the C_{13} acetate group as well as a method to introduce the C_1 isopropenyl group in a stereoselective way. Previous synthetic work by others has either exploited the chiral pool (8, 9), a diastereoselective alkylation (5), or an intramolecular Nozaki–Hiyama–Kishi reaction (7) to introduce the isopropenyl group, whereas the

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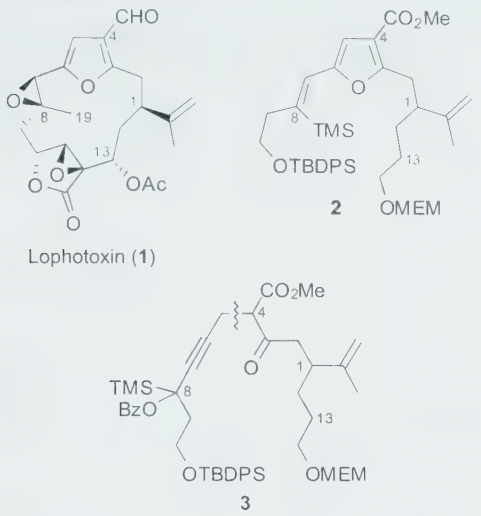
Fig. 1. Lophotoxin and the structures of synthetic intermediates.



configuration of the C_{13} substituent was not addressed (5, 6) or of no concern (7–9). In this paper, we wish to report on our findings for the stereoselective introduction of these two stereogenic carbons. A modification of our initial set of conditions, which uses microwave irradiation for the furan cyclization reaction, is also disclosed.

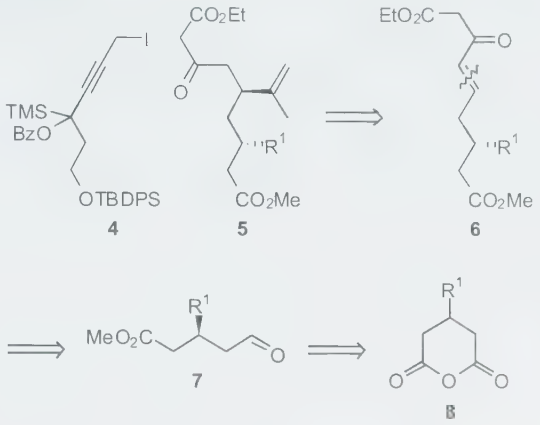
Results and discussions

β-Keto esters, such as **3**, are rapidly constructed by an alkylation reaction with propargylic iodide (**4**) (11) (Scheme 1). Segment **5** would need to be constructed in a stereocontrolled fashion. Further simplification of **5** provides **6**, which can be assembled from aldehyde **7** and an appropriate phosphonate by a Horner–Wadsworth–Emmons olefination. Finally, the highly symmetrical nature of aldehyde **7** led us to consider the use of a catalytic desymmetrization reaction of cyclic *meso*-anhydride (**8**) with an alcohol (13) to create the stereocenter at C_{13}.

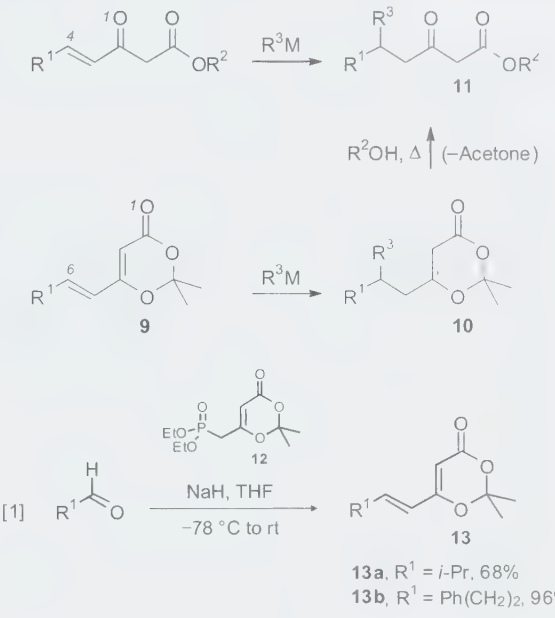
We initially envisioned that a conjugate 1,4-addition of an isopropenyl group to the unsaturated β-keto ester would be a straightforward means to introduce the C_1 side chain in **6**. However, owing to the ease of enolization of this particular type of substrate, we opted for an indirect route in which the 1,3-dicarbonyl unit would be revealed at a later stage (Scheme 2). We further anticipated that confinement of the β-keto ester to a [1,3]dioxin-4-one ring system, such as in **9**, would solve the problem, however, instead of a conjugate 1,4-addition, this required an extended 1,6-additon reaction. Thermolysis of adduct **10** in the presence of an alcohol (R^2OH) would then provide a number of different β-keto esters **11**, and an even greater number of derivatives could be obtained if other heteronucleophiles such as thiols or amines were to be used instead.

To test the feasibility of this route, [1,3]dioxin-4-ones (**13**) were prepared from phosphonate (**12**) (14) and either isobutyraldehyde or hydrocinnamaldehyde according to a literature procedure (15) and used as model substrates (eq. [1]).

Scheme 1. Strategy for the incorporation of the C_{13} stereogenic carbon center.

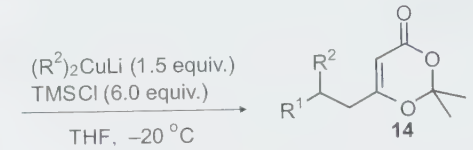


Scheme 2. Strategy for the incorporation of the C_1 stereogenic carbon center.



After some optimization of the reaction conditions, it was found that the addition of these extended Michael acceptors to solutions of Gillman-type organocuprates (R_2CuLi) containing chlorotrimethylsilane (16) at low temperature cleanly afforded the desired 1,6-addition products in high yields (Table 1). A small survey of different organocuprates revealed that simple alkyl groups were readily added (Table 1, entries 1–4), as were aromatic (Table 1, entries 5 and 6) and even silicon-based groups (17) (Table 1, entries 7 and 8). The addition of sterically encumbered organocuprates such as $(t\text{-Bu})_2CuLi$ also proceeded to afford the 1,6-addition adduct, albeit in low yields (Table 1, entries 9 and 10). However, the low yields observed were not because of a lack of reactivity during the 1,6-addition, but rather the result of a

Table 1. 1,6-Addition of organocuprates to [1,3]dioxin-4-ones **13**.



Entry	Substrate	$(R^2)_2CuLi$	Yield (%)
1	**13a**	Me_2CuLi	91
2	**13b**	Me_2CuLi	77
3	**13a**	Et_2CuLi	88
4	**13b**	Et_2CuLi	92
5	**13a**	Ph_2CuLi	79
6	**13b**	Ph_2CuLi	66
7	**13a**	$(PhMe_2Si)_2CuLi$	60
8	**13b**	$(PhMe_2Si)_2CuLi$	61
9	**13a**	$t\text{-}Bu_2CuLi$	17
10	**13b**	$t\text{-}Bu_2CuLi$	43

nonselective protonation step of the intermediate extended silyl enol ether formed after the 1,6-addition. No reaction occured when less reactive sp-hybridized organocopper reagents (RC≡CCu) or organocuprates [$(RC{\equiv}C)_2CuLi$] were used. It should be pointed out that in all cases studied using these sets of conditions, no adducts derived from 1,4- or 1,2-addition were isolated (18).

Having established that the extended conjugate addition reaction was possible, we next turned our attention toward the preparation of fragment **5** for our synthesis of lophotoxin. As we discussed previously, we planned on introducing the stereocenter at C_{13} by a catalytic desymmetrization reaction on cyclic *meso*-anhydrides **8** (Scheme 3). These were conveniently prepared according to a literature procedure (19) from commercially available diethyl 3-hydroxyglutarate by protection of the free hydroxyl group as a silyl ether to give **15**, followed by exhaustive saponification and dehydration of the resulting disodium acid salt with acetic anhydride. The TBDMS-protected cyclic anhydride **8a** was obtained as an off-white solid upon recrystallization of the crude material after the dehydration step, whereas the TBDPS-protected anhydride **8b** had to be filtered rapidly over a pad of silica gel pretreated with acetic anhydride to remove silanes before recrystallization was successful.[3]

Although there are a number of reported procedures to effect the desymmetrization of the cyclic anhydride **8a** (20–22), we opted for a method recently developed by Deng and co-workers (23) that employs modified cinchona alkaloids, initially adapted for the catalytic asymmetric dihydroxylation of alkenes (24) (Table 2). Using substoichiometric amounts (30 mol%) of $(DHQD)_2AQN$ in the presence of an excess of methanol at low temperature, Deng and co-workers (23) converted cyclic *meso*-anhydrides **8** (R^1 = Me, *i*-Pr) to acids **16** in good yields and high values of ee (Table 2, entries 1 and 2). When these optimized conditions were applied to the TBDMS-protected cyclic anhydride **8a**, a similar conversion to the desired acid was obtained (Table 2, entry 3). Longer reaction times resulted in higher conversions (Table 2, entry 4), however extensive desilylation of the product in both cases precluded the use of this substrate. Fortunately, when the TBDPS-protected cyclic anhydride **8b** was submitted to the desymmetrization reaction, conversions of 75%–85% were obtained, and more importantly, ^1H NMR analysis of the crude mixture indicated that no desilylation of **16** had occurred (Table 2, entry 5). An aliquot of the crude acid, accumulated from seven desymmetrizations under identical conditions, was reduced to the corresponding alcohol and treated with dil. HCl to provide the cyclic lactone **18** (Scheme 4) (25). Comparison of the chiral HPLC trace of this material with the racemic material prepared using quinuclidine as the organocatalyst (Table 2, entry 7) showed that the desymmetrization reaction occurred with a high level of enantioselectivity (95% ee). Finally, conducting the desymmetrization of **8b** at a higher temperature (–20 °C, Table 2, entry 6) resulted in a com-

Scheme 3. Preparation of cyclic anhydrides **8**. Reagents and conditions: (*a*) chlorosilane, imidazole, CH_2Cl_2, rt (**15a**, R^1 = OTBDMS, 92%; **15b**, R^1 = OTBDPS, 96%); (*b*) NaOH, MeOH, rt, 24–40 h; (*c*) Ac_2O, C_6H_6, Δ, 1.5 h (**8a**, R^1 = OTBDMS, 80%; **8b**, R^1 = OTBDPS, 46%).

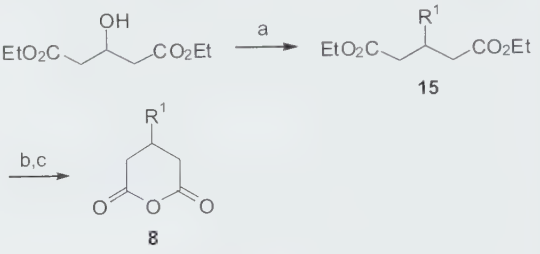
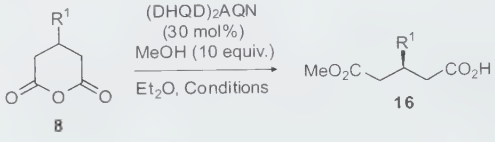


Table 2. Catalytic desymmetrization of cyclic *meso*-anhydrides **8** with $(DHQD)_2AQN$.

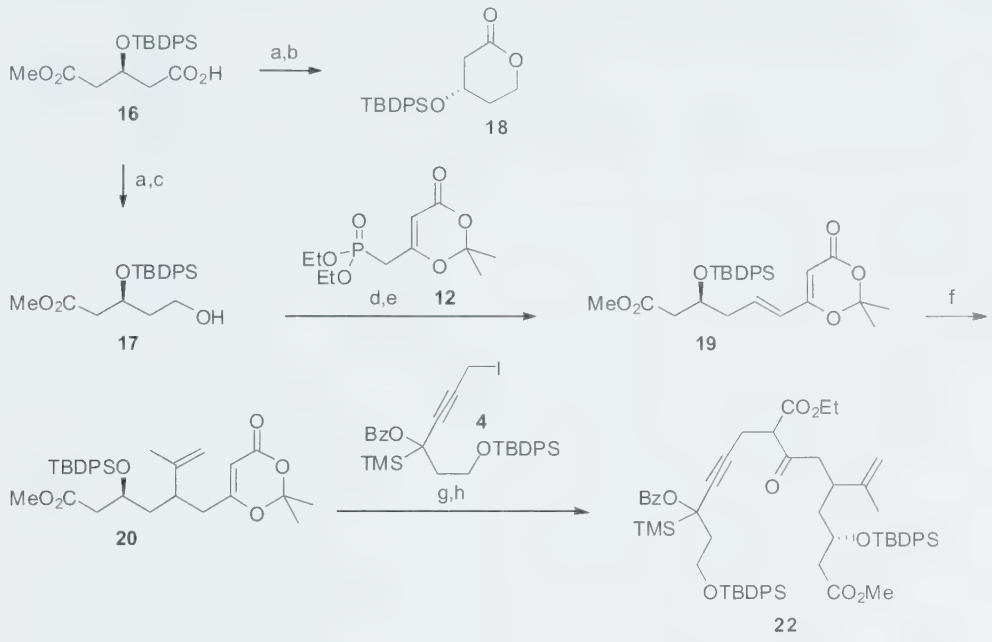


Entry	R^1	Conditions (°C, h)	Conversion (%)	ee (%)
1[a]	Me	–40, 43[a]	70[a,b]	91
2[a]	*i*-Pr	–40, 43[a]	72[a,b]	90
3	OTBDMS (**8a**)	–40, 41	65[c]	Nd[d]
4	OTBDMS (**8a**)	–40, 70	90–95[c]	Nd
5	OTBDPS (**8b**)	–40, 70	75–85[e]	95
6	OTBDPS (**8b**)	–20, 70	100	88
7	OTBDPS (**8b**)	–40, 70	96[f]	—

[a]Data from ref. 23.
[b]Isolated yield.
[c]Extensive desilylation of the product was observed.
[d]Nd (not determined).
[e]Conversions from seven desymmetrizations under identical conditions.
[f]Quinuclidine was used as a catalyst.

[3]Extensive desilylation occurs during the two-step sequence leading to lower yields of **8b**.

Scheme 4. Preparation of furan cyclization precursor **22**. Reagents and conditions: (*a*) BH_3·DMS, THF, rt, 15–17 h; (*b*) 10% HCl, rt, 1 h (38% from **8b**); (*c*) satd. aq. $NaHCO_3$, rt, 20 min (71% from **8b**); (*d*) TPAP (5 mol%), NMO, 4 Å MS, MeCN–CH_2Cl_2 (1:9), 30 min; (*e*) **12**, NaH, THF, –78 °C to rt, 1 h (49%, two steps); (*f*) CuI, 2-lithiopropene, TMSCl, THF, –20 °C, 16 h (94%, 1:1 dr); (*g*) EtOH, toluene, Δ; (*h*) NaH, **4**, THF, 0 °C to rt (77%, two steps).



plete conversion to the acid, albeit with lower selectivity (88% ee).

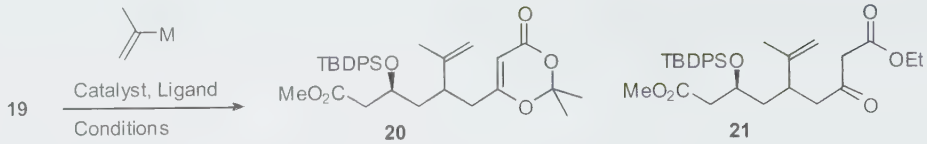
With an efficient and stereoselective solution for introducing the protected alcohol at C_{13}, we proceeded with our synthesis of fragment **5**. Reduction of the acid function in **16** with the borane – dimethyl sulfide complex followed by basic aqueous work up gave the alcohol **17** in good overall yield from cyclic *meso*-anhydride **8b**. Ley–Griffith oxidation of this alcohol to the aldehyde (26) followed by a Horner–Wadsworth–Emmons olefination with the stabilized phosphonate **12** (15) provided the 1,6-addition precursor **19** as a single isomer. Using 3 equiv. of the organocuprate derived from 2-lithiopropene, addition to the extended Michael acceptor occurred smoothly to provide **20** in high yield as a 1:1 mixture of diastereomers. Thermolysis of the [1,3]dioxin-4-one ring with ethanol in refluxing toluene revealed the β-keto ester (**21**) (see Table 3) that was then alkylated with the previously reported iodide **4** (11) to give the furan cyclization precursor **22** in good yield as a mixture of stereoisomers.

We were not surprised by the lack of stereocontrol obtained for the 1,6-addition of the organocuprate to [1,3]dioxin-4-one (**19**) (Scheme 4). By analogy to the diastereoselective 1,4-addition of copper-based organometallic reagents to Michael acceptors possessing a stereogenic center at the δ position under substrate control (27), we anticipated low levels of selectivity for the 1,6-addition. This gave us the opportunity to develop a catalytic asymmetric variant of the 1,6-addition reaction, and since stoichiometric copper-based reagents were effective, we initially screened for copper catalysts (Table 3). These studies proved quite disappointing; indeed, using conditions optimized for the catalytic asymmetric 1,4-addition of diorganozincs to enones (28), no reaction occurred and the starting material was recovered unchanged (Table 3, entry 1). The addition of chlorotrimethylsilane had no effect on the outcome of the reaction and even the use of Et_2Zn, which is often employed as a nucleophile in catalytic asymmetric conjugate additions, failed as well.

Over the past decade, rhodium catalysts have received increasing attention as alternatives to copper catalysts for the catalytic asymmetric 1,4-addition reaction, especially since the pioneering work by the research groups of Miyaura and Hayashi (29). However, a serious concern arises when considering the experimental conditions employed; most of the procedures involve heating at elevated temperatures in a binary solvent mixture composed of water and a cosolvent. We feared that thermal fragmentation of the [1,3]dioxin-4-one ring would lead to the α,β-unsaturated methyl ketone derived from **19** by a sequence that involves addition of 1 equiv. of water to an acyl ketene intermediate, followed by intramolecular decarboxylation of the resulting β-keto acid. As shown in Table 3 (entry 2), these concerns were confirmed when an addition of lithium 2-propenylborate in the presence of 1 equiv. of water (30) resulted in hydrolysis of **19** and isolation of the α,β-unsatured ester (65%).

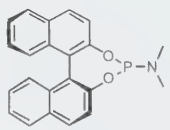
Recent findings by Feringa and co-workers (31) and Genêt and co-workers (32) have shown that potassium organotrifluoroborates (RBF_3K), a class of air- and moisture-stable organometallic reagents, can be used as substitutes for boronic acids in the rhodium-catalyzed asymmetric 1,4-addition to enones using phosporamidites or

Table 3. Catalytic asymmetric 1,6-addition to [1,3]dioxin-4-one **19**.

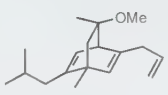


Entry	Substrate	M	Catalyst (mol%), Ligand (mol%)	Conditions	Yield **20**,**21** (%)	dr[a]
1	**19**	$(\frac{}{}\!\!\rangle_2$Zn	$Cu(OTf)_2$ (5), $\mathbf{L_1}$ (10)	Toluene, –20 °C	0	—
2	**19**	$B(OMe)_3Li$	$Rh(acac)(eth)_2$ (4), Binap (6.5)	Dioxane H_2O (1 equiv.), Δ	0	—
3	**19**	BF_3K	$Rh(acac)(eth)_2$ (4), $\mathbf{L_1}$ (13)	EtOH, 83 °C	23,41	1.7:1
4	**19**		$Rh(acac)(eth)_2$ (4), $\mathbf{L_2}$ (6)	EtOH, 82 °C	21,38	4.0:1
5	**24**[b]		$Rh(acac)(eth)_2$ (4), $\mathbf{L_2}$ (6)	EtOH, 78 °C	27,32	3.7:1

[a] Diastereomeric ratio determined by ^{1}H NMR
[b] Reaction performed on the acetate-protected derivative.



$\mathbf{L_1}$ (MonoPhos™)



$\mathbf{L_2}$ (Carreira's diene)

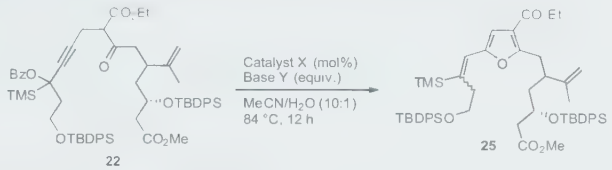
bidentate phosphines as chiral ligands. Of particular interest to us was the fact that these reactions can be performed in the absence of water (pure EtOH) and at lower temperatures (70 °C) (31), so that addition could occur before any significant cleavage of the [1,3]dioxin-4-one ring could take place. Gratifyingly, on our first try with Monophos™ ($\mathbf{L_1}$, see bottom of Table 3) in a heated ethanolic solution, we obtained a mixture of 1,6-addition products **20** and **21** in a moderate combined yield, albeit in low diastereoselectivity (Table 3, entry 3). We then turned our attention to chiral bidentate phosphine ligands such as (*R*)-Binap, (*R*,*R*)-Me-Duphos, and (*S*,*S*)-Chiraphos, however, the use of these ligands seemed to considerably diminish the activity of the catalytic system and only starting material was recovered.

Another class of promising chiral ligands for the catalytic asymmetric 1,4-addition are chiral dienes (33), which have been disclosed recently by Hayashi et al. (34) and Carreira and co-workers (35). We chose to prepare Carreira's diene (see $\mathbf{L_2}$, bottom of Table 3) from commercially available carvone. After heating **19** with the organotrifluoroborate in the presence of a rhodium catalyst, we were able to isolate the addition products **20** and **21** in a moderate combined yield as a 4:1 mixture of isomers (Table 3, entry 4) (36). Performing the reaction with a different neutral rhodium catalyst, $\{[RhCl(eth)_2]_2\}$ gave similar results (64% combined yield, 3.1:1 dr), whereas lower temperatures (57–60 °C) resulted in lower conversions.[4] We also attempted the reaction with the acetate-protected derivative **24** (Table 3, entry 5) as well as the free-hydroxyl derivative **23**, however, no increase in selectivity was observed with the former and the latter appeared to be unreactive.

Since we were unable to prepare the 1,6-addition products **20** and (or) **21** with high levels of stereoselectivity, we decided to resume our synthesis of lophotoxin with the 1:1 mixture of diastereomers obtained in high yield from the organocuprate addition (Scheme 4). The stage was now set for the key cyclization step that would produce the 2,3,5-trisubstituted furan ring and stereoselectively generate the olefin with the appropriate geometry, all in a single transition-metal-catalyzed event. Unfortunately, treatment of the α-propargyl β-keto ester **22** under our previously optimized conditions (11) gave only trace amounts of furan **25** (Table 4, entry 1). Although the starting material had been completely consumed, as judged by ^{1}H NMR analysis, no identifiable products could be isolated from the crude reaction mixture. After a number of unsuccessful attempts, we decided to conduct control experiments and we were quite surprised to see that treatment of **22** with only K_2CO_3, present under otherwise identical reaction conditions, resulted in rapid desilylation (TMS group) of the starting material (ca. 1 h, Table 4, entry 2). In light of this result, we decided to screen for other catalyst–base combinations and we were pleased to see that the use of $Pd(PPh_3)_4$ and $NaOAc{\cdot}3H_2O$ provided a reasonable yield of furan **25** as a 6.8:1 mixture of isomers (Table 4, entry 3). The addition of more base (Table 4, entry 4) or the use of related bases (Table 4, entries 5

[4] Comparable diastereomeric ratios (3.9:1) were obtained.

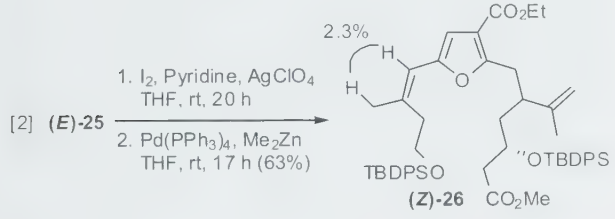
Table 4. Transition-metal-catalyzed cyclization of α-propargyl β-keto ester **22**.



Entry	Catalyst X (mol%)	Base Y (equiv.)	*E*/*Z* (ratio)[a]	Yield (%)
1	$Pd(OAc)_2$ (5), dppf (6)	K_2CO_3 (1.1)	—	Nd[b]
2	none	K_2CO_3 (1.1)	—	0
3	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$ (1.1)	6.8:1	49
4	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$ (5.0)	6.8:1	51
5	$Pd(PPh_3)_4$ (15)	NaOBz (1.1)	5.4:1	44
6	$Pd(PPh_3)_4$ (15)	$NaOPiv{\cdot}H_2O$ (1.1)	5.5:1	53
7	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$ (1.1), 2,6-lutidine (1.1)	6.6:1	56

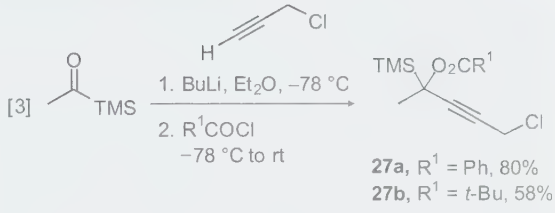
and 6) led to almost identical results, as did the combination of $NaOAc{\cdot}3H_2O$ and an organic base (Entry 7).

Comparison of the ^1H NMR spectra of **25** with our previously described furan **2** (Fig. 1) indicated that the major isomer formed during the reaction was the undesired (*E*)-isomer.[5] To verify the olefin configuration, we converted the vinylsilane moiety to the corresponding iodide and performed a Negishi cross-coupling reaction with dimethylzinc that yielded furan **26** (eq. [2]). A 1D-nOe analysis allowed us to assign the stereochemistry of the major isomer as **(*Z*)-26** since an nOe enhancement was observed between the hydrogen atoms of the newly introduced methyl group and the hydrogen atom of the alkene, establishing that the TMS group in **25** was located *trans* to the furan ring.



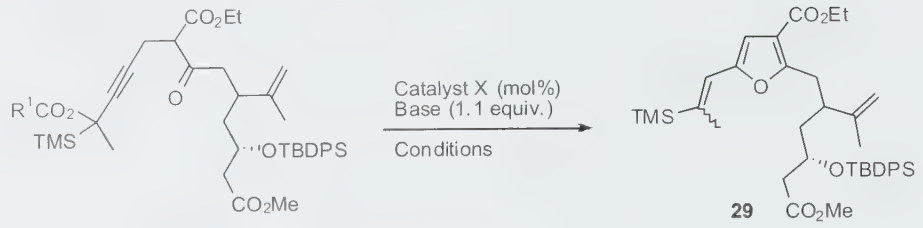
Our inability to gain access to **(*Z*)-25** forced a reconsideration of our strategy to close the macrocyclic ring in lophotoxin. Instead of relying on the furan cyclization reaction to set the stereochemistry as shown in **(*Z*)-25** and then attach the C_{19} methyl group, we decided to prepare furan **(*E*)-29** (Table 5) that already had an attached C_{19} methyl group and to use the vinylsilane moiety for further transformations. In addition to being more convergent, this approach gave us the opportunity to focus on a different bond disconnection in which C_8 and C_9 would be joined together by a transition-metal-catalyzed intramolecular cross-coupling reaction. In any event, we prepared the α-propargyl β-keto esters **28** from β-keto ester **21** and the appropriate halides **27** (eq. [3]).

When substrate **28a** (R^1 = Ph) was subjected to the original cyclization conditions, virtually no furan was formed and the starting material decomposed (Table 5, entry 1). Using the modified set of conditions [$Pd(PPh_3)_4$–$NaOAc{\cdot}3H_2O$] we were pleased to see that cyclization had occured, although we were alarmed by the much lower isolated yield (Table 5, entry 2). Another product, possibly arising from migration of the benzoate group across the alkyne, was recovered from this reaction in ca. 32% yield. Since the benzoate might be too readily eliminated, we prepared the pivaloate derivative **28b** (R^1 = *t*-Bu) and were relieved to see that under the new set of conditions, the desired furan **29** was formed once again in moderate yield (Table 5, entry 3). To decrease the reaction times and possibly minimize side reactions, we next turned our attention to the use of microwave irradiation to promote the cyclization reaction. Gratifyingly, heating **28b** for only 40 min in the microwave under otherwise identical reaction conditions led to furan **29** in a comparable yield and high selectivity (Table 5, entry 4). While screening for other transition-metal catalysts, we were pleased to find that the allylpalladium chloride dimer was also an effective catalyst for the cyclization. In this case, both pivalate and benzoate derivatives could be used and the furan was obtained in acceptable yields (Table 5, entries 5 and 6). Although the (*E*/*Z*) selectivity was severely diminished, isomerization of the furan mixture with a catalytic amount (5–10 mol%) of $(PhSe)_2$ in THF at reflux produced pure **(*E*)-29** in high yield (Table 5, entry 5). With a more practical route to this furan in hand, we are currently exploring a strategy that involves further modification of the protected β-hydroxy ester fragment followed by an intramolecular transition-metal-



[5] The ^1H NMR chemical shift of the TMS group is particularly diagnostic. Indeed, in **2** the TMS group has a δ of 0.11 ppm, whereas the major isomer in **25** has a δ of 0.00 ppm and the minor isomer has a δ of 0.09 ppm.

Table 5. Transition-metal-catalyzed cyclization of α-propargyl β-keto esters **28**.



28 29

Entry	R^1	Catalyst X (mol%)	Base (1.1 equiv.)	Conditions[a]	E/Z (ratio)[b]	Yield (%)
1	Ph (**28a**)	$Pd(OAc)_2$ (5), dppf (6)	K_2CO_3	A	—	Nd[c]
2	Ph (**28a**)	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$	A	5.1:1	30
3	*t*-Bu (**28b**)	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$	A	6.6:1	53
4	*t*-Bu (**28b**)	$Pd(PPh_3)_4$ (15)	$NaOAc{\cdot}3H_2O$	B	8.6:1	51
5	*t*-Bu (**28b**)	$[(\eta^3\text{-}C_3H_5)PdCl]_2$ (7.5), dppf (15)	None	C	1.4:1	59 (50[d])
6	Ph (**28a**)	$[(\eta^3\text{-}C_3H_5)PdCl]_2$ (7.5), dppf (15)	None	C	1.5:1	54

Reagents and conditions: (A) MeCN–H_2O (10:1); (B) MeCN–H_2O (10:1), 100 °C, μW, 40 min; (C) THF, 100 °C, μW, 20 min.
[b] Isomeric ratio determined by ^1H NMR.
[c] Nd (not determined)
[d] Yield of pure (*E*)-**29** from **28** after isomerization with $(PhSe)_2$.

catalyzed cross-coupling reaction with the vinylsilane moiety. These results will be disclosed in due course.

Conclusion

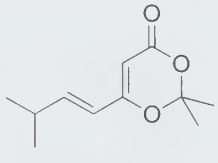
We have shown that a catalytic desymmetrization reaction using a modified cinchona alkaloid allows for the stereoselective incorporation of the C_{13} substituent present in lophotoxin from a simple prochiral cyclic anhydride. A newly developed, highly regioselective 1,6-addition reaction of organocuprates to unsaturated [1,3]dioxin-4-ones provided a means to introduce the C_1 isopropenyl group, and encouraging preliminary results have established that a rhodium-catalyzed asymmetric 1,6-addition reaction provides moderate levels of diastereocontrol. Problems encountered with the transition-metal catalyzed furan cyclization reaction have led to modifications of our original thermal procedure and to the development of a microwave-assisted variant. We are currently applying these modifications toward the total synthesis of lophotoxin and other members of the furanocembranolide family of natural products.

Experimental

General methods

All moisture-sensitive reactions were performed under an atmosphere of N_2 and glassware was flame-dried under vacuum prior to use. Et_2O and THF were dried by distillation over Na–benzophenone. Distilled hexane and ethyl acetate were used for chromatographic purifications. Toluene and CH_2Cl_2 were purified by filtration through activated alumina. TMSCl was distilled over CaH_2 and kept in a dessicator. $(DHQD)_2AQN$ was prepared according to a literature procedure (24). Unless otherwise stated, all other reagents and solvents were used as received. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F-254 plates (particle size 0.040–0.055 mm, 230–400 mesh) and visualization was accomplished with a 254 nm UV light and (or) by staining with a basic $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% aq. NaOH solution). NMR spectra were recorded at 300 MHz and 76 MHz for ^1H NMR and ^{13}C NMR, respectively, using a Bruker AVANCE 300 MHz spectrometer at 21 °C in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), hextet (hex), multiplet (m), broad (b)), coupling constants, and integration. IR spectra were obtained on a Nicolet AVATAR 360 FT-IR ESP spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Optical rotations were measured on a PerkinElmer 241 polarimeter. Microwave reactions were run on a CEM Discover instrument.

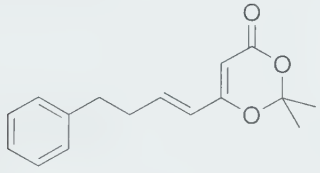
2,2-Dimethyl-6-(3-methylbut-1-enyl)[1,3]dioxin-4-one (13a)



To a solution of phosphonate **12** (1.11 g, 3.99 mmol) in THF (20 mL) cooled to 0 °C was added NaH (192 mg of a 60% mineral dispersion, 4.80 mmol). The ice bath was removed and the reaction mixture was stirred at rt for 30 min, cooled to –78 °C, and treated with isobutyraldehyde (400 μL, 4.4 mmol). The solution was allowed to gradually warm to rt and stirred for 1 h. One drop of satd. aq. $NaHCO_3$ was added and the mixture was stirred for 5 min (to complete the deprotonation step). After adding satd. aq. $NaHCO_3$ (50 mL), the reaction was transferred to a separatory funnel and extracted with Et_2O (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), filtered,

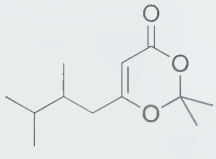
concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 532 mg of **13a** (68%) as a colourless oil. R_f 0.26 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2963, 2872, 1731, 1653, 1592, 1391, 1374, 1273, 1206, 1018. ^1H NMR ($CDCl_3$) δ: 6.54 (dd, J = 15.6, 6.8 Hz, 1H), 5.85 (dd, J = 15.6, 1.4 Hz, 1H), 5.26 (s, 1H), 2.46 (hexd, J = 6.8, 1.4 Hz, 1H), 1.72 (s, 6H), 1.08 (d, J = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ: 163.5, 161.8, 148.5, 119.6, 106.0, 93.1, 31.1, 24.8 (2), 21.3 (2). HR-MS (EI) *m/e* calcd. for $C_{11}H_{16}O_3$: 196.1099; found: 196.1102.

2,2-Dimethyl-6-(4-phenylbut-1-enyl)[1,3]dioxin-4-one (13b)



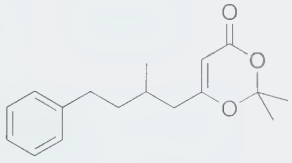
To a solution of phosphonate **12** (1.95 g, 7.01 mmol) in THF (50 mL) cooled to 0 °C was added NaH (240 mg of a 60% mineral dispersion, 6.00 mmol). The ice bath was removed and the reaction mixture was stirred at rt for 30 min, cooled to –78 °C, and treated with hydrocinnamaldehyde (730 µL, 5.0 mmol). The solution was allowed to gradually warm to rt and stirred for 1 h. One drop of satd. aq. $NaHCO_3$ was added and the mixture was stirred for 5 min (to complete the deprotonation step). After adding satd. aq. $NaHCO_3$ (50 mL), the reaction was transferred to a separatory funnel and extracted with Et_2O (4 × 50 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 1.23 g of **13b** (96%) as a colourless oil. R_f 0.20 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2999, 2941, 1725, 1653, 1592, 1390, 1274, 1205, 1020. ^1H NMR ($CDCl_3$) δ: 7.34–7.18 (m, 5H), 6.61 (dt, J = 15.5, 7.1 Hz, 1H), 5.93 (dt, J = 15.6, 1.4 Hz, 1H), 5.25 (s, 1H), 2.82–2.76 (m, 2H), 2.58–2.50 (m, 2H), 1.72 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 163.1, 161.9, 141.2, 140.6, 128.4 (2), 128.2 (2), 126.1, 122.9, 106.2, 93.4, 34.6, 34.4, 24.9 (2). HR-MS (EI) *m/e* calcd. for $C_{16}H_{18}O_3$: 258.1256; found; 258.1254.

6-(2,3-Dimethylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14a)



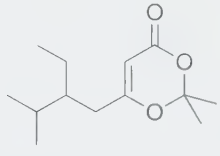
To a suspension of CuI (143 mg, 0.751 mmol) in THF (2.5 mL) cooled to –78 °C was added dropwise a solution of MeLi in Et_2O (1.6 mol/L, 940 µL, 1.5 mmol). The cold bath was removed and the mixture was stirred at rt for 30 min. The resulting colourless solution was then cooled to –78 °C and TMSCl (380 µL, 3.0 mmol) was added. After stirring for ca. 5 min, a solution of **13a** (98.8 mg, 0.503 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 18 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (4 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 97 mg of **14a** (91%) as a colourless oil. R_f 0.36 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2961, 2876, 1735, 1633, 1390, 1272, 1205, 1013. ^1H NMR ($CDCl_3$) δ: 5.23 (s, 1H), 2.29 (dd, J = 14.1, 5.0 Hz, 1H), 1.96 (dd, J = 14.1, 9.4 Hz, 1H), 1.75–1.70 (m, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.65–1.59 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.7, 161.2, 106.1, 94.0, 38.5, 36.0, 31.8, 25.2, 24.7, 19.8, 17.7, 15.0. HR-MS (ESI–POS) *m/e* calcd. for $C_{12}H_{20}O_3Na$: 235.1310 [M + Na]; found: 235.1299.

2,2-Dimethyl-6-(2-methyl-4-phenylbutyl)[1,3]dioxin-4-one (14b)



Following the previous procedure for the 1,6-addition of Me_2CuLi, [1,3]dioxin-4-one **13b** (124 mg, 0.480 mmol) gave 101 mg (77%) of **14b** as a colourless oil. R_f 0.29 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2998, 2929, 1732, 1633, 1390, 1272, 1204, 1014. ^1H NMR ($CDCl_3$) δ: 7.32–7.27 (m, 2H), 7.22–7.15 (m, 3H), 5.22 (s, 1H), 2.73–2.67 (m, 1H), 2.63–2.57 (m, 1H), 2.28 (dd, J = 14.2, 6.1 Hz, 1H), 2.07 (dd, J = 14.2, 7.9 Hz, 1H), 1.86 (hex, J = 6.4 Hz, 1H), 1.73–1.67 (m, 1H), 1.67 (s, 3H), 1.66 (s, 3H), 1.56–1.47 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 170.8, 161.1, 141.9, 128.3 (2), 128.2 (2), 125.8, 106.1, 94.2, 41.0, 38.3, 33.1, 30.1, 25.0, 24.9, 19.3. HR-MS (ESI–POS) *m/e* calcd. for $C_{17}H_{22}O_3Na$ [M + Na]: 297.1467; found: 297.1447.

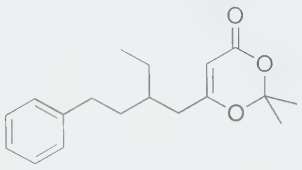
6-(2-Ethyl-3-methylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14c)



To a suspension of CuI (143 mg, 0.751 mmol) in THF (2.0 mL) cooled to 0 °C was added dropwise a 0.39 mol/L solution of EtLi in benzene–cyclohexane (90:10, 3.8 µL, 1.5 mmol) and the mixture was stirred at 0 °C for 30 min. The resulting dark black solution was then cooled to –78 °C and TMSCl (380 µL, 3.0 mmol) was added. After stirring for ca. 5 min, a solution of **13a** (97.6 mg, 0.497 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 17 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under

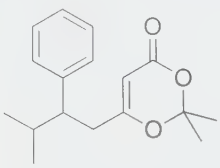
reduced pressure, and purified by chromatography on SiO_2 to afford 99 mg of **14c** (88%) as a colourless oil. R_f 0.35 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2961, 2876, 1735, 1632, 1464, 1389, 1272, 1205, 1015. ^1H NMR ($CDCl_3$) δ: 5.24 (s, 1H), 2.21 (dd, J = 14.4, 6.0 Hz, 1H), 2.06 (dd, J = 14.4, 7.7 Hz, 1H), 1.82–1.72 (m, 1H), 1.69 (s, 6H), 1.53–1.42 (m, 1H), 1.42–1.17 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H), 0.88 (d, J = 7.3 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 172.3, 161.3, 106.1, 94.0, 42.8, 34.9, 28.6, 25.1, 24.9, 22.8, 19.0, 18.6, 11.6. HR-MS (EI) *m/e* calcd. for $C_{10}H_{16}O_2$: 168.1150 [M – CH_3COCH_3]; found: 168.1148.

6-(2-Ethyl-4-phenylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14d)



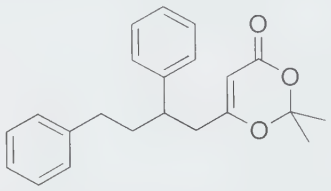
Following the previous procedure for the 1,6-addition of Et_2CuLi, [1,3]dioxin-4-one **13b** (131 mg, 0.507 mmol) gave 134 mg (92%) of **14d** as a colourless oil. R_f 0.28 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2998, 2935, 1731, 1631, 1455, 1390, 1272, 1204, 1014. ^1H NMR ($CDCl_3$) δ: 7.32–7.26 (m, 2H), 7.22–7.14 (m, 3H), 5.23 (s, 1H), 2.67–2.57 (m, 2H), 2.26–2.19 (m, 2H), 1.73–1.60 (m, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.49–1.36 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.2, 161.2, 142.0, 128.3 (2), 128.2 (2), 125.8, 106.2, 94.2, 37.7, 36.1, 34.7, 32.7, 25.5, 25.0, 24.9, 10.4. HR-MS (EI) *m/e* calcd. for $C_{18}H_{24}O_3$: 288.1725; found: 288.1727.

2,2-Dimethyl-6-(3-methyl-2-phenylbutyl)-[1,3]dioxin-4-one (14e)



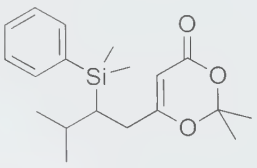
To a suspension of CuI (143 mg, 0.751 mmol) in THF (2.5 mL) cooled to 0 °C was added dropwise a solution of PhLi (1.0 mol/L) in cyclohexane–Et_2O (70:30, 1.5 mL, 1.5 mmol). After stirring at 0 °C for 30 min, the mixture was cooled to –78 °C, at which point a dense precipitate formed. TMSCl (380 µL, 3.0 mmol) was added and after ca. 5 min a solution of **13a** (99.2 mg, 0.506 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 18 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (4 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 110 mg of **14e** (79%) as a colourless oil. R_f 0.31 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2960, 2873, 1731, 1633, 1454, 1390, 1272, 1204, 1014. ^1H NMR ($CDCl_3$) δ: 7.29–7.24 (m, 2H), 7.22–7.17 (m, 1H), 7.10–7.06 (m, 2H), 5.05 (s, 1H), 2.76 (dd, J = 14.2, 4.3 Hz, 1H), 2.73–2.66 (m, 1H), 2.52 (dd, J = 14.2, 11.1 Hz, 1H), 1.84 (apparent hex, J = 6.8 Hz, 1H), 1.51 (s, 3H), 1.32 (s, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 170.7, 161.2, 141.4, 128.4 (2), 128.1 (2), 126.6, 106.2, 94.5, 49.5, 36.9, 33.6, 25.4, 24.0, 20.6, 20.1. HR-MS (EI) *m/e* calcd. for $C_{14}H_{16}O_2$: 216.1150 [M – CH_3COCH_3]; found: 216.1150.

6-(2,4-Diphenylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14f)



Following the previous procedure for the 1,6-addition of Ph_2CuLi, [1,3]dioxin-4-one **13b** (128 mg, 0.496 mmol) gave 110 mg (66%) of **14f** as a colourless oil. R_f 0.24 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3027, 2999, 2939, 2858, 1728, 1632, 1495, 1454, 1390, 1272, 1204, 1014. ^1H NMR ($CDCl_3$) δ: 7.36–7.31 (m, 2H), 7.29–7.23 (m, 3H), 7.21–7.15 (m, 3H), 7.12–7.07 (m, 2H), 5.07 (s, 1H), 2.97–2.89 (m, 1H), 2.60 (dd, J = 14.5, 6.4 Hz, 1H), 2.56–2.40 (m, 3H), 2.05–1.88 (m, 2H), 1.53 (s, 3H), 1.46 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 169.8, 161.0, 142.6, 141.6, 128.6 (2), 128.29 (2), 128.26 (2), 127.5 (2), 126.8, 125.8, 106.3, 94.5, 42.3, 40.7, 38.1, 33.3, 25.0, 24.6. HR-MS (EI) *m/e* calcd. for $C_{19}H_{18}O_2$: 278.1307 [M – CH_3COCH_3]; found: 278.1303.

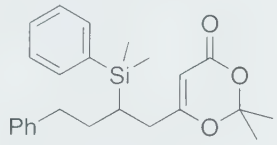
6-[2-(Dimethylphenylsilanyl)-3-methylbutyl]-2,2-dimethyl[1,3]dioxin-4-one (14g)



To a suspension of CuI (143 mg, 0.751 mmol) in THF (1.0 mL) cooled to –20 °C was added dropwise a solution of $PhMe_2SiLi$ in THF (0.40 mol/L, 3.8 µL, 1.5 mmol), and the mixture was stirred at –20 °C for 4 h. TMSCl (380 µL, 3.0 mmol) was added and the mixture was stirred for ca. 5 min after which a solution of **13a** (95.4 mg, 0.486 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The reaction mixture was stirred at –20 °C for ca. 15 h, stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (4 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 97 mg of **14g** (60%) as a colourless oil. R_f 0.42 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2998, 2957, 2872, 1732, 1630, 1427, 1389, 1271, 1205, 1111, 1016. ^1H NMR ($CDCl_3$) δ: 7.54–7.47 (m,

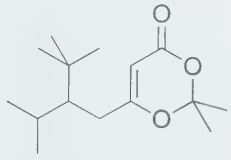
2H), 7.39–7.33 (m, 3H), 5.17 (s, 1H), 2.30–2.22 (m, 2H), 1.98–1.92 (m, 1H), 1.63 (s, 3H), 1.60 (s, 3H), 1.31–1.26 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.36 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 172.6, 161.2, 138.3, 133.7 (2), 129.0, 127.8 (2), 106.1, 93.5, 31.4, 29.8, 28.7, 25.2, 24.6, 22.0, 21.3, –2.2, –3.1. HR-MS (EI) *m/e* calcd. for $C_{18}H_{25}O_3Si$: 317.1573 [M – CH_3]; found: 317.1557.

6-(2-(Dimethyl(phenyl)silyl)-4-phenylbutyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (14h)



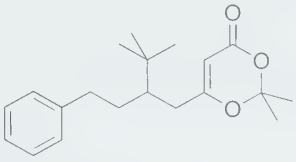
Following the previous procedure for the 1,6-addition of $(PhMe_2Si)_2CuLi$, [1,3]dioxin-4-one **13b** (129 mg, 0.499 mmol) gave 121 mg (61%) of **14h** as a colourless oil. R_f 0.26 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2999, 2950, 2859, 1729, 1629, 1389, 1272, 1204, 1112, 1014. ^{1}H NMR ($CDCl_3$) δ: 7.53–7.48 (m, 2H), 7.42–7.36 (m, 3H), 7.28–7.23 (m, 2H), 7.20–7.16 (m, 1H), 7.05–7.01 (m, 2H), 5.19 (s, 1H), 2.61–2.53 (m, 1H), 2.53–2.46 (m, 1H), 2.38 (dd, J = 14.9, 4.5 Hz, 1H), 2.16 (dd, J = 14.9, 9.6 Hz, 1H), 1.83–1.75 (m, 1H), 1.67–1.59 (m, 1H, hidden under two s), 1.65 (s, 3H), 1.64 (s, 3H), 1.32–1.25 (m, 1H), 0.363 (s, 3H), 0.360 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.9, 161.0, 141.8, 137.2, 133.8 (2), 129.3, 128.3 (2), 128.1 (2), 127.9 (2), 125.8, 106.2, 93.8, 35.2, 34.3, 31.9, 25.1, 24.7, 22.1, –4.1, –4.2. HR-MS (EI) *m/e* calcd. for $C_{24}H_{30}O_3Si$: 394.1964; found: 394.1953.

6-(2-Isopropyl-3,3-dimethylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14i)



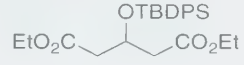
To a suspension of CuI (143 mg, 0.751 mmol) in THF (2.5 mL) cooled to –78 °C was added dropwise a solution of *t*-BuLi in pentane (1.4 mol/L, 1.1 µL, 1.5 mmol). The mixture was stirred at –78 °C for 30 min and then TMSCl (380 µL, 3.0 mmol) was added. After stirring for ca. 5 min, a solution of **13a** (101 mg, 0.515 mmol) in THF (1.5 mL, 1.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 15 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (30 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 22 mg of **14i** (17%) as a colourless oil. R_f 0.53 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2960, 1733, 1630, 1389, 1271, 1205, 1016. ^{1}H NMR ($CDCl_3$) δ: 5.29 (s, 1H), 2.22 (d, J = 5.6 Hz, 2H), 2.11–2.06 (m, 1H), 1.69 (s, 6H), 1.50 (td, J = 5.7, 1.9 Hz, 1H), 0.93–0.92 (m, 12H), 0.87 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 174.1, 161.5, 106.1, 93.2, 49.9, 34.9, 30.4, 28.6 (3), 27.7, 25.2, 25.0, 24.4, 18.3. HR-MS (EI) *m/e* calcd. for $C_{15}H_{27}O_3$: 255.1960 [M + H]; found: 255.1964.

6-(3,3-Dimethyl-2-phenethylbutyl)-2,2-dimethyl[1,3]dioxin-4-one (14j)



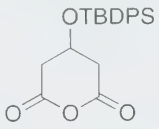
Following the previous procedure for the 1,6-addition of $(t\text{-Bu})_2CuLi$, [1,3]dioxin-4-one **13b** (130 mg, 0.503 mmol) gave 68 mg (43%) of **14j** as a colourless oil. R_f 0.33 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3026, 2960, 1732, 1630, 1454, 1389, 1272, 1204, 1014. ^{1}H NMR ($CDCl_3$) δ: 7.32–7.25 (m, 2H), 7.22–7.13 (m, 3H), 5.32 (s, 1H), 2.74–2.67 (m, 1H), 2.58–2.51 (m, 1H), 2.47 (dd, J = 15.0, 4.2 Hz, 1H), 2.07 (dd, J = 15.0, 7.5 Hz, 1H), 1.90–1.82 (m, 1H), 1.71 (s, 6H), 1.53–1.48 (m, 1H), 1.46–1.37 (m, 1H), 0.91 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 172.7, 161.2, 142.1, 128.4 (2), 128.2 (2), 125.9, 106.2, 93.8, 45.1, 35.9, 35.6, 33.9, 33.4, 27.5 (3), 25.3, 24.9. HR-MS (EI) *m/e* calcd. for $C_{17}H_{22}O_2$: 258.1620 [M – $(CH_3)_2CO$]; found: 258.1616.

3-(tert-Butyldiphenylsilanyloxy)pentanedioic acid diethyl ester (15, R^1 = OTBDPS)



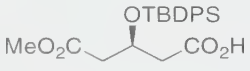
To a solution of imidazole (1.36 g, 20.0 mmol) in CH_2Cl_2 (20 mL) at rt was added TBDPSCl (2.47 mL, 9.50 mmol). After stirring for 10 min at rt, a solution of diethyl 3-hydroxyglutarate (2.04 g, 10.0 mmol) in CH_2Cl_2 (5, 2, and 1 mL rinses) was added to the white suspension. The reaction was stirred at rt for 16 h after which it was stopped by the addition of water (25 mL) and diluted with Et_2O (125 mL). The mixture was then transferred to a separatory funnel, extracted, the layers separated, and the organic layer was washed with brine (25 mL). The aqueous layers were combined and extracted with Et_2O (50 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 4.05 g of **15** (96%) as a white solid; mp 44–46 °C. R_f 0.48 (20% EtOAc–hexane). FT-IR (KBr, cm^{-1}): 2966, 1740, 1378, 1268, 1227, 1145, 1107, 1026. ^{1}H NMR ($CDCl_3$) δ: 7.70–7.66 (m, 4H), 7.47–7.35 (m, 6H), 4.55 (qn, J = 6.0 Hz, 1H), 4.08–3.97 (m, 4H), 2.60 and 2.54 (AB of ABX, J = 15.2, 6.3 and 15.2, 5.9 Hz, 4H), 1.19 (t, J = 7.1 Hz, 6H), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 170.8 (2), 135.8 (4), 133.5 (2), 129.7 (2), 127.6 (4), 67.2, 60.3 (2), 41.8 (2), 26.8 (3), 19.2, 14.1 (2). HR-MS (EI) *m/e* calcd. for $C_{24}H_{31}O_5Si$: 427.1941 [M – CH_3]; found: 427.1931.

3-[(tert-Butyldiphenylsilyl)oxy]pentanedioic anhydride (8b, R^1 = OTBDPS)



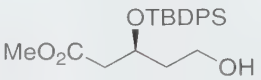
To a solution of diester **15** (8.85 g, 20.0 mmol) in MeOH (30 mL) was added NaOH pellets (2.00 g, 50.0 mmol) and the mixture was stirred vigorously at rt for 38 h. The resulting yellowish suspension was concentrated under reduced pressure and kept under high vacuum. The flaky solid was then crushed into smaller pieces, suspended in a mixture of benzene (40 mL) and Ac_2O (30 mL) and heated to reflux for 1.5 h. During this time, the colour changed to a deep purple. After cooling to rt, the reaction was stopped by the addition of brine (200 mL) and the mixture was transferred to a separatory funnel with $CHCl_3$ (400 mL). After extraction, the layers were separated and the organic layer was washed with satd. aq. $NaHCO_3$ (3 × 200 mL). The organic layer was then dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 [pretreated with hexane containing 1% Ac_2O, solvent gradient from pure hexane (+1% Ac_2O) to 20% EtOAc–hexane (+1% Ac_2O)] to afford 3.40 g of **8b** (46%) as a white solid. Recrystallization from a hot mixture of hexane–EtOAc (20:1) provided white needles; mp 107 to 108 °C (hexane–EtOAc 20:1). R_f 0.27 (20% EtOAc–hexane containing 1% Ac_2O). FT-IR (KBr, cm^{-1}): 2932, 1817, 1765, 1429, 1348, 1262, 1191, 1111, 1070, 1044. ^{1}H NMR ($CDCl_3$) δ: 7.71–7.56 (m, 4H), 7.55–7.35 (m, 6H), 4.31 (qn, J = 3.2 Hz, 1H), 2.86 (dd, J = 16.0, 3.6 Hz, 2H), 2.58 (dd, J = 16.0, 2.4 Hz, 2H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 165.3 (2), 135.8 (4), 132.4 (2), 130.6 (2), 128.3 (4), 62.9, 38.9 (2), 26.9 (3), 19.2. HR-MS (EI) *m/e* calcd. for $C_{17}H_{15}O_4Si$: 311.0740 [M – C_4H_9]; found: 311.0744.

(S)-((3-tert-Butyldiphenylsilyl)oxy)pentanedioic acid monomethyl ester (16)



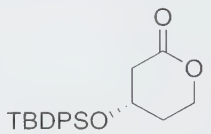
To a previously dried flask containing cyclic anhydride **8b** (1.09 g, 2.96 mmol) was added Et_2O (100 mL). The solution was cooled to –40 °C, $(DHQD)_2AQN$ (760 mg, 0.887 mmol) was added and the mixture was stirred for about 20 min. MeOH (1.20 mL, 29.6 mmol) was then added and the reaction was stirred at –40 °C for 70–72 h, stopped by the addition of 10% aq. HCl (90 mL) at –40 °C, and allowed to warm to rt. After transferring to a separatory funnel, the mixture was extracted, the layers were separated, and the aqueous layer was reextracted with EtOAc (2 × 100 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide 1.25 g of the crude acid **16** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.70–7.65 (m, 4H), 7.48–7.35 (m, 6H), 4.51 (qn, J = 6.1 Hz, 1H), 3.56 (s, 3H), 2.69–2.53 (m, 4H), 1.03 (s, 9H). The ^{1}H NMR spectra was identical with the one reported in ref. 25. This material was combined with other crude desymmetrized material to provide 7.29 g of product. The catalyst was recovered by basifying the acidic aqueous layer with KOH pellets (a yellow precipitate formed). The aqueous layer was then extracted with Et_2O until the organic layer remained colourless. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The recovered catalyst was purified by chromatography on SiO_2 with 5% MeOH–$CHCl_3$ containing 0.5% aq. NH_4OH before being reused.

(S)-3-((tert-Butyldiphenylsilyl)oxy)-5-hydroxypentanoic acid, methyl ester (17)



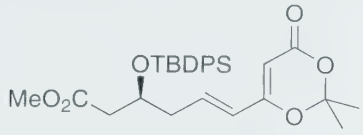
To a solution of crude acid **16** (7.29 g, 19.8 mmol) in THF (100 mL) at rt was added a solution of BH_3·DMS in THF (2.0 mol/L, 30 mL, 60 mmol) and the mixture was stirred for 15 h. The reaction was stopped by slowly adding satd. aq. $NaHCO_3$ (350 mL) and stirred vigorously for 20 min. The mixture was then transferred to a separatory funnel and extracted with Et_2O (3 × 300 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 5.41 g of **17** (71%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 7.74–7.65 (m, 4H), 7.48–7.37 (m, 6H), 4.38 (qn, J = 5.9 Hz, 1H), 3.70–3.61 (m, 2H), 3.54 (s, 3H), 2.55 (d, J = 6.4 Hz, 2H), 1.86–1.80 (m, 1H), 1.78–1.72 (m, 1H), 1.62 (bt, J = 5.5 and 5.2 Hz, 1H), 1.06 (s, 9H). The ^{1}H NMR spectra was identical with the one reported in ref. 25.

(S)-3-((tert-Butyldiphenylsilyl)oxy)-5-hydroxypentanoic acid lactone (18)



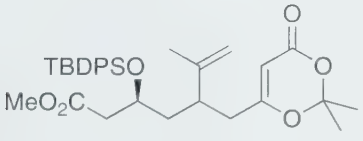
To a solution of crude acid **16** (115 mg, 0.287 mmol) in THF (2.0 mL) at rt was added a solution of BH_3·DMS in THF (2.0 mol/L, 430 µL, 0.86 mmol) and the mixture was stirred for 17 h. The reaction was stopped by slowly adding 10% HCl (3.5 mL) and stirred vigorously for 1 h. The mixture was then transferred to a separatory funnel and extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 38 mg of **18** (38%) as a colourless oil. $[\alpha]_D$ –12.3 (*c* 7.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.67–7.62 (m, 4H), 7.50–7.37 (m, 6H), 4.63 (ddd, J = 11.3, 8.6, 4.5 Hz, 1H), 4.28–4.18 (m, 2H), 2.59 (d, J = 4.9 Hz, 2H), 1.94–1.75 (m, 2H), 1.08 (s, 9H). The ^{1}H NMR spectra was identical with the one reported in ref. 25. The enantiomeric excess was determined by chiral HPLC (Chiralcel OD) using *i*-PrOH–hexane (1.0%) at a flow rate of 1.0 mL/min (R_t minor = 22.8 min, R_t major = 24.5 min).

3-(tert-Butyldiphenylsilanyloxy)-6-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)hex-5-enoic acid methyl ester (19)



To a stirred solution of alcohol **17** (5.41 g, 14.0 mmol) in a mixture of CH_2Cl_2 (63 mL) and CH_3CN (7 mL) at rt was added NMO (2.46 g, 21.0 mmol) and 4 Å molecular sieves (7.0 g). TPAP (246 mg, 0.700 mmol) was added in three portions over a period of 20 min and the resulting mixture was stirred for 30 min at rt. The dark black mixture was then filtered over Celite with CH_2Cl_2 and the filtrate was concentrated under reduced pressure. The resulting oil was rapidly purified by chromatography on SiO_2 with EtOAc–hexanes (20%) to afford 4.23 g of the corresponding aldehyde (79%) as a colourless oil. A solution of phosphonate **12** (4.28 g, 15.4 mmol) in THF (100 mL) cooled to 0 °C was treated with 95% NaH (317 mg, 13.2 mmol). The cold bath was removed and the mixture was stirred at rt for 20 min. After cooling to –78 °C, a solution of the aldehyde (4.23 g, 11.0 mmol) in THF (5 mL, 5 mL rinse) was added, the bath was removed, and the reaction was allowed to gradually warm to rt and was stirred at that temperature for 1 h. One drop of satd. aq. $NaHCO_3$ was added and the mixture was stirred for 5 min (to complete the deprotonation step). After adding additional satd. aq. $NaHCO_3$ (300 mL), the mixture was transferred to a separatory funnel and extracted with Et_2O (3 × 300 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 3.50 g of **19** (49% from alcohol) as a colourless oil. $[\alpha]_D$ 58.0 (*c* 0.21, $CHCl_3$). R_f 0.33 (30% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2932, 2858, 1728, 1655, 1592, 1428, 1390, 1274, 1206, 1111, 1020. ^1H NMR ($CDCl_3$) δ: 7.76–7.60 (m, 4H), 7.52–7.33 (m, 6H), 6.44 (dt, *J* = 15.5, 7.5 Hz, 1H), 5.78 (d, *J* = 15.6 Hz, 1H), 5.18 (s, 1H), 4.29 (qn, *J* = 6.0 Hz, 1H), 3.57 (s, 3H), 2.54 (A of ABX, J_{AB} = 15.2, J_{AX} = 6.4 Hz, 1H), 2.48–2.36 (m, 3H), 1.67 (s, 6H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 171.3, 162.7, 161.9, 137.4, 135.81 (2), 135.78 (2), 133.4, 133.3, 129.8 (2), 127.6 (4), 125.2, 106.2, 93.8, 69.5, 51.5, 41.7, 40.2, 26.8 (3), 24.9 (2), 19.2. HR-MS (EI) *m/e* calcd. for $C_{25}H_{27}O_6Si$: 451.1577 [M – C_4H_9]; found: 451.1575.

(3S)-Methyl 3-(tert-butyldiphenylsilyloxy)-5-((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)-6-methylhept-6-enoate (20)

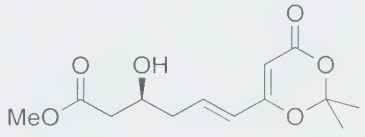


A solution of *t*-BuLi in pentane (1.2 mol/L, 33 mL, 40 mmol) cooled to –78 °C was diluted with THF (33 mL) and 2-bromopropene (1.78 mL, 20.0 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min, then at 0 °C for 30–45 min. To a suspension of CuI (1.10 g, 5.78 mmol) in THF (20 mL) cooled to –78 °C was added the solution of 2-lithiopropene (39 mL, 12 mmol). The dark black mixture was stirred at –78 °C for 30 min and then TMSCl (3.0 mL, 24 mmol) was added. After stirring for ca. 5 min, a solution of **19** (981 mg, 1.93 mmol) in THF (6.0 mL, 2 × 2.0 mL rinse) was added. The mixture was stirred at –78 °C for 30 min, then at –20 °C for ca. 16 h. The reaction was stopped by adding satd. aq. $NaHCO_3$ (100 mL) at –20 °C, then warmed to rt, transferred to a separatory funnel, and extracted with Et_2O (4 × 100 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 999 mg of **20** (94%) as a colourless oil. R_f 0.38 (30% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2933, 2858, 1732, 1633, 1428, 1390, 1272, 1205, 1111, 1015. ^1H NMR ($CDCl_3$) δ: 7.75–7.62 (m, 4H), 7.51–7.34 (m, 6H), 5.08 and 5.05 (s, 1H), 4.66–4.62 (m, 1H), 4.54 and 4.41 (br s, 1H), 4.14–4.03 (m, 1H), 3.59 and 3.54 (s, 3H), 2.65–2.26 (m, 3H), 2.11–1.97 (m, 2H), 1.67–1.47 (m, 2H), 1.65 and 1.64 (s, 3H), 1.60 and 1.58 (s, 3H), 1.49 and 1.21 (s, 3H), 1.04 and 1.02 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 171.6 [171.3], 170.0 [169.8], 161.16 [161.09], 144.4 [144.3], 135.9 (8), 133.9 [133.7], 133.6 [133.5], 129.8 (4), 127.6 (8), 113.9 [113.3], 106.3 (2), 94.2 [94.1], 68.6 [68.4], 51.41 [51.36], 42.6 [41.2], 40.8 [40.7], 40.8 [40.4], 37.8 [37.4], 26.9 (3) [26.8 (3)], 25.40 [25.36], 25.0 [24.9], 19.3 [19.2], 17.6 [17.3]. HR-MS (ESI–POS) *m/e* calcd. for $C_{32}H_{42}O_6NaSi$: 573.2648 [M + Na]; found: 573.2642.

Rhodium-catalyzed asymmetric 1,6-addition of potassium isopropenyl organotrifluoroborate to 19 in the presence of Carreira's diene

To a dry sealed tube was added the diene ligand (3.6 mg, 0.014 mmol), $Rh(acac)(eth)_2$ (3 mg, 0.01 mmol), and EtOH (0.5 mL) and the mixture was stirred at rt for 15 min. A solution of **19** (117 mg, 0.230 mmol) in EtOH (0.75 mL, 0.75 mL rinse) was then added, followed by potassium isopropenyl organotrifluoroborate (37) (102 mg, 0.689 mmol). The reaction mixture was stirred at 82 °C for 24 h, cooled to rt, and treated with satd. aq. $NaHCO_3$ (15 mL). The mixture was transferred to a separatory funnel and extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 27.2 mg (21%) of **20** and 47.5 mg of **21** (38%).

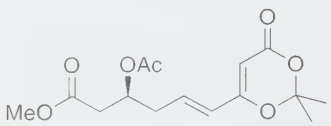
6-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxyhex-5-enoic acid methyl ester (23)



To a solution of **19** (234 mg, 0.460 mmol) in THF (5.5 mL) in a plastic tube was added HF·pyridine (600 µL, 23 mmol) and the mixture was stirred vigorously at rt for 3 days. The reaction was stopped by dropwise addition to

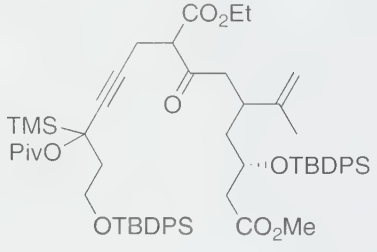
satd. aq. $NaHCO_3$ (75 mL). After adding solid $NaHCO_3$ to the aqueous solution, the mixture was transferred to a separatory funnel and extracted with Et_2O (4 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 34 mg (15%) of starting material **19** and 101 mg of **23** (81%) as a colourless oil. $[\alpha]_D$ 5.9 (*c* 2.38, CH_2Cl_2). R_f 0.17 (50% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3454, 2999, 2952, 1728, 1651, 1592, 1392, 1276, 1204, 1067, 1020. ^1H NMR ($CDCl_3$) δ: 6.59 (dt, *J* = 15.6, 7.6 Hz, 1H), 6.01 (d, *J* = 15.6 Hz, 1H), 5.28 (s, 1H), 4.23–4.13 (m, 1H), 3.74 (s, 3H), 3.10 (d, *J* = 3.6 Hz, 1H), 2.54 (A of ABX, J_{AB} = 16.7, J_{AX} = 3.4 Hz, 1H), 2.51–2.40 (m, 3H), 1.72 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 172.8, 162.7, 161.9, 137.2, 125.1, 106.4, 93.9, 66.9, 51.8, 40.6, 39.4, 24.9 (2). HR-MS (EI) *m/e* calcd. for $C_{13}H_{16}O_5$: 252.0998 [M – H_2O]; found: 252.0999.

(S,E)-Methyl 3-acetoxy-6-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)hex-5-enoate (24)



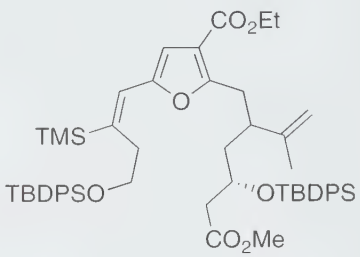
To a solution of **23** (51.2 mg, 0.189 mmol) in pyridine (1.56 mL, 19.3 mmol) was added Ac_2O (910 μL, 9.6 mmol) and the mixture was stirred at rt for 6.5 h. After concentrating under reduced pressure, the resulting mixture was purified by chromatography on SiO_2 to afford 56.4 mg (95%) of **24** as a colourless oil. $[\alpha]_D$ 11.9 (*c* 1.96, CH_2Cl_2). R_f 0.37 (50% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2999, 2954, 1732, 1656, 1594, 1438, 1376, 1244, 1020. ^1H NMR ($CDCl_3$) δ: 6.45 (dt, *J* = 15.5, 7.5 Hz, 1H), 5.98 (dt, *J* = 15.6, 1.3 Hz, 1H), 5.36–5.27 (m, 1H), 5.28 (s, 1H), 3.69 (s, 3H), 2.64 (A of ABX, J_{AB} = 15.8, J_{AX} = 7.3 Hz, 1H), 2.59–2.52 (m, 2H), 2.04 (s, 3H), 1.71 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 170.3, 170.1, 162.5, 161.9, 135.6, 125.8, 106.5, 94.3, 68.8, 51.9, 38.2, 37.0, 25.0, 24.9, 20.9. HR-MS (EI) *m/e* calcd. for $C_{13}H_{16}O_5$: 252.0998 [M – CH_3CO_2H]; found: 252.0998.

(7S)-Dimethyl 2-(4-(benzoyloxy)-6-(tert-butyldiphenylsilyloxy)-4-(trimethylsilyl)hex-2-ynyl)-7-(tert-butyldiphenylsilyloxy)-3-oxo-5-(prop-1-en-2-yl)nonanedioate (22)



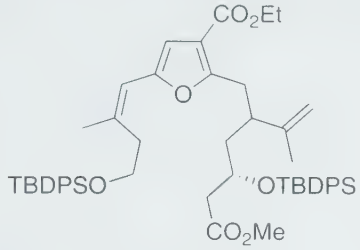
To a solution of [1,3]dioxin-4-one **20** (999 mg, 1.81 mmol) in toluene (20 mL) was added EtOH (530 μL, 9.1 mmol). The solution was heated at reflux for ca. 1.5 h until TLC analysis showed complete consumption of the starting material. The solution was then concentrated under reduced pressure and kept under high vacuum. The crude β-keto ester was redissolved in THF (20 mL) and cooled to 0 °C. The septum was temporarily removed to allow the quick introduction of 98% NaH (52 mg, 2.2 mmol) and the mixture was stirred at 0 °C for ca. 20 min. Afterwards, a solution of iodide **4** [prepared from the corresponding chloride (1.86 g, 3.30 mmol) and NaI (679 mg, 4.53 mmol) in refluxing acetone (15 mL)] in THF (6.0 mL, 6.0 mL rinse) was added and the reaction was gradually warmed to rt, while maintaining the flask in the cold bath. After stirring overnight, the reaction mixture was concentrated under reduced pressure and filtered over a pad of SiO_2 with EtOAc–hexane (20%). This material was then purified by chromatography on SiO_2 to afford 1.50 g of **22** (77%, two steps) as a colourless oil. Since this α-propargyl β-keto ester exists as a mixture of up to four different diastereomers, it was not characterized.

Ethyl 5-((E)-4-(tert-butyldiphenylsilyloxy)-2-(trimethylsilyl)but-1-enyl)-2-((4S)-4-(tert-butyldiphenylsilyloxy)-6-methoxy-6-oxo-2-(prop-1-en-2-yl)hexyl)furan-3-carboxylate (25)



A solution of α-propargyl β-keto ester **22** (76.0 mg, 0.0713 mmol) in a mixture of MeCN (1.0 mL) and H_2O (100 μL) was subjected to three freeze–pump–thaw cycles. Afterwards, $NaOAc{\cdot}3H_2O$ (10.7 mg, 0.0784 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) were added and the mixture was stirred at 87 °C for 2 h. After cooling to rt, the crude mixture was filtered over a pad of SiO_2 with 20% EtOAc–hexane and concentrated under reduced pressure. This material was then purified by chromatography on SiO_2 to afford 33.2 mg of **25** (49%, 6.8:1 mixture of (*E*)–(*Z*)-isomers) as a colourless oil. R_f 0.28 (10% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3071, 2931, 2857, 1741, 1716, 1590, 1428, 1388, 1230, 1111. ^1H NMR ($CDCl_3$) δ: 7.75–7.59 (m, 8H), 7.46–7.31 (m, 12H), 6.75 and 6.71 (s, 1H), 6.45 and 6.42 (s, 1H), 4.58 and 4.46 (brs, 1H), 4.46 and 4.41 (brs, 1H), 4.32–4.20 (m, 2H), 4.18–4.03 (m, 1H), 3.71–3.61 (m, 2H), 3.55 and 3.49 (s, 3H), 2.94–2.72 (m, 4H), 2.61–2.33 (m, 2H), 1.75–1.48 (m, 3H), 1.57 and 1.21 (s, 3H), 1.33 and 1.30 (t, *J* = 7.2 Hz, 3H), 1.063 and 1.056 (s, 9H), 1.00 (s, 9H), –0.003 and –0.004 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 172.0 [171.5], 163.8 [163.7], 160.0 [159.7], 151.1 [151.0], 145.7 [144.9], 140.04 [139.99], 135.94, 135.88, 135.8, 135.6, 135.2, 134.8, 134.2, 133.8, 133.62, 133.58, 129.5, 127.7, 127.6, 127.5, 127.4, 126.6 [126.4], 115.6, 112.85 [112.80], 110.0, 69.0 [68.9], 62.5, 60.1, 51.33 [51.27], 43.2, 43.0, 42.5 41.0, 40.1, 39.6, 34.7, 32.4 [32.3], 26.9, 26.8, 26.5, 19.2, 19.1, 19.0, 18.0, 16.9, 14.33 [14.28], 0.14, –1.8.

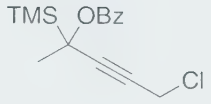
Ethyl 5-((Z)-4-(tert-butyldiphenylsilyloxy)-2-methylbut-1-enyl)-2-((4S)-4-(tert-butyldiphenylsilyloxy)-6-methoxy-6-oxo-2-(prop-1-en-2-yl)hexyl)furan-3-carboxylate (26)



To a solution of I_2 (105 mg, 0.414 mmol) in THF (0.5 mL) was added pyridine (50 µL, 0.62 mmol) followed by $AgClO_4$ (85 mg, 0.41 mmol). The mixture was stirred at rt for 15 min, then a solution of furan **25** (97.4 mg, 0.103 mmol) in THF (1.0 mL, 2 × 0.5 mL rinse) was added. After stirring at rt for 19 h, the crude reaction mixture was filtered over a pad of Celite with Et_2O (25 mL). The solution was transferred to a separatory funnel and extracted with a mixture of 10% aq. $Na_2S_2O_3$ (10 mL) and satd. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted again with Et_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 113 mg of crude vinyl iodide. The iodide was redissolved in THF (1.0 mL) and subjected to two freeze–pump–thaw cycles. The degassed solution was then cooled to 0 °C and $Pd(PPh_3)_4$ (6.0 mg, 0.0052 mmol) was added, followed by a 2.0 mol/L solution of Me_2Zn in toluene (160 µL, 0.32 mmol). The cold bath was removed and the reaction was stirred at rt for ca. 17 h, stopped by adding H_2O (5 mL), and transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 5 mL), the organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 57.5 mg of **26** (63%, 4.7:1 mixture of (*Z*)-(*E*)-isomers) as a colourless oil. R_f 0.28 (10% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3071, 2931, 2857, 1740, 1715, 1600, 1428, 1385, 1227, 1111. ^1H NMR ($CDCl_3$) δ: 7.74–7.61 (m, 8H), 7.45–7.33 (m, 12H), 6.47 and 6.45 (s, 1H), 6.02 and 6.00 (s, 1H), 4.54 and 4.43 (brs, 1H), 4.43 and 4.37 (brs, 1H), 4.31–4.20 (m, 2H), 4.16–4.04 (m, 1H), 3.87–3.79 (m, 2H), 3.55 and 3.50 (s, 3H), 2.98–2.77 (m, 2H), 2.77–2.59 (m, 2H), 2.55–2.35 (m, 2H), 1.86 and 1.85 (s, 3H), 1.71–1.50 (m, 3H), 1.56 and 1.09 (s, 3H), 1.32 and 1.30 (t, J = 7.2 Hz, 3H), 1.041 and 1.038 (s, 9H), 1.01 and 1.00 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 172.0 [171.5], 163.93 [163.90], 159.2 [158.9], 151.05 [150.97], 145.8 [145.0], 137.43 [137.38], 135.91, 135.88, 135.81, 135.6, 135.2, 134.8, 134.2, 133.9, 133.7, 133.6, 133.5, 129.5, 127.7, 127.6, 127.5, 127.4, 115.37 [115.24], 115.15 [115.08], 112.7, 107.7 [107.6], 69.0 [68.9], 62.3, 60.0, 51.31 [51.25], 43.3, 43.0, 42.4, 41.0, 40.3, 39.7, 36.6, 32.3 [32.2], 26.9, 26.8, 26.5, 25.2, 19.2, 19.1, 18.4, 18.0, 17.0, 14.4 [14.3].

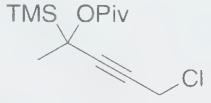
5-Chloro-2-(trimethylsilyl)pent-3-yn-2-yl benzoate (27a)

A solution of *n*-BuLi (1.6 mol/L, 4.4 mL, 7.0 mmol) in Et_2O (40 mL) was cooled to –78 °C and treated with propargyl chloride (540 µL, 7.5 mmol). After stirring at



–78 °C for 20 min, acetyltrimethylsilane (720 µL, 5.0 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min and benzoyl chloride (870 µL, 7.8 mmol) was added. The reaction was allowed to gradually warm up to rt, while maintained in the cold bath and stirred overnight. The reaction was stopped by adding H_2O (50 mL) and the mixture was transferred to a separatory funnel. After extraction, the organic layer was separated and the aqueous layer was extracted once more with Et_2O (50 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 1.2 g of **27a** (80%) as a yellow-orange oil. For the full spectral characterization of this compound, see ref. 11.

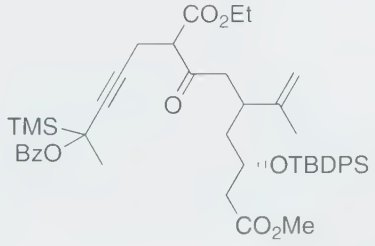
5-Chloro-2-(trimethylsilyl)pent-3-yn-2-yl pivalate (27b)



A solution of *n*-BuLi (1.6 mol/L, 8.8 mL, 14 mmol) in Et_2O (80 mL) cooled to –78 °C was treated with propargyl chloride (1.09 mL, 15.0 mmol). After stirring at –78 °C for 20 min, acetyltrimethylsilane (1.43 mL, 9.98 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min and trimethylacetyl chloride (1.85 mL, 15.0 mmol) was added. The reaction mixture was allowed to gradually warm up to rt, while maintained in the cold bath and stirred overnight. The reaction was stopped by adding H_2O (100 mL) and transferred to a separatory funnel. After extraction, the organic layer was separated and the aqueous layer was extracted once more with Et_2O (100 mL). The organic layers were combined, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 to afford 1.59 g of **27b** (58%) as a yellow-orange oil. R_f 0.22 (5% EtOAc–hexane). FT-IR (neat, cm^{-1}): 2970, 1737, 1479, 1367, 1262, 1144, 1060. ^1H NMR ($CDCl_3$) δ: 4.24 (s, 2H), 1.62 (s, 3H), 1.19 (s, 9H), 0.19 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 177.1, 87.6, 82.4, 67.2, 39.2, 31.3, 27.1 (3), 21.1, –4.2. HR-MS (EI) *m/e* calcd. for $C_{13}H_{23}O_2SiCl$: 274.1156; found: 274.1154.

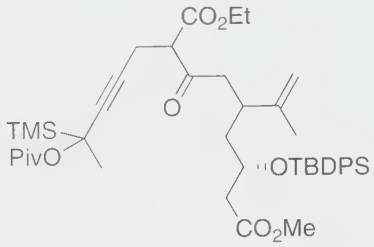
(7S)-1-Ethyl 9-methyl 2-(4-(benzoyloxy)-4-(trimethylsilyl)pent-2-ynyl)-7-(tert-butyldiphenylsilyloxy)-3-oxo-5-(prop-1-en-2-yl)nonanedioate (28a)

Following the same procedure as for the preparation of α-propargyl β-keto ester **22**, the alkylation of β-keto ester **21**



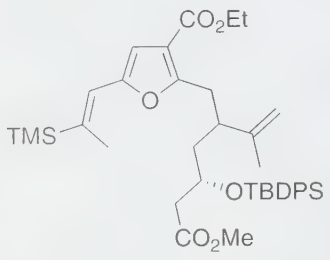
[prepared from [1,3]dioxin-4-one **20** (422 mg, 0.765 mmol)] with the iodide derived from **27a** (406 mg, 1.38 mmol) gave 580 mg (95%, two steps) of **28a** as a colourless oil. Since this α-propargyl β-keto ester exists as a mixture of up to four different diastereomers, it was not characterized.

(7S)-1-Ethyl 9-methyl 7-(tert-butyldiphenylsilyloxy)-3-oxo-2-(4-(pivaloyloxy)-4-(trimethylsilyl)pent-2-ynyl)-5-(prop-1-en-2-yl)nonanedioate (28b)



Following the same procedure as for the preparation of α-propargyl β-keto ester **22**, the alkylation of β-keto ester **21** [prepared from [1,3]dioxin-4-one **20** (387 mg, 0.703 mmol)] with the iodide derived from **27b** (349 mg, 1.27 mmol) gave 350 mg (64%, two steps) of **28b** as a colourless oil. Since this α-propargyl β-keto ester exists as a mixture of up to four different diastereomers, it was not characterized.

Ethyl 2-((4S)-4-(tert-butyldiphenylsilyloxy)-6-methoxy-6-oxo-2-(prop-1-en-2-yl)hexyl)-5-((E)-2-(trimethylsilyl)prop-1-enyl)furan-3-carboxylate (29)



In a microwave tube, a solution of **28b** (84.3 mg, 0.108 mmol) in THF (500 μL) was subjected to three freeze–pump–thaw cycles. To the degassed solution was then added allylpalladium chloride dimer (3.0 mg, 0.0082 mmol) and dppf (9.0 mg, 0.016 mmol) and the mixture was stirred vigorously at rt for ca. 5 min (during this time a voluminous precipitate formed). The microwave tube was then heated with stirring in the microwave reactor for 20 min (100 °C, 300 W) and then cooled to rt. The crude, wine-red reaction mixture was filtered over a pad of SiO_2 with 20% EtOAc–hexane. This material was then purified by chromatography on SiO_2 to afford 43.5 mg of **29** (59%) as a colourless oil. The diastereomeric mixture of furans was dissolved in THF (500 μL) and $(PhSe)_2$ (1.0 mg, 0.0032 mmol) was added. The solution was heated at 70 °C for 16 h in a sealed tube, then cooled to rt, and concentrated under reduced pressure. This material was purified by chromatography on SiO_2 to afford 36.8 mg of pure ***E*-29** (50% from **28b**) as a colourless oil. R_f 0.55 (20% EtOAc–hexane). FT-IR (neat, cm^{-1}): 3072, 2954, 2857, 1742, 1715, 1597, 1428, 1229, 1111. ^1H NMR ($CDCl_3$) δ: 7.73–7.60 (m, 4H), 7.45–7.31 (m, 6H), 6.55 and 6.54 (s, 1H), 6.44 and 6.37 (apparent q, J = 1.5 and 1.6 Hz, 1H), 4.59 and 4.48 (bs, 1H), 4.46 and 4.43 (bs, 1H), 4.31–4.19 (m, 2H), 4.18–4.04 (m, 1H), 3.56 and 3.50 (s, 3H), 3.00–2.75 (m, 2H), 2.63–2.36 (m, 2H), 2.01 and 2.00 (d, J = 1.6 and 1.6 Hz, 3H), 1.75–1.49 (m, 3H), 1.56 and 1.16 (s, 3H), 1.34 and 1.31 (t, J = 7.1 and 7.1 Hz, 3H), 1.00 (s, 9H), 0.14 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 171.9 [171.5], 163.9 [163.8], 159.4 [159.1], 151.83 [151.79], 145.7 [145.1], 140.2 [140.0], 135.92 (2) [135.88 (2)], 135.85 (2) [135.77 (2)], 134.2 [133.8], 133.6 (2), 129.6 (3), 129.5, 127.5 (6), 127.4 (2), 124.3 [124.2], 115.5 (2), 112.8 [112.6], 109.74 [109.71], 69.0 [68.8], 60.0 (2), 51.3 [51.2], 43.0 [42.9], 42.5 [41.0], 40.1 [39.6], 32.3 (2), 26.9 (3) [26.8 (3)], 19.2 (2), 18.0 [17.1], 17.1 (2), 14.34 [14.28], –2.3 (6). HR-MS (ESI–POS) *m/e* calcd. for $C_{39}H_{54}O_6NaSi_2$: 697.3357 [M + Na]; found: 697.3303.

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Synthesis of a hindered C_2-symmetric hydrazine and diamine by a crisscross cycloaddition of citronellal azine[1]

Barry B. Snider, James F. Grabowski, Roger W. Alder, Bruce M. Foxman, and Lin Yang

Abstract: Crisscross cycloaddition of citronellal azine (**6**) with 2 equiv. of TFA and powdered 3 Å molecular sieves in CH_2Cl_2 at reflux for 22 h afforded 37% of the desired C_2-symmetric hydrazine **7** and 5%–10% of diastereomer **8** in which one of the 6–5 ring fusions is cis. Methylation of the hydrazine of **7** and reduction of the resulting salt (**9**) with Li in NH_3 cleaved the N—N bond to give secondary tertiary amine **10** in 97% yield. Eschweiler–Clarke methylation afforded the C_2-symmetric bis tertiary amine **11** in 69% yield. Racemic products were obtained in initial attempts at asymmetric catalysis using **7** or **11** as asymmetric bases, using bistertiary amine **11** as a ligand analogous to sparteine for alkyllithiums, or using the lithium amide from secondary tertiary amine **10** as an asymmetric base. Apparently, the proton is buried in the core of **11**, leaving a hydrophobic surface; the free counterion is not an asymmetric catalyst. Diamine **11** may be too hindered to complex to *s*-BuLi. Tertiary amine **11** (pK_{a1} = 24.7) is more basic than DBU (pK_a = 24.3) in CH_3CN, in good agreement with theory.

Key words: crisscross cycloaddition, azine, dipolar cycloaddition, calculation of pK_a.

Résumé : La cycloaddition croisée de l'azine du citronellal (**6**) à l'aide de 2 équivalents d'acide trifluoroacétique et de tamis moléculaires 3 Å en poudre, dans du CH_2Cl_2 au reflux, pendant 22 heures, conduit à la formation de l'hydrazine (**7**) de symétrie C_2 recherchée avec un rendement de 37 % ainsi qu'à environ 5 % à 10 % du diastéréomère **8** dans lequel la fusion des cycles à cinq et à six chaînons est cis. La méthylation de l'hydrazine **7** et la réduction du sel **9** qui en résulte avec du Li dans de l'ammoniac permet de clivé la liaison N—N pour conduire à la formation de l'amine secondaire tertiaire **10** avec un rendement de 97 %. Une méthylation de Eschweiler–Clarke fournit la bisamine tertiaire de symétrie C_2 (**11**) avec un rendement de 60 %. On n'a obtenu que des produits racémiques dans les essais initiaux de catalyse asymétrique en utilisant les bases asymétriques **7** ou **11**, en utilisant la bisamine tertiaire **11** comme ligand analogue à la spartéine pour les alkyllithiens ou en utilisant l'amide de lithium dérivé de l'amine secondaire tertiaire **10** comme base asymétrique. Il semble que le proton est enfoui à l'intérieur du composé **11** qui ne laisse qu'une surface hydrophobe; le contre-ion libre n'est pas un catalyseur asymétrique. Il est possible que la diamine **11** soit trop encombrée pour se complexer au *s*-BuLi. L'amine tertiaire **11** (pK_{a1} = 24,7) est plus basique que la DBU (pK_a = 24,3) dans le CH_3CN, ce qui est en bon accord avec la théorie.

Mots clés : cycloaddition croisée, azine, cycloaddition dipolaire, calcul de pK_a.

[Traduit par la Rédaction]

Introduction

Both inter- and intra-molecular crisscross cycloadditions of azines with two alkenes are well-known as routes to 1,5-diazabicyclo[3.3.0]octanes, which are tetralkylhydrazines embedded in the ring fusion of a bicyclo[3.3.0] ring system (see Scheme 1) (1, 2). In an intermolecular example, the azine of hexafluoroacetone (**1**) reacted with 2 equiv. of methyl acrylate in benzene at 80 °C for 8 days to give 64% of adduct **2** and minor amounts of regio- and stereo-isomers (2*b*). Reaction of 2-allyloxy-1-naphthalenecarboxaldehyde (**3**) with 0.5 equiv. of hydrazine dihydrochloride in EtOH at

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Dedicated to Alfred Bader in honor of the contributions that he and the Aldrich Chemical Company, which he founded and developed, have made to the development of organic chemistry over the past half century. RWA thanks Alfred Bader for his enthusiastic promotion of Proton Sponge®.

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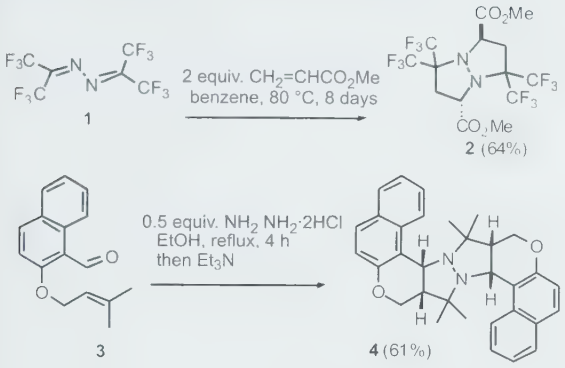
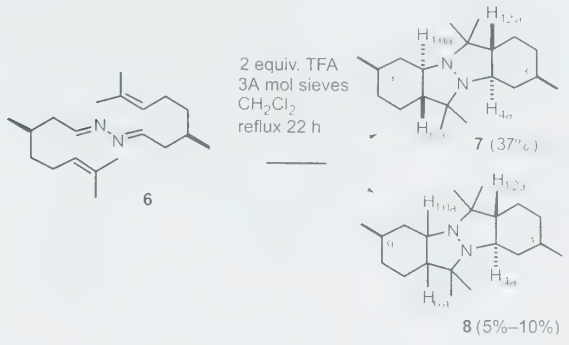
Scheme 1. Examples of crisscross cycloadditions.



Scheme 2. Crisscross cycloaddition of azine **6**.



reflux for 4 h provided the azine, which underwent a crisscross cycloaddition to give **4** in 61% yield (*2a*, *2c*). We were intrigued by the possibility of using this reaction with the azine of a readily available chiral aldehyde, such as citronellal, to obtain a chiral C_2-symmetric product that might be of value as an asymmetric catalyst. C_2-Symmetric diamines have been widely used in asymmetric synthesis (3), as has sparteine, which is not C_2-symmetric (4). The intramolecular cycloaddition of citronellal phenylhydrazone has been reported, although the stereochemistry of the product has not been well-characterized (5). Kobayashi et al. (6) have also explored asymmetric cycloadditions of related unsaturated acylhydrazones.

Results and discussion

Crisscross cycloaddition of 6

Initial attempts at forming the azine **6** of (*R*)-citronellal (**5**) with hydrazine dihydrochloride under various conditions afforded complex mixtures of azine **6**, hydrazones, hemiacetals, hemiaminals, and (or) the ene adduct, isopulegol. Eventually we found that treatment of neat (*R*)-citronellal (**5**) with 0.5 equiv. of anhydrous hydrazine for 10 min at 0–25 °C afforded azine **6** quantitatively as a 100:20:1 mixture of *E*,*E*-, *E*,*Z*-, and *Z*,*Z*-isomers, respectively, as determined by analysis of the chemical shift of the CH=N protons (7).

Heating a solution of azine **6** with 2 equiv. of TFA and powdered 3 Å molecular sieves in CH_2Cl_2 at reflux for 22 h afforded 37% of the desired C_2-symmetric hydrazine **7** and 5%–10% of diastereomer **8** in which one of the 6–5 ring fusions is cis (see Scheme 2). Lower yields were obtained without molecular sieves, with either more or less TFA, with other acids or BF_3·Et_2O, or by combining azine formation and crisscross cycloaddition in a single step.

The structures of both **7** and **8** were established by spectroscopic analysis and X-ray structure determination. The ^{13}C NMR spectrum of **7** has only 10 different carbons, establishing that the molecule is symmetrical. The ^1H NMR spectrum of **7** is also simple. H_{4a} and H_{10a} both absorb at δ 2.65 as a ddd (J = 11.0, 11.0, 3.7 Hz). The 11.0 Hz coupling constant between both H_{4a} and H_{12a} and H_{10a} and H_{6a} establishes that the ring fusions are trans with antiperiplanar hydrogens. The cycloaddition should proceed preferentially to give products with the methyl groups attached to C_3 and C_6 equatorial, permitting the assignment of **7** as the major product.

The ^{13}C NMR spectrum of the minor product **8** has 20 different carbons. H_{4a} absorbs at δ 2.17 as a ddd (J = 11.0, 11.0, 3.1 Hz). The 11.0 Hz coupling constant between H_{4a} and H_{12a} establishes that the ring fusion is trans. H_{10a} absorbs at δ 3.01 as a ddd (J = 8.5, 8.5, 5.5 Hz), establishing that the other ring fusion is cis. Assuming that the cycloaddition gave only products with equatorial methyl groups, the minor product must be **8**.

Crystallographic analysis[3]

Figures 1 and 2 show the structures of **7** and **8** determined by X-ray crystallographic analysis. The orientation of the lone pairs in the core 1,5-diazabicyclo[3.3.0]octanes is quite different in the two adducts. In the major adduct **7**, the lone pairs are syn with a calculated torsion angle of 12° (see Scheme 3). The numbering corresponds to that used for the crystallographic data. The nitrogens are pyramidal and are 0.45 and 0.44 A above the plane formed by the three substituents. In the minor adduct **8**, the lone pairs are anti with a calculated torsion angle of 177°. The molecule is flattened with the nitrogens only 0.11 and 0.23 A above the plane formed by the three substituents. In syn isomers such as **7**, the torsion angles C_1-N_1-N_2-C_{11} (117.8°) and C_{17}-N_1-N_2-C_7 (141.4°) are much less than 180° and differ significantly. In anti isomers, such as **8**, the torsion angles C_1-N_1-N_2-C_{11} (169.3°) and C_{17}-N_1-N_2-C_7 (174.7°) are both close to 180°. In syn isomers such as **7**, the torsion angle between the lone pairs (12°) is calculated to be the average of C_1-N_1-N_2-C_7 (12.2°) and C_{17}-N_1-N_2-C_{11} (11.4°). In anti isomers such as **8**, the torsion angle between the lone pairs (177°) is calculated

[3] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5052. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 289019 and 28920 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Fig. 1. Molecular structure of **7**.

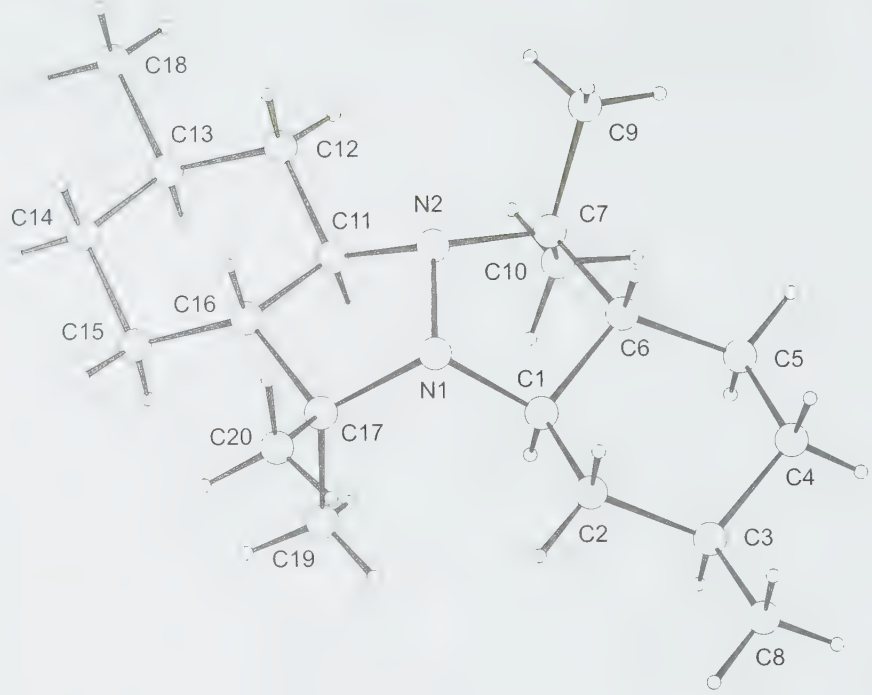
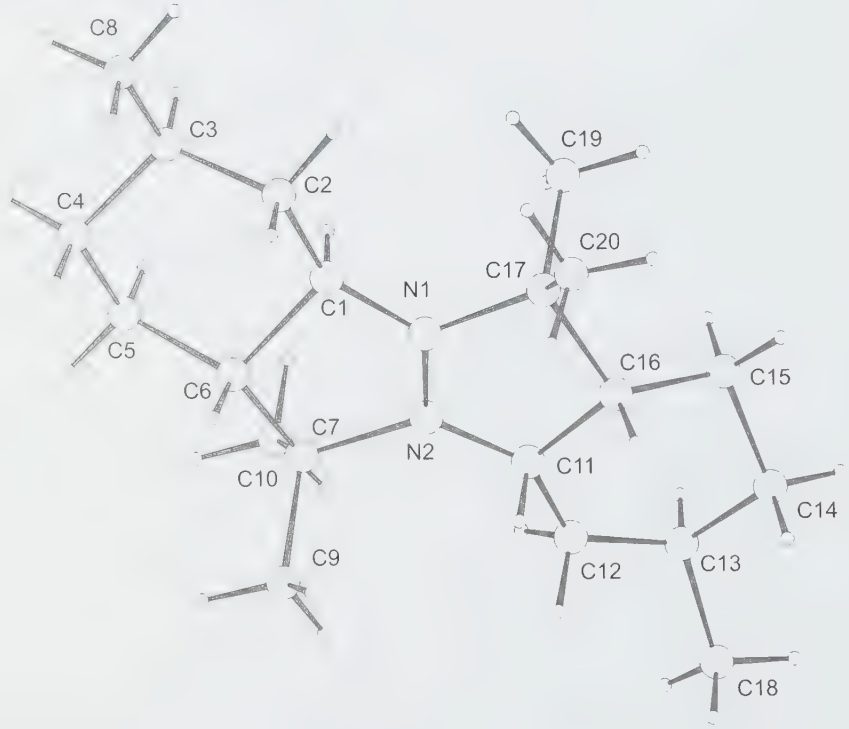
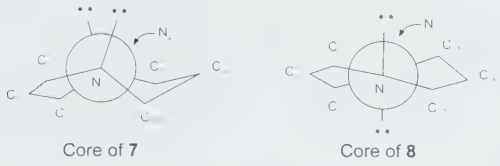


Fig. 2. Molecular structure of **8**.



Scheme 3. 1,5-Diazabicylo[3.3.0]octane cores of **7** and **8** showing lone pair torsion angles.



to be 180° minus half the difference between C_1-N_1-N_2-C_7 (23.9°) and C_{17}-N_1-N_2-C_{11} (18.5°).

A search of the Cambridge Structural Database (CSD) found structures of seven 1,5-diazabicyclo[3.3.0]octanes whose CSD refcodes, lone pair torsion angles, and out of plane distances, respectively, are listed in the following. Five of these have syn lone pairs comparable to **7**: BETGOW, 48.3°, 0.45 Å, 0.45 Å (2*b*); BETGUC, 23.8°, 0.35 Å, 0.35 Å (2*b*); BETHAJ, 23.2°, 0.35 Å, 0.35 Å (2*b*); FEDYAP, 44.8°, 0.54 Å, 0.56 Å (2*i*); and WIWFAJ, 36.6°, 0.52 Å, 0.52 Å (2*g*). The other two have anti lone pairs comparable to **8**: LEKHIS, 179.8°, 0.44 Å, 0.43 Å (2*e*); and LEKHIS, 175.3°, 0.46 Å, 0.42 Å (2*e*).

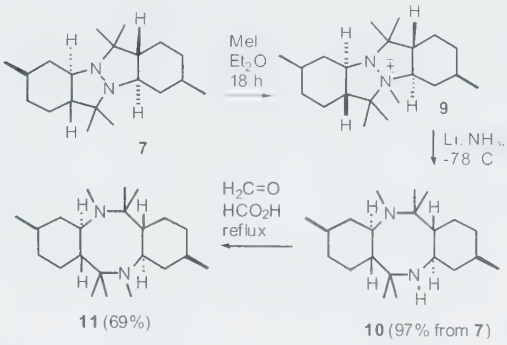
Preparation of 10 and 11

Hydrazines are less basic than amines (8) and are sensitive to oxidation. We therefore explored the reductive cleavage of **7** to give a bis secondary amine. Although hydrazines have been reduced hydrogenolytically (9) or by dissolving metal reductions (10), initial attempts to reduce **7** by either method were unsuccessful. Apparently, steric hindrance and the electron-donating alkyl substituents retard the reduction. We activated the system toward reduction by methylation (11). A solution of **7** was treated with excess (10 equiv.) MeI in ether for 18 h at 25 °C to give **9** (see Scheme 4). Slow addition of a THF solution of **9** to excess Li in NH_3 at –78 °C afforded secondary tertiary amine **10** in 97% yield from **7**. It is important to make sure that excess Li is present because $LiNH_2$ acts as a nucleophile to convert **9** back to **7** with the formation of $MeNH_2$. Eschweiler–Clarke methylation (12) of **10** with formic acid and aqueous formaldehyde at reflux for 19 h afforded the C_2-symmetric tertiary amine **11** in 69% yield.

Evaluation of 7, 10, and 11 as catalysts

We now turned our attention to exploring the use of hydrazine **7** and amines **10** and **11** for asymmetric catalysis. Methanolysis of *cis*-1,2-cyclohexanedicarboxylic anhydride in ether (13) was very slow with **7** as the catalyst and very rapid with **11** as the catalyst. In both cases racemic product was obtained. Attempted deprotonation of *N*-Boc pyrrolidine with *s*-BuLi and **11**, analogously to that reported with *s*-BuLi and sparteine (14) was unsuccessful. Attempted asymmetric deprotonation of cyclohexene oxide with LDA and **10** as described by Asami for other chiral secondary tertiary amines (15) gave racemic 2-cyclohexen-1-ol. The nitrogens of **11** are very basic and quite hindered. The NMR spectrum of diamine **11** in CD_3OD is identical to that of the monotrifluoroacetate salt indicating that the free amine is fully converted to the ammonium methoxide. Apparently, the proton is buried in the core leaving a hydrophobic surface and the reactive methoxide is not an asymmetric catalyst.

Scheme 4. Conversion of hydrazine **7** to amines **10** and **11**.



Diamine **11** may be too hindered to complex to *s*-BuLi. It is also possible that the distance between and (or) alignment of the lone pairs make **11** a poor ligand for Li. The presence of the two geminal dimethyl groups makes the nitrogens very hindered so that **11** is not effective as an asymmetric catalyst or ligand.

Determination of the pK_a of 11 in MeCN

Cyclic diamines are much more basic than simple amines because there is lone pair repulsion in the free diamine and the ammonium salt is stabilized by a strong intramolecular hydrogen bond. 1,4-Dimethyl-1,4-diazacyclooctane has a pK_{a1} in H_2O of 11.9 (15). We determined the pK_{a1} of **11** relative to DBU (**12**) in CD_3CN by adding 0.4 equiv. of TFA to a CD_3CN solution of 1 equiv. of DBU and 1 equiv. of **11**. The NMR spectrum showed three species. Amine **11** (0.72 equiv.) and **11**-H^+ (0.28 equiv.) are observed as separate species that equilibrate slowly on the NMR timescale as has been previously observed for other polyamines (16). DBU is observed as a single rapidly equilibrating species that is 14% protonated by comparison with values for DBU and DBU-H^+. We established that this mixture was at equilibrium by adding the components in various orders. These data establish that **11** is more basic than DBU by 0.4 pK_a units. Using a value of 24.3 for the pK_a of DBU in CH_3CN (17), the pK_{a1} of **11** is 24.7. A similar experiment in DMSO showed that only DBU was protonated, indicating that DBU (pK_a = 13.9, ref. 17) is much more basic than **11** in DMSO.

Calculation of the pK_a of 11

Calculation of proton affinities (PA), gas-phase basicities (GB), and solution pK_a values have been extensively developed in recent years and might help us understand the basicity of **11**. Liptak and Shields (18) have shown that it is possible to calculate absolute aqueous pK_a values with chemical accuracy and their methods have been applied with considerable success to calculate pK_a values in several solvents for one special class of strong neutral bases, the diaminocarbenes, by Magill et al. (19). Unfortunately, the most reliable methods (e.g., CBS-QB3) are far too computationally intensive to be applied to molecules the size of **11**. Magill and Yates' (20) recent results suggest that two good options for larger species are (*a*) CBS-4M and (*b*) B3LYP/6-311+G** and method (*b*) has been used here. This procedure uses geometries, zero point energies, and thermal and entropy corrections from the well-established B3LYP/6-

Table 1. Calculated (B3LYP/6-311+G**//B3LYP/6-31G*) PA and pK_a values for amines **11–15**.

Diamine	Gas-phase PA (kJ mol^{-1})	pK_a (MeCN)[a]	pK_a (DMSO)[b]	$\Delta E(1)$ (kJ mol^{-1})	$\Delta E(2)$ (kJ mol^{-1})
11	1074	24.4	14.7	98	59
12	1052	23.9	12.1		
13a	1028	18.1	8.5		
13b	1089	23.2	11.1		
14	1046	23.5	14.0	1	–9
15	1078	28.3	18.7	42	–6
16	1105	30.4	20.9	43	–23

[a] Relative to Me_3N, pK_a = 17.61.
[b] Relative to Me_3N, pK_a = 8.4.

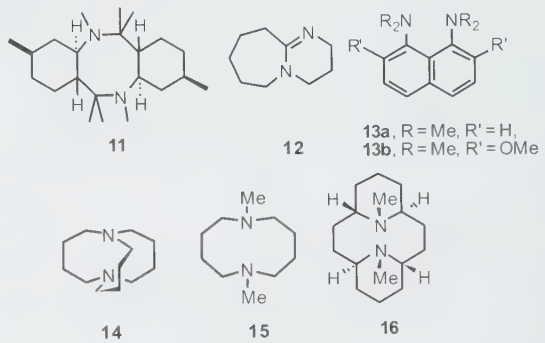
31G* level of theory. pK_a values have been calculated relative to the pK_a values for Me_3NH^+ of 17.61 in MeCN and 8.4 in DMSO, as described previously (21).

DFT calculations were performed with the Jaguar program package (22), using Becke's three-parameter exchange functional (23) with the correlation functional of Lee et al. (B3LYP) (24). All species were characterized by full geometry optimization with the standard 6-31G* basis set, and minima were characterized by analytical frequency calculations. Single point calculations were then carried out with the 6-311+G** basis set. Calculations simulating the solvents MeCN and DMSO employed the Poisson–Boltzmann continuum solvent model as implemented in the Jaguar program, with the assumption that geometries, zero point energy, and thermodynamic parameters could be transferred from the gas-phase calculations. These procedures lead to pK_a values of 11.9 (H_2O), 18.1 (MeCN), and 8.5 (DMSO) for the original proton sponge **13a** compared with experimental values of 12.1 (25), 18.62 (17*a*), and 7.5 (26, 27), respectively. The pK_a value of **13b** in DMSO is calculated to be 11.1 (experimental value, 11.5, ref. 28). While the general level of agreement in MeCN seems relatively good, it is worth noting that the calculated pK_a difference between **13b** and **15** in DMSO is 3.9, compared with a measured value of only 0.4 (15, 21).

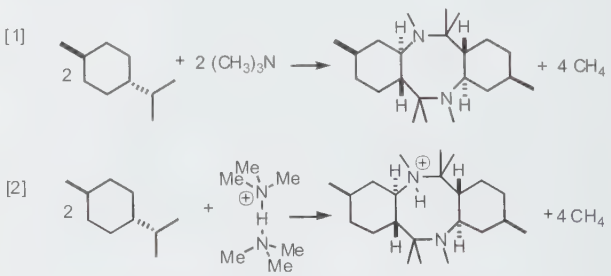
Monte Carlo multiple minimum conformational searches (29, 30) were carried out to find low energy conformations for diamine **11** and the monoprotonated ion, using the MMFFs force field in MacroModel (31, 32). One conformation was clearly preferred for the ion, with a strong N···H-N$^+$ bond (2.66 Å distance between nitrogens; N···H-N angle, 140.9°). The cyclohexane rings are in the expected chair form, and the eight-membered ring is in a twist boat form. The conformational situation for diamine **11** was less clear and therefore, five low energy structures from a MacroModel search for the diamine were submitted to B3LYP/6-31G* calculation. The preferred structure was found to have the same conformation as the protonated ion, with the nitrogen atoms separated by 2.90 Å; this structure was used for the PA and pK_a calculations.

PA and pK_a values for amines **11–16** (see Chart 1) are listed in Table 1. The gas-phase PA results should be regarded as rather reliable. They show that diamine **11** is a substantially stronger base than the flexible 10-membered ring diamine **14**, in spite of having a hydrogen bond that is further from the linear ideal. This presumably reflects greater strain relief on protonation.

Chart 1. Structures of amines whose calculated PA and pK_a values are shown in Table 1.



Scheme 5. Theoretical eqs. [1] and [2] used for assessing strain relief in calculations of PA and pK_a values.



As described previously (21), a convenient way to assess this strain relief is by comparison of the calculated energy changes associated with eqs. [1] and [2] in which the strained diamine and protonated ion are formally constructed from unstrained components (see Scheme 5). The B3LYP/6-31G* computed vales for $\Delta E(1)$ and $\Delta E(2)$ are shown in Table 1. The value of $[\Delta E(1) - \Delta E(2)]$ for **11** (39 kJ mol^{-1}) is considerably greater than for **14** and approaches that for **15**, but is still much smaller than that for **16** (66 kJ mol^{-1}). We conclude that this strain relief is the major factor that determines the PA of these diamines. The increased strain in diamine **11**, when compared with its protonated ion, will be partly due to lone pair – lone pair repulsion, but forcing the nitrogen atoms to move to 2.90 Å, compared with 2.66 Å in the protonated ion, necessarily increases the strain elsewhere in the molecule.

There is much more uncertainty about the calculated pK_a values, since these rely on the performance of the solvation

model. In fact, the calculated pK_a values in MeCN for **11** and **12** are in reasonable agreement with the experimental relative pK_a data. Note that the calculations suggest that, in this solvent, **11** has a rather low pK_a value considering its PA, and is nearer to **14** than **15** in calculated pK_a. This of course reflects a relatively high (calculated) solvation energy for the diamine. There is no simple way of assessing whether this is correct, but we note that diamine **11** has a larger purely hydrophobic surface than the other diamines being used for comparison. While the calculated pK_a values in MeCN are in (possibly fortuitously) quite good agreement with experiment, the calculated values in DMSO are in poor agreement. We can offer no simple explanation, beyond noting that results for DMSO, using the Poisson–Boltzmann continuum solvent model, as implemented in the Jaguar program, have been less satisfactory than for MeCN, as noted earlier.

Conclusion

We have developed an efficient route to C_2-symmetric hydrazine **7** and diamine **11**. Initial trials suggest that the bis tertiary amine **11** is too hindered to function as an asymmetric catalyst or ligand. We are currently exploring routes to less hindered C_2-symmetric tricyclic amines that lack the two geminal dimethyl substituents.

Experimental section

General procedures

NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated, chemical shifts are reported in δ, and coupling constants in Hz. The silica gel used for chromatography was deactivated with methanol unless otherwise indicated. IR spectra are reported in cm^{-1}.

(*R*)-Citronellal azine (6)

Anhydrous hydrazine (0.28 mL, 9.0 mmol) was added dropwise to (*R*)-(+)-citronellal (**5**, 3.26 mL, 2.77 g, 18.0 mmol) at 0 °C and the resulting mixture was stirred at 25 °C for 10 min. The mixture was diluted with CH_2Cl_2 (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give 2.637 g (98%) of **6** as a 100:20:1 mixture of *E,E*-, *E,Z*-, and *Z,Z*-isomers (7), respectively, as a clear oil. IR (neat): 1651. ^{1}H NMR: 7.88 (t, 2, *J* = 6.1, *E,E*-isomer), 7.56 (t, 1, *J* = 5.8, *E,Z*-isomer), 7.15 (t, 1, *J* = 5.5, *E,Z*-isomer) 7.07–7.02 (t, 2, *J* = 5, *Z,Z*-isomer), 5.09 (tq, 2, *J* = 8.5, 1.2), 2.35 (ddd, 2, *J* = 14.0, 8.5, 6.1, *E,E*-isomer), 2.19 (ddd, 2, *J* = 14.0, 8.0, 6.1, *E,E*-isomer), 2.07–1.95 (m, 4), 1.84–1.76 (m, 2), 1.68 (s, 6), 1.60 (s, 6), 1.45–1.36 (m, 2), 1.30–1.21 (m, 2), 0.97 (d, 6, *J* = 6.7). ^{13}C NMR: 165.0 (2C), 131.5 (2C), 124.3 (2C), 39.6 (2C), 36.8 (2C), 30.9 (2C), 25.7 (2C), 25.4 (2C), 19.6 (2C), 17.6 (2C).

(3*R*,4a*R*,6a*R*,9*R*,10a*R*,12a*R*)-Dodecahydro-3,6,6,9,12,12-hexamethyl-1*H*,6*H*-indazolo[2,1-*a*]indazole (7) and (3*R*,4a*R*,6a*R*,9*R*,10a*S*,12a*R*)-dodecahydro-3,6,6,9,12,12-hexamethyl-1*H*,6*H*-indazolo[2,1-*a*]indazole (8)

TFA (1.4 mL, 18 mmol) was added to a suspension of azine **6** (2.616 g, 8.591 mmol) and 3 A powdered molecular sieves (1.024 g) in dry CH_2Cl_2 (300 mL) and the resulting suspension was stirred and heated at reflux for 22 h. The suspension was cooled and water (60 mL) was added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give 3.632 g of a yellow oil. Flash chromatography on silica gel (hexanes–acetone, 3:2) and subsequent deprotonation with satd. $NaHCO_3$ solution gave 495 mg (19%) of 60% pure **8** as a clear wax. Elution with MeOH and subsequent deprotonation with satd. $NaHCO_3$ solution gave 975 mg (37%) of **7** as an orange wax. Data for **7**: IR (CH_2Cl_2): 1688. ^{1}H NMR: 2.65 (ddd, 2, *J* = 11.0, 11.0, 3.7, H_{4a}, H_{10a}), 1.84–1.60 (m, 8), 1.44–1.41 (m, 2), 1.19–1.09 (m, 2), 1.14 (s, 6), 0.98–0.87 (m, 4), 0.96 (s, 6), 0.92 (d, 6, *J* = 6.7). ^{13}C NMR: 58.2 (2C), 58.1 (2C), 57.6 (2C), 41.1 (2C), 34.5 (2C), 30.9 (2C), 28.4 (2C), 24.3 (2C), 22.2 (2C), 19.3 (2C). HRMS (EI) calcd. for $C_{20}H_{36}N_2$: 304.2878 (M^+); found: 304.2882

TFA (2 drops, excess) was added to a solution of **7** in $CDCl_3$ to give **7**·TFA: ^{1}H NMR: 2.92 (ddd, 2, *J* = 11.7, 11.4, 4.0, $H_{4a(10a)}$), 2.20 (ddd, 2, *J* = 12.3, 11.4, 3.2, $H_{12a(6a)}$), 1.91 (br d, 2, *J* = 11.7, $H_{4eq(10eq)}$), 1.78 (br d, 2, *J* = 13.2, $H_{2eq(8eq)}$), 1.73 (br dd, 2, *J* = 11.5, 3.2, $H_{1eq(7eq)}$), 1.44–1.38 (m, 2, $H_{3ax(9ax)}$), 1.41 (s, 6), 1.36 (ddd, 2, *J* = 11.7, 11.7, 11.4, $H_{4ax(10ax)}$), 1.15 (s, 6), 1.15 (br ddd, 2, *J* = 12.3, 11.5, 2.9, $H_{1ax(7ax)}$), 1.05 (m, 2, $H_{2ax(8ax)}$), 0.99 (d, 6, *J* = 6.2). A 1D NOESY experiment showed NOEs from $H_{4a(10a)}$ at δ 2.9 to $H_{12a(6a)}$ at δ 2.2 (small), to $H_{4eq(10eq)}$ at δ 1.91 (large), to $H_{3ax(9ax)}$ at δ 1.44–1.38 (small), to $H_{4ax(10ax)}$ at δ 1.36 (small), to $H_{1ax(7ax)}$ at δ 1.15 (small), and to the methyl group at δ 1.15.

Flash chromatography of 495 mg of 60% pure **8** on silica gel (Et_2O) gave 118 mg (5%) of **8** as a clear wax. ^{1}H NMR: 3.01 (ddd, 1, *J* = 8.5, 8.5, 5.5, H_{10a}), 2.17 (ddd, 1, *J* = 11.0, 11.0, 3.1, H_{4a}), 1.94–1.90 (m, 2, H_{6a}, H_{12a}), 1.86–1.78 (m, 2), 1.76–1.69 (m, 1), 1.58–1.48 (m, 3, including H_{10eq}), 1.47–1.39 (m, 1, H_{4eq}), 1.36–1.31 (m, 2), 1.27–1.18 (m, 2, including H_{10ax}), 1.12–1.05 (m, 1), 1.11 (s, 3), 1.10 (s, 3, 12-CH_3), 1.00 (s, 3, 6-CH_3), 0.98–0.86 (m, 1, H_{4ax}), 0.93 (d, 3, *J* = 6.7), 0.90 (d, 3, *J* = 6.1, 9-CH_3), 0.90 (s, 3, 6-CH_3), 0.77–0.72 (m, 1). ^{13}C NMR: 60.7, 58.5, 56.7, 54.2, 50.2, 38.2, 35.3, 34.2, 31.2, 31.1, 28.7, 26.5, 25.2, 25.0, 23.2, 22.42, 22.41, 21.8, 16.7 (one carbon was not observed). A 1D NOESY experiment showed NOEs from H_{10a} at δ 3.01 to H_{6a} at δ 1.94–1.90 (large), to H_{10eq} at δ 1.58–1.48 (small), to H_{10ax} at δ 1.27–1.18 (large), to 12-CH_3 at δ 1.10, and to 9-CH_3 at δ 0.90 (small). A 1D NOESY experiment showed NOEs from H_{4a} at δ 2.17 to H_{12a} at δ 1.94–1.90 (small), to H_{4eq} at δ 1.47–1.39 (large), to 6-CH_3 at δ 1.00 (large), to H_{4ax} at δ 0.98–0.86 (small), and to 6-CH_3 at δ 0.90 (small).

(3*R*,4a*R*,6a*R*,9*R*,10a*R*,12a*R*)-Hexadecahydro-3,5,6,6,9,12,12-heptamethyldibenzo[*b*,*f*][1,5]diazocine (10)

Iodomethane (0.56 mL, 9.06 mmol) was added to a solution of **7** (276 mg, 0.906 mmol) in dry Et_2O (18 mL) and the resulting solution was stirred at 25 °C for 18 h. The solution was concentrated under reduced pressure to give monomethylated iodide **9** as a white residue.

Crude **9** was dissolved in dry THF (12 mL) and the solution was added dropwise to a dark blue mixture of dry NH_3 (30 mL) and lithium metal at –78 °C. More lithium was

added immediately after the solution became lighter blue so that an excess of solvated electrons was always present. After the addition was complete, the mixture was stirred at reflux (–33 °C) for 1 h. NH_4Cl (3 g) was added and the NH_3 was evaporated. The residue was dissolved in water (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with 1 mol/L NaOH solution (100 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure to give 283 mg (97%) of >95% pure **10** as a red liquid. IR (neat): 3349. ^{1}H NMR: 3.83 (br s, 1, NH), 2.83 (br dd, 1, J = 11.0, 11.0), 2.49 (br dd, 1, J = 10.4, 10.4), 2.37 (s, 3), 2.12–1.93 (m, 4), 1.76–1.64 (m, 4), 1.44–1.18 (m, 5), 1.17 (s, 3), 1.12–1.01 (m, 1), 1.04 (s, 3), 1.00–0.78 (m, 2), 0.96 (s, 3), 0.95 (s, 3), 0.934 (d, 3, J = 6.7), 0.927 (d, 3, J = 6.1). ^{13}C NMR: 68.7, 60.1, 59.8, 56.4, 50.8, 49.0, 43.6, 38.5, 37.0, 36.0, 35.8, 34.6, 34.1, 31.3, 30.6, 29.7, 28.6, 25.4, 23.8, 22.6, 21.9.

(3*R*,4a*R*,6a*R*,9*R*,10a*R*,12a*R*)-Hexadecahydro-3,5,6,6,9,11,12,12-octamethyldibenzo[*b*,*f*][1,5]diazocine (11)

Formic acid (0.17 mL, 4.42 mmol) and 37% formaldehyde in water (0.17 mL, 2.30 mmol) were added in succession to **10** (283 mg, 0.883 mmol) at 0 °C. The resulting solution was heated at reflux for 19 h. The solution was cooled and 2 mol/L HCl (3 mL) was added. The aqueous solution was extracted with Et_2O (2 × 5 mL) to remove less polar impurities and made basic with 2 mol/L NaOH solution. The aqueous solution was saturated with NaCl and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give 205 mg (69%) of **11** as a white wax. IR (CH_2Cl_2): 2956, 2921, 2772. ^{1}H NMR: 2.38–2.27 (m, 2), 2.32 (s, 6), 2.18–1.98 (m, 4), 1.81–1.73 (m, 2), 1.72–1.62 (m, 2), 1.35–1.15 (m, 4), 1.12–0.82 (m, 4), 0.97 (s, 6), 0.92 (d, 6, J = 6.7), 0.89 (s, 6). ^{1}H NMR (CD_3CN): 2.40–2.29 (m, 2), 2.37 (s, 6), 2.25–2.10 (m, 2), 2.09–2.00 (m, 2), 1.82–1.72 (m, 2), 1.71–1.62 (m, 2), 1.38–1.24 (m, 2), 1.22–1.12 (m, 2), 1.11–0.92 (m, 4) 1.00 (s, 6), 0.94 (s, 6), 0.92 (d, 6, J = 6.7). ^{1}H NMR (CD_3OD): 3.07 (ddd, 2, J = 11.6, 11.3, 2.4), 2.67 (s, 6), 2.44 (ddd, 2, J = 11.3, 11.0, 3.1), 2.18 (br dd, 2, J = 11.6, 2.4), 1.90 (br ddd, 2, J = 12.2, 6.7, 3.0), 1.77 (br d, 2, J = 12.2), 1.54–1.40 (m, 2), 1.41 (ddd, 2, J = 11.6, 11.6, 11.6), 1.27 (s, 6), 1.26 (s, 6), 1.31–1.08 (m, 4), 1.03 (d, 6, J = 6.1). ^{13}C NMR: 67.0 (2C), 58.5 (2C), 49.9 (2C), 38.4 (2C), 36.8 (2C), 36.5 (2C), 34.3 (2C), 30.1 (2C), 22.6 (2C), 22.4 (2C), 22.3 (2C). HRMS (EI) calcd. for $C_{22}H_{42}N_2$: 334.3348 (M^+); found: 334.3356.

TFA (120 µL, 10^{-1} mol/L in $CDCl_3$, 12 µmol, 1 equiv.) was added to a solution of 4 mg (12 µmol) **11** in $CDCl_3$ to give **11**·TFA. ^{1}H NMR: 3.00 (br dd, 2, J = 11.9, 11.5), 2.71 (s, 6), 2.27 (ddd, 2, J = 11.5, 10.4, 2.4), 2.16 (br d, 2, J = 11.0), 1.89–1.79 (m, 4), 1.56–1.42 (m, 2), 1.28 (s, 6), 1.23 (s, 6), 1.23 (br ddd, 2, J = 11.9, 10.4, 9.8), 1.16 (br ddd, 2, J = 14.0, 14.0, 11.9), 1.08–0.94 (m, 2), 1.01 (d, 6, J = 6.7). The NMR spectrum did not change on addition of an additional 120 µL of TFA solution.

TFA (2 drops, excess) was added to a solution of **11** in CD_3CN to give **11**·TFA. ^{1}H NMR (CD_3CN): 2.97 (ddd, 2, J = 11.6, 11.3, 2.4), 2.57 (d, 6, J = 3.1), 2.36 (ddd, 2, J = 11.3, 10.6, 3.1), 2.10 (ddd, 2, J = 10.6, 1.8, 1.8), 1.85–1.74 (m, 2), 1.71 (br d, 2, J = 9.2), 1.49–1.30 (m, 4), 1.28–1.02 (m, 2), 1.18 (s, 12), 1.01–0.88 (m, 2), 0.97 (d, 6, J = 6.1).

Determination of the pK_a of 11 in CH_3CN

TFA (3.5 µmol, 0.4 equiv., 2.7 µL of a 1.3 mol/L solution in CD_3CN prepared by diluting TFA (100 µL, 148 mg, 1.3 mmol) to a final volume of 1 mL) was added to a solution of DBU (8.7 µmol, 13 µL of a 6.7×10^{-1} mol/L solution in CD_3CN prepared by diluting DBU (100 µL, 102 mg, 0.67 mmol) to a final volume of 1 mL) and **11** (2.9 mg, 8.7 µmol) in CD_3CN (1.0 mL). The resulting solution was monitored for 4 days at 25 °C by ^{1}H NMR. DBU was calculated to be 14% protonated from the ^{1}H NMR shift (δ 3.155, t, J = 5.5) relative to $DBUH^+$ (δ 3.279, br s) and to the DBU/**5** solution (δ 3.135, t, J = 5.5) prior to adding TFA. Diamine **11** was calculated to be 28% protonated from an integration of **11** at δ 2.09–1.72 (m, 4) and **11**-H^+ at δ 2.97 (ddd, 2, J = 11.6, 11.3, 2.4). Based on the pK_a of DBU (24.34 (17*a*)), the p*K*a of **11** was calculated to be 24.7. An identical mixture was obtained adding DBU to a solution of TFA and diamine **11** in CD_3CN.

Determination of the pK_a of 11 in DMSO

TFA (3.5 µmol, 0.40 equiv., 2.7 µL of a 1.3 mol/L solution in DMSO-d_6, prepared by diluting TFA (100 µL, 148 mg, 1.3 mmol) to a final volume of 1 mL) was added to a solution of DBU (8.7 µmol, 13 µL of a 6.7×10^{-1} mol/L solution in DMSO-d_6, prepared by diluting DBU (100 µL, 102 mg, 0.67 mmol) to a final volume of 1 mL) and **11** (2.9 mg, 8.7 µmol) in DMSO-d_6 (1.0 mL) and the resulting solution was monitored for 3 h at 25 °C by ^{1}H NMR. DBU was calculated to be 37% protonated from the ^{1}H NMR shift (δ 3.150, br s) relative to $DBUH^+$ (δ 3.248, br s) and to the DBU/**11** solution (δ 3.093, t, J = 5.2) prior to adding TFA. Diamine **5** was calculated to be completely unprotonated. The peaks for **11** at δ 2.12–1.93 (m, 4) were present and those for **11**-H^+ at δ 2.99 (br dd, 2, J = 10.4, 10.4) were absent.

A solution of TFA (3.5 µmol, 2.7 µL of a 1.3 mol/L stock solution in DMSO-d_6) and **11** (2.9 mg, 8.7 µmol) in DMSO-d_6 (1.0 mL) showed the presence of a mixture of **11** and **11**-H^+ (48:52) based on integration of the peaks for **11** at δ 2.12–1.93 (m, 4) and for **11**-H^+ at δ 2.99 (br dd, 2, J = 10.4, 10.4). Addition of DBU (8.7 µmol, 13 µL of a 6.7×10^{-1} mol/L solution in DMSO-d_6) gave a spectrum identical to that described above with DBU absorbing at δ 3.151 and only unprotonated **11**.

Acknowledgements

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Bis(ether) derivatives of tetrakis(2-hydroxyphenyl)ethene — Direct synthesis of (*E*)- and (*Z*)-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene via the McMurry olefination reaction[1]

Mee-Kyung Chung, Paul Fancy, and Jeffrey M. Stryker

Abstract: The direct synthesis of sterically hindered, partially etherified derivatives of tetrakis(2-hydroxyphenyl)ethene is reported by using the McMurry reductive olefination reaction on a range of differentially substituted 2,2′-dialkoxybenzophenone substrates. Three orthogonal protection strategies are demonstrated, incorporating β-silylethyl, 3-butenyl, and *tert*-butyl protecting groups, respectively, into the starting benzophenones. The latter proved most efficient, with both the McMurry coupling and deprotection steps occurring concomitantly under the McMurry conditions to directly yield the desired bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene as a 1:1 mixture of *E*- and *Z*-diastereoisomers.

Key words: preorganized polyaryloxide ligands, McMurry olefination, titanium trichloride, supramolecular chemistry, tetrakis(2-hydroxyphenyl)ethene, 2,2′-disubstituted benzophenone.

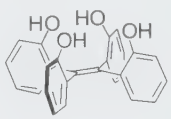
Résumé : On a réalisé la synthèse directe de dérivés stériquement encombrées et partiellement éthérifiés du tétrakis(2-hydroxyphényl)éthène en appliquant la réaction d'oléfination réductrice de McMurry à une large série de 2,2′-alkoxybenzophénones substituées. On a démontré les stratégies de protection orthogonale en incorporant respectivement des groupes protecteurs β-silyléthyle, butén-3-yle et *tert*-butyle dans les benzophénones de départ. Le dernier s'avère le plus efficace alors que les étapes de couplage de McMurry et de déprotection se produisent d'une façon concomitante dans les conditions de McMurry pour conduire directement au bis(2-hydroxyphényl)éthène-bis(2-methoxyphényl)éthène recherché sous la forme de mélange 1 : 1 des diastéréoisomères *E*- et *Z*-.

Mots clés : ligands polyaryloxydes préorganisés, oléfination de McMurry, trichlorure de titane, chimie supramoléculaire, tétrakis(2-hydroxyphényl)éthène, benzophénone 2,2′-disubstituée.

[Traduit par la Rédaction]

Introduction

Structurally preorganized polydentate ligands based on tetrakis(2-hydroxyphenyl)ethene (**I**) constitute a topologically distinct alternative to the ubiquitous calix[4]arene class (1, 2). The roughly square binding array and conformational rigidity imposed by the planarity of the ethylene core allows the construction of highly bridged polymetallic coordination complexes of unusual robustness, providing unique structural and functional models for oxo-surface coordination (1*a*, 3). To expand the potential of this system for applications to coordination chemistry, the preparation of partially etherified tetrakis(2-hydroxyphenyl)ethene ligands (e.g., **II**) has also been reported, both by direct synthesis and by selective dealkylation reactions starting with tetrakis(2-methoxyphenyl)ethene (4).



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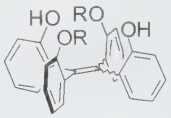

II

The original synthesis of tetrakis(2-hydroxyphenyl)ethene derivatives required a two-step conversion of a 2,2′-dialkoxybenzophenone to the corresponding diaryldiazomethane, followed by acid-catalyzed generation of the tetrakis(2-alkoxyphenyl)ethene. We recently introduced (5) an improved synthesis of tetrakis(2-substituted) tetraphenylethenes by direct conversion of the 2,2′-dialkoxybenzophenone into the corresponding tetraphenylethene using the McMurry reductive olefination reaction (6). Historically, bis(ortho-substituted) benzophenones have been identified as unsuitable for the McMurry reaction, leading instead to competitive reduction of the diarylketone and (or) formation of the

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Dedicated to Dr. Alfred Bader, who did well, certainly, and then did good; with deepest admiration and respect. Eppes fun gornisht — "From nothing, something".

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coupled but over-reduced tetrasubstituted ethane (7). 2,2′-Dimethoxybenzophenone itself is reported to produce tetrakis(2-methoxyphenyl)*ethane* nearly exclusively (7*a*), presumably a consequence of the high degree of steric congestion in the vicinity of the carbonyl functionality. Despite this negative precedent, however, meticulous optimization of McMurry reaction conditions has led to a remarkably general McMurry procedure for the preparation of sterically hindered tetrakis(2-substituted) tetraphenylethenes in moderate to excellent yields, a significant expansion in the scope of this important olefination reaction (5). To explain this success, the intervention of a previously unrecognized *substrate-based electronic effect* was postulated, contravening the steric limitations inherent to this substrate class.

To improve upon our syntheses of bis(ether) derivatives of tetrakis(2-hydroxyphenyl)ethene, our McMurry protocol has been challenged by a series of orthogonally protected 2,2′-dialkoxybenzophenones, some of considerable steric encumbrance. In this communication, we report the successful extension of the McMurry olefination protocol to this expanded range of unsymmetrically disubstituted substrates, culminating in a single-step olefination–deprotection procedure for the synthesis of (*E*)- and (*Z*)-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene.

Results and discussion

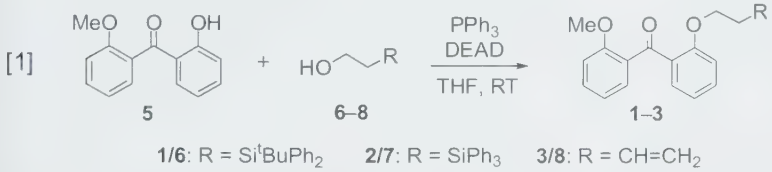
Thus, four unsymmetrically functionalized 2,2′-dialkoxybenzophenones (**1**–**4**) were selected for investigation, each designed to produce a tetrakis(2-alkoxyphenyl)ethene derivative capable of undergoing selective deprotection to give the targeted bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene. Benzophenones **1**–**3** were directly prepared by the dehydrative etherification of 2-hydroxy-2′-methoxybenzophenone [(2-hydroxyphenyl)(2-methoxyphenyl)methanone] (**5**) (4) and the corresponding functionalized alcohols **6**–**8** (8) under Mitsunobu-type conditions (eq. [1]) (9).[3] The final substrate, 2-*tert*-butoxy-2′-methoxybenzophenone (**4**), was prepared in good yield by the directed ortho-lithiation of *tert*-butoxybenzene (**9**) (*n*-BuLi, TMEDA) (10) followed by condensation with the known Weinreb amide, 2-methoxy-*N*-methoxy-*N*-methyl benzamide (**10**) (eq. [2]) (11, 12).

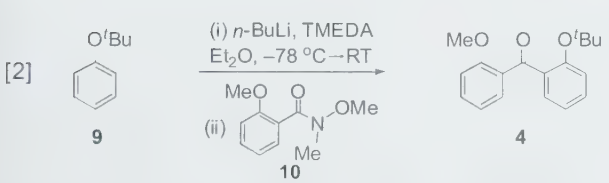
For each substrate, treatment under the previously optimized McMurry reaction conditions ($TiCl_3$ or $TiCl_3$·1.5DME, Zn(Cu), DME, RT)[3] proceeded in moderate to good yields to give the desired olefination product, albeit as an approximately 1:1 mixture of (*E*)- and (*Z*)-isomers (Table 1). The β-silylethyl and butenyl ethers **1**–**3** were converted to the expected bis(2-methoxyphenyl)-bis(2-alkoxyphenyl)ethene derivatives **11**–**13**, respectively (Table 1, entries 2–4). For comparison, the results obtained from McMurry coupling of the symmetrical 2,2′-dimethoxybenzophenone under the same conditions are also provided in Table 1 (entry 1) (5). Although it was anticipated that the steric bulk of the β-silylethyl protecting groups might produce a diastereoselective McMurry reaction, the reactions were entirely nonselective, suggesting that the silyl substituents are too remote from the reactive carbonyl functionality to influence the stereochemistry of the reaction.

For bis[2-(3-butenyloxyphenyl]-bis(2-methoxyphenyl)ethene (**13**), selective deprotection of the butenyloxy moiety was accomplished using catalytic $RhCl_3$·$3H_2O$ (13) in ethanol (reflux, 24 h).[3] In this way, the readily separable mixture of (*E*)- and (*Z*)-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene (**14**) (ca. 1:1) was obtained, spectroscopically identical with authentic material (4). With due consideration of the attractive results obtained from the reactions of **4** (vide infra), the deprotection of the β-silylethyl ether derivatives **11** and **12** was not pursued in this investigation.

Among the four substrates, the *tert*-butyl ether derivative **4** provided the most compelling and, not coincidentally, the most synthetically valuable result. Despite our original expectation that the steric bulk of the *tert*-butyl substituent might completely inhibit the McMurry reaction, the desired olefination reaction nonetheless proceeds in good yield, *accompanied by the serendipitous in situ deprotection of the* tert-*butyl ether groups*. Thus, a mixture of (*E*)- and (*Z*)-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethenes (**14**) (ca. 1:1) was obtained *directly* from the McMurry reaction (Table 1, entry 5).[3]

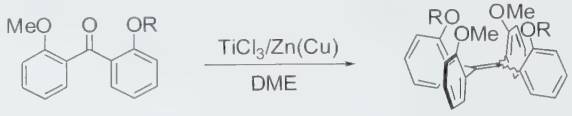
A series of control experiments provides some insight into this unexpected transformation. Although the preparation of the low-valent titanium reagent by reduction of $TiCl_3$ with Zn(Cu) also produces $ZnCl_2$ as a by-product, the Lewis acid-

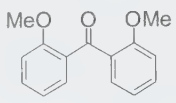
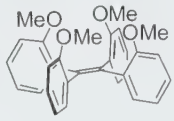
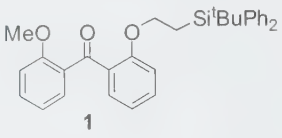
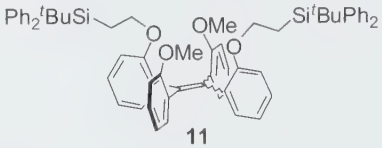
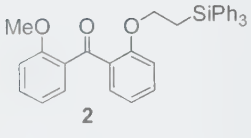
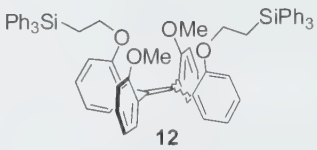
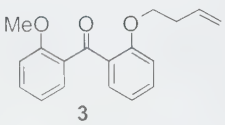
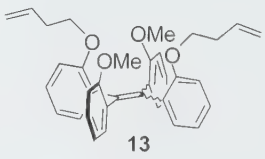
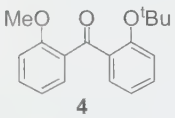
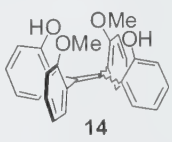




[3] Supplementary data (experimental procedures for the preparation of unsymmetrical ketones (**1**-**4**) and McMurry reactions (**11**–**14**) and the deprotection of **13**; spectroscopic and analytical data) for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5056. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Table 1. McMurry olefination reactions of 2,2′-bis(*ortho*-alkoxy)benzophenones **1–4**.



Entry	Ketone	Olefin derivatives[a]	Isolated yield (%)
1[b]			76[c], 73[d]
2	 1	 11	69[e] (*E*/*Z* = 1)
3	 2	 12	57[e] (*E*/*Z* = 1)
4	 3	 13	48[e] (*E*/*Z* = 1)
5	 4	 14	45[f,g] (*E*/*Z* = 1), 64[h] (*E*/*Z* = 1)

Note: Reagents and conditions: (*i*) $TiCl_3$ (6 equiv.), Zn(Cu) (3 equiv.), DME, 80 °C, 14 h; (*ii*) RT, substrate. Details provided as Supplementary information (see footnote 3).

[a] Product(s) and *E*/*Z* ratio by spectroscopic analysis. Complete characterization data are provided as Supplementary information (see footnote 3).

[b] See ref. 5.

[c] 1,1,2,2-(2′-Methoxyphenyl)ethane was also isolated in 15% yield.

[d] Large-scale experiment (4.12 g, 17.0 mmol of ketone).

[e] The corresponding tetraarylethane was isolated in ~5% yield.

[f] 1,2-Bis(2′-hydroxyphenyl)-bis(2′-methoxyphenyl)ethane was isolated in 17% yield.

[g] Product identification by comparison to literature data (see ref. 4).

[h] $TiCl_3$·1.5DME was used as the titanium source and the McMurry reagent preparation step was omitted in this procedure.

ity of this compound is significantly moderated by coordination to DME. In independent trials, anhydr. $ZnCl_2$ in DME only slowly mediates cleavage of the *tert*-butyl ether in **4**.[4] Moreover, the reaction of 2-hydroxy-2′-methoxybenzophenone (**5**) with $TiCl_3$–Zn(Cu) under otherwise identical reaction conditions produces no detectable olefination product; the McMurry reaction of **4** clearly involves the reductive coupling of the intact substrate.[5] Steric effects, evidently, do

[4] The conversion of **4** to **5** using equimolar anhydr. $ZnCl_2$ in DME proceeds 12% to completion after being left overnight at ambient temperature.

[5] After standard aqueous work up, **5** was recovered in 87% yield.

not significantly limit the scope of the McMurry reaction for the production of hindered tetraphenylethenes (5). Whether the in situ deprotection of the *tert*-butyl ether occurs on the surface of the low-valent titanium or by subsequent reaction with DME-solvated $ZnCl_2$ remains undetermined. The replacement of unsolvated $TiCl_3$ powder with the $TiCl_3$·1.5 DME complex and elimination of the reagent preparation period (14) provides significantly higher yields of bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene (**14**) (Table 1, entry 5), although the origin of this improvement is not obvious.[6] Finally, despite the close proximity of the sterically bulky *tert*-butyl substituents to the reactive carbonyl functionality, the McMurry olefination of **4** remains inexplicably stereorandom, consistently returning a 1:1 mixture of (*E*)- and (*Z*)-isomers.

Despite this lack of diastereoselectivity, the steric tolerance of this McMurry olefination protocol is quite remarkable, providing unexpectedly general access to sterically encumbered ortho-substituted tetraphenylethenes. Further extension in the scope of this reaction remains under investigation.

Optimized experimental procedure

McMurry reaction of 4 using $TiCl_3$·1.5 DME[3]

All operations were performed under an atmosphere of argon. In a glovebox, an oven-dried, 50 mL Schlenk flask was charged with $TiCl_3$·1.5 DME (0.62 g, 4.0 mmol) and Zn(Cu) (0.13 g, 2.0 mmol). After removal from the glovebox, anhydr. DME (12.0 mL) was added at ambient temperature under an argon flow. An oven-dried 25 mL Schlenk flask was charged with **4** (0.20 g, 0.69 mmol) and anhydr. DME (6.0 mL) under an atmosphere of argon. The resulting solution was transferred to the slurry of low-valent titanium by cannula under a flow of argon and the reaction mixture stirred at ambient temperature for 18 h, with the progress of the reaction monitored by analytical TLC. After completion of the reaction, the reaction mixture was quenched cautiously with 5 mL of water. The resulting suspension was extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles removed on the rotary evaporator. Flash chromatography of the crude product on silica gel using a gradient solvent system of CH_2Cl_2–hexanes provided 0.220 g of 1,2-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene (**14**) as a 1:1 mixture of (*E*)- and (*Z*)-isomers (64% yield). Stereochemical assignments and separation of the isomers by selective crystallization or column chromatography has been previously reported (4).

Acknowledgements

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[6] The use of unsolvated $TiCl_3$ (rather than the $TiCl_3$·1.5 DME complex) in this so-called instant method leads to low yields of the desired product and the formation of unidentified, inseparable by-products.

Fabrication of patterned organic thin film by low-energy electron beam lithography and surface-initiated ring-opening metathesis polymerization[1]

Zhebo Ding and Bruce Ganem

Abstract: High densities of immobilized polymer brushes have been created on solid supports in a spatially addressable fashion. Octadecyltrichlorosilane was self-assembled on a silicon substrate to form an inert monolayer. The substrate was then patterned by low-energy electron beam lithography. Finally, the exposed region was back-filled with a second functionalized silane and the pattern was further amplified by surface-initiated ring-opening metathesis polymerization. The patterned substrate was imaged by scanning electron microscopy and atomic force microscopy.

Key words: patterned thin film, e-beam lithography, ring-opening metathesis polymerization, polymer brushes.

Résumé : On a préparé des brosses de polymères de hautes densités immobilisés sur des supports solides dans des arrangements qui peuvent être adressés d'une façon spatiale. On a réalisé un autoassemblage de l'octadécyltrichlorosilane sur un substrat de silicium qui à conduit à la formation d'une monocouche inerte. On a ensuite lithographié le substrat à l'aide de la méthode par faisceau d'électrons de basse énergie. Enfin, on a rempli la région exposée avec un deuxième silane fonctionnalisé et on a amplifié le patron par une polymérisation de métathèse avec ouverture de cycle initiée par la surface. On a obtenu une image du patron du substrat à l'aide de microscopie électronique à balayage et par microscopie des forces atomiques.

Mots clés : film mince avec un patron, lithographie à l'aide d'un faisceau électronique, polymérisation de métathèse avec ouverture de cycle, brosses de polymère.

[Traduit par la Rédaction]

Introduction

The ability to immobilize organic compounds on solid supports in a spatially addressable fashion is of interest in combinatorial chemistry, high-throughput screening, genetic analysis, controlled drug delivery, and trace analyte detection (1). High densities of surface-bound organic substances may be achieved using polymer brushes, which are long polymer chains anchored to the surface that extend away from the attachment sites. Such systems may be assembled either by grafting functionalized polymers onto the surface (2) or by inducing radical (3), cationic (4), or anionic (5) polymerization reactions at surface-bound initiators.

The use of ring-opening metathesis polymerization (ROMP) reactions catalyzed by well-defined and highly active metal alkylidenes (6) represents an attractive alternative approach. The living nature of ROMP reactions provides control of organic thin film thickness and chemical composition. Recently, Weck et al. (7*a*) and Kim et al. (8) reported successful surface-initiated ROMP reactions using an initiator anchored on gold and Si–SiO_2 surfaces, respectively. Pattern generation in polymeric films was achieved by combining microcontact printing (μ-CP) and surface-initiated polymerization (9). Recently, imprint lithography has been demonstrated to fabricate sub-100 nm features (10) for biotechnological applications such as antibody or cell–cell interaction assays (11). Here, we report a simple method for creating high densities of immobilized polymer brushes on solid supports in a spatially addressable fashion as an alternative to imprint lithographic technique.

Electron beam lithography is commonly used in semiconductor manufacturing and can produce precisely aligned, high-resolution patterns. Because direct substrate contact is not required, the method offers advantages over μ-CP or scanned probe lithography (SPL) for patterning surfaces that display complex features (12). Moreover, no mask is needed for electron beam lithography. The creation of features as small as 6 nm in width has been achieved by electron beam

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This paper is dedicated to Dr. Alfred Bader on the occasion of his 80th birthday.

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[1]This article is part of a Special Issue dedicated to Dr. Alfred Bader.
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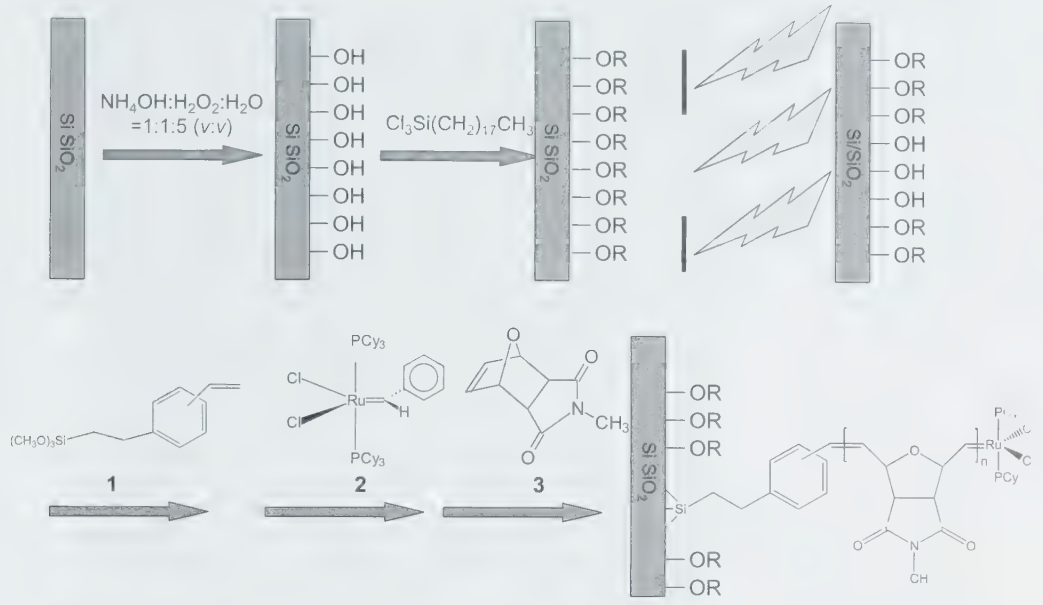
Fig. 1. Formation of patterned organic thin films by low-energy electron beam lithography and surface-initiated ring-opening metathesis polymerization.



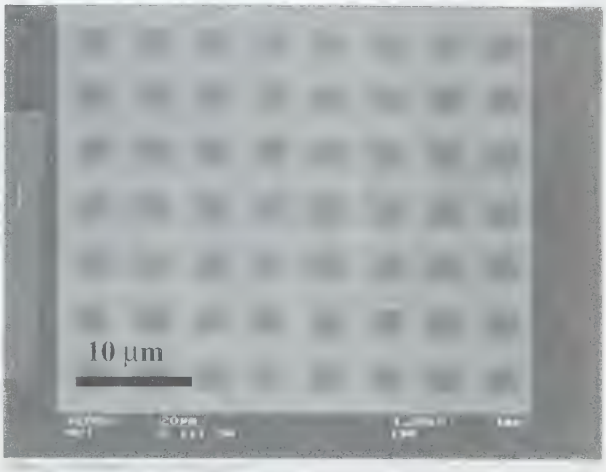
lithography on self-assembled monolayers (SAMs) (13). Low-energy electron beam lithography has recently attracted attention because of its easy operation, low cost, and biological compatibility. Here, we describe a simple and convenient method for fabricating patterned organic thin films using a combination of low-energy electron beam lithography and surface-initiated ROMP.

Methods

A monolayer of octadecyltrichlorosilane (OTS) was self-assembled on a Si–SiO_2 substrate (Fig. 1), then patterned sacrificially by low-energy electron beam lithography. Next, the exposed region was back-filled with a second functionalized silane and the pattern was further amplified by surface-initiated ROMP. Overall, the process is simple and compatible with simple dip and rinse laboratory protocols.

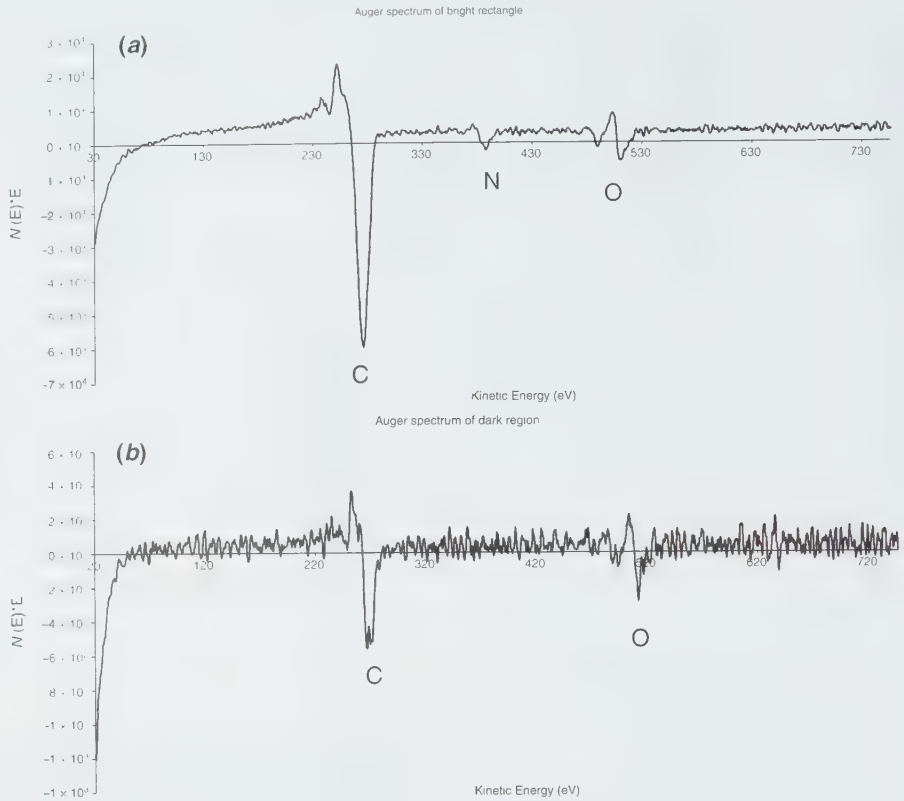
To prepare a hydroxyl group terminated Si–SiO_2 substrate for monolayer deposition, a silicon wafer was first rinsed several times with acetone and 2-propanol. The wafer was then immersed in a boiling solution containing 1:1:5 (by volume) of 30% aqueous hydrogen peroxide, 28%–30% ammonium hydroxide, and deionized water for 10 min, then rinsed with deionized water and dried with flowing argon gas. Self-assembled monolayers of OTS (Sigma-Aldrich) were formed on the clean silicon surface by immersing the cleaned substrate in a 2 mmol/L OTS solution in toluene overnight under argon. The sample was then sonicated in toluene for 5 min, rinsed with toluene, dried with argon, and annealed at 130 °C for 20 min. The contact angle of prepared OTS-modified silicon surfaces was measured to be 113 ± 3°, indicating the complete coverage of the self-assembled monolayers (14). Monolayers were judged to be stable for at least two months when stored in a desiccator at room temperature, since no significant decrease in contact angle was observed.

Fig. 2. SEM image of patterned polymer film of **3** on a Si–SiO_2 substrate.



A scanning electron microscope (LEO Electron Microscopy, Inc.Nano Technology Systems Division, Carl Zeiss SMT), equipped with a pattern generator and alignment system (JC Nabity Lithography Systems, Bozeman, Montana), was used for electron beam lithography. Typical electron beam exposures were conducted at an accelerating voltage of 2 kV and doses of 500 μC/cm^2. After electron beam exposure, the sample was further developed in the UV–ozone

Fig. 3. Auger electron spectra of (*a*) the region modified by polymer film of **3** and (*b*) the OTS-modified region. Spectra were taken at an extraction voltage of 3 kV and an electron current of 20 nA. Samples were tilted at a 60° angle.



cleaner (UVOCS Inc., Montgomeryville, Pennsylvania) for 45 s to remove the decomposed monolayer and to regenerate the chemically active hydroxyl groups. It has been shown (15) that UV–ozone exposure is sufficient to remove damaged monolayers without significantly reducing the hydrophobicity of unexposed areas. After surface cleaning, the substrate was immediately immersed in a toluene solution containing 4% (by volume) styrylethyltrimethoxysilane (**1**, SETS, Gelest Inc., Morrisville, Pennsylvania) and 2% (by volume) triethylamine (Fluka) overnight to back-fill the exposed area. The substrate was then sonicated in toluene for 5 min, rinsed with toluene, and dried with argon. Grubbs catalyst $[(Cy_3P)_2Cl_2Ru{=}CHPh]$ (16) (**2**) was then immobilized at the styryl-terminated regions by dipping the patterned substrate into a 33 mmol/L CH_2Cl_2 solution of **2** for 3 h. After extensive rinsing with distilled CH_2Cl_2, the sample was subsequently exposed to a 0.4 mol/L CH_2Cl_2 solution of *exo-N*-methyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (**3**) for 16 h to allow the growth of polymer brushes on the surface.

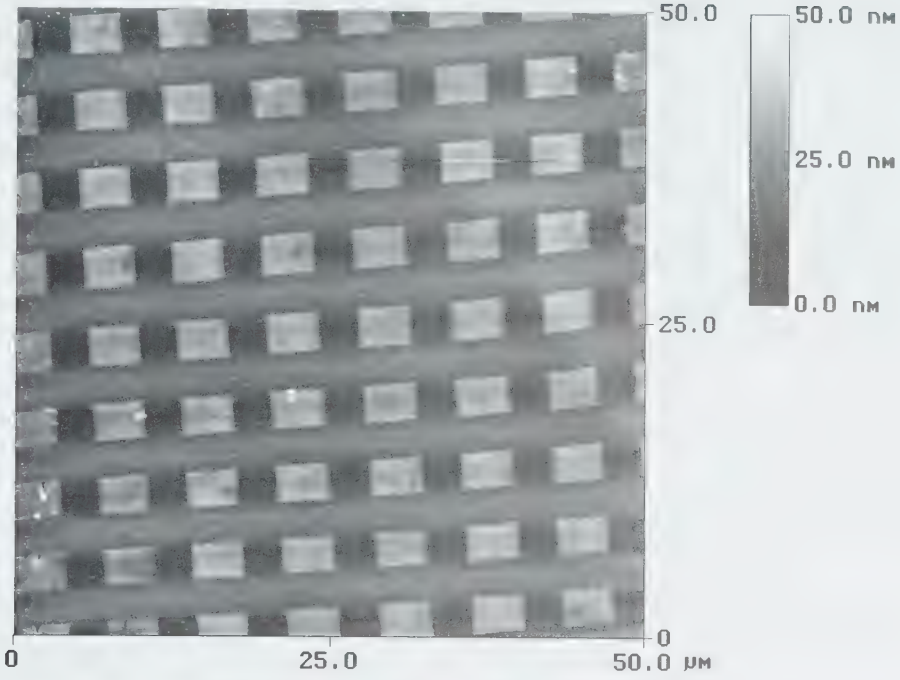
Spatially localized polymer brushes synthesized by surface-initiated ROMP on the patterned functionalized surfaces were imaged by scanning electron microscopy (SEM) and atomic force microscopy (AFM). Figure 2 shows a low-resolution SEM image of the patterned polymer film. The dark rectangles in the image (3 μm × 2 μm) represent regions where polymer brushes were formed, while light regions represent unaffected areas of OTS monolayers.

Insights into the chemical composition of the dark and light regions in Fig. 2 came from Auger electron spectroscopy. A scanning Auger microprobe (SAM) was used to establish unique elemental signatures in each region (Fig. 3). Using this technique, dark regions in the SEM image corresponded to polymer brushes, as confirmed by the carbon, nitrogen, and oxygen elemental signatures in the Auger spectrum (Fig. 3*a*). The Auger spectrum of light regions (Fig. 3*b*) matched spectra of authentic samples of uniform OTS monolayers.

Further analysis of the polymer brushes was carried out using AFM. A 50 μm × 50 μm tapping mode AFM scan of the patterned polymer film (Fig. 4) showed very well-defined boundaries between regions where polymer brushes were formed (bright rectangles) and regions covered with OTS (dark areas). The regions of the surface exposed to the electron beam were covered by uniform polymer films. Estimates from the AFM image indicated that the polymer brush thickness was ~30 nm, which is in good agreement with ellipsometry data.[3]

[3] Ellipsometry results were obtained using uniform polymer films produced under identical experimental conditions.

Fig. 4. Tapping mode AFM image of patterned polymer film of **3** on Si–SiO_2 substrate.



Conclusion

In conclusion, a simple surface chemical process has been developed for fabricating patterned organic thin films using low-energy electron beam lithography and surface-initiated ROMP. All processes were conducted in solution at ambient temperature by simple dip and rinse procedures. The use of low-energy electron beam lithography makes it possible to generate higher resolution patterns on surfaces, while locally varying the density of attached materials. The use of this technique for the site-specific anchoring of concentrated quantities of small-molecule drugs, peptides, or diagnostic proteins as polymer brush deposits on surfaces is currently being explored.

Acknowledgments

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A silyl-mediated [3+2] photochemical cycloaddition[1]

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Abstract: The generation of larger rings from intermediate cyclobutanes via a two-step [2+2] photocycloaddition – ring expansion, known as the de Mayo reaction, has been widely applied in synthesis. Herein a one-step synthesis of cyclopentanoids has been developed based on the photochemical irradiation of an enone in the presence of an allylsilane. The ability of the silyl moiety to stabilize the intermediate biradical is believed to be responsible for this unique transformation where one normally expects to see the [2+2] cyclobutane adduct.

Key words: [2+2] photocycloaddition – ring expansion, allylsilanes, cyclopentanoids, photochemical.

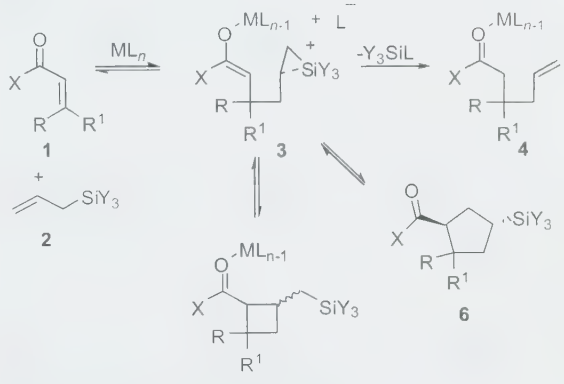
Résumé : La génération de cycles plus grands à partir d'intermédiaires cyclobutanes, par le biais d'une séquence en deux étapes comportant une photocycloaddition [2+2] suivie expansion de cycle, connue sous le nom de réaction de de Mayo, est très souvent utilisée en synthèse. Dans ce travail, on décrit une synthèse en une étape de cyclopentanoïdes qui repose sur l'irradiation photochimique d'une énone en présence d'un allylsilane. On croit que la possibilité pour la portion silane de stabiliser l'intermédiaire biradicalaire est responsable de cette transformation unique au cours de laquelle on s'attend normalement à obtenir une addition cyclobutane [2+2].

Mots clés : photocycloaddition [2+2] – expansion de cycle, allylsilanes, cyclopentanoïdes, photochimie.

[Traduit par la Rédaction]

Since the seminal work on the allylation reaction between allyltrimethylsilane and α,β-unsaturated ketones was disclosed by Hosomi and Sakurai (1), there has been a great deal published regarding the expansion of the scope and utility of allylsilanes in such reactions (2). This methodology has been expanded to include ring formation when the allylsilanes involved possess "bulky groups" on silicon to provide cyclobutane and cyclopentane products via Lewis acid catalyzed [2+2] and [3+2] annulation, respectively (3–5). The general addition process for allylsilanes onto unsaturated substrates is illustrated in Scheme 1. Siliranium ion intermediate **3** is central to all possible products of initial conjugate addition. In the case of enone substrates (X = alkyl), if Y is large (e.g., isopropyl) the principal product isolated is the five-membered ring adduct **6**, which appears to be both the thermodynamic and kinetic product (6, 7). When Y is methyl, the allylation product **4**, i.e., the Sakurai product, is the major adduct isolated. In the case of unsaturated ester substrates (e.g., X = OR), the formation of both four- and five-membered rings is also with precedent (8, 9). In these situations, the cyclobutane is typically the kinetic product and the cyclopentane **6** forms from **5** over time in the presence of the Lewis acid, presumably via intermediate **3**.

Scheme 1.



The primary driving force behind nucleophilic reactions involving allylsilanes is the presence of the silicon moiety, which activates the olefin and stabilizes the intermediate carbocation that is generated β to itself during the addition process by strong hyperconjugative effects (see intermediate **3**) (10). Thus, the silyl group is electron-rich and strongly σ-donating. The larger and more electron-rich the ligands on silicon, the more nucleophilic, hence reactive, the allylsilane becomes (11). Further, the larger the ligands on silicon, the more the silyl moiety resists protodesilylation.

It is known that radicals show similar stabilization as do cations when positioned β to silicon, but little has been done with this synthetically. We were interested in trying to exploit this feature of silicon in the development of new cyclization reactions. The photochemical excitation of enones in

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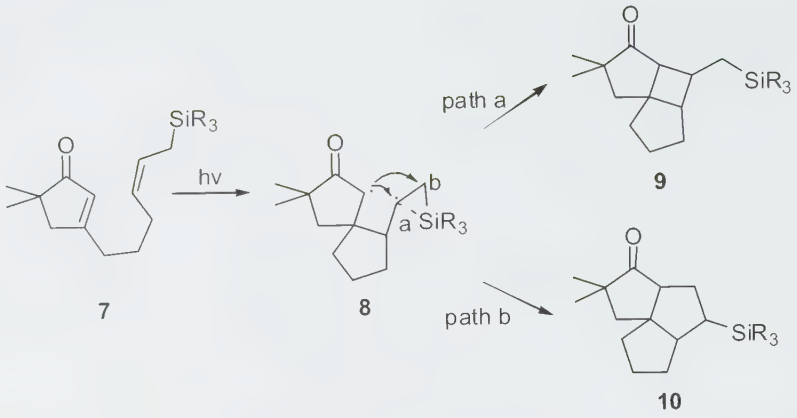
Scheme 2.

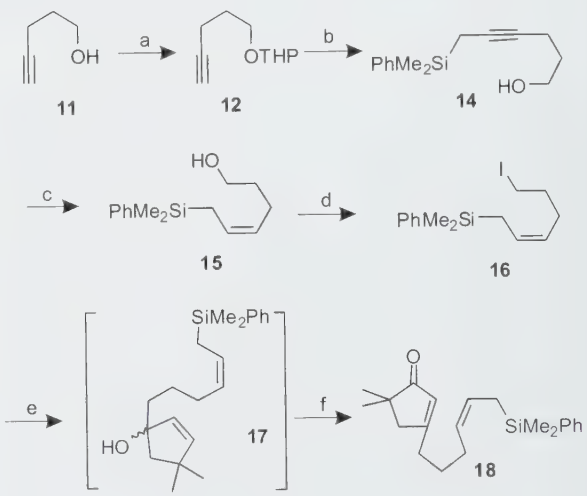


the presence of ground-state alkenes is a reliable and well-established method for the production of radicals. If the alkene was in fact an allylsilane, then the silyl component could become directly involved during the photoaddition itself, thus giving rise to new ringed structures directly upon irradiation. We envisioned that this methodology could be used for the production of five-membered rings and this is demonstrated in our approach to the angular triquinane framework shown in Scheme 2. In this case, it is an intramolecular photoaddition that would lead, presumably, to the intermediate biradical **8**, which would be stabilized by hyperconjugation. This would place radical character at both position *a* and *b*. Closure at *a* would lead to cyclobutane **9**, whereas *b* would provide cyclopentane **10**, which posseses the triquinane ring structure in one overall transformation from **7**.

Our synthetic approach to photoprecursor **18** began with 4-pentyn-1-ol (**11**, Scheme 3). Protection of the alcohol followed by alkyne deprotonation and electrophilic capture with dimethylphenylsilylmethyl iodide provided the corresponding allylsilane. Deprotection (**14**) and controlled hydrogenation with P2 catalyst provided the requisite *cis*-olefin geometry in **15**, which we determined was necessary to deliver the required stereochemistry in the triquinane structure through the ring-forming steps later on (see Scheme 4). Conversion of the alcohol to the corresponding iodide (**16**) provided the substrate for metal–halogen exchange and 1,2-addition to 4,4-dimethylcyclopent-2-en-1-one, yielding **17**. Finally, chromium-mediated [1,3] rearrangement and concomitant oxidation provided photoprecursor **18** cleanly and in good recovery.

The optimized photochemical step is outlined in Scheme 4. Initially, we attempted the reaction under a variety of conditions. In cyclohexane solvent, all other parameters being the same as those in Scheme 4, the Norrish type I cleavage product (i.e., the aldehyde) was the principal one isolated. All reactions attempted using a Hanovia 450 W Hg medium pressure lamp failed to provide any identifiable cycloadducts. However, we did observe isomerization of the allylsilane double bond geometry, which could happen by one of at least two possible mechanisms. The reaction could proceed to the biradical intermediate (**19**), but under these reaction conditions, reversion to starting material is faster than closure to product, thus scrambling olefin geometry.

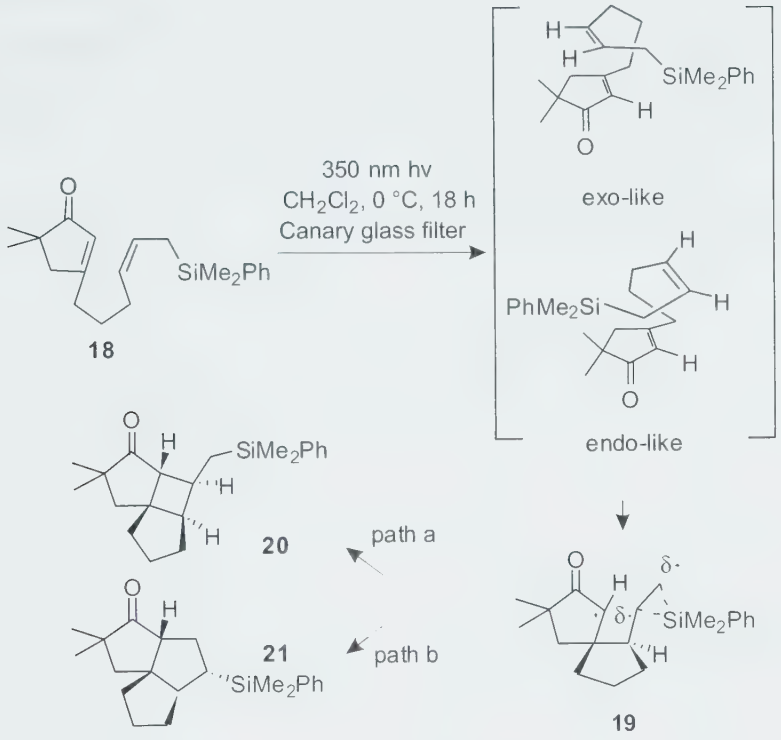
Scheme 3. Reagents and conditions: (*a*) DHP, PPTS (cat.), CH_2Cl_2, rt, 82%; (*b*) (1*i*) *n*-BuLi, THF, –78 °C, (1*ii*) $PhMe_2SiCH_2I$ (**13**), reflux; (2) H_2SO_4 (cat.), MeOH, rt, 99%; (*c*) H_2 (1 atm, 1 atm = 101.325 kPa), $Ni(AcAc)_2$, $4H_2O$ (cat.), $NaBH_4$ (cat.), Et_3N, EtOH, rt, 75%; (*d*) I_2, PPh_3, Et_3N, MeCN, rt, 76%; (*e*) (*i*) *t*-BuLi (2.2 equiv.), Et_2O, –78 °C, (*ii*) 4,4-dimethylcyclopent-2-en-1-one; (*f*) PDC, CH_2Cl_2, rt, 99%.



Conversely, and more likely, the double bond could be getting excited, either directly or by triplet transfer, and relaxation occurs with olefin scrambling. We reasoned that if we could eliminate light of wavelengths less than 300 nm, at least direct excitation of the allylsilane would be eliminated with certainty. This meant that Pyrex with a 280 nm cutoff was not a suitable filter, so we opted to use uranium (canary) glass that possesses a 314 nm cutoff (12). As mentioned, attempts with the Hg lamp failed, but prolonged irradiation with a low power Rayonet reactor equipped with 350 nm lamps led to two products (**20** and **21**) in equal amounts (yield = 60%) that were purified by preparative HPLC.

Assuming that the intramolecular addition followed the "rule of 5" (13), leading to the linearly fused and not crossfused photoadduct, the trajectory of the olefin to the enone could follow an "endo-like" or "exo-like" arrangement

Scheme 4.



(see Scheme 4). The endo approach would lead to a highly congested transition state, which is exacerbated by the presence of the *gem*-dimethyl moiety that we installed in the photoprecursor, which is present in the general structure of all angular triquinanes and is therefore necessary. Further to this mechanistic assessment, the structures of **20** and **21** were assigned on the basis of 1D and 2D proton NMR spectra, including COSY and nOe that are in the Supporting information.[3]

There are a few examples in the literature pertaining to the use of olefins that are substituted with structural moieties, which can lead to cycloadducts other than the expected [2+2] photoproducts from the biradical intermediates that are presumably formed on the reaction pathway (14). Indeed, vinylcyclopropane and 1,6-hexadiene derivatives have been used to directly produce six- and seven-membered rings during irradiation with suitable enones. These systems were used as mechanistic probes to determine the initial site of bond formation during the addition process itself. Interestingly, when compound **18** was treated with a variety of Lewis acids (i.e., Me_2AlCl, $EtAlCl_2$, and $TiCl_4$), decomposition of the substrate (**18**) was observed, indicating that the ring expansion is a unique photochemical outcome. To our knowledge, no photoaddition has been conducted that directly leads to the formation of a cyclopentane ring. Further, the silyl moiety is a latent alcohol that can be used to modify the photoadduct to deliver the methyl group and unsaturation at the C-9 site, which is common in the structure of triquinanes.

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Synthesis and characterization of 2,7-bis(2-pyridyl)-1,8-diazaanthraquinone — A redox-active ligand designed for the construction of supramolecular grids[1]

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Abstract: Double condensation of 2-acetylpyridine with 1,3-diaminobenzene-4,6-dicarboxaldehyde affords 2,7-bis(2-pyridyl)-1,8-diazaanthracene, which was subsequently oxidized to the corresponding quinone. Electrochemical studies indicate two reversible reduction processes corresponding to semiquinone and hydroquinonate formation. Electron-withdrawing pyridine groups and the nitrogen atoms make this somewhat more easily reduced than anthraquinone. This compound is redox-active and can be reduced to its radical anion, a potential spin-bearing ligand for the construction of [2 × 2] metallo-grid structures.

Key words: quinone, grid, supramolecular, bistridentate, electrochemistry, metallosupramolecular chemistry.

Résumé : La double condensation de la 2-acétylpyridine avec du 1,3-diaminobenzène-4,6-dicarboxaldéhyde conduit à la formation de 2,7-bis(2-pyridyl)-1,8-diazaanthrène qui s'oxyde subséquemment en quinone correspondante. Des études électrochimiques indiquent qu'il existe deux processus de réductions réversibles qui correspondent à la formation de la semiquinone et de l'hydroquinonate. Par comparaison avec l'anthraquinone, les groupes pyridines et les atomes d'azote électroattracteurs rendent cette réduction plus facile. Ce composé est actif dans un système redox et il peut être réduit en anion radical, un ligand qui pourrait s'avérer utile comme porteur de spin dans la construction de structures en grilles métalliques [2 × 2].

Mots clés : quinone, grille, supramoléculaire, bistridentate, électrochimie, chimie métallosupramoléculaire.

[Traduit par la Rédaction]

Introduction

The designed assembly of metal–ligand architectures — metallosupramolecular chemistry — is an immensely popular contemporary facet of coordination chemistry. Judicious ligand design, coupled with the thermodynamic control that spurs the self-assembly of metal ions and multidentate receptor ligands, has led to a plethora of well-defined geometric shapes (1) as well as coordination polymers (2) and networks. The ultimate product is contingent on ligand topology in addition to its compatibility with different metal ions. This field of research is spurred by the promise of applications based on the potential function (magnetic, optical, catalytic, etc.) of these materials.

One of the more intensively studied classes of discrete metallosupramolecular structures are the so-called "grids" (3). This architectural class is characterized by ligands with multiple polydentate binding sites situated so as to enforce a regular $m \times n$ array of octahedrally or tetrahedrally coordinated metal ions. Figure 1 schematically depicts the assembly of a 2 × 2 grid based on bisbidentate or bistridentate ligands in conjunction with tetrahedrally or octahedrally coordinated metal ions, respectively. A huge number of grids have been prepared, many of which form in high yield simply from reactions of the free ligand and a metal ion source. The structural diversity is impressive and includes larger grids ($n \times n$, $n \geq 3$) (4), rectangular ($n \times m$, $n \neq m$) grids, grids with incompletely filled metal sites (5), and even grids with extraneous (noncoordinated) ligands intercalated into the grid (6).

Beyond their attractive structural features, the properties of grid molecules have been heavily studied. The incorporation of redox-active metals into grid structures can lead to a rich redox chemistry (7), and the magnetic (8) properties of these materials have also been investigated. In all these cases the redox- or spin-active component of the grids are the metal ions; the ligands play an important structural role but can be described as only passive contributors to the electronic functionality of the grids. No examples of metallosupramolecular grids based on redox-active or spin-containing ligands have yet been reported, although we have described the synthesis of a stable radical containing an analogue of **2** designed for such purposes (9).

Herein we present the design and synthesis of a new bistridentate ligand (**5**), which has been designed specifically

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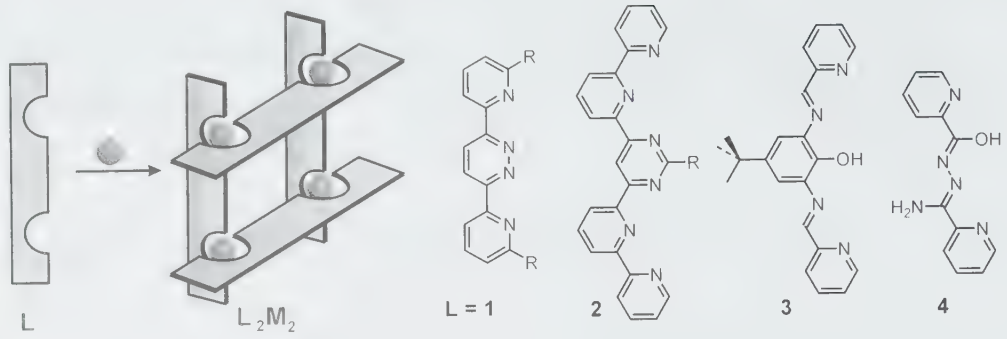
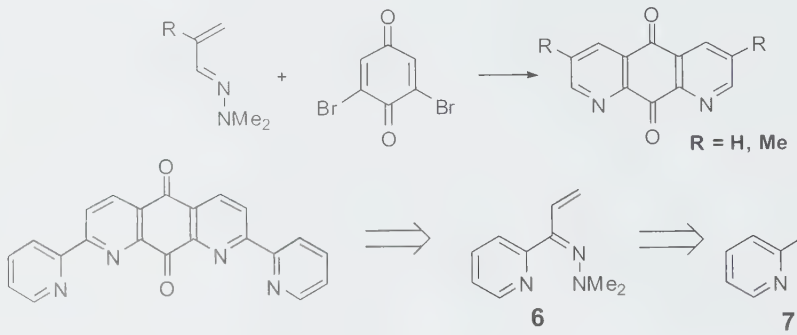
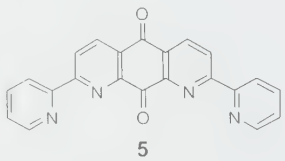
Fig. 1. Schematic of the assembly of a 2 × 2 grid with selected examples of L.



Scheme 1.



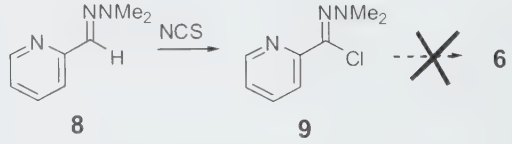
for 2 × 2 grid assembly and has the potential to play an active role in electronic (redox, magnetic, optical, etc.) properties of the assembled grid. The metal-binding sites present in **5** are analogous to those found in **3**, i.e., suited for 2 × 2 grid assembly based on octahedrally coordinated metals. However, **5** is distinguished by the presence of the *p*-(anthra)quinone functional unit embedded in the structure. Quinones are well-known to be redox active and form stable radical anions and dianions. Moreover, metal complexes of *o*-quinones possess a number of very interesting physicochemical properties such as strong magnetic exchange between metal- and semiquinone-based spins and molecular bistability (valence tautomerism) (10). The incorporation of quinone-type functional units into supramolecular assemblies is quite rare (11). The molecular structure of **5** has an appropriate topology of metal binding sites for the formation of 2 × 2 grid structures, and the presence of the *p*-quinone component offers the possibility of magnetically coupled metal–ligand arrays or even grid structures capable of exhibiting valence tautomerism.



Synthesis

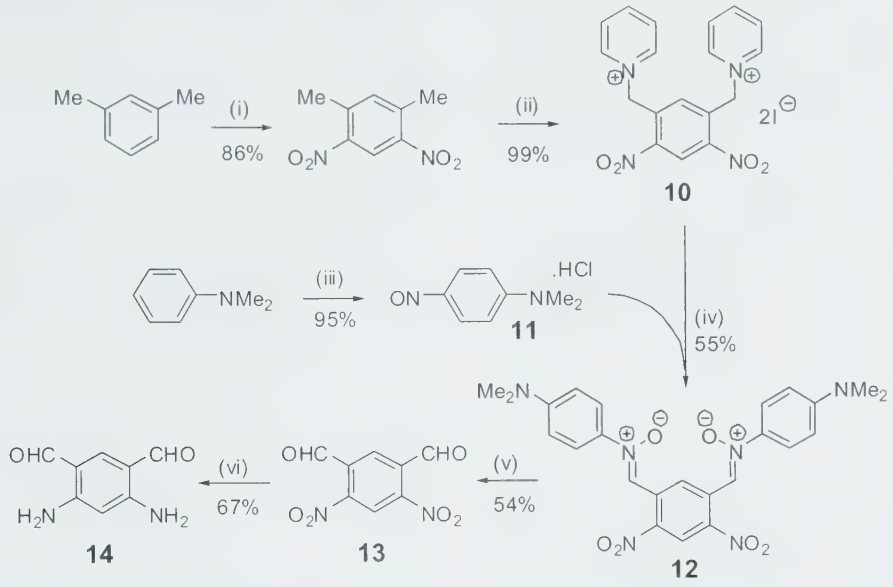
Diaza-9,10-anthraquinones are commonly prepared through hetero-Diels–Alder reactions of 1,4-benzoquinones or quinoline–diones and azadienes (Scheme 1) (12). Our initial attempts to construct **5** were based on this strategy, for which the azadiene **6** was identified as a key intermediate. However, attempts to prepare this substrate from the reaction of (2-pyridyl) vinyl ketone (**7**), prepared by oxidation of the corresponding secondary alcohol (13) with *N*,*N*-dimethylhydrazine, failed. We then turned to a different strategy to prepare **6**, outlined in Scheme 2. 2-Pyridinecarboxaldehyde-*N*,*N*-dimethylhydrazone (14) was chlorinated with NCS to give **9**. Attempts to convert **9** to azadiene **6** through reactions with vinyl nucleophiles (Grignard, lithium reagents) led to no reaction or extensive substrate decomposition. Addition of late metal catalysts did not improve these reactions. Therefore, a different route was sought.

Scheme 2.



The successful synthesis of **5** is outlined in Schemes 3 and 4. The key intermediate is 4,6-diamino-1,3-benzenedicarboxaldehyde (**14**), which was made by slight modification of literature procedures (Scheme 3) (15). *m*-Xylene was bisnitrated and subsequently refluxed with I_2 for 16 h in pyridine to give the air-sensitive bis(pyridinium)diiodide salt (**10**). This salt was reacted with *p*-nitrosodimethylaniline hydrochloride (**11**) (16) to give the bis(imine) oxide (**12**), which was deprotected to give 4,6-dinitro-1,3-benzaldehyde (**13**). Attempts to reduce **13** to the diamine using the literature method (15) failed in our hands. This problem was solved by adopting the protocol described for the reduction of 6-nitro-

Scheme 3. Reagents and conditions: (*i*) HNO_3 (concd.) O °C to rt; (*ii*) pyridine–I_2, 95 °C; (*iii*) 2HCl, $NaNO_2$; (*iv*) **11**, EtOH – 10% NaOH (–5 to 5 °C); (*v*) H_2SO_4 (6 N), toluene, 65 °C; (*vi*) $FeSO_4·7H_2O$, EtOH–H_2O–NH_4OH, 80 C.



Scheme 4. Reagents and conditions: (*i*) 2-acetylpyridine (20 equiv.), 10% KOH, EtOH, 100 °C; (*ii*) CH_3COOH, CrO_3–H_2O, Δ.

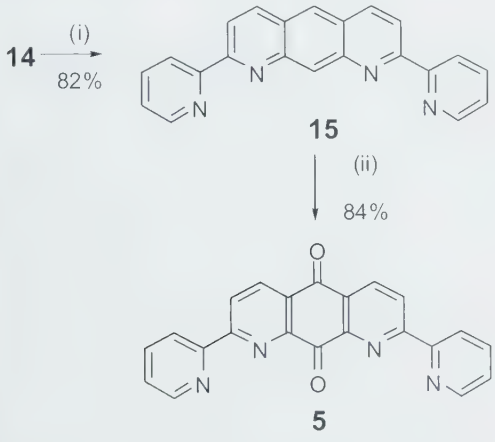
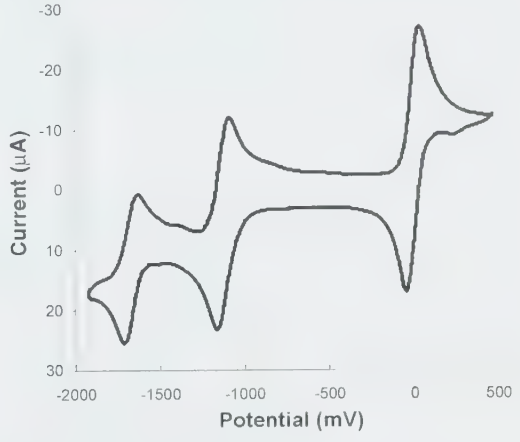


Fig. 2. Cyclic voltammogram of 2,7-dipyridyl-1,8-diaza-9,10-anthraquinone. The redox process at 0 mV is the ferrocene/ferrocenium redox couple, added as an internal reference.

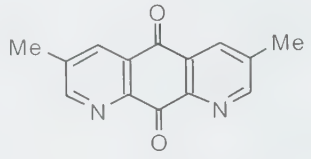


piperinal (17), i.e., aq. $FeSO_4·7H_2O$ in EtOH–H_2O followed by addition of 30% NH_4OH at 80 °C. This facilitated formation of **14** in 67% yield.

Dialdehyde **14** then underwent a double condensation reaction with an excess of 2-acetylpyridine to give 2,7-bis(2-pyridyl)-1,8-diazaanthracene (**15**) in excellent yield. We note the potential use of this compound as a bisbidendate ligand in its own right. The oxidation of **15** to target quinone **5** was initially attempted using V_2O_5 and $NaClO_3$, similar to the oxidation of anthracene to anthraquinone (16), but this method was plagued with dismal conversions and recovery of mostly starting material. Aqueous chromium trioxide in glacial acetic acid proved to be a more effective alternative. Upon cooling the reaction after refluxing for 30 min, quinone **5** precipitated and was isolated in 84% yield. The IR spectrum of **5** shows two carbonyl stretches at 1703 and 1662 cm^{-1}. The UV–vis spectrum showed four intense absorptions at 230, 260, 285, and 315 nm. Other spectroscopic and analytical tools confirmed the structure and purity of **5**.

The redox properties of **5** were probed electrochemically. The cyclic voltammogram of **9** (Fig. 2) has two reversible reduction waves at potentials of E_1° = –1.13 V and E_2° = –1.67 V vs. the ferrocene/ferrocenium redox couple. Table 1 presents the reduction potentials of this compound along with corresponding data for several other compounds. 9,10-Anthraquinone is considerably more difficult to reduce (E_1° = –1.39 V, E_2° = –1.86 V) than 1,4-benzoquinone (E_1° = –0.96 V, E_2° = –1.56 V) because of the effects of annelation. The introduction of two nitrogen atoms at the 1,8 positions (i.e., 1,8-diazaanthraquinone (**16**); made according to literature methods (12*b*)) renders this compound slightly more easily

Table 1. Reduction potentials of *p*-quinones in CH_2Cl_2.



16

Compound	E_1° (V)	E_2° (V)
1,4-Benzoquinone	–0.96	–1.56
9,10-Anthraquinone	–1.39	–1.86
16	–1.24	–1.77
5	–1.13	–1.67

reduced (E_1° = –1.24 V, E_2° = –1.77 V) and the title compound has yet still higher reduction potentials (E_1° = –1.13 V, E_2° = –1.67 V) because of the electron-withdrawing 2-pyridyl substituents. Based on this, reduction of **5** should be chemically possible by reaction with cobaltocene (oxidation potential, E_1° = –1.33 V). This was found to be the case as evidenced by a striking color change from pale yellow to deep red on adding cobaltocene to a solution of **5**. However, the presumed cobaltocenium salt of the radical anion of **5** was exceptionally reactive and could not be isolated, as is often the case in *p*-quinones with low reduction potentials. Despite this shortcoming, we anticipate the radical anion of **5** to gain stability upon coordination as observed in other *p*-dioxolene systems (18).

Experimental

General considerations

All reagents were purchased from Sigma-Aldrich and used as received. All solvents were dried and distilled under argon prior to use (ether, Na–benzophenone, CH_2Cl_2, CaH_2). Infrared spectra were recorded on a PerkinElmer FT-IR spectrometer using KBr pellets. NMR spectra were acquired on a Bruker AMX500 spectrometer in $CDCl_3$. Mass spectra were recorded on a Kratos Concept IH mass spectrometer system. UV–vis data were collected on a Cary 100 SCAN spectrophotometer. The electrochemical experiments were performed using a CV-50W voltammetric analyzer (BAS) at room temperature (22 ± 2 °C). Cyclic voltammetry experiments were performed in CH_2Cl_2 containing 0.1 mol/L of *n*-Bu_4NBF_4 under argon. A carbon electrode (BAS, diameter 3.0 mm) was used as the working electrode. Platinum and silver wires were used as the auxiliary and reference electrodes, respectively. The working electrode was polished on alumina before use. *iR* compensations were applied for all experiments. All peak potentials are reported vs. an internal reference (ferrocene/ferrocenium). Elemental analyses were performed by Canadian Microanalytical Services Ltd., Vancouver, British Columbia.

Synthesis of 2-pyridyl-*N*,*N*-dimethylaminochloroimine (9)

A CH_2Cl_2 solution (35 mL) of 2-pyridinecarboxaldehyde dimethylhydrazone (2.03 g, 13.6 mmol) was slowly treated with *N*-chlorosuccinimide in small portions. After stirring overnight, the solvent was removed under reduced pressure and hexanes were added. The succinimide by-product precipitated and was filtered. The yellow-orange filtrate was cooled to afford crystals of **9**. Yield: 1.67 g (67%). ^{1}H NMR ($CDCl_3$, ppm) δ: 8.6 (d, 1H), 7.9 (d, 1H), 7.6 (dd, 1H), 7.2 (dd, 1H), 2.9 (s, 6H). ^{13}C NMR ($CDCl_3$, ppm) δ: 152.1, 149.0, 136.3, 131.9, 124.1, 122.3, 46.7.

Synthesis of 1,3-diamino-4,6-benzenedicarboxaldehyde (14)

A solution of 4,6-dinitro-1,3-benzaldehyde (**13**) (1.6 g, 7.1 mmol) in EtOH–H_2O (50:50, 80 mL) was brought to reflux and then a solution of ferrous sulfate heptahydrate (36.8 g, 0.132 mol) in H_2O (80 mL) was added to the vigorously stirred reaction mixture, followed by ammonium hydroxide (36 mL) while refluxing. The thick black slurry was refluxed for an additional hour. Thereafter, the hot solution was suction filtered using a large Büchner funnel. Finally, hot ethanol (approx. 50 mL) was used to wash the residue to make sure all the product was filtered through. The filtrate was then brought to a boil and refiltered to remove any metallic black residue that may not have been eliminated the first time. The resultant yellow filtrate was boiled to reduce the volume (to approximately one-third) and on cooling, crude **14** (light brown) precipitated, which was isolated by another filtration. The product was recrystallized using a H_2O–EtOH (5:1) mixture. Yield: 0.780 g (67%). Characterization data (^{1}H and ^{13}C NMR) of **14** was the same as reported previously (15).

Synthesis of 2,7-dipyridyl-1,8-diazaanthracene (15)

KOH (10%, 0.4 mL) was added to a solution of 1,3-diamino-4,6-benzenedicarboxaldehyde (**14**, 0.300 g 1.83 mmol) and of 2-acetylpyridine (4.432 g, 36.5 mmol) at 100–110 °C. The solution was stirred for an additional 15 min. Thereafter, 15 mL of ethanol was added to the mixture and boiled for a short time (~2 min). The reaction mixture was cooled, filtered, and the yellow residue washed with EtOH and dried in vacuo to give **15,** which was recrystallized from hot EtOH. Yield: 0.500 g (82%); mp 239 to 240 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.40 (m, 2H, H18, H23), 7.92 (m, 2H, H17, H22), 8.37 (s, 1H, H10), 8.44 (d, 2H, H4, H5, ^3J = 8.8 Hz), 8.61 (d, 2H, H3, H6, ^3J = 8.8 Hz), 8.76–8.80 (m, 4H, H16, H19, H21, H24), 9.07 (s, 1H, H9). ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 119.2 (C3, C6), 122.3 (C18, C23), 124.4 (C16, C21), 126.4 (C10), 127.0 (C11, C14), 129.3 (C9), 136.9, 137.0 (C4, C5, C17, C22), 146.7 (C12, C13), 149.1 (C19, C24), 155.9 (C15, C20), 157.5 (C2, C7). LSIMS: 335 $[M + H]^+$. Anal. calcd. for $C_{22}H_{14}N_4$ (%): C 79.02, H 4.22, N 16.76; found: C 78.73, H 4.23, N 16.74.

Synthesis of 2,7-dipyridyl-1,8-diaza-9,10-anthraquinone (2,7-DIP-DAAQ) (5)

To **15** (0.600 g, 1.80 mmol) in a two-necked flask, mounted by a reflux condenser, was added glacial acetic acid (6 mL), then the flask stoppered. The reaction mixture was brought to reflux, and while that was underway, CrO_3 (4 equiv. mol) were dissolved in H_2O (0.6 mL), followed by glacial acetic acid (3 mL). The heat source was removed from the reaction mixture and the mixture was dropped into the stirring reaction mixture over a course of ~10 min. The

reaction was then refluxed for a further 10–15 min. Pure 2,7-DIP-DAAQ usually precipitates on cooling, but if it did not, the reaction solution at room temperature was precipitated into ice-cold water (30 mL) with continued stirring for another 10–15 min (cold conditions must be maintained). Filtration afforded a crude yellow residue that was washed thoroughly with hot water, cold water, and diethyl ether. Recrystallization from glacial acetic acid afforded **5**. Yield: 0.550 g (84%); mp 316 °C. UV–vis (CH_2Cl_2, nm) λ_{max} (ε): 230 (20 100 (mol/L)$^{-1}$ cm^{-1}), 260 (22 100 (mol/L)$^{-1}$ cm^{-1}), 285 (23 100 (mol/L)$^{-1}$ cm^{-1}), 315 (27 500 (mol/L)$^{-1}$ cm^{-1}). Pertinent IR stetches (cm^{-1}): 1703 (m), 1662 (s), 1589 (s), 1330 (s). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.46 (m, 2H, H18, H23), 7.96 (m, 2H, H17, H22), 8.76–8.79 (m, 4H, H3–H6), 8.85 (d, 2H, H16, H21, ^3J = 8.1 Hz), 8.97 (d, 2H, H19, H24, ^3J = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 123.2 (C18, C23), 125.4 (C3, C6, C16, C21), 129.8 (C11, C14), 136.4 (C17, C22), 137.4 (C4, C5), 148.8 (C12, C13), 149.4 (C19, C24), 154.1 (C15, C20), 161.2 (C2, C7), 180.1, 182.0 (C9, C10). HRMS calcd. for $C_{22}H_{12}N_4O_2$: 364.10; found: 364.0955 ± 0.0016. Anal. calcd. for $C_{22}H_{12}N_4O_2$ (%): C 72.52, H 3.32, N 15.38; found: C 72.77, H 3.38, N 15.37.

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Synthesis and aldol cyclotrimerization of 4,7-di-*tert*-butylacenaphthenone[1]

Aaron W. Amick, Keith S. Griswold, and Lawrence T. Scott

Abstract: An efficient gram scale synthesis of the previously unknown 4,7-di-*tert*-butylacenaphthenone (**3b**) is reported. The facile isomerization of epoxide **9b** to ketone **3b** occurs simply on stirring a solution of **9b** with silica gel at room temperature. Aldol cyclotrimerization of **3b** with titanium tetrachloride gives 2,5,8,11,14,17-hexa-*tert*-butyldecacyclene (**1b**) in 58% isolated yield. X-ray crystal structures have been obtained for the synthetic intermediates 4,7-di-*tert*-butylacenaphthene (**2b**) and 4,7-di-*tert*-butylacenaphthylene (**8b**).

Key words: aromatic, decacyclene, hydrocarbon, nonalternant, polycyclic.

Résumé : On a mis au point une synthèse efficace au niveau du gramme de la 4,7-di-*tert*-butylacénaphténone, un composé antérieurement inconnu. L'isomérisation facile de l'époxyde **9b** en cétone **3b** se produit simplement en agitant une solution du composé **9b** avec du gel de silice, à la température ambiante. La cyclotrimérisation aldolique du composé **3b** en présence de tétrachlorure de titane conduit au 2,5,8,11,14,17-hexa-*tert*-butyldécacyclène (**1b**) qui a été isolé avec un rendement de 58 %. Faisant appel à la diffraction des rayons X, on a déterminé les structures cristallines des intermédiaires de synthèse 4,7-di-*tert*-butylacénaphtène (**2b**) et 4,7-di-*tert*-butylacénaphtylène (**8b**).

Mots clés : aromatique, décacyclène, hydrocarbure, nonalternant, polycyclique.

[Traduit par la Rédaction]

Introduction

Decacyclene (**1a**), annulated with additional aromatic rings and (or) substituted with strategically placed chlorine atoms, has served admirably in our laboratory for some years now as the core structure of synthetic precursors to geodesic polyarenes ranging from bowl-shaped polycyclic aromatic hydrocarbons to the I_h fullerene, C_{60} (1). The parent decacyclene (**1a**) was first prepared in 1883 (2) by an oxidative trimerization of acenaphthene (**2a**) (3), which, in turn, was isolated from coal tar. Unfortunately, this simple method is not well-suited for the regioselective cyclotrimerization of unsymmetrical acenaphthene derivatives (4). For this purpose, we have relied on the acid-catalyzed head-to-tail cyclic aldol trimerization of compounds related to acenaphthenone (**3a**, Fig. 1) (1).

Other triply annulated benzene rings with threefold symmetry have been prepared by aldol cyclotrimerizations of cyclic ketones since the 19th century (5); however, the success of the reaction depends on the particular system in ways that are still poorly understood. Some cases work spectacularly well, e.g., 1-indanone (**4**), 85% yield (6), whereas closely related systems sometimes fail miserably, e.g., 1-tetralone (**5**), 0% yield (7).

We recently surveyed the literature on such reactions in an attempt to uncover correlations between the outcome of attempted aldol cyclotrimerizations and structural features in the cyclic ketones, and at least one prerequisite for success did emerge (8). Some critical factors that can scuttle these reactions have been identified (8, 9); however, others remain obscure. Thus, it is still not possible to predict with confidence which cyclic ketones will give triply annulated benzene rings in high yield by aldol cyclotrimerizations.

Fortunately for us, the tricyclic and tetracyclic ketones **6** and **7** and certain chlorinated derivatives thereof, provide triply annulated benzene rings in high yield by aldol cyclotrimerizations (9, 10). We have been especially puzzled, however, by the relatively low yield of decacyclene (**1a**) produced under a variety of conditions from acenaphthenone (**3a**), a five-membered ring aromatic ketone that closely resembles both indanone (**4**) and the larger ketones **6** and **7** (11).

By following the buildup and disappearance of the various intermediates involved in this reaction, we hoped to learn more about what makes the aldol cyclotrimerization of acenaphthenone such a comparatively poor reaction. The low solubility of decacyclene and of the two aldol dimers (E and Z) of **3a**, unfortunately, hampered our ability to obtain reliable data, so we decided to incorporate solubilizing groups at the 4 and 7 positions, where they would not impose any steric hindrance to the reactions. The hexa-*tert*-butyldecacyclene (**1b**) expected from cyclotrimerization of 4,7-di-*tert*-butylacenaphthenone (**3b**), in fact, is already a known compound (3, 12) and its solubility in normal organic solvents bodes well for the mechanistic studies we have

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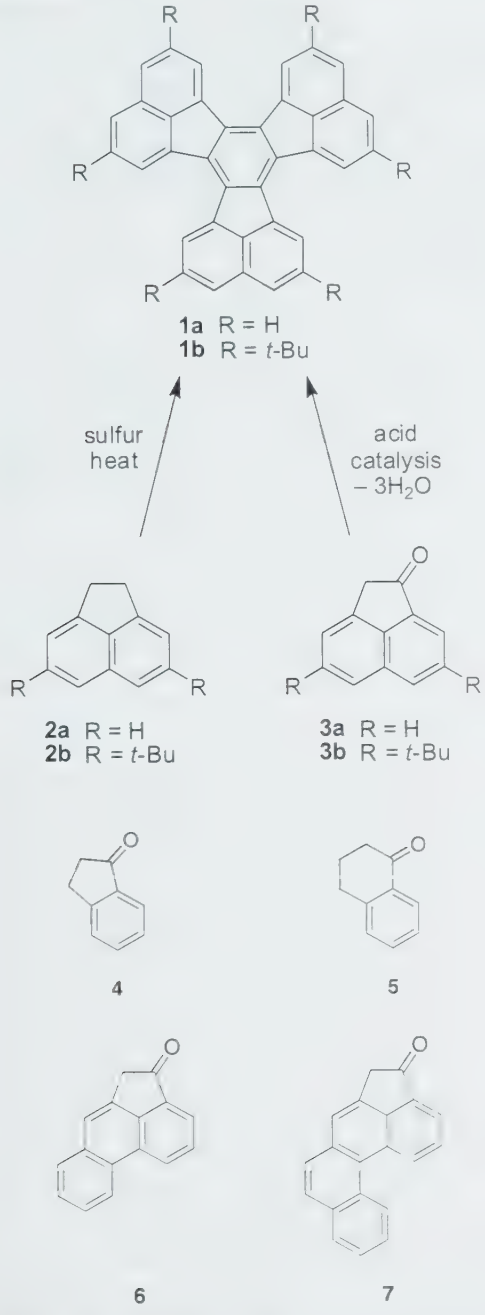
Fig. 1. Decacyclenes (**1**) by oxidative cyclotrimerization of acenaphthenes (**2**) and by aldol cyclotrimerization of acenaphthenones (**3**)



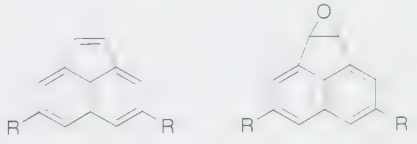
planned. Our purpose is not to compete with the published syntheses of **1b**, which have been achieved both by direct Friedel–Crafts alkylation of **1a** (12) and by oxidative cyclotrimerization of **2b** (3). Rather, we hope to use the alternative synthesis of **1b** from **3b** as a case study with which to probe the factors that influence the interconnected maze of competing pathways involved in aldol cyclotrimerization reactions.

Synthesis and cyclotrimerization of 4,7-di-*tert*-butylacenaphthenone (3b)[3]

The di-*tert*-butylation of acenaphthene (**2a**) under Friedel–Crafts conditions to give 4,7-di-*tert*-butylacenaphthene (**2b**) was first reported by Peters in 1942 (13). The structure of the product was initially misassigned, but Peters corrected the assignment himself in 1950 to the one shown (**2b**) (14).

A further complication in the literature on compounds of this class derives from the intermingling of at least three different numbering schemes for the acenaphthene ring system. Peters consistently refers to compound **2b** as "2 : 5-di-*tert*-butylacenaphthene", in accord with "Richter's numbering of the acenaphthene system",[4] which numbers the carbon atoms of the five-membered ring last. In this paper, we use the *Chemical Abstracts* numbering scheme, which numbers the two carbon atoms of the five-membered ring first.

The unsaturated hydrocarbon, 4,7-di-*tert*-butylacenaphthylene (**8b**), has been prepared from **2b** by dehydrogenation with DDQ in refluxing benzene (15). A third numbering scheme led the authors who first reported this reaction to name the compound "3,6-di-*tert*-butylacenaphthylene", but the structure is the one shown here (**8b**). We have made no significant modifications to the procedures for synthesizing **2b** and **8b**, but report here the UV–vis spectra of both hydrocarbons and the ^{13}C NMR spectrum of **8b** for the first time. Because there are some discrepancies concerning the melting points and NMR chemical shifts of **2b** (13, 14, 16–19) and **8b** (15), we report our melting points and NMR data as well, including copies of the full spectra for the first time in the Supplementary material.[5]



8a R = H
8b R = *t*-Bu

9a R = H
9b R = *t*-Bu

The usual route to substituted acenaphthenones involves benzylic acetoxylation with Pb_3O_4 in acetic acid, followed

[3] *Chemical Abstracts* name: 4,7-bis(1,1-dimethylethyl)-1(2*H*)-acenaphthylenone or 4,7-di-*tert*-butyl-1(2*H*)-acenaphthylenone

[4] See footnote on page 729 in ref. 14.

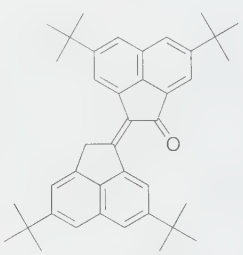
[5] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5051. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 279886 (**2b**) and 279887 (**8b**) contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Fig. 2. X-ray crystal structures of 4,7-di-*tert*-butylacenaphthene (**2b**, left) and 4,7-di-*tert*-butylacenaphthylene (**8b**, right).

by saponification of the acetate to the alcohol and oxidation to the ketone (17). In the present case, we have found that the readily available epoxide (**9b**) rearranges in high yield to 4,7-di-*tert*-butylacenaphthenone (**3b**) under exceptionally mild conditions (i.e., stirring in solution with silica gel at room temperature).

Preliminary attempts to promote an aldol cyclotrimerization of the substituted acenaphthenone **3b** by treatment with various Lewis acids and Brønsted acids gave only low yields of hexa-*tert*-butyldecacyclene (**1b**). The best conditions found so far (58% isolated yield) entail heating a solution of **3b** and titanium tetrachloride (6 equiv.) in 1,2-dichloroethane to reflux for 4.5 h, with a constant flow of N_2 bubbling through the solvent to sweep out the HCl that is formed.

From a reaction run under other conditions, we isolated and characterized the aldol dimer, 4,7,4′,7′-tetra-*tert*-butyl-1,1′-biacenaphthylenyliden-2-one (**10**), a presumed intermediate in the trimerization. The solubility imparted by the *tert*-butyl groups to all the species present in this reaction has allowed us to begin monitoring these aldol cyclotrimerizations by NMR spectroscopy, and detailed studies that are currently underway with a variety of catalysts, stoichiometries, solvents, temperatures, times, etc., will be reported in due course.



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X-ray crystal structures of 2b and 8b

Through our ongoing collaboration with the solid-state NMR group of Grant and Pugmire and co-workers in Utah (20), we learned that the motion of individual molecules in crystals of acenaphthylene (**8a**) has prevented the experimental determination of chemical shift tensors for the carbon atoms in this archetypal nonalternant hydrocarbon. We speculated that the *tert*-butyl groups on **8b** should anchor the molecules in the crystal and thereby eliminate the motion. As an added bonus, the incorporation of so many aliphatic hydrogen atoms near the acenaphthylene core would be expected to shorten the relaxation times for the carbon nuclei and allow faster data acquisition. Grant and Pugmire expressed an interest in both the saturated and the unsaturated hydrocarbons, so we supplied them with samples of both **2b** and **8b**.

When we were informed that analysis of the solid-state NMR data would be facilitated by a knowledge of the exact geometries of the molecules, we obtained X-ray crystal structures for both **2b** and **8b** (Fig. 2).[5]

Conclusions

The previously unknown 4,7-di-*tert*-butylacenaphthenone (**3b**) can now be prepared on a gram scale by an efficient three-step synthesis from commercially available acenaphthene (**2a**). The facile isomerization of epoxide **9b** to ketone **3b** occurs simply on stirring a solution of **9b** with silica gel at room temperature. Preliminary efforts to effect the aldol trimerization of **3b** have given the substituted decacyclene **1b** in 58% isolated yield, and the stage is now set for more detailed mechanistic studies. X-ray crystal structures have been obtained for the synthetic intermediates **2b** and **8b**.

Experimental

General

Melting points are corrected.

4,7-Di-*tert*-butylacenaphthene (2b)

The synthesis was carried out in a manner similar to that reported by Gill et al. (18) and the product was obtained as colorless needles by recrystallization from glacial acetic acid (twice) and ethanol (95%, once); mp 162.5–163.5 °C (lit. value (13) mp 162 to 163 °C; lit. value (14) mp 162.5–163.5 °C; lit. value (16) mp 162 to 163 °C; lit. value (17) mp 167.0–168.0 °C; lit. value (19) mp 164 °C). UV–vis (CH_2Cl_2) λ_{max} (log ε): 235 (5.61), 284 (4.50). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.58 (s, 2H), 7.39 (s, 2H), 3.39 (s, 4H), 1.42 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 151.08, 144.88, 136.11, 130.56, 117.34, 117.27, 35.43,

31.80, 30.66. HRMS ESI (*m/z*) calcd. for $C_{20}H_{26}$: 266.2034 $[M]^+$; found: 266.2035.

4,7-Di-*tert*-butylacenaphthylene (8b)

A 250 mL round bottom flask was charged with 4,7-di-*tert*-butylacenaphthene (**2b**, 5.16 g, 19.3 mmol), DDQ (6.61 g, 29.1 mmol), and benzene (100 mL). The mixture was heated to reflux, and the progress of the reaction was monitored by GC–MS until it reached completion (ca. 4 h). The benzene was evaporated from the reaction mixture under reduced pressure to give a dark blue solid. This solid was then redissolved in dichloromethane and run through an alumina plug to remove any latent DDQ and hydroquinone. This organic solution was evaporated under reduced pressure to give 4.41 g of a yellow crystalline solid (88% yield); mp 114.5–117 °C (lit. value (15) mp 108 to 109 °C). UV–vis (CH_2Cl_2) λ_{max} (log ε): 235 (5.51), 331 (4.39). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.79 (d, J = 1.1 Hz, 2H), 7.76 (d, J = 1.1 Hz, 2H), 7.08 (s, 2H), 1.46 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 150.90, 138.84, 129.40, 127.09, 125.26, 122.42, 121.93, 35.61, 31.79. HRMS ESI (*m/z*) calcd. for $C_{20}H_{24}$: 264.1878 $[M]^+$; found: 264.1882.

4,7-Di-*tert*-butylacenaphthenone (3b)

A sample of 4,7-di-*tert*-butylacenaphthylene (2.00 g, 7.60 mmol) was added to a solution of freshly washed *m*-chloroperoxybenzoic acid (2.00 g, 11.4 mmol), dichloromethane (50 mL), and saturated aqueous sodium bicarbonate (50 mL). The reaction mixture was stirred and the reaction progress was monitored by GC–MS. Upon completion of the reaction (2 h), the organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The product was redissolved in dichloromethane and silica gel (ca. 50 g) was added. This slurry was stirred at 25 °C for approximately 6 h. The silica gel was filtered off and washed with dichloromethane. Evaporation of the organic solvent under reduced pressure gave a reddish-orange, oily solid. This product was dissolved in hexanes and evaporated under reduced pressure yielding 1.70–1.91 g (80%–90% over several runs) of a reddish-orange, crystalline solid; mp 81–83 °C. UV–vis (CH_2Cl_2) λ_{max} (log ε): 234 (5.45), 287 (4.47). IR (KBr, cm^{-1}): 1718 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.06 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 7.74 (s, 1H), 7.52 (d, J = 1.0 Hz, 1H), 3.82 (s, 2H), 1.46 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 203.72, 151.90, 151.86, 140.25, 134.14, 134.07, 130.45, 127.16, 119.44, 119.24, 118.72, 42.50, 35.66, 35.64, 31.67, 31.47. HRMS ESI (*m/z*) calcd. for $C_{20}H_{24}O$: 280.1827 $[M]^+$; found: 280.1823.

2,5,8,11,14,17-Hexa-*tert*-butyldecacyclene (1b)

A 100 mL two-necked flask was charged with 4,7-di-*tert*-butylacenaphthenone (0.200 g, 0.714 mmol), dichloroethane (16 mL), and titanium tetrachloride (4.3 mmol, 0.47 mL). The reaction mixture was heated to reflux for 4.5 h with a constant flow of N_2 bubbling through the solvent. When the reaction was complete, as determined by TLC, the mixture was poured into a solution of 10% HCl and ice and extracted with dichloromethane. The organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure.The dark product thus obtained was purified by column chromatography on neutral alumina with hexane–dichloromethane (75:25) to give 0.097 g of a dark yellow crystalline solid (58%). UV–vis (CH_2Cl_2) λ_{max} (log ε): 234 (5.53), 280 (4.86), 350 (4.70). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.97 (s, 6H), 7.93 (s, 6H), 1.66 (s, 54H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 151.00, 137.01, 136.37, 131.37, 129.57, 122.14, 121.80, 35.84, 31.99. HRMS ESI (*m/z*) calcd. for $C_{60}H_{66}$: 786.5165 $[M]^+$; found: 786.5168.

4,7,4′,7′-Tetra-*tert*-butyl-1,1′-biacenaphthylenyliden-2-one (10)

A sample of 4,7-di-*tert*-butylacenaphthenone (0.200 g, 0.714 mmol) and anhydrous ethanol (16 mL) were added to a pressure vessel under N_2 and the mixture was cooled to –78 °C. Titanium tetrachloride (0.034 g, 0.178 mmol) was added via syringe and the vessel was sealed. The reaction mixture was stirred in an oil bath at 90 °C for 1 h and subsequently quenched with 10% HCl. The product was extracted into dichloromethane, which was then dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by preparative TLC on alumina with hexane–dichloromethane (75:25) as the eluent, yielding 0.005 g (2.4%) of a bright yellow solid: mp 246–256 °C (dec). UV–vis (CH_2Cl_2) λ_{max} (log ε): 234 (5.28), 289 (4.56), 440 (4.25). IR (KBr, cm^{-1}): 1692 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 10.03 (d, J = 1.6 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 8.03 (s, 1H), 7.92 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 0.8 Hz, 1H), 7.71 (s, 1H), 7.64 (d, J = 0.8 Hz, 1H), 4.68 (s, 2H), 1.60 (s, 9H), 1.58 (s, 9H), 1.49 (s, 9H), 1.48 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 193.39, 152.27, 151.76, 151.69, 151.18, 150.92, 138.78, 138.27, 138.21, 136.53, 135.94, 133.52, 130.68, 130.33, 129.89, 126.33, 126.30, 123.84, 119.91, 119.88, 119.26, 118.65, 118.06, 41.00, 35.94, 35.88, 35.71, 35.44, 31.88, 31.73, 31.66. HRMS ESI (*m/z*) calcd. for $C_{40}H_{46}O$: 542.3549 $[M]^+$; found: 542.3558.

The stereochemistry around the double bond in this dimer is assigned as (Z) on the basis of ^{1}H NMR chemical shift arguments. Both dimers can be seen in solution, although only this one was isolated and characterized. The lowest field chemical shift for the E-dimer is seen at δ 8.98 ppm, which is very close to lowest field chemical shift for the cyclic trimer (**1b**, 8.90 ppm). The structural similarity between the sterically crowded fjord regions of **1b** and the E-dimer accounts for the near coincidence of their lowest field proton chemical shifts. By contrast, the lowest field chemical shift for the Z-dimer is seen at δ 10.03 ppm, more than 1.00 ppm lower field than that for the E-dimer and for **1b**. The proximity of the fjord region hydrogen in the Z-dimer to the carbonyl group (**10**) accounts for its exceptionally low field chemical shift. Presumably, the E-and Z-dimers interconvert through a common dienol during the aldol trimerization reaction.

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Effect of crown ether ring size on binding and fluorescence response to saxitoxin in anthracylmethyl monoazacrown ether chemosensors[1]

Hua Mao, John B. Thorne, Jennifer S. Pharr, and Robert E. Gawley

Abstract: Convenient macrocyclization synthetic routes for the preparation of different-sized monoaza anthracylmethyl crown ether chemosensors (15-crown-5, 18-crown-6, 21-crown-7, 24-crown-8, and 27-crown-9) are described. Evaluation of these crowns as chemosensors for saxitoxin revealed that the larger crowns have moderately higher binding constants, with the 27-crown-9 chemosensor having the largest binding constant (2.29×10^5 $(mol/L)^{-1}$). Fluorescence enhancements of 100% were observed at saxitoxin concentrations of 5 μmol/L, which is close to the detection limit in mouse bioassay.

Key words: anthracene, crown ethers, saxitoxin, paralytic shellfish poison (PSP), binding constants; chemosensors.

Résumé : On décrit des voies de synthèse pratiques à base de macrocyclisations pour la préparation de senseurs chimiques à base des monoaza anthracylméthyl éthers couronnes de tailles différentes, 15-courone-5, 18-couronne-6, 21-couronne-7, 24-couronne-8 et 27-couronne-9. L'évaluation de ces couronnes comme senseurs chimiques pour la saxitoxine révèle que les couronnes les plus grosses présentent les constantes de fixation les plus élevées, alors que le senseur chimique à base de 27-couronne-9 est associée à la constante de fixation la plus élevée, soit $2,29 \times 10^{-5}$ $(mol/L)^{-1}$ On a observé des augmentations de la fluorescence de 100 % à des concentrations de 5 μmol/L, valeur qui est proche de la limite de détection dans les bioessais à l'aide de souris.

Mots clés : anthracène, éthers couronnes, saxitonine, intoxication paralysante par les mollusques, constantes de fixation, senseurs chimiques.

[Traduit par la Rédaction]

Harmful algal blooms (HABs) are linked to many cases of human poisoning each year. Economic losses and costs to the fishing industry, public health, and tourism are estimated to be $40 000 000US annually as of the late 1990s (1). The toxins produced by HABs, as well as many other analytes of interest to members of the biomedical community, are "small molecules". Saxitoxin (STX) (Fig. 1) is such a small molecule because of its neurotoxicity and is the most toxic component of the paralytic shellfish poisons (PSPs) (2). Its activity is manifested through the binding of the toxin to voltage-gated sodium channels and blocking sodium ion transport across neuronal membranes. In 1996, saxitoxin was included on the United States government's list of "Select Agents" (potential terrorist weapons). It is one of only three small molecules on the list; the rest are viruses (e.g., Ebola), bacteria (e.g., *Yersenia pestis*), and proteins (e.g., ricin, abrin).

Mouse bioassay is the current method used by government agencies to detect saxitoxin and its derivatives (3), but for both ethical and economic reasons, an alternative would be highly beneficial. We have been working for several years to develop fluorescent chemosensors for the detection of saxitoxin and have recently made significant advances. Specifically, we have shown that arylmethylcrowns are selective for the detection of saxitoxin over sodium, potassium, and calcium ions (4), as well as several organic analytes (5), including tetrodotoxin (Fig. 1) (6). The latter point is clinically relevant since saxitoxin and tetrodotoxin bind, competitively, to the same site on voltage-gated sodium channels and produce the same clinical symptoms (7, 8).

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This paper is dedicated to Alfred Bader in recognition of his many contributions, both personal and professional, to the chemical enterprise.

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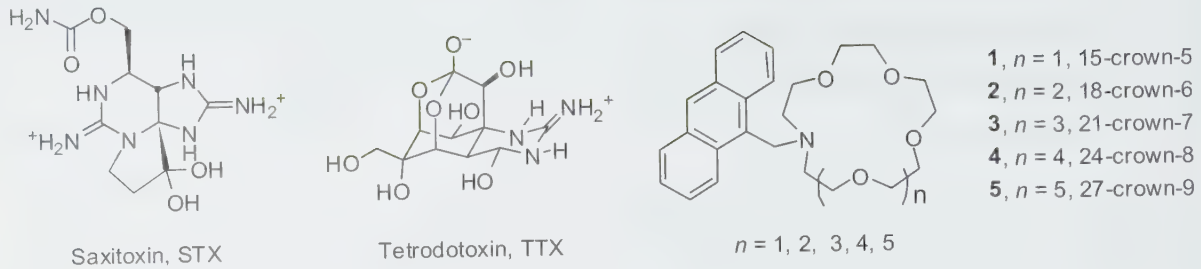
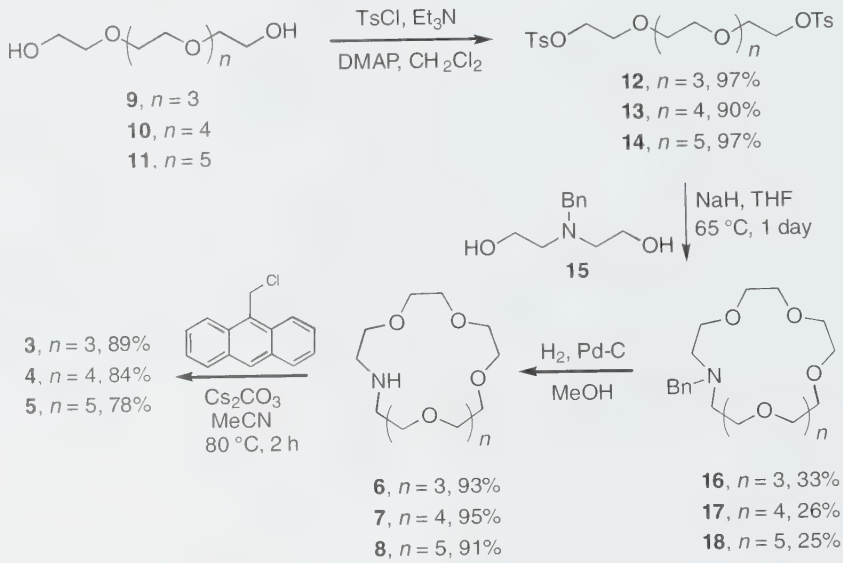
Fig. 1.



Scheme 1.



Until now we have focused on the 18-crown-6 monoaza- or diaza-crown ethers, with anthracene, coumarin, or acridine fluorophores. In early work, Cram and co-workers showed that 27-crown-9 crown ether is the optimum size to host a guanidinium guest (9, 10). Since saxitoxin (Fig. 1) is a bisguanidinium dication, we explored larger crown sizes to determine the effect on binding, using the anthracene fluorophore as sensor. Thus, crown ethers **1**–**5** were prepared and evaluated for fluorescence response to saxitoxin: 15-crown-5 (**1**, n = 1), 18-crown-6 (**2**, n = 2), 21-crown-7 (**3**, n = 3), 24-crown-8 (**4**, n = 4), and 27-crown-9 (**5**, n = 5) (Fig. 1).

Synthesis

Anthracylmethyl crown ethers **1** and **2** were originally prepared by de Silva and co-workers (11). They were made by alkylation of monoazacrowns with 9-(chloromethyl)anthracene. Anthracylmethyl crowns **3**–**5** were similarly prepared by alkylation of monoazacrowns **6**–**8**, as shown in Scheme 1. The diols **9** and **10** are commercially available. Diol **11** was prepared in three steps from diethylene glycol and triethylene glycol according to a literature procedure (12) with some modifications (using benzyl instead of allyl as the protecting group). Ditosylation of polyethylene glycols **9**–**11** afforded ditosylates **12** (13), **13** (14), and **14**, respectively, which were cyclized with *N*-benzyldiol **15** using sodium hydride to afford the *N*-benzyl crowns **16**–**18** in modest yields. Hydrogenolysis of **16**–**18** to crowns **6**–**8** proceeded smoothly and alkylation with chloromethyl anthracene afforded the sensors **3**–**5**. The synthetic steps all proceeded in excellent yields with the exception of the macrocyclization, which is typically low-yielding (10).[3]

Titrations

A solution of each crown ether in methanol was titrated against saxitoxin using the fluorescence response of anthracene at an excitation wavelength of 372 nm and an emission wavelength of 420 nm. The concentration of the crown ethers was held constant at 10^{-6} mol/L, while the

[3] Supplementary data (^{1}H and ^{13}C NMR spectra for compounds **3**–**8** and **12**–**18** and typical binding isotherms for the titration of crowns **1**–**4**) for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5060. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

concentration of the toxin was varied by successive dilutions with a 10^{-6} mol/L solution of the crown ether. Beginning with 150 µL of a solution of 1 µmol/L crown sensor (**1–5**) and a starting STX concentration of 100 µmol/L, binding isotherms were obtained by successive removal of 50 µL aliquots and replacement with 50 µL of a 1 µmol/L crown solution. Fluorescence measurements for each dilution were made after a 4 min equilibration. Binding constants for each anthracylmethyl crown ether were obtained by curve fitting of the intensity at 420 nm to a standard rectangular hyperbolic equation for 1:1 binding (15). The binding constant was determined according to the equation

$$\frac{F}{F_0} = \frac{1 + \left(\frac{k_{11}}{k_{crown}}\right) K_{11}[STX]}{1 + K_{11}[STX]}$$

where F and F_0 are the observed fluorescence intensities in the presence and absence of STX, respectively, k_{crown} and k_{11} are constants related to fluorescence intensities of the crown and the 1:1 crown·STX complex, respectively, K_{11} is the binding constant for the 1:1 complex, and [STX] is the equilibrium concentration of unbound saxitoxin (15). The equation describes a hyperbolic binding isotherm and the binding constant (K_{11}) was obtained by a nonlinear least-squares curve-fitting program. One of the isotherms for saxitoxin binding to **5** is shown in Fig. 2. The binding constants (K_{11}) for the five crown sensors are listed in Table 1. Each value is the average of at least two runs and each run had a correlation coefficient for the least-squares fit of ≥0.98.

Discussion

The sensing mechanism is illustrated by the following equilibrium

$$\text{Toxin} + \text{Crown} \overset{K_{11}}{\rightleftharpoons} \text{Toxin·Crown}$$

where K_{11} is the binding (equilibrium) constant for formation of the 1:1 Toxin·Crown complex. In sensors such as **1–5**, the fluorescent chromophore having a benzylic nitrogen is only weakly fluorescent owing to photoinduced electron transfer (PET) (16). Upon complexation of the toxin, PET is turned off and the chromophore fluoresces normally. The usual mechanism invoked for this type of PET quenching is complexation of a ligand to the benzylic nitrogen lone pair. The binding model that we believe is operative in saxitoxin sensing involves hydrogen bonding of the crown ether to one of the guanidiniums (C-8, Fig. 1), as shown in Fig. 3 (5). Monte Carlo searching of possible docked structures failed to identify a low energy structure having a hydrogen bond to the benzylic nitrogen (5). Note that the second guanidinium appears to π stack with the anthracene fluorophore. We suggest that this π stacking perturbs the relative energies of the chromophore HOMO and the nitrogen lone pair, thus "turning off" the PET (5). This hypothesis is supported by the fact that sodium, potassium, calcium (4), guanidinium (5, 17), and ammonium ions (5, 17), all of which are known to bind to crown ethers, produce no fluorescence enhancement with these sensors in alcohol solvents containing small amounts of water. Further support is found in the failure of

Fig. 2. Typical binding isotherm for titration of saxitoxin from 10^{-4} mol/L to 5×10^{-7} mol/L vs. anthracylmethyl 27-crown-9 chemosensor **5** (10^{-6} mol/L). A 50% fluorescence enhancement is observed at 1 µmol/L [STX] and 100% enhancement is observed at 5 µmol/L [STX].

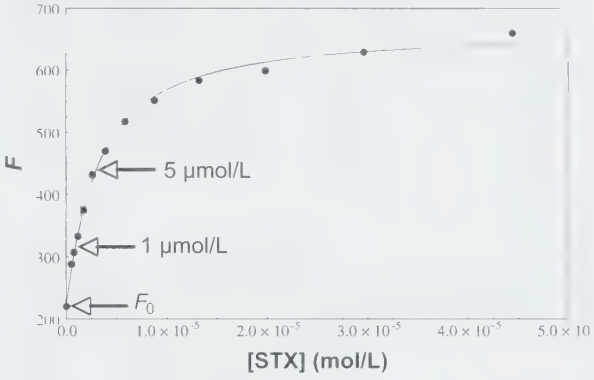


Table 1. Binding constants of saxitoxin to crown sensors **1–5** in methanol.

Crown sensor	Binding constant (K_b, $(mol/L)^{-1}$)
1	4.93×10^4
2	5.3×10^4
3	4.68×10^4
4	1.07×10^5
5	2.29×10^5

Note: Each K_{11} is the average of at least two runs. Correlation coefficients of ≥0.98 were calculated for each fit.

Fig. 3. Molecular mechanics model of STX docked to anthracylmethyl 18-crown-6 (global minimum) (5). Note the absence of a hydrogen bond to the benzylic nitrogen.

tetrodotoxin (Fig. 1), a toxin having many hydrogen bond donors but only one guanidinium and which binds competitively to saxitoxin in sodium channels to produce any fluorescence enhancement (6).

Three factors can contribute to an increase in fluorescence intensity upon binding of the toxin: (1) a large binding constant, which increases the relative concentration of the fluorescing Toxin·Crown complex over the unbound Crown; (2) a chromophore having a high molar absorptivity (extinction coefficient); and (3) a high fluorescence quantum yield, such that a high fraction of incident light is absorbed and a high fraction of absorbed light is emitted when PET is turned off. Anthracene has one of the highest fluorescence quantum

yields known (~0.4–0.8, depending on conditions). The fluorescence enhancement by saxitoxin in these sensors has not shown significant dependence on the chromophore (anthracene (5, 17), coumarin (4), or acridine (6)), so our efforts have focussed primarily on increasing the binding constant by making modifications to the crown ether.

In a full paper (5), we reported the synthesis and binding constants of 11 anthracylmethyl 18-crown-6 ethers, 10 of which were diazacrowns with additional substituents added to the crown ring — opposite the anthracylmethyl group — in the hope of increasing the binding constant. Although replacement of one oxygen with a nitrogen doubled the binding constant, further substitution failed to produce any improvement.

In early work on the binding of guanidinium ions to crown ethers, molecular models were used to postulate six hydrogen bonds between guanidinium ion and 27-crown-9 ethers (9, 10). The hypothesis was supported by the solubilization of (otherwise insoluble) guanidinium ion in chloroform by benzo-27-crown-9. The binding model invoked hydrogen bonding between the six guanidinium N-Hs and six of the nine oxygens of the crown ether. Although this binding model cannot be employed for saxitoxin, the large number of hydrogen bond donors in the toxin prompted the question whether a larger crown might show enhanced binding. Interestingly, neither ammonium ion nor guanidinium ion produced any fluorescence enhancement in **2** in ethanol (5, 17). The results of the current study reveal increased binding as the size of the crown ring increases. A control experiment shows that guanidinium ion fails to enhance the fluorescence of **5**; if anything, a slight suppression is observed in methanol.

Summary

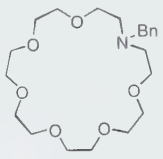
Anthracylmethyl crown ether chemosensors show enhanced binding over smaller crowns. This may be due to the fact that there are more heteroatoms in the crown and (or) that the larger crown is simply more flexible. Either effect could offer more sites for hydrogen bonding to the toxin. Our results show that simple chemosensors such as these could be developed for the detection of saxitoxin and possibly other PSP toxins, at concentrations comparable to those at which mice are sensitive.

Experimental section

General methods

IR spectra were recorded as thin films between NaCl plates or as KBr pellets. ^{1}H and ^{13}C NMR were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to residual chloroform; coupling constants are reported in Hz. ESI mass spectra were obtained by flow injection on a quadrupole ion trap mass spectrometer with methanol as the carrier solvent. High-resolution ESI mass spectra (HRMS/ESI) were obtained by using direct flow injection on a 9.4 T Fourier transform mass spectrometer. Dry solvents were freshly distilled before use: dichloromethane was distilled from calcium hydride and THF from sodium–benzophenone. Methanol, acetonitrile, and ethyl acetate were used as received. The hexane used in column chromatography was distilled before use. Water refers to high purity water that was obtained from the Milli-Q purification system. All reactions were performed under a nitrogen atmosphere.

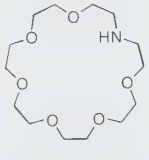
N-Benzyl monoaza-21-crown-7 (16)



To a solution of pentaethylene glycol (5.00 g, 21.0 mmol) in CH_2Cl_2 (120 mL) was added Et_3N (8.8 mL, 63.0 mmol), DMAP (1.28 g, 10.5 mmol), and TsCl (8.41 g, 44.1 mmol) at 0 °C. After stirring at RT for 1 h, NH_4Cl (satd. aq. sol., 50 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 20 mL), the organic phase was dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel using EtOAc–hexane (50%:50%), which gave **12** as an oil (11.2 g, 97%).

To a solution of bistosylate **12** (11.2 g, 20.5 mmol) in anhydr. THF (150 mL) was added *N*-benzyl diol **15** (4.00 g, 20.5 mmol) and NaH (2.46 g, 61.4 mmol; 60% dispersion in mineral oil, the oil was removed from the product chromatographically). The mixture was heated at 65 °C for 18 h. After cooling to RT, NH_4Cl (satd. aq. sol., 100 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 30 mL). The organic phase was dried with $MgSO_4$, evaporated under reduced pressure, and the residue was purified on alumina using EtOAc–hexane (50%:50%), which gave an oil (2.69 g, 33%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3523, 2870, 1643, 1453, 1124. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.78 (t, 4H, J = 5.8 Hz, CH_2), 3.57–3.68 (m, 26H, CH_2), 7.19–7.33 (m, 5H, CH-Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.78 (CH_2), 59.66 (CH_2-Bn), 70.00, 70.63, 70.78, 70.83, 70.90 (CH_2), 126.78, 128.11, 128.83 (*C*H-Ar), 139.71 (*C*-Ar). MS *m/e*: 398 [M^+ + 1]. HRMS calcd. for $C_{21}H_{36}NO6$ 398.2542 [MH^+]; found: 398.2531. Anal. calcd. for $C_{21}H_{35}NO_6$: C 63.45, H 8.87; found: C 63.29, H 8.88.

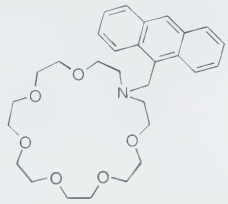
1-Aza-21-crown-7 (6)



A solution of **16** (2.69 g, 6.76 mmol) in MeOH (50 mL) containing Pd-C (10%, 200 mg) was stirred under 1 atm H_2 (balloon, 1 atm = 101.325 kPa) overnight. The catalyst was filtered through Celite and washed with MeOH (5 × 10 mL). After evaporation, the residue was purified on alumina using MeOH–EtOAc (15%:85%), which gave a colorless oil (1.94 g, 93%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3504, 2874, 1648, 1460, 1353, 1110. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.71

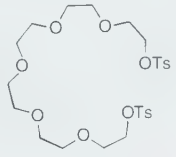
(t, 4H, J = 4.9 Hz, CH_2), 2.90 (1H, br, NH), 3.51–3.59 (m, 24H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 49.25 (CH_2), 70.53, 70.57, 70.69, 70.75 (CH_2). MS *m/e*: 308 [M^+ + 1]. HRMS calcd. for $C_{14}H_{30}NO_6$: 308.2073 [MH^+]; found: 308.2061.

1-(Anthracen-9-ylmethyl)-aza-21-crown-7 (3)



To a solution of **16** (0.301 g, 0.976 mmol) in anhydr. CH_3CN (30 mL) was added 9-(chloromethyl)anthracene (0.221 g, 0.976 mmol) and Cs_2CO_3 (0.954 g, 2.93 mmol). The mixture was heated at 80 °C for 2 h. After cooling to RT, NH_4Cl (satd. aq. sol., 30 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 20 mL), the organic phase was dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified on SiO_2 using EtOAc–MeOH (90%:10%), to give an oil (0.432 g, 89%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3487, 2868, 1630, 1451, 1117. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.90 (t, 4H, J = 5.7 Hz, CH_2), 3.56–3.73 (m, 24H, CH_2), 4.64 (s, 2H, CH_2), 7.44–7.55 (m, 4H, CH-Ar), 8.00 (d, 2H, J = 8.9 Hz, CH-Ar), 8.41 (s, 1H, CH-Ar), 8.60 (d, 2H, J = 8.9 Hz, CH-Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.75 (CH_2), 53.86 (CH_2), 70.10, 70.44, 70.85 (CH_2), 124.80, 125.35, 125.52, 127.41, 128.89 (CH-Ar), 130.57, 131.41, 131.43 (C-Ar). MS *m/e*: 498 [M^+ + 1]. HRMS calcd. for $C_{29}H_{40}NO_6$: 498.2855 [MH^+]; found: 498.2838.

Hexaethylene glycol ditosylate (13)



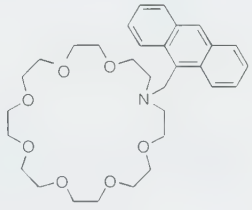
To a solution of hexaethylene glycol (3.36 g, 11.9 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Et_3N (5.0 mL, 35.7 mmol), DMAP (1.45 g, 5.96 mmol), and TsCl (5.68 g, 29.78 mmol). After stirring at RT for 30 min, NH_4Cl (satd. aq. sol., 20 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 20 mL) and the combined organic phase was dried with $MgSO_4$, condensed, and the residue was purified on silica gel using EtOAc–hexane (80%:20%) to EtOAc (100%), which gave a colorless oil (6.34 g, 90%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 2957, 2871, 1596, 1450, 1361, 1181. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.41 (s, 6H, CH_3-Ts), 3.54 (s, 8H, CH_2), 3.56–3.62 (m, 8H, CH_2), 3.63–3.66 (m, 4H, CH_2), 4.10–4.13 (m, 4H, CH_2), 7.30–7.33 (m, 4H, CH-Ts), 7.74–7.77 (m, 4H, CH-Ts). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.61 (CH_3-Ts), 68.60, 69.31, 70.45, 70.50, 70.55, 70.66 (6 × CH_2), 127.92 and 129.84 (8 × CH-Ar), 132.90 and 144.84 (4 × C-Ar). MS *m/e*: 591 [M^+ + 1]. Anal. calcd. for $C_{26}H_{38}O_{11}S_2$: C 52.87, H 6.48; found: C 52.75, H 6.59.

1-Aza-24-crown-8 (7)

To a solution of bistosylate **13** (19.56g, 33.1 mmol) in anhydr. THF (150 mL) was added *N*-benzyl diol **15** (6.45 g, 33.1 mmol) and NaH (3.97 g, 99.3 mmol; 60% dispersion in mineral oil, the oil was removed from the product chromatographically). The mixture was heated at 65 °C for 18 h. After cooling to RT, NH_4Cl (satd. aq. sol., 100 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 30 mL) and the combined organic phase was dried with $MgSO_4$, condensed, and the residue was purified on alumina using EtOAc–hexane (80%:20%), which gave compound **17** as an oil (3.85 g, 26%).

A solution of **17** (3.85 g, 8.71 mmol) in MeOH (50 mL) containing Pd-C (10%, 200 mg) was stirred under 1 atm H_2 (balloon) overnight. The catalyst was filtered through Celite and washed with MeOH (5 × 10 mL). After evaporation, the residue was purified on alumina using MeOH–EtOAc (15%:85%), which gave a colorless oil (2.91 g, 95%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3490, 2872, 1649, 1461, 1352, 1109. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.39 (s, br, NH), 2.72 (t, 4H, J = 5.1 Hz, CH_2), 3.51–3.60 (m, 28H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 49.09 (CH_2), 70.44, 70.56, 70.66, 70.67, 70.70, 70.80 (CH_2). MS *m/e*: 352 [M^+ + 1]. HRMS calcd. for $C_{16}H_{34}NO_7$: 352.2335 [MH^+]; found: 352.2326.

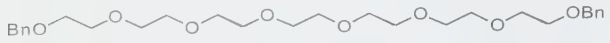
1-(Anthracen-9-ylmethyl)-aza-24-crown-8 (4)



To a solution of **7** (0.837 g, 2.38 mmol) in anhydr. CH_3CN (50 mL) was added 9-(chloromethyl)anthracene (0.450 g, 1.98 mmol) and Cs_2CO_3 (1.29 g, 3.96 mmol). The mixture was heated at 80 °C for 2 h. After cooling to RT, NH_4Cl (satd. aq. sol., 30 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 20 mL) and the combined organic phase was dried with $MgSO_4$, evaporated, and purified on alumina using EtOAc–hexane (60%:40%), which gave an oil (0.903 g, 84%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3486, 2868, 1636, 1452, 1119. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.90 (t, 4H, J = 5.7 Hz, CH_2), 3.55-

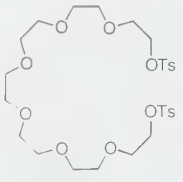
3.69 (m, 28H, CH_2), 4.64 (s, 2H, CH_2), 7.43–7.54 (m, 4H, CH-Ar), 8.00 (d, 2H, J = 8.9 Hz, CH-Ar), 8.40 (s, 1H, CH-Ar), 8.58 (d, 2H, J = 8.9 Hz, CH-Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.84 (*C*H_2), 53.79 (*C*H_2), 70.08, 70.46, 70.80, 70.82, 70.84, 70.87 (*C*H_2), 124.81, 125.36, 125.52, 127.41, 128.89 (*C*H-Ar), 130.58, 131.41, 131.43 (*C*-Ar). MS *m/e*: 542 [M^+ + 1]. HRMS calcd. for $C_{31}H_{44}NO_7$: 542.3118 [MH^+]; found: 542.3099.

1-((2-(2-(2-(2-(2-(2-(benzyloxy)ethoxy)ethoxy)-ethoxy)ethoxy)ethoxy)ethoxy)methyl)benzene



To a solution of triethylene glycol bistosylate (5.02 g, 10.93 mmol, synthesized according to literature procedure (13) with some modifications) in anhydr. THF (100 mL) was added 2-(2-(benzyloxy)ethoxy)ethanol (4.50 g, 22.96 mmol) and NaH (2.20 g, 54.68 mmol; 60% dispersion in mineral oil, the oil was removed from the product chromatographically). The mixture was heated at 65 °C for 1.5 h. After cooling to RT, NH_4Cl (satd. aq. sol., 100 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 30 mL) and the combined organic phase was dried with $MgSO_4$, evaporated, and the residue was purified on SiO_2 using EtOAc, which gave the product as an oil (4.825 g, 87%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3572, 2870, 1454, 1106. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.62–3.71 (m, 28H, CH_2), 4.58 (s, 4H, CH_2), 7.26–7.34 (m, 10H, CH-Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 69.44, 70.59, 70.61, 70.66, 73.23 (*C*H_2), 127.59, 127.74, 128.36 (*C*H-Ar), 138.29 (*C*-Ar). MS *m/e*: 507 [M^+ + 1]. Anal. calcd. for $C_{28}H_{42}O_8$: C 66.38, H 8.36; found: C 66.09, H 8.30.

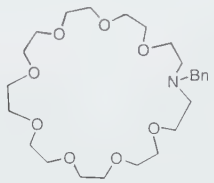
Heptaethylene glycol ditosylate (14)



The bisbenzyl ether prepared above (4.825 g, 9.52 mmol) was dissolved in MeOH (50 mL) containing Pd-C (10%, 300 mg) and stirred under 1 atm H_2 pressure (balloon) overnight. The catalyst was filtered through Celite and washed with MeOH (5 × 20 mL). After evaporation, the product (heptaethylene glycol) was obtained as a colorless oil (2.52 g, 81%) and used without further purification or characterization.

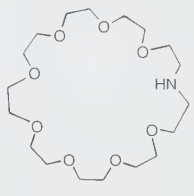
To this heptaethylene glycol (2.52 g, 7.73 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (3.2 mL, 23.2 mmol), DMAP (0.472 g, 3.87 mmol), and TsCl (3.09 g, 16.23 mmol) at 0 °C. After stirring at RT for 1 h, NH_4Cl (satd. aq. sol., 20 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 30 mL) and the combined organic phase was dried with $MgSO_4$, evaporated, and the residue was purified on silica gel using EtOAc to afford a colorless oil (4.71 g, 96%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3525, 2872, 1598, 1457, 1182. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 6H, CH_3-Ts), 3.56–3.68 (m, 24H, CH_2), 4.12–4.15 (m, 4H, CH_2), 7.32–7.34 (m, 4H, CH-Ts), 7.76–7.79 (m, 4H, CH-Ts). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.63 (*C*H_3-Ts), 68.63, 69.28, 70.48, 70.52, 70.54, 70.58, 70.70 (*C*H_2), 127.95 and 129.84 (*C*H-Ar), 132.95 and 144.82 (*C*-Ar). MS *m/e*: 635 [M^+ + 1]. Anal. calcd. for $C_{28}H_{42}O_{12}S_2$: C 52.98, H 6.67; found: C 53.16, H 6.59.

***N*-Benzyl monoaza-27-crown-9 (18)**



To a solution of bistosylate **14** (2.164 g, 3.41 mmol) in anhydr. THF (50 mL) was added *N*-benzyl diol **15** (0.798 g, 4.09 mmol) and NaH (0.545 g, 13.6 mmol; 60% dispersion in mineral oil, the oil was removed from the product chromatographically). The mixture was heated at 65 °C for 18 h. After cooling to RT, NH_4Cl (satd. aq. sol., 50 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 30 mL) and the combined organic phase was dried with $MgSO_4$, evaporated, and the residue was purified on alumina using EtOAc–hexane (80%:20%), which gave an oil (0.414 g, 25%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3525, 2871, 1644, 1456, 1113. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.79 (t, 4H, J = 5.9 Hz, CH_2), 3.52–3.71 (m, 34H, CH_2), 7.23–7.40 (m, 5H, CH-Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.79 (*C*H_2), 59.85 (*C*H_2-Bn), 69.93, 70.53, 70.75 (*C*H_2), 126.84, 128.15, 128.88 (*C*H-Ar), 139.45 (*C*-Ar). MS *m/e*: 486 [M^+ + 1]. HRMS calcd. for $C_{25}H_{44}NO_8$: 486.3067 [MH^+]; found: 486.3049. Anal. calcd. for $C_{25}H_{43}NO_8$: C 61.83, H 8.93; found: C 61.81, H 9.06.

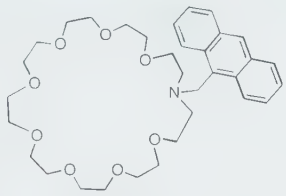
1-Aza-27-crown-9 (8)



A solution of **18** (0.369 g, 0.759 mmol) in MeOH (15 mL) containing Pd-C (10%, 50 mg) was stirred under 1 atm of H_2 (balloon) overnight. The catalyst was filtered through Celite and washed with MeOH (5 × 10 mL). After evaporation, the residue was purified on alumina using MeOH–EtOAc (15%:85%), which gave a colorless oil (0.274 g, 91%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3452, 2915, 1649, 1461, 1103. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, br, NH), 2.80 (t, 4H, J = 5.0 Hz, CH_2), 3.58–3.69 (m, 32H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 49.16 (*C*H_2), 70.52, 70.60, 70.71, 70.75

(CH_2). MS *m/e*: 396 [M^+ + 1]. HRMS calcd. for $C_{18}H_{38}NO_8$: 396.2597 [MH^+]; found: 396.2580. Anal. calcd. for $C_{18}H_{37}NO_8$: C 54.66, H 9.43; found: C 54.38, H 9.48.

1-(Anthracen-9-ylmethyl)-aza-27-crown-9 (5)



To a solution of **8** (0.210 g, 0.530 mmol) in anhydr. CH_3CN (20 mL) was added 9-(chloromethyl)anthracene (0.109 g, 0.482 mmol) and Cs_2CO_3 (0.314 g, 0.964 mmol). The mixture was heated at 80 °C for 2 h. After cooling to RT, NH_4Cl (satd. aq. sol., 30 mL) was added. The reaction mixture was extracted three times with CH_2Cl_2 (3 × 20 mL) and the combined organic phase was dried with $MgSO_4$, evaporated, and the residue was purified on alumina using EtOAc–hexane (60%:40%), which gave an oil (0.221 g, 78%). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3449, 2870, 1646, 1108. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.89 (t, 4H, J = 5.8 Hz, CH_2), 3.50–3.67 (m, 32H, CH_2), 4.64 (s, 2H, CH_2), 7.44–7.54 (m, 4H, CH-Ar), 7.99 (d, 2H, J = 8.8 Hz, CH-Ar), 8.41 (s, 1H, CH-Ar), 8.58 (d, 2H, J = 8.8 Hz, CH-Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.94 (CH_2), 53.79 (CH_2), 70.02, 70.32, 70.51, 70.69 (CH_2), 124.82, 125.33, 125.53, 127.42, 128.89 (*C*H-Ar), 130.52, 131.39, 131.42 (*C*-Ar). MS *m/e*: 586 [M^+ + 1]. HRMS calcd. for $C_{33}H_{48}NO_8$: 586.3380 [MH^+]; found: 586.3354.

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1,4,8,11-Tetra[2-aryl-1-diazenyl]-1,4,8,11-tetraazacyclotetradecanes — Synthesis, characterization, and X-ray crystallography of the first tetrakistriazenes to be reported[1]

Jeffery D. Clarke, Keith Vaughan, and Valerio Bertolasi

Abstract: The reactions of a series of arene diazonium salts with 1,4,8,11-tetraazacyclotetradecane (cyclam) afford the novel compounds, the 1,4,8,11-tetra[2-aryl-1-diazenyl]-1,4,8,11-tetraazacyclotetradecanes (**1a**–**1f**), which are the first examples of tetrakistriazenes to be reported. The tetrakistriazenes were characterized by IR spectroscopy, proton and carbon NMR, elemental analysis, high resolution electrospray mass spectrometry, and X-ray crystallography. The analogous reaction of a diazonium salt with 1,4,7-triazacyclononane or 1,5,9-triazacyclododecane yields the tristriazenes **2**, **3a**, and **3b**. The structures of compounds **1c** and **1e** were solved by X-ray crystallography at low temperature (150 K). Both molecules display a conformation where the four phenyltriazenyl groups point alternately upwards and downwards with respect to the mean macrocyclic plane.

Key words: triazene, tetrakistriazene, cyclam, tetraazacyclotetradecane, X-ray, NMR, cyclic polyamines.

Résumé : Les réactions d'une série de sels d'arènediazonium avec le 1,4,8,11-tétraazacyclotétradécane (= cyclame) conduit à la formation de nouveaux composés, les 1,4,8,11-tétra[2-aryl-1-diazényl]-1,4,8,11-tétraazatétradécanes (**1a**–**1f**) qui sont les premiers exemples de tétrakistriazènes à être rapportés. On a caractérisé les tétrakistriazènes par spectroscopie IR, par RMN du ^{1}H et du ^{13}C, par analyse élémentaire, par spectrométrie de masse à haute résolution à l'aide d'une ionisation par électronébulisation, et par diffraction des rayons X. La réaction analogue d'un sel de diazonium avec le 1,4,7-triazacyclononane ou le 1,5,9-triazacyclododécane conduit à la formation des tristriazènes **2**, **3a** et **3b**. Les structures des composés **1c** et **1e** ont été résolues par diffraction des rayons X à basse température (150 K). Les deux molécules présentent chacune une conformation dans laquelle les quatre groupes phényltriazényles sont orientés alternativement vers le haut et vers le bas par rapport au plan macromoléculaire moyen.

Mots clés : triazène, tétrakistriazène, cyclame, tétraazacyclotétradécane, rayons X, RMN, polyamines cycliques.

[Traduit par la Rédaction]

Introduction

1,4,8,11-Tetraazacyclotetradecane (cyclam) forms the most stable complexes with transition metal ions from both a thermodynamic and a kinetic viewpoint, among cyclic polyamines of varying ring size (1). The proclivity of cyclam to coordinate to Ni^{II} has been used to advantage in the template synthesis reaction (2), whereas covalent attachment of cyclam to a DNA-intercalator molecule, such as anthraquinone (3), influences interaction with DNA, causing substantially enhanced unwinding of the DNA. Metal complexation to the cyclam portion of the adduct increases the effect still further and metal-binding to DNA can cause sequence selective binding (4). Bicyclam derivatives composed of two cyclam units linked by an aliphatic linker have been identified as potent inhibitors of HIV type 1 and type 2 (5). This is just a fragment of the intense and vast literature dealing with the chemistry and pharmacology of cyclam. Surprisingly, the potential of cyclam to undergo diazo coupling reactions has apparently not been explored previously.

The reaction of a diazonium salt with a simple secondary amine is the conventional way to synthesize a stable triazene, e.g., $ArN{=}N{-}NR_2$ (6). Many triazenes have been shown to possess antitumor properties in experimental models (7) and a few triazenes are used clinically in the treatment of human malignant melanoma (8) and brain tumors (9). Bistriazenes are compounds that contain two triazene units in the same molecule; the chemistry of bistriazenes has recently been reviewed (10). Compounds that contain three or four triazene units per molecule, i.e., tristriazenes and

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This paper is dedicated to the invaluable contribution of Dr. Alfred Bader, whose entrepreneurial skills have provided starting materials for the pursuit of organic synthesis in laboratories everywhere.

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[1]This article is part of a Special Issue dedicated to Dr. Alfred Bader.

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tetrakistriazenes, are hitherto unknown, so it is with great satisfaction that we report here the synthesis of the first known examples of the classes of tristriazenes and tetrakistriazenes from the diazonium coupling reaction with the cyclic polyamines, 1,4,7-triazacyclononane, 1,5,9-triazacyclododecane, and 1,4,8,11-tetraazacyclotetradecane (cyclam). The potential medicinal chemistry resulting from the combination of the polyamine and triazene units in the same drug molecule is an exciting prospect.

Experimental

Melting points were determined on a hot-stage melting point apparatus and are uncorrected. IR spectra were obtained using Nujol mulls. ^{1}H and ^{13}C NMR chemical shifts were recorded in $CDCl_3$ or d_6-DMSO solutions at 27 °C (unless stated otherwise) and are relative to TMS as internal standard. Accurate mass measurements were performed by ESI-MS. The sample was dissolved in methanol or methanol–chloroform. The solution concentration was approximately 50–100 μmol/L. It was infused at a flow rate of 30 μL/min. For accurate mass measurement of $(M + H)^+$, tetralysine KKKK or Angiotensin III was used as the reference compound. The mass of $(M + H)^+$ from tetralysine was used as the lock mass.

Synthesis of the 1,4,8,11-tetra[2-aryl-1-diazenyl]-1,4,8,11-tetraazacyclotetradecanes (1a–1f)

General procedure

A solution of the aromatic amine (0.005 mol) in 3 mol/L hydrochloric acid (5.0 mL) was cooled to 0 °C and diazotized with a solution of sodium nitrite (0.38 g) in water (1.5 mL). A solution of 1,4,8,11-tetraazacyclotetradecane (0.20 g) in water (2.0 mL), with 3 mol/L HCl (0.5 mL) added, was added slowly with stirring to the cold diazonium salt solution and the mixture was left stirring for 0.5 h. The solution was then neutralized with saturated sodium bicarbonate solution, stirred in the cold for a further 1.0 h, and then filtered by vacuum filtration to afford the following tetrakistriazenes.

1,4,8,11-Tetra[2-(p-cyanophenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (1a)

Off-white powder, yield 80%, mp 251–254 °C (ethyl acetate). IR (cm^{-1}) ν_{max}: 2223 (CN), 844 (OOP). ^{1}H NMR (500 MHz, d_6-DMSO) δ: 2.17 (4H, v br), 3.84 (8H, br), 4.15 (8H, br s, H_a), 7.45 (8H, d, J = 6.7 Hz), 7.75 (8H, d, J = 6.7 Hz). MS (ESI+) *m/z* calcd. for $C_{38}H_{36}N_{16}$: 716 $(M + Na)^+$; found: 739.2.

1,4,8,11-Tetra[2-(p-nitrophenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (1b)

Yellow powder, yield 90%, mp 263 to 264 °C (from dimethylsulfoxide). IR (cm^{-1}) ν_{max}: 1514, 1333 (nitro group), 854 (OOP). ^{1}H NMR (500 MHz, d_6-DMSO) δ: 2.18 (4H, br), 3.93 (8H, br), 4.20 (8H, br s), 7.57 (8H, d, J = 9.0 Hz), 8.24 (8H, d, J = 9.5 Hz). Second species (rotamer with 40% relative intensity) δ: 2.94 (br), 3.99 (br), 4.20 (br), 7.42 (br), 8.31 (d, J = 9.0 Hz). Anal. calcd. for $C_{34}H_{36}N_{16}O_8$: C 51.25, H 4.55; found: C 51.14, H 4.57.

1,4,8,11-Tetra[2-(p-methoxycarbonylphenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (1c)

Pale yellow prisms, yield 75%, mp 215–217 °C (toluene). IR (cm^{-1}) ν_{max}: 1716 (C=O), 1278 (C-O), 859 (OOP). ^{1}H NMR (500 MHz, 47 °C, $CDCl_3$) δ: 2.19 (4H, quintet, J = 6.7 Hz), 3.79 (8H, t, J = 6.7 Hz), 3.91 (12H, s), 4.11 (8H, s), 7.33 (8H, d, J = 8.5 Hz), 7.92 (8H, d, J = 8.6 Hz). ^{13}C NMR (15 MHz, $CDCl_3$) δ: 30.40, 51.76, 120.21, 130.50, 145.03, 153.61, 166.75. HRMS (ESI) *m/z* calcd. for $C_{42}H_{49}N_{12}O_8$: 849.3796 $(M + H)^+$; found: 849.3799. Anal. calcd. for $C_{91}H_{104}N_{24}O_{16}$: C 61.07, H 5.82, N 18.79; found: C 61.24, H 5.95, N 18.45.

1,4,8,11-Tetra[2-(p-acetylphenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (1d)

Reddish-brown powder, yield 65%, mp 182–184 °C (ethanol). IR (cm^{-1}) ν_{max}: 1672 (C=O), 841 (OOP). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.19 (4H, br), 2.58 (12H, s), 3.80 (8H, br), 4.15 (8H, s), 7.35 (8H, d, J = 8.2 Hz), 7.84 (8H, d, J = 8.2 Hz). Anal. calcd. for $C_{42}H_{48}N_{12}O_4$: C 64.26, H 6.16; found: C 63.84, H 6.31.

1,4,8,11-Tetra[2-(p-methylphenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (1e)

White needles, yield 40%, mp 139 to 140 °C (ethanol). IR (cm^{-1}) ν_{max}: 825 (OOP). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.14 (4H, quintet, J = 6.7 Hz), 2.33 (12H, s), 3.73 (8H, t, J = 6.8 Hz), 4.02 (8H, s), 7.07 (8H, d, J = 8.2 Hz), 7.26 (8H, d, J = 8.2 Hz). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ: 21.04, 27.09, 49.54, 120.53, 129.44, 135.37, 148.32. HSQC NMR (125.77 MHz, $CDCl_3$) δ: 51.38 correlates with proton signal at 3.73 ppm. HRMS (ESI) *m/z* calcd. for $C_{38}H_{49}N_{12}$: 673.4203 $(M + H)^+$; found: 673.4202.

1,4,8,11-Tetra[2-(p-bromophenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (1f)

Off-white powder, yield 86%, mp 198 to 199 °C (propanol). IR (cm^{-1}) ν_{max}: 828 (OOP). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.12 (4H, quintet, J = 6.6 Hz), 3.72 (8H, t, J = 6.6 Hz), 4.04 (8H, s), 7.18 (8H, d, J = 8.5 Hz), 7.365 (8H, d, J = 8.5 Hz). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ: 26.99, 49.44, 119.18, 122.15, 131.92, 149.25. Anal. calcd. for $C_{34}H_{36}N_{12}Br_4$: C 43.90, H 3.89, N 18.03; found: C 44.07, H 3.87, N 17.74.

Application of this procedure with 1,5,9-triazacyclododecane in place of cyclam afforded the tristriazene **2**.

1,5,9-Tri[2-(p-cyanophenyl)-1-diazenyl]-1,5,9-triazacyclododecane (2)

Red-brown powder, yield 57%, mp 172–175 °C (ethanol). IR (cm^{-1}) ν_{max}: 2221 (CN), 844 (OOP). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.32 (6H, br quintet), 3.88 (12H, t, J = 6.0 Hz), 7.47 (6H, d, J = 8.5 Hz), 7.61 (6H, d, J = 8.5 Hz). Anal. calcd. for $C_{30}H_{30}N_{12}$: C 64.50, H 5.41; found: C 64.26, H 5.39.

Application of the general procedure with 1,4,7-triazacyclononane in place of cyclam afforded the tristriazenes **3a** and **3b**.

Table 1. Crystal data of compounds **1c** and **1e**.

Compound	**1c**	**1e**
Formula	$C_{42}H_{48}N_{12}O_8 \cdot {}^{1/2}(C_7H_8)$	$C_{38}H_{48}N_{12}$
M_r	894.99	672.88
Crystal system	Triclinic	Triclinic
Space group	*P*-1	*P*-1
a (Å)	11.6051(4)	11.7168(3)
b (Å)	11.9153(5)	17.2582(5)
c (Å)	17.1696(8)	20.0360(7)
α (°)	95.044(2)	106.296(1)
β (°)	94.902(2)	103.975(1)
γ (°)	106.145(3)	100.614(2)
V (Å^3)	2 256.7(2)	3 632.9(2)
Z	2	4
$D_{calcd.}$ (g cm^{-3})	1.317	1.230
F(000)	946	1440
μ (cm^{-1})	0.93	0.77
Temperature (K)	150	150
Crystal form, color	Irregular, colorless	Prismatic, colorless
Crystal size (mm)	0.16 × 0.10 × 0.07	0.25 × 0.10 × 0.05
θ_{min}–θ_{max} (°)	2.48–20.81	2.55–22.21
Measured reflections	33 849	53 975
Index ranges	$-11 \le h \le 11$, $-11 \le k \le 11$, $-17 \le l \le 17$	$-12 \le h \le 12$, $-18 \le k \le 18$, $-21 \le l \le 20$
Unique reflections	4 695	9 150
R_{int}	0.090	0.123
Obs. reflections [$F^2 \ge 2\sigma(F^2)$]	2 738	5 277
$R(F^2)$ (Obs. reflections)	0.0504	0.0566
$wR(F^2)$ (All reflections)	0.1294	0.1393
No. of parameters	617	901
GOF	0.969	1.006
$\Delta\rho_{min}$, $\Delta\rho_{max}$	–0.20, 0.19	–0.24, 0.27

1,4,7-Tri[2-(p-cyanophenyl)-1-diazenyl]-1,4,7-triazacyclononane (3a)

Light-brown powder, yield 88%, mp 253–256 °C (ethanol). IR (cm^{-1}) ν_{max}: 2222 (CN), 845 (OOP). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.95–4.37 (12H, m), 7.45 (6H, d, *J* = 8.4 Hz), 7.60 (6H, d, *J* = 8.4 Hz). Anal. calcd. for $C_{27}H_{24}N_{12}$: C 62.78, H 4.68, N 32.54; found: C, 62.87, H 4.64, N 31.84.

1,4,7-Tri[2-(p-methylphenyl)-1-diazenyl]-1,4,7-triazacyclononane (3b)

Cream-coloured needles, yield 61.5%, mp 152–155 °C (ethanol). IR (cm^{-1}) ν_{max}: 822 (OOP). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (9H, s), 3.91 (6H, v br), 4.19 (6H, v br), 7.12 (6H, d, *J* = 8.1 Hz), 7.31 (6H, d, *J* = 8.2 Hz). ^{13}C NMR (125.77 MHz, 223 K, $CDCl_3$) δ: 21.51, 53.18, 120.54, 129.83, 135.75, 148.10. Second species (rotamer) δ: 21.51, 49.28, 120.6, 129.7, 135.9, 147.9. Anal. calcd. for $C_{27}H_{33}N_9$: C 67.06, H 6.88, N 26.07; found: C 66.76, H 6.60, N 25.82.

Crystallography

X-ray diffraction data for compounds **1c** and **1e** were collected at low temperature (150 K) on a Nonius Kappa CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.7107 Å).[3] The structures were solved by direct methods (SIR97) (11) and refined (SHELXL-97) (12) by full-matrix least-squares with anisoptropic non-H and hydrogen atoms included on calculated positions riding on their carrier atoms. The methoxy carbonyl moiety C41, O7, O8, C42 in **1c** is disordered and the methyl group $C42H_3$ has been refined over two positions with the respective occupancies of 0.579(9) and 0.421(9). The crystal contains half a molecule of toluene per molecule of **1c**, disordered around a crystallographic centre of symmetry. It has been refined over

[3] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5059. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 276886 and 292214 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Table 2. Selected bond distances and angles in 1,4,8,11-tetra[2-(*p*-methoxycarbonylphenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (**1c**).

Bond distances (Å)	
N1—N2	1.340(4)
N1—C1	1.469(5)
N1—C10	1.463(5)
N2—N3	1.277(5)
N3—C11	1.427(5)
N4—N5	1.309(4)
N4—C2	1.457(5)
N4—C3	1.467(4)
N5—N6	1.287(4)
N6—C19	1.428(5)
N7—N8	1.341(4)
N7—C5	1.465(5)
N7—C6	1.465(5)
N8—N9	1.277(5)
N9—C27	1.426(4)
N10—N11	1.314(4)
N10—C7	1.466(4)
N10—C8	1.456(5)
N11—N12	1.283(5)
N12—C35	1.419(4)
Bond angles (°)	
N2-N1-C1	114.3(3)
N2-N1-C10	123.5(3)
C1-N1-C10	120.8(3)
N1-N2-N3	113.2(3)
N2-N3-C11	112.9(3)
N5-N4-C2	123.8(3)
N5-N4-C3	117.3(3)
C2-N4-C3	118.7(3)
N4-N5-N6	114.9(3)
N5-N6-C19	110.7(3)
N8-N7-C5	114.7(3)
N8-N7-C6	121.6(3)
C5-N7-C6	119.7(3)
N7-N8-N9	112.7(3)
N8-N9-C27	112.9(3)
N11-N10-C7	122.3(3)
N11-N10-C8	118.0(3)
C7-N10-C8	119.2(3)
N10-N11-N12	115.2(3)
N11-N12-C35	110.8(3)

Table 3. Selected bond distances and angles in 1,4,8,11-tetra[2-(*p*-methylphenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (**1e**).

	Molecule A	Molecule B
Bond distances (Å)		
N1—N2	1.344(3)	1.332(4)
N1—C1	1.453(5)	1.464(4)
N1—C10	1.474(4)	1.472(5)
N2—N3	1.273(4)	1.274(4)
N3—C11	1.426(4)	1.430(4)
N4—N5	1.322(4)	1.336(4)
N4—C2	1.449(5)	1.446(5)
N4—C3	1.461(4)	1.465(5)
N5—N6	1.284(5)	1.268(5)
N6—C18	1.426(4)	1.434(4)
N7—N8	1.345(4)	1.337(4)
N7—C5	1.469(5)	1.473(4)
N7—C6	1.458(5)	1.462(5)
N8—N9	1.272(5)	1.278(3)
N9—C25	1.430(4)	1.413(4)
N10—N11	1.347(4)	1.330(4)
N10—C7	1.449(4)	1.456(4)
N10—C8	1.456(5)	1.456(5)
N11—N12	1.279(5)	1.279(5)
N12—C32	1.427(4)	1.435(4)
Bond angles (°)		
N2-N1-C1	121.8(3)	122.0(3)
N2-N1-C10	114.6(3)	115.3(3)
C1-N1-C10	121.6(3)	118.7(3)
N1-N2-N3	113.4(3)	115.4(3)
N2-N3-C11	112.1(3)	111.3(3)
N5-N4-C2	122.3(3)	122.3(3)
N5-N4-C3	118.6(3)	116.3(3)
C2-N4-C3	119.1(3)	119.4(3)
N4-N5-N6	114.6(3)	113.6(3)
N5-N6-C18	111.0(3)	112.2(3)
N8-N7-C5	114.1(3)	114.3(3)
N8-N7-C6	120.8(3)	121.5(3)
C5-N7-C6	119.9(3)	118.8(3)
N7-N8-N9	113.8(3)	114.5(3)
N8-N9-C25	112.3(3)	112.0(3)
N11-N10-C7	120.9(3)	122.4(3)
N11-N10-C8	117.4(3)	115.6(3)
C7-N10-C8	119.1(3)	119.8(3)
N10-N11-N12	112.6(3)	114.8(3)
N11-N12-C32	113.2(3)	110.4(3)

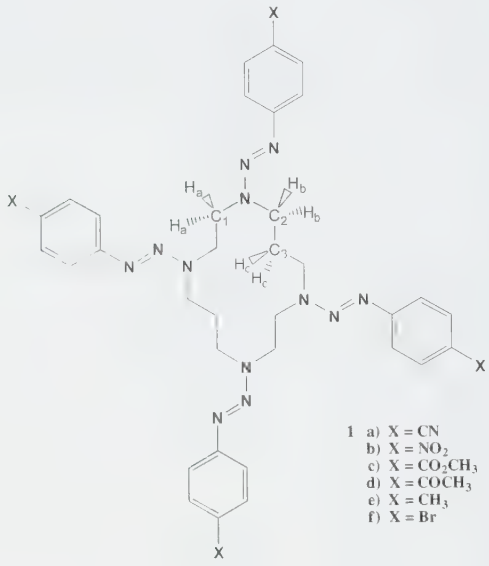
two positions with occupancies of 0.5. All other calculations were performed using the PARST system of programs (13).

The crystal data and refinement parameters are summarized in Table 1. Selected bond distances and angles are given in Tables 2 and 3.

Results and discussion

1,4,8,11-Tetraazacyclotetradecane (cyclam) reacted favorably in aqueous solution with a variety of diazonium salts to afford the novel 1,4,8,11-tetra[2-aryl-1-diazenyl]-1,4,8,11-tetraazacyclotetradecanes (**1a–1f**) in excellent yields, as high as 90%. The diazonium salt was used in 25% excess above the required stoichiometric ratio of 4:1. Raising the amount of diazonium salt to 50% excess had little effect on the yield, with the exception of the *p*-bromo derivative (**1f**) that went from 35% to 86% yield. The 1,4,8,11-tetra[2-aryl-1-diazenyl]-1,4,8,11-tetraazacyclotetradecanes are stable solids that crystallize, mostly from polar solvents, and it was possible to grow small crystals from two of the compounds in the series for X-ray crystallography. The tetrakistriazenes have been identified by spectroscopic methods. The IR spectra display the characteristic bands of the particular aryl substituents, e.g., nitrile, carbonyl, and nitro groups. The ^{1}H NMR spectra are consistent with the assigned structures, although significant broadening of NMR signals was evident

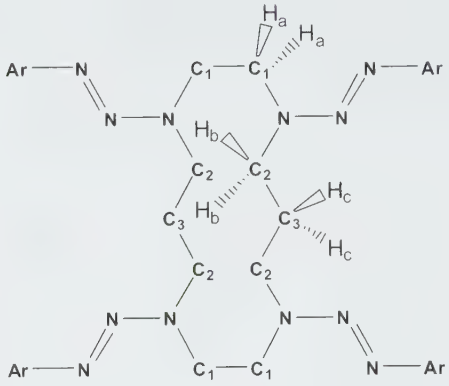
owing to the familiar phenomenon of restricted rotation around the N—N bonds of the triazene moieties (14). The protons attached to the carbon atoms of the 14-membered macrocyclic ring are clearly distinguished (see proton and carbon labelling in Fig. 1 to clarify the following discussion).



The eight equivalent protons of the ethylene spacers, labeled H_a attached to C_1, give rise to a singlet at ca. 4.2 ppm, integrating for 8H as expected, with varying line width from quite sharp in **1e** and **1f** to very broad in **1b**. The multiplicity of the protons of the propylene spacers, H_b and H_c, is resolved in compounds **1c**, **1e**, and **1f**. In these spectra, the H_b protons appear as an eight-proton triplet at ca. 3.8 ppm and the H_c protons are resolved as a four-proton quintet at ca. 2.2 ppm. The analogous signals in the spectra of **1a**, **1b**, and **1d** are too broad for the multiplicity to show. In all compounds (**1a**–**1f**) the aromatic protons give rise to the expected AA′BB′ pattern and the protons of the methyl groups in the X-substituents of **1c**–**1e** are observed at the predicted chemical shifts.

A VT NMR experiment was conducted with compound **1c** in $CDCl_3$ to attempt to slow down the rotational equilibrium in the triazene units so that resolution would be improved. However, lowering the temperature of the solution of **1c** resulted in further broadening of the proton signals, while raising the temperature to 47 °C gave a nicely resolved spectrum with the triplet of H_b and the quintet of H_c clearly evident. Evidently, raising the temperature of the solution causes the faster exchange of rotamers and individual multiplets are observed. A different manifestation of the dynamic rotation is observed in the case of the *p*-nitro derivative (**1b**); this tetrakistriazene affords a proton spectrum with two clear sets

Fig. 1. Proton and carbon labelling in structures **1a**–**1f**.



of broad signals that we ascribe to the rotamers resulting from the restricted rotation around the N—N bond (14). This total doubling of the spectra is only seen in the case of the *p*-nitro compound; the strongly electron-withdrawing nitro group promotes the resonance (eq. [1]) that gives the N—N bond greater double-bond character.

^{13}C NMR analysis was not feasible with compounds **1a**, **1b**, and **1d** owing to the combination of low solubility and the broadening of NMR signals because of rotational dynamics. However, compounds **1c** and **1f** gave partial ^{13}C NMR spectra with not all macrocyclic ring carbons showing. Only compound **1e** gave a complete set of ^{13}C signals, with the aid of HSQC spectroscopy (Fig. 2) to detect the signal from C2. These limited data give the general assignments of C1 at 49.5 ppm, C2 at 51.0 ppm, and C3 at ca. 27.0 ppm, together with the predicted aromatic carbon signals.

Further analytical evidence for the structures of the tetrakistriazenes was obtained from elemental analysis of compounds **1b**–**1f** and from electrospray mass spectrometry with compounds **1a**, **1c**, and **1e**. The molecular ions of these compounds did not survive the conditions of electron ionization mass spectrometry. Unequivocal proof of the novel tetrakistriazene structure is evident in the X-ray crystallography of compounds **1c** and **1e**.

An ORTEP (15) view of the molecule of the tetrakistriazene **1c** is shown in Fig. 3, in which the molecule is viewed more or less through the plane of the cyclam core. The best view of the 14-membered macrocycle (without substituents for the sake of clarity) is shown in the ORTEP diagram of Fig. 4. The molecule of **1c** displays a conformation where the four phenyltriazenyl groups point alternately upwards and downwards with respect to the mean macrocyclic plane. All the phenyltriazenyl groups are almost planar and those on the same side are roughly parallel, but the phenyl ring couples (C11-C16)–(C27-C32) and (C19-C24)–(C35-C40) form angles of 11.0(2)° and 10.2(1)°, respectively. An important point to make regarding this structure is the conjugation degree within the triazene moieties that is greater for

[1]

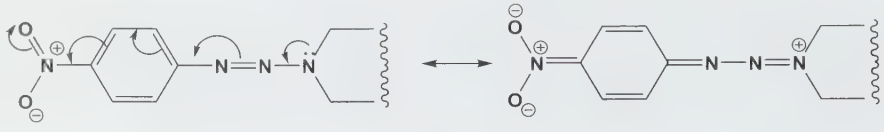


Fig. 2. High-field region of the HSQC ($CDCl_3$) spectrum of 1,4,8,11-tetra[2-(*p*-tolyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (**1e**), showing the correlation of protons H_a, H_b, and H_c with carbons C1, C2, and C3, respectively.

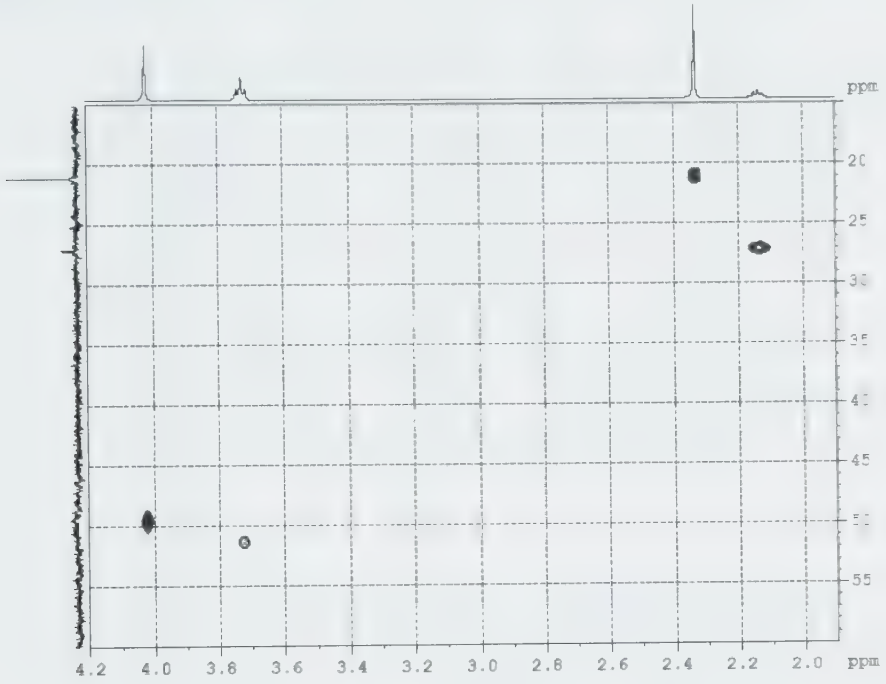
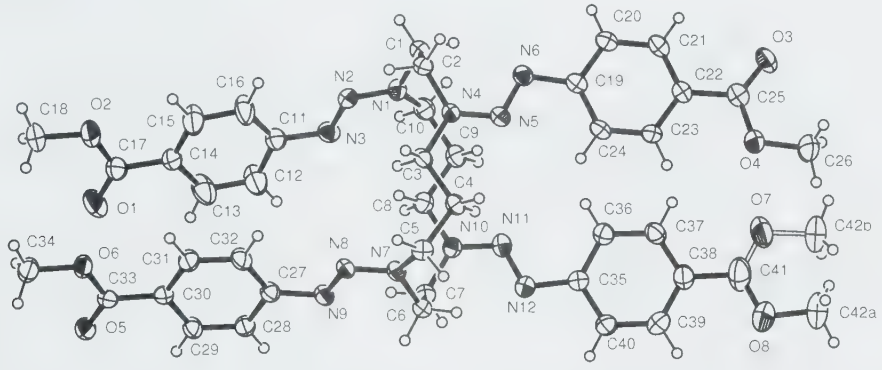


Fig. 3. ORTEP view of 1,4,8,11-tetra[2-(*p*-methoxycarbonyl-phenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (**1c**), displaying the thermal ellipsoids at 40% probability.

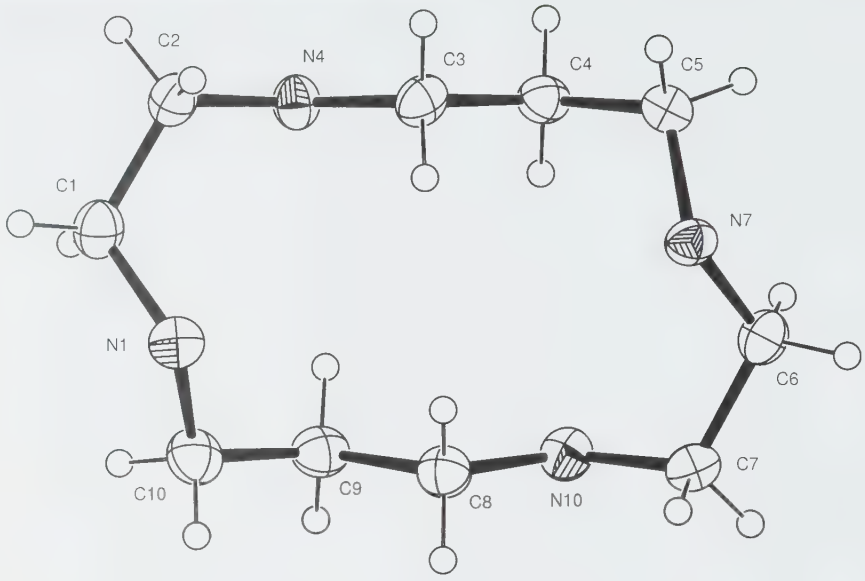


N4-N5=N6 and N10-N11=N12 situated on one side with respect to N1-N2=N3 and N7-N8=N9 on the other side.

Although the N1—N2 and N7—N8 single bonds of 1.340(4) and 1.341(4) Å and the N2=N3 and N8=N9 double bonds of 1.277(5) and 1.277(5) Å indicate significant conjugation within the triazene moieties, the corresponding distances for the other triazenes, N4—N5 = 1.309(4) Å, N5=N6 = 1.287(4) Å, N10—N11 = 1.314(4) Å, and N11=N12 = 1.283(5) Å, show, however, a much more pronounced degree of conjugation. The macrocycle shown in Fig. 3 displays a rectangular cavity with the following internal distances: N1··N7 = 5.311(4) Å, N4·N10 = 4.527(4) Å, N4·C9 = 3.609(5) Å, and N10·C4 = 3.623(5) Å.

The structure of the *p*-tolyl analogue in the series (**1e**) is quite complicated because the asymmetric unit contains two independent molecules; the ORTEP diagrams of these two species are shown in Figs. 5*a* and 5*b*, which clearly support our conclusions that the connectivity in this compound is the tetrakistriazene structure. The best projections of the 14-membered macrocycles (without substituents) are shown in Figs. 6*a* and 6*b*. Both molecules display similar conformations with respect to those observed in compound **1c**, where the four phenyltriazenyl groups point alternately upwards and downwards from the mean macrocyclic plane. All the phenyltriazenyl groups are almost planar and the phenyl groups, on the same sides, form the following dihedral angles: C11-C16-C25-C30 of 15.9(1)° and 3.7(1)° and C18-C23-C32-C37 of 10.4(1)° and 11.8(1)° for molecules A and B, respectively. All the triazene groups display similar conjugations with N—N single bonds in the range 1.32–1.35 Å

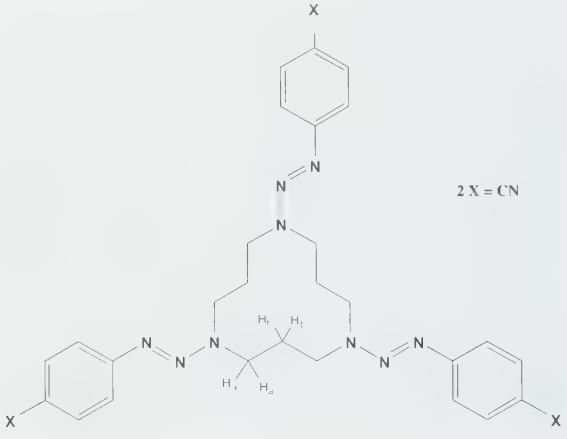
Fig. 4. ORTEP view of the heterocyclic cyclam core of the molecule of **1c**.



and N=N double bonds in the range 1.27–1.28 Å. The macrocycles, shown in Figs. 6*a* and 6*b*, exhibit slightly different conformations displaying cavities with the following internal distances: N1···N7 = 5.378(4) Å, N4···N10 = 4.470(4) Å, N4···C9 = 3.564(5) Å, and N10···C4 = 3.586(5) Å for molecule A; N1···N7 = 5.346(4) Å, N4···N10 = 4.556(4) Å, N4···C9 = 3.665(5) Å, and N10···C4 = 3.663(5) for molecule B.

This paper represents a major advance in the chemistry of triazenes, moving in one leap from the bistriazene front to the previously unknown tetrakistriazene. Of course, there is a missing link in this picture, which is the tristriazene represented by structures **2** and **3**. Accordingly, we investigated the reaction of 1,5,9-triazacyclododecane with *p*-cyanobenzenediazonium chloride, which afforded the tristriazene, 1,5,9-tri[2-(*p*-cycanophenyl)-1-diazenyl]-1,5,9-triazacyclododecane (**2**). The ^{1}H NMR spectrum of **2** is decidedly simple and consistent with the tristriazene structure. The protons of the three equivalent three-carbon spacers appear as the expected six-proton quintet at 2.32 ppm, assigned to the protons H_b of the central methylene groups, and a 12-proton triplet at 3.88 ppm, assigned to the protons H_a of the N-CH_2 groups.

Reaction of 1,4,7-triazacyclononane with diazonium salts afforded the tristriazenes **3a** and **3b**. However, the NMR spectra of these molecules are not as simple as expected; in principle, the protons of the triazacyclononane methylene groups should be equivalent. In the ^{1}H NMR spectrum of **3b**, the peaks are broad but, significantly, they integrate for the correct number of protons. The tolyl methyl protons resonate at 2.34 ppm with an integration for nine protons and the broadened aromatic AA′BB′ system integrates for 12 protons. The methylene protons of the heterocyclic ring appear as two very broad signals at 3.91 and 4.19 ppm, each integrating for 6H. We suggest that these two methylene signals can be assigned to the axial and equatorial hydrogen atoms



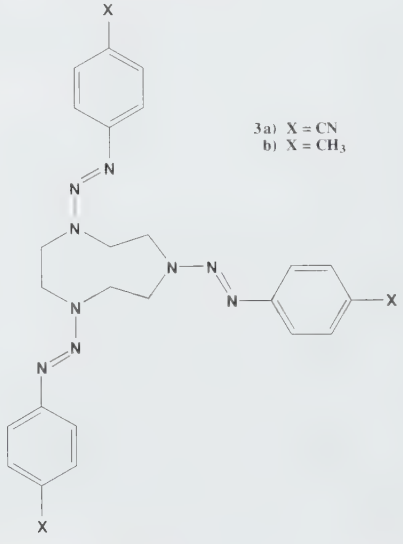
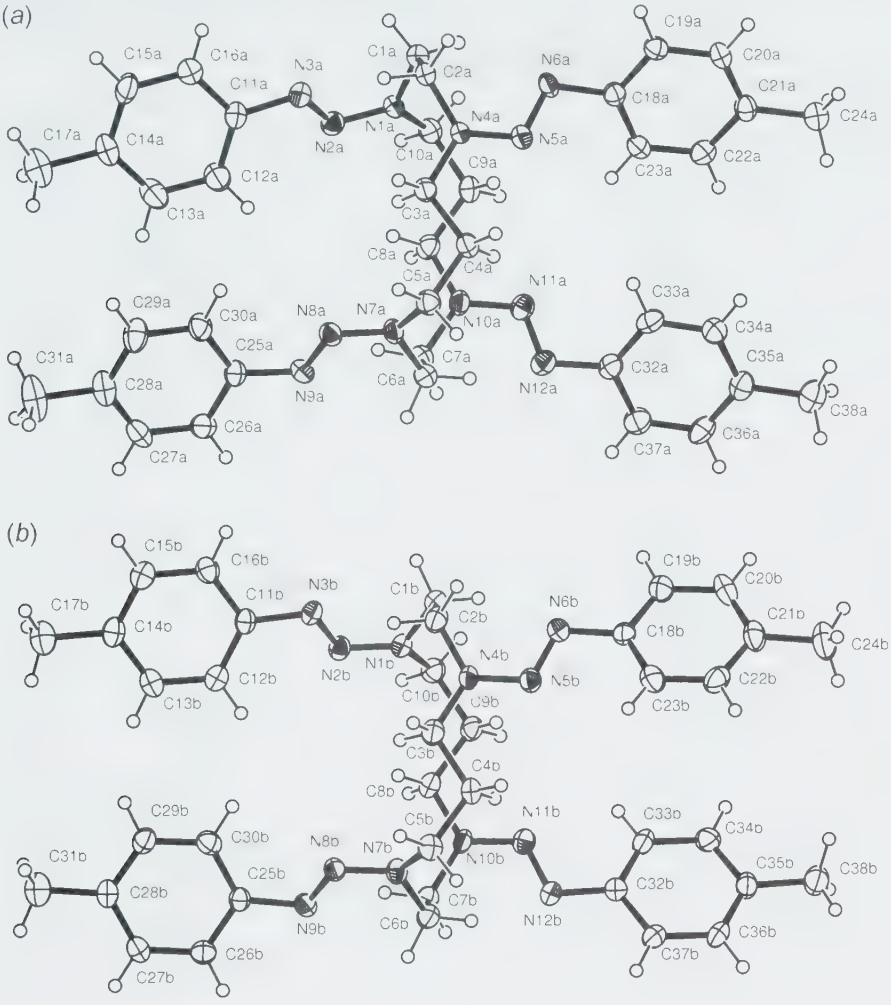


Fig. 5. ORTEP views of the two independent molecules of 1,4,8,11-tetra[2-(*p*-methylphenyl)-1-diazenyl]-1,4,8,11-tetraazacyclotetradecane (**1e**), displaying the thermal ellipsoids at 40% probability.



in the nine-membered ring (see Fig. 7). The broadening of the signals is ascribed to the rotational dynamics of the triazene moieties (14). Indeed, the two rotameric forms of **3b** are clearly seen in the ^{13}C NMR spectrum, and each carbon atom is detected. The relative intensity of the signals from the two rotamers indicates that the major rotamer is present in 60%–70% abundance. Significantly, the equivalent carbon atoms of the heterocyclic ring are detected at 49.28 and 53.18 ppm.

Tristriazene **3a** did not have sufficient solubility to enable ^{13}C NMR analysis, but the ^{1}H NMR spectrum of **3a** showed a complex set of signals for the methylene protons of the heterocyclic ring. The multiplet observed in the range 3.95–4.37 ppm could be interpreted as a group of signals centred around 4.03 ppm and a second group around 4.25 ppm. The two groups are assigned to the axial and equatorial hydrogens (Fig. 6) and the multiple peaks in each group could be assigned to the various rotamers arising from the restricted rotation around the N—N bond in the triazenes (14).

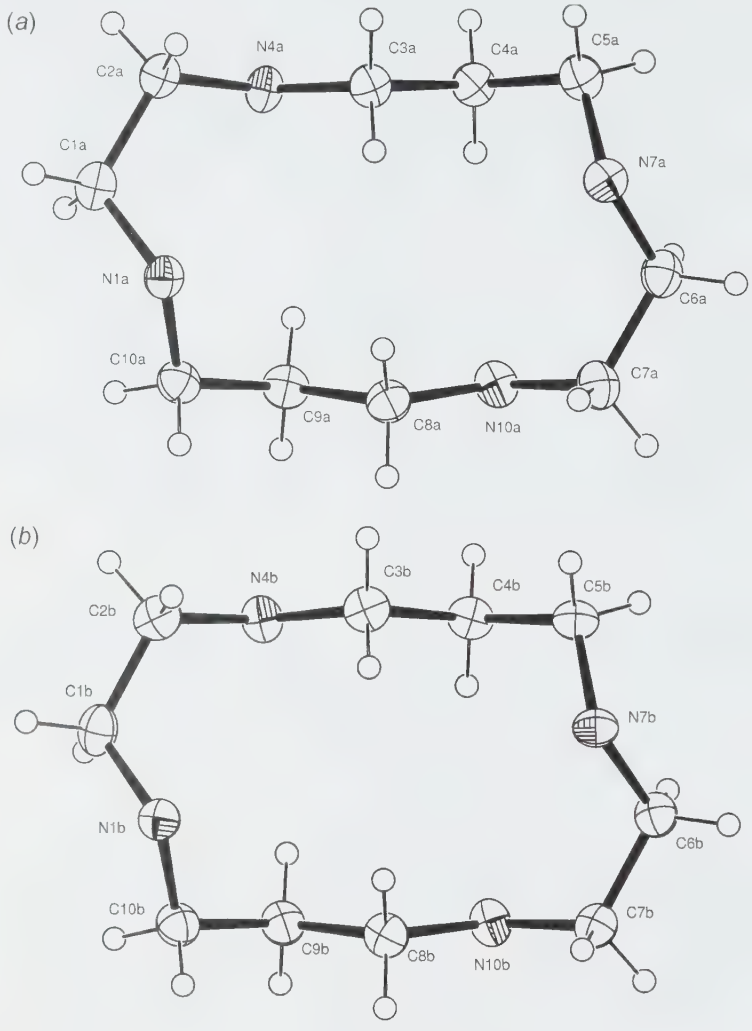
Conclusion

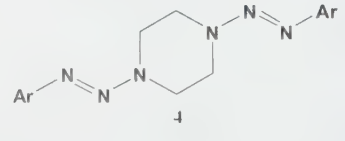
The results reported in this paper clearly show that tristriazenes and tetrakistriazenes can be synthesized and characterized. These results further our extensive research into the synthesis of bistriazenes of various types. Notably, our recent studies have been involved with the general synthesis of triazene derivatives of 1,*x*-diazacycloalkanes. For example, diazonium coupling with piperazine affords the stable bis-1,4-di-(2-aryl-1-diazenyl)-piperazines (**4**) (16). Analogous coupling of diazonium salts with homopiperazines affords the bistriazene series **5** (17).

Acknowledgements

The authors are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for a Discovery Grant to the principal author (KV) and an Undergraduate Summer Research Award (2004) to Jeff Clarke. Financial

Fig. 6. ORTEP views of the best projections of the 14-membered macrocycles (without substituents) of compound **1e**.





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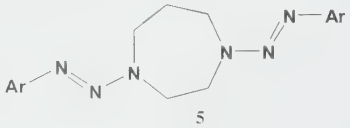

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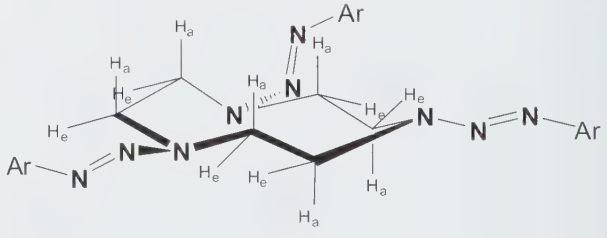
Fig. 7. A representation of the tristriazene structure **3** showing the orientation of the axial (H_a) and equatorial (H_e) hydrogen atoms of the triazacyclononane ring.



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A chiral auxiliary cleavable by ring-closing alkene metathesis — Efficient synthesis of chiral nonracemic cycloalkenes[1]

Luc Boisvert, Francis Beaumier, and Claude Spino

Abstract: *p*-Menthane-3-carboxaldehyde is a readily available chiral auxiliary used to prepare cycloalkenes and heterocycles bearing a chiral tertiary or quaternary carbon of high enantiomeric purity. The auxiliary is available in both enantiomeric forms and is inexpensive and recyclable. It is cleaved by a ring-closing alkene metathesis reaction directly yielding the cycloalkene.

Key words: chiral auxiliary, cleavage reaction, cyclization, ring-closing alkene metathesis, enantioenriched cycloalkenes.

Résumé : Le *p*-menthane-3-carboxaldéhyde est utilisé comme auxiliaire chiral pour fabriquer des cycloalcènes et des hétérocycles contenant un centre carboné tertiaire ou quaternaire de pureté énantiomérique élevée. L'auxiliaire est disponible dans les deux séries énantiomériques et est peu dispendieux et recyclable. Il est clivé par une réaction de fermeture de cycle par métathèse d'alcènes menant directement au cycloalcène.

Mots clés : auxiliaire chiral, réaction de clivage, cyclisation, fermeture de cycle par métathèse d'alcènes, cycloalcènes énantioenrichis.

Introduction

Chiral auxiliaries are exceptionally useful tools in synthetic organic chemistry because many of them achieve high levels of asymmetric induction on a wide range of substrates (1). One inherent drawback to their use is the need to install and cleave the auxiliary, which adds two chemical steps to the synthesis of the target molecule. This disadvantage can, however, be minimized if one of these two steps consists of a chemical transformation that would have been carried out eventually as part of the synthetic plan. This is not the case for the majority of chiral auxiliaries found in the literature that are cleaved either by addition–elimination reactions on polarized π systems (e.g., hydride reduction of C=O functional groups) or by hydrolysis of acetal-like functionalities (1). In addition, while other auxiliary-specific cleaving reactions have been developed (e.g., ozonolysis of C=C bonds (2) or hydrogenolysis of benzylic groups (3)), there is still a need to widen the arsenal of available methods to cleave chiral auxiliaries.

In this report, we disclose the cleavage of a chiral auxiliary by ring-closing alkene metathesis (RCM) (4) to yield highly enantioenriched cycloalkenes. To the best of our knowledge, this constitutes the first example of a chiral auxiliary cleavable by a RCM reaction (5, 6). Using our strategy, the cleavage of the auxiliary becomes intrinsic to the synthetic strategy and does not add extra steps en route to the final target.

Synthesis of RCM precursors[3]

The sequence of reactions starts with the synthesis of allylic alcohols **7a**–**7e** from *p*-menthane-3-carboxaldehyde **3** (7). These allylic alcohols were prepared by one of three methods (Scheme 1 and Table 1).

Method A involves the $AlMe_3$-promoted addition of vinyllithium reagents **6a** to aldehyde **3** (8). In this manner, a mixture of diastereomeric allylic alcohols, which are easily separated by flash chromatography, is obtained with selectivities ranging from ca. 10:1 to more than 100:1, favouring the Felkin–Ahn adducts (i.e., **7** as illustrated). Method B involves the addition of vinylalanes **6b**, generated by the zirconium-catalyzed methylalumination of alkynes (9) to aldehyde **3**. In Method C, lithium acetylides **2** are added to aldehyde **3** in the presence of dry cerium trichloride to afford a mixture of diastereomeric propargylic alcohols **4** (10).

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[3]Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5067. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

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Scheme 1.

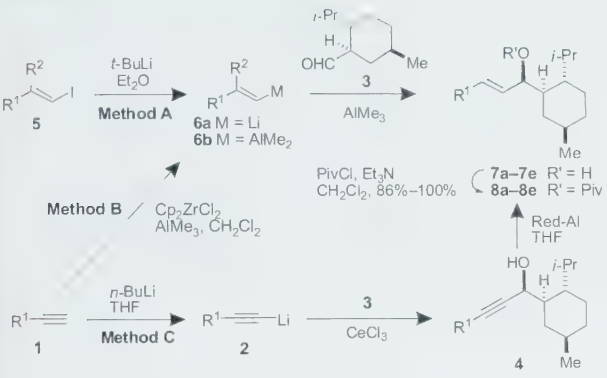


Table 1. Preparation of allylic alcohols **7a**–**7e** (cf. Scheme 1).

Entry	R1	R2	Compound	Yield of **7**[a] (%), (dr)
1	Bn	H	**7a**	64,[b] 170:1
2	$TBSOCH_2$	H	**7b**	43,[c] 3.5:1[d]
3	Bn	Me	**7c**	76,[e] 11:1
4	$TBSO(CH_2)_4$	Me	**7d**	68,[e] 11:1
5	$MOMOCH_2$	H	**7e**	37,[c] 3.1:1[d]

[a]Isolated yield of diastereomerically pure allylic alcohol **7**.
[b]Method A.
[c]Method C (yield of **7** over two steps).
[d]DR of **4** from the addition of **2** to **3**.
[e]Method B.

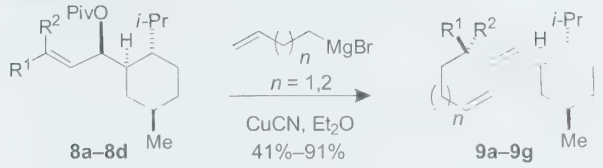
These propargylic alcohols are easily separated and converted to geometrically pure *E* allylic alcohols **7** by reduction with Red-Al. The alcohols **7a**–**7e** were then converted to the corresponding allylic pivalate esters **8a**–**8e** in excellent yields.

Cyanocuprates, derived from Grignard reagents, displaced the pivalate esters stereospecifically (anti to the leaving group with complete transfer of chirality) with 100% stereoselectivity (reaction on the conformer with minimized $A^{1,3}$ strain, yielding *E* alkenes) and with exclusive S_N2' regioselectivity (no S_N2 adduct detected by GC) (7, 11). Thus, cuprate adducts **9a**–**9g** (precursors to five- and six-membered rings for the subsequent RCM reactions) were prepared from pivalate esters **8a**–**8d** (Scheme 2). It should be noted that both absolute stereochemistries at the newly created chiral center in adducts **9** are accessible since both enantiomers of *p*-menthane-3-carboxaldehyde **3** are available, the double-bond geometry in **8** can be controlled, and the order of introduction of the different substituents on the new chiral center can be varied (7).

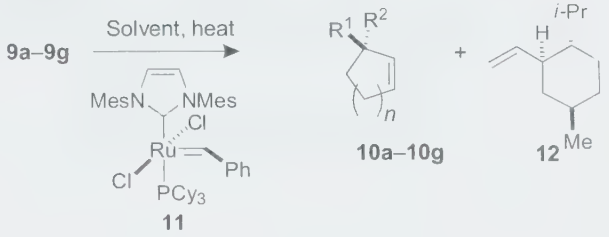
RCM reactions

After screening different ruthenium-based metathesis catalysts (see Supplementary data),[3] it was found that the formation of cycloalkenes **10** by a RCM reaction was best performed using the Grubbs–Nolan catalyst **11** (12) (Scheme 3). For precursors of five-membered rings bearing a tertiary carbon center (**9a** and **9c**) very mild conditions (**11** (1 mol%), CH_2Cl_2, 40 °C, 3 h) resulted in smooth transformation to cycloalkenes **10a** and **10c** (Table 2, entries 1 and

Scheme 2.



Scheme 3.



3). The only detectable (^{1}H NMR) products in the crude reaction mixtures were the cycloalkenes **10** and compound **12**.

Cyclization of precursors of six-membered rings bearing a tertiary carbon center (**9b** and **9d**) necessitated harsher conditions (**11** (10 mol%), $ClCH_2CH_2Cl$, 83 °C, 3 h) to avoid the formation of the corresponding dimers **13b** and **13d** by a competitive cross-metathesis reaction (Fig. 1). Under these conditions, the RCM reactions occurred smoothly to provide cycloalkenes **10b** and **10d** in good yields (Table 2, entries 2 and 4), with only trace amounts of **13** being detected.

Adducts **9e**–**9g**, bearing a quaternary carbon, presented a greater challenge. Minimizing the production of dimer **13** was crucial because when **13e** (derived from **9e**) was treated under RCM conditions (with or without an atmosphere of ethylene), no useful amount of **10e** could be obtained. Ultimately, it was found that higher dilution and temperatures were efficient in decreasing the amount of **13**. However, these conditions sometimes caused side-reactions, like the well-documented alkene isomerization (13), such that cycloalkenes **10e** and **10g** were contaminated with small amounts of inseparable alkene regioisomers **14e** and **14g**, respectively (Fig. 1).

Many strategies were tried to inhibit the formation of **14** (see Supplementary data),[3] but none gave reproducible results. Although the isomerization could not be completely suppressed, cycloalkene **10e** could be obtained in 79% yield as an acceptable 31:1 mixture of **10e** and **14e** by maintaining strictly anhydrous conditions and limiting the reaction time. In the same manner, **10g** was obtained in 70% yield as a 42:1 mixture of **10g** and **14g**. The fact that the RCM proceeds at all on substrates **9e** and **9g** is very satisfying, given the presence of an allylic quaternary center and a bulky menthyl fragment on each side of the *E* double bond (14).

It is perhaps not surprising, given the above results, that we have not yet succeeded in forming six-membered rings bearing a quaternary carbon. Compound **9f** afforded mostly dimer **13f** and degradation products under various conditions: RCM adduct **10f** was never observed, nor was by-product **12** (Table 2, entry 6).

The enantiomeric purity (determined by GC or HPLC analysis against racemic samples) of each RCM adduct was

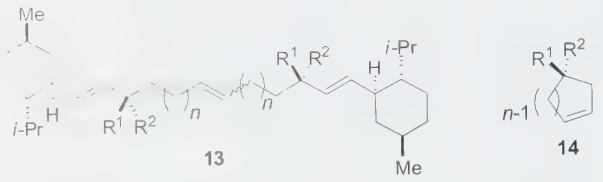
Table 2. Yields and enantiomeric ratios of cycloalkenes **10a–10g**.

Entry	9	R1	R2	*n*	10	Yield of 10 (%)[a]	er (%)
1	**9a**	Bn	H	1	**10a**	81	—[b]
2	**9b**	Bn	H	2	**10b**	84	>99:1[c]
3	**9c**	$TBSOCH_2$	H	1	**10c**	87	>98:2[d]
4	**9d**	$TBSOCH_2$	H	2	**10d**	73	>98:2[d]
5	**9**	Bn	Me	1	**10**	79[b]	97:3[e]
6	**9f**	Bn	Me	2	**10f**	0	—
7	**9g**	$TBSO(CH_2)_4$	Me	1	**10g**	70[b]	—[b]

Note: General conditions: **11** (1–10 mol%), CH_2Cl_2 or $ClCH_2CH_2Cl$ (0.01–0.002 mol/L), reflux, 3 h (see Supplementary data).[1]

[a]Isolated yield of **10** after flash chromatography.
[b]See text.
[c]Determined by HPLC analysis.
[d]Determined by GC analysis on the free alcohol.
[e]Determined by HPLC analysis on the allylic oxidation derivative.

Fig. 1. By-products from RCM reactions.



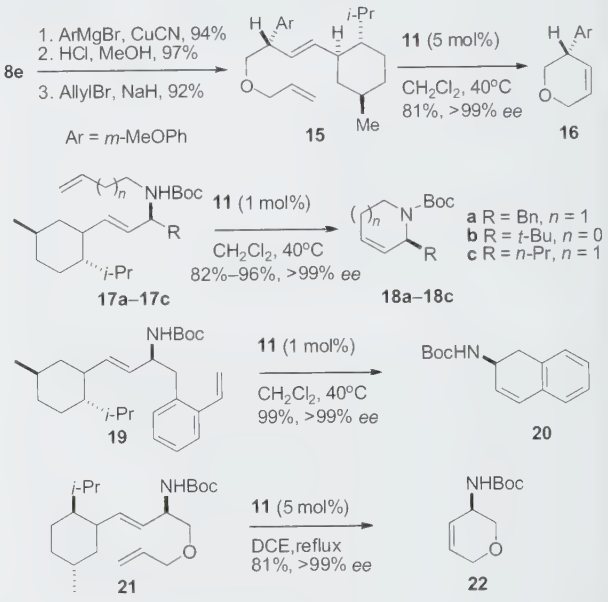
found to be excellent. For entries 1 and 7 of Table 2, we were unable to achieve complete resolution of the cycloalkene enantiomers, but their enantiomeric ratios are likely to be equally high. By-product **12** can be easily recovered by flash chromatography in yields of 70%–80% and, if desired, can be recycled back to aldehyde **3** by ozonolysis.

It is possible to envisage the application of our strategy to the preparation of a wide variety of highly enantioenriched cycloalkenes. Among the most interesting candidates, heterocycles are highly desirable (15). As an example, diene **15** (obtained in three steps from pivalate ester **8e**) was submitted to a RCM reaction to furnish dihydropyran **16** in 81% yield and >99% ee (as determined by HPLC analysis) (Scheme 4). *N*-Heterocycles, prepared by a different route (16), were also obtained by a similar RCM cleavage strategy as shown in Scheme 4. Dehydropiperidine **18a** and **18c**, pyrrolidine **18b**, and dihydroquinoline **20** were formed in excellent yield under much milder conditions (1 mol% catalyst in refluxing dichloromethane). Dihydropyran **22** required higher catalyst loading and higher temperature. We are currently embarked on the total synthesis of several alkaloids using this methodology.

Conclusion

We have achieved the first cleavage of a chiral auxiliary by a RCM reaction. This unprecedented method of cleavage has the merit of increasing the complexity of the substrate during the cleavage of the auxiliary, while not adding any extra steps to a synthetic plan aimed at synthesizing cycloalkenes. The sequence described herein allows the synthesis of enantioenriched cycloalkenes bearing a tertiary or quaternary chiral carbon in just four steps starting from readily available starting materials (vinyliodides or alkynes).

Scheme 4.



We are currently expanding the methodology to include more diverse and complex structures.

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Triazene derivatives of (1,*x*-)diazacycloalkanes. Part VI. 3-({5,5-Dimethyl-3-[2-aryl-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-aryl-1-diazenyl]imidazolidines — Synthesis, characterization, and X-ray crystal structure[1,2]

Keith Vaughan, Shasta Lee Moser, Reid Tingley, M. Brad Peori, and Valerio Bertolasi

Abstract: Reaction of a series of diazonium salts with a mixture of formaldehyde and 1,2-diamino-2-methylpropane affords the 3-({5,5-dimethyl-3-[2-aryl-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-aryl-1-diazenyl]imidazolidines (**1a**–**1f**) in excellent yield. The products have been characterized by IR and NMR spectroscopic analysis, elemental analysis, and X-ray crystallography. The X-ray crystal structure of the *p*-methoxycarbonyl derivative (**1c**) establishes without question the connectivity of these novel molecules, which can be described as linear bicyclic oligomers with two imidazolidinyl groups linked together by a one-carbon spacer. This is indeed a rare molecular building block. The molecular structure is corroborated by ^{1}H and ^{13}C NMR data, which correlates with the previously published data of compounds of types **5** and **6** derived from 1,3-propanediamine. The triazene moieties in the crystal of **1c** display significant π conjugation, which gives the N—N bond a significant degree of double-bond character. This in turn causes restricted rotation around the N—N bond, which leads to considerable broadening of signals in both the ^{1}H and ^{13}C NMR spectra. The molecular ion of the *p*-cyanophenyl derivative (**1b**) was observed using electrospray mass spectrometry (ES + Na). The mechanism of formation of molecules of type **1** is proposed to involve diazonium ion trapping of the previously unreported bisimidazolidinyl methane (**13**).

Key words: triazene, bistriazene, imidazolidine, synthesis, X-ray crystallography, NMR spectroscopy.

Résumé : Les réactions d'une série de sels de diazonium avec un mélange de formaldéhyde et de 1,2-diamino-2-méthylpropane conduit à la formation des 3-({5,5-diméthyl-3-[2-aryl-1-diazényl]-1-imidazolidinyl}méthyl)-4,4-diméthyl-1-[2-aryl-1-diazényl]imidazolidines (**1a**–**1f**) avec d'excellents rendements. On a caractérisé les produits par leurs spectres IR et RMN, par analyse élémentaire et par diffraction des rayons X. La structure cristalline ainsi déterminée pour le dérivé *p*-méthoxycarbonyle (**1c**) permet d'établir sans ambiguïté la connectivité dans ces nouvelles molécules qui peuvent être décrites comme des oligomères bicycliques linéaires comportant deux groupes imidazolidinyles reliés par un groupe d'espacement formé d'un atome de carbone, ce qui est un élément moléculaire d'assemblage assez rare. La structure moléculaire est corroborée par les données de la RMN du ^{1}H et du ^{13}C qui permettent d'établir une corrélation avec les données publiées antérieurement au sujet de composés des types **5** et **6** dérivés de la 1,3-propanediamine. Dans les portions triazènes présentes dans la structure cristalline du composé **1c** on retrouve une conjugaison π importante qui donne à la liaison N—N un caractère important de double liaison. Ce caractère provoque une restriction autour de la liaison N—N et, par voie de conséquence, un élargissement considérable dans les spectres RMN du ^{1}H et du ^{13}C. Dans le spectrogramme de masse obtenu en faisant appel à une ionisation par électronébulisation, on peut observer l'ion moléculaire du dérivé *p*-cyanophényle (**1b**). On suggère que le mécanisme de formation des molécules de type **1** implique un piégeage par l'ion diazonium du bisimidazolidinyméthane (**13**) qui n'avait pas encore été rapporté antérieurement.

Mots clés : triazène, bistriazène, imidazolidine, synthèse, cristallographie à l'aide de rayons X, spectroscopie RMN.

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Introduction

Imidazolidines are ubiquitous in pharmacology, medicinal chemistry, biochemistry, and various chemical studies. A number of imidazolidine carbonyl derivatives have recently been shown to exhibit antinociceptive activity (1) and several substituted thioxo-imidazolidine compounds have been evaluated for schistosomicidal activity (2). A structure–activity relationship of some new antiarrhythmic 5-arylideneimidazolidine-2,4-diones has been established (3) and the compounds were devoid of significant side effects. In the area of asymmetric synthesis, chiral imidazolidine ligands have been synthesized from *N,N′*-dialkylated cyclohexanediamine derivatives with excellent levels of enantiomeric excess (4). A novel imidazolidine derivative is formed spontaneously from the reaction of triethylenetetramine, salicylaldehyde, and benzaldehyde in methanol (5); this reaction has some significance to the chemistry reported in this paper. On a different playing field, a pentamethylimidazolidine embedded in polyethylene has been used as a radical probe to investigate the orientation distribution function of certain anisotropic paramagnetic species (6), and in a theoretical study, structural, electronic, and energetic information has been elucidated for three imidazolidinone derivatives (7).

This paper reports the synthesis and characterization of a series of new bis(imidazolyl)methanes, the novel 3-({5,5-dimethyl-3-[2-aryl-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-aryl-1-diazenyl]imidazolidines (**1a**–**1f**), from the diazonium coupling reaction with a mixture of formaldehyde and 1,2-diamino-2-methylpropane. These new bistriazenes exhibit the linear bicyclic structure similar to other bistriazenes derived from 1,3-propanediamines previously reported (8). However, these structures are diametrically different from the molecules of type **2**, obtained by analogous reaction with ethylenediamine (9), which have a distinctly different bridged bicyclic (or "cagelike") structure. Evidently, we have discovered a crossover in the molecular architecture of the products (**2**) derived from ethylenediamine itself (**3**) compared with the products (**1**) derived from the branched chain molecule, 1,2-diamino-2-methylpropane (**4**) (Scheme 1).

Experimental section

All reagents were reagent grade materials purchased from the Sigma-Aldrich Chemical Co. Ltd. and were used without further purification. Melting points were determined on a Fisher-Johns melting point apparatus (Fisher Scientific Inc.) and are uncorrected. Infrared spectra were obtained using Nujol mulls, unless otherwise stated, on a PerkinElmer 299 spectrophotometer or with a Brucker Vector 22 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained using either the Anasazi Instruments 60 MHz EFT spectrometer at Saint Mary's University or the Bruker 250 MHz spectrophotometer at the Atlantic Regional Magnetic Resonance Centre at Dalhousie University, both located in Halifax, Nova Scotia. Chemical shifts were recorded in $CDCl_3$ solutions at 20 °C and are relative to TMS as the internal standard. Elemental analysis was carried out at the Canadian Microanalytical Laboratory, Delta, British Columbia.

Synthesis of the 3-({5,5-dimethyl-3-[2-aryl-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-aryl-1-diazenyl]imidazolidines (1a–1f)

General procedure

The appropriate aromatic amine (0.015 mol) was dissolved in 3 mol/L of hydrochloric acid (20.0 mL) and the resulting solution was cooled to 0 °C. The hydrochloride solution was diazotized with a solution of sodium nitrite (1.15 g) in water (minimum volume) and the diazonium salt solution was left in the cold with stirring for 0.5 h. The solution was neutralized with saturated sodium bicarbonate solution and then 37% aqueous formaldehyde (5.0 mL) was added, while the temperature was kept below 0 °C. An aliquot of 1,2-diamino-2-methylpropane (0.015 mol) was dissolved in water and was then slowly added to the neutralized formaldehyde – diazonium salt mixture. After stirring for a further 0.5 h, the mixture was again basified with saturated sodium bicarbonate and the product that precipitated at this point was isolated by vacuum filtration, dried, and recrystallized from either ethanol, an ethanol – ethyl acetate mixture, or a hexanes – ethyl acetate mixture, to afford the following products.

*3-({5,5-Dimethyl-3-[2-(**p**-nitrophenyl)-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-(**p**-nitrophenyl)-1-diazenyl]imidazolidine (1a)*

Yellow crystals; yield 87%; mp 135–138 °C (ethanol – ethyl acetate). IR (Nujol, cm^{-1}) ν_{max}: 848, 1338, 1507. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.27 (12H, s), 3.51 (2H, s), 3.88 (4H, br s), 4.59 (4H, br s), 7.48 (4H, d, J = 9.0 Hz), 8.17 (4H, d, J = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz, ppm) δ: 22.0, 58.2, 120.7, 125.0, 145.0. Anal. calcd. for $C_{23}H_{30}N_{10}O_4$ (%): C 54.1, H 5.9, N 27.5; found: C 53.9, H 5.8, N 27.1.

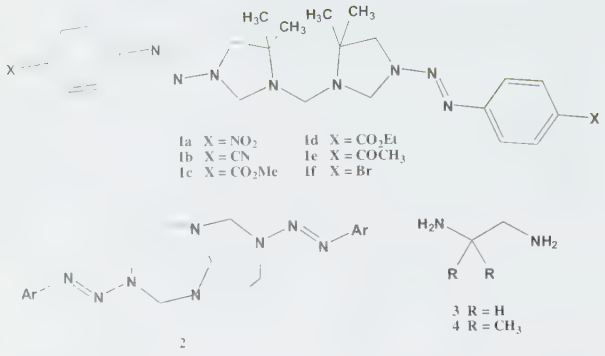
*3-({5,5-Dimethyl-3-[2-(**p**-cyanophenyl)-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-(**p**-cyanophenyl)-1-diazenyl]imidazolidine (1b)*

Cream prisms; yield 97%; mp 198–200 °C (hexanes – ethyl acetate). IR (Nujol, cm^{-1}) ν_{max}: 848, 2219. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.26 (12H, s), 3.50 (2H, s), 3.65 (4H, br s), 4.59 (4H, br s), 7.46 (4H, d, J = 8.5 Hz), 7.59 (4H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz, ppm) δ: 22.0 (br), 58.3, 60.0 (br), 68.0 (br), 69.4 (br), 108.5, 119.6, 121.3, 133.3, 154.3. MS (ES^+ + Na) m/z: 493 (M^+ + 23). Anal. calcd. for $C_{25}H_{30}N_{10}$ (%): C 63.8, H 6.4, N 29.8; found: C 63.7, H 6.3, N 29.8.

*3-({5,5-Dimethyl-3-[2-(**p**-methoxycarbonylphenyl)-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-(**p**-methoxycarbonylphenyl)-1-diazenyl]imidazolidine (1c)*

Amber needles; yield 87%; mp 178–181 °C (ethanol - ethyl acetate). IR (Nujol, cm^{-1}) ν_{max}: 860, 1710. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.25 (12H, s), 3.49 (2H, s), 3.75 (4H, br s), 3.89 (6H, s, O-Me), 4.67 (4H, br s), 7.46 (4H, d, J = 8.5 Hz), 8.00 (4H, d, J = 8.6 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz, ppm) δ: 22.0, 26.7, 58.2, 60.5, 120.5, 125.5, 129.7, 154.7, 197.6. Anal. calcd. for $C_{27}H_{36}N_8O_4$ (%): C 60.4, H 6.7, N 20.9; found: C 59.6, H 6.7, N 20.2.

Scheme 1.



3-({5,5-Dimethyl-3-[2-(p-ethoxycarbonylphenyl)-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-(p-ethoxycarbonylphenyl)-1-diazenyl]imidazolidine (1d)

Yellow needles; yield 92%; mp 139–144 °C (ethanol). IR (Nujol, cm^{-1}) ν_{max}: 860, 1708. ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.22 (12H, s), 1.36 (6H, t, J = 7.0 Hz), 3.46 (2H, s), 3.72 (4H, br s), 4.33 (4H, q, J = 7.1 Hz), 4.66 (4H, br s), 7.44 (4H, d, J = 8.6 Hz), 8.00 (4H, d, J = 8.6 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz, ppm) δ: 14.4, 21.7, 58.1, 60.3, 60.8, 68.0 (br), 70.0 (w br), 120.3, 127.2, 130.6, 154.4, 166.6. Anal. calcd. for $C_{29}H_{40}N_8O_4$ (%): C 61.7, H 7.1, N 19.8; found: C 61.6, H 7.2, N 19.3.

3-({5,5-Dimethyl-3-[2-(p-acetylphenyl)-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-(p-acetylphenyl)-1-diazenyl]imidazolidine (1e)

Cream-coloured needles; yield 60%; mp 159–163 °C (ethanol). IR (Nujol, cm^{-1}) ν_{max}: 833, 1672. ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.25 (12H, s), 2.58 (6H, s), 3.49 (2H, s), 3.75 (4H, br s), 4.68 (4H, br s), 7.46 (4H, d, J = 8.5 Hz), 7.94 (4H, d, J = 8.6 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz, ppm) δ: 22.0, 26.7, 58.2, 60.6, 120.5, 125.5, 129.7, 154.7, 197.6. Anal. calcd. for $C_{27}H_{36}N_8O_2$ (%): C 64.3, H 7.2, N 22.2; found: C 64.5, H 7.1, N 22.4.

3-({5,5-Dimethyl-3-[2-(p-bromophenyl)-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-(p-bromophenyl)-1-diazenyl]imidazolidine (1f)

Pale yellow needles; yield 91%; mp 157–160 °C (ethanol). IR (Nujol, cm^{-1}) ν_{max}: 831. ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.23 (12H, s), 3.46 (2H, s), 3.70 (4H, br s), 4.63 (4H, br s), 7.28 (4H, d, J = 8.8 Hz), 7.45 (4H, d, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz, ppm) δ: 21.9, 58.2, 60.4, 68.0, 119.0, 122.2, 132.0, 150.0. Anal. calcd. for $C_{23}H_{30}N_8Br_2$ (%): C 47.7, H 5.2, N 19.4; found: C 47.3, H 5.1, N 19.1.

Crystallography

X-ray diffraction data were collected on a Nonius Kappa CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.7107 Å). Data sets were integrated using the Denzo-SMN package (10) and corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR97) (11) and refined (SHELXL-97) (12) by full-matrix least-squares with anisotropic non-H and the hydrogen atoms included on calculated positions, riding on their carried atoms. All other calculations were accomplished using the PARST system of programs (13). Crystal data are given in Table 1.[4] Selected bond distances and angles are given in Table 2.

Table 1. Crystal data of compound **1c**.

Compound	**1c**
Formula	$C_{27}H_{36}N_8O_4$
M_r	536.64
Crystal system	Monoclinic
Space group	$P2_1/a$
a (Å)	13.9425(3)
b (Å)	7.1444(2)
c (Å)	28.6998(9)
β (°)	97.272(1)
V (Å^3)	2835.82(13)
Z	4
$D_{calcd.}$ (g cm^{-3})	1.257
$F(000)$	1 144
μ (cm^{-1})	0.874
Temperature (K)	295
Crystal form, colour	Prismatic, colourless
Crystal size (mm)	0.43 × 0.19 × 0.12
θ_{min}–θ_{max} (°)	3.4–27.5
Measured reflections	8624
Index ranges	$-18 \le h \le 18$; $-9 \le k \le 9$; $-37 \le l \le 36$
Unique reflections	6502
R_{int}	0.027
Obs. reflections [$F^2 \ge 2\sigma(F^2)$]	3792
$R(F^2)$ (Obs. reflections)	0.0466
$wR(F^2)$ (All reflections)	0.1311
No. of parameters	358
GoF	1.017
$\Delta\rho_{min}$, $\Delta\rho_{max}$	–0.129, 0.135

Results and discussion

Reaction of a mixture of 1,2-diamino-2-methylpropane and formaldehyde with an arene diazonium salt afforded the new bistriazene series, the 3-({5,5-dimethyl-3-[2-aryl-1-diazenyl]-1-imidazolidinyl}methyl)-4,4-dimethyl-1-[2-aryl-1-diazenyl]imidazolidines (**1a–1f**); in all but one case, the yields are very high, in the range 87%–97%. These new bistriazenes have two 4,4-dimethylimidazolidinyl moieties connected together via a single methylene group bridging

[4] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5065. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 246660 contains the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

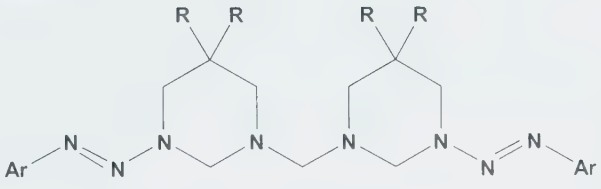
Table 2. Selected bond lengths and angles in compound **1c**.

Bond lengths (Å)	
N1—C1	1.423(2)
N1—N2	1.276(2)
N2—N3	1.319(2)
N3—C9	1.448(2)
N3—C11	1.440(2)
N4—C10	1.486(2)
N4—C11	1.456(2)
N4—C14	1.444(2)
C9—C10	1.520(3)
N8—C20	1.426(2)
N7—N8	1.274(2)
N6—N7	1.329(2)
N6—C16	1.447(2)
N6—C17	1.446(2)
N5—C15	1.488(2)
N5—C17	1.454(2)
N5—C14	1.450(2)
C15—C16	1.532(2)
Bond angles (°)	
N2-N1-C1	112.2(2)
N1-N2-N3	113.3(2)
N1-N3-C9	124.7(1)
N2-N3-C11	119.8(2)
C9-N3-C11	112.6(1)
C10-N4-C11	107.2(1)
C10-N4-C14	116.5(1)
C11-N4-C14	113.0(1)
N4-C14-N5	109.0(1)
N7-N8-C20	111.9(1)
N6-N7-N8	112.8(1)
N7-N6-C16	124.4(1)
N7-N6-C17	118.0(1)
C16-N6-C17	111.8(1)
C15-N5-C17	106.5(1)
C14-N5-C15	116.3(1)
C14-N5-C17	112.0(1)

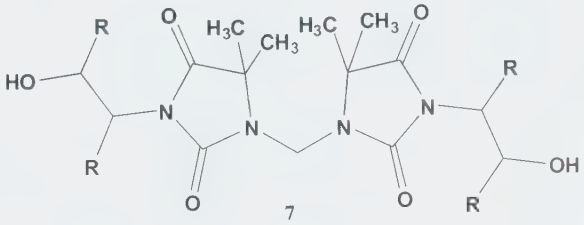
the N3 nitrogens; the available N1 nitrogens are coupled to the aryldiazenyl groups. This is a very similar type of molecular architecture to that previously reported (8) for the hexahydropyrimidine series, **5** and **6**. Molecules of types **1**, **5**, and **6** can be described as linear bicyclic bistriazenes, whereas the contrasting structure (**2**) can be described as a bridged bicyclic bistriazene with a cagelike structure. All compounds in the series **1a**–**1f** are stable crystalline solids, whereas the compounds of series **5** and **6** showed variable stability with a certain tendency to decompose (Scheme 2).

Molecules of type **1**, with two imidazole groups bridged by a single carbon atom are quite rare. Habermeier and Porret (14) reported a series of 1,1′-methylene-bis(hydantoins) (**7**). It is intriguing to note that the dimethyl branching positions in **1** are identical to those in the hydantoin (**7**), which raises the question regarding the possible existence of isomers of the new compounds of series **1**. Such isomers would have the structures shown in **8** and **9**; however, it is clear from the crystal structure elucidation of

Scheme 2.



5 R = H
6 R = CH_3



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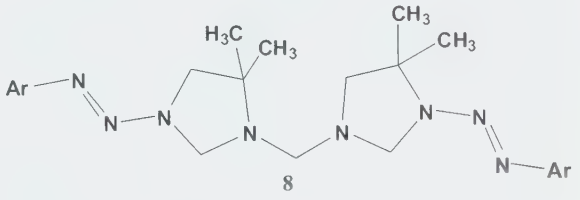

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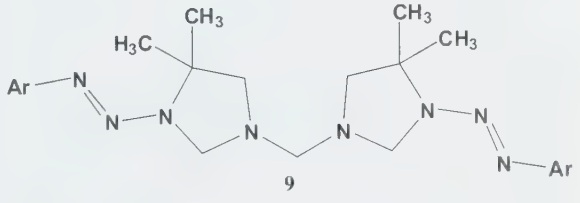

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compound **1c** that we do indeed have the novel structure **1** in which the methyl branches essentially face each other in an intuitively unlikely stereochemical combination.

An ORTEP (15) view of compound **1c** is shown in Fig. 1. The compound is built up by two equivalent fragments in the S-cis orientation, with respect to the N4-C14-N5 bridge. The planar phenyltriazenyl groups are mutually slightly rotated by an angle of 39.57(6)° and both the triazene moieties in the anti configuration display significant π conjugation. Both the imidazolidine five-membered rings adopt a twist conformation as shown in Table 3 (16).

The intuitive reasoning that suggests that structure **1c** should be sterically crowded is not supported by the ORTEP diagram in Fig. 1. The molecule of **1c** adopts a folded conformation that brings the triazene moieties fairly close together, but not close enough to invoke π–π stacking interactions. This folding of the molecule, which is similar to the folding observed in the X-ray structures of molecules of types **5** and **6** (17, 18), relieves any steric strain that would build up between the methyl branching groups. The folded conformation is also seen clearly in the crystal packing diagram, as displayed in Fig. 2, which is determined only by

Fig. 1. Thermal ellipsoid plot (ORTEP) of **1c**. Thermal ellipsoids are drawn at the 30% probability level.

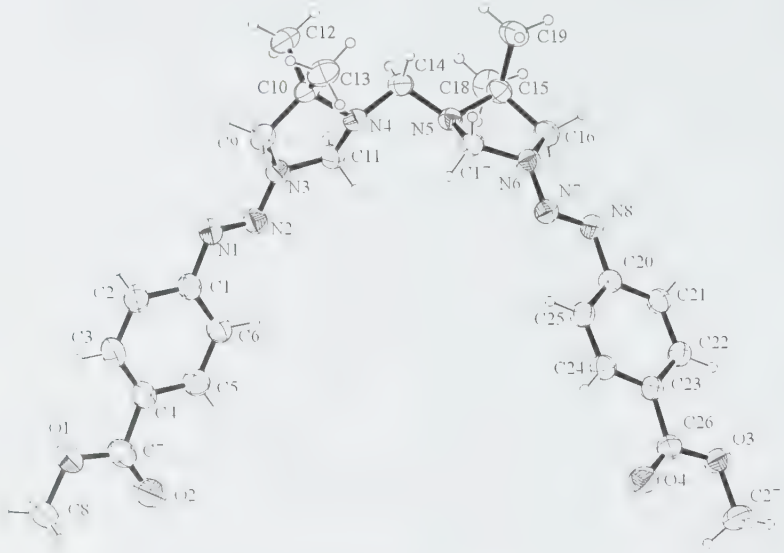


Fig 2. The crystal packing of **1c** viewed down the crystallographic *b* axis.

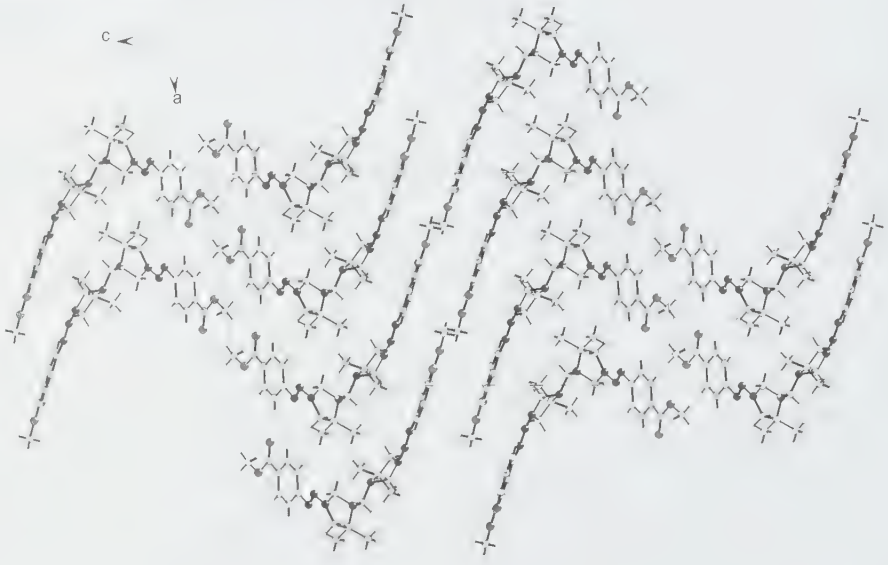


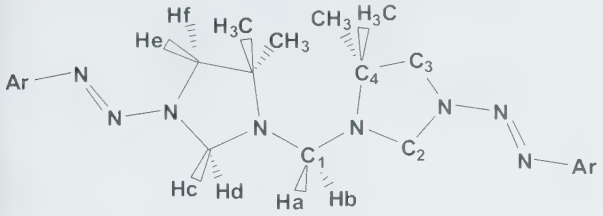
Table 3. Puckering parameters and ring conformations (16).

Ring	ϕ_2 (°)	q_2 (Å)	Conformation
N3-C9-C10-N4-C11	–88.6(3)	0.349(2)	$^4T_3$
N6-C16-C15-N5-C17	–83.3(2)	0.368(2)	$^4T_3$

van der Waals interactions. There is an inherent flow to the 3D structure shown in Fig. 2; the crystal is built up of layers of strings of molecules, but each string is like a sine wave. This repeating sine curve is made possible by the inherent curvature of each molecule derived from the folded conformation. It would appear that the ends of the molecules in each string are held together by the van der Waals attraction between the dipole moments of the terminal ester (COOMe) groups.

Further identification of the compounds in the series **1a**–**1f** is based on spectroscopic evidence. In the IR spectra of the new bistriazenes, the functional groups in the parasubstituents give rise to the predicted bands of either nitro, cyano, or carbonyl groups. Discussion of the supporting NMR data will be facilitated with reference to the proton and carbon labels in Fig. 3. In the ^{1}H NMR spectra, the protons of the methyl substituents give rise to a 12-proton singlet at ca. 1.25 ppm and the protons (H_a, H_b) of the bridging methylene group also give a sharp singlet at ca. 3.5 ppm. The equivalent methylene groups (H_c, H_d) give rise to a somewhat broadened singlet at ca. 4.6–4.7 ppm. The singlet

Fig. 3. Labelling of some hydrogen and carbon atoms in structure **1** to assist with the discussion of NMR data.



arising from the other methylene protons (H_e, H_f) at ca. 3.7–3.9 ppm is similarly broadened. This broadening of the signals of protons in close proximity to the triazene moiety is quite familiar and is attributed to the restricted rotation around the N—N bond in the triazene because of the partial double bond character of this group (19). The aromatic protons appear as the predictable AA′BB′ patterns.

The ^{13}C NMR spectra also show signs of the rotational dynamics in the triazene units referred to in the preceding paragraph. The carbon signals of carbon atoms C1, C2, and C3 are often so broad as to be impossible to detect. The carbon atom at C4, well away from the triazene units, is clearly seen in all spectra at ca. 58 ppm. The carbon atoms of the methyl substituents are also clearly evident at ca. 22 ppm. The C3 carbon is visible in four out of six spectra and is readily assigned to the chemical shift at ca. 60 ppm. The carbon atoms at C1 and C2 are more difficult to detect and when they are seen, the signals are weak and broad, but we can say with reasonable certainty that C1 occurs at ca. 68 ppm and C2 occurs at ca. 70 ppm. These chemical shift assignments show a strong correlation with the chemical shift assignments previously reported (8) for the compounds of series **5**.

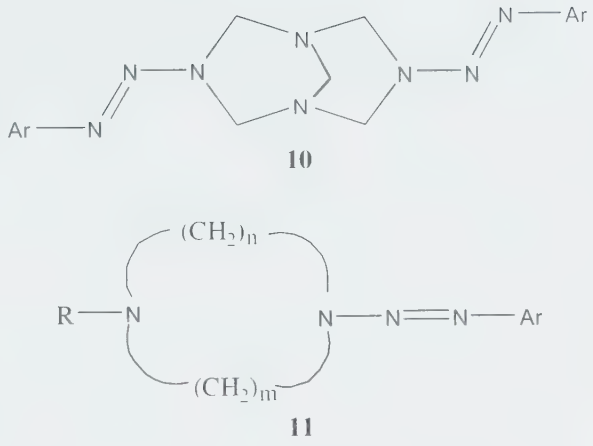
The stability of the compounds of series **1** did not extend to the analysis by mass spectrometry. Attempts to record mass spectra of these compounds by EI instrumentation did not succeed; no molecular ions were observed. However, in one case, that of **1b**, we were successful in seeing the molecular ion under ES^+ conditions with sodium as the charged cation.

Conclusion

It appears, from our ongoing studies, that the interaction of a diazonium salt with a mixture of formaldehyde and an alkanediamine [$NH_2(CH_2)_nNH_2$] gives rise to two distinct types of oligomer. Bistriazenes of types **2** (9) and **10** (20) are examples of the bridged bicyclic bistriazene, whereas the compounds of series **1** and **5** exemplify the linear bicyclic bistriazene. The new compounds of series **1**, reported here, clearly belong to the linear bicyclic class, providing further evidence that there is a crossover in the molecular architecture going from ethylenediamine (**3**) (two-carbon spacer) to the branched two-carbon spacer (**4**). This type of crossover was also observed in the transition from ethylenediamine to propanediamine in structures **5** and **6** (17, 18) (Scheme 3).

This paper is part VI in a series that describes the synthesis of a variety of triazenes and bistriazenes that fit the general classification of 1-aryldiazenyl-(1,*x*)-diazacycloalkanes

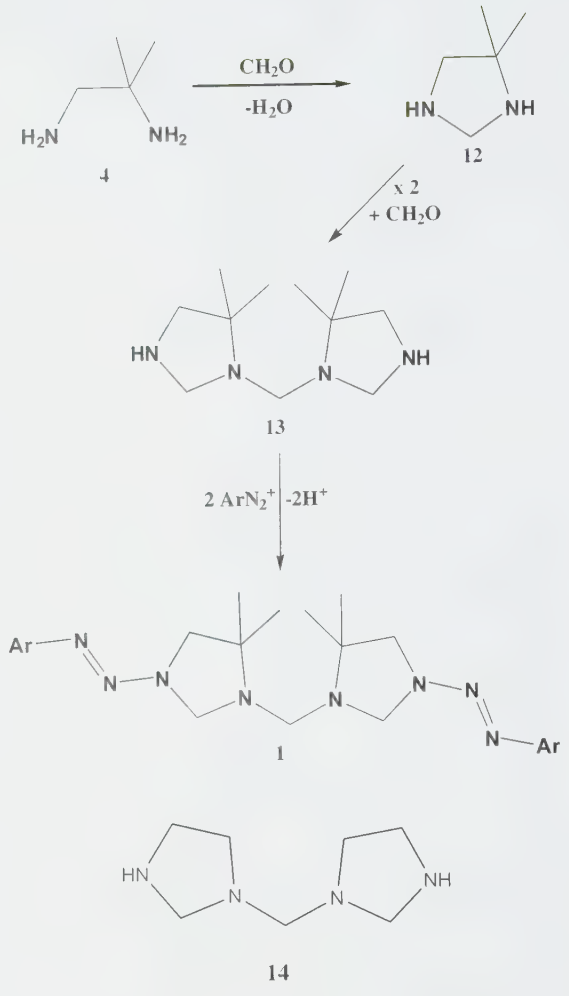
Scheme 3.



described by the general structure **11**, where m = 1 or 2 and n = 2, 3, 4, or 5. The new compounds of series **1** fit to the general structure **11** where m = 1 and n = 2. Previously, we reported new triazenes derived from piperazine (21, 22) ($m = n = 2$) and homopiperazine (23) (m = 2, n = 3). In future papers in this series, we will report more examples of the linear bicyclic bistriazene derived from other diamines, such as 1,4-diaminobutane and 1,5-diaminopentane. Evidently, the linear bicyclic bistriazene, reported here in the new compounds of series **1**, appears to be the normal type of molecular architecture in this field of chemistry.

However, there may be a more prevailing reason why these new compounds of type **1** are significant and that is the presence of the imidazolidine ring. Although well-known stable molecules like imidazolidine-2,4-dione ("hydantoin") (used to prepare amino acids (24)) and the essential growth factor, biotin, contain a 2-oxoimidazolidine ring in their structure, the parent imidazolidine is not so well-known. Direct hydrogenation of imidazole is difficult and it has been said by no less a figure of heterocyclic chemistry than Adrien Albert (25) that "imidazolidine appears to be unknown". However, the *N*,*N*′-diethyl derivative is readily prepared by reaction of *N*,*N*′-diethylethylenediamine and formaldehyde. This observation, and the work of Bera et al. (5), gives us a clue as to how the molecules of type **1** are formed (Scheme 4). Condensation of **4** with formaldehyde could afford the 4,4-dimethylimidazolidine (**12**), which in turn undergoes a dimerization–condensation to give the dimer **13**. Reaction of **13** with the diazonium ion then affords the observed product **1**. It would seem that the importance of the results reported here lies in the fact that the diazonium coupling reaction "traps out" the elusive intermediate bisimidazolidinyl methane **13**, which has previously not been reported. In fact, it would appear that the central moiety of our new compounds of series **1**, i.e., the saturated bis(imidazolidinyl)-methane unit (**14**), is virtually unknown. Although the CA files contain numerous molecules that contain the skeleton of **14**, all known compounds with this skeleton are either oxo-substituted derivatives, i.e., hydantoin-like molecules, such as **7**, or they are aromatic benzimidazolidine derivatives.

Scheme 4.



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The regioselective α-alkylation of the benzophenone imine of glycinamide, alaninamide, and related derivatives[1]

Martin J. O'Donnell, Jeremy D. Keeton, Vien Van Khau, and John C. Bollinger

Abstract: The benzophenone imine of glycinamide was alkylated using ion pair extraction (RX, 10% aq. NaOH, Bu_4NHSO_4 (1 equiv.), CH_2Cl_2, rt) to give the α-monosubstituted products, which were then alkylated a second time using stronger basic conditions (KO-*t*-Bu, THF, 0 °C, RX). Crystal structures of the Schiff bases of glycinamide, an α-monosubstituted and an α,α-disubstituted product were reported.

Key words: benzophenone imines, Schiff bases, alkylation, ion pair extraction (IPE), phase-transfer catalysis (PTC), anhydrous base, X-ray crystal structures.

Résumé : L'alkylation de la benzophénone imine du glycinamide par extraction par paire d'ions (RX, NaOH aqueux à 10%, Bu_4HSO_4 (1 équiv.), CH_2Cl_2, température ambiante) conduit à des produits α-monosubstitués qui sont alkylés une deuxième fois dans des conditions plus basiques (KO-*t*-Bu, THF, 0 °C, RX). Les structures cristallines des bases de Schiff du glycinamide, d'un produit α-monosubstitué et d'un produit α,α-disubstitué ont été déterminées.

Mots clés : imines de la benzophénone, bases de Schiff, alkylation, extraction par paire d'ions (EPI), catalyse par transfert de phase (CTP), base anhydre, structures cristallines par diffraction des rayons X.

[Traduit par la Rédaction]

Introduction

The development of new methods for the synthesis of unnatural α-amino acids has been the focus of our research for many years. The first general synthesis of α-amino acids by phase-transfer catalysis (PTC) was reported in 1978 (1). On treatment with base, the benzophenone imines of glycine alkyl esters (**1**) function as glycine anion equivalents for reaction with electrophiles to yield higher amino acid derivatives **2** (Scheme 1, pK_a experimental (calculated), refs. 2 and 3)) (4). A key tenet in this chemistry is the ability to achieve selective monoalkylation of **1** to give **2** under mild ("normal") PTC conditions, although a second alkylation to form **3** can be accomplished using stronger basic conditions (5). The possibility of stopping the reaction at the monoalkylation stage is attributed to $A_{1,3}$ strain in products **2** (6). The lower acidity of the monoalkylation product **2** compared with starting material **1** (2) has also been applied for the selective monophenylation of **1** (7), in the catalytic enantioselective alkylation for the synthesis of monoalkyl products without concomitant racemization under basic PTC conditions (8–10), and in the regioselective solution (**1**, OR = amino acid ester (11)) and on-resin (**1**, R = Merrifield, Wang, Rink, or Weinreb resin (12)) monoalkylation of a benzophenone-protected glycine residue in a peptide without either N-alkylation or alkylation of a C-terminal glycine or higher amino acid residue. Additionally, the on-resin enantioselective syntheses of α-alkyl amino acids have been achieved by both alkylation and Michael addition reactions (13).

While monoalkylations of the aldimines of glycine esters ($ArCH{=}NCH_2CO_2R$, **4a**, Ar = 4-ClC_6H_4, R = Et; pK_a (DMSO) 18.8 (19) (refs. 2 and 3)) are possible (14), the similar acidities of the unsubstituted (e.g., **4a**) and monosubstituted (e.g., **5a**) derivatives (2) can lead to overalkylation and (or) racemization of products **5** by deprotonation–reprotonation. In contrast, PTC alkylation of the aldimine of a monoalkyl amino ester is generally the method of choice to prepare α,α-dialkylated amino acid derivatives (Scheme 2) (15). Similarly, the aldimine activating group has been used for preparation of α-phenyl-α-alkyl amino acid derivatives by phenylation of the α-alkyl derivatives (16) and the regioselective solution (11) and on-resin (17) N-terminal α-carbon alkylation of peptides containing an N-terminal non-

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Dedicated to Dr. Alfred Bader for his contributions to humanity.

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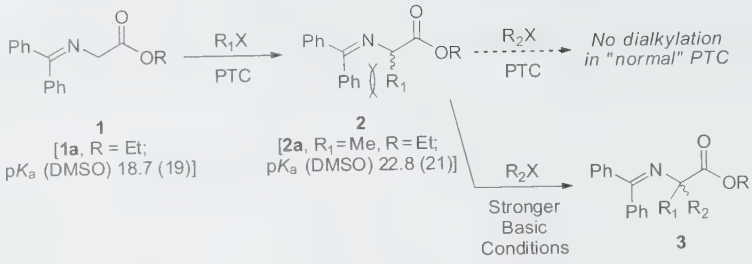
Scheme 1. Selective monoalkylation of benzophenone imine glycinates.



1
[**1a**, R = Et;
pK_a (DMSO) 18.7 (19)]

2
[**2a**, R_1=Me, R=Et;
pK_a (DMSO) 22.8 (21)]

3

glycine residue. A limitation of this methodology for the preparation of α,α-dialkyl amino acids from their glycine counterparts is the need to change activating groups from ketimine (Ph_2C=N-) (Scheme 1, **1** to **2**) to aldimine (ArCH=N-) (Scheme 2). As noted earlier (5), stronger base may be used to prepare the α,α-dialkylated products (Scheme 1, **2** to **3**). Additionally, on-resin tandem alkylations of benzophenone imine protected glycinates have been achieved by initial alkylation under PTC-like conditions followed by introduction of a second group at the α-carbon using stronger base (18).

The successful alkylation chemistry of the Schiff bases of glycine alkyl esters (**1**) and higher amino acid esters (**5**) prompted us to extend this methodology to the selective α-carbon alkylations of amino amides as a route to α-substituted and α,α-disubstituted amides (19). Reports of the enantioselective synthesis of monosubstituted amino amides by PTC have recently appeared (20).

Enzymatic resolution of racemic α-substituted and α,α-disubstituted amino acid amides has been developed by the DSM group (21) for preparing these important compounds and their associated α-amino acids in optically pure form from the racemic or optically enriched products. One synthetic route involves alkylation of **1b**, hydrolysis of the monoalkylated benzophenone imine of glycine methyl ester (**2**, R = Me, R_1 = alkyl), and conversion to the amide by treatment with ammonia (21*g*). A route to the α,α-disubstituted derivatives involved preparation of the aldimine of a monosubstituted amino acid amide (**7**) followed by alkylation under PTC conditions to give **8** (Scheme 3) (21*c*).

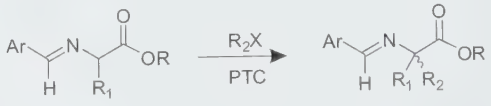
A more efficient route to the α,α-disubstituted derivatives of amino acid amides would be to start with the benzophenone imine of glycinamide (**10**) (prepared from benzophenone imine (**9**) and glycinamide), carry out a selective monoalkylation to (**11**), and then, *without changing the imine-protecting group*, do a second alkylation to give **12**. In this paper we report the successful accomplishment of this goal (Scheme 4).

Results and discussion

Prediction of the acidities of the benzophenone imines of glycinamide and their monoalkylated derivatives

Although the experimental acidities of the imines of glycinamide and their monoalkyl derivatives are not available, it was possible to use CAMEO to obtain qualitative theoretical acidities (DMSO) of these compounds (Fig. 1).[3]

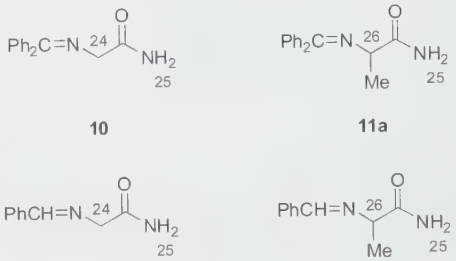
Scheme 2. Alkylation of a higher amino acid derivative by PTC.



5
[**5a**, Ar=4-ClC_6H_4, R_1=Me, R=Et;
pKa (DMSO) 19.2 (21)]

6

Fig. 1. Calculated acidities (pK_a in DMSO) using CAMEO for the benzophenone imines of glycinamide and alaninamide.



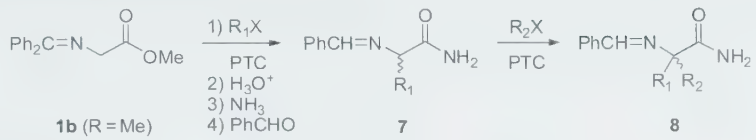
10 **11a**

13 **7a**

The predicted acidities of the α-protons in glycinamide imines (**10** or **13**, α-CH pK_a = 24) are only an order of magnitude greater than the acidities of the NH protons on the unsubstituted amides (**10** or **13**, NH pK_a = 25). This small effect is certainly not, by itself, sufficient to predict selective α-monoalkylation over N-alkylation. Additionally, as in the amino acid ester cases (2*a*), both the benzophenone imines and aldimines were predicted to have the same acidities and the monoalkyl derivatives were both predicted to be 10^2 less acidic than their glycinamide counterparts. As in the ester cases, the potential major acid-weakening effect in the benzophenone imine of alaninamide (**11a**) was not predicted. If this effect were taken into account, one would predict that the α-proton in **11a** would be even less acidic (higher pK_a) than those in **10**. Thus, it would be expected that the second alkylation of **10** would occur at nitrogen rather than at the α-carbon. Even though these qualitative theoretical predictions do not bode well for achieving the desired selective mono- and di-alkylations in the amino acid amide imines, we proceeded with experimental studies of these alkylation reactions.

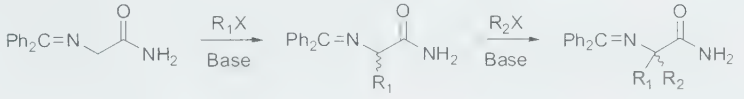
[3] Previous alkylation and Michael addition studies of three active methylene derivatives (cyanoacetamide, acetoacetamide, and malonamide) containing an unsubstituted amide and the predicted pK_as (DMSO) of these compounds are summarized in the Supplementary material.

Scheme 3. DSM route to α-alkyl amino amides and α,α-dialkyl amino amides.



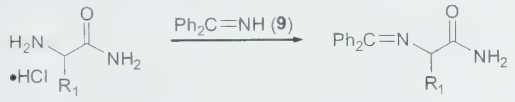
1b (R = Me) **7** **8**

Scheme 4. Selective mono- and di-alkylation of the benzophenone imine of glycinamide.



10 **11** **12**

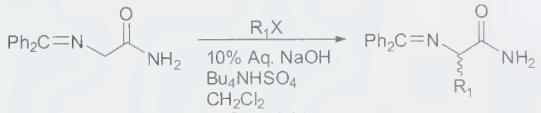
Scheme 5. Synthesis of the Schiff base of glycinamide (**10**) and alaninamide (**11a**) by transimination.



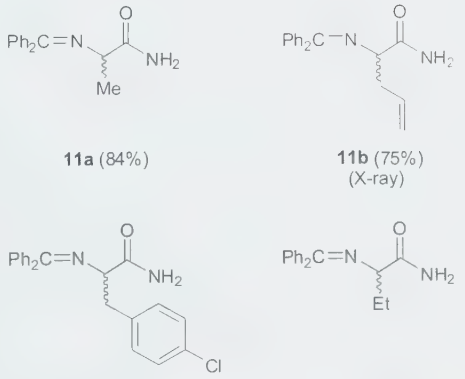
14 (R_1 = H)
15 (R_1 = Me)

10 (R_1 = H) (70%, X-ray)
11a (R_1 = Me) (96%)

Scheme 6. Alkylation of the benzophenone imine of glycinamide (**10**) by ion pair extraction to form the α-monosubstituted derivatives **11**.



10 **11**



11a (84%)

11b (75%) (X-ray)

11c (72%)

11d (73%)

Preparation and monoalkylation of the benzophenone imine of glycinamide

The benzophenone imine of glycinamide (**10**) (22, 23) was prepared from glycinamide hydrochloride **14** and benzophenone imine by transimination following a protocol similar to that developed for preparation of the related imines of glycine and monoalkyl amino acid esters (Scheme 5) (24). Since glycinamide hydrochloride is relatively insoluble in dichloromethane, the reaction was refluxed overnight in 1,2-dichloroethane with triethylamine (1 equiv.). Removal of solvent followed by recrystallization gave **10** (70%) as white crystals. An X-ray crystal structure, which will be discussed later, was obtained for **10**.

Alkylations of the Schiff base of glycinamide **10** were accomplished by ion pair extraction (IPE) using representative active (methyl, allyl, or benzyl) or less active (ethyl) halides, 10% aq. NaOH, and tetrabutylammonium hydrogen sulfate (TBAH, 1.2 equiv.) in dichloromethane at room temperature overnight (Scheme 6) (1*a*, 25). After work-up, the crude products were purified by column chromatography (silica gel was prewashed with 1% triethylamine because of the acid lability of the imine). Notably, under these mild alkylation conditions, the Cα-monoalkylated products (**11a**–**11d**) were obtained in good yield (72%–84%). An X-ray crystal structure, to be discussed later, was obtained of the α-monoalkylated product **11b**.

Alternatively, **11a** was prepared in 96% yield by transimination of alaninamide hydrochloride with benzophenone imine (DMF, rt, overnight).

Model study — Allylation of the benzophenone imine of alaninamide

A model alkylation study for the proposed regioselective Cα-alkylation of the Schiff base of alaninamide (**11a**) to prepare the α,α-dialkylated product was conducted using allyl bromide as the alkylating agent with a variety of bases and reaction conditions (Scheme 7). In addition to the desired C-monoalkylated product **12a**, four other alkylation products are possible in this reaction (**16**–**19**) (Fig. 2). The calculated pK_a values (CAMEO) of the α-CH and NH protons in these products are given for reference (see Fig. 1 for predicted pK_a values of **10** and **11a**).

The reactions were conveniently monitored by TLC (Fig. 3). The optimized TLC system provides for separation of the starting material (**11a**), the desired C-allylated target (**12a**), the N-allylated product (**16**), the two possible diallylated derivatives (**17** and **18**), and the triallylated compound (**19**), as well as the hydrolysis product, benzophenone. Identities of the various spots were determined using mass spectral analysis and ^{1}H NMR.

Allylation of Schiff base **11a** was studied using a variety of bases and reaction conditions (Table 1). The alkylation was first conducted using IPE conditions, however no reaction was observed (Table 1, entry 1) (1*a*, 25). IPE conditions using 50% aq. NaOH gave only trace amounts of desired

Scheme 7. Model study for regioselective α-C alkylation of the Schiff base of alaninamide (**11a**).

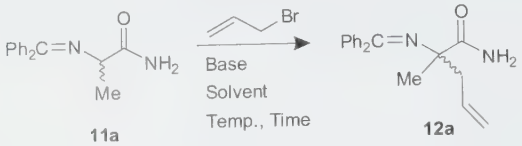
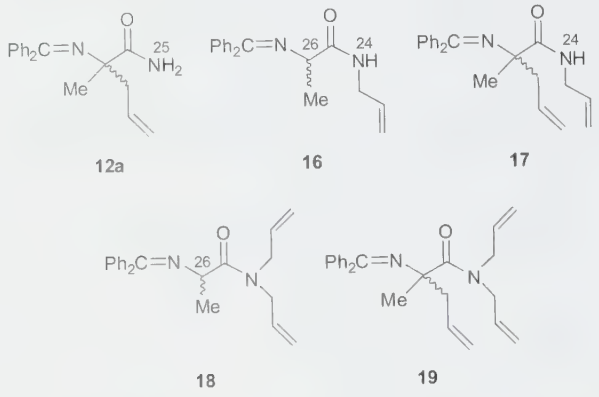
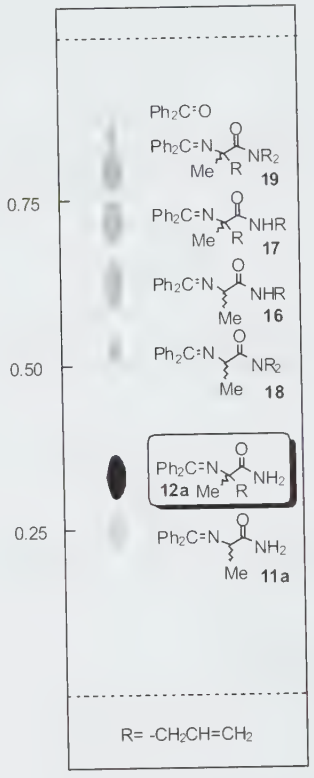


Fig. 2. Possible products from the alkylation of the Schiff base of alaninamide (**11a**) with allyl bromide.



product (**12a**) (Table 1, entry 2). Next, alkylation was performed under nonaqueous conditions using the Schwesinger base BTPP (*tert*-butylimino-tri(pyrrolidino)phosphorane, 0.9 equiv.) to again give only trace amounts of product. BTPP is a relatively strong, organic soluble, nonionic base used successfully for the α-alkylation of resin-bound Schiff base derivatives of amino acids and peptides (26). From these first experiments, it was apparent that stronger conditions were needed to effect α-alkylation. Thus, alkylation was next attempted using sodium ethoxide (in EtOH) in the presence of catalytic TBAB in anhydrous acetonitrile (Table 1, entry 4) (5). In this case, no reaction was observed because of the insolubility of **11a** in acetonitrile. In a second set of reactions using the same reagents, the EtOH was first removed from NaOEt and then acetonitrile was added, but again the reaction was unsuccessful because of the insolubility of the starting Schiff base (Table 1, entry 4). LDA in anhydr. THF gave only trace amounts of product (Table 1, entry 5). The same conditions were applied using LiHMDS, but again only trace amounts of desired product were observed (Table 1, entry 6) (27). With KHMDS, the target α-monoalkylated product (**12a**) was obtained in 24% yield (Table 1, entry 7). The final and most effective base used was KO-*t*-Bu (Table 1, entries 8–10) (27). When the reaction was carried out at ambient temperature or –78 °C, 42%–46% and 34%–48% yields, respectively, of **12a** were obtained (Table 1, entries 8 and 9). Optimal conditions were obtained using Schiff base **11a** (1 equiv.), KO-*t*-Bu (1.2 equiv.), and allyl bromide (1.2 equiv.) in THF at 0 °C for 3 h to give product **12a** in 55%–61% yield (Table 1, entry 10). The addition of LiCl (5 equiv.), which has often proven to be an effective additive in alkylation and other anionic reactions (28), using the KO-*t*-Bu conditions at rt, 0 °C, or –78 °C gave only trace amounts of product as did other solvents (DMF or *tert*-butyl alcohol) with KO-*t*-Bu (TLC, LC–MS, and ^{1}H NMR).

Fig. 3. TLC data for products from the allylation of the Schiff base of alaninamide (**11a**).



Flash chromatography:
Hexanes/EtOAc/Et_3N
75:25:1

The reaction conditions were studied further by using 0.9 equiv. of both allyl bromide and KO-*t*-Bu to understand which of the various possible alkylations was occurring and in what order. Hopefully, selective monoalkylation at the α position to form **12a** would occur first and further alkylation would not be problematic when less than 1 equiv. of base and alkylating reagent was used. If more than 1 equiv. of base and alkylating agent was used, selective Cα-monoalkylation (**12a**) could occur followed by N-alkylation (to **17**), and possibly N,N-dialkylation (to **19**).

The results from the model experiment showed that, even when less than 1 equiv. of base and alkylating reagent were used, the reaction gave mixtures of mono-, di-, and tri-alkylation products (Fig. 2). From the earlier experimental results (Table 1), in which the desired C-allylated product was obtained in up to 61% yield, it is apparent that the predicted pK_a values (Figs. 1 and 2) provide only a very qualitative estimate of the various pK_as.

Finally, the alkylation reaction of **11a** with allyl bromide was examined after 5 min by TLC to see if the product distribution was affected by time. At this time, all of the products shown in Fig. 3 were present.

Table 1. α-Allylation of the benzophenone imine of alaninamide (**11a**) to form **12a** (base study).

Entry	Base	Solvent	Other	Temp. (°C)	Time (h)	**12a** (%)
1	10% Aq. NaOH	CH_2Cl_2	TBAH[a]	rt	18	No rxn.
2	50% Aq. NaOH	CH_2Cl_2	TBAH[a]	rt	18	Trace
3	BTPP[b]	CH_2Cl_2	—	rt	18	Trace
4	NaOEt	CH_3CN	TBAB[c]	—	—	No rxn.[d]
5	LDA	THF	—	–78	3	Trace
6	LiHMDS	THF	—	–78	3	Trace
7	KHMDS	THF	—	–78	3	24
8	KO-*t*-Bu	THF	—	rt	3	42–46
9	KO-*t*-Bu	THF	—	–78	3	34–48
10	KO-*t*-Bu	THF	—	0	3	55–61

[a]Bu_4NHSO_4 (1 equiv.).
[b]*tert*-Butylimino-tri(pyrrolidino)phosphorane.
[c]Bu_4NBr (cat.).
[d]Starting material insoluble.

Alkylation of the Schiff base of monosubstituted amino amides to give α,α-disubstituted derivatives

Using the optimized results from the model alkylation study described previously, several target molecules were made by following the general procedure for alkylation of the benzophenone imine of a monosubstituted amino amide. Further alkylations included benzylation and alkylation with less reactive alkyl halides as well as a Michael addition. The model conditions used, unless otherwise noted, were as follows: KO-*t*-Bu (2.38 mmol) was added to the benzophenone imine of a monosubstituted α-amino amide (1.98 mmol) dissolved in anhydr. THF at 0 °C and the reaction mixture was stirred at 0 °C for 20 min. The alkylating agent (2.38 mmol) was added and the reaction mixture was stirred at 0 °C for an additional 3 h. After work-up, the crude product was purified by flash chromatography using silica that was prewashed with hexanes–EtOAc–triethylamine (75:25:1). The product was then recrystallized from dichloromethane–hexanes (1:15). Four monoalkylated starting materials (**11a**–**11d**, Scheme 6) were used to prepare 10 new α,α-disubstituted products (**12a**–**12e** and **12g**–**12k**, Fig. 4).

The alkylation of **11a** with allyl derivatives gave the highest yields for all alkylations studied (Fig. 4, products **12a**–**12d**). Alkylation of Schiff base **11a** with allyl bromide, 4-bromo-2-methyl-2-butene, 3-bromo-2-methylpropene, and cinnamyl bromide, gave the respective Schiff bases (**12a**–**12d**) in 36%–61% isolated yield. An X-ray crystal structure, which will be discussed later, was obtained for dialkylated product **12b**.

The alkylation of Schiff base **11a** using non-allylic halides was examined next (Fig. 4, products **12e**–**12h**). Alkylation with 4-chlorobenzyl bromide gave the Schiff base **12e** (53%) while methylation gave a complex mixture of products, likely owing to the reactivity and small size of the methyl group. Alkylation of **11a** with iodoethane gave **12g** (24%) while 1-iodo-2-methylpropane gave **12h** (25%). Alkylation with two α-haloesters, methyl bromoacetate, and *tert*-butyl bromoacetate, did not give the desired α-alkylated products (LC–MS and ^{1}H NMR).

Alkylation of the Schiff base of higher amino amides using the general procedure for the alkylation of **11a** was also studied (Fig. 4, products **12i**–**12k**). The Schiff base starting materials (**11b**–**11d**) were prepared earlier by IPE from the Schiff base of glycinamide (**10**, Scheme 6). These three monoalkylated Schiff base glycinamides (**11b**–**11d**) were then subjected to allylation and benzylation. In all cases, the allylation of the benzophenone imines of these higher amino amides did yield the desired products, although in low yields. Allylation of Schiff base **11b** gave **12i** (21%), **11c** yielded **12j** (25%), and **11d** gave **12k** (13%). For the synthesis of Schiff base **12j**, the addition of 4-chlorobenzyl bromide to Schiff base **11b** gave only a 10% yield of product. This compared with the higher yield (25%) of the same product (**12j**) obtained by allylation of the benzylated starting material **11c**.

Methylation of Schiff bases **11b** and **10** gave a mixture of products (TLC and LC–MS) and it was not possible to isolate the desired α-alkylated product, which was present only in trace amounts, from the crude reaction mixture. Methylation of **11d** gave the N-monoalkylated product (45%) and methylation of **11c** yielded less than 10% of product **12e**, compared with the 53% yield for the reverse order of alkylation of the Schiff base alaninamide **11a** using *p*-chlorobenzyl bromide.

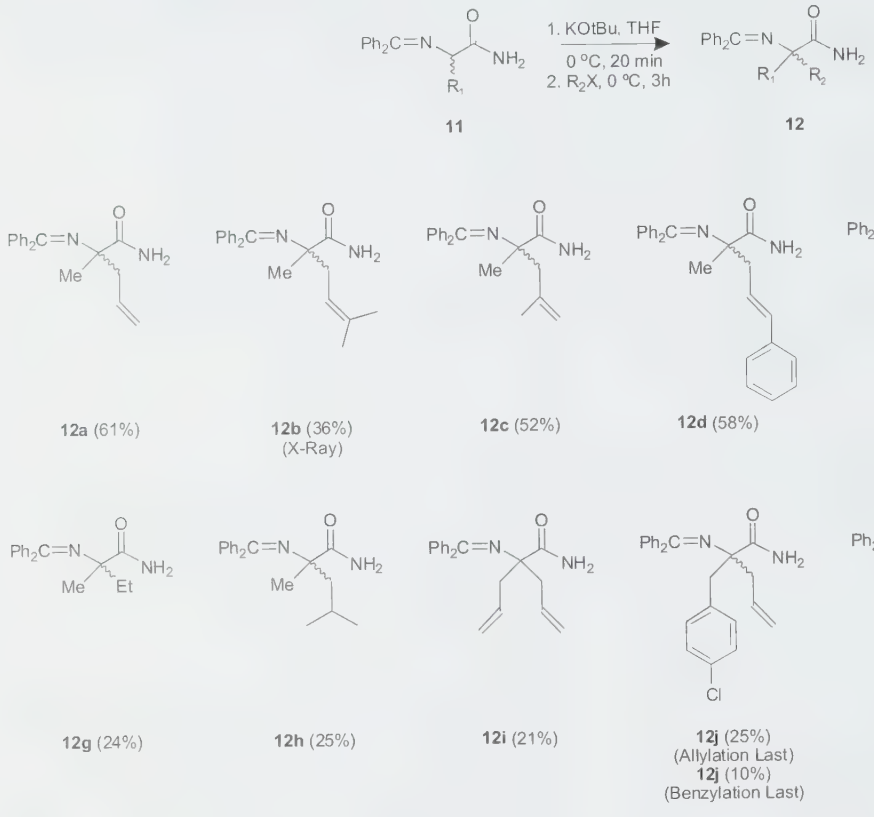
Michael addition of the Schiff base of alaninamide

The Schiff base of alaninamide (**11a**) was reacted with the Michael acceptor (*tert*-butyl acrylate) to give the Schiff base **20** (32%) (Scheme 8). Schiff base **11a** (1.98 mmol) was dissolved in anhydr. THF, then *tert*-butyl acrylate (2.38 mmol) was added, followed by KO-*t*-Bu (0.238 mmol), and the reaction mixture was stirred at 0 °C for 3 h. This reaction was optimal with 0.12 molar equiv. of KO-*t*-Bu rather than the normal 1.2 equiv. in the case of alkylation. Attempted Michael addition with methyl acrylate did not give the desired product as monitored by LC–MS, while use of acrylonitrile gave the N,N-dialkylated product (^{1}H NMR and LC–MS) and only trace amounts of monoalkylated product (LC–MS).

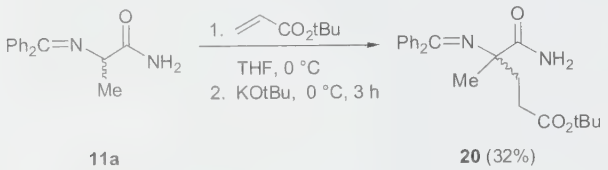
X-ray crystal structures of the benzophenone imine of amino amides

The X-ray crystal structures of the benzophenone imines of the unsubstituted (**10**), a monosubstituted (**11b**), and a disubstituted (**12b**) amino amide were obtained (Fig. 5). A

Fig. 4. Alkylation of the benzophenone imines of monosubstituted amino amides (**11**) with KO-*t*-Bu to form the α,α-disubstituted products **12**.



Scheme 8. Michael addition of the benzophenone imine of alaninamide with *tert*-butyl acrylate.



summary of the crystallographic data is given in Table 2.[4] In addition to confirming the structures of these products, several other points are of interest in this series of compounds.

The *cis*-phenyl group (Ph_c) on the imine is considerably farther out of planarity with the imine double bond than is the *trans*-phenyl group (Ph_t). This is due to $A_{1,3}$ strain (6) in the mono- and di-substituted derivatives, where the effect is more pronounced than in the unsubstituted case. Interestingly, the sum of these two values (Σ) increases in going from **10** (Σ = 88°) to **11b** (Σ = 92°) to **12b** (Σ = 99°). As a comparison, in the unsubstituted Schiff base esters ($Ph_2C{=}NCH_2CO_2Et$, **1a**, Σ = 71°; $Ph_2C{=}NCH_2CO_2$-*t*-Bu, **1c**, Σ = 86° (4)) and in the α-benzyl or α-phenyl substituted Schiff base esters ($Ph_2C{=}NCH(CH_2C_6H_4$-4-Cl$)CO_2$-*t*-Bu, **2c**, Σ = 97° (4); $Ph_2C{=}NCH(Ph)CO_2Et$, **2d**, Σ = 82° (7)). The X-ray structure of an α,α-disubstituted Schiff base ester in this series was not determined.

The bond lengths to the quaternary α-carbon in the disubstituted Schiff base amide (**12b**) relative to the other two compounds in the series are also of interest. Three of the four bonds to the α-carbon are the longest in the series: the Cα—N_{imine} bond(1.477 Å), the Cα—Me bond (1.536 Å), and the Cα-C_{CO} bond (1.555 Å), which is a result of the steric congestion about the quaternary α-carbon in **12b**.

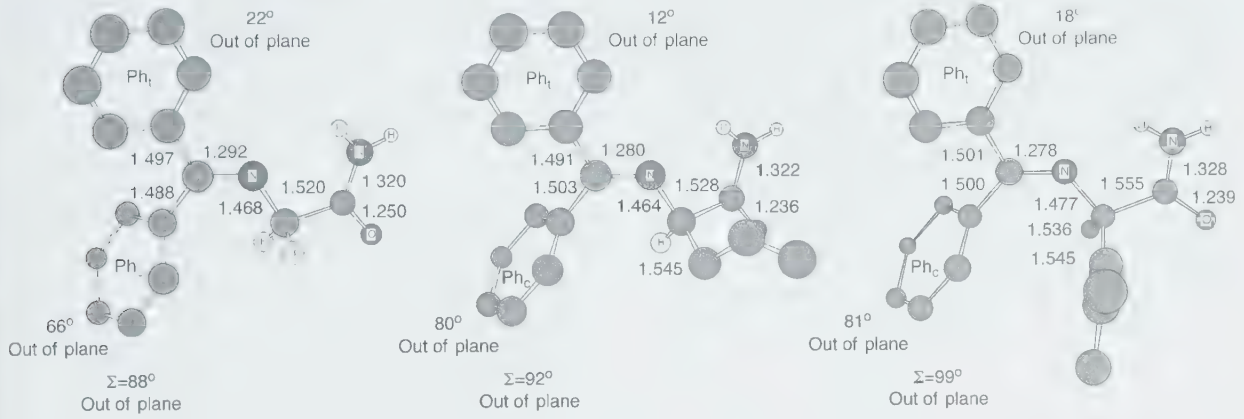
Experimental

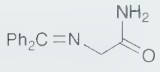
General

Unless otherwise noted, all manipulations were carried out under an inert atmosphere (argon) in glassware dried

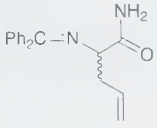
[4] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5057. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 296438, 296439, and 296437 (compounds **10**, **11b**, and **12b**, respectively) contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Fig. 5. Crystal structures of representative unsubstituted, α-monosubstituted, and α,α-disubstituted amino amide derivatives.

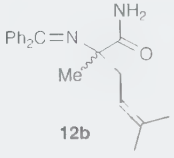




10



11b



12b

with a heat gun. THF was freshly distilled before use from sodium benzophenone ketyl. Sure Seal™ bottles of potassium *tert*-butoxide (1.0 mol/L in THF and 1.0 mol/L in *tert*-butyl alcohol), sodium ethoxide (21 wt% in denatured ethyl alcohol), lithium diisopropylamine (2.0 mol/L in heptane–THF–ethylbenzene), potassium bis(trimethylsilyl)amide (0.5 mol/L in toluene), lithium bis(trimethylsilyl)amide (1.0 mol/L in THF), and all solvents other than THF were purchased from the Sigma-Aldrich Chemical Co.

Nuclear magnetic resonance (NMR) spectra were recorded on a 300 MHz Varian Gemini spectrometer. Infrared (IR) spectra were obtained neat in thin films on NaCl plates (oils) using a Matteson Genesis FT-IR. Elemental analyses were performed by Midwest Microlabs, Indianapolis, Indiana. High-resolution mass spectrometry was run in the FAB mode at Indiana University. Melting points were determined in open-end capillaries using a Thomas-Hoover Unimelt melting apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum sheets with UV visualization. Column chromatography was performed using silica gel (60 Å, 40–63 μm standard grade gel) with the solvent systems described in the individual procedures. Liquid chromatography – mass spectrometry (LC–MS) was performed on a Waters 2795 liquid chromatograph, a Waters 996 photodiode array, a Sedex 75 light scatterer, and a Waters Micromass ZQ mass spectrometer. The mobile-phase solvent was 90% H_2O – 5% ACN – 5% – 0.2% formic acid buffer at approximately pH 3.0.

X-ray crystallography was performed at the Molecular Structure Center at Indiana University. X-ray diffraction data were collected using a Bruker diffractometer with SMART 6000 CCD detector. Structures were solved via the SHELXTL program suite (29). Further structure determination details are available in CIF form in the Supplementary material.[4]

Preparation of the benzophenone imines of glycinamide and alaninamide by transimination

2-[(Diphenylmethylene)amino]acetamide (10)

Glycinamide hydrochloride (**14**, 5.00 g, 45.2 mmol) and 1,2-dichloroethane (60 mL) were added to a dried 250 mL three-necked round-bottomed flask equipped with a reflux condenser, a magnetic stirrer, and an argon source. Diphenylketimine (7.6 mL, 45.2 mmol), triethylamine (6.93 mL, 49.7 mmol), and 1,2-dichloroethane (20 mL) were added by syringe to a separate dry 50 mL round-bottomed flask equipped with an argon source. The mixture was stirred for 5 min and was added slowly by cannula under argon to the reaction flask. The mixture was refluxed under argon overnight, cooled, filtered, and the solvent was removed under reduced pressure to give a light yellow solid. Recrystallization from hexanes–EtOAc (2:3 by volume) gave **10** as white crystals (7.55 g, 70%); mp 160–163 °C (lit value (22) mp 162 to 163 °C). IR (cm^{-1}): 1681, 3442. ^1H NMR δ: 3.96 (s, 2H, CH_2), 5.55–5.75 (br s, 2H, NH_2), 7.10–7.70 (m, 10H, aromatic). ^{13}C NMR ($CDCl_3$) δ: 58.2, 128.9, 129.8, 130.0, 130.1, 130.5, 130.6, 132.3, 137.6, 140.4, 156.7, 172.0, 175.1.

(±)-2-[(Diphenylmethylene)amino]propanamide (11a)

(±)-Alaninamide hydrochloride (**15**, 1.00 g, 8.03 mmol) followed by anhydr. DMF (50 mL) were added to a dried 250 mL round-bottomed flask equipped with a magnetic stirrer. The solution was stirred at room temperature under argon for 30 min or until the solid was completely dissolved. Benzophenone imine (1.45 g, 8.03 mmol) was added dropwise via syringe to the alaninamide solution under argon at room temperature. The reaction mixture was stirred at room temperature under argon overnight. The solution was

Table 2. Crystallographic data.

Crystal	**10**	**11b**	**12b**
Emperical formula	$C_{15}H_{14}N_2O$	$C_{18}H_{18}N_2O$	$C_{21}H_{24}N_2O$
Formula mass	238.28	278.34	320.42
Colour, habit	Multifaceted, colourless	Plate, colourless	Colourless, block
Crystal dimensions (mm)	0.5×0.5×0.25	0.5×0.3×0.08	0.26×0.18×0.14
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	*C*2/*c*	*P*-1	*P*-1
Z	8	6	4
a (Å)	26.640(6)	11.1428(3)	8.9409(7)
b (Å)	5.9821(14)	12.9776(3)	11.6696(8)
c (Å)	18.643(4)	16.5402(4)	17.8861(13)
α (°)	90.00	92.3530(10)	102.943(2)
β (°)	118.543(5)	99.9610(10)	95.127(2)
γ (°)	90.00	101.0850(10)	97.676(2)
Collection ranges	$-31 \le h \le 27$, $-7 \le k \le 7$, $-20 \le l \le 22$	$-15 \le h \le 15$, $-18 \le k \le 18$, $-23 \le l \le 23$	$-12 \le h \le 12$, $-16 \le k \le 16$, $25 \le l \le 25$
Temperature (K)	120(2)	120(2)	117(2)
Volume (Å^3)	2609.8(10)	2304.97(10)	1788.7(2)
D_{calcd} (Mg m^{-3})	1.213	1.203	1.190
Radiation (Å)	MoKα (λ = 0.710 73)	MoKα (λ = 0.710 73)	MoKα (λ = 0.710 73)
Absorption coeff (μ, mm^{-1})	0.078	0.075	0.073
Absorption correction	Semiempirical	Semiempirical	Numerical
F(000)	1008	888	688
θ range for data (°)	2.44–29.97	2.07–30.01	3.50–29.86
Observed reflections	7106	42 952	38 005
Independent reflections	2302	13 452	7930
Data/restraints/parameters	2302/0/219	13452/0/815	7930/0/625
Maximum shift/error	0.003	0.002	0.001
GOF on F^2	0.995	1.462	1.553
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0698$, $wR_2 = 0.1749$	$R_1 = 0.0461$, $wR_2 = 0.0960$	$R_1 = 0.0457$, $wR_2 = 0.1007$
R indices (all data)	$R_1 = 0.1109$, $wR_2 = 0.2293$	$R_1 = 0.0739$, $wR_2 = 0.1038$	$R_1 = 0.0648$, $wR_2 = 0.0963$
Absolute structure parameter	NA	NA	NA
Extinction coefficient	NA	NA	NA
Largest diff peak and hole (e Å^{-3})	0.368 and –0.395	0.352 and –0.227	0.432 and –0.215

quenched with H_2O (100 mL), Et_2O (100 mL) was added, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with H_2O (3 × 100 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The solid was washed with hexanes (5 × 20 mL) to give **11a** as a white solid (1.94 g, 96%). Recrystallization from CH_2Cl_2–hexanes (1:15) gave the product as a fine white powder (see the following analytical data).

General procedure for the alkylation of the benzophenone imine of glycinamide (10) by IPE to form the α-monosubstituted products 11

Aqueous NaOH (10%, 2.52 mmol) followed by tetrabutylammonium hydrogen sulfate (1.03 mmol) were added to a dried 25 mL round-bottomed flask equipped with a magnetic stirrer and the reaction mixture was stirred for 5 min. The benzophenone imine of glycinamide (**10**, 0.84 mmol) was dissolved in dichloromethane (1.5 mL) and then added dropwise via syringe to the reaction mixture. The solution was stirred for 3 min and then the system was placed under argon. The alkylating agent (4.2 mmol) was added dropwise via syringe and the reaction mixture was stirred at room temperature under argon overnight. The reaction mixture was transferred to a separatory funnel and distilled water (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The organic layer was washed with distilled water (3 × 10 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give the crude product. The product was purified by flash column chromatography (SiO_2, first washed with hexanes–EtOAc–Et_3N (90:10:1)) using EtOAc–hexanes (50:50) to EtOAc–hexanes (85:15) gave the purified products **11**.

(±)-2-[(Diphenylmethylene)amino]propanamide (11a)

The general procedure described in the previous section using 10% aq. NaOH (0.9 g, 2.52 mmol), tetrabutylammonium hydrogen sulfate (0.351 g, 1.03 mmol), **10** (0.200 g, 0.84 mmol) in dichloromethane (1.5 mL), and

iodomethane (0.593 g, 4.2 mmol) gave solid product **11a** (177 mg, 84%); mp 120–123 °C. IR (cm^{-1}): 1651, 3451. ^1H NMR δ: 1.35 (d, 3H, J = 7.4 Hz, CH_3), 4.00 (q, 1H, J = 6.9 Hz, CH), 5.30–5.45 (br s, 2H, NH_2), 7.00–7.70 (m, 10H, aromatic). ^{13}C NMR ($CDCl_3$) δ: 22.3, 63.0, 128.9, 129.8, 130.1, 130.3, 130.4, 130.5, 132.2, 137.2, 140.7, 170.5, 178.5. Anal. calcd. for $C_{16}H_{16}N_2O$: C 76.17, H 6.39, N 11.10; found: C 76.36, H 6.50, N 11.14.

(±)-2-[(Diphenylmethylene)amino]-4-pentenamide (11b)

The general procedure described previously using 10% aq. NaOH (11.65 g, 31.5 mmol), tetrabutylammonium hydrogen sulfate (4.38 g, 12.9 mmol), **10** (2.50 g, 10.5 mmol) in dichloromethane (20 mL), and allyl bromide (5.07 g, 42.0 mmol) gave a glassy oil, which was purified by flash column chromatography (SiO_2, first washed with hexanes–EtOAc–Et_3N (90:10:1)) using EtOAc–hexanes (50:50) to EtOAc–hexanes (85:15) to give **11b** as a white solid (2.20 g, 75%); mp 78–80 °C. IR (cm^{-1}): 1686, 3448. ^1H NMR δ: 2.54 (t, 2H, J = 6.6 Hz, CH_2), 4.07 (t, 1H, J = 5.9 Hz, CH), 5.04 (m, 2H, CH_2), 5.44 (br s, 1H, NH), 5.68 (m, 1H, CH), 6.82 (br s, 1H, NH), 7.10–7.66 (m, 10H, aromatic). ^{13}C NMR ($CDCl_3$) δ: 39.8, 65.9, 117.7, 127.8, 128.2, 128.6, 128.7, 128.9, 130.6, 134.0, 135.7, 139.3, 169.8, 175.3. Anal. calcd. for $C_{18}H_{18}N_2O$: C 77.67, H 6.52, N 10.06; found: C 77.36, H 6.52, N 10.00.

(±)-2-[(Diphenylmethylene)amino]-3-(4-chlorophenyl)propanamide (11c)

The general procedure described previously using 10% aq. NaOH (11.6 g, 31.5 mmol), tetrabutylammonium hydrogen sulfate (4.38 g, 12.9 mmol), **10** (2.50 g, 10.5 mmol) in dichloromethane (22 mL), and 4-chlorobenzyl bromide (2.65 g, 12.9 mmol) gave a white solid, which was purified by flash column chromatography (SiO_2, first washed with hexanes–EtOAc–Et_3N (90:10:1)) using EtOAc–hexanes (50:50) to EtOAc–hexanes (85:15) to give the alkylated product **11c** as a white solid (2.74 g, 72%); mp 181 to 182 °C. IR (cm^{-1}): 1681, 3441. ^1H NMR δ: 3.01 (dd, 1H, J = 9.6, 13.2 Hz, CH), 3.15 (dd, 1H, J = 3.3, 12.9 Hz, CH), 4.17 (q, 1H, J = 4.2 Hz, CH), 5.38 (br s, 1H, NH), 6.55 (d, 2H, J = 6.6 Hz, CH), 6.73 (br s, 1H, NH), 6.94–7.59 (m, 14H, aromatic). ^{13}C NMR ($CDCl_3$) δ: 42.4, 69.1, 128.9, 129.8, 130.1, 130.2, 132.3, 132.9, 133.9, 136.8, 137.8, 140.7, 171.9, 176.5. HRMS m/z calcd. for $C_{22}H_{20}N_2OCl$: 363.1186 ($M + Na^+$); found: 363.1252.

(±)-2-[(Diphenylmethylene)amino]butanamide (11d)

The general procedure described previously using 10% aq. NaOH (11.6 g, 31.5 mmol), tetrabutylammonium hydrogen sulfate (4.38 g, 12.9 mmol), **10** (2.50 g, 10.5 mmol) in dichloromethane (25 mL), and iodoethane (2.01 g, 12.9 mmol) gave a light yellow solid, which was purified by flash column chromatography (SiO_2, first washed with hexanes–EtOAc–Et_3N (90:10:1)) using EtOAc–hexanes (50:50) to EtOAc–hexanes (85:15) to give **11d** as a white solid (2.05 g, 73%); mp 116 to 117 °C. IR (cm^{-1}): 1686, 3451. ^1H NMR δ: 0.88 (t, 3H, J = 7.4 Hz, CH_3), 1.78–1.85 (m, 2H, CH_2), 3.93 (q, 1H, J = 3.9 Hz, CH), 5.41 (br s, 1H, NH), 6.80 (br s, 1H, NH), 7.10–7.68 (m, 10H, aromatic). ^{13}C NMR ($CDCl_3$) δ: 11.7, 30.3, 68.8, 129.3, 129.8, 130.2, 130.3, 130.4, 132.2, 137.4, 140.9, 171.0, 177.6. Anal. calcd. for $C_{17}H_{18}N_2O$: C 76.66, H 6.81, N 10.52; found: C 76.94, H 6.84, N 10.55.

General procedure for the alkylation of the benzophenone imines of α-monosubstituted amino amides (11) using KO-*t*-Bu to form the α,α-disubstituted products 12

The benzophenone imine of a monosubstituted α-amino amide (**11**, 1.98 mmol) and anhydr. THF (5 mL) were added at room temperature to a dried 15 mL round-bottomed flask containing a magnetic stirrer and an argon source. The solution was cooled to 0 °C and KO-*t*-Bu (1.0 mol/L in THF, 2.38 mmol) was added dropwise via syringe. The reaction mixture was stirred at 0 °C for 20 min. The alkylating agent (2.38 mmol) was added dropwise via syringe to the reaction mixture at 0 °C and the solution was stirred for 3 h. The reaction mixture was quenched with satd. NH_4Cl (5 mL), H_2O (10 mL), and CH_2Cl_2 (15 mL) were added. The layers were separated, the organic layer was washed with H_2O (2 × 10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (silica was washed with hexanes–EtOAc–Et_3N, 75:25:1) to give, in most cases, a solid product. Recrystallization from CH_2Cl_2–hexanes (1:15) gave the purified products **12**.

(±)-2-[(Diphenylmethylene)amino]-2-methyl-4-pentenamide (12a) and by-products (16–19)

The general procedure described in the previous section using **11a** (0.500 g, 1.98 mmol) and allyl bromide (0.287 g, 2.38 mmol) gave product **12a** as a white solid (0.35 g, 61%); mp 127–129 °C. R_f 0.39 (hexanes–EtOAc, 7:3). IR (cm^{-1}): 1682, 3438. ^1H NMR δ: 1.23 (s, 3H, CH_3), 2.25 (dd, 1H, J = 6.3, 14.3 Hz, CH), 2.69 (dd, 1H, J = 7.4, 14.7 Hz, CH), 5.05 (m, 2H, CH_2), 5.56 (bs, 1H, NH), 5.71–5.82 (m, 1H, CH), 7.12–7.52 (m, 10H, aromatic). ^{13}C NMR ($CDCl_3$) δ: 24.7, 43.9, 67.8, 117.6, 127.9, 128.0, 128.1, 128.6, 130.3, 133.6, 138.3, 166.9, 179.1. Anal. calcd. for $C_{19}H_{20}N_2O$: C 78.05, H 6.89, N 9.58; found: C 77.94, H 6.93, N 9.62.

Selected analytical data for the by-products

N-Allylated product **16**: R_f 0.62 (hexanes–EtOAc, 7:3). Selected ^1H NMR signals: 1.30 (d, 3H, CH_3), 4.00 (q, 1H, CH), 5.0–6.0 (m, 3H, vinyl of one allyl). LC–MS: 293. Cα,N-Diallylated product **17**: R_f 0.71 (hexanes–EtOAc, 7:3). Selected ^1H NMR signals: 1.23 (s, 3H, CH_3), 5.0–6.0 (m, 6 H, vinyls of two allyls). LC–MS: 333. N,N-Diallylated product **18**: R_f 0.52 (hexanes–EtOAc, 7:3). Selected ^1H NMR signals: 1.30 (d, 3H, CH_3), 4.00 (q, 1H, CH), 5.0–6.0 (m, 6H, vinyls of two allyls). LC–MS: 333. Cα,N,N-Triallylated product **19**: R_f 0.77 (hexanes–EtOAc, 7:3). Selected ^1H NMR signals: 1.23 (s, 3H, CH_3), 5.0–6.0 (m, 9H, vinyls of three allyls). LC–MS: 373.

(±)-2-[(Diphenylmethylene)amino]-2,5-dimethyl-4-hexenamide (12b)

The general procedure described previously using **11a** (0.500 g, 1.98 mmol) and 4-bromo-2-methyl-2-butene (0.355 g, 2.38 mmol) gave product **12b** as a white solid

(0.226 g, 36%); mp 127–129 °C. IR (cm^{-1}): 1638, 3442. ^1H NMR δ: 1.21 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.12 (dd, 1H, J = 5.9, 14.7 Hz, CH), 2.70 (dd, 1H, J = 7.3, 15.5 Hz, CH), 5.09 (m, 1H, CH), 5.59 (br s, 1H, NH), 7.18–7.53 (m, 10H, aromatic), 7.96 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 18.0, 24.5, 25.9, 38.6, 67.8, 119.2, 127.9, 128.1, 128.4, 130.2, 134.1, 138.4, 141.2, 179.6. Anal. calcd. for $C_{21}H_{24}N_2O$: C 78.71, H 7.55, N 8.74; found: C 78.51, H 7.59, N 8.74.

(±)-2-[(Diphenylmethylene)amino]-2,4-dimethyl-4-pentenamide (12c)

The general procedure described previously using **11a** (0.500 g, 1.98 mmol) and 3-bromo-2-methylpropene (0.320 g, 2.38 mmol) gave product **12c** as a white solid (0.314 g, 52%); mp 122 to 123 °C. IR (cm^{-1}): 1686, 3443. ^1H NMR δ: 1.28 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.96 (d, 1H, J = 16.2 Hz, CH), 2.80 (d, 1H, J = 16.2 Hz, CH), 4.76 (d, 2H, J = 26.5 Hz, CH_2), 5.56 (br s, 1H, NH), 7.21–7.52 (m, 10H, aromatic), 8.13 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 25.7, 28.5, 47.5, 68.8, 114.7, 129.3, 129.5, 129.6, 129.8, 130.1, 131.8, 139.9, 142.8, 143.2, 167.7, 181.3. HRMS *m/z* calcd. for $C_{20}H_{23}N_2O$: 307.1732 for (M + Na^+); found: 307.1797.

(±)-2-[(Diphenylmethylene)amino]-2-methyl-(5E)-phenyl-4-pentenamide (12d)

The general procedure described previously using **11a** (0.500 g, 1.98 mmol) and cinnamyl bromide (0.466 g, 2.38 mmol) gave product **12d** as a white solid (0.423 g, 58%); mp 149 to 150 °C. IR (cm^{-1}): 1686, 3442. ^1H NMR δ: 1.26 (s, 3H, CH_3), 2.40 (dd, 1H, J = 7.0, 13.6 Hz, CH), 2.84 (dd, 1H, J = 7.4, 14.0 Hz, CH), 5.55 (br s, 1H, NH), 6.15 (m, 1H, CH), 6.39 (d, 1H, J = 14.6 Hz, CH), 7.16–7.53 (m, 15H, aromatic), 7.94 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 26.4, 44.8, 69.8, 126.9, 127.8, 128.7, 129.5, 129.7, 129.8, 130.0, 130.3, 131.9, 134.4, 139.2, 140.0, 142.7, 168.7, 180.6. Anal. calcd. for $C_{25}H_{24}N_2O$: C 81.49, H 6.57, N 7.60; found: C 81.29, H 6.61, N 7.63.

(±)-2-[(Diphenylmethylene)amino]-2-(4-chlorophenyl)propanamide (12e)

The general procedure described previously using **11a** (0.500 g, 1.98 mmol) and 4-chlorobenzyl bromide (0.490 g, 2.38 mmol) in anhydr. THF (1 mL) gave product **12e** as a white solid (0.392 g, 53%); mp 147–149 °C. IR (cm^{-1}): 1686, 3444. ^1H NMR δ: 1.14 (s, 3H, CH_3), 2.87 (d, 1H, J = 14.0 Hz, CH), 3.25 (d, 1H, J = 13.2 Hz, CH), 5.39 (bs, 1H, NH), 7.05–7.50 (m, 14H, Ar). ^{13}C NMR ($CDCl_3$) δ: 26.4, 44.8, 69.8, 126.9, 127.8, 128.7, 129.5, 129.7, 129.8, 130.0, 131.9, 134.4, 139.2, 140.0, 142.7, 168.7, 180.6. Anal. calcd. for $C_{23}H_{21}ClN_2O$: C 73.30, H 5.62, Cl 9.41, N 7.43; found: C 73.06, H 5.62, Cl 9.52, N 7.43.

(±)-2-[(Diphenylmethylene)amino]-2-methylbutanamide (12g)

The general procedure described previously using **11a** (0.500 g, 1.98 mmol) and iodoethane (0.371 g, 2.38 mmol) gave of product **12g** as a white solid (0.129 g, 24%); mp 137 to 138 °C. IR (cm^{-1}): 1680, 3436. ^1H NMR δ: 0.87 (t, 3H, J = 7.6 Hz, CH_3), 1.22 (s, 3H, CH_3), 1.45 (m, 1H, CH), 1.96 (m, 1H, CH), 6.20 (br s, 1H, NH), 7.20–7.53 (m, 10H, aromatic), 8.14 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 10.7, 26.7, 33.9, 69.9, 129.3, 129.6, 129.7, 130.1, 131.8, 140.1, 142.8, 167.9, 181.7. Anal. calcd. for $C_{18}H_{20}N_2O$: C 77.11, H 7.19, N 9.99; found: C 76.83, H 7.28, N 9.82.

(±)-2-[(Diphenylmethylene)amino]-2,4-dimethylpentanamide (12h)

The general procedure described previously using **11a** (0.500 g, 1.98 mmol) and 1-iodo-2-methylpropane (0.437 g, 2.38 mmol) gave product **12h** as a white solid (0.150 g, 25%); mp 136–138 °C. IR (cm^{-1}): 1700, 3061. ^1H NMR δ: 0.86 (d, 3H, J = 6.6 Hz, CH_3), 0.93 (d, 3H, J = 6.6 Hz, CH_3), 1.16 (s, 3H, CH_3), 1.42 (dd, 1H, J = 5.1, 14.0 Hz, CH), 1.80 (m, 1H, CH), 1.97 (dd, 1H, J = 8.1, 14.0 Hz, CH), 5.57 (br s, 1H, NH), 7.19–7.53 (m, 10H, aromatic), 8.19 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 24.2, 25.8, 26.9, 28.4, 49.6, 68.9, 129.0, 129.6, 129.7, 129.8, 130.1, 130.2, 131.8, 140.1, 142.8, 167.8, 182.2. HRMS *m/z* calcd. for $C_{20}H_{25}N_2O$: 309.1889 (M + Na^+); found: 309.1961.

2-[(Diphenylmethylene)amino]-2-(2-propenyl)-4-pentenamide (12i)

The general procedure described previously using **11b** (0.500 g, 1.79 mmol) and allyl bromide (0.266 g, 2.16 mmol) gave the product **12i** as a solid (0.119 g, 21%); mp 138–140 °C. IR (cm^{-1}): 1691, 3435. ^1H NMR δ: 2.23 (dd, 2H, J = 6.3, 14.3 Hz, CH_2), 2.67 (dd, 2H, J = 7.4, 13.2 Hz, CH_2), 5.05 (m, 4H, CH_2), 5.73 (m, 2H, CH), 7.26–7.48 (m, 10H, aromatic), 8.72 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 43.6, 72.7, 119.3, 128.9, 129.7, 129.8, 130.5, 131.9, 134.7, 139.9, 142.8, 168.7, 179.4. Anal. calcd. for $C_{21}H_{22}N_2O$: C 79.21, H 6.96, N 8.80; found: C 79.34, H 7.01, N 8.80.

(±)-2-(4-Chlorobenzyl)-2-[(diphenylmethylene)amino]-4-pentenamide (12j) by allylation

The general procedure described previously using **11c** (0.500 g, 1.38 mmol) and allyl bromide (0.196 g, 1.65 mmol) gave product **12j** as a solid (0.139 g, 25%); mp 143 to 144 °C. IR (cm^{-1}): 1686, 2360, 3442. ^1H NMR δ: 2.27 (dd, 1H, J = 5.9, 14.7 Hz, CH), 2.71 (dd, 1H, J = 7.4, 14.7 Hz, CH), 2.89 (d, 1H, J = 14.0 Hz, CH), 3.23 (d, 1H, J = 14.7 Hz, CH), 5.05 (d, 2H, J = 12.5 Hz, CH_2), 5.53 (br s, 1H, NH), 5.72 (m, 1H, CH), 7.09–7.49 (m, 14H, aromatic), 7.93 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 43.3, 45.3, 72.8, 119.7, 128.9, 129.7, 129.8, 129.9, 130.6, 132.1, 132.6, 133.8, 134.4, 137.2, 139.8, 142.6, 168.7, 178.7. HRMS *m/z* calcd. for $C_{25}H_{24}N_2OCl$: 403.1499 (M + Na^+); found: 403.1595.

(±)-2-(4-Chlorobenzyl)-2-[(diphenylmethylene)amino]-4-pentenamide (12j) by benzylation

The general procedure described previously using **11b** (0.250 g, 0.90 mmol) and 4-chlorobenzyl bromide (0.222 g, 1.08 mmol) in THF (1 mL) gave product **12j** as a solid (0.036 g, 10%). See previous analytical data.

(±)-2-[(Diphenylmethylene)amino]-2-ethyl-4-pentenamide (12k)

The general procedure described previously using **11d** (0.500 g, 1.87 mmol) and allyl bromide (0.273 g,

2.25 mmol) gave the product **12k** as a solid (0.075 g, 13%); mp 136 to 137 °C. IR (cm^{-1}): 1679, 3447. ^1H NMR δ: 0.85 (t, 3H, J = 7.4 Hz, CH_3), 1.43 (m, 1H, CH), 1.94 (m, 1H, CH), 2.20 (dd, 1H, J = 6.6, 14.7 Hz, CH), 2.64 (dd, 1H, J = 7.4, 14.7 Hz, CH), 5.03 (m, 2H, CH_2), 5.74 (m, 2H, CH_2), 7.24–7.49 (m, 10H, aromatic), 8.33 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 1.6, 10.3, 32.3, 44.1, 44.2, 119.0, 128.6, 129.6, 129.7, 129.8, 129.9, 130.3, 131.6, 131.8, 133.9, 135.0, 168.2, 187.5. Anal. calcd. for $C_{20}H_{22}N_2O$: C 78.40, H 7.24, N 9.14; found: C 78.28, H 7.26, N 9.13.

Michael addition of the benzophenone imine of alaninamide

1,1-Dimethylethyl (±)-5-amino-4-[(diphenylmethylene)amino]-4-methyl-5-oxopentanoate (20)

2-[(Diphenylmethylene)amino]propanamide (**11a**, 0.500 g, 1.98 mmol) and anhydr. THF (5 mL) were added at room temperature to a dried 15 mL round-bottomed flask containing a magnetic stirrer and an argon source. The solution was cooled to 0 °C and *tert*-butyl acrylate (0.305 g, 2.38 mmol) followed by KO-*t*-Bu (1.0 mol/L in THF, 0.238 mL, 0.238 mmol) were added dropwise via syringe. The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with satd. NH_4Cl (5 mL), H_2O (10 mL), and CH_2Cl_2 (15 mL) were added. The layers were separated, the organic layer was washed with H_2O (2 × 10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (silica was washed with hexanes–EtOAc–Et_3N, 75:25:1) to give product **20** as a white solid (0.242 g, 32%). Recrystallization from CH_2Cl_2–hexanes (1:15) gave the purified product; mp 161 to 162 °C. IR (cm^{-1}): 1686, 3438. ^1H NMR δ: 1.20 (s, 3H, CH_3), 1.38 (s, 9H, *tert*-butyl), 1.77–1.81 (m, 2H, CH_2), 6.10 (br s, 1H, NH), 7.22–7.52 (m, 10H, aromatic), 8.03 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 24.3, 24.9, 28.0, 30.5, 31.1, 33.1, 34.7, 62.1, 66.8, 125.8, 125.9, 127.7, 128.1, 128.2, 128.4, 128.5, 128.6, 130.4, 138.1, 140.9, 145.3, 146.0, 167.3, 172.2, 172.7, 179.4, 179.8. HRMS *m/z* calcd. for $C_{23}H_{29}N_2O_3$: 381.2100 ($M + Na^+$); found: 381.2187.

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Cyclotrimerization approach to unnatural structural modifications of pancratistatin and other amaryllidaceae constituents — Synthesis and biological evaluation[1]

Tomas Hudlicky, Michael Moser, Scott C. Banfield, Uwe Rinner, Jean-Charles Chapuis, and George R. Pettit

Abstract: The phenanthridone core of pancratistatin lacking all aromatic oxygenation was prepared by cyclotrimerization of acetylene-containing scaffolds **30** and **41**, reflecting the natural and the C-1 epi configuration, respectively, of the amino inositol moiety. The cobalt-catalyzed formation of the aromatic core led to bisTMS derivatives **39** and **48**, as well as bisacetyl derivative **51**. The effectiveness of cyclotrimerization of the natural or trans series was compared with that of the cis series. In addition, the yields of cyclotrimerization were compared for propargylic amines and propargylic amides. Eleven derivatives, including the fully hydroxylated phenantridone **39**, were tested against seven cancer cell lines. Three of the compounds displayed activities only an order of magnitude less than those of 7-deoxypancratistatin. Full experimental and spectral details are provided for all key compounds and future projections for the preparation of unnatural analogs of Amaryllidaceae constituents are advanced, along with some new insight into the minimum pharmacophore of pancratistatin.

Key words: cyclotrimerization, alkaloids, cobalt catalyst.

Résumé : Faisant appel à une cyclotrimérisation des dérivés acétyléniques **30** et **41** qui reflètent respectivement les configurations naturelle et C-1-épi, on a préparé la phénanthridone, le squelette fondamental de la pancratistatine ne comportant pas d'oxygène aromatique. La formation catalysée par le cobalt du noyau fondamental à conduit aux dérivés bisTMS **39** et **48** ainsi qu'au dérivé bisacétylé **51**. On a comparé l'efficacité de la cyclotrimérisation de la série nature ou trans avec celle de la série cis. De plus, on a comparé les rendements des cyclotrimérisations avec des amines et des amides propargyliques. Onze dérivés, y compris la phénantridone totalement hydroxylé (**39**) ont été évalués contre sept souches de cancer. Trois de ces composés présentent des activités qui ne sont qu'un ordre de grandeur inférieures à celle de la 7-désoxypancratistatine. On rapporte l'ensemble des détails expérimentaux et spectraux relatifs à tous les intermédiaires clés. Les projections relatives à la préparation d'analogues non naturels des constituants de l'Amaryllidaceae sont avancées et l'on possède déjà de nombreuses pistes nouvelles concernant la nature du pharmacophore minimal de la pancratistatine.

Mots clés : cyclotrimérisation, alcaloïdes, catalyseur de cobalt.

[Traduit par la Rédaction]

Introduction

Pancratistatin (**1**) and its congeners (Fig. 1) have been at the forefront of activities in both synthetic and medicinal communities (1). All four naturally occurring constituents have been synthesized by many creative approaches (2–5), and significant effort has been devoted to the investigation of the mode of action (6), active pharmacophore (7), and more bioavailable agents (8). To date many truncated versions of the key constituents have been prepared (9) and evaluated for activities against several cancer cell lines. From the results of these evaluations, several generalizations

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Dedicated to Dr. Alfred Bader in recognition of his service to the organic chemistry community.

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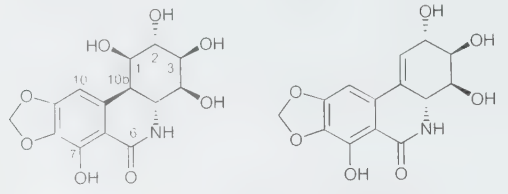
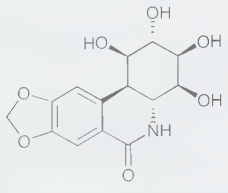
Fig. 1. Amaryllidaceae constituents (**1**–**4**) and some recently synthesized unnatural mimics (**5**–**7**).

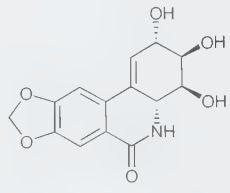


Pancratistatin (**1**)

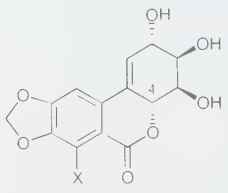
Narciclasine (**2**)



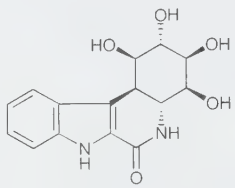
7-Deoxypancratistatin (**3**)



Lycoricidine (**4**)



5 Lactone narciclasine mimic, X = OH
6 Lactone lycoricidine mimic, X = H



7 β-Carboline-1-one mimic

have emerged with regard to the structural elements essential to activity. First, the hydroxyphenanthridone moiety is thought to be essential to high activity of pancratistatin and narciclasine; its deletion, as in 7-deoxypancratistatin and lycoricidine, leads to a significant drop in activity (10). Second, the amino inositol motif is also essential, save for small changes at C-1 and C-2; deletion of the hydroxyls at these positions or altering substitution patterns at C-1 does not altogether eliminate activity (7, 11). Various unnatural derivatives with specific deletions in the hydroxylated ring have been tested. A recent article established that the minimum requirement for activity is the 2,3,4-triol pattern found in all active constituents (11). Third, deletion of some of the aromatic oxygenation lowers activity significantly (12). Fourth, recently synthesized lactone mimics **5** and **6**, in both configurations at C-4, were found inactive, suggesting that the phenanthridone unit is essential for retention of activity (13). Finally, an indole mimic of pancratistatin (**7**) recently prepared in our laboratory possessed borderline activity against one cell line (Table 1) (14).

These observations, as well as the bioavailability studies, indicate that the greatest opportunity for structural alterations exists in modifications of the aromatic core of the natural product. To prepare a large number of derivatives, a diversity-oriented synthesis strategy (DOS) is the most efficient way to generate libraries of compounds for testing. Rather than synthesize uniquely functionalized aryl residues for eventual attachment to the amino inositol unit, we have chosen the cyclotrimerization approach portrayed in Fig. 2, which is based on acetylene- and nitrile-containing scaffolds and their cobalt-catalyzed trimerization to aromatic (15) and heteroaromatic (16) variants of the pancratistatin type. This unique transformation was discovered in 1864 by Berthelot (17), who prepared benzene by passing acetylene over hot copper. We note that Berthelot's paper, published in 1866, is usually cited as the event of original discovery (17*b*, 17*c*). This is not the correct citation and for historical interest we include the original description of his 1864 experiment here:

Il est un cas de condensation de l'acetylene naissant très-remarquable et qui mérite un examen particulier, bien que la démonstration en soit plutôt vraisemblable que rigoureusement établie: c'est la condensation de l'acétylène en benzine. Entre la formule de l'acétylène, C^4H^2, et celle de la benzine $C^{12}H^6$, c'est-à-dire entre les poids de ces deux corps ramenés à l'état gazeux et au même volume, il existe une relation très-simple; la deuxième formule est triple de la première :

$$3\ C^4H^2 = C^{12}H^6.$$

Or cette relation n'existe pas seulement entre les formulas des deux corps; mais on peut admettre que, dans certaines circonstances que nous allons signaler, l'acétylène naissant se transforme réellement en benzine. Voici ces circonstances.

Nous avons vu précédemment (p. 286) qu'en faisant passer un courant de vapeur de formène trichloré (chloroforme), C^2HCl^3, sur du cuivre chauffé au rouge, le chlore est absorbé et l'acétylène prend naissance. Répétons cette expérience avec le formène tribromé (bromoforme), C^2HBr^3, nous obtiendrons de la benzine. Nous sommes donc autorisés à penser que 3 molécules d'acétylène naissant peuvent se condenser en une seule molécule de benzine : la benzine serait alors du triacétylène.

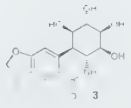
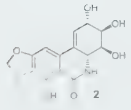
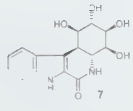
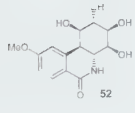
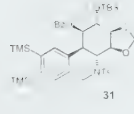
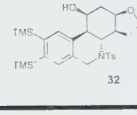
This is an example of condensation of the nascent acetylene that is very remarkable and deserves a close examination, even though the demonstration is rather plausible then rigorously established: it is the condensation of the acetylene into benzene. There is a very simple relationship between the formula of acetylene, C_4H_2, and the formula of benzene, $C_{12}H_6$, specifically between the weight of equal volumes of those two bodies in the gas state: the second formula is triple of the first:

$$3\ C_4H_2 = C_{12}H_6.$$

Now such relation does not just exist between the formulas of the two bodies; but we can admit that under certain particular circumstances that we may point to, nascent acetylene is actually transformed to benzene. We have already seen (p.286) that by passing a stream of gaseous trichlorinated formene (chloroform), C_2HCl_3, over red-hot copper, chlorine is absorbed and acetylene is generated. By repeating this experience with tribrominated formene (bromofrom), C_2HBr_3, we would obtain some benzene. This leads us to think that three molecules of nascent acetylene could combine to form a single molecule of benzene. Thus benzene would be a triacetylene.

The reaction enjoyed moderate attention and, indeed, exhibited moderate yields in most of the documented examples in the literature, including recent applications (18). An ex-

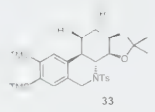
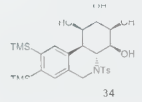
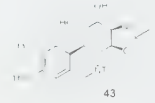
Table 1. Evaluation of the activities of aromatic deoxygenated TMS derivatives of 7-deoxypancratistatin.

		Murine P388 lumphocytic leukemia and human cancer cell results (GI_{50} values in μg/mL)						
Entry	Compound	Murine P388 lymphocytic leukemia	Pancreas BXPC-3	Breast MCF-7	CNS SF-268	Lung NCI-H460	Colon KM20L2	Prostate DU-145
2	 3	0.44				0.29	0.22	
3	 2	0.0012	0.026	0.019	0.021	0.032	0.021	0.011
4	 7	18.3	>10	>10			>10	
5	 52	4.3	4.9	4.4	3.3	2.8	3.6	2.6
6	 31	> 10	> 10	> 10	> 10	> 10	> 10	> 10
7	 32		3.6	2.2	3.8	4.7	3.1	13.1

ception to such critique is found in the classic application of cyclotrimerization to the total synthesis of estrone by Funk and Vollhardt in 1977 (19), shown in Fig. 3. Despite the attention this synthesis received, only once more was this technique featured in a total synthesis effort — an approach to morphine also disclosed by Vollhardt and co-workers (20) (Fig. 3). In the estrone synthesis, the initial cyclization furnished a low yield of **13** in addition to the intermediate benzocyclobutane, which, under the conditions of the reaction, underwent [4+2] cyclization to **13** in a total yield of 71%. In the approach to morphine, benzofuran **15** yielded the tetracyclic morphine skeleton as a single diastereomer with C-5, C-9, and C-13 correctly set, indicating the potential for adjustment to the total synthesis of morphine itself, once appropriate substitution parameters for the incipient quaternary center at C-13 were designed. The emphasis on multicomponent reactions and cascade processes, so prevalent in the last decade or so (21, 22), seemed in sharp contrast to the apparent underutilization of cyclotrimerization techniques that satisfy both of these criteria. We reasoned that the modest yields reported in most of the applications could be addressed though appropriate reaction engineering and optimization of conditions. The benefits that would be harvested in the area of structure and activity relationships (SAR) for the analogs of the pancratistatin group of compounds seemed to outweigh the uncertainty and expectations of moderate yields in the construction of aromatic nuclei of the analogs.

In this manuscript we report the successful synthesis of several pancratistatin analogs by a high-yielding cyclotri-

Table 1 (*concluded*).

Entry	Compound	Murine P388 lymphocytic leukemia	Pancreas BXPC-3	Breast MCF-7	CNS SF-268	Lung NCI-H460	Colon KM20L2	Prostate DU-145
		Murine P388 lumphocytic leukemia and human cancer cell results (GI_{50} values in μg/mL)						
8	 33	3.0	1.7	1.5	1.6	1.7	1.6	1.6
9	 34	3.3	1.7	1.7	1.6	1.7	1.4	1.8
10	 43	3.9						

Note: Compounds 36, 37, 38, 39, 44, and 48 are marginally inactive to completely inactive in the p388 leukemia cell lines.

merization protocol from fully functionalized scaffolds of type **9** (23). The biological evaluation of the analogs, also reported herein, provided some surprising results and cast some uncertainty on the previously held views regarding some of the structural features deemed essential for biological function.

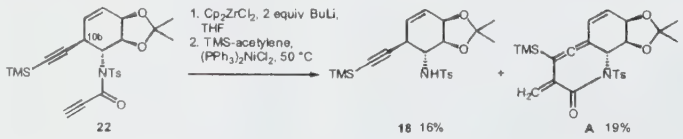
Results and discussion

The original intent of our study was the investigation of a de *novo* approach to pancratistatin (**1**) from scaffold **9** in which the acetylene partners would provide a triply silylated arene that could be converted to the fully oxygenated core of pancratistatin. Portrayed in Scheme 1 are the results of this particular approach, which met with abject failure because of the steric issues associated with multiply silylated sites or perhaps random desilylation processes similar to those observed when Rainier used an iron-based catalyst (24). Only the cobalt-coordinated tetracycle **20** was isolated in low yield from the reactions of bisacetylene **19** (Scheme 1). The final cycloaddition of bis(trimethylsilyl)acetylene (BTMSA) did not lead to the fully silylated arene **21**, presumably because of steric crowding.

When $Ni(COD)_2$ was employed as a catalyst, the cyclotrimerization of **22** gave an interesting dimeric product (**23**) in 47% yield. The use of a zirconium catalyst (25) did not lead to dimeric **23** and gave other products.[3]

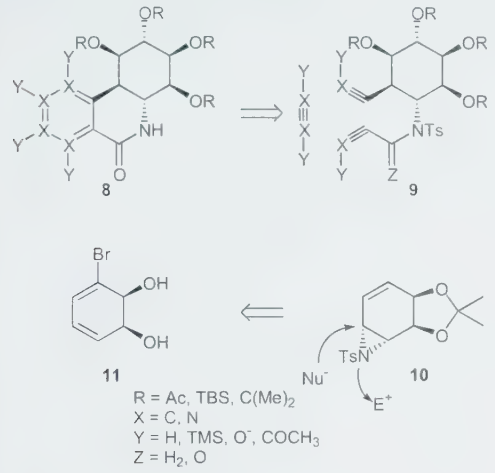
Adjustments in the strategic plan led to the construction of simpler scaffolds unencumbered by TMS groups and cyclotrimerization attempts to attain a 7-deoxypancratistatin

[3] The exposure of propargylic amide **22** to a zirconium-based catalyst led to some unusal results. The propargylic amide was lost and tosylamide **18** was recovered, in addition to an unusual structure, tentatively identified as cyclic allene **A**, which may result in an ene reaction between the propargyl group and the hydrogen at 10b.



A [(1*R*,2*S*,6*R*)-4,4-Dimethyl-12-methylene-14-(4-methylphenylsulfonyl)-11-trimethylsilyl-3,5-dioxa-14-azatricyclo-[7.5.0.$0^{2,6}$]tetradeca-7,9,10-trien-13-one]: $[\alpha]^{28}_{D}$ +79.0 (c 0.95, $CHCl_3$). R_f 0.81 (hexanes – ethyl acetate, 4:1). IR ($CHCl_3$, cm^{-1}) ν: 3683, 3020, 2962, 2932, 2401, 2167, 1736, 1660, 1598, 1509, 1374, 1308, 1278, 1251, 1216, 1189, 1176, 1091, 1063, 950, 908, 847, 757, 669, 582. ^1H NMR (300 MHz, $CDCl_3$, 50 °C, ppm) δ: 8.00 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.11 (s, 1H), 5.80 (dd, *J* = 9.9, 3.1 Hz, 1H), 5.64 (d, *J* = 10.2 Hz, 1H), 4.71 (t, *J* = 5.0 Hz, 1H), 4.63 (d, *J* = 4.8 Hz, 1H), 4.40 (m, 1 H), 2.43 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 0.14 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 145.6, 142.7, 135.5, 129.8, 128.9, 128.0, 125.1, 121.5, 110.7, 104.0, 77.5, 74.4, 69.8, 62.9, 41.0, 28.1, 27.0, 22.0, 0.0. MS (EI) *m/z* (relative intensity): 456 (M^+ CH_3, 30), 415 (10), 414 (30), 413 (23), 259 (11), 258 (30), 242 (7), 230 (10), 220 (5), 215 (5), 161 (6), 156 (8), 155 (29), 149 (11), 140 (5), 139 (13), 129 (6), 108 (5), 107 (7), 106 (12), 105 (9), 99 (6), 98 (11). HRMS (EI) calcd. for $C_{23}H_{26}O_5NSSi$-CH_3: 456.1301; found: 456.1289.

Fig. 2. Cyclotrimerization approach to aromatic core variants of pancratistatin.



substitution pattern instead. These efforts were divided into three distinct areas: (*i*) synthesis of building blocks exhibiting the stereochemistry of the "natural" or trans series, with respect to stereochemical configuration at C-1 and C-2; (*ii*) synthesis of the corresponding "unnatural" or cis series; and (*iii*) comparison of the overall efficiency of these two approaches with one that would employ propargyl amides vs. propargyl amines. Upon attaining the nucleus of Amaryllidaceae constituents, all of these approaches would be evaluated and the best one chosen for the eventual production of analogs.

Cyclotrimerization of scaffolds in the trans or natural series

The intermediate reflecting the natural amino inositol configuration was synthesized as shown in Scheme 2 (23). Vinylaziridine **10** (26) was reacted with the aluminum complex prepared from lithium (trimethylsilyl)acetylene to provide **18** in 69% yield. After column chromatography, the product of this reaction was treated with 2,2-dimethoxypropane (DMP) and acetone to reprotect the diol liberated in the portion of the mixture by the action of $AlCl_3$. The reprotected compound was used without further purification. The tosylaziridine **18** was first converted to the cis-diol **24** by the action of OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO) (44% yield, 76% conversion), and the cyclic sulfate **25** was then generated in 82% yield by treatment with SO_2Cl_2 and NEt_3. Cyclic sulfates, whose reactivity resembles that of epoxides (27), are easily opened with weak nucleophiles such as ammonium benzoate. Such opening generates the required trans relationship at C-1/C-2 of pancratistatin, as has been previously demonstrated (27*b*). Treatment of **25** with ammonium benzoate generated, surprisingly, a mixture of the desired **26**, as a minor product accompanied by the elimination product **27**, displaying the substitution parameters of narciclasine or lycoricidine. Investigation of this reaction revealed that **27** does not originate in **26** nor is it derived from **25** by syn elimination. Careful experimentation revealed that the likely source of **27** is the intramolecular elimination of proton at C-10b by the intermediate sulfate anion **25a** as shown in Fig. 4. Further study is required to optimize the production of either **26** or **27**, the latter containing the structural features of narciclasine.

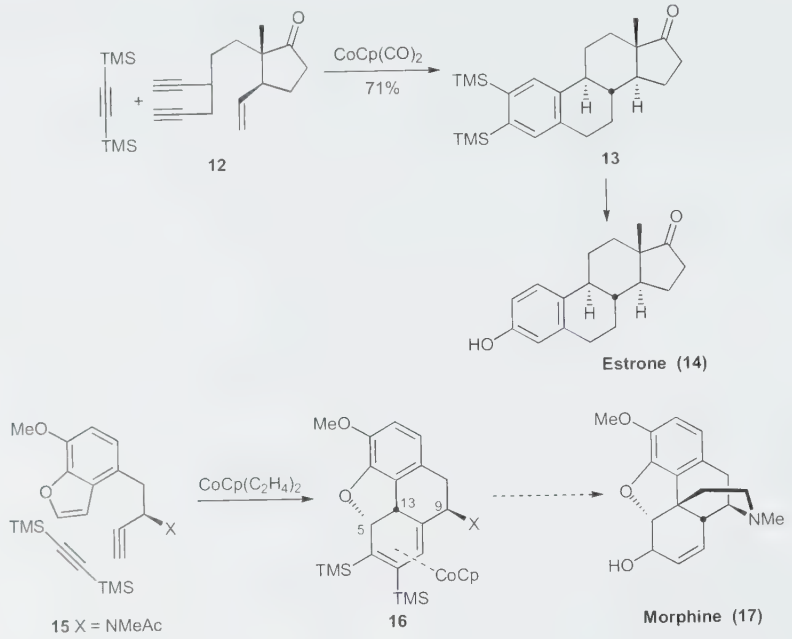
The TMS group was removed with tetrabutylammonium triphenyldifluorosilicate (TBAT) in 84% yield from acetylene **26** to avoid previously encountered problems with steric bulk at the incipient C-10 of the aromatic nucleus. Following the protection of the C-2 alcohol as a TBS ether (89%), tosylamide **29** was alkylated with propargyl bromide to yield the required compound **30** in 79% yield. As mentioned above, the prospects for high yields in the cyclotrimerization were not promising based on the rather modest yields reported throughout the literature. Yet, after optimization, acetylene derivative **30** was converted to tetracyclic tosylamide **31** in 83% yield (slow addition over 36 h of a mixture of **30**, catalyst, and BTMSA to a heated solution of BTMSA, which was recovered by distillation upon completion of the reaction). Tosylamide **31** was converted to fully deprotected tetraol **34** (as shown in Scheme 3) to provide compounds lacking the phenanthridone carbonyl group for biological evaluation. Oxidation of **31** to the state of phenanthridone proved somewhat arduous, proceeding in 15% yield to **35** with $NaIO_4$–$RuCl_3$. Oxidation studies on bisbenzoate **37** led to the same results under these conditions. With the reaction buffered by solid Na_2CO_3, the oxidation occurred more slowly to give **38** in 33% yield. This material was subjected to reductive detosylation with sodium naphthalide, during which a partial loss of the benzoate groups occurred as a result of the basic conditions. The crude material was treated first under stronger basic conditions CH_3ONa in MeOH) then under acidic conditions (Dowex 50WX8-100 in MeOH) to provide the 7-deoxypancratistatin nucleus having TMS groups in place of the aromatic oxygenation. The preparation of this key compound in 14 steps and 0.3% overall yield starting from aziridine **10** signified the successful validation of the cyclotrimerization strategy as an approach to compounds with variations in the aromatic core.

Cyclotrimerization of scaffolds in the cis or unnatural series

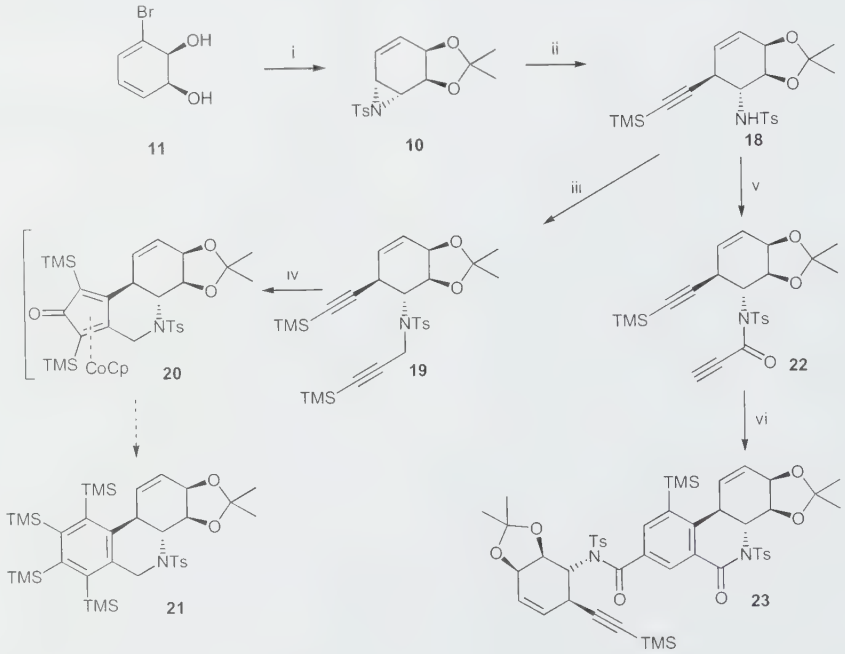
The unnatural or cis series intermediate was synthesized as shown in Scheme 4. The purpose of this approach was twofold. First, it would avoid the lack of selectivity in the cyclic sulfate opening encountered with **25**, leaving this reaction for the latter part of the synthesis. Second, it would provide the analogs with unnatural C-1 configuration for biological testing. The bisbenzoate **41** was subjected to cyclotrimerization under the optimized conditions applied to compound **30** in the trans series and provided tetracycle **42** in 87% yield (as shown in Scheme 5).

Deprotection of the benzoate and generation of the cyclic sulfate was accomplished in high yield and *trans*-benzoate alcohol **36** was generated in essentially quantitative yield. Upon exposure of **44** to ammonium benzoate in dimethylformamide (DMF) in this series, the elimination to the narciclasine/lycoricidine manifold was not observed. A possible explanation may lie in the relative acidities of propargylic vs. benzylic protons at C-10b in **25** vs. **44**, respectively. Fully deprotected analogs **34** (lacking the phenanthridone carbonyl) and **39** (containing the amide) were ob-

Fig. 3. Applications of cyclotrimerization strategy in total synthesis (Vollhardt's estrone and morphine).



Scheme 1. Cyclotrimerization approach to fully silylated aromatic core. Reagents and conditions: (*i*) DMP, *p*-TSA, acetone, rt, then PhINTs, $Cu(acac)_2$, H_3CCN, 0 °C to rt, then *n*-Bu_3SnH, AIBN, THF, reflux, 25% over three steps; (*ii*) BuLi, TMS–acetylene, $AlCl_3$, toluene, 0 °C to rt, then DMP, *p*-TSA, acetone, rt, 69% over two steps; (*iii*) BuLi, TMS – propargyl bromide, $(n\text{-}Bu)_4NI$, THF, rt, 46% (66% by conversion); (*iv*) $CpCo(CO)_2$, BTMSA, 140 °C; (*v*) BuLi, propiolic acid anhydride, THF, 0 °C to rt, 46%; (*vi*) $Ni(COD)_2$, PPh_3, toluene, BTMSA, rt, 47%.



Scheme 2. Scaffold for cyclotrimerization in the trans or natural series. Reagents and conditions: (*i*) BuLi, TMS–acetylene, $AlCl_3$, toluene, 0 °C to rt; (*ii*) DMP, acetone, rt, 69% over two steps; (*iii*) OsO_4, NMO, CH_2Cl_2, rt, 44% (76% by conversion); (*iv*) SO_2Cl_2, NEt_3, CH_2Cl_2, 0 °C to rt, 82%; (*v*) $H_5C_6COONH_4$, DMF, 70 °C, then H_2O, H_2SO_4, THF, rt; (*vi*) TBAT, H_3CCN, rt, 84%; (*vii*) TBSCl, imidazole, DMF, rt, 89%; (*viii*) NaHMDS, propargyl bromide, $(n\text{Bu})_4NI$, THF, –0 °C to rt, 79%.

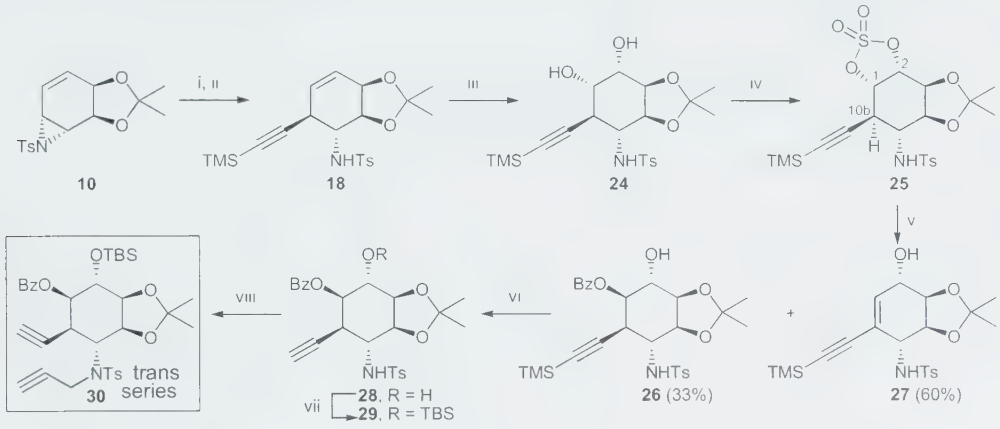
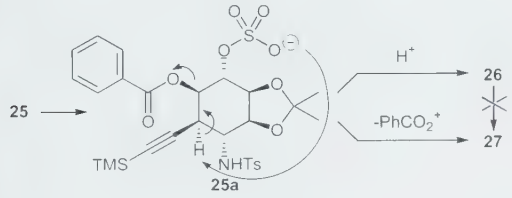


Fig. 4. Generation of enyne **25**.



tained in a manner similar to that employed in the trans series. Overall, the cis series synthesis of phenanthridone **48** proved to be three times higher yielding because of higher selectivity in the cyclic sulfate opening. The eventual synthesis of C-1 epimeric analogs would originate in the cis-diol **24**.

Cyclotrimerization of propargyl amides

To avoid the modest yields of benzylic oxidation in the tetracycles **31** and **37**, we chose to investigate the cyclotrimerization protocol on propargylic amides, which could be easily generated by acylation of tosylamide **18**. Initially, the enyne **45**, obtained by acylation of **18** with propiolic acid anhydride, was chosen for this purpose (as shown in Scheme 6). Cyclotrimerization of this material furnished metal complex **46** in 11% yield and with apparent isomerization of the olefin to the configuration representing 2-deoxylycoricidine. When **47** was synthesized from **40** in 35% yield over two steps (cis series) and subjected to the same optimized conditions for cyclotrimerization, the tetracyclic phenanthridone **48** was obtained in 5% yield. It remains unclear whether these low yields are a function of unfavorable rotamer population of the imides such as **45** or **47** or whether the additional basic oxygen interferes with the catalytic cycle by complexation with the catalyst. Apparently these issues did not prevent the aforementioned cyclotrimerization of amide **22** to the dimeric phenanthridone **23** obtained in 47% yield (Scheme 1).

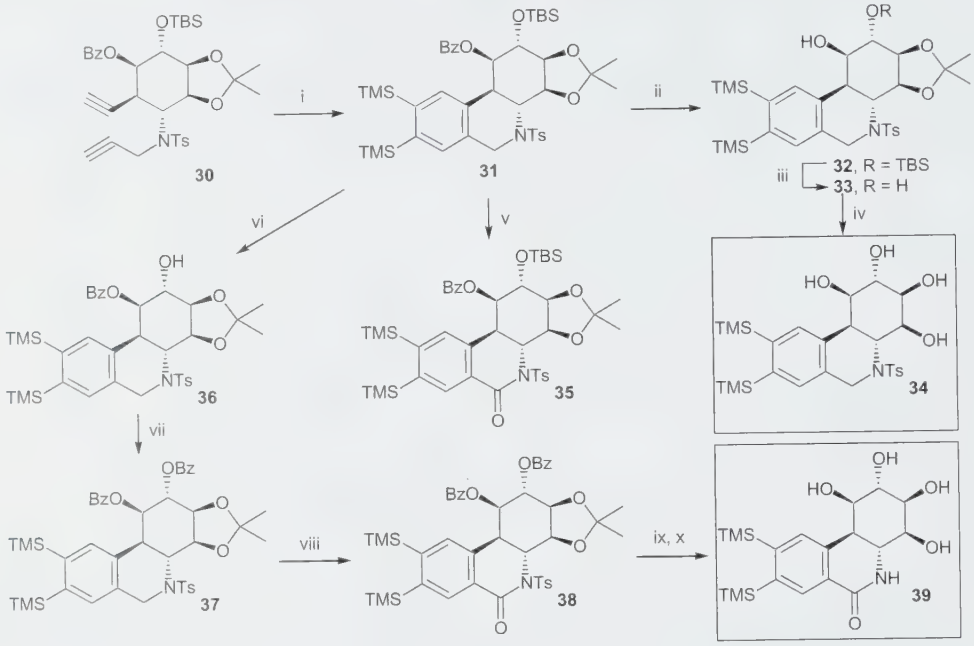
Synthesis of the bisacetyl derivative of 7-deoxypancratistatin

As a prelude to a de novo synthesis of one of the Amaryllidaceae constituents, we decided to prepare the bisacetyl derivative **51** shown in Scheme 7. Both arylsilanes and acetophenones should respond to Tamao oxidation (28) or Baeyer–Villiger oxidation (29), respectively, as means of generating the required oxygenation of the aromatic nucleus. Having noticed the experimental difficulties experienced by Vollhardt and Funk (19) in establishing the phenolic unit in estrone from a TMS group, we thought the bis(acetyl)arene would provide an alternative way to accomplish this task. To this end, the cyclotrimerization of bisacetylene **41** (cis series) was performed with hex-3-yne-2,5-diol protected as a bisTBS ether **49**. Tetracycle **50** was obtained as a mixture of diastereomers in 31% yield. The mixture was treated with tetrabutylammonium fluoride (TBAF) and oxidized to the bisacylated tetracycle **51** in 51% yield over two steps. In future endeavors, the oxidation of this compound to acetyl catechols will be pursued as the means of establishing the C-8/C-9 oxygenation of pancratistatin-type constituents.

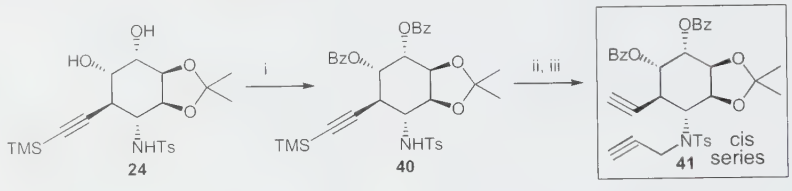
Biological evaluation

Several of the compounds in both the trans or natural and the C-1 epimeric series were evaluated in the cancer cell line series listed in Table 1. The activity profiles of pancratistatin, 7-deoxypancratistatin, and narciclasine (Table 1, entries 1, 2, and 3, respectively) are shown for comparison, along with two unnatural analogs previously synthesized in our laboratory (Table 1, entries 4 and 5). Some rather surprising and unexpected results were obtained. While the fully protected core of 7-deoxypancratistatin (Table 1, entry 6) is essentially inactive, the partially deprotected intermediates (Table 1, entries 7 and 8), as well as the fully deprotected tetraol (Table 1, entry 9) are quite active, having activities only 10-fold less than those of 7-deoxypancratistatin. This is surprising for several reasons: First, it has been widely held that the phenathridone amide carbonyl is essential for activity, since Chapleur and co-workers (13) demonstrated that

Scheme 3. Cyclotrimerization of the trans scaffold. Reagents and conditions: (*i*) $CpCo(CO)_2$, BTMSA, xylene, 140 °C, 83%; (*ii*) NaOMe, MeOH, rt, 99%; (*iii*) TBAF, THF, rt, 85%; (*iv*) Dowex 50WX8-100, MeOH, 70 °C, 79%; (*v*) $NaIO_4$, $RuCl_3$, CH_3CN–CCl_4–H_2O, rt, 15%; (*vi*) TBAF, THF, rt, 84%; (*vii*) BzCl, pyridine, rt, 86%; (*viii*) $NaIO_4$, $RuCl_3$, Na_2CO_3, CH_3CN–CCl_4–H_2O, rt, 33%; (*ix*) Na-naphthalide, THF, –65 °C, then NaOMe, MeOH, rt, 32%; (*x*) Dowex 50WX8-100, MeOH, 70 °C, 94%.



Scheme 4. Scaffold for cyclotrimerization in the cis or unnatural series. Reagents and conditions: (*i*) BzCl, pyridine, 0 °C to rt, 80%; (*ii*) TBAT, H_3CCN, rt, 76%; (*iii*) NaHMDS, propargyl bromide, $(n\text{Bu})_4NI$, THF, –70 °C to rt, 94%.

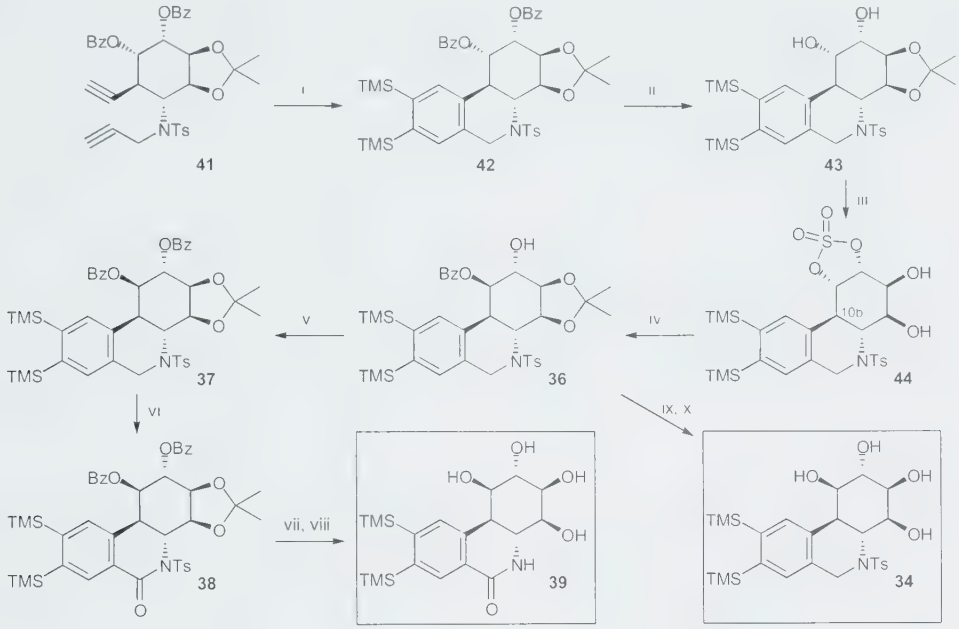


the lactone analogs **5** and **6** are inactive. Second, these compounds represent the first examples of pancratistatin analogs that retain activity despite the absence of all aromatic oxygenation, in addition to lacking the amide moiety. Third, and very surprising, these derivatives have shown greater activity than the fully deprotected bisTMS derivative **39** (Table 1, entry 16) in which the phenanthridone amide is present. This difference in activity may also be ascribed to the fact that a tosyl group is a common pharmacophore and several truncated derivatives of pancratistatin containing tosyl groups were shown to be more active than those lacking it (9*c*). As it has been assumed that the phenolic hydroxyl and the amide may be required as a donor–acceptor pair for hydrogen bonding, our results indicate that these requirements may be offset by other structural features. The only other active compound was the C-1 epimeric diol (Table 1, entry 10), where activity supports the observation that changes at C-1 of the pharmacophore do not drastically alter biological profiles. The fact that four of the intermediates displayed profiles only an order of magnitude lower that those of 7-deoxypancratistatin is promising and will guide us in further design of unnatural analogs with variable functionality in the aromatic core.

Summary and conclusion

The successful synthesis of several analogs of pancratistatin was achieved by the cobalt-catalyzed cyclotrimerization of acetylenic scaffolds with BTMSA and protected 2,5-hex-3-yne. Both configurations at the C-1 hydroxylated aminoinositol unit were examined, with the unnatural, or cis series, being clearly a higher-yielding and more efficient process. The cyclotrimerizations of bisacetylenes with *N*-propargylic substituents were also much higher yielding than the corresponding processes that employed the propargylic amides. The attainment of bisacetyl derivative **51** bodes well for eventual installation of the methylenedioxy unit via the Baeyer–Villiger reaction in a de novo synthesis of 7-

Scheme 5. Cyclotrimerization of the cis scaffold. Reagents and conditions: (*i*) $CpCo(CO)_2$, BTMSA, xylene, 140 °C, 87%; (*ii*) 1% NaOH, MeOH, rt, 99%; (*iii*) SO_2Cl_2, NEt_3, CH_2Cl_2, 0 °C to rt, 70%; (*iv*) $H_5C_6COONH_4$, DMF, 70 °C, 99%; (*v*) BzCl, pyridine, rt, 86%; (*vi*) $NaIO_4$, $RuCl_3$, Na_2CO_3, CH_3CN–CCl_4–H_2O, rt, 33%; (*vii*) Na-naphthalide, THF, –65 °C, then NaOMe, MeOH, rt, 32%; (*viii*) Dowex 50WX8-100, MeOH, 70 °C, 94%; (*ix*) NaOMe, MeOH, rt, 99%; (*x*) Dowex 50WX8-100, MeOH, 70 °C, 79%.

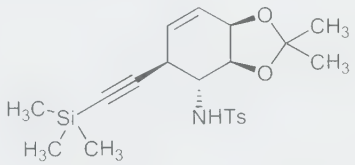


deoxypancratistatin. Based on the surprising and promising results of biological activity, it now seems prudent to proceed further with the preparation of diversely functionalized analogs of Amaryllidaceae constituents.

Experimental section

All nonaqueous reactions were conducted in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. Methylene chloride was distilled from calcium hydride; THF and toluene were dried over potassium/benzophenone. Analytical thin-layer chromatography was performed on Silicycle 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using silica gel 60 (230–400 mesh). Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a PerkinElmer One FT-IR spectrometer. Optical rotation was measured on a PerkinElmer 341 polarimeter at a wavelength of 589 nm. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Brucker spectrometer. All chemical shifts are referenced to TMS or residual undeuterated solvent ($CHCl_3$). The data for the proton spectra are reported as follows: chemical shift (multiplicity, singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m), coupling constants (Hz), integration). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm (δ) relative to solvent resonance as internal standard. Combustion analysis were performed by Chemisar Laboratories Inc., Guelph, Ontario. Mass spectra and high-resolution mass spectra were performed by the analytical division at Brock University, St. Catharines, Ontario.

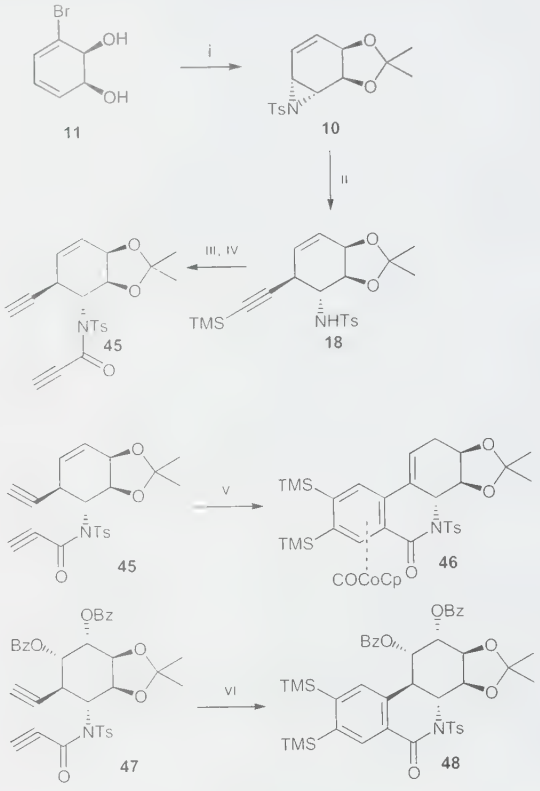
N-[(1*R*,2*R*,5*R*,6*S*)-2-(2-Trimethylsilylethynyl)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-4-methylbenzenesulfonamide (18)



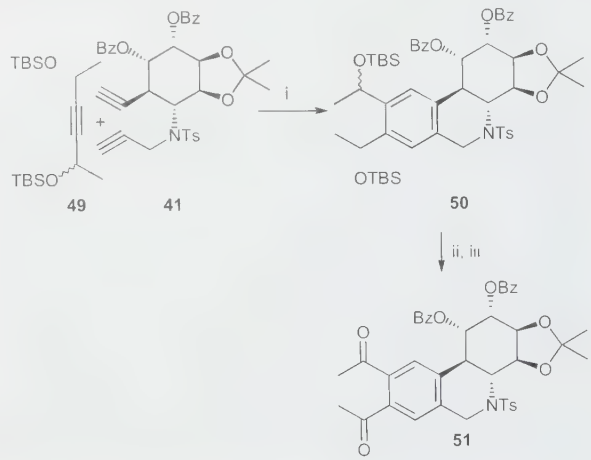
$C_{21}H_{29}NO_4SSi$
419.61 g/mol

To a solution of of (trimethylsilyl)acetylene (2.75 g, 28.00 mmol) in 40 mL toluene was added BuLi (1.6 mol/L, 17.50 mL, 28.00 mmol) at 0 °C. During the addition, a heavy white precipitate formed. The reaction mixture was stirred at 0 °C for 10 min before $AlCl_3$ (1.24 g, 9.33 mmol) was added. After stirring for a further 10 min, aziridine **10** (1.00 g, 3.11 mmol), dissolved in 5 mL toluene, was added dropwise. Additional $AlCl_3$ (622 mg, 4.67 mmol) was added and the suspension was allowed to warm to room temperature over 18 h. The reaction was quenched by addition of 1 mol/L HCl (100 mL) and diluted with ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried over

Scheme 6. Propargyl amide series. Reagents and conditions: (*i*) DMP, *p*-TSA, acetone, rt, then PhINTs, $Cu(acac)_2$, H_3CCN, 0 °C to rt, then *n*-Bu_3SnH, AIBN, THF, reflux, 25% over three steps; (*ii*) BuLi, TMS–acetylene, $AlCl_3$, toluene, 0 °C to rt, then DMP, *p*-TSA, acetone, rt, 69% over two steps; (*iii*) BuLi, propiolic acid anhydride, THF, 0 °C to rt, 46%; (*iv*) TBAT, H_3CCN, rt, 61%; (*v*) $CpCo(CO)_2$, BTMSA, xylene, 140 °C, 11%; (*vi*) $CpCo(CO)_2$, BTMSA, xylene, 140 °C, 5%.

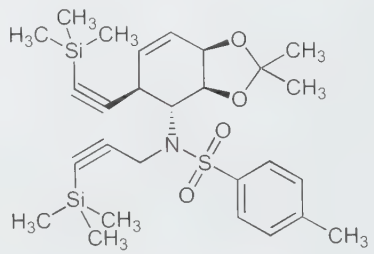


Scheme 7. Bisketone approach. Reagents and conditions: (*i*) $CpCo(CO)_2$, xylene, 140 °C, 31%; (*ii*) TBAF, THF, rt, 72%; (*iii*) IBX, DMSO, rt, 71%.



$MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 2:1 to 1:2) afforded the title compound and the corresponding free diol. The diol was dissolved in 40 mL of acetone and protected by addition of 2,2-dimethoxypropane (486 mg, 4.67 mmol) and *p*-TSA (0.2 g). After 15 min the solution was diluted with ethyl acetate (200 mL), washed with satd. aq. $NaHCO_3$ (3 × 40 mL) and brine (40 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure affording 900 mg of pure acetonide **18** (2.14 mmol, 69%); mp 168 °C. $[\alpha]^{21}_D$ +30.2 (*c* 0.20, CH_2Cl_2). R_f 0.48 (hexanes – ethyl acetate, 2:1). IR ($CHCl_3$, cm^{-1}) ν: 3269, 3020, 2401, 2176, 1600, 1427, 1375, 1330, 1251, 1216, 1159, 1094, 1075, 972, 928, 846, 759, 669. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.83 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 2H), 5.83 (m, 2H), 4.63 (d, *J* = 8.0 Hz, 1H), 4.50 (m, 1H), 4.05 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.60 (q, *J* = 8.3 Hz, 1H), 3.14 (d, *J* = 8.4 Hz, 1H), 2.41 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 0.14 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 143.2, 138.9, 130.4, 129.4, 127.5, 124.6, 110.1, 103.5, 87.9, 76.5, 71.8, 56.8, 34.6, 27.9, 25.9, 21.6, 0.0. MS (EI) *m/z* (relative intensity): 420 (MH^+, 0.6), 419 (M^+, 1.6), 255 (12), 254 (76), 253 (17), 207 (20), 191 (11), 190 (20), 175 (26), 171 (10), 155 (28), 149 (16), 147 (11), 139 (43), 124 (17), 123 (10), 121 (16), 117 (7), 107 (10), 105 (10), 100 (10), 99 (82), 98 (57), 97 (11), 92 (15), 91 (100), 89 (10), 85 (10), 84 (13), 83 (15), 77 (12), 75 (24), 73 (64), 65 (16), 59 (11), 58 (14), 57 (10), 45 (14), 44 (18), 43 (56), 41 (11). HRMS (EI) calcd. for $C_{21}H_{29}O_4NSSi$: 419.1587; found: 419.1582. Anal. calcd. for $C_{21}H_{29}O_4NSSi$: C 60.11, H 6.97; found: C 60.33, H 7.07.

(3a*S*,4*R*,5*R*,7a*R*)-2,2-Dimethyl-4-[4-methylphenyl(3-trimethylsilyl-2-propynyl)sulfonamido]-5-(2-trimetylsilyl-1-ethynyl)-3a,4,5,7a-tetrahydro-1,3-benzodioxole (19)

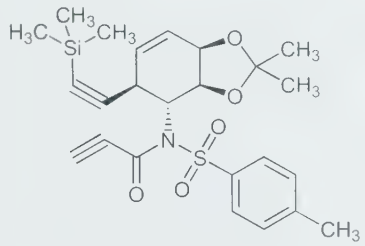


$C_{27}H_{39}NO_4SSi2$
529.84 g/mol

To a solution of of tosylamide **18** (200 mg, 0.48 mmol) in 3 mL THF was added BuLi (1.6 mol/L, 0.30 mL, 0.48 mmol) at 0 °C under argon. The solution was stirred for 5 min and trimethylsilyl propargyl bromide (0.37 mL, 2.38 mmol) and a catalytic amount of $N(n\text{-}Bu)_4I$ were added. The reaction mixture was allowed to stir for 1 h at 0 °C and then it was warmed to room temperature and stirred for 16 h. The reaction was quenched by the addition of satd. aq. NH_4Cl (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was

removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 7:1 to 2:1) afforded sulfonamide **19** (115 mg, 0.22 mmol, 46%) and starting material **18** (40 mg, 20%). R_f 0.63 (hexanes – ethyl acetate, 5:1). IR ($CHCl_3$, cm^{-1}) ν: 2959, 2926, 2180, 1599, 1497, 1381, 1347, 1249, 1216, 1159, 1095 1068, 1016, 1000, 972, 920, 843, 814, 760, 734, 699, 666, 642, 596, 568, 544, 482. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.01 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 5.91 (m, 2H), 4.62 (m, 2H), 4.17 (m, 1H), 4.10 (d, J = 7.3 Hz, 2H), 3.77 (d, J = 10.5 Hz, 1H), 2.42 (s, 3H), 1.53 (s, 3H), 1.34 (s, 3H), 0.18 (s, 9H), 0.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 143.0, 138.0, 132.8, 129.1, 128.5, 123.3, 109.8, 104.2, 100.6, 90.5, 88.0, 77.3, 74.0, 72.7, 61.3, 33.2, 28.0, 25.8, 21.6, 0.0, –0.4. MS (EI) *m/z* (relative intensity): 529 (M^+, 0.2), 514 ($M^+ - CH_3$, 4.1), 366 (12), 365 (27), 364 (100), 347 (12), 215 (16), 209 (28), 207 (15), 168 (11), 155 (10), 149 (17), 139 (66), 111 (15), 97 (11), 91 (47), 84 (10), 83 (33), 75 (16), 73 (86), 71 (12), 59 (16), 53 (13), 43 (32). HRMS (EI) calcd. for $C_{27}H_{39}O_4NSSi$: 529.2138; found: 529.2144.

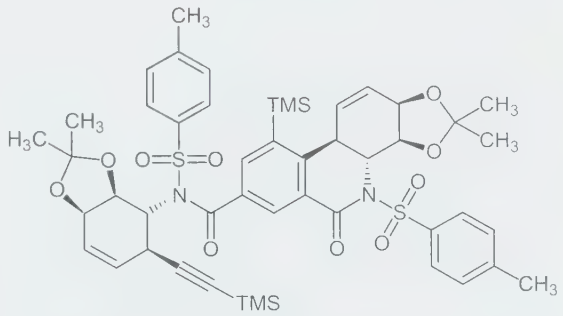
_N_-[(1_R_,2_R_,5_R_,6_S_)-2-(2-Trimethylsilylethynyl)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-_N_-propioloyl-4-methylbenzenesulfonamide (22



$C_{24}H_{29}NO_5SSi$
471.64 g/mol

To a solution of of acetonide **18** (250 mg, 0.60 mmol) in 5 mL THF was added BuLi (1.6 mol/L, 0.41 mL, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (87 mg, 0.72 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by the addition of satd. aq. NH_4Cl (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 3:1) afforded the tosylamide **22** (128 mg, 0.27 mmol, 46%) as a slightly yellow foam. $[\alpha]^{21}_D$ +29.2 (*c* 0.25, CH_2Cl_2). R_f 0.71 (hexanes – ethyl acetate, 3:1). IR ($CHCl_3$, cm^{-1}) ν: 3297, 3021, 2988, 2961, 2177, 2110, 1932, 1795, 1739, 1675, 1597, 1494, 1457, 1366, 1307, 1250, 1216, 845, 756. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.03 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.98 (m, 2H), 5.11 (m, 1H), 4.74 (m, 2H), 4.25 (d, J = 10.8 Hz, 1H), 3.23 (s, 1H), 2.43 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 153.7, 145.2, 136.0, 132.6, 130.1, 129.2, 123.3, 110.6, 103.4, 89.6, 82.7, 75.5, 73.7, 72.8, 65.8, 34.0, 27.9, 25.8, 21.9, –0.2. MS (EI) *m/z* (relative intensity): 471 (MH^+, 0.1), 456 (9), 306 (19), 258 (7), 248 (16), 242 (7), 224 (7), 207 (7), 191 (24), 190 (72), 176 (8), 175 (35), 161 (7), 159 (7), 157 (7), 156 (10), 155 (90), 151 (6), 149 (9), 147 (9), 139 (15), 131 (7), 124 (11), 123 (8), 121 (7), 119 (5), 117 (6), 115 (6), 112 (8), 109 (5), 108 (6), 107 (5), 105 (7), 100 (7), 99 (7), 98 (9), 97 (10), 92 (13), 91 (100), 90 (5), 89 (9), 85 (7), 84 (7), 83 (12), 79 (5), 77 (8), 75 (19), 74 (10), 73 (77), 71 (6), 70 (7), 69 (9), 65 (13), 64 (10), 63 (5), 60 (6), 59 (12), 58 (8), 57 (9), 56 (5), 55 (8), 53 (30), 51 (5), 45 (14), 44 (17), 43 (49), 42 (6), 41 (10). HRMS (EI) calcd. for $C_{21}H_{29}O_4NSSi$: 471.1536; found: 471.1527.

_N_-[(1_R_,2_R_,5_R_,6_S_)-2-Trimethylsilylethynyl-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-_N_-(4-methylphenylsulfonyl)-(3a_S_,3b_R_,9b_R_,10_R_,11a_S_)-2,2-dimethyl-5-oxo-9-trimethylsilyl-3a,3b,4,5,9b,11a-hexahydro[1,3]dioxolo[4,5-*c*]phenanthridine-10-en-7-carboxamide (23)

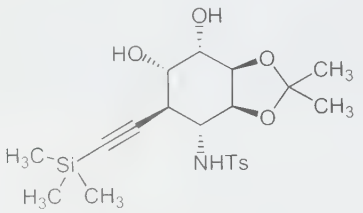


$C_{48}H_{58}N_2O_{10}S_2Si_2$
943.28 g/mol

To a solution of of bis(cyclooctadiene)nickel(0) (15 mg, 0.06 mmol) and triphenylphosphine (57 mg, 0.22 mmol) in 5 mL toluene was added bisacetylene **22** (86 mg, 0.18 mmol), immediately followed by of (trimethylsilyl)acetylene (27 mg, 0.27 mmol, 39 μL) at room temperature under argon. The solution was stirred overnight, quenched by the addition of satd. aq. NH_4Cl (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 5:1) afforded the cyclotrimerized dimer **23** (40 mg, 0.04 mmol, 47%) as a slightly yellow oil. $[\alpha]^{28}_D$ +53.6 (*c* 0.74, $CHCl_3$). R_f 0.64 (hexanes – ethyl acetate, 4:1). IR ($CHCl_3$, cm^{-1}) ν: 3430, 3020, 2172, 1686, 1677, 1598, 1374, 1253, 1216, 1171, 1076, 845, 756. ^1H NMR (300 MHz, $CDCl_3$, 50 °C, ppm) δ: 8.30 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 7.9 Hz, 1H), 7.49 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.16 (m, 2H), 7.08 (d, J = 7.9 Hz, 1H), 5.16 (m, 4H), 5.55 (m, 1H), 4.76 (m, 3H), 4.58 (m, 1H), 4.42 (m, 1H), 4.20 (d, J = 10.8 Hz, 1H), 3.63 (t, J = 10.5 Hz, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 1.38 (m, 12H), 0.49 (s, 9H), 0.16 (s, 9H). MS (EI) *m/z* (relative intensity): 943 (M^+, 0.1), 927 (0.1), 456 (9), 256 (7), 255 (8), 254 (47), 253 (12), 231 (5), 229 (15), 207 (19), 206 (6), 191 (12), 190 (27), 189 (6), 176 (7),

175 (18), 161 (6), 156 (6), 155 (32), 151 (5), 149 (20), 147 (8), 145 (5), 140 (6), 139 (39), 135 (6), 133 (5), 131 (10), 129 (6), 123 (6), 121 (10), 119 (9), 117 (8), 116 (6), 115 (5), 109 (5), 108 (6), 107 (7), 105 (7), 100 (8), 99 (45), 98 (36), 97 (12), 95 (7), 93 (7), 92 (13), 91 (86), 90 (6), 89 (9), 86 (5), 85 (10), 84 (16), 83 (12), 82 (5), 81 (8), 79 (6), 77 (10), 75 (24), 74 (12), 73 (100), 71 (15), 70 (13), 69 (19), 67 (7), 65 (17), 64 (6). HRMS (EI) calcd. for $C_{48}H_{58}O_{10}N_2S_2Si_2$-$CH_3$: 927.2837; found: 927.2824.

(3a*S*,4*R*,5*R*,6*S*,7*S*,7a*S*)-6,7-Dihydroxy-2,2-dimethyl-4-(4-methylphenylsulfonamido)-5-(2-trimethylsilyl-1-ethynyl)perhydro-1,3-benzodioxole (24)

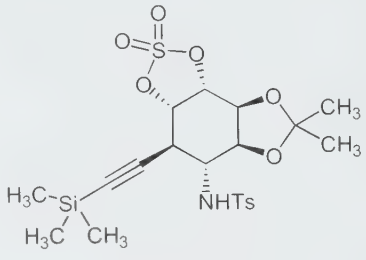


$C_{21}H_{31}NO_6SSi$
453.63 g/mol

To a solution of of (trimethylsilyl)acetylene **18** (1.55 g, 3.68 mmol) in 40 mL CH_2Cl_2 was added *N*-methylmorpholine-*N*-oxide (5.18 mg, 4.42 mmol) and six small crystals of OsO_4. The reaction mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of satd. aq. $NaHSO_3$ (50 mL), the organic and the aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 1:1) afforded diol **24** (768 mg, 1.69 mmol, 46%) as white crystals (mp 87 °C) and the starting material (488 mg, 1.16 mmol, 32%). $[\alpha]^{21}_D$ +32.5 (*c* 0.45, $CHCl_3$). R_f 0.37 (hexanes – ethyl acetate, 1:1). IR ($CHCl_3$, cm^{-1}) ν: 3684, 3577, 3359, 3020, 2991, 2962, 2903, 2401, 2178, 1731, 1599, 1519, 1423, 1383, 1375, 1334, 1306, 1250, 1216, 1160, 1093, 1066, 929, 848, 814, 771, 669, 627, 598, 557, 512, 460. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.79 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.80 (d, *J* = 9.4 Hz, 1H), 4.11 (m, 3H), 4.01 (d, *J* = 5.8, 1H), 3.89 (m, 1H), 3.26 (s, 2H), 2.80 (t, *J* = 5.5 Hz, 1H), 2.42 (s, 3H), 1.41 (s, 3H), 1.25 (s, 3H), 0.13 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 143.5, 138.4, 129.8, 127.2, 109.5, 102.5, 89.6, 78.1, 77.4, 72.5, 69.9, 54.9, 36.9, 27.9, 25.9, 21.7, 0.0. MS (EI) *m/z* (relative intensity): 438 (M^+ – CH_3, 28), 380 (7), 366 (11), 351 (7), 322 (15), 282 (6), 254 (12), 242 (6), 226 (13), 225 (24), 224 (8), 222 (9), 212 (6), 211 (9), 194 (7), 193 (6), 180 (7), 178 (8), 172 (5), 171 (8), 157 (6), 156 (6), 155 (60), 154 (5), 153 (7), 152 (6), 151 (6), 150 (6), 149 (16), 141 (7), 140 (11), 139 (27), 129 (8), 128 (5), 125 (12), 124 (8), 123 (6), 109 (5), 108 (7), 107 (7), 101 (14), 100 (16), 99 (15), 98 (14), 97 (7), 92 (14), 91 (100), 90 (5), 89 (6), 86 (5), 85 (11), 84 (14), 83 (8), 77 (8), 75 (29), 74 (10), 73 (84), 72 (5), 71 (8), 70 (33), 69 (9), 65 (15), 64 (6), 63 (5), 61 (7), 60 (6), 59 (29), 58 (9), 55 (10), 53 (8), 45 (14), 44 (9), 43 (57), 42 (6), 41 (8). HRMS (EI) calcd. for $C_{21}H_{31}O_6NSSi$-CH_3: 438.1407; found: 438.1400. Anal. calcd. for $C_{21}H_{31}O_6NSSi$: C 55.60, H 6.89; found: C 55.20, H 7.02.

(3a*S*,4*R*,5*R*,5a*S*,8a*S*,8b*S*)-*N*-(7,7-Dimethyl-2,2-dioxo-4-trimethylsilanylethynyl hexahydro-1,3,6,8-tetraoxa-2λ^6-thia-*as*-indacen-5-yl)-4-methylbenzenesulfonamide (25)

To a solution of diol **24** (150 mg, 0.33 mmol) in 5 mL dry



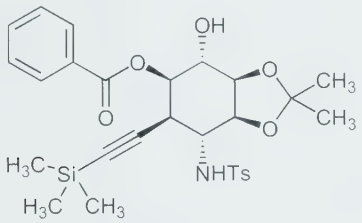
$C_{21}H_{29}NO_8S_2Si$
515.67 g/mol

CH_2Cl_2 was added triethylamine (0.37 mL, 2.65 mmol) at 0 °C. The solution was stirred for 10 min and SO_2Cl_2 (0.99 mL, 1.0 mol/L solution, 0.99 mmol) was added dropwise. After the addition, the solution was allowed to warm to room temperature and was stirred for 3 h. Further addition of triethylamine (0.37 mL, 2.65 mmol) and SO_2Cl_2 (0.99 mL, 1.0 mol/L solution, 0.99 mmol) led to total consumption of the starting material (2 h). The reaction mixture was diluted with CH_2Cl_2 (30 mL) and extracted with water (2 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes – ethyl acetate, 2:1) afforded cyclic sulfate **25** (140 mg, 0.27 mmol, 82%); mp 169 °C. $[\alpha]^{26}_D$ –51.5 (*c* 1.40, $CHCl_3$). R_f 0.89 (hexanes – ethyl acetate, 3:7). IR ($CHCl_3$, cm^{-1}) ν: 3684, 3617, 3374, 3020, 2964, 2928, 2401, 2182, 1721, 1599, 1520, 1496, 1404, 1334, 1307, 1291, 1252, 1216, 1160, 1093, 1013, 985, 924, 848, 813, 759, 669, 548, 505, 475, 462, 454. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.81 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 5.03 (m, 3 H), 4.48 (m, 1H), 4.14 (m, 1H), 3.52 (m, 1H), 3.04 (m, 1H), 2.43 (s, 3H), 1.38 (s, 3H), 1.19 (s, 3H), 0.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 143.6, 138.3, 129.5, 127.5, 110.6, 98.1, 93.3, 82.4, 80.7, 77.3, 73.4, 54.4, 36.0, 27.4, 25.2, 21.7, –0.2. MS (EI) *m/z* (relative intensity): 500 (M^+ – CH_3, 15), 391 (16), 309 (7), 244 (5), 243 (35), 242 (100), 238 (6), 234 (5), 233 (5), 231 (6), 229 (9), 228 (8), 225 (8), 222 (6), 207 (5), 206 (6), 205 (8), 204 (18), 191 (6), 190 (7), 180 (6), 178 (6), 177 (8), 176 (8), 175 (6), 171 (6), 169 (5), 167 (9), 165 (12), 164 (8), 163 (13), 162 (7), 161 (9), 160 (5), 159 (5), 156 (7), 155 (34), 153 (7), 152 (6), 151 (10), 150 (9), 149 (41), 147 (6), 140 (6), 139 (16), 138 (5), 137 (11), 135 (10), 133 (7), 129 (7), 127 (6), 126 (8), 125 (8), 124 (9), 123 (11), 122 (5), 121 (7), 119 (9), 115 (5), 113 (8), 112 (9), 111 (15), 110 (7), 109 (12), 108 (7), 107 (7), 105 (7), 102 (6), 100 (7), 99 (10), 98 (10), 97 (21), 96 (9), 95 (15), 93 (5), 92 (9), 91 (42), 89 (6), 85 (21), 84 (13), 83 (23), 82 (10), 81 (16), 80 (7), 79 (7), 77 (6), 76 (8), 75 (11), 73 (26), 72 (6), 71 (48), 70 (23), 69 (45), 68 (9), 67 (12), 65

(9), 64 (6), 59 (8), 58 (13), 57 (48), 56 (18), 55 (40), 54 (6), 53 (9), 51 (5), 45 (5), 43 (65), 42 (8), 41 (29). HRMS (EI) calcd. for $C_{21}H_{29}O_8NS_2Si$-CH_3: 500.0869; found: 500.0846. Anal. calcd. for $C_{21}H_{29}O_8NS_2Si$: C 48.91, H 5.67; found: C 49.32, H 5.86.

(3a*S*,4*S*,5*R*,6*R*,7*R*,7a*S*)-4-Hydroxy-2,2-dimethyl-7-(4-methylphenylsulfonamido)-5-phenylcarbonyloxy-6-(2-trimethylsilyl-1-ethynyl)perhydro-1,3-benzodioxole (26)

To a solution of cyclic sulfate **25** (462 mg, 0.90 mmol) in 5 mL dry DMF was added ammonium benzoate (312 mg,

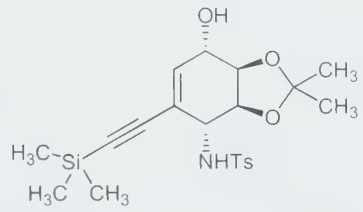


$C_{28}H_{35}NO_7SSi$
557.73 g/mol

2.24 mmol). The reaction mixture was heated to 70 °C for 2 h, then cooled to 40 °C and the DMF was removed under reduced pressure. The residue was suspended in 25 mL THF before 3 drops of H_2O and H_2SO_4 were added. The resulting mixture was stirred for 1.5 h and then quenched with satd. aq. $NaHCO_3$ (25 mL) and diluted with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 2:1) afforded benzoate **26** (167 mg, 0.30 mmol, 33%); mp 105 °C. $[\alpha]^{22}_D$ –38.4 (*c* 0.98, $CHCl_3$). R_f 0.19 (hexanes – ethyl acetate, 2:1). IR ($CHCl_3$, cm^{-1}) ν: 3275, 2924, 2853, 2323, 2177, 1702, 1601, 1452, 1383, 1332, 1275, 1249, 1219, 1159, 1119, 1093, 1069, 1027, 845, 814, 761, 712, 664, 568, 550. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.07 (d, *J* = 7.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 7.28 (d, *J* = 7.2 Hz, 2H), 5.75 (d, *J* = 7.1 Hz, 1H), 5.31 (dd, *J* = 4.2, 7.7 Hz, 1H), 4.30 (m, 1H), 4.23 (m, 1H), 4.08 (m, 2H), 3.26 (m, 1H), 3.16 (s, 1H), 2.41 (s, 3H), 1.50 (s, 3H), 1.24 (s, 3H), 0.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.7, 143.7, 138.1, 133.7, 130.3, 129.9, 128.7, 127.6, 110.0, 101.1, 90.5, 78.5, 77.5, 72.2, 70.5, 66.6, 54.3, 36.2, 28.2, 26.0, 21.8, 0.0. MS (EI) *m/z* (relative intensity): 542 ($M^+ - CH_3$, 2.1), 366 (10), 351 (8), 276 (16), 264 (6), 263 (27), 225 (8), 224 (8), 212 (5), 180 (5), 179 (6), 169 (6), 155 (22), 151 (6), 150 (8), 149 (8), 141 (8), 140 (8), 139 (14), 137 (7), 135 (6), 133 (7), 132 (7), 127 (12), 126 (8), 125 (13), 124 (8), 123 (13), 122 (37), 121 (9), 120 (7), 113 (11), 112 (12), 111 (23), 110 (7), 109 (14), 108 (30), 107 (7), 106 (9), 105 (58), 104 (12), 101 (6), 100 (8), 99 (19), 98 (18), 97 (38), 96 (10), 95 (17), 94 (7), 93 (10), 92 (13), 91 (60), 89 (5), 87 (5), 86 (7), 85 (61), 84 (21), 83 (53), 82 (13), 81 (19), 80 (11), 79 (9), 78 (9), 77 (32), 75 (8), 74 (6), 73 (15), 72 (7), 71 (65), 70 (34), 69 (53), 68 (11), 67 (15), 65 (16), 64 (7), 63 (6), 60 (7), 59 (12), 58 (11), 57 (100), 56 (22), 55 (57), 54 (7), 53 (11), 52 (9), 51 (19), 50 (12), 47(6), 45 (11), 44 (27), 43 (94), 42 (15), 41 (38). HRMS (EI) calcd. for $C_{28}H_{35}O_7NSSi$-CH_3: 542.1669; found: 542.1660.

(3a*S*,4*R*,7*S*,7a*R*)-7-Hydroxy-2,2-dimethyl-4-(4-methylphenylsulfonamido)-5-(2-trimethylsilyl-1-ethynyl)-3a,4,7,7a-tetrahydro-1,3-benzodioxole (27)

To a solution of cyclic sulfate **25** (462 mg, 0.90 mmol) in 5 mL dry DMF was added ammonium benzoate (312 mg,

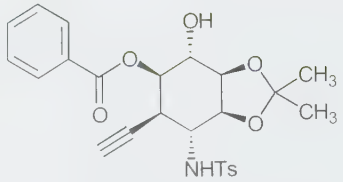


$C_{21}H_{29}NO_5SSi$
435.61 g/mol

2.24 mmol). The reaction mixture was heated to 70 °C for 2 h, then cooled to 40 °C and the excess DMF was removed under reduced pressure. The residue was suspended in 25 mL THF and 3 drops of H_2O and H_2SO_4 were added. The resulting mixture was stirred for 1.5 h, quenched with satd. aq. $NaHCO_3$ (25 mL), and diluted with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 2:1) afforded allyl alcohol **27** (234 mg, 0.54 mmol, 60%); mp 131 °C. $[\alpha]^{22}_D$ –42.7 (*c* 0.30, $CHCl_3$). R_f 0.33 (hexanes –ethyl acetate, 2:1). IR ($CHCl_3$, cm^{-1}) ν: 3318, 3020, 2928, 2401, 2149, 1726, 1600, 1424, 1384, 1332, 1251, 1216, 1158, 1094, 1060, 926, 865, 846, 814, 771, 669, 603, 550, 515. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.80 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.37 (d, *J* = 5.2 Hz, 1H), 5.76 (d, *J* = 9.5 Hz, 1H), 4.51 (m, 1H), 4.38 (m, 1H), 4.32 (m, 1H), 3.96 (dd, *J* = 3.2, 9.4 Hz, 1H), 3.16 (s, 1H), 2.42 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 0.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 143.3, 137.8, 137.3, 129.6, 127.4, 125.0, 109.0, 102.3, 98.0, 77.6, 77.6, 66.2, 53.9, 26.4, 24.5, 21.7, –0.2. MS (EI) *m/z* (relative intensity): 420 ($M^+ - CH_3$, 6), 349 (9), 337 (7), 336 (15), 335 (61), 212 (16), 206 (6), 205 (7), 204 (8), 192 (6), 190 (6), 181 (8), 180 (43), 178 (12), 177 (9), 176 (11), 175 (6), 165 (5), 155 (14), 150 (6), 149 (18), 139 (15), 120 (13), 107 (8), 105 (6), 104 (6), 101 (6), 100 (7), 97 (13), 96 (6), 95 (5), 92 (12), 91 (75), 90 (5), 85 (16), 84 (7), 83 (9), 81 (5), 77 (8), 75 (25), 74 (12), 73 (100), 71 (13), 70 (6), 69 (12), 65 (13), 60 (6), 59 (13), 58 (7), 57 (12), 55 (11), 45 (11), 44 (6), 43 (44), 42 (8), 41 (13). HRMS (EI) calcd. for $C_{21}H_{29}O_5NSSi$: 435.1536; found: 435.1534. Anal. calcd. for $C_{21}H_{29}O_5NSSi$: C 57.90, H 6.71; found: C 57.45, H 7.00.

(3a*S*,4*S*,5*R*,6*R*,7*R*,7a*S*)-4-Hydroxy-2,2-dimethyl-7-(4-methylphenylsulfonamido)-5-phenylcarbonyloxy-6-(1-ethynyl)perhydro-1,3-benzodioxole (28)

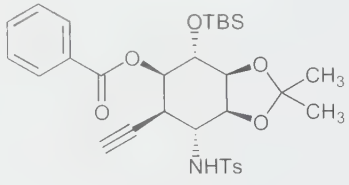
To a solution of TMS-protected acetylene **26** (436 mg, 0.78 mmol) in 15 mL dry acetonitrile was added TBAT (633 mg, 1.17 mmol). The reaction mixture was stirred at



$C_{25}H_{27}NO_7S$
485.55 g/mol

room temperature for 4 h, quenched with satd. aq. NH_4Cl (25 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 1:1) afforded alcohol **28** (318 mg, 0.65 mmol, 84%) as white crystals; mp 103 °C. $[\alpha]^{19}_D$ –23.4 (*c* 0.85, $CHCl_3$). R_f 0.41 (hexanes – ethyl acetate, 1:1). IR ($CHCl_3$, m^{-1}) ν: 440, 3288, 3155, 2988, 2254, 1726, 1697, 1600, 1453, 1375, 1331, 1279, 1247, 1222, 1163, 1119, 1095, 1069, 908, 815, 734, 651, 545.^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.06 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2 H), 7.58 (m, 1H), 7.44 (m, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.59 (d, *J* = 8.0 Hz, 1H), 5.31 (dd, *J* = 3.6, 6.8 Hz, 1H), 4.33 (m, 1H), 4.23 (m, 1H), 4.08 (m, 2H), 3.19 (m, 1H), 3.03 (s, 1H), 2.38 (s, 3H), 2.02 (d, *J* = 2.7 Hz, 1H), 1.51 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.7, 143.6, 138.2, 133.7, 130.2, 129.7, 129.5, 128.7, 127.6, 109.9, 79.6, 78.5, 77.4, 73.2, 72.4, 69.4, 54.3, 34.6, 28.0, 26.1, 21.7. MS (EI) *m/z* (relative intensity): 470 (M^+ – CH_3, 3.2), 377 (6), 362 (5), 263 (7), 225 (8), 179 (16), 155 (17), 150 (7), 139 (9), 134 (8), 132 (5), 123 (5), 122 (24), 108 (8), 106 (13), 105 (100), 92 (8), 91 (48), 85 (6), 80 (6), 78 (7), 77 (34), 75 (8), 73 (11), 71 (5), 70 (11), 69 (7), 65 (11), 59 (7), 58 (5), 57 (8), 55 (8), 53 (5), 51 (13), 50 (7), 45 (7), 44 (13), 43 (25), 41 (11). HRMS (EI) calcd. for $C_{25}H_{27}O_7NS$-CH_3: 470.1273; found: 470.1283. Anal. calcd. for $C_{25}H_{27}O_7NS$: C 61.84, H 5.60; found: C 61.45, H 5.36.

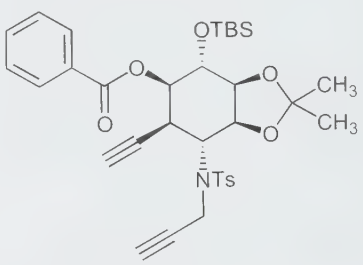
(3a*S*,4*S*,5*R*,6*R*,7*R*,7a*S*)-2,2-Dimethyl-7-(4-methylphenylsulfonamido)-4-(*tert*-butyldimethylsilyloxy)-5-phenylcarbonyloxy-6-(1-ethynyl)perhydro-1,3-benzodioxole (29)



$C_{31}H_{41}NO_7SSi$
599.81 g/mol

To a solution of alcohol **28** (290 mg, 0.60 mmol) in 4 mL dry DMF were added imidazole (204 mg, 2.99 mmol) and TBSCl (451 mg,2.99 mmol). The reaction mixture was stirred at room temperature for 18 h, quenched with water (20 mL) and, after stirring for an additional 10 min, extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 9:1) afforded TBS-protected alcohol **29** (319 mg, 0.53 mmol, 89%) as white crystals; mp 83 °C. $[\alpha]^{19}_D$ –36.9 (*c* 1.20, $CHCl_3$). R_f 0.33 (hexanes – ethyl acetate, 5:1). IR ($CHCl_3$, cm^{-1}) ν: 3309, 3066, 2988, 2955, 2931, 2896, 2859, 2254, 1720, 1601, 1586, 1495, 1472, 1463, 1452, 1383, 1373, 1328, 1272, 1221, 1160, 1112, 1094, 1081, 1054, 1027, 1005, 987, 909, 840, 814, 781, 734, 664, 650, 579, 564, 549, 514, 466. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.08 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 5.29 (d, *J* = 7.5 Hz, 1H), 5.23 (m, 1H), 4.32 (m, 1H), 4.10 (m, 1H), 4.08 (m, 2H), 3.09 (m, 1H), 2.38 (s, 3H), 1.83 (d, *J* = 2.3 Hz, 1H), 1.52 (s, 3H), 1.26 (s, 3H), 0.86 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 165.8, 143.1, 139.2, 133.5, 130.1, 129.9, 129.3, 128.6, 127.7, 109.6, 80.1, 78.5, 77.7, 73.8, 72.7, 67.4, 55.0, 33.3, 28.1, 26.2, 25.8, 21.7, 18.1, –4.8, –4.9. MS (EI) *m/z* (relative intensity): 584 (M^+ – CH_3, 3.7), 420 (9), 378 (5), 377 (18), 363 (6), 362 (20), 288 (5), 207 (7), 206 (7), 192 (6), 191 (32), 181 (5), 180 (15), 179 (89), 155 (12), 139 (5), 129 (5), 106 (9), 105 (100), 91 (34), 85 (5), 77 (20), 75 (14), 73 (32), 59 (6), 57 (9), 43 (13), 41 (7). HRMS (EI) calcd. for $C_{31}H_{41}O_7NSSi$-CH_3: 584.2138; found: 584.2150. Anal. calcd. for $C_{31}H_{41}O_7NSSi$: C 62.08, H 6.89; found: C 61.86, H 6.64.

(3a*S*,4*S*,5*R*,6*R*,7*R*,7a*S*)-2,2-Dimethyl-7-(4-methylphenyl(2-propynyl)sulfonamido)-4-(*tert*-butyldimethylsilyloxy)-5-phenylcarbonyloxy-6-(1-ethynyl)perhydro-1,3-benzodioxole (30)

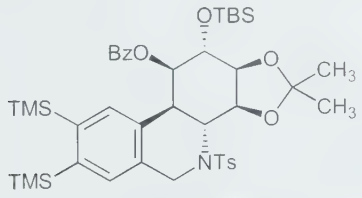


$C_{34}H_{43}NO_7SSi$
637.86 g/mol

To a solution of tosylamide **29** (411 mg, 0.69 mmol) in 11 mL of dry THF was added NaHMDS (0.82 mL, 0.82 mmol) at –70 °C. The reaction mixture was stirred for 0.5 h, while warming up to 0 °C. TMS – propargyl bromide (408 mg, 3.43 mmol) and $(n\text{-Bu})_4NI$ (252 mg, 0.69 mmol) were added. The reaction mixture was stirred at room temperature for 6 h, quenched with satd. aq. NH_4Cl (30 mL), extracted with ethyl acetate (3 × 30 mL), dried over Na_2SO_4, and the solvent was evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 9:1) afforded imide **30** (345 mg, 0.54 mmol, 79%) as colourless foam. $[\alpha]^{19}_D$ –37.5 (*c* 0.24, $CHCl_3$). R_f 0.54 (hexanes – ethyl acetate, 3:1). IR ($CHCl_3$, cm^{-1}) ν: 3309, 3068, 2987, 2956, 2931, 2896, 2859, 2255, 2125, 1722, 1601, 1586, 1495, 1472, 1463, 1453, 1384, 1373, 1351, 1331, 1308, 1269, 1221, 1159, 1095, 1027, 1006, 990, 961, 910, 865, 840, 815, 781, 734, 712, 666, 650, 599, 583, 546, 467. ^{1}H NMR (300 MHz,

$CDCl_3$, ppm) δ: 8.18 (d, J = 8.1 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.59 (m, 1H), 7.47 (m, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.35 (m, 1H), 4.84 (m, 2H), 4.42 (m, 1H), 4.15 (m, 3H), 3.64 (m, 1H), 2.42 (s, 3H), 2.22 (m, 1H), 2.00 (d, J = 2.2 Hz, 1H), 1.64 (s, 3H), 1.36 (s, 3H), 0.94 (s, 9H), 0.25 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 165.9, 143.5, 137.8, 133.4, 130.2, 129.9, 129.4, 128.6, 128.5, 109.7, 80.5, 78.7, 78.5, 74.9, 74.7, 73.9, 73.0, 66.6, 58.7, 30.9, 28.2, 26.3, 25.8, 25.8, 21.7, 18.1, –4.8, –5.0. MS (EI) *m/z* (relative intensity): 622 ($M^+ - CH_3$, 2.6), 522 (7), 401 (6), 400 (19), 245 (7), 222 (9), 192 (7), 191 (35), 181 (6), 180 (15), 179 (94), 167 (7), 155 (18), 150 (7), 149 (23), 139 (15), 137 (8), 135 (6), 129 (8), 122 (5), 113 (6), 111 (6), 109 (5), 106 (9), 105 (100), 97 (10), 95 (8), 92 (9), 91 (48), 85 (14), 84 (6), 83 (14), 81 (10), 77 (19), 75 (13), 73 (41), 71 (18), 70 (12), 69 (23), 67 (6), 66 (6), 65 (7), 59 (6), 57 (34), 56 (12), 55 (22), 53 (5), 43 (27), 41 (21). HRMS (EI) calcd. for $C_{34}H_{43}O_7NSSi$-CH_3: 622.2295; found: 622.2284. Anal. calcd. for $C_{34}H_{43}O_7NSSi$: C 64.02, H 6.79; found: C 63.82, H 6.94.

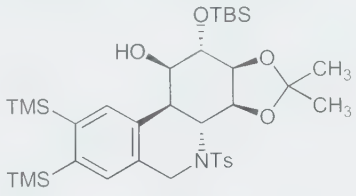
(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-10-phenylcarbonyloxy-11-(*tert*-butyldimethylsilyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (31)



$C_{42}H_{61}NO_7SSi_3$
808.26 g/mol

To a solution of $CpCo(CO)_2$ (5 μL) in BTMSA (12 mL) were added dropwise with a syringe pump bisacetylene **30** (324 mg, 0.51 mmol) and $CpCo(CO)_2$ (5 μL) dissolved in xylene (2 mL) and BTMSA (8 mL) at 140 °C over 30 h. During this slow addition, extra catalyst was added directly into the reaction mixture in aliquots: 5 μL after 5 h and 3 μL after 20 and 29 h. The reaction mixture was heated under argon for further 12 h. BTMSA and xylene were removed under high vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 9:1). The cyclotrimerized product **31** was isolated as crystalline foam in 83% yield (341 mg, 0.42 mmol); mp 97 °C. $[\alpha]^{22}_D$ +17.6 (*c* 0.65, $CHCl_3$). R_f 0.60 (hexanes – ethyl acetate, 3:1). IR ($CHCl_3$, cm^{-1}) ν: 2956, 2930, 2857, 1724, 1601, 1511, 1452, 1348, 1267, 1251, 1219, 1160, 1109, 957, 839, 757, 712, 670, 627, 560, 536, 515. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.15 (d, J = 7.6 Hz, 2H), 7.73 (m, 1H), 7.58 (m, 2H), 7.38 (m, 4H), 6.63 (d, J = 7.9 Hz, 2H), 5.96 (s, 1H), 4.85 (m, 2H), 4.49 (m, 4H), 3.12 (d, J = 11.9 Hz, 1H), 2.21 (s, 3H), 1.91 (s, 3H), 1.59 (s, 3H), 1.05 (s, 9H), 0.45 (s, 9H), 0.35 (m, 12H), 0.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 165.6, 145.9, 143.6, 141.9, 137.1, 134.5, 133.2, 132.7, 130.7, 130.1, 129.6, 128.5, 128.4, 127.5, 109.1, 79.4, 77.3, 76.1, 71.6, 68.5, 57.0, 48.5, 35.8, 28.2, 26.1, 25.7, 21.3, 18.0, 1.8, 1.8, –4.9, –5.2. MS (EI) *m/z* (relative intensity): 750 ($M^+ - C(CH_3)_3$, 15), 692 (6), 653 (6), 652 (11), 596 (8), 595 (16), 594 (12), 572 (5), 571 (10), 570 (19), 562 (8), 496 (7), 495 (5), 472 (6), 471 (6), 430 (6), 415 (6), 414 (12), 179 (22), 167 (7), 155 (8), 151 (5), 150 (5), 149 (29), 139 (7), 137 (6), 135 (6), 129 (5), 127 (5), 125 (10), 123 (9), 121 (6), 113 (8), 112 (8), 111 (18), 110 (7), 109 (13), 106 (6), 105 (55), 99 (9), 98 (12), 97 (34), 96 (11), 95 (20), 91 (14), 88 (6), 87 (5), 86 (37), 85 (32), 84 (65), 83 (35), 82 (13), 81 (20), 77 (10), 75 (10), 74 (5), 73 (41), 72 (6), 71 (51), 70 (29), 69 (54), 68 (10), 67 (16), 60 (7), 59 (7), 58 (8), 57 (96), 56 (37), 55 (80), 54 (7), 53 (7), 51 (6), 49 (12), 47 (14), 45 (9), 44 (7), 43 (100), 42 (17), 41 (73). HRMS (EI) calcd. for $C_{42}H_{61}O_7NSSi_3$-$C(CH_3)_3$: 750.2772; found: 750.2772.

(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-11-(*tert*-butyldimethylsilyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridin-10-ol (32)

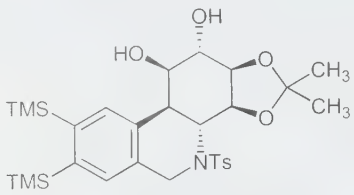


$C_{35}H_{57}NO_6SSi_3$
704.15 g/mol

To a solution of benzoate **31** (110 mg, 0.13 mmol) in 1 mL THF was added 0.5 mL of a 2.25 mol/L solution of freshly prepared sodium methoxide in methanol. The reaction was stirred for 10 min, quenched with NH_4Cl (3 mL), and diluted with ethyl ether (10 mL). The organic phase was separated and washed with $NaHCO_3$ (3 mL) and satd. NaCl solution (3 mL). After drying over $MgSO_4$ and filtration, the solvent was removed under vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 3:1). The product **32** was isolated as crystalline foam in 99% yield (88 mg, 0.12 mmol); mp 97 °C. $[\alpha]^{22}_D$ +14.2 (*c* 0.60, CH_2Cl_2). R_f 0.40 (hexanes – ethyl acetate, 3:1). IR (CH_2Cl_2, cm^{-1}) ν: 3516, 2986, 2954, 2931, 2898, 2859, 2253, 1912, 1738, 1599, 1553, 1495, 1471, 1463, 1455, 1407, 1383, 1371, 1361, 1346, 1308, 1250, 1220, 1161, 1122, 1091, 1007, 977, 948, 910, 858, 839, 811, 780, 756, 734, 700, 675, 656, 628, 605, 577, 559, 540, 513, 472. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.36 (d, J = 8.1 Hz, 2H), 7.24 (s, 1H), 7.15 (s, 1H), 6.86 (d, J = 7.8 Hz, 2H), 5.07 (m, 1H), 4.65 (dd, J_1 = 75.0 Hz, J_2 = 17.1 Hz, 2H), 4.26 (m, 3H), 4.04 (m, 1H), 2.82 (d, J = 12.9 Hz, 1H), 2.34 (m, 1H), 2.24 (s, 3H), 1.57 (s, 3H), 1.41 (s, 3H), 0.92 (s, 9H), 0.33 (s, 9H), 0.28 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 144.7, 143.7, 142.3, 137.8, 134.0, 133.2, 133.0, 132.2, 128.6, 127.4, 109.4, 79.1, 75.3, 73.5, 69.2, 58.5, 51.4, 36.3, 28.5, 26.1, 25.6, 21.4, 17.9, 1.8, 1.8, –5.0, –5.1. MS (EI) *m/z* (relative intensity): 689 ($M^+ - CH_3$, 5), 688 (7), 648 (10), 647 (18), 646 (32), 588 (7), 550 (11), 549 (22), 548 (50), 491 (9), 490 (14), 476 (5), 460 (9), 459

(14), 458 (33), 457 (34), 433 (8), 432 (9), 430 (10), 428 (6), 414 (7), 385 (5), 316 (6), 315 (7), 304 (6), 303 (7), 302 (5), 276 (8), 275 (15), 274 (24), 258 (5), 243 (5), 202 (8), 159 (14), 149 (10), 139 (9), 131 (10), 129 (11), 124 (9), 123 (6), 121 (6), 119 (7), 117 (8), 115 (6), 105 (10), 101 (7), 100 (7), 98 (5), 97 (6), 92 (8), 91 (21), 88 (9), 86 (45), 85 (10), 84 (69), 82 (6), 81 (11), 77 (9), 75 (35), 74 (13), 73 (100), 71 (6), 70 (5), 69 (10), 59 (11), 58 (6), 57 (11), 56 (8), 55 (10), 51 (6), 49 (9), 47 (18), 45 (9), 43 (24), 41 (15). HRMS (EI) calcd. for $C_{35}H_{57}O_6NSSi_3$-CH_3: 688.2980; found: 688.3006. Anal. calcd. for $C_{35}H_{57}O_6NSSi_3$: C 59.70, H 8.16; found: C 59.36, H 7.83.

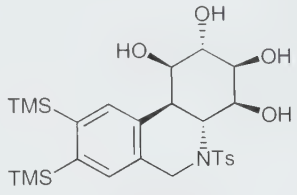
(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridin-10,11-diol (33)



$C_{29}H_{43}NO_6SSi_2$
589.89 g/mol

To a solution of TBS-protected alcohol **32** (49 mg, 0.07 mmol) in 0.1 mL THF was added 84 µL of a 1.0 mol/L solution of TBAF in THF. The reaction was stirred for 10 min at room temperature, quenched with NH_4Cl (3 mL) and diluted with ethyl ether (5 mL). The organic phase was separated and extracted three times with ethyl ether (3 mL). After drying over $MgSO_4$ and filtration, the solvent was removed under vacuum and the residue was purified by column chromatography (pentane –ethyl ether, 3:1). The deprotected diol **33** was isolated as crystalline foam in 85% yield (35 mg, 0.06 mmol); mp 91 °C. $[\alpha]^{22}_D$ +33.7 (*c* 0.39, CH_2Cl_2). R_f 0.57 (hexanes – ethyl acetate, 1:2). IR (CH_2Cl_2, cm^{-1}) ν: 3469, 2987, 2956, 2931, 2253, 1771, 1725, 1634, 1599, 1495, 1453, 1384, 1376, 1342, 1307, 1250, 1221, 1159, 1121, 1091, 1058, 974, 911, 872, 856, 840, 811, 790, 734, 675, 650, 626, 578, 561, 542. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.45 (d, J = 8.4 Hz, 2H), 7.36 (s, 1H), 7.19 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 4.88 (dd, J_1 = 8.7 Hz, J_2 = 6.0 Hz, 1H), 4.45 (m, 3H), 4.28 (t, J = 5.4 Hz, 1H), 4.18 (m, 1H), 4.07 (dd, J_1 = 12.0 Hz, J_2 = 8.7 Hz, 1H), 2.88 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 2.58 (d, J = 2.7 Hz, 1H), 2.27 (s, 3H), 2.21 (d, J = 4.8 Hz, 1H), 1.58 (s, 3H), 1.37 (s, 3H), 0.32 (s, 9H), 0.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 145.4, 143.8, 142.5, 137.3, 134.5, 132.9, 132.6, 131.8, 128.9, 127.6, 109.9, 78.3, 76.2, 72.5, 71.4, 57.3, 49.2, 38.4, 28.1, 25.7, 21.5, 1.9, 1.9. MS (EI) *m/z* (relative intensity): 574 (M^+ – CH_3, 0.1), 458 (5), 155 (5), 149 (15), 111 (11), 109 (6), 105 (7), 99 (6), 98 (19), 97 (37), 96 (9), 95 (10), 91 (9), 87 (18), 86 (6), 85 (29), 84 (23), 83 (38), 82 (10), 81 (15), 77 (5), 75 (14), 73 (19), 72 (5), 71 (50), 70 (45), 69 (87), 68 (13), 67 (11), 60 (8), 59 (9), 58 (11), 57 (82), 56 (45), 55 (72), 54 (6), 53 (5), 44 (5), 43 (100), 42 (15), 41 (60). HRMS (EI) calcd. for $C_{29}H_{43}O_6NSSi_2$: 589.2350; found: 589.2322. Anal. calcd. for $C_{29}H_{43}O_6NSSi_2$: C 59.05, H 7.35; found: C 58.72, H 6.92.

(1*S*,2*S*,3*S*,4*S*,4a*R*,10b*R*)-5-(4-Methylphenylsulfonyl)-8,9-di(trimethylsilyl)-1,2,3,4,4a,5,6,10b-octahydro-1,2,3,4-phenanthridinetetraol (34)

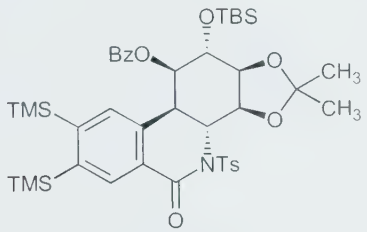


$C_{26}H_{39}NO_6SSi_2$
549.83 g/mol

To a solution of acetonide **33** (27 mg, 0.05 mmol) in MeOH (0.5 mL) was added 1 drop of water and a spatula tip of strong acidic Dowex 50WX8-100 ion exchange resin. The reaction was heated for 4 h at 70 °C, dried by addition of $MgSO_4$, and filtered. The solvent was removed under vacuum and the residue was diluted in $CHCl_3$ and filtered again. After removal of the solvent, the deprotected tetraol **34** was isolated as an oily solid in 79% yield (20 mg, 0.04 mmol). $[\alpha]^{22}_D$ +23.9 (*c* 0.61, CH_2Cl_2). R_f 0.44 (hexanes – ethyl acetate, 1:2). IR (CH_2Cl_2, cm^{-1}) ν: 3410, 2954, 2926, 2902, 2253, 1793, 1646, 1599, 1494, 1450, 1409, 1331, 1307, 1289, 1265, 1249, 1186, 1153, 1122, 1089, 1063, 1020, 970, 909, 856, 840, 811, 735, 673, 650, 629, 582, 565, 539, 481. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.42 (s, 1H), 7.25 (d, J = 6.0 Hz, 2H), 7.14 (s, 1H), 6.85 (d, J = 8.1 Hz, 2H), 4.69 (d, J = 16.2 Hz, 1H), 4.49 (s, 1H), 4.36 (m, 3H), 4.27 (d, J = 10.5 Hz, 1H), 4.03 (m, 1H), 3.57 (brs, 4H) 2.91 (d, J = 11.7 Hz, 1H), 2.21 (s, 3H), 0.32 (s, 9H), 0.28 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 145.5, 143.0, 143.0, 134.7, 134.3, 133.9, 132.2, 131.3, 128.9, 127.6, 74.9, 70.8, 70.4, 69.6, 55.3, 47.9, 38.9, 21.4, 1.9, 1.9. MS (EI) *m/z* (relative intensity): 534 (M^+ – CH_3, 5), 467 (5), 466 (11), 460 (8), 459 (15), 458 (36), 457 (5), 450 (6), 430 (6), 396 (6), 395 (12), 394 (35), 387 (8), 386 (26), 342 (6), 324 (6), 323 (5), 322 (13), 316 (5), 304 (7), 303 (7), 302 (8), 288 (6), 287 (5), 286 (6), 276 (6), 275 (10), 274 (21), 273 (5), 272 (7), 258 (6), 257 (5), 256 (8), 252 (6), 244 (6), 242 (6), 234 (9), 232 (6), 231 (8), 230 (8), 229 (8), 228 (11), 216 (6), 215 (17), 214 (52), 213 (21), 212 (5), 206 (9), 205 (7), 204 (12), 203 (8), 202 (15), 200 (6), 193 (10), 191 (5), 190 (7), 189 (6), 188 (9), 187 (14), 186 (15), 185 (7), 184 (5), 181 (6), 171 (5), 167 (6), 162 (6), 159 (6), 158 (7), 157 (8), 156 (11), 155 (8), 149 (19), 143 (6), 141 (6), 140 (10), 139 (15), 138 (6), 137 (37), 136 (16), 135 (8), 134 (6), 133 (8), 132 (5), 131 (12), 130 (10), 129 (13), 128 (8), 127 (7), 126 (7), 124 (15), 122 (5), 116 (6), 115 (7), 113 (7), 112 (5), 111 (10), 110 (9), 109 (10), 108 (8), 107 (10), 105 (7), 99 (11), 98 (31), 97 (18), 96 (8), 95 (13), 93 (10), 92 (22), 91 (52), 90 (5), 83 (8), 81 (22), 80 (8), 79 (8), 78 (5), 77 (13), 76 (5), 75 (27), 74 (13), 73 (100), 71 (31), 69 (22), 68 (8), 67 (12), 65 (14), 64 (9), 63 (6), 60 (11), 59 (5), 57 (56), 56 (15), 55 (38), 54

(6), 53 (7), 45 (23), 43 (43), 41 (28). HRMS (EI) calcd. for $C_{26}H_{39}O_6NSSi_2$: 549.2037; found: 549.2031.

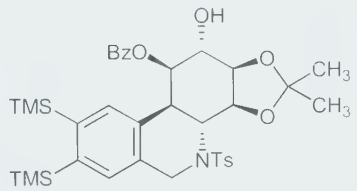
(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-5-oxo-10-phenylcarbonyloxy-11-(*tert*-butyldimethylsilyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (35)



$C_{42}H_{59}NO_8SSi_3$
822.24 g/mol

To a suspension of tosylamide **31** (20 mg, 0.02 mmol) in CH_3CN–CCl_4–H_2O (2:2:3, 0.5 mL) were added $NaIO_4$ (22 mg, 0.10 mmol) and a catalytic amount of $RuCl_3 \cdot H_2O$. After 3 h, $NaIO_4$ (15 mg) and another catalytic amount of $RuCl_3 \cdot H_2O$ were added. The reaction mixture was stirred at room temperature overnight. After another addition of $NaIO_4$ (15 mg) and another catalytic amount of $RuCl_3 \cdot H_2O$ the next day, the starting material was fully converted. The heterogeneous reaction was diluted with CH_2Cl_2 (25 mL) and extracted with water. The organic phase was dried with Na_2SO_4, filtered, and purified by flash chromatography (hexanes – ethyl acetate, 2:1). The oxidized product **35** was isolated as colorless oil in 15% yield (3 mg, 0.003 mmol). $[\alpha]^{22}{}_D$ –97.8 (*c* 0.09, CH_2Cl_2). R_f 0.63 (hexanes – ethyl acetate, 3:1). IR ($CHCl_3$, cm^{-1}) ν: 3055, 2986, 2957, 2930, 2857, 2305, 1721, 1697, 1600, 1581, 1509, 1452, 1422, 1363, 1265, 1221, 1175, 1148, 1108, 1068, 939, 895, 880, 840, 739, 705, 656, 636, 603, 544, 516, 476. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.38 (m, 3H), 7.64 (m, 3H), 7.44 (m, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.24 (m, 2H), 5.93 (s, 1H), 5.74 (m, 1H), 4.57 (m, 1H), 4.44 (s, 1H), 4.34 (m, 1H), 3.94 (m, 1H), 2.45 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 0.99 (s, 9H), 0.32 (s, 3H), 0.25 (m, 21H). MS (EI) *m/z* (relative intensity): 764 (M^+ – $C(CH_3)_3$, 4), 610 (7), 445 (5), 432 (6), 431 (11), 430 (25), 422 (5), 421 (12), 358 (6), 356 (9), 332 (10), 331 (28), 307 (9), 302 (7), 217 (5), 215 (7), 189 (8), 181 (6), 180 (11), 179 (43), 169 (6), 167 (10), 165 (5), 155 (8), 151 (7), 150 (8), 141 (9), 140 (7), 139 (11), 137 (8), 135 (10), 129 (8), 127 (8), 126 (6), 125 (11), 124 (11), 123 (16), 122 (9), 121 (20), 119 (24), 117 (9), 113 (9), 112 (10), 111 (21), 110 (8), 109 (16), 107 (7), 106 (10), 105 (100), 100 (7), 99 (13), 98 (16), 97 (38), 96 (13), 95 (25), 93 (8), 92 (11), 91 (35), 89 (6), 88 (98), 87 (12), 86 (37), 85 (55), 84 (44), 83 (46), 82 (36), 81 (32), 80 (6), 79 (9), 78 (5), 77 (27), 76 (6), 75 (14), 74 (10), 73 (73), 72 (11), 71 (65), 70 (44), 69 (71), 68 (14), 67 (20), 65 (10). HRMS (EI) calcd. for $C_{42}H_{59}O_8NSSi_3$-$C(CH_3)_3$: 764.2565; found: 764.2597. HRMS (EI) calcd. for $C_{42}H_{59}O_8NSSi_3$-CH_3: 806.3034; found: 806.3073.

(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-11-Hydroxy-2,2-dimethyl-4-(4-methylphenylsulfonyl)-10-phenylcarbonyloxy-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (36)

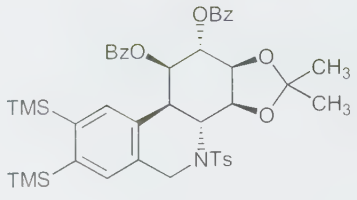


$C_{36}H_{47}NO_7SSi_2$
694.00 g/mol

To a solution of cyclic sulfate **44** (344 mg, 0.53 mmol) in dry DMF (8 mL) was added ammonium benzoate (184 mg, 1.32 mmol). The reaction mixture was heated to 70 °C for 2 h, then cooled to 40 °C, and the DMF was removed under reduced pressure. The residue was suspended in THF (8 mL) before 1 drop each of H_2O and H_2SO_4 were added. The resulting mixture was stirred for 1.5 h and then quenched with satd. aq. $NaHCO_3$ (30 mL) and diluted with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated at reduced pressure. Benzoate **36** (410 mg, 0.59 mmol, 99%) was obtained as foamy white crystals and used without further purification; mp 91 °C. $[\alpha]^{27}{}_D$ +63.7 (*c* 1.00, CH_2Cl_2). R_f 0.38 (hexanes – ethyl acetate, 2:1). IR (CH_2Cl_2, cm^{-1}) ν: 3019, 2954, 2401, 1719, 1602, 1494, 1452, 1384, 1346, 1318, 1269, 1250, 1216, 1159, 1115, 1091, 1070, 955, 876, 841, 810, 757, 714, 669, 627, 564, 456. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.92 (d, *J* = 8.1 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 2 H), 7.18 (d, *J* = 7.8 Hz, 2 H), 6.59 (d, *J* = 8.1 Hz, 2 H), 5.87 (m, 1 H), 4.66 (m, 2H), 4.35 (m, 4H), 3.04 (m, 2H), 2.10 (s, 3H), 1.71 (s, 3H), 1.40 (s, 3H), 0.28 (s, 9H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.8, 146.0, 143.9, 142.2, 137.2, 134.8, 133.7, 132.8, 132.4, 130.8, 129.9, 128.8, 128.7, 127.7, 109.8, 78.3, 76.9, 73.0, 71.0, 56.7, 47.6, 37.0, 29.9, 28.1, 25.9, 21.6, 1.9, 1.8. MS (EI) *m/z* (relative intensity): 693 (2), 484 (8), 472 (9), 471 (23), 317 (12), 316 (37), 285 (5), 169 (20), 155 (6), 149 (8), 147 (6), 139 (5), 123 (8), 122 (44), 121 (5), 119 (14), 111 (6), 106 (7), 105 (74), 97 (10), 95 (7), 91 (22), 88 (11), 86 (63), 85 (12), 84 (100), 83 (11), 82 (9), 81 (10), 78 (6), 77 (44), 75 (9), 74 (10), 73 (56), 71 (12), 70 (7), 69 (26), 67 (7), 65 (6), 60 (6), 59 (8), 57 (21), 56 (7), 55 (19), 52 (5), 51 (25), 50 (13), 49 (21), 47 (25), 45 (12), 44 (8), 43 (34), 42 (6), 41 (18). HRMS (EI) calcd. for $C_{36}H_{47}O_7NSSi_2$: 693.9979; found: 693.2603. Anal. calcd. for $C_{36}H_{47}O_7NSSi_2$: C 62.30, H 6.83; found: C 62.18, H 6.70.

(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-10,11-di(phenylcarbonyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (37)

To a solution of of alcohol **36** (142 mg, 0.21 mmol) in pyridine (1 mL) was added benzoyl chloride (35 μL,

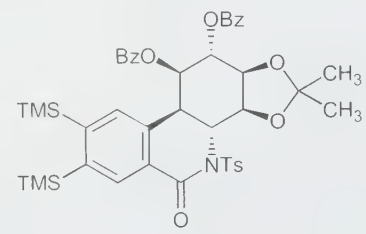


$C_{43}H_{51}NO_8SSi_2$
798.10 g/mol

0.31 mmol) at 0 °C. The ice bath was removed and the reaction mixture was stirred for 4 h at room temperature. The reaction was quenched with 5 drops of MeOH, diluted with ethyl acetate (50 mL), and washed with 1.0 mol/L HCl (2 × 20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 5:1) afforded dibenzoate **37** (140 mg, 0.18 mmol, 86%) as foamy white crystals; mp 107 °C. $[\alpha]^{25}_D$ –12.7 (*c* 1.39, CH_2Cl_2). R_f 0.62 (hexanes – ethyl acetate, 2:1). IR ($CHCl_3$, cm^{-1}) ν: 3020, 2954, 1726, 1602, 1585, 1493, 1452, 1407, 1384, 1373, 1349, 1316, 1249, 1218, 1170, 1159, 1093, 1070, 1027, 983, 954, 858, 841, 811, 711, 670, 627, 578, 562, 550, 532, 514, 462. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.10 (m, 4H), 7.59 (m, 2H), 7.48 (m, 4H), 7.25 (m, 4H), 6.45 (d, J = 8.1 Hz, 2H), 6.21 (s, 1H), 5.74 (t, J = 2.4 Hz, 1H), 4.77 (d, J = 16.5 Hz, 1H), 4.71 (dd, J_1 = 5.4 Hz, J_2 = 10.2 Hz, 1H), 4.50 (m, 2H), 4.34 (d, J = 16.2 Hz, 1H), 3.04 (d, J = 11.7 Hz, 1H), 2.05 (s, 3H), 1.84 (s, 3H), 1.47 (s, 3H), 0.31 (s, 9H), 0.20 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 165.1, 164.3, 146.3, 144.0, 141.9, 136.6, 134.6, 133.6, 133.4, 132.6, 131.9, 130.3, 130.1, 129.8, 129.7, 128.8, 128.5, 128.4, 128.4, 128.3, 127.4, 109.8, 76.3, 70.0, 68.3, 56.1, 47.4, 38.0, 27.9, 25.9, 21.3, 1.7, 1.6. MS (EI) *m/z* (relative intensity): 798 (M^+, 4), 797 (6), 642 (6), 476 (7), 340 (7), 179 (5), 149 (5), 123 (6), 122 (31), 106 (8), 105 (100), 97 (8), 95 (5), 91 (10), 84 (6), 83 (9), 77 (37), 74 (6), 73 (23), 71 (10), 70 (5), 69 (10), 67 (6). HRMS (EI) calcd. for $C_{43}H_{51}O_8NSSi_2$: 797.2874; found: 797.2863. Anal. calcd. for $C_{43}H_{51}O_8NSSi_2$: C 64.71, H 6.44; found: C 64.71, H 6.50.

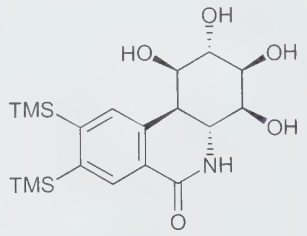
(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-5-oxo-10,11-di(phenylcarbonyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (38)

To a suspension of tosylamide **37** (141 mg, 0.18 mmol) in CH_3CN–CCl_4–H_2O (4:4:3, 11 mL) was added a solution of Na_2CO_3 (60 mg) and $NaIO_4$ (340 mg, 1.59 mmol) in H_2O (3 mL). A catalytic amount of $RuCl_3 \cdot H_2O$ (1 mg) was added and the reaction was stirred at room temperature. After 3 h, the same amount of $NaIO_4$ buffered with Na_2CO_3 and another catalytic amount of $RuCl_3 \cdot H_2O$ were added. The reaction mixture was stirred at room temperature overnight. After another addition of the same amount of oxidant the next day and one additional hour, the starting material was fully converted. The heterogeneous reaction was diluted with CH_2Cl_2 (25 mL) and washed with water and brine. The organic phase was dried with Na_2SO_4, filtered, and purified by flash chromatography (hexanes – ethyl acetate, 3:1). The oxidized product **38** was isolated as colorless oil in 33% yield (48 mg, 0.059 mmol); mp 105 °C. $[\alpha]^{23}_D$ –72.5 (*c* 0.65, CH_2Cl_2). R_f 0.74 (hexanes – ethyl acetate, 2:1). IR (CH_2Cl_2, cm^{-1}) ν: 3057, 2956, 2927, 2856, 2306, 1968, 1729, 1698, 1600, 1582, 1494, 1452, 1365, 1315, 1266, 1221, 1176, 1093, 1070, 1027, 955, 857, 843, 740, 710, 666, 637, 608, 587, 545. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.35 (s, 1H), 8.34 (d, J = 6.9 Hz, 2H), 8.11 (d, J = 6.9 Hz, 2H), 7.62 (m, 3H), 7.48 (m, 4H), 7.34 (d, J = 8.4 Hz, 2H), 7.25 (m, 2H), 6.17 (t, J = 3.3 Hz, 1H), 5.82 (t, J = 3.6 Hz, 1H), 5.70 (dd, J_1 = 5.7 Hz, J_2 = 8.4 Hz, 1H), 4.69 (dd, J_1 = 8.7 Hz, J_2 = 12.6 Hz, 1H), 4.52 (m, 1H), 3.94 (dd, J_1 = 3.3 Hz, J_2 = 12.6 Hz, 1H), 2.45 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 0.25 (s, 9H), 0.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.9, 165.1, 164.6, 154.8, 146.0, 144.1, 138.5, 135.6, 133.8, 133.3, 131.6, 130.0, 129.6, 129.1, 129.0, 128.9, 128.7, 128.2, 127.3, 109.9, 74.6, 73.5, 68.8, 68.5, 63.0, 40.1, 28.3, 26.1, 21.7, 1.6, 1.3 (two signals missing). MS (EI) *m/z* (relative intensity): 796 (M^+ – CH_3, 0.4), 477 (6), 356 (5), 355 (6), 331 (6), 179 (6), 122 (5), 106 (8), 105 (100), 97 (7), 91 (13), 85 (6), 83 (8), 81 (7), 77 (19), 73 (19), 71 (8), 69 (14), 67 (5). HRMS (EI) calcd. for $C_{43}H_{49}O_9NSSi_2$-CH_3: 796.2432; found: 796.2444.



$C_{43}H_{49}NO_9SSi_2$
812.09 g/mol

(1*R*,2*S*,3*S*,4*S*,4a*R*,10b*R*)-1,2,3,4-Tetrahydroxy-8,9-di(trimethylsilyl)-1,2,3,4,4a,5,6,10b-octahydro-6-phenanthridinone (39)

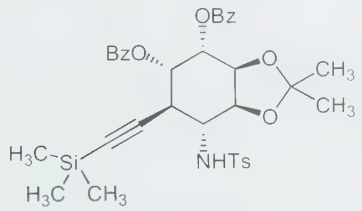


$C_{19}H_{31}NO_5Si_2$
409.62 g/mol

To a solution of of tosylate **38** (39 mg, 0.05 mmol) in THF (0.5 mL) under argon was added a 0.4 mol/L solution of sodium naphthalide (at –65 °C) until the green colour persisted. The reaction was quenched with satd. aq. NH_4Cl and extracted with CH_2Cl_2 (6 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the organic solvent was removed under reduced pressure. The residue was dissolved in MeOH. After addition of a 2.25 mol/L solution

of sodium methoxide (64 μL), the reaction mixture was stirred for 20 min. The solution was quenched with satd. aq. NH_4Cl and extracted with CH_2Cl_2 (6 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the organic solvent was removed under vacuum. Flash column chromatography of the residue (pentane – diethyl ether, 1:2) afforded a diol (7 mg, 0.02 mmol, 32%). The diol (6 mg, 0.01 mmol) was dissolved in MeOH and heated to reflux for 4 h after addition of a spatula tip of Dowex 50WX8-100. The ion exchange resin was removed by filtration and the solvent was removed under reduced pressure. Flash column chromatography of the residue ($CHCl_3$–MeOH, 6:1) afforded tetraol **39** (5 mg, 0.01 mmol, 25% over three steps); mp 213 °C. $[\alpha]^{23}_D$ +60.5 (*c* 0.15, MeOH). R_f 0.38 ($CHCl_3$–MeOH, 6:1). IR ($CHCl_3$, cm^{-1}) ν: 3385, 2953, 2926, 1705, 1652, 1600, 1586, 1447, 1410, 1375, 1318, 1250, 1217, 1155, 1128, 1093, 1055, 955, 857, 838, 757, 667, 630, 572, 549. ^1H NMR (300 MHz, CD_3OD, ppm) δ: 8.31 (s, 1H), 7.79 (s, 1H), 4.87 (s, 5H), 4.61 (m, 1H), 4.22 (t, J = 3.3 Hz, 1H), 4.05 (m, 1H), 3.95 (m, 2H), 3.33 (m, 1H), 0.41 (s, 9H), 0.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 168.3, 153.0, 145.3, 139.0, 134.9, 132.7, 129.1, 75.1, 72.1, 72.0, 70.2, 51.6, 41.1, 2.0, 1.9. MS (ESI) *m/z* (relative intensity): 454 ([M + formate]$^-$, 72), 444 ([M + Cl]$^-$, 100), 408 ([M – H]$^-$, 2), 394 (7), 311 (5), 265 (8), 171 (17), 111 (7), 89 (12). HRMS (ESI) calcd. for $C_{42}H_{61}O_7NSSi_3$ + Cl^-: 444.1429; found: 444.1429.

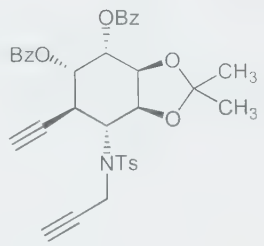
(3a*S*,4*S*,5*S*,6*R*,7*R*,7a*S*)-2,2-Dimethyl-7-(4-methylphenylsulfonamido)-4,5-di(phenylcarbonyloxy)-6-(2-trimethylsilyl-1-ethynyl)perhydro-1,3-benzodioxole (40)



$C_{35}H_{39}NO_8SSi$
661.84 g/mol

To a solution of of diol **24** (721 mg, 1.59 mmol) in pyridine (5 mL) was added benzoyl chloride (0.44 mL, 3.82 mmol) at 0 °C. The ice bath was removed and the reaction mixture was stirred for 1.5 h at room temperature. The reaction was quenched with 10 drops of MeOH, diluted with ethyl acetate (150 mL), and washed with 1.0 mol/L HCl (3 × 20 mL), water (20 mL), and brine (20 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 6:1 to 3:1) afforded dibenzoate **40** (840 mg, 1.27 mmol, 80%) as white crystals; mp 149 °C. $[\alpha]^{23}_D$ –99.9 (*c* 4.50, CH_2Cl_2). R_f 0.71 (hexanes – ethyl acetate, 2:1). IR ($CDCl_3$, cm^{-1}) ν: 3673, 3264, 3066, 3034, 2988, 2961, 2938, 2901, 2255, 2183, 1966, 1911, 1728, 1601, 1585, 1493, 1452, 1384, 1374, 1329, 1316, 1274, 1248, 1222, 1162, 1094, 1070, 1026, 1003, 910, 848, 814, 792, 734, 711, 686, 662, 650, 575, 548, 512, 466. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.95 (m, 4H), 7.79 (d, J = 8.1 Hz, 2H), 7.56 (m, 2H), 7.42 (m, 4H), 7.28 (d, J = 8.4 Hz, 2H), 5.86 (dd, J_1 = 2.7 Hz, J_2 = 4.2 Hz, 1H), 5.68 (dd, J_1 = 2.7 Hz, J_2 = 8.1 Hz, 1H), 5.04 (d, J = 7.5, 1H), 4.38 (m, 2H), 3.87 (m, 1H), 3.23 (t, J = 7.8 Hz, 1H), 2.42 (s, 3H), 1.51 (s, 3H), 1.31 (s, 3H), 0.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 165.3, 165.3, 143.6, 138.8, 133.9, 133.7, 130.1, 130.1, 129.8, 129.7, 129.6, 128.9, 128.8, 127.6, 110.6, 101.6, 90.5, 78.1, 75.1, 71.8, 69.7, 57.4, 36.4, 28.1, 26.3, 21.9, 0.0. MS (EI) *m/z* (relative intensity): 646 (M^+ – CH_3, 3), 282 (6), 214 (11), 155 (7), 122 (9), 106 (10), 105 (100), 91 (15), 77 (21), 73 (8), 69 (9), 57 (6), 55 (6), 43 (11), 41 (6). HRMS (EI) calcd. for $C_{35}H_{39}O_8NSSi$: 661.2166; found: 661.2158. Anal. calcd. for $C_{35}H_{39}O_8NSSi$: C 63.52, H 5.94; found: C 63.97, H 5.95.

(3a*S*,4*S*,5*S*,6*R*,7*R*,7a*S*)-6-(1-Ethynyl)-2,2-dimethyl-7-[4-methylphenyl(propynyl)sulfonamido]-4,5-di(phenylcarbonyloxy)perhydro-1,3-benzodioxole (41)

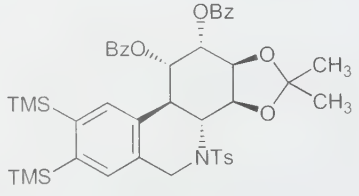


$C_{35}H_{33}NO_8S$
627.70 g/mol

To a solution of TMS-protected acetylene **40** (976 mg, 1.48 mmol) in dry acetonitrile (35 mL) was added TBAT (1.19 g, 2.21 mmol). The reaction mixture was stirred at room temperature for 1.5 h, quenched with satd. aq. NH_4Cl (50 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 4:1 to 2:1) afforded unprotected acetylene (664 mg, 1.13 mmol, 76%) as white crystals. To these crystals (418 mg,0.71 mmol) dissolved in THF (2 mL) was added NaHMDS (1.0 mol/L, 0.85 mL, 0.85 mmol) at –70 °C under argon. The reaction mixture was allowed to warm up to 0 °C over a period of 20 min and was further stirred for 10 min at this temperature. Propargyl bromide (422 mg, 3.54 mmol) and (nBu)$_4$NI (262 mg, 0.71 mmol) were added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by addition of satd. aq. NH_4Cl (40 mL) and extracted with ethyl acetate (4 × 40 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 3:2) afforded tosylamide **41** (419 mg, 0.67 mmol, 94%; 71% over two steps) as crystalline foam ; mp 86 °C. $[\alpha]^{23}_D$ –99.0 (*c* 1.40, CH_2Cl_2). R_f 0.29 (hexanes – ethyl acetate, 3:1). IR (CH_2Cl_2, cm^{-1}) ν: 3300, 3064, 2988, 2939, 2593, 2126, 1918, 1732, 1602, 1586, 1494, 1452, 1386, 1374, 1352,

1328, 1274, 1247, 1222, 1157, 1097, 1071, 1037, 1003, 921, 894, 854, 817, 736, 710, 667, 578, 564, 545, 526, 460. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.04 (d, J = 7.5 Hz, 2H), 7.92 (m, 4H), 7.52 (m, 1H), 7.43 (m, 3H), 7.30 (m, 4H), 5.95 (m, 1H), 5.70 (dd, J_1 = 2.1 Hz, J_2 = 9.6 Hz, 1H), 4.99 (dd, J_1 = 5.7 Hz, J_2 = 8.7 Hz, 1H), 4.40 (m, 1H), 4.22 (m, 3H), 4.00 (m, 1H), 2.38 (s, 3H), 2.22 (s, 1H), 2.05 (d, J = 1.5 Hz, 1H), 1.65 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 165.0, 164.8, 143.6, 137.2, 133.5, 133.1, 129.8, 129.7, 129.3, 129.0, 128.5, 128.3, 128.0, 110.6, 79.9, 78.1, 75.0, 75.0, 74.2, 73.3, 71.3, 68.5, 62.6, 36.5, 36.4, 33.2, 28.0, 26.0, 21.5. MS (EI) *m/z* (relative intensity): 612 ($M^+ - CH_3$, 1), 472 (11), 414 (5), 355 (7), 246 (5), 232 (5), 214 (8), 190 (16), 189 (97), 173 (7), 171 (6), 170 (7), 155 (7), 149 (14), 139 (8), 137 (11), 136 (5), 129 (5), 123 (7), 122 (9), 121 (9), 119 (5), 106 (11), 105 (100), 97 (7), 95 (8), 92 (9), 91 (24), 85 (7), 83 (9), 82 (6), 81 (26), 78 (6), 77 (21), 73 (11), 71 (12), 70 (6), 69 (61), 68 (8), 67 (7), 65 (7), 60 (10), 59 (5), 57 (23), 56 (9), 55 (19), 45 (8), 43 (32), 41 (24), 40 (9), 39 (10). HRMS (EI) calcd. for $C_{35}H_{33}O_8NS$-CH_3: 612.1692; found: 612.1682.

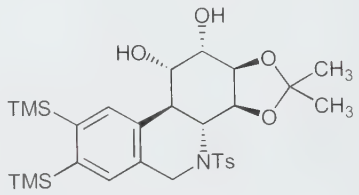
(3a*S*,3b*R*,9b*R*,10*S*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-10,11-di(phenylcarbonyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (42)



$C_{43}H_{51}NO_8SSi_2$
798.10 g/mol

To a solution of $CpCo(CO)_2$ (5 μL) in BTMSA (12 mL) bisacetylene **41** (370 mg, 0.59 mmol), $CpCo(CO)_2$ (5 μL) dissolved in xylene (2 mL), and BTMSA (8 mL) were added dropwise with a syringe pump at 140 °C over 30 h. During this slow addition, extra catalyst was added directly into the reaction mixture in aliquots: 3 μL after 5 h, 5 μL after 20 h, and 3 μL after 29 h. The reaction mixture was heated under argon for further 12 h. BTMSA and xylene were removed under high vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 9:1). The cyclotrimerized product **42** was isolated as crystalline foam in 87% yield (407 mg, 0.51 mmol); mp 131 °C. $[\alpha]^{23}_D$ +43.1 (*c* 0.75, CH_2Cl_2). R_f 0.37 (hexanes – ethyl acetate, 3:1). IR ($CDCl_3$, cm^{-1}) ν: 3065, 3034, 2986, 2954, 2901, 2255, 1911, 1729, 1602, 1586, 1493, 1452, 1384, 1374, 1348, 1316, 1272, 1251, 1218, 1178, 1162, 1120, 1093, 1069, 1027, 1002, 971, 910, 874, 856, 839, 812, 784, 734, 670, 649, 628, 564, 519. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.89 (d, J = 7.5 Hz, 2H), 7.85 (d, J = 8.7 Hz, 2H), 7.52 (m, 4H), 7.34 (m, 4H), 7.26 (m, 2H), 7.04 (d, J = 8.1 Hz, 2H), 6.19 (dd, J_1 = 5.4 Hz, J_2 = 8.4 Hz, 1H), 5.70 (dd, J_1 = 5.1 Hz, J_2 = 9.3 Hz, 1H), 4.98 (t, J = 7.5 Hz, 1H), 4.76 (dd, J_1 = 7.2 Hz, J_2 = 9.0 Hz, 1H), 4.59 (dd, J_1 = 16.5 Hz, J_2 = 60.0 Hz, 2H), 4.03 (dd, J_1 = 8.4 Hz, J_2 = 12.6 Hz, 1H), 3.28 (dd, J_1 = 8.7 Hz, J_2 = 12.6 Hz, 1H), 2.31 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H), 0.39 (s, 9H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 165.4, 165.3, 146.2, 144.3, 142.7, 137.4, 133.6, 133.3, 133.1, 132.6, 132.5, 131.4, 129.7, 129.7, 129.3, 129.1, 129.0, 128.3, 128.1, 127.5, 110.7, 76.9, 73.7, 69.7, 69.5, 58.1, 48.0, 39.4, 27.5, 25.1, 21.4, 1.8, 1.6. MS (EI) *m/z* (relative intensity): 430 (2), 256 (5), 230 (11), 167 (5), 149 (19), 137 (11), 136 (6), 129 (15), 123 (9), 122 (5), 121 (7), 113 (6), 112 (10), 111 (7), 109 (8), 197 (6), 105 (19), 98 (7), 97 (12), 96 (6), 95 (15), 93 (9), 91 (8), 87 (5), 85 (12), 84 (13), 83 (19), 82 (10), 81 (41), 79 (7), 77 (10), 73 (23), 71 (26), 70 (21), 69 (100), 68 (16), 67 (15), 61 (6), 60 (19), 58 (6), 57 (49), 56 (31), 55 (46), 54 (6), 53 (8), 45 (12), 44 (12), 43 (59), 42 (15), 41 (67). HRMS (EI) calcd. for $C_{43}H_{51}O_8NSSi_2$: 797.2874; found: 797.2885.

(3a*S*,3b*R*,9b*R*,10*S*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine-10,11-diol (43)

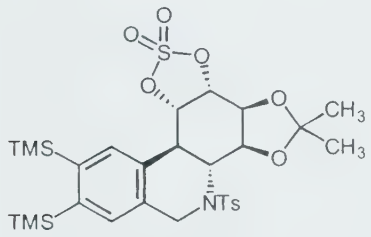


$C_{29}H_{43}NO_6SSi_2$
589.89 g/mol

Protected diol **42** (100 mg, 0.13 mmol) was dissolved in a 1% sodium hydroxide solution in methanol (2 mL) and stirred for 1 h at room temperature. The reaction was quenched with NH_4Cl and extracted with CH_2Cl_2. The organic solvents were dried over Na_2SO_4 and removed under high vacuum. The residue was purified by column chromatography (hexanes – ethyl acetate, 3:1 to 1:1). The diol **43** was isolated as foamy crystals in 99% yield (73 mg, 0.12 mmol); mp 121 °C. $[\alpha]^{25}_D$ +35.5 (*c* 1.50, CH_2Cl_2). R_f 0.18 (hexanes – ethyl acetate, 2:1). IR (CH_2Cl_2, cm^{-1}) ν: 3406, 3055, 2954, 2927, 2871, 1727, 1599, 1495, 1455, 1376, 1347, 1266, 1250, 1213, 1160, 1124, 1091, 1072, 1042, 1002, 972, 931, 877, 858, 840, 740, 704, 672, 656, 602, 563, 546, 519, 486, 479, 467, 463, 455. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.65 (s, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.21 (s, 1H), 6.98 (d, J = 8.1 Hz, 2H), 4.74 (t, J = 7.8 Hz, 1H), 4.56 (d, J = 16.2 Hz, 1H), 4.35 (m, 3H), 3.91 (m, 1H), 3.75 (m, 1H), 3.11 (s, 1H), 2.87 (s, 1H), 2.67 (dd, J_1 = 8.1 Hz, J_2 = 12.3 Hz, 1H), 2.29 (s, 3H), 1.54 (s, 3H), 1.33 (s, 3H), 0.33 (s, 9H), 0.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 145.6, 143.9, 142.5, 137.4, 133.9, 133.8, 132.3, 132.1, 128.9, 127.4, 110.3, 77.1, 75.8, 70.3, 68.8, 57.0, 47.6, 41.0, 27.7, 25.0, 21.5, 1.9, 1.9. MS (EI) *m/z* (relative intensity): 574 ($M^+ - CH_3$, 13), 471 (12), 459 (10), 458 (22), 435 (23), 434 (65), 432 (11), 429 (13), 428 (29), 342 (11), 335 (17), 322 (20), 285 (21), 274 (12), 185 (10), 169

(79), 155 (30), 150 (15), 149 (19), 147 (27), 139 (15), 133 (10), 131 (13), 129 (17), 125 (14), 124 (14), 123 (14), 119 (45), 111 (21), 109 (21), 105 (15), 97 (38), 96 (17), 95 (28), 92 (12), 91 (65), 85 (23), 84 (14), 83 (32), 82 (17), 81 (31), 79 (14), 77 (14), 73 (51), 71 (33), 70 (21), 69 (75), 68 (14), 67 (22), 65 (15), 59 (12), 57 (55), 56 (19), 55 (61), 53 (11), 45 (15), 44 (15), 43 (100), 42 (15), 41 (54). HRMS (EI) calcd. for $C_{29}H_{43}O_6NSSi_2$-CH_3: 574.2115; found: 574.2099. Anal. calcd. for $C_{29}H_{43}O_6NSSi_2$: C 59.05, H 7.35; found: C 58.77, H 7.37.

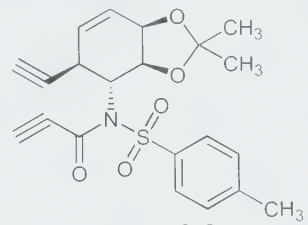
(3a*S*,3b*R*,6a*S*,6b*R*,12b*R*,12c*S*)-5,5-Dimethyl-7-(4-methylphenylsulfonyl)-10,11-di(trimethylsilyl)-3a,3b,6a,6b,7,8,12b,12c-octahydro-1,3,4,6-tetraoxa-2-thia-7-azadicyclopenta[*a*,*c*]phenanthrene-2,2-dioxide (44)



$C_{29}H_{41}NO_8S_2Si_2$
651.94 g/mol

To a solution of diol **43** (494 mg, 0.84 mmol) in dry CH_2Cl_2 (20 mL) was added triethylamine (5 mL) at 0 °C. The solution was stirred for 10 min and SO_2Cl_2 (1.0 mol/L solution, 15 mL) were added dropwise via syringe pump over a period of 2 h. Additional NEt_3 (5 mL) and SO_2Cl_2 (15 mL) were added over a period of 2 h for full conversion (TLC). The reaction mixture was diluted with CH_2Cl_2 (30 mL), quenched with satd. aq. NH_4Cl (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes – ethyl acetate, 5:1) afforded cyclic sulfate **44** (383 mg, 0.59 mmol, 70%); mp 110 °C. $[\alpha]^{26}_D$ +24.6 (*c* 0.40, CH_2Cl_2). R_f 0.66 (hexanes – ethyl acetate, 2:1). IR ($CHCl_3$, cm^{-1}) ν: 3462, 3021, 2963, 2870, 1732, 1597, 1456, 1385, 1355, 1308, 1249, 1213, 1182, 1162, 1127, 1090, 1056, 995, 919, 883, 840, 795, 756, 669, 627, 562. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.42 (m, 3H), 7.28 (s, 1H), 7.00 (d, J = 8.1 Hz, 2H), 5.35 (dd, J_1 = 7.2 Hz, J_2 = 9.6 Hz, 1H), 5.04 (t, J = 7.2 Hz, 1H), 4.75 (m, 2H), 4.63 (d, J = 16.2 Hz, 1H), 4.27 (d, J = 16.2 Hz, 1H), 3.69 (dd, J_1 = 8.1 Hz, J_2 = 12.3 Hz, 1H), 2.99 (t, J = 10.8 Hz, 1H), 2.30 (s, 3H), 1.57 (s, 3H), 1.34 (s, 3H), 0.34 (s, 9H), 0.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 145.0, 144.0, 141.3, 135.1, 131.7, 130.8, 129.6, 128.8, 127.3, 125.6, 109.8, 80.9, 78.0, 75.1, 73.0, 54.3, 45.2, 36.5, 25.5, 22.9, 19.7, 0.0, 0.0. MS (EI) *m*/*z* (relative intensity): 636 ($M^+ - CH_3$, 1), 88 (11), 86 (65), 84 (100), 73 (6), 69 (6), 49 (21), 47 (27), 43 (6). HRMS (EI) calcd. for $C_{29}H_{41}O_8NS_2Si_2$-CH_3: 636.1577; found: 636.1556. Anal. calcd. for $C_{29}H_{41}O_8NS_2Si_2$: C 53.43, H 6.34; found: C 53.52, H 6.47.

(3a*S*,4*R*,5*R*,7a*R*)-5-(1-Ethynyl)-2,2-dimethyl-4-[4-methylphenyl(propioloyl)sulfonamido]-3a,4,5,7a-tetrahydro-1,3-benzodioxolone (45)

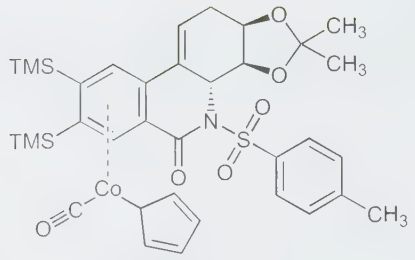


$C_{21}H_{21}NO_5S$
399 46 g/mol

To a solution of acetonide **18** (250 mg, 0.60 mmol) in THF (5 mL) was added BuLi (1.6 mol/L, 0.41 mL, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (87 mg, 0.72 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by addition of satd. aq. NH_4Cl (20 mL) and the aqueous phase extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 3:1) afforded a bisacetylene (128 mg, 0.27 mmol, 46%) as a slightly yellow foam. To a solution of this bisacetylene (150 mg, 0.32 mmol) in acetonitrile (5 mL) was added TBAT (340 mg, 0.63 mmol). The reaction mixture was stirred at room temperature for 30 h, then diluted with 30 mL ethyl acetate, and washed with satd. aq. NH_4Cl (3 × 10 mL) and with brine (10 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 3:1) afforded the bisacetylene **45** (77 mg, 0.19 mmol, 61%) as a colorless oil. $[\alpha]^{21}_D$ +30.3 (*c* 0.25, CH_2Cl_2). R_f 0.40 (hexanes – ethyl acetate, 3:1). IR ($CHCl_3$, cm^{-1}) ν: 3298, 3021, 2989, 2937, 2876, 2591, 2403, 2109, 1917, 1732, 1674, 1597, 1511, 1495, 1485, 1456, 1429, 1399, 1366, 1309, 1270, 1246, 1216, 1189, 1172, 1141, 1120, 1085, 1067, 1027, 1019, 998, 971, 946, 923, 897, 865, 830, 813, 757. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.97 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 9.5 Hz, 2H), 5.98 (m, 2H), 5.07 (m, 1H), 4.70 (m, 2H), 4.21 (d, J = 10.4 Hz, 1H), 3.24 (s, 1H), 2.39 (s, 3H), 2.16 (s, 1H), 1.48 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 153.6, 145.4, 136.0, 132.6, 129.7, 129.2, 123.6, 110.6, 83.0, 81.5, 75.2, 73.4, 72.9, 72.7, 65.4, 32.9, 27.8, 25.8, 21.9. MS (EI) *m*/*z* (relative intensity): 384 ($MH^+ - CH_3$, 8), 306 (18), 248 (11), 228 (7), 224 (10), 204 (12), 170 (9), 156 (8), 155 (77), 152 (9), 139 (11), 135 (20), 119 (22), 118 (46), 107 (5). HRMS (EI) calcd. for $C_{21}H_{21}O_5NS$-CH_3: 384.0906; found: 384.0898.

Carbonyl-η^1-cyclopentadienyl-η^6-(3a*S*,3b*R*,11a*R*)-2,2-dimethyl-4-(4-methylphenylsulfonyl)-7,8-di(trimethylsilyl)-3a,3b,4,5,11,11a-hexahydro[1,3]dioxolo[4,5-*c*]-phenanthridin-5-onylcobalt (46)

A solution of bisacetylene **45** (165 mg, 0.43 mmol) and $CpCo(CO)_2$ (10 μL) in BTMSA (10 mL) and xylene (10 mL) was added with a syringe pump to a refluxing solu-

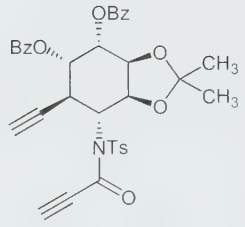


$C_{35}H_{44}CoNO_6SSi_2$
721.91 g/mol

tion of $CpCo(CO)_2$ (10 µL) in BTMSA (25 mL) over a period of 35 h. After the addition was completed, the reaction mixture was refluxed for an additional 6 h. The solvent was removed under reduced pressure (0.1 mbar, 1 bar = 100 kPa). The reddish brown residue was purified by flash column chromatography (pentane to ether – pentane, 1:1) and afforded the cobalt complex **46** (33 mg, 0.05 mmol, 11%) as a yellow oil. $[\alpha]^{26}_D$ +27.6 (*c* 0.23, $CHCl_3$). R_f 0.53 (hexanes –ethyl acetate, 3:1). IR ($CHCl_3$, cm^{-1}) ν: 3261, 3019, 2958, 2934, 2873, 2401, 1693, 1599, 1521, 1496, 1456, 1383, 1375, 1328, 1287, 1272, 1251, 1216, 1158, 1096, 1071, 969, 928, 857, 841, 812, 757, 669. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.00 (s, 1H), 7.51 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 6.01 (d, *J* = 7.7 Hz, 1H), 5.91 (m, 1H), 5.71 (d, *J* = 9.8 Hz, 1H), 4.57 (m, 1H), 4.18 (m, 3H), 4.00 (m, 1H), 3.61 (m, 1H), 2.18 (s, 3H), 1.58 (m, 2H), 1.33 (s, 3H), 1.18 (s, 3H), 0.23 (s, 9H), 0.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 169.5, 152.6, 144.8, 141.7, 141.0, 140.0, 136.3, 136.1, 135.7, 129.5, 129.1, 128.8, 126.9, 124.3, 109.9, 79.5, 79.3, 72.7, 65.9, 60.4, 41.8, 30.5, 28.7, 28.2, 26.2, 25.9, 21.6, 1.9, 1.8. MS (FAB) *m/z* (relative intensity): 744 (M^+ + Na, 0.1). MS (EI) *m/z* (relative intensity): 656 (M^+ – Cp, 4.8), 614 (5), 613 (11), 505 (7), 501 (8), 500 (20), 460 (9), 459 (21), 458 (8), 420 (6), 419 (14), 418 (38), 358 (6), 357 (13), 356 (7), 343 (6), 341 (7), 340 (7), 329 (5), 325 (8), 294 (7), 288 (6), 279 (5), 255 (8), 254 (37), 253 (23), 228 (6), 205 (6), 171 (6), 155 (18), 149 (17), 141 (5), 140 (7), 139 (33), 124 (8), 100 (11), 99 (65), 98 (52), 97 (6), 95 (8), 92 (11), 91 (58), 85 (7), 83 (9), 81 (5), 77 (6), 75 (18), 74 (11), 73 (100), 71 (13), 69 (13), 67 (5), 65 (10). HRMS (EI) calcd. for $C_{35}H_{44}O_6NSSi_2Co$-CO: 693.1811; found: 693.1807.

(3a*S*,4*S*,5*S*,6*R*,7*R*,7a*S*)-6-(1-Ethynyl)-2,2-dimethyl-7-[4-methylphenyl(propioloyl)sulfonamido]-4,5-di(phenylcarbonyloxy)perhydro-1,3-benzodioxole (47)

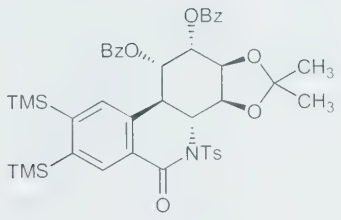
To a solution of TMS-protected acetylene **40** (976 mg, 1.48 mmol) in dry acetonitrile (35 mL) was added TBAT (1.19 g, 2.21 mmol). The reaction mixture was stirred at room temperature for 1.5 h, quenched with satd. aq. NH_4Cl (50 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. Column chromatography (hexanes – ethyl acetate, 4:1 to 2:1) afforded unprotected acetylene (664 mg, 1.13 mmol, 76%) as white crystals. To a solution of this material (210 mg, 0.36 mmol) in THF (6 mL) was added NaHMDS (1.0 mol/L, 0.43 mL, 0.43 mmol) at –70 °C under argon. The reaction mixture was allowed to warm to 0 °C over a period of 20 min and was further stirred for 10 min at this temperature. Propiolic acid anhydride (130 mg, 1.07 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by addition of satd. aq. NH_4Cl (20 mL) and the aqueous phase extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 3:2) afforded an unseparable 3:2 rotamer mixture of tosylamide **47** (128 mg, 0.27 mmol, 46%) as oily white crystals; mp 121 °C. $[\alpha]^{23}_D$ –124.6 (*c* 1.05, CH_2Cl_2). R_f 0.62 (hexanes – ethyl acetate, 2:1). IR (CH_2Cl_2, cm^{-1}) ν: 3292, 3055, 2987, 2831, 2686, 2522, 2411, 2306, 2113, 1731, 1677, 1602, 1551, 1422, 1363, 1266, 1189, 1173, 1116, 1095, 1071, 1055, 1027, 896, 853, 740, 705, 618, 574, 546. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.15 (m, 3H), 8.02 (m, 1H), 7.97 (m, 2H), 7.58 (m, 1H), 7.49 (m, 3H), 7.40 (m, 4H), 6.06 (m, 1H), 5.72 (dd, J_1 = 2.1 Hz, J_2 = 10.2 Hz, 1H), 5.35/4.96 (m, 1H), 4.96 (m, 1H), 4.46 (m, 2H), 3.30/3.18 (m, 1H), 2.45/2.43 (s, 3H), 2.19/2.14 (m, 1H), 1.74/1.64 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 165.3, 165.1/164.9, 153.2, 145.4/145.2, 136.7, 133.7, 133.3/133.2, 130.9/130.0, 129.9, 129.9, 129.6, 129.4/129.3, 129.2/129.0, 128.7, 128.4/128.3, 111.2/111.0, 83.6/83.2, 79.4/79.0, 75.9/75.4, 75.2/75.1, 74.4/74.1, 74.0/73.2, 71.2/71.1, 68.3/68.1, 62.8, 33.8/31.5, 27.9/27.8, 26.2/26.0, 21.7. MS (EI) *m/z* (relative intensity): 626 (M^+ – CH_3, 1), 122 (9), 119 (5), 105 (47), 91 (8), 88 (19), 86 (100), 84 (100), 77 (14), 64 (16), 53 (15), 51 (11), 49 (31), 48 (6), 47 (37), 44 (7), 43 (17). HRMS (EI) calcd. for $C_{35}H_{31}O_9NS$-CH_3: 626.1485; found: 626.1495.



$C_{35}H_{31}NO_9S$
641.69 g/mol

(3a*S*,3b*R*,9b*R*,10*S*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-5-oxo-10,11-di(phenylcarbonyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (48)

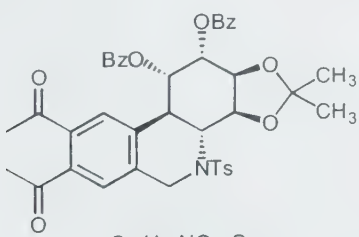
To a solution of $CpCo(CO)_2$ (2 µL) in BTMSA (6 mL), bisacetylene **47** (105 mg, 0.16 mmol) and $CpCo(CO)_2$ (2 µL) dissolved in xylene (1 mL) and BTMSA (4 mL) were added dropwise with a syringe pump at 140 °C over 30 h. During this slow addition, extra catalyst was added directly into the reaction mixture in aliquots: 2 µL after 5 h and after 20 h, and 1 µL after 29 h. After 5 h and after 20 h, additional $CpCo(CO)_2$ (2 µL) was added, and after 29 h, additional $CpCo(CO)_2$ (1 µL) was added. The reaction mixture was heated under argon for a further 12 h. BTMSA and



$C_{43}H_{49}NO_9SSi_2$
812.09 g/mol

xylene were removed at high vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 9:1). The cyclotrimerized product **48** was isolated as a colourless oil in 5% yield (7 mg, 0.01 mmol). $[\alpha]^{22}_D$ –20.9 (*c* 0.25, CH_2Cl_2). R_f 0.32 (hexanes – ethyl acetate, 4:1). IR (CH_2Cl_2, cm^{-1}) ν: 3061, 2987, 2957, 2928, 2856, 1728, 1704, 1601, 1584, 1494, 1452, 1405, 1366, 1316, 1266, 1219, 1189, 1175, 1094, 1027, 1003, 963, 841, 816, 739, 712, 672, 660, 638, 602, 572, 545, 512. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.44 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 2H), 8.13 (s, 1H), 8.07 (m, 2H), 7.99 (m, 2H), 7.64 (m, 1H), 7.52 (m, 3H), 7.39 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.44 (s, 1H), 5.85 (dd, J_1 = 7.2 Hz, J_2 = 10.8 Hz, 1H), 5.25 (dd, J_1 = 2.4 Hz, J_2 = 7.2 Hz, 1H), 4.98 (t, *J* = 7.2 Hz, 1H), 3.90 (t, *J* = 11.1 Hz, 1H), 3.76 (d, *J* = 12.0 Hz, 1H), 2.45 (s, 3H), 1.49 (s, 3H), 1.32 (s, 3H), 0.44 (s, 9H), 0.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.4, 165.5, 165.5, 155.6, 146.7, 144.2, 138.4, 137.9, 136.7, 133.8, 133.4, 131.1, 129.9, 129.8, 129.3, 129.2, 129.0, 128.8, 128.8, 128.4, 126.8, 110.4, 75.4, 73.5, 72.0, 70.5, 66.1, 46.1, 27.6, 25.5, 21.7, 1.7, 1.6. MS (EI) *m/z* (relative intensity): 796 ($M^+ - CH_3$, 1), 525 (6), 477 (5), 179 (5), 149 (7), 129 (8), 106 (9), 105 (100), 98 (7), 97 (13), 96 (6), 95 (8), 91 (13), 85 (10), 84 (9), 83 (17), 82 (8), 81 (13), 77 (16), 73 (25), 71 (17), 70 (10), 69 (30), 68 (6), 67 (8). HRMS (EI) calcd. for $C_{43}H_{49}O_9NSSi_2$-CH_3: 796.2432; found: 796.2399. Anal. calcd. for $C_{43}H_{49}O_9NSSi_2$: C 63.60, H 6.08; found: C 63.46, H 6.00.

(3a*S*,3b*R*,9b*R*,10*S*,11*S*,11a*S*)-7,8-Diacetyl-2,2-dimethyl-4-(4-methylphenylsulfonyl)-10,11-di(phenylcarbonyloxy)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (51)



$C_{41}H_{39}NO_{10}S$
737.82 g/mol

To a solution of 2,5-di(*tert*-butyldimethylsilyloxy)-3-hexyne (1.00 g) in $CpCo(CO)_2$ (5 μL), bisacetylene **41** (108 mg, 0.17 mmol) and $CpCo(CO)_2$ (5 μL) dissolved in xylene (5 mL) were added dropwise with a syringe pump at 140 °C over 30 h. During and after this slow addition, extra catalyst was added directly into the reaction mixture in aliquots: 5 μL after 5, 17, 29, and 41 h. The reaction mixture was heated under argon for a further 12 h. Xylene was removed at high vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 9:1 to 6:1). All four diastereoisomers of the cyclotrimerized product **50** were isolated as crystalline foam in 31% overall yield (52 mg, 0.05 mmol). MS (EI) *m/z* (relative intensity): 954 ($M^+ - CH_3$, 0.1), 912 (10), 526 (12), 253 (12), 179 (12), 147 (11), 106 (12), 105 (100), 91 (16), 77 (17), 75 (27), 73 (33).

The mixture of diastereoisomers was dissolved in THF (0.5 mL), treated with TBAF (1.0 mol/L solution in THF, 0.55 mL) and stirred for 2 h. The reaction mixture was quenched with satd. NH_4Cl solution and extracted three times with diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated to dryness. Column chromatography (hexanes – ethyl acetate, 1:2) gave a mixture of four diastereomeric diols (29 mg, 0.04 mmol, 72%), used immediately in the next step. IR ($CDCl_3$, cm^{-1}) ν: 3417, 3019, 2978, 2929, 2857, 1727, 1601, 1452, 1384, 1375, 1347, 1316, 1276, 1216, 1160, 1092, 1070, 1027, 758, 713, 668.

To the diastereomeric diols (17 mg, 0.02 mmol) dissolved in DMSO (1 mL) was added *o*-iodoxybenzoic acid (IBX, (75 mg, 0.28 mmol). The reaction mixture was stirred for 1 day, diluted with diethyl ether, and washed four times with water. The ether phase was dried over $MgSO_4$, filtered, and evaporated to dryness. The pure product **51** was obtained by column chromatography (ethyl ether – pentane, 2:1) as a white crystalline single diastereomer in 71% yield (12 mg, 0.02 mmol); mp 119 °C. $[\alpha]^{23}_D$ +38.6 (*c* 0.06, CH_2Cl_2). R_f 0.48 (hexanes – ethyl acetate, 1:1). IR ($CDCl_3$, cm^{-1}) ν: 3020, 2926, 2855, 1759, 1727, 1602, 1510, 1452, 1316, 1273, 1216, 1162, 1092, 1068, 1027, 933, 814, 758, 710, 667, 548. ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ: 7.89 (2m, 4H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.58 (m, 1H), 7.52 (m, 1H), 7.52 (s, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.08 (s, 1H), 6.12 (dd, J_1 = 4.8 Hz, J_2 = 8.6 Hz, 1H), 5.74 (dd, J_1 = 4.7 Hz, J_2 = 7.9 Hz, 1H), 5.03 (dd, J_1 = 6.8 Hz, J_2 = 8.8 Hz, 1H), 4.73 (t, *J* = 7.4 Hz, 1H), 4.62 (d, *J* = 16.8 Hz, 1H), 4.53 (d, *J* = 16.7 Hz, 1H), 4.00 (dd, J_1 = 8.9 Hz, J_2 = 12.6 Hz, 1H), 3.43 (dd, J_1 = 8.9 Hz, J_2 = 12.6 Hz, 1H), 2.41 (s, 3 H), 2.35 (s, 3H), 2.20 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ: 201.7, 200.0, 165.4, 165.3, 143.8, 139.3, 138.6, 137.7, 137.4, 136.4, 133.8, 133.5, 129.8, 129.8, 129.4, 128.6, 128.4, 127.5, 126.2, 125.1, 110.8, 96.1, 76.2, 74.1, 70.1, 69.8, 59.4, 48.5, 39.6, 30.3, 29.2, 27.8, 27.7, 25.4, 21.5. MS (EI) *m/z* (relative intensity): 737 (M^+, 0.1), 133 (14), 105 (6), 89 (41), 87 (18), 73 (11), 59 (12), 45 (100). HRMS (EI) calcd. for $C_{41}H_{39}O_{10}NS$: 737.2295; found: 737.2306.

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Novel electrophilic ipso acylation – detosylation reaction of pyrroles[1]

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Abstract: A pyrrole and two pyrroloindoles that are substituted with a *p*-toluenesulfonyl group undergo an ipso acylation – detosylation reaction with acid chlorides and aluminum chloride to afford the corresponding acyl-substituted pyrroles and pyrroloindoles.

Key words: pyrrole, pyrroloindole, ipso acylation, detosylation, Friedel–Crafts reaction.

Résumé : Sous l'action de chlorures d'acides et de chlorure d'aluminium, un pyrrole et deux pyrroindoles substitués par un groupe *p*-toluènesulfonyle subissent des réactions d'acétylation-détosylation ipso qui conduisent à la formation des pyrroles et pyrroindoles correspondants substitués par un groupe acyle.

Mots clés : pyrrole, pyrroindole, acétylation ipso, détosylation, réaction de Friedel–Crafts.

[Traduit par la Rédaction]

Introduction

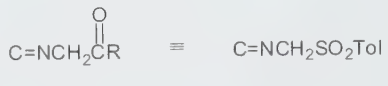
Whereas electrophilic ipso substitution (1) of aromatic and heteroaromatic compounds, including organosilanes (2), organostannanes (3), and several other substrates (4), is well-documented, there appear to be no examples of organosulfones undergoing electrophilic ipso substitution. For example, treatment of 3-phenyl-4-(*p*-toluenesulfonyl)furan with acetyl chloride and $AlCl_3$ gives only the expected electrophilic product, 2-acetyl-3-phenyl-4-(*p*-toluenesulfonyl)furan (5). On the other hand, free radical ipso stannylation – detosylation reactions of 1-(phenylsulfonyl)-2-(*p*-toluenesulfonyl) indole and related heterocycles have been described (6).

Results and discussion

In connection with our interest in the closely related Barton–Zard (7), van Leusen (8), and Montforts (9) syntheses of pyrroles (10), we had occasion to examine the Friedel–Crafts acylation of 4-ethyl-2-(*p*-toluenesulfonyl)pyrrole (**4**). This compound was readily prepared by treating either 2-nitrobutyl acetate (**1**) (11) or 2-nitro-1-butene (**2**) (12) with TosMIC (**3**) (13) and DBU in the presence of isopropanol Scheme 1). Treatment of **4** with acetyl chloride in the presence of aluminum chloride affords 2-acetyl-4-ethylpyrrole (**5**) and not the expected 2-acetyl-3-ethyl-5-(*p*-toluenesulfonyl)pyrrole (**6**). The characteristic odor of *p*-toluenesulfonyl chloride (**7**) in the reaction mixture was indicative of this novel transformation. To confirm the regiochemistry of **5**, we synthesized 2-acetyl-3-ethylpyrrole (**8**) by hydrolysis (K_2CO_3, MeOH, reflux, 78%) of the known 2-acetyl-3-ethyl-1-(phenylsulfonyl)pyrrole (14). Direct comparison of these two pyrroles reveals that the product of the acetylation of **4** was clearly **5** and not **8**. We view this ipso acylation – detosylation reaction as involving ipso electrophilic attack at C-5 in **4** followed by chloride attack on the sulfonyl group to give *p*-toluenesulfonyl chloride and pyrrole **5**.

This ipso acylation – detosylation was extended to the synthesis of acylated pyrroloindoles (Scheme 2). Thus, treatment of pyrrolo[2,3-*b*]indole **10** and pyrrolo[3,4-*b*]indole **13** with acetyl chloride and valeryl chloride in the presence of aluminum chloride affords the acylated analogues **11** and **14**, respectively. Pyrroloindoles **10** and **13** were synthesized with TosMIC from indoles **9** and **12**, respectively, according to our earlier method (10).

In summary, we have discovered a novel electrophilic ipso acylation – detosylation reaction of α-tosylpyrroles. In the context of van Leusen and Barton–Zard pyrrole syntheses, the reagent TosMIC (**3**) can be viewed as a synthetic equivalent for α-isocyanoketones (**15**). Compounds related to **15** have previously been generated from α-metalated oxazoles (15), but they have not been employed in these pyrrole ring syntheses.



15 **3**

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Dedicated to Dr. Alfred Bader, organic chemistry pioneer and art connoisseur extraordinaire. Thank you for giving us decades of wonderful service and for rejuvenating our appreciation of art.

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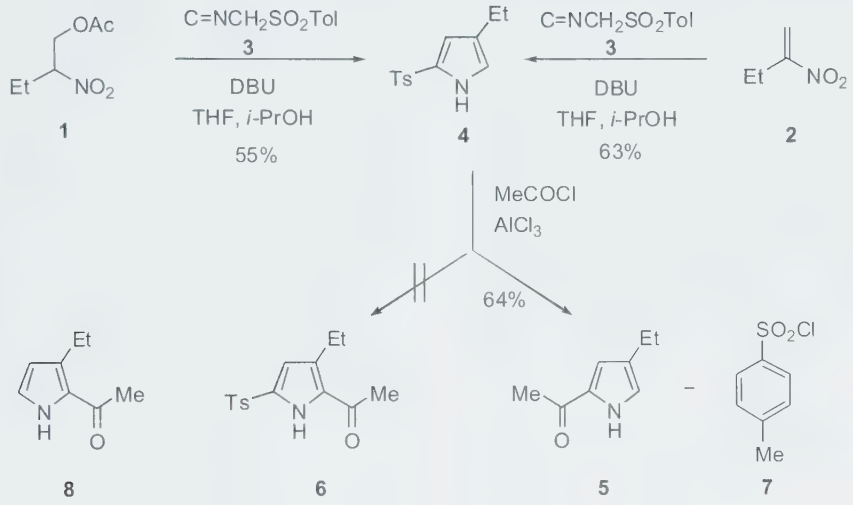
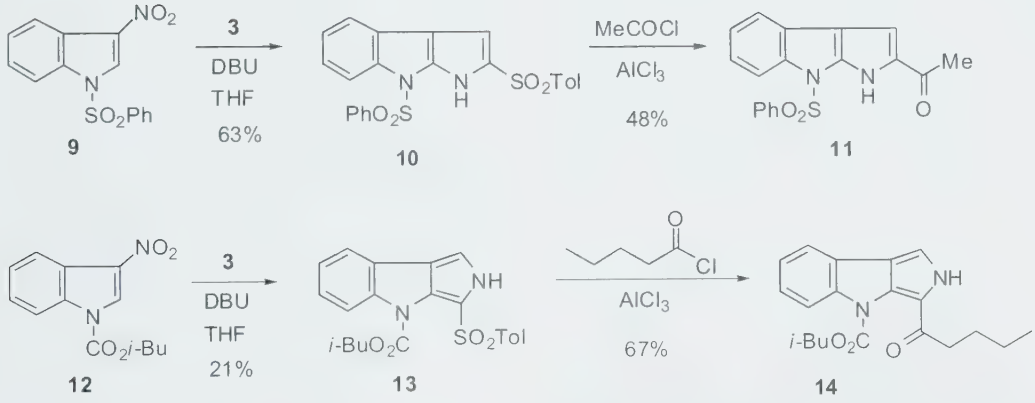
Scheme 1.



Scheme 2.



Experimental

Melting points were determined using open capillary tubes and are uncorrected. Thin-layer chromatography (TLC) was performed on regular TLC plates. Visualization of developed plates was achieved with a 254 nm UV lamp and (or) with iodine. Flash chromatography utilized 230–400 mesh silica gel 60. ^{1}H NMR and ^{13}C NMR were run at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm using the solvent residual proton or carbon signal ($CDCl_3$: H, 7.27, C, 77.23) as an internal reference. The apparent multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), broad (br)), number of protons, and coupling constants (in Hz) are reported in that order in parenthesis after the chemical shift. Infrared spectra (IR) are reported in reciprocal centimeters and were obtained using neat compounds (neat), solid KBr pellets (KBr), polyethylene IR cards (PE), or polytetrafluoroethylene IR cards (PTFE). High-resolution mass spectrometry (HRMS) was performed at the University of Illinois (Urbana-Champaign, Illinois) mass spectrometry laboratory or by the SOCAL Mass Spectrometry Facility at the University of California (Riverside, California). Elemental analyses were performed by Atlantic Microlabs, Inc. (Norcross, Georgia). Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium-benzophenone ketyl. Diisopropylamine, dichloromethane, xylenes, and triethylamine were distilled from calcium hydride. Acetyl chloride, hexanoyl chloride, trimethylsilyl chloride, and valeryl chloride were distilled from 0.1% quinoline. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and were used without further purification. All reactions were performed under a positive nitrogen atmosphere with magnetic stirring unless otherwise noted. All glassware was oven-dried at >130 °C and allowed to cool in a desiccator (Drierite®) before assembly under positive nitrogen.

2-Nitro-1-butanol

A modification of a literature procedure was utilized (11). To a 0 °C stirred solution of sodium hydroxide (4.20 g, 105 mmol) dissolved in distilled water (40 mL) was added 1-nitropropane (8.91 g, 100 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature (rt) for 1 h. Upon recooling to 0 °C, the reaction mixture was treated with an aqueous solution of formalin

(37%, 8.52 g, 105 mmol) dropwise via addition funnel over 10 min and then the reaction mixture was stirred at rt for 7 h. Upon recooling to 0 °C, the reaction mixture was treated with acetic acid (6.60 g, 110 mmol) dropwise and stirred for 3 h. The aqueous solution was extracted with ether (5 × 50 mL) and the combined organic extracts were washed with brine (200 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a yellow oil (20 g) that was purified by vacuum distillation through a Vigreux column. The desired product was obtained as a colorless oil. Yield: 6.57 g, 55.1 mmol, 55%; bp 124 to 125 °C at 10 Torr (1 Torr = 133.322 4 Pa) (lit. value (11) bp 90–92 °C at 3 Torr). ^{1}H NMR ($CDCl_3$) δ: 4.51–4.59 (m, 1H) 3.89–4.10 (m, 2H), 1.81–2.06 (m, 3H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 90.8, 63.1, 23.5, 10.4.

2-Nitrobutyl acetate (1)

A modification of the literature procedure for synthesizing β-nitroacetates was utilized (16). To a 0 °C stirred solution of 2-nitro-1-butanol (5.59 g, 47.0 mmol) dissolved in CH_2Cl_2 (50 mL) was added acetic anhydride (5.72 g, 56.0 mmol) followed by *p*-toluenesulfonic acid monohydrate (380 mg, 2.0 mmol). The reaction mixture was stirred at 0 °C and then at rt for 8 h. Removal of the solvent in vacuo gave a residue (10 g) that was purified by vacuum distillation through a Vigreux column. The desired product **1** was obtained as a light yellow oil. Yield: 6.57 g, 40.1 mmol, 86%; bp 88 to 89 °C at 4 Torr (lit. value (11) bp 70–72 °C at 2 Torr). ^{1}H NMR ($CDCl_3$) δ: 4.62–4.69 (m, 1H), 4.41–4.43 (m, 2H), 2.07 (s, 3H), 1.80–2.06 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 170.5, 87.8, 63.8, 23.9, 20.8, 10.2.

2-Nitro-1-butene (2) (Caution: Lachrymator and foul smelling)

A modification of the literature procedure for the synthesis of 2-nitropropene was utilized (17). A round-bottomed flask (100 mL) fitted with a Vigreux column and short-path distillation apparatus was charged with 2-nitro-1-butanol (11.9 g, 0.100 mol) and phthalic anhydride (29.6 g, 0.200 mol) and was partially evacuated (under water aspirator pressure). The reaction mixture was heated in an oil bath to 150 °C for 30 min and then to 200 °C. The desired product **2** distilled over with water into an ice-cooled receiving flask. The aqueous layer was separated and the organic layer was dried over sodium sulfate. The desired product **2** was obtained as a blue-green oil. Yield: 4.48 g, 0.0443 mol, 44%; bp 76–84 °C at 40 Torr (lit. value (12) bp 108 °C at 61 Torr). IR (neat, cm^{-1}) υ_{max}: 3132, 2980, 2942, 2882, 1524, 1465, 1436, 1347, 1258. ^{1}H NMR ($CDCl_3$) δ: 6.44 (s, 1H), 5.55 (s, 1H), 2.64 (q, J = 7.2 Hz, 2H,), 1.18 (t, J = 7.2 Hz, 3H,). ^{13}C NMR ($CDCl_3$) δ: 159.8, 116.3, 23.6, 11.8.

4-Ethyl-2-(*p*-toluenesulfonyl)pyrrole (4)

To a rt stirred solution of 2-nitro-1-butene (**2**) (202 mg, 2.00 mmol) and tosylmethyl isocyanide (**3**) (586 mg, 3.00 mmol) dissolved in THF (3 mL) and 2-propanol (3 mL) was added a solution of DBU (457 mg, 3.00 mmol) dissolved in THF (3 mL) and 2-propanol (3 mL). The reaction mixture was stirred at rt for 20 h. Removal of the solvent in vacuo gave a brown oil (1.8 g) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 1:1; CH_2Cl_2–hexanes, 3:1). After eluting a brightly colored yellow impurity (R_f 0.38; CH_2Cl_2–hexanes, 3:1), the desired product **4** was obtained as a yellow amorphous solid. Yield: 372 mg, 80% pure by ^{1}H NMR, 1.25 mmol, 63% yield based on NMR integration. Recrystallization (CH_2Cl_2–hexanes, 1:4) gave **4** as off-white needles; mp 94 to 95 °C. R_f 0.15 (CH_2Cl_2–hexanes, 3:1). IR (PTFE, cm^{-1}) υ_{max}: 3306 (NH), 2964, 2924, 2872, 1595, 1494, 1440, 1379, 1301, 1202, 1146. ^{1}H NMR ($CDCl_3$) δ: 8.90 (br s, 1H), 7.80–7.83 (m, 2H), 7.26 (m, 2H), 6.70–6.75 (m, 2 H), 2.45 (q, 2H, J = 7.5 Hz), 2.39 (s, 3H), 1.15 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 143.9, 139.9, 130.0, 129.0, 127.7, 127.0, 121.1, 114.8, 21.7, 20.0, 15.0. MS *m/z* (%): 250 (M^+ + 1), 249 (M^+), 234 (100%), 184, 170, 142, 127, 110, 91, 78, 65. Anal. calcd. for $C_{13}H_{15}NO_2S$: C 62.63, H 6.06, N 5.62, S 12.83; found: C 62.57, H 6.05, N 5.56, S 12.95.

2-Acetyl-4-ethylpyrrole (5)

To a 0 °C stirred suspension of aluminum chloride (333 mg, 2.50 mmol) in CH_2Cl_2 (5 mL) was added freshly distilled (from quinoline) acetyl chloride (79 mg, 1.00 mmol) and the mixture was stirred for 15 min and then treated with a solution of 4-ethyl-2-(*p*-toluenesulfonyl)pyrrole (**4**) (125 mg, 0.500 mmol) dissolved in CH_2Cl_2 (5 mL) dropwise. The reaction mixture was stirred at 0 °C for 1 h and then was poured onto ice (20 g). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (60 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave an orange oil (0.3 g) that was purified by flash chromatography (hexanes; CH_2Cl_2). The title compound **5** was obtained as a yellow oil. Yield: 44 mg, 0.32 mmol, 64%. R_f 0.16 (CH_2Cl_2–EtOAc, 10:1). UV (EtOH) λ_{max} (nm): 208, 250, 302. IR (PTFE, cm^{-1}) υ_{max}: 3257 (NH), 2960, 2920, 2851, 1633 (C=O), 1568, 1479, 1432, 1397, 1322. ^{1}H NMR ($CDCl_3$) δ: 9.82 (br s, 1H), 6.77–6.87 (m, 2H), 2.52 (q, 2H, J = 7.5 Hz), 2.42 (s, 3H), 1.17–1.26 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 188.1, 132.0, 128.6, 122.8, 116.5, 25.5, 20.0, 15.4. MS *m/z* (%): 138 (M^+ + 1), 137 (M^+), 122 (100%), 104, 94, 77, 67. HRMS *m/z* calcd. for $C_8H_{11}NO$: 137.0841 (M^+); found: 137.0841.

2-Acetyl-3-ethylpyrrole (8)

To a rt stirred solution of 3-ethyl-2-acetyl-1-(phenylsulfonyl)pyrrole (14) (83 mg, 0.30 mmol) dissolved in methanol (5 mL) was added potassium carbonate (170 mg, 1.2 mmol) and the reaction mixture was heated to reflux for 7 h and then allowed to cool to rt. Removal of the solvent in vacuo gave an orange oil (0.5 g) that was partitioned between distilled water (20 mL) and ether (20 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were washed with brine (60 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a yellow oil (40 mg) that was purified by flash chromatography (hexanes; CH_2Cl_2). The desired product **8** was obtained as a light yellow amorphous solid. Yield: 32 mg, 0.23 mmol, 78%; mp 64 to 65 °C. R_f 0.18 (CH_2Cl_2). UV (EtOH) λ_{max} (nm): 206, 292. IR (PTFE, cm^{-1}) υ_{max}: 3271 (NH), 2967, 1622 (C=O), 1532, 1478, 1407, 1325, 1201, 1136. ^{1}H NMR ($CDCl_3$) δ:

9.43 (br s, 1H), 6.92–6.94 (m, 1H), 6.17–6.19 (m, 1H), 2.82 (q, 2H, J = 7.5 Hz), 2.47 (s, 3H), 1.30 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 187.9, 134.2, 123.3, 111.5, 111.4, 28.0, 21.3, 15.1. MS m/z (%): 138 (M^+ + 1), 137 (M^+), 122 (100%), 94, 80, 67. HRMS m/z calcd. for $C_8H_{11}NO$: 137.0841 (M^+); found: 137.0842.

1,8-Dihydro-4-(phenylsulfonyl)-2-(*p*-toluenesulfonyl)pyrrolo[2,3-*b*]indole (10)

To a stirred solution of 3-nitro-1-(phenylsulfonyl)indole (**9**) (18) (151 mg, 0.500 mmol) dissolved in THF (10 mL) was added a solution of tosylmethyl isocyanide (**3**) (117 mg, 0.600 mmol) dissolved in THF (5 mL) followed by neat DBU (183 mg, 1.20 mmol). The clear yellow reaction mixture was stirred at rt for 22 h. Removal of solvent in vacuo gave a crude orange oil (500 mg) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 3:1; CH_2Cl_2). The desired product **10** was obtained as a white amorphous solid (150 mg). Trituration (hexanes, 2 × 5 mL) gave **10** as a gray flaky solid. Yield: 142 mg, 0.315 mmol, 63%; mp 212–214 °C (dec). Two recrystallizations (CH_2Cl_2–cyclohexane, 2:1) gave **10** as white crystals; mp 236–238 °C. R_f 0.50 (CH_2Cl_2). UV (EtOH) λ_{max} (nm): 210, 274 (sh), 300, 346 (sh). IR (KBr, cm^{-1}) υ_{max}: 3256 (NH), 2928, 1540, 1528, 1447, 1419, 1374, 1318, 1181. ^{1}H NMR ($CDCl_3$) δ: 9.78 (bs, 1H), 7.88–7.92 (m, 3H), 7.74–7.76 (m, 2H), 7.48–7.54 (m, 2H), 7.22–7.37 (m, 6H), 7.11 (d, 1H, J = 1.8 Hz), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 144.3, 139.6, 138.5, 137.6, 136.4, 134.8, 130.2, 129.6, 128.8, 127.2, 126.9, 125.0, 124.6, 124.3, 120.1, 114.8, 113.4, 107.6, 21.8. MS m/z (%): 473.1 $(M + Na)^+$. Anal. calcd. for $C_{23}H_{18}N_2O_4S_2$: C 61.32, H 4.03, N 6.22, S 14.23; found: C 61.35, H 4.04, N 6.23, S 14.36.

2-Acetyl-1,8-dihydro-8-(phenylsulfonyl)pyrrolo[2,3-*b*]indole (11)

To a 0 °C stirred suspension of aluminum chloride in CH_2Cl_2 (5 mL) was added acetyl chloride (79 mg, 1.0 mmol) and the mixture was stirred for 15 min. The reaction mixture was treated with a solution of 1,8-dihydro-2-(*p*-toluenesulfonyl)-4-(phenylsulfonyl)pyrrolo[2,3-*b*]indole (**10**) (225 mg, 0.500 mmol) dissolved in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 0 °C for 2 h and then at rt for 30 min. The reaction was poured onto ice (20 g) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a yellow oil (0.6 g) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 1:1; CH_2Cl_2–hexanes, 3:1). The desired product **11** was obtained as a white amorphous solid. Yield: 82 mg, 0.24 mmol, 48%; mp 222–225 °C. Recrystallization (CH_2Cl_2–hexanes) gave **11** as light brown crystals; mp 230 to 231 °C. R_f 0.18 (CH_2Cl_2). UV (EtOH) λ_{max} (nm): 206, 224, 254 (sh), 332. IR (PTFE, cm^{-1}) υ_{max}: 3304 (NH), 2917, 2851, 1633, 1555, 1488, 1440, 1380, 1285, 1201, 1171. ^{1}H NMR ($CDCl_3$) δ: 9.87 (br s, 1H), 7.93–7.96 (m, 1H), 7.81–7.85 (m, 2H), 7.27–7.59 (m, 6H), 7.11 (d, 1H, J = 1.5 Hz), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 187.9, 139.1, 139.0, 136.9, 134.7, 132.9, 129.6, 127.0, 124.9, 124.7, 124.4, 120.0, 114.9, 113.5, 108.2, 25.3. MS m/z (%): 338 (M^+), 197 (100%), 169, 155, 127, 101, 77. Anal. calcd. for $C_{18}H_{14}N_2O_3S$: C 63.89, H 4.17, N 8.28, S 9.47; found: C 64.04, H 4.07, N 8.20, S 9.34.

2-Methyl-1-propyl 2,4-dihydro-3-(*p*-toluenesulfonyl)pyrrolo[3,4-*b*]indole-4-carboxylate (13)

To a rt stirred solution of 2-methyl-1-propyl 3-nitroindole-1-carboxylate (**12**) (18) (1.84 g, 7.00 mmol) and tosylmethyl isocyanide (**3**) (1.56 g, 8.00 mmol) dissolved in THF (50 mL) was added DBU (1.22 g, 8.00 mmol) and the reaction mixture was stirred at rt for 20 h. Removal of the solvent in vacuo gave a brown oil (4 g) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 3:1; CH_2Cl_2). The desired product **13** was obtained as a brown amorphous solid (615 mg, 1.50 mmol, 21%) that was purified by a second round of column chromatography (hexanes; CH_2Cl_2–hexanes, 1:1). The yellow powder thus obtained was recrystallized (CH_2Cl_2–hexanes) to give **13** as fine yellow needles; mp 177 to 178 °C. R_f 0.23 (CH_2Cl_2). UV (EtOH) λ_{max} (nm): 206, 222 (sh), 254 (sh), 278, 315 (sh), 324. IR (PTFE, cm^{-1}) υ_{max}: 3283 (NH), 2958, 1731 (C=O), 1595, 1515, 1448, 1417, 1379, 1317, 1199, 1139. ^{1}H NMR ($CDCl_3$) δ: 9.60 (br s, 1H), 8.32 (br s, 1H), 8.24–8.26 (m, 1H), 7.89 (d, 2H, J = 8.1 Hz), 7.34–7.49 (m, 2H), 7.24 (d, 2H, J = 8.1 Hz), 7.03 (br s, 1H), 4.23 (d, 2H, J = 4.8 Hz), 2.35 (s, 3H), 2.14 (br s, 1H), 1.06 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 151.4, 144.2, 143.2, 139.7, 131.4, 130.1, 127.4, 126.6, 123.8, 122.8, 121.5, 120.0, 116.1, 115.5, 107.2, 73.1, 28.1, 21.7, 19.3. HRMS m/z calcd. for $C_{22}H_{22}N_2O_4S$: 410.1300 (M^+); found: 410.1294. Anal. calcd. for $C_{22}H_{22}N_2O_4S$: C 64.37, H 5.40, N 6.82, S 7.81; found: C 64.46, H 5.51, N 6.85, S 7.76.

2-Methyl-1-propyl 2,4-dihydro-3-valerylpyrrolo[3,4-*b*]-indole-4-carboxylate (14)

To a 0 °C stirred suspension of aluminum chloride (200 mg, 1.50 mmol) in CH_2Cl_2 (5 mL) was added freshly distilled (from 0.1% quinoline) valeryl chloride (72 mg, 0.60 mmol) and this was stirred for 15 min. The reaction mixture was treated with a solution of 2-methyl-1-propyl 2,4-dihydro-3-(*p*-toluenesulfonyl)pyrrolo[3,4-*b*]indole-1-carboxylate (**13**) (123 mg, 0.300 mmol) dissolved in CH_2Cl_2 (10 mL) dropwise. The reaction mixture was stirred at 0 °C for 15 min and then was poured onto ice (20 g). The aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a tan amorphous solid (0.2 g) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 1:1; CH_2Cl_2–hexanes, 3:1). The desired product **14** was obtained as an off-white amorphous solid (68 mg, 0.20 mmol, 67%, mp 166–168 °C). Recrystallization (EtOAc–hexanes) gave **14** as white needles; mp 173 to 174 °C. R_f 0.48 (H_2Cl_2–MeOH, 98:2). UV (EtOH) λ_{max} (nm): 206, 233 (sh), 246 (sh), 277 (sh), 286, 311 (sh), 344 nm. IR (KBr) υ_{max} (cm^{-1}): 3236 (NH), 2956, 2870, 1728 (C=O), 1627 (C=O), 1506, 1460, 1402, 1390, 1319, 1268, 1219. ^{1}H NMR ($CDCl_3$) δ: 10.04 (br s, 1H), 8.43 (br s, 1H), 8.00–8.02 (m, 1H), 7.43–7.48 (m, 1H), 7.33–7.38 (m, 1H), 7.13 (br s, 1H), 4.27 (d, 2H, J = 6.3 Hz), 3.12 (t, 2H, J = 7.2 Hz), 2.12–2.22 (m, 1H), 1.82–1.92 (m, 2H), 1.48–1.60 (m, 2H), 1.10 (d, 6H, J =

6.9 Hz), 1.02 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 190.1, 151.6, 143.4, 131.8, 126.8, 123.5, 122.6, 122.5, 121.0, 118.5, 116.3, 107.5, 73.2, 40.5, 28.2, 26.7, 22.8, 19.4, 14.3. MS *m/z* (%): 340 (M^+, 100%), 298, 283, 242, 198, 183, 156, 127, 101, 77. Anal. calcd. for $C_{20}H_{24}N_2O_3$: C 70.57, H 7.11, N 8.23; found: C 70.32, H 7.11, N 8.13.

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Catalysis with palladium colloids supported in poly(acrylic acid)-grafted polyethylene and polystyrene[1]

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Abstract: Grafts of poly(acrylic acid) on polyethylene powder (PE-*g*-PAA) or polystyrene (PS-*g*-PAA) can be used to support Pd(0) crystallites that function like a homogeneous Pd(0) catalyst in some reactions. These Pd–PE-*g*-PAA catalysts were active in allylic substitution reactions in the presence of added phosphine ligand. A catalyst analogous to the Pd–PE-*g*-PAA powder catalyst on polystyrene (Pd–PS-*g*-PAA) was similarly active for allylic substitution and could also be used in Heck reactions at 80–100 °C in *N*,*N*-dimethylacetamide (DMA). Analysis of the product solutions for Pd leachate and a correlation of the Pd leaching with product formation in the allylic substitution chemistry for both types of catalysts suggests that the active catalysts in these reactions are leached from the support. In the case of the allylic substitution reaction, external triphenylphosphine and substrate together are required for the chemistry and Pd leaching.

Key words: catalysis, palladium, allylic substitution, grafted polystyrene, supported catalysts.

Résumé : Les produits de greffage d'acide polyacrylique sur de la poudre de polyéthylène (PE-*g*-APA) ou de polystyrène (PS-*g*-APA) peuvent être utilizés comme support de cristallites de Pd(0) qui, dans certaines réactions, peuvent fonctionner comme catalyseur de Pd(0). Ces catalyseurs de Pd–PE-*g*-APA mis en présence d'un ligand phosphine sont actifs dans les réactions de substitution allylique. Un catalyseur analogue au catalyseur en poudre Pd–PE-*g*-APA sur du polystyrène (Pd–PS-*g*-APA) est aussi actif pour la réaction de substitution allylique et il peut aussi être utilizé dans les réactions de Heck, à des températures allant de 80 à 100 °C, dans le *N*,*N*-diméthylacétamide (DMA). Une analyse des solutions de produits pour rechercher la présence de Pd qui aurait été lessivé ainsi qu'une corrélation du Pd de lessivage avec la formation de produit dans la chimie de la substitution allylique pour les deux types de catalyseur suggère que les catalyseurs actifs dans ces réactions sont lessivés de leur support. Dans le cas de la réaction de substitution allylique, la présence simultanée de la triphénylphosphine externe et du substrat sont requis pour la chimie et le lessivage du Pd.

Mots clés : catalyse, palladium, substitution allylique, polystyrène greffé, catalyseurs sur un support.

[Traduit par la Rédaction]

Introduction

The use of supported heterogeneous catalysts is well-established. Palladium catalysts are among the most common examples of such species. For example, catalysts like Pd–C are widely used for hydrogenation of alkenes (1). They have the virtue of wide availability, relatively low costs for handling and preparation, and activity that is often as good or better than that of the more "novel" hydrogenation catalysts reported from time to time.

While hydrogenation is an important reaction, other palladium-catalyzed processes, such as allylic substitutions and cross-coupling chemistry, are of more current interest. A variety of palladium catalysts have been developed for these purposes (2). Some years ago we had noted that classical Pd–C catalysts, under relatively mild conditions (i.e., at reaction temperatures <100 °C) (3, 4), exhibit reactivity resembling that of the well-established homogeneous Pd catalyst, tetrakis(triphenylphosphine)palladium(0). Specifically, we found that both a supported Pd(0) species prepared from an organometallic derivative of cross-linked polystyrene (5) and simple Pd–C could effectively catalyze allylic substitution of allyl acetates by nucleophiles like secondary amines. In these cases, catalysis was most effective in the presence of a soluble phosphine with reactions sometimes occurring at room temperature.

The importance of new sorts of catalysts, including adventitiously formed or designed colloidal metal catalysts for various catalytic reactions including cross-coupling reactions, has recently received increased attention (6–11). For example, we and others have noted the exceptional reactivity of Pd(0) colloidal catalysts, presumably generated in situ from Pd(II) palladacycle compounds during cross-coupling chemistry (12–17). These studies suggest that further explo-

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ration of ways to support and use Pd colloids merit attention. Our studies of these putative Pd colloids formed from SCS–Pd(II) precursors noted that those species were more soluble in polar phases than in nonpolar phases (14). Since we recently developed some new sorts of immobilized polar poly(acrylic acid) graft phases on polyethylene powders and on DVB cross-linked polystyrene resins, we have sought to explore these supported phases as supports for catalytically active Pd colloids. We have shown that Pd colloids formed and supported in these poly(acrylic acid) phases are active catalysts. While they are competent catalysts for hydrogenations, their activity is not significantly different then the more readily available and simpler Pd–C catalysts in hydrogenation catalysis.

While catalytic activity, especially reactivity in a reaction as simple as alkene hydrogenation, is often easy to demonstrate and assay, the identity of the actual species that leads to catalysis is not always clear. Indeed, it can even be difficult to determine whether the actual catalyst is soluble or insoluble (18). Such issues are even more complex when the chemistry is carried out with supported palladium colloids. For example, while we assumed a soluble Pd species was generated in our earlier studies (3, 4), a three-phase test using a polymer-supported Pd species (a soluble phosphine) and a second polymer-supported substrate failed to detect a soluble catalyst. We rationalized this result at the time on the basis that the actual phosphine-ligated Pd colloidal catalyst could still be present but could be unreactive to a second insoluble supported substrate (3). More recent work from several laboratories using various procedures, including Rebek's three-phase test (19), has been more successful in showing that homogeneous catalysts are responsible for the catalysis seen in other systems with "heterogeneous" catalysts (12, 19–24).

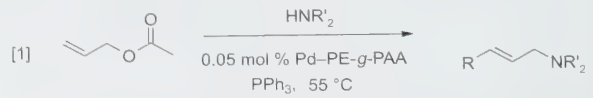
Here we describe work where we have shown that the Pd colloids in poly(acrylic acid) grafted polystyrene, which we used previously in hydrogenation reactions, are active in Heck catalysis and also in allylic substitution chemistry. While the analogous polyethylene-supported catalysts cannot be used in Heck chemistry (the required temperatures are incompatible with the underlying polymer), the polyethylene-bound catalysts exhibit Pd(0)-like reactivity in allylic substitutions of allylic acetates and amines. While we did not achieve the sort of notable reactivity we and others have seen in other putative Pd colloidal catalysts (12–17), we have been able to show that, in the case of these Pd colloids in a grafted polystyrene matrix or supported on polyethylene powder, Pd leaching is associated with the observed Pd(0)-like chemistry. The simplest explanation for these results is that soluble phosphine-free (Heck catalysis) or phosphine-ligated Pd species (allylic substitutions), derived from the interfacially supported Pd colloids in both the poly(acrylic acid)-grafted polyethylene powder and the poly(acrylic acid)-grafted DVB cross-linked polystyrene resin, are the active catalysts.

Results and discussion

We recently described several sorts of supported palladium catalysts using a poly(acrylic acid) graft on polyethylene powder (PE-*g*-PAA) or a poly(acrylic acid) graft within DVB cross-linked polystyrene beads (PS-*g*-PAA) as supports (19, 20, 25). Such colloidal catalysts have precedent both in our earlier work with polystyrene-supported palladium colloids (3, 4) and in other reports where supported thin films or inorganic matrices support analogs of homogeneous catalysts (3, 4, 8, 26–31).

The synthesis and characterization of both the PE-*g*-PAA and PS-*g*-PAA supports and catalysts were previously described, and the syntheses of these catalysts are summarized in Schemes 1 and 2. As shown in both schemes, the formation of a PE-*g*-PAA or a PS-*g*-PAA supported Pd colloid involved ion exchange of palladium acetate onto a PE- or PS-bound carboxylate group with subsequent reduction of the Pd(II) carboxylate ionically attached to the polymer graft. The Pd–PE-*g*-PAA and Pd–PS-*g*-PAA catalysts contained about 0.01 or 1.1 mmol of Pd per gram of support, respectively, based on digestion of the polymers and analysis of the residue for Pd by ICP metal analysis. In the case of the Pd–PE-*g*-PAA catalyst, imaging of the catalyst by XPS spectroscopy showed that the Pd colloids were distributed throughout a 50–100 μm region on the surface of the powder (Fig. 1). In the case of the Pd–PS-*g*-PAA, the Pd colloidal particles were mostly within the polystyrene bead.

The use of the Pd–PE-*g*-PAA and Pd–PS-*g*-PAA catalysts for catalytic hydrogenation reactions were described previously (19, 20). Both catalysts were found to be fully recyclable and no Pd leachate was detected in those studies. Of more interest in this study was that these catalysts also catalyze some Pd(0)-like reactions. Specifically, the PE-bound Pd colloids were effective in promoting allylic substitution reactions between secondary amines and allyl acetate (eq. [1]). Such reactions were not successful if no added phosphine was present in solution, but were successful in the presence of 5 mol% added triphenylphosphine (Table 1).



The reactivity in the presence of added phosphine ligands of the Pd–PE-*g*-PAA catalyst could be due to activation of the Pd colloids within the polymer matrix by the added triphenylphosphine. Alternatively, formation of tetrakis(triphenylphosphine)palladium or formation of some less-defined soluble phosphine-ligated Pd(0) species could explain the observed chemistry. As noted above, we had previously been unsuccessful at using a three-phase test to detect such soluble intermediates in a related system (3). Here we used several other approaches that together provide convincing evidence that a soluble Pd species is formed in these catalytic reactions.

To ascertain the origin of the catalysis, several experiments were performed. First, XPS analysis of Pd crystallites in a hyperbranched graft of Pd–PE-*g*-PAA showed a Pd $3d^{3/2}$ peak at 333.3 eV. This peak was discernibly different than the peak for a previously described immobilized molecular catalyst — a Pd(0) complex prepared using the same polymer that had been further modified to contain aminodiphenylphosphinopropyl ligands (i.e., Pd(0)-DPPA–PE-*g*-PAA; DPPA is diphenylphosphinopropylamide containing a phosphine ligand that was covalently coupled to poly(acrylic

Scheme 1. Synthesis of Pd–PE-*g*-PAA catalysts.

acid)-grafted PE via an amide bond) (25). No evidence was obtained for the presence of phosphine in the recovered PE support after a reaction, suggesting that added phosphine was not sorbed into the resin. Catalysts analogous to the Pd–PE-*g*-PAA could also be prepared by deliberate oxidation of the phosphine ligands in a Pd(0)-DPPA–PE-*g*-PAA catalyst — a process that converted the light yellow Pd(0)-DPPA–PE-*g*-PAA powder into a grey powder and produced a new peak for oxidized phosphine in XPS spectroscopy and a Pd(0) species with a Pd $3d^{3/2}$ peak such as that seen for the Pd crystallites in Pd–PE-*g*-PAA.

While the original Pd(0)-DPPA–PE-*g*-PAA catalyst was active in allylic substitution, after oxidation, both this recovered catalyst, now containing Pd(0) colloids, and the Pd–PE-*g*-PAA catalyst behaved similarly in that they had no activity in allylic substitution unless external phosphine was present (Fig. 2). These reactions catalyzed by Pd(0) colloids were also accompanied by Pd leaching. Using ICP–MS (inductively coupled plasma – mass spectroscopy) analysis, ca. 2% to 3% Pd leaching was seen in the reaction between allyl acetate and diethylamine with external phosphine. Pd leaching was not seen with Pd(0)-DPPA–PE-*g*-PAA catalysts that

Scheme 2. Synthesis of Pd–PAA-*g*-PS catalysts.

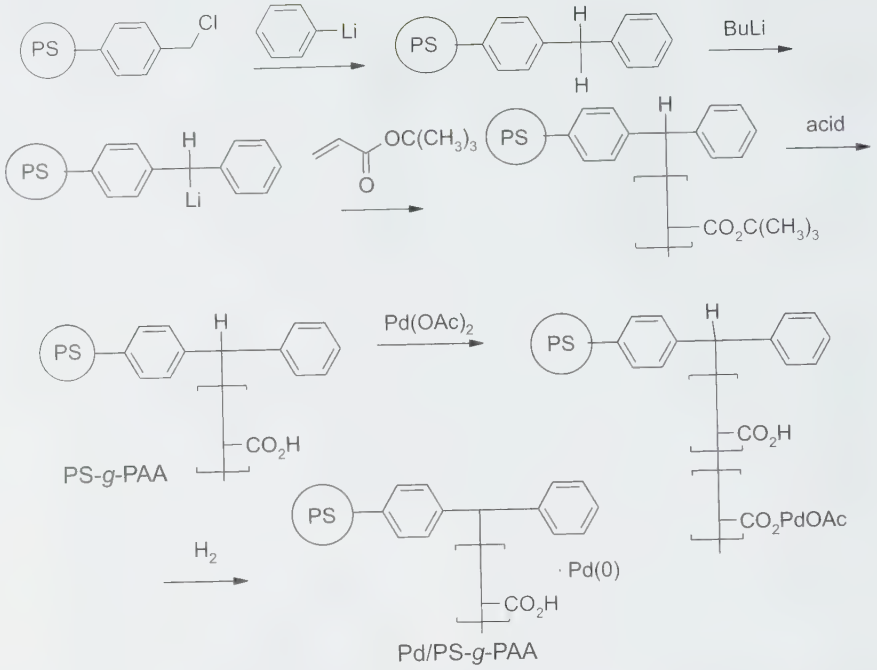
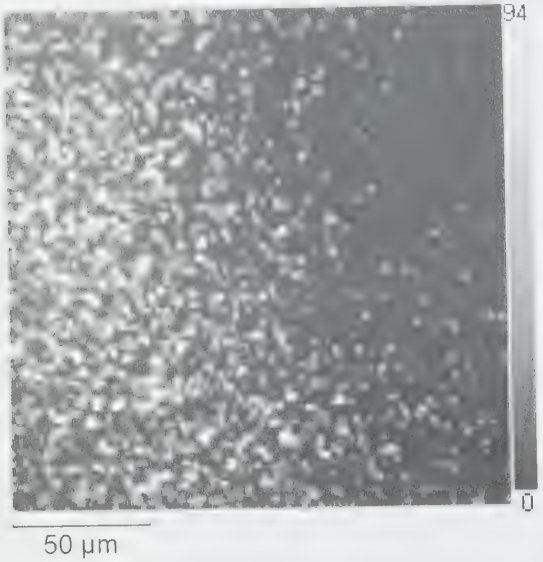


Fig. 1. XPS image of a Pd–PE-*g*-PAA powder. The white regions represent the presence of Pd 3d electrons. The left side of the image is focused on a Pd–PE-*g*-PAA particle, and the edge of the three-dimensional particle roughly transects the photograph.



contained covalently bound phosphine ligands within the functional polymer support that formed analogs of a molecular Pd(0) catalyst (25). Taken together, these results are consistent with an explanation such as that proposed previously (3) for the activity of these Pd–PE-*g*-PAA colloidal catalysts, which is based on leaching of a phosphine-ligated Pd catalyst or a Pd cluster.

Table 1. Allylic substitution reactions of allyl acetate with Pd–PE-*g*-PAA.

-R″	PPh_3 (mol%)	Time (h)	Conversion (%)[a]
Diethylamine	0.00	24	—[b]
Diethylamine	0.05	6/6	99, 99[c]
Pyrrolidine	0.05	20	99

Note: Reactions were carried out at 55 °C on a 20 mmol scale, typically without any added solvent.

[a]GC analysis showed that the conversion of starting material to product was 99%. Isolated yields of allylic amines in similar reactions were typically ca. 90%.

[b]No product was detected.

[c]Conversions for a second cycle using the Pd–PE-*g*-PAA catalyst with a fresh addition of 5 mol% triphenylphosphine.

These PE-bound Pd(0) species could not be used in Heck catalysis. No Heck catalysis was seen at 55 °C, and heating to higher temperatures led to thermal reorganization of the grafted PE powder (melting that produced a material that became inactive in hydrogenation or allylic substitution with or without added phosphine). However, immobilized poly(acrylic acid) grafts on a more thermally robust polymer, which are analogous to the Pd–PE-*g*-PAA powder catalysts described previously, can be prepared on DVB crosslinked polystyrene supports as shown in Scheme 2. Ion exchange of $Pd(OAc)_2$ with the immobilized poly(acrylic acid) followed by reduction, produced immobilized Pd(0) colloids that had hydrogenation activity analogous to that seen with Pd–C or to Pd crystallites immobilized within hyperbranched poly(acrylic acid) grafts on PE powder (20).

While the PE-supported Pd colloids could not be used in Heck catalysis because of temperature limitations, Pd colloids supported on more thermally robust DVB crosslinked polystyrene were active in Heck catalysis (eq. [2]).

Table 2. Heck catalysis with Pd–PS-*g*-PAA.

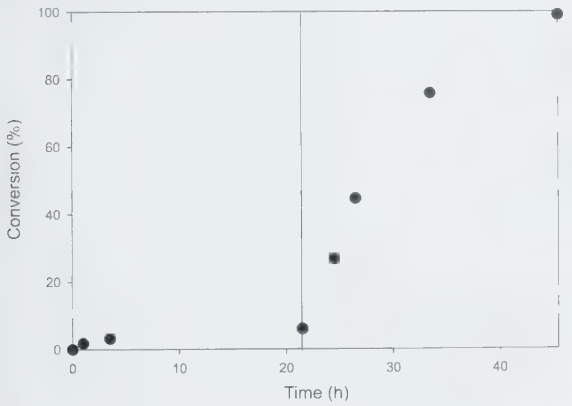
Substrate aryl iodide	Heck acceptor	Catalyst	Yield (%)[a]
4-Iodotoluene	*tert*-Butyl acrylate	Pd–PS-*g*-PAA	99
4-Iodotoluene	*tert*-Butyl acrylate	Pd–C[b]	75
Iodobenzene	*tert*-Butylstyrene	Pd–PS-*g*-PAA	100
4-Iodoanisole	*tert*-Butylbenzene	Pd–PS-*g*-PAA	94
4-Iodoanisole	*N,N*-Dimethylacrylamide	Pd–PS-*g*-PAA	95
4-Iodoanisole	*N,N*-Dimethylacrylamide	Pd–C	36
Iodobenzene	*tert*-Butyl acrylate	Pd–PS-*g*-PAA	100
4-Bromoacetophenone	*tert*-Butyl acrylate	Pd–PS-*g*-PAA	81
4-Bromoacetophenone	*N,N*-Dimethylacrylamide	Pd–PS-*g*-PAA	66

Note: Reactions were carried out on a 2 mmol scale in 10 mL of *N,N*-dimethylacrylamide using 2.5 mmol of Et_3N as a base at 80 °C for 36 h (or at 100 °C for 24 h). The Heck acceptor was present in 20 mol% excess. The PS-*g*-Pd catalyst contained 0.11 mol% of Pd. The Pd–C species used was 10% Pd–C (Sigma-Aldrich). Yields were measured by GC using dodecane as an internal standard. The catalyst was present at 0.1 mol%.

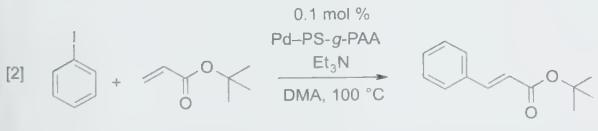
[a]Isolated yields were typically 10% lower for reactions carried out on a 5 or 10 mmol scale.

[b]The catalyst was present at 0.5 mol%.

Fig. 2. Allylic substitution of allyl acetate using diethylamine with a Pd(0) catalyst containing Pd(0) crystallites and no phosphine ligands within the interface. After 24 h, external PPh_3 was introduced to the reaction mixture, a step that did lead to allylic substitution product formation.



As shown in Table 2, good yields in small scale reactions were obtained with a variety of aryl iodides. However, unactivated aryl bromides and aryl chlorides were not substrates, even if added to a reaction along with a more reactive aryl iodide. The activity of the Pd–PS-*g*-PAA catalysts was also compared to Pd–C — a simple catalyst that also has modest activity in Heck catalysis. The PS-*g*-PAA immobilized Pd colloids were found to be more active. These cross-coupling reactions occurred without any added phosphine ligand present.



Recycling the Pd species in a polystyrene resin in Heck catalysis was tested using the Heck reaction between iodobenzene and *tert*-butyl acrylate (eq. [2]) as a model reaction. The first cycle was complete in 6 h by GC analysis. The catalyst was recovered by pouring off the reaction solution after centrifugation. Fresh reagents and solvent were then added to the catalyst for the second cycle (Table 3). After 6 h, the reaction had proceeded to 95% conversion by GC analysis. During the third recycling experiment the reaction went to only 46% conversion after 6 h. After washing the catalyst by Soxhlet extraction with MeOH for 24 h, a fourth cycle went to 99% conversion after 9 h. Presumably, the reaction salts had built up in the resin, inhibiting the reaction. Such fouling of a recovered catalyst by salt byproducts is a potential general problem for any recoverable catalyst that employs a relatively polar phase.

Table 3. Recycling experiments using Pd–PS-*g*-PAA in the Heck reaction of *tert*-butyl acrylate and iodobenzene (eq. [2]).

Cycle	Conversion (%)	Time (h)
1	99	6
2	95	6
3	46	6
4	99	9

Note: After the third cycle, the catalyst was recovered and washed in a Soxhlet apparatus with MeOH for 24 h

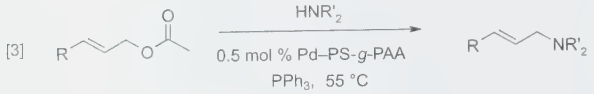
Trace metal analysis (ICP–MS) of an acid-digested aliquot from the first reaction cycle showed 2.1% leaching of Pd. This result is in accord with other suggestions that activity of a heterogeneous Pd catalyst involves oxidative addition and formation of a soluble Pd species (2).

The Pd–PS-*g*-PAA catalyst is also active for allylic substitution chemistry (Table 4). As was true for Pd–PE-*g*-PAA catalysts, the presence of external triphenylphosphine is required for these reactions to proceed. A series of allylic substitution reactions using allyl acetate or cinnamyl acetate reacting with diethylamine or piperidine were performed (eq. [3]). The reaction between allyl acetate and diethylamine went to only 38% conversion in 18 h without the presence of external triphenylphosphine. With external phosphine, the reaction goes to complete conversion in 1 h. The reaction between cinnamyl acetate and diethylamine was even more dependant on external phosphine. After 24 h without any external phosphine, no reaction was seen by GC analysis. A reaction in the presence of added triphenylphosphine was completed within 8 h.

Table 4. Results for allylic substitution reactions with Pd–PS-*g*-PAA.

-R	-R′	PPh_3 (mmol)	Time (h)	Conversion (%)
-H	$-CH_2CH_3$	—	18	38
-H	$-CH_2CH_3$	0.1	1	99
-Ph	$-CH_2CH_3$	—	24	0
-Ph	$-CH_2CH_3$	0.1	8	99
-H	$-CH_2CH_2CH_2CH_2CH_2-$	0.05	1	99

Note: These reactions were carried out in THF at 60 °C on a 10 or 20 mmol scale.

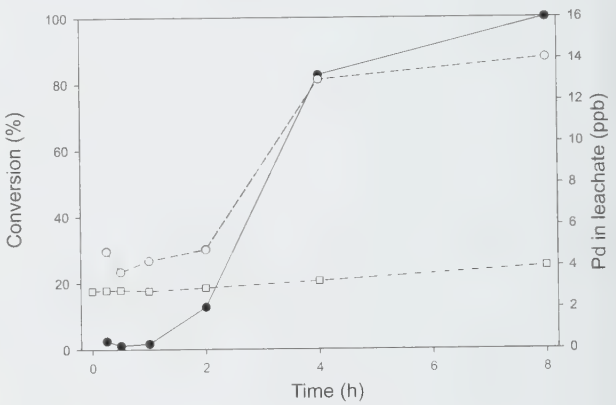


A more detailed study showed that these reactions appear to involve Pd leachates as the active catalyst. An induction period of ca. 2 h was observed for the formation of the cinnamyl acetate and diethylamine product. Interestingly, the progress of these allylic substitution reactions using Pd–PS-*g*-PAA catalysts with added triphenylphosphine were correlated with leaching of palladium into solution. In these studies, the first experiment was designed to monitor the Pd leaching into solution from the Pd–PS-*g*-PAA catalyzed allylic substitution reaction between cinnamyl acetate and diethylamine with triphenylphosphine present. During the course of the 8 h reaction between cinnamyl acetate and diethylamine, aliquots were removed from solution. The aliquots were digested in acid and analyzed by ICP–MS. Figure 3 shows the results from this experiment. The results show very little Pd leaching into solution during the induction period. As product forms, the Pd concentration in the reaction mixture increases. A second control reaction that had only triphenylphosphine and Pd–PS-*g*-PAA catalyst showed almost no palladium leaching for 8 h, the time required for complete conversion of starting materials to product. This suggests that the substrates cause the leaching of Pd and that the active catalytic species is generated with the presence of triphenylphosphine. In this case the Pd–PS-*g*-PAA catalyst serves as a reservoir of Pd for the reaction. These results are in accord with previous results from our group where the three-phase test for a soluble Pd catalyst failed using a polymer-supported allylic ester substrate and Pd–C- and polystyrene-supported Pd(0) catalysts (3). These results showed no reaction between a polystyrene-bound allyl ester and diethylamine using a heterogeneous Pd catalyst with triphenylphosphine in solution. However, as shown here, that result is understandable since in that experiment the substrate and Pd source were both heterogeneous. Assuming that this is also the case presently, the soluble phosphine alone would not cause the Pd leaching and no reaction would occur.

Conclusion

Hyperbranched grafts of poly(acrylic acid) on polyethylene powder or polystyrene can be used to support Pd(0) crystallites that function as a homogeneous Pd(0) catalyst in some reactions. These Pd–PE-*g*-PAA catalysts were active in allylic substitution reactions in the presence of added phosphine ligand. A catalyst analogous to the Pd–PE-*g*-PAA powder catalyst on polystyrene (Pd–PS-*g*-PAA) was similarly active for allylic substitution and could also be used in Heck reactions at 80 °C in *N*,*N*-dimethylacetamide (DMA). Analysis of the solution for Pd and a correlation of the Pd leaching with product formation in the allylic substitution chemistry for both types of catalysts suggests that the active catalysts in these reactions are leached from the support. In the case of the allylic substitution reaction, external triphenylphosphine and substrate together are required for the chemistry and Pd leaching.

Fig. 3. A Pd–PS-*g*-PAA catalyzed allylic substitution reaction between cinnamyl acetate and diethyl amine carried out in the presence of 0.5 mol% of added triphenylphosphine in THF at 60 °C. The various plots show the extent of reaction in the presence of added triphenylphosphine as a function of reaction time (●), the concentration of Pd in the leachate as a function of time (○), and the concentration of leachate in a reaction with the same catalyst and the same amount of triphenylphosphine and amine but no cinnamyl acetate substrate (□). No reaction was observed in the absence of triphenylphosphine over a 24 h period under the same reaction conditions.



Experimental section

General methods

Merrifield Resin (RGEN100) was obtained from the American Peptide Company, Inc. (Sunnyvale, California) as a 100–200 mesh resin and had a loading of 1.05 mmol of $ClCH_2$ groups per gram. Other reagents and solvents were obtained from the Sigma-Aldrich Chemical Company and were used as received unless noted otherwise. X-ray photoelectron spectra were obtained on a Kratos Axis Ultra XPS

(Manchester, UK) using a monochromatic Al K_α source (400 W) in a UHV environment (ca. 5×10^{-9} torr (1 torr = 133.3224 Pa). During acquisition, surfaces were kept from charging by the application of low energy electrons. Surface elemental composition was determined by normalized integration of the resulting peaks using Kratos software (Kratos Analytical, Chestnut Ridge, New York). ^1H and ^{13}C NMR spectroscopy experiments were carried out using Mercury 300, Unity 300, or Unity 500 spectrometers. GC analyses were carried out using a Shimazdu Model 2010 GC. All glassware used in the experiments in which trace metal analysis was performed was soaked in a 1 mol/L HNO_3 acid bath for at least 12 h prior to the experiment.

Preparation of Pd–PS-*g*-PAA

A reported procedure was used (20). The product Pd catalyst was prepared on a 12 g scale. The Pd loading of the Pd(II)–PS-*g*-PAA prepared in this manner was 1.27 mmol/g, based on gravimetric analysis of the exchange of $Pd(OAc)_2$ and the sodium salt of the poly(acrylic acid)-grafted polystyrene. Subsequent reduction of this Pd(II) salt in the poly(acrylic acid) graft produces a product (Pd–PS-*g*-PAA) that was used in the catalytic studies. Analysis by ICP–MS of a solution of the residue after combustion and acid digestion of this Pd–PS-*g*-PAA product in triplicate showed that the Pd loading of this polystyrene-supported Pd product was 1.1 mmol of Pd per gram of Pd–PS-*g*-PAA.

Preparation of Pd–PE-*g*-PAA powder

Following a literature procedure (19), a poly(acrylic acid) hyperbranched graft on a PE powder sample (1.3 g) was first stirred with a pH 9 buffer for 2 h to deprotonate the $-CO_2H$ groups of the graft. The resulting carboxylate-containing polymer was then suspended in 25 mL of an acetone–water (4:1) mixture with 20 mg of $Pd(OAc)_2$. This solution was stirred at room temperature for 24 h then filtered and washed with dilute acidic ethanol and ethanol. The yellowish powder was suspended in EtOH and reduced with H_2 in a Parr apparatus to yield the Pd–PE-*g*-PAA catalyst that was used in these studies. To determine the Pd loading, this powder sample was combusted in a crucible at 650 °C for 2 h. The residue was digested in acid and ICP–MS analysis of the residue for Pd showed that Pd loading was ca. 0.01 mmol of Pd per gram of Pd–PE-*g*-PAA powder.

Typical procedure for Heck catalysis with 10% Pd–C or Pd–PS-*g*-PAA

An aryl iodide such as iodotoluene (2.0 mmol), 2.4 mmol (0.3139 g, 98%) of *tert*-butyl acrylate, 2.5 mmol of triethylamine, along with 0.01 mmol of the Pd catalyst (e.g., 9 mg of Pd–PS-*g*-PAA) were added to a 50 mL flask. Then 10 mL of DMA was added to the mixture and the reaction was heated to 80 °C.

Typical procedure for allylic substitutions with Pd–PS-*g*-PAA

A mixture of 2.0 mmol (0.36 g) of cinnamyl acetate, 2.4 mmol (0.21 g) of morpholine, 0.1 mmol (0.264 g) of triphenylphosphine, and 0.01 mmol (9.0 mg) of Pd–PS-*g*-PAA were added to a 50 mL reaction flask along with 10 mL of THF. The reaction mixture was heated to 60 °C and agitated with a wrist-action shaker. The progress of the reaction was checked using GC.

General procedure for Heck catalysis, recycling, and leachate analysis using Pd–PS-*g*-PAA

Iodobenzene (5 mmol), *tert*-butyl acrylate (6 mmol), triethylamine (7.5 mmol), and 0.5 mol% Pd(0)-PAA–PS (0.025 mmol of Pd, 22.5 mg of resin) were added to a 40 mL centrifuge tube along with 25 mL of DMA. This mixture was heated to 100 °C and agitated using a wrist-action shaker until GC analysis showed the reaction was complete. After the reaction was complete, the catalyst was separated by centrifugation and decantation. The catalyst isolated in this manner could then be reused in a subsequent reaction. To analyze for Pd leaching, ca. 25% of the decanted solution from this reaction was evaporated to dryness and then heated on a hot plate with 20 mL of concentrated sulfuric acid for 24 h. The solution was diluted to 50 mL using 1% HCl and analyzed by ICP–MS. In a typical analysis, a reaction that started with 2.65 mg of Pd had 56 μg of Pd in total in this solution corresponding to 2.1% leaching.

General procedure for allylic substitution reactions and leachate analysis using Pd–PS-*g*-PAAC

Cinnamyl acetate (10 mmol, 1.76 g) and diethylamine (24 mmol, 1.75 g) were combined with triphenylphosphine (0.2 mmol, 52.4 mg) and Pd(0)-PAA–PS (0.5 mol%, 45 mg of resin) in 20 mL of distilled THF in a 40 mL centrifuge tube. This mixture was degassed by freeze–pump–thaw cycles three times and then backfilled with N_2. The reaction tube was heated to 55 °C and agitated using a wrist-action shaker. A control reaction was also carried out at the same time using the same amount of catalyst, phosphine, and solvent but without any cinnamyl acetate. GC analysis of aliquots was carried out as the reaction progressed. The remainder of each aliquot was digested by heating in concd. H_2SO_4 for 24 h. The concentrated digest was diluted to 25 mL with 1% HCl and then analyzed by ICP–MS.

Pd–PE-*g*-PAA catalyzed allylic substitution reactions

Allyl acetate (18.8 mmol, 1.8852 g), piperidine (37.8 mmol, 3.2125 g), triphenylphosphine (0.01 mmol, 26.4 mg), and 400 mg of Pd–PE-*g*-PAA powder were combined in a 20 mL flask. This mixture was degassed three times by freeze–pump–thaw, backfilled with N_2, and then heated to 55 °C. After 20 h, the allyl acetate had been completely consumed based on GC analysis.

Acknowledgments

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Design and synthesis of selenonium and sulfonium ions related to the naturally occurring glucosidase inhibitor salacinol[1]

Hui Liu and B. Mario Pinto

Abstract: Four series of analogues of the naturally occurring glucosidase inhibitor salacinol were synthesized for structure–activity studies with different glycosidase enzymes. The target zwitterionic compounds were synthesized by means of nucleophilic attack at the least-hindered carbon atom of the 1,3-cyclic sulfates derived from D-glucose and D-mannose by the isopropylidene-protected 1,4-anhydro-4-thio- and seleno-D-allitols and the 4-thio- and seleno-L-allitols. Deprotection of the coupled products afforded the novel sulfonium and selenonium ions containing polyhydroxylated acyclic chains of four and six carbons, with different stereochemistry at the stereogenic centers and with 1,4-anhydro-4-seleno or 4-thio-D- or L- alditol heterocyclic rings. The compounds showed no significant activity against recombinant human maltase glucoamylase (MGA), a critical intestinal glucosidase involved in the processing of oligosaccharides of glucose into glucose itself.

Key words: glycosidase inhibitors, zwitterionic, selenonium salts, sulfonium salts, cyclic sulfates, L-ascorbic acid, D-gulonic-γ-lactone.

Résumé : Afin de pouvoir faire des études de structure–activité avec divers enzymes glycosides, on a réalisé la synthèse de quatre séries d'analogues du salacinol, un inhibiteur naturel de glucosidase. Les composés zwitterioniques cibles ont été synthétisés par le biais d'une attaque nucléophile au niveau de l'atome de carbone le moins encombré de sulfates 1,3-cycliques obtenus à partir du D-glucose et du D-mannose par des 1,4-anhydro-4-thio- et 1,4-anhydro-4-séléno-D-allitols et des 4-thio- et 4-séléno-L-allitols. La déprotection des produits de couplage fournit des nouveaux ions sulfonium et sélénonium qui contiennent des chaînes acycliques polyhydroxylées de quatre et de six carbones, avec des stéréochimies différentes au niveau des centres stéréogènes et hétérocycles 1,4-anhydro-4-séléno- et 1,4-anhydro-4-thio-D- ou L-alditols. Ces composés ne présentent aucune activité significative contre la maltase glucoamylase humaine recombinante (MGA), une glucosidase intestinale critique dans la transformation des oligosaccharides du glucose en glucose.

Mots clés : inhibiteurs de glycosidase, zwitterion, sels de sélénonium, sels de sulfonium, sulfates cycliques, acide L-ascorbique, γ-lactone de l'acide D-gulonique.

[Traduit par la Rédaction]

Introduction

Glycosidases are responsible for the hydrolysis of poly- and oligo-saccharides into monomers or the cleavage of bonds between sugars and non-carbohydrate aglycons. In recent years, much attention has focused on the synthesis and development of glycosidase inhibitors because of an increasing awareness of the vital role played by sugars in biological processes and because of their therapeutic potential (1, 2). In the case of patients suffering from Type II diabetes, the management of blood glucose levels is crucial since their insulin secretion may be normal, but the entry into cells of glucose (normally mediated by insulin) is compromised (3). Glycosidase inhibitors can be used to inhibit the activity of intestinal glucosidases that break down oligosaccharides to glucose. This enzyme inhibition delays glucose absorption into the blood and results in a lowering or smoothing of the blood glucose levels (4, 5).

There are two generally accepted mechanisms for the enzymatic hydrolysis of a glycosidic bond, proceeding either with the inversion or retention of configuration at the anomeric center (6, 7). In either case, protonation of the exocyclic oxygen leads to cleavage of the glycosidic bond with subsequent formation of an oxacarbenium ion. To generate potent glycosidase inhibitors, an attractive approach is to create compounds that mimic the oxacarbenium ion transition state in the enzyme-catalyzed reaction. Some naturally occurring compounds, such as acarbose (**1**) and voglibose (**2**) (Chart 1), are potent glycosidase inhibitors and presumably mimic the oxacarbenium ion, at least in binding to active site carboxylate residues via the protonated nitrogen atom (8, 9).

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Dedicated, with respect, to Dr. Alfred Bader for his impact on the field of chemistry.

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[1]This article is part of a Special Issue dedicated to Dr. Alfred Bader.

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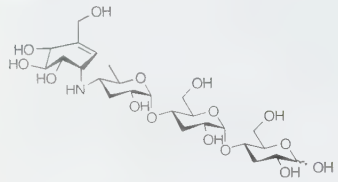
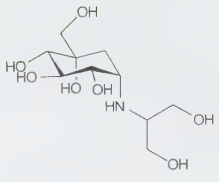
Chart 1.

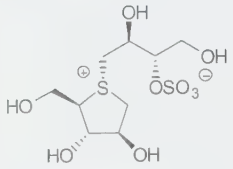


acarbose (**1**)

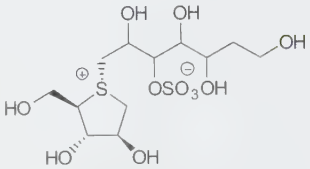


voglibose (**2**)

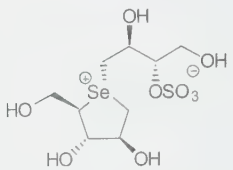
Chart 2.



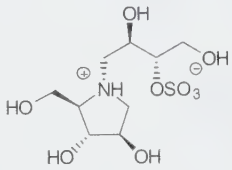
salacinol (**3**)



kotalanol (**4**)



blintol (**5**)

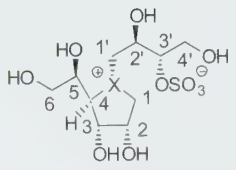


ghavaminol (**6**)

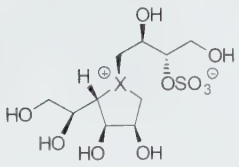
Recently, a new class of glycosidase inhibitors, including salacinol (**3**) and kotalanol (**4**) (Chart 2), with an intriguing inner-salt sulfonium sulfate structure was isolated from the roots and stems of the plant *Salacia reticulata* (10–12). The compounds were shown to be inhibitors of intestinal glucosidase enzymes that attenuate the undesirable spike in blood glucose that is experienced by diabetics after consuming a meal rich in carbohydrates. It is postulated that the inhibition of glucosidases by salacinol and kotalanol is due to their ability to mimic both the shape and charge of the oxocarbenium ion-like transition state involved in the enzymatic reactions.

In our current research program, we have undertaken a limited structure–activity study of salacinol and related compounds. The synthesis of salacinol and its ammonium and selenonium analogues have been reported by us and others (13–17). Analogues containing six-membered heterocyclic rings and some chain-extended analogues of salacinol have also been synthesized (18–21). Some of these analogues exhibited inhibitory activities in the micromolar range for recombinant human maltase glucoamylase, an intestinal glucosidase (20, 21). The studies also showed an interesting variation in the inhibitory power of these compounds against glycosidase enzymes of different origin (14–17, 22). In particular, the stereochemistry at the different stereogenic centers as well as the nature of the heteroatom play significant roles in discrimination between glycosidase enzymes. The molecular basis for this selectivity is being investigated through structural studies of the enzyme-bound inhibitors using molecular modeling in conjunction with conformational analysis by NMR techniques (23) and X-ray crystallography (24).

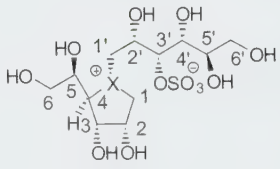
Chart 3.



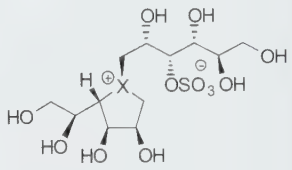
7 X = Se
8 X = S



9 X = Se
10 X = S



11 X = Se
12 X = S



13 X = Se
14 X = S

To further understand the enzyme discrimination of related compounds, we now describe the synthesis of new analogues of salacinol analogues **7**–**14** based on novel seleno- and thio-alditols derived from D-gulonic-γ-lactone and L-ascorbic acid (Chart 3).

Results and discussion

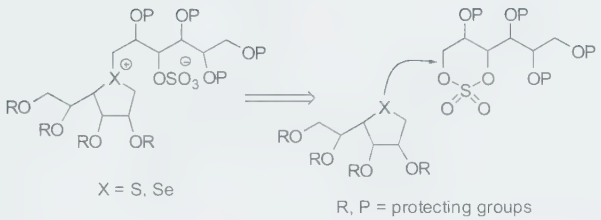
The analogues **7**–**14** can be synthesized by alkylation of a protected anhydroalditol at the ring heteroatom with terminal 1,3-cyclic sulfates. The protected anhydroalditols and the cyclic sulfates can be synthesized from the appropriate carbohydrate starting materials (Scheme 1).

The choice of protecting groups for the thio- and seleno-anhydroalditols and the cyclic sulfates, however, merited careful consideration, especially in the case of the selenonium analogues. Hydrogenolysis and strongly basic conditions proved to be problematic deprotection steps for similar selenonium analogues; thus, these conditions needed to be avoided (15–17). Therefore, we chose to use isopropylidene and benzylidene acetals as the protecting groups for the thio- and seleno-anhydroalditols **15**–**18** and the cyclic sulfates **19** and **20** since these acetals are both labile to acidic hydrolysis (Chart 4).

Our previous work also suggested that the release of ring strain in the opening of bicyclic sulfates was beneficial (14–17). Therefore, the benzylidene acetal at the 2,4-positions of the cyclic sulfates **19** and **20** played dual roles as protecting groups and reaction facilitators for the coupling reactions with compounds **15**–**18**. After the coupling reactions, the products could then be readily deprotected by simple treatment with trifluoroacetic acid.

The synthesis of the isopropylidene-protected 1,4-anhydro-4-seleno-D-allitol (**15**) and 1,4-anhydro-4-thio-D-allitol (**16**) started from the commercially available D-gulonic-γ-lactone (**21**, Scheme 2). 2,3,5,6-Di-*O*-isopropylidene-D-gulonic-γ-lactone (**22**) (25) was reduced with sodium borohydride to afford the corresponding diol **23**. Compound

Scheme 1.



Scheme 2.

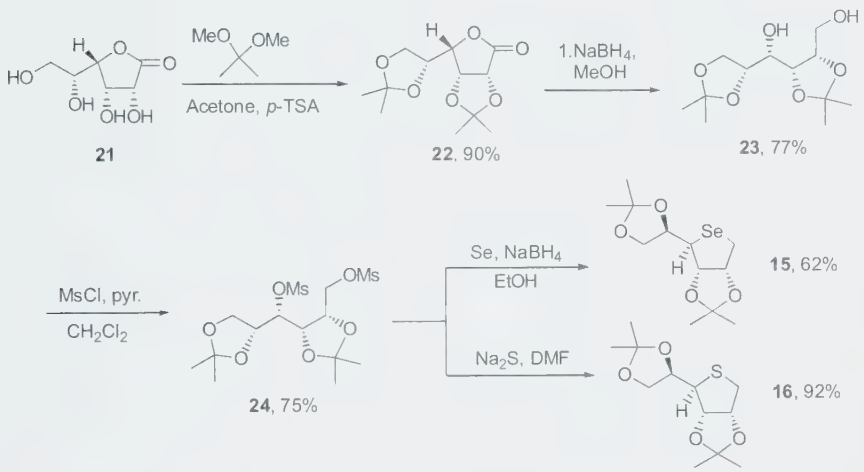
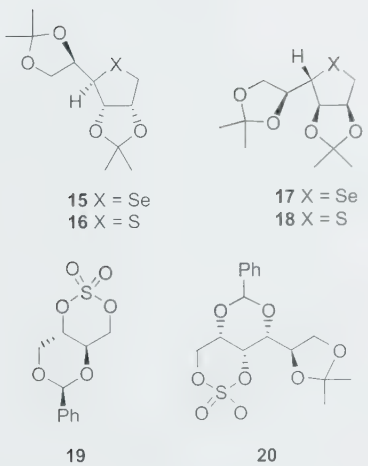


Chart 4.

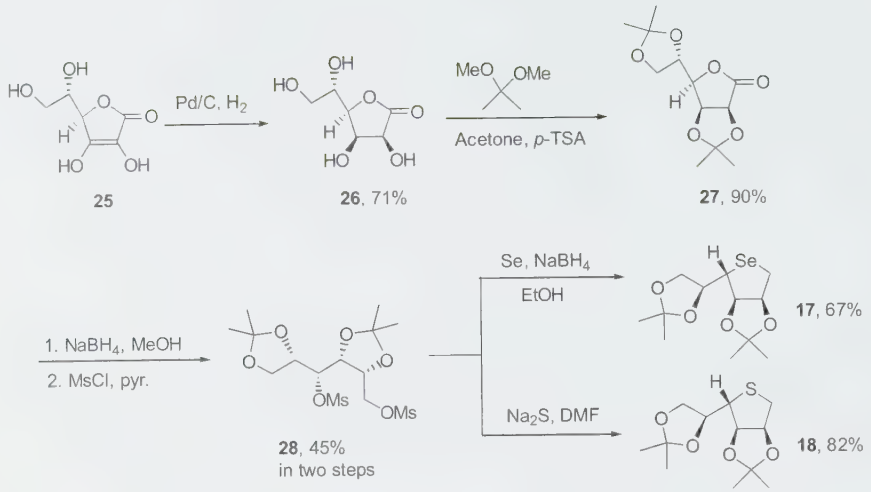


23 was then converted to the dimesylate **24** by treatment with methanesulfonyl chloride and pyridine in 80% yield (26). When the dimesylate **24** was reacted with selenium metal and sodium borohydride in EtOH at 60–65 °C, the isopropylidene-protected 1,4-anhydro-4-seleno-D-allitol **15** was obtained in 62% yield. The isopropylidene-protected 1,4-anhydro-4-thio-D-allitol **16** was prepared in 92% yield by treatment of the dimesylate **24** with sodium sulfide in DMF (Scheme 2).

Although the enantiomeric isopropylidene-protected 1,4-anhydro-4-seleno-L-allitol (**17**) and 1,4-anhydro-4-thio-L-allitol (**18**) could, in principle, be prepared from L-gulonic-γ-lactone, the high cost of this starting material made these syntheses unrealistic. Thus, inexpensive and commercially available L-ascorbic acid (**25**) was used as the starting material to give the L-gulonic-γ-lactone (**26**) in 71% yield (27) (Scheme 3). Compound **26** was then treated with 2,2-dimethoxypropane in dry acetone containing *p*-toluenesulfonic acid as a catalyst to give 2,3,5,6-di-*O*-isopropylidene-L-gulonic-γ-lactone (**27**) (25). The lactone **27** was subsequently reduced with sodium borohydride to afford the corresponding diol that was, in turn, converted to the dimesylate **28** by treatment with methanesulfonyl chloride and pyridine. When the dimesylate **28** was reacted with selenium metal and sodium borohydride in EtOH at 60–65 °C, the isopropylidene-protected 1,4-anhydro-4-seleno-L-allitol **17** was obtained in 67% yield. The isopropylidene-protected 1,4-anhydro-4-thio-L-allitol **18** was prepared in 82% yield by treatment of the dimesylate **28** with sodium sulfide in DMF.

Since salacinol **3** and its selenonium analogue, blintol (**5**) (Chart 2), are the most active, so far, of this class of glycosidase inhibitors against human maltase glucoamylase, we first concentrated on the coupling reactions of **15** and **16** with the cyclic sulfate **19**, which would yield the identical side chain present in salacinol and blintol (Scheme 4). The solvent chosen for the coupling reactions was the unusual solvent 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which offers significant advantage in these types of coupling reactions compared with other solvents (15–17). The cyclic sulfates **19**, prepared as described previously (16), were reacted with **15** and **16**, to give the corresponding protected

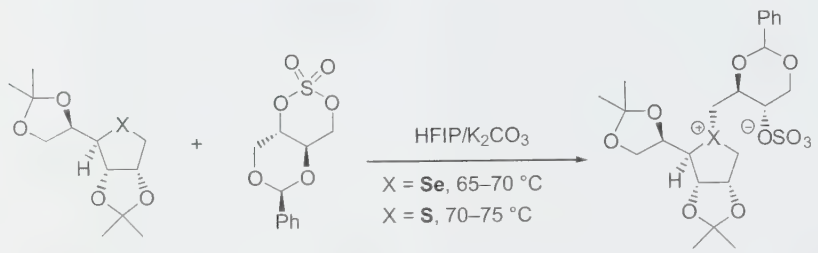
Scheme 3.



25 **26**, 71% **27**, 90%

28, 45% in two steps **17**, 67% **18**, 82%

Scheme 4.



15 X = Se
16 X = S

19

29 X = Se, 90%
30 X = S, 94%

selenonium and sulfonium sulfates **29** and **30**, respectively (Scheme 4).

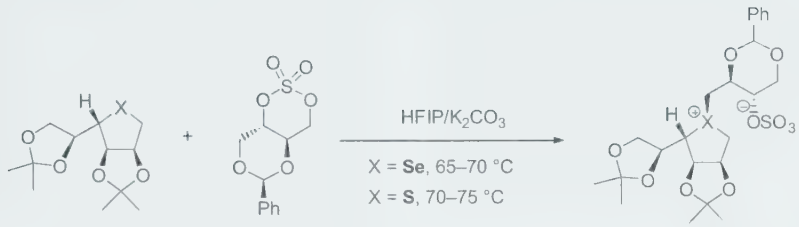
The coupling reactions of enantiomeric **17** and **18** with the cyclic sulfate **19** were carried out analogously, to give the corresponding protected selenonium and sulfonium sulfates **31** and **32**, respectively (Scheme 5).

We next turned our attention to the possibility of attaching longer side chains to the anhydroalditols **15**–**18**. Our interest in longer side chains stemmed from the fact that kotalanol **4**, which has a seven-carbon side chain instead of four-carbon side chain of the salacinol, exhibits stronger inhibitory activities toward certain glycosidase enzymes. Since the exact stereochemistry of kotalanol **4** is not yet known, it is necessary and important to study the structure–activity relationships of these types of compounds systematically by attaching side chains with different chain lengths and different stereochemistry at the stereogenic centers to the heterocyclic rings of the anhydroheteroalditols. The cyclic sulfate **20**, which consisted of a protected polyhydroxylated six-carbon chain (19), was chosen for this purpose. The cyclic sulfate **20** reacted with **15** and **16** and their enantiomers **17** and **18** in HFIP to give the corresponding protected selenonium and sulfonium compounds **33**–**36**, respectively (Scheme 6).

The reactivity of **15**–**18** with cyclic sulfates **19** and **20** varied slightly. With the same anhydroalditols, the cyclic sulfate **19** was more reactive than the cyclic sulfate **20**, also resulting in higher yields of the coupling reactions. Thus, the coupling reactions with the cyclic sulfate **19** usually proceeded in yields of 90%–95%, while the cyclic sulfate **20** typically gave yields of 70%–80%, with the remainder consisting of starting materials and a small amount of decomposition products. With the same cyclic sulfate, the selenoalditols were slightly more reactive than their sulfur counterparts, as demonstrated by the different reaction temperatures required in the coupling reactions. The reactivities of the enantiomeric pairs, compounds **15**–**17** and **16**–**18** with the cyclic sulfates **19** and **20** were virtually the same. Selectivity for attack at the primary center of the cyclic sulfates **19** and **20** over possible alternative attack at the secondary center by compounds **15**–**18** was invariably excellent, and in no case were isolable quantities of the regioisomers detected. In the case of the coupling reaction of **15** and L-allitol **17** with the cyclic sulfates **19** and **20**, there was a small amount (5%–10%) of the stereoisomer formed through electrophilic attack on the β face of the seleno-D-allitol **15** and the α face of the seleno-L-allitol **17** to give products that were diastereomeric at the selenonium center, but could not be isolated in pure form. However, this type of minor product was not detected in the reactions of the corresponding thioallitols.

The deprotection of the coupled products **29**–**36** was carried out by treatment with trifluoroacetic acid (Scheme 7). After rinsing away the cleaved protecting groups with dichloromethane, the resulting residues were purified by flash

Scheme 5.

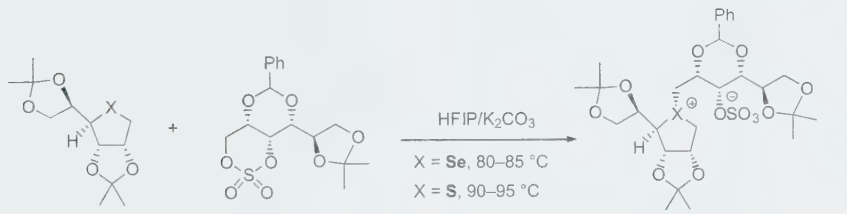


17 X = Se
18 X = S

19

31 X = Se, 90%
32 X = S, 92%

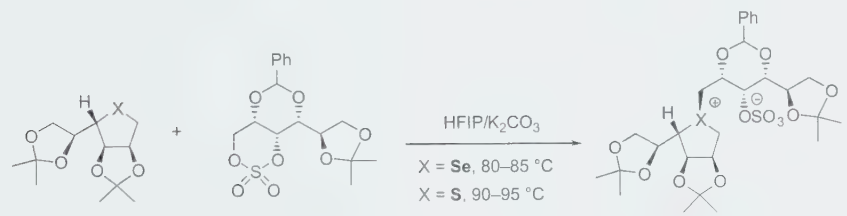
Scheme 6.



15 X = Se
16 X = S

20

33 X = Se, 70%
34 X = S, 82%



17 X = Se
18 X = S

20

35 X = Se, 67%
36X = S, 79%

chromatography to yield compounds **7**–**10** as amorphous, hygroscopic solids. In the cases of compounds **33**–**36**, however, some of the benzylidene acetal protecting group (up to 30% by NMR measurements) remained even after prolonged (up to 48 h) treatment with TFA. The remaining benzylidene acetal was eventually cleaved by hydrogenolysis in 80% acetic acid to give the corresponding deprotected products **11**–**14** as amorphous, hygroscopic solids. The yields of compounds **11**–**14** were low, partly because of the adsorption of the products on the Pd–C catalyst. Compounds **7**–**14** were characterized by spectroscopic methods. The MALDI-TOF mass spectra of compounds **7**–**14** showed major fragmentation peaks ($M + Na^+ - SO_3$) together with the molecular ion peaks ($M + Na^+$) of much lower intensities.

The absolute stereochemistry at the heteroatom center of compounds **7**–**14** was established by 1D-NOE NMR spectroscopy. For example, in the 1D-NOE spectrum of compound **8** (Fig. 1), the H-4 to H-1′b correlation was clearly exhibited, implying that these two hydrogens are syn-facial. Therefore, C-1′ of the side chain must be anti to C-5 of the sulfonium salt ring.

As a final point of interest, compounds **7**–**14** were screened against recombinant human maltase glucoamylase (MGA), a critical intestinal glucosidase involved in the processing of oligosaccharides of glucose into glucose itself. The compounds showed no significant activity.[3]

Conclusions

Four series of analogues of the naturally occurring glucosidase inhibitor salacinol were synthesized. These analogues contained the acyclic chains of salacinol and extended acyclic chains of six carbons, as well as ring heteroatom substitution (Se, S). In addition, the heterocyclic ring bore the D- or L-allitol configuration. These syntheses utilized the 1,3-cyclic sulfates derived from commercially available D-glucose and D-mannose. The isopropylidene and benzylidene acetal protecting groups on the coupled products ensured facile deprotection with TFA to yield the final compounds **7**–**14**. The compounds showed no inhibitory activity against human maltase glucoamylase.

Experimental section

General

Optical rotations were measured at 23 °C. ^1H and ^{13}C

[3]L. Sim and D.R. Rose. Unpublished data.

Scheme 7.

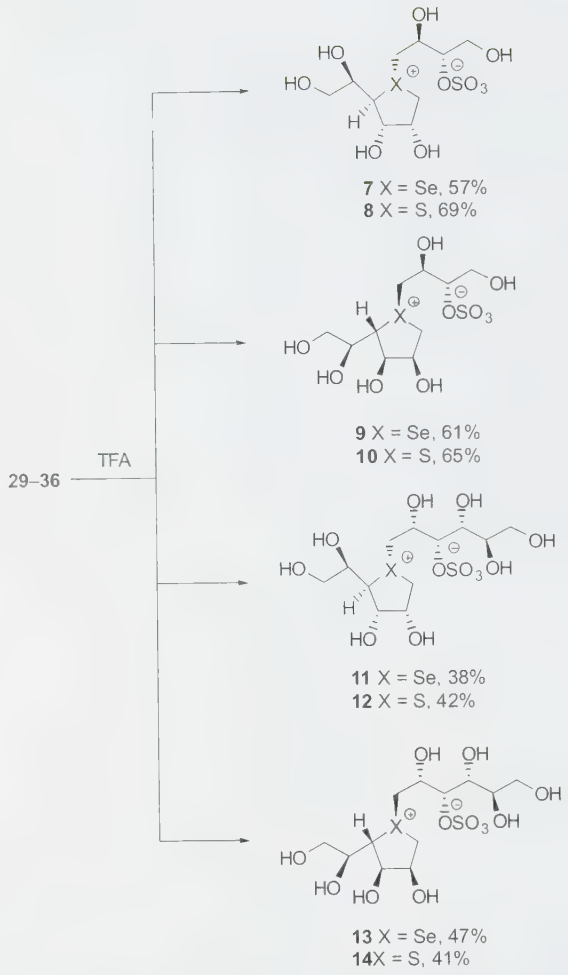
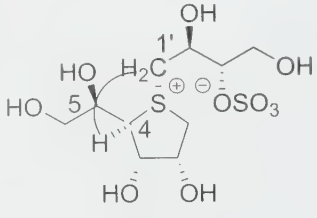


Fig. 1. NOE correlation observed in the 1D-NOE spectrum of compound **8**.



NMR spectra were recorded at 500 and 125 MHz, respectively. All assignments were confirmed with the aid of two-dimensional ^{1}H and ^{1}H (COSYDFTP) or ^{1}H and ^{13}C (INVBTP) experiments using standard Bruker pulse programs. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). MALDI mass spectra were obtained on a PerSeptive Biosystems Voyager DE time-of-flight spectrometer for samples dispersed in a 2,5-dihydroxybenzoic acid matrix. High-resolution mass spectra were obtained by the electrospray ionization (ESI) technique, using a ZabSpec oaTOF mass spectrometer at 10 000 RP.

2,3,5,6-Di-*O*-isopropylidene-1,4-di-*O*-methanesulfonyl-D-gulitol (24)

2,3,5,6-Di-*O*-isopropylidene-1,4-di-*O*-methanesulfonyl-D-gulitol (**24**) was prepared by the literature method (26) with slight variations. To a solution of commercially available D-gulonic-γ-lactone **21** (10.0 g, 56.1 mmol) in dry acetone (200 mL), 2,2-dimethoxypropane (40 mL, 0.32 mmol) was added at RT. To this solution, *p*-toluenesulfonic acid (200 mg) was added as a catalyst. The progress of the reaction was followed by TLC analysis of the aliquots (hexane–EtOAc, 1:1). When the starting material **21** had been essentially consumed, the reaction was stopped by addition of triethylamine (1 mL) to the reaction mixture. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography (hexane–EtOAc, 1:1) to give compound **22** as a white solid (13.1 g, 90%). The NMR spectrum of compound **22** matched that of the published data (25). The lactone **22** (5.0 g, 19.3 mmol) was dissolved in THF (20 mL) and MeOH (50 mL) was then added. To this solution, $NaBH_4$ was added portionwise at 0 °C. The progress of the reaction was followed by TLC analysis of the aliquots (hexane–EtOAc, 1:1). When the starting material **22** had been consumed, the solvent was evaporated under reduced pressure. The residue was redissolved in EtOAc (50 mL), washed with aqueous tartaric acid solution (2 × 10 mL) and brine (50 mL), and dried over Na_2SO_4. Purification by column chromatography (hexane–EtOAc, 2:1) yielded compound **23** as a colourless syrup (3.9 g, 77%). The NMR spectrum of compound **23** matched that of the published data (26). The diol **23** (5.0 g, 19.1 mmol) was dissolved in CH_2Cl_2 (50 mL) and the solution was added dropwise to a mixture of pyridine (100 mL) and methanesulfonyl chloride (6 mL, 77.5 mmol) and cooled to 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to RT for 6 h. When TLC analysis of the aliquots (hexane–EtOAc, 1:1) showed total consumption of the starting material, the reaction mixture was poured into ice water, extracted with CH_2Cl_2 (3 × 100 mL), washed with brine (50 mL), and dried over Na_2SO_4. Purification by column chromatography (hexane–EtOAc, 2:1) yielded compound **24** as a colourless syrup (5.9 g, 75%). $[\alpha]^{22}_D$ –46° (*c* 1, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 4.87 (dd, 1H, $J_{3,4}$ = 5.8 Hz, $J_{4,5}$ = 4.7 Hz, H-4), 4.56 (ddd, 1H, $J_{1b,2}$ = 6.0 Hz, $J_{1a,1b}$ = 12.0 Hz, H-1b), 4.56–4.48 (m, 2H, H-2, H-3, H-1a), 4.48 (dd, 1H, H-1a), 4.46 (ddd, 1H, H-5), 4.14 (dd, 1H, $J_{5,6b}$ = 6.8 Hz, $J_{6a,6b}$ = 8.7 Hz, H-6b), 4.02 (dd, 1H, $J_{5,6a}$ = 6.7 Hz, H-6a), 3.23, 3.14 (2 s, 6H, 2 × OSO_2CH_3), 1.51, 1.41, 1.38, 1.34 (4 s, 12H, 4 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 110.1, 109.6 ($(CH_3)_2C(OR)_2$), 79.1 (C-4), 75.6 (C-3), 75.0 (C-2), 74.9 (C-1), 68.7 (C-5), 65.4 (C-6), 38.8, 36.7 (2 × OSO_2CH_3), 26.9, 25.6, 25.1, 25.0 (4 × CH_3). Anal. calcd. for $C_{14}H_{26}O_{10}S_2$: C 40.18, H 6.26; found: C 40.35, H 6.14.

2,3,5,6-Di-*O*-isopropylidene-1,4-di-*O*-methanesulfonyl-L-gulitol (28)

To a solution of commercially available L-ascorbic acid **25** (30.0 g, 0.17 mmol) in distilled water (200 mL), palladium

on activated carbon (10%, 1.0 g) was added as a catalyst at RT. The reaction mixture was placed in a steel reaction vessel and underwent hydrogenation (100 psi, 1 psi = 6.894 757 kPa) at 60 °C for 48 h. The progress of the reaction was followed by TLC analysis of the aliquots (EtOAc–MeOH–H_2O, 10:3:1). When the starting material **25** had been essentially consumed, the reaction was stopped and the reaction mixture was filtered under vacuum and washed with water (2 × 50 mL). The filtrate and the wash were combined and the water was then evaporated under reduced pressure. The residue was recrystallized from methanol – ethyl acetate to give compound **26** as a white solid (21.5 g, 71%). The NMR spectrum of compound **26** matched that of the published literature (26). To a suspension of the lactone **26** (10.0 g, 56.1 mmol) in dry acetone (200 mL), 2,2-dimethoxypropane (40 mL, 0.32 mmol) was added at RT. To this mixture, *p*-toluenesulfonic acid (200 mg) was added as a catalyst. The progress of the reaction was followed by TLC analysis of the aliquots (hexane–EtOAc, 1:1). When the starting material **26** had been essentially consumed, the reaction was stopped by addition of triethylamine (1 mL). The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography (hexane–EtOAc, 1:1) to give compound **27** as a white solid. The NMR spectrum of compound **26** matched that of the published data (25). Lactone **27** (5.0 g, 19.3 mmol) was dissolved in THF (20 mL) and MeOH (50 mL) was then added. To this solution, $NaBH_4$ was added portionwise at 0 °C. The progress of the reaction was followed by TLC analysis of the aliquots (hexane–EtOAc, 1:1). When the starting material **27** had been consumed, the solvent was evaporated under reduced pressure. The residue was redissolved in EtOAc (50 mL), washed with aqueous tartaric acid solution (2 × 10 mL) and brine (50 mL), and dried over Na_2SO_4. After evaporating the solvent, the crude diol was used directly in the next step. The crude diol was dissolved in CH_2Cl_2 (50 mL). The solution was added dropwise to a mixture of pyridine (100 mL) and methanesulfonyl chloride (6 mL, 77.5 mmol) and cooled to 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then allowed to warm to RT for 6 h. When TLC analysis of the aliquots (hexane–EtOAc, 1:1) showed total consumption of the starting material, the reaction mixture was poured into ice water, extracted with CH_2Cl_2 (3 × 100 mL), washed with brine (50 mL), and dried over Na_2SO_4. Purification by column chromatography (hexane–EtOAc, 2:1) yielded compound **28** as a colourless syrup (3.6 g, 45% for two steps). $[\alpha]^{22}_D$ +54° (*c* 4, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 4.87 (dd, 1H, $J_{3,4}$ = 6.1 Hz, $J_{4,5}$ = 4.8 Hz, H-4), 4.57 (ddd, 1H, $J_{1b,2}$ = 6.0 Hz, $J_{1a,1b}$ = 12.0 Hz, H-1b), 4.56–4.48 (m, 3H, H-2, H-3, H-1a), 4.45 (ddd, 1H, H-5), 4.13 (dd, 1H, $J_{5,6b}$ = 6.7 Hz, $J_{6a,6b}$ = 8.6 Hz, H-6b), 4.03 (dd, 1H, $J_{5,6a}$ = 6.6 Hz, H-6a), 3.24, 3.15 (2 s, 6H, 2 × OSO_2CH_3), 1.52, 1.41, 1.38, 1.34 (4 s, 12H, 4 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 114.3, 113.8 ($(CH_3)_2C(OR)_2$), 83.3 (C-4), 79.7 (C-3), 79.0 (C-2), 78.9 (C-1), 72.9 (C-5), 69.6 (C-6), 43.0, 40.9 (2 × OSO_2CH_3), 31.3, 29.9, 29.3, 29.2 (4 × CH_3). Anal. calcd. for $C_{14}H_{26}O_{10}S_2$: C 40.18, H 6.26; found: C 39.89, H 6.02.

1,4-Anhydro-2,3,5,6-di-*O*-isopropylidene-4-seleno-D-allitol (15)

To a suspension of grey selenium metal (1.6 g, 20.2 mmol) and 95% EtOH (100 mL), $NaBH_4$ was added portionwise until the black Se color disappeared. To this mixture, a solution of the dimesylate **24** (7.0 g, 16.8 mmol) in THF (10 mL) was added and the reaction mixture was heated at 70 °C for 12 h. The solvent was evaporated under reduced pressure, the residue was redissolved in EtOAc, washed with water (20 mL) and brine (20 mL), and dried over Na_2SO_4. After evaporating the solvent, the crude product was purified by column chromatography (hexane EtOAc, 3:1) to give **15** as a colourless oil (3.2 g, 62%). $[\alpha]^{22}_D$ +152° (*c* 1, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 4.98 (ddd, 1H, $J_{1b,2}$ = 4.5 Hz, H-2), 4.91 (dd, 1H, $J_{2,3}$ = 5.6 Hz, H-3), 4.12 (dd, 1H, $J_{6a,6b}$ = 8.4 Hz, $J_{5,6b}$ = 6.4 Hz, H-6b), 4.04 (ddd, 1H, $J_{5,6a}$ = 5.9 Hz, $J_{4,5}$ = 5.8 Hz, H-5), 3.71 (dd, 1H, H-6a), 3.18 (m, 1H, H-4), 3.16 (dd, 1H, $J_{1a,1b}$ = 12.8 Hz, H-1b), 2.78 (dd, 1H, H-1a), 1.42, 1.38, 1.29, 1.28 (4 s, 12H, 4 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 110.3, 109.8 ($(CH_3)_2C(OR)_2$), 85.6 (C-3), 83.9 (C-2), 76.4 (C-5), 69.0 (C-6), 57.7 (C-4), 37.4 (C-1), 26.5, 26.0, 25.1, 24.1 (4 × CH_3). Anal. calcd. for $C_{12}H_{20}O_4Se$: C 46.91, H 6.56; found: C 46.67, H 6.37.

1,4-Anhydro-2,3,5,6-di-*O*-isopropylidene-4-thio-D-allitol (16)

To a solution of the dimesylate **24** (5.0 g, 11.9 mmol) in DMF (80 mL), $Na_2S{\cdot}9H_2O$ (4.0 g, 16.7 mmol) was added and the reaction mixture was heated at 90 °C for 12 h. The reaction mixture was poured into water (100 mL), extracted with Et_2O (4 × 50 mL), washed with water (10 × 20 mL), and dried over Na_2SO_4. After evaporating the solvent, the crude product was purified by column chromatography (hexane–EtOAc, 3:1) to give **16** as a colourless oil (2.9 g, 92%). $[\alpha]^{22}_D$ +127° (*c* 1, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 5.04 (ddd, 1H, $J_{1b,2}$ = 4.7 Hz, H-2), 4.91 (dd, 1H, $J_{2,3}$ = 5.6 Hz, H-3), 4.15–4.12 (m, 1H, H-4), 4.13 (dd, 1H, H-6b), 3.68 (ddd, 1H, $J_{5,6a}$ = 6.7 Hz, $J_{4,5}$ = 9.2 Hz, $J_{5,6b}$ = 8.2 Hz, H-5), 3.45 (dd, 1H, $J_{6a,6b}$ = 8.5 Hz, H-6a), 3.29 (dd, 1H, $J_{1a,1b}$ = 11.2 Hz, H-1b), 2.92 (dd, 1H, H-1a), 1.42, 1.38, 1.29, 1.27 (4 s, 12H, 4 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 109.9, 109.8 ($(CH_3)_2C(OR)_2$), 87.1 (C-3), 85.3 (C-2), 77.1 (C-5), 69.6 (C-6), 52.6 (C-4), 29.7 (C-1), 26.6, 26.2, 25.2, 24.1 (4 × CH_3). Anal. calcd. for $C_{12}H_{20}O_4S$: C 55.36, H 7.74; found: C 55.64, H 7.72.

1,4-Anhydro-2,3,5,6-di-*O*-isopropylidene-4-seleno-L-allitol (17)

To a suspension of grey selenium metal (1.4 g, 18.7 mmol) and EtOH (100 mL, 95%), $NaBH_4$ was added portionwise until the black Se color disappeared. To this mixture, a solution of the dimesylate **28** (6.0 g, 14.3 mmol) in THF (10 mL) was added and the reaction mixture was heated at 65–70 °C for 12 h. The solvent was evaporated under reduced pressure and the residue was redissolved in EtOAc, washed with water (20 mL) and brine (20 mL), and dried over Na_2SO_4. After evaporating the solvent, the crude product was purified by column chromatography (hexane–EtOAc, 3:1) to give **17** as a colourless oil (2.9 g, 67%). $[\alpha]^{22}_D$ −143° (*c* 1, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 5.03 (ddd, 1H, H-2), 4.91 (dd, 1H, $J_{2,3}$ = 5.6 Hz, H-3), 4.15–4.10 (m, 2H, H-5, H-6b), 3.68 (dd, 1H, $J_{5,6a}$ = 8.9 Hz, $J_{6a,6b}$ = 11.4 Hz, H-6a), 3.45 (dd, 1H, H-4), 3.27 (dd, 1H, $J_{1b,2}$ = 4.7 Hz, $J_{1a,1b}$ = 12.0 Hz, H-1b), 2.92 (dd, 1H, $J_{1b,2}$ = 0.7 Hz,

H-1a), 1.42, 1.37, 1.29, 1.27 (4 s, 12H, 4 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 110.0, 109.8 ($(CH_3)_2C(OR)_2$), 87.1 (C-3), 85.3 (C-2), 77.1 (C-5), 69.6 (C-6), 52.6 (C-4), 29.8 (C-1), 26.6, 26.2, 25.3, 24.1 (4 × CH_3). Anal. calcd. for $C_{12}H_{20}O_4Se$: C 46.91, H 6.56; found: C 46.76, H 6.66.

1,4-Anhydro-2,3,5,6-di-*O*-isopropylidene-4-thio-L-allitol (18)

To a solution of the dimesylate **28** (5.0 g, 11.9 mmol) in DMF (80 mL), $Na_2S·9H_2O$ (4.0 g, 16.7 mmol) was added and the reaction mixture was heated at 90 °C for 12 h. The reaction mixture was poured into water (100 mL), extracted with Et_2O (4 × 50 mL), washed with water (10 × 20 mL), and dried over Na_2SO_4. After evaporating the solvent, the crude product was purified by column chromatography (hexane–EtOAc, 3:1) to give **18** as a colourless oil (2.5 g, 82%). $[\alpha]^{22}_D$ −139° (*c* 1, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 4.99 (ddd, 1H, H-2), 4.92 (dd, 1H, $J_{2,3}$ = 5.6 Hz, H-3), 4.12 (dd, 1H, $J_{6a,6b}$ = 8.2 Hz, $J_{5,6b}$ = 6.4 Hz, H-6b), 4.04 (ddd, 1H, H-5), 3.71 (dd, 1H, $J_{5,6a}$ = 5.9 Hz, H-6a), 3.19–3.15 (m, 1H, H-4), 3.17 (dd, 1H, H-1b), 2.80 (dd, 1H, $J_{1a,1b}$ = 12.9 Hz, H-1a), 1.42, 1.38, 1.29, 1.28 (4 s, 12H, 4 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 110.3, 109.8 ($(CH_3)_2C(OR)_2$), 85.6 (C-3), 83.9 (C-2), 76.3 (C-5), 69.0 (C-6), 57.7 (C-4), 37.4 (C-1), 26.5, 26.0, 25.1, 24.1 (4 × CH_3). Anal. calcd. for $C_{12}H_{20}O_4S$: C 55.36, H 7.74; found: C 55.16, H 7.58.

General procedure for the preparation of sulfonium and selenonium sulfates 29–36

A mixture of **15**, **16**, **17**, or **18**, and the cyclic sulfate **19** or **20** in HFIP (1,1,1,3,3,3-hexafluoroisopropanol) was placed in a reaction vessel and K_2CO_3 (20 mg) was added. The stirred reaction mixture was heated in a sealed tube at the indicated temperature for the indicated time, as given later. The progress of the reaction was followed by TLC analysis of the aliquots (EtOAc–MeOH, 10:1). When the limiting reagent had been essentially consumed, the mixture was cooled, diluted with CH_2Cl_2, and evaporated to give a syrupy residue. Purification by column chromatography (EtOAc to EtOAc–MeOH, 10:1) gave the purified sulfonium salts and selenonium salts **29**–**36**.

1,4-Anhydro-2,3,5,6-di-O-isopropylidene-1-[(S)-[(2′S,3′S)-2′,4 -benzylidenedioxy-3′-(sulfooxy)butyl]selenonio]-D-allitol inner salt (29)

The reaction of compound **15** (500 mg, 1.63 mmol) with the cyclic sulfate **19** (530 mg, 1.94 mmol) in HFIP (2.0 mL) for 12 h at 80–85 °C gave compound **29** as a colourless, amorphous solid (850 mg, 90% based on **15**). $[\alpha]^{22}_D$ +12° (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 7.56–7.38 (m, 5H, H-Arom.), 5.74 (s, 1H, C*H*Ph), 5.52 (ddd, 1H, $J_{1b,2}$ = 5.2 Hz, $J_{2,3}$ = 5.7, H-2), 5.27 (dd, 1H, H-3), 4.78 (ddd, 1H, ddd, 1H, $J_{5,6b}$ = 7.3 Hz, $J_{5,6a}$ = 5.2 Hz, $J_{4,5}$ = 3.8 Hz, H-5), 4.62 (dd, 1H, H-4), 4.46–4.37 (m, 4H, H-1′b, H-2′, H-3′, H-4′b), 4.28 (dd, 1H, $J_{1'a,1'b}$ = 13.4 Hz, $J_{1'a,2'}$ = 3.8 Hz, H-1′a), 4.25 (dd, 1H, $J_{6a,6b}$ = 9.5 Hz, $J_{5,6b}$ = 7.3 Hz, H-6b), 4.10 (dd, 1H, $J_{1b,2}$ = 5.2 Hz, $J_{1a,1b}$ = 15.4 Hz, H-1b), 3.97 (dd, 1H, H-1a), 3.96 (dd, 1H, $J_{5,6a}$ = 5.2 Hz, H-6a), 3.78 (m, 1H, H-4′a), 1.64, 1.42, 1.38, 1.32 (4 s, 18H, 4 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 142.3, 133.9, 133.0, 131.1 (C-Ar), 116.9, 115.7 (2 $(CH_3)_2C(OR)_2$), 106.1 (*C*HPh), 89.9 (C-3), 89.8 (C-2), 81.3 (C-2′), 79.0 (C-5), 73.9 (C-4), 73.5 (C-4′), 71.8 (C-6), 71.5 (C-3), 52.8 (C-1), 50.4 (C-1′), 30.3, 30.1, 28.2, 27.1 (4 × *C*H_3). HRMS calcd. for $C_{23}H_{33}O_{10}SSe$: 581.0594 (M + H^+); found: 581.0597.

1,4-Anhydro-2,3,5,6-di-O-isopropylidene-1-[(S)-[(2′S,3′S)-2′,4′-benzylidenedioxy-3′-(sulfooxy)butyl]sulfonio]-D-allitol inner salt (30)

The reaction of compound **16** (500 mg, 1.92 mmol) with the cyclic sulfate **19** (630 mg, 2.31 mmol) in HFIP (2.0 mL) for 12 h at 70–75 °C gave compound **30** as a colourless, amorphous solid (960 mg, 94% based on **16**). $[\alpha]^{22}_D$ +1.2° (*c* 0.1, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 7.56–7.38 (m, 5H, H-Arom.), 5.74 (s, 1H, C*H*Ph), 5.52 (ddd, 1H, $J_{1b,2}$ = 5.2 Hz, $J_{2,3}$ = 5.7 Hz, H-2), 5.26 (dd, 1H, H-3), 4.79 (ddd, 1H, ddd, 1H, $J_{5,6b}$ = 7.4 Hz, $J_{5,6a}$ = 5.1 Hz, $J_{4,5}$ = 3.9 Hz, H-5), 4.63 (dd, 1H, H-4), 4.49–4.36 (m, 4H, H-1′b, H-2′, H-3′, H-4′b), 4.28 (dd, 1H, $J_{1'a,1'b}$ = 13.4 Hz, $J_{1'a,2'}$ = 3.7 Hz, H-1′a), 4.25 (dd, 1H, $J_{6a,6b}$ = 9.4 Hz, H-6b), 4.10 (dd, 1H, $J_{1b,2}$ = 5.2 Hz, $J_{1a,1b}$ = 14.4 Hz, H-1b), 3.97 (dd, 1H, H-1a), 3.97 (dd, 1H, $J_{5,6a}$ = 5.1 Hz, H-6a), 3.78 (m, 1H, H-4′a), 1.64, 1.42, 1.38, 1.32 (4s, 18H, 4 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 138.5, 129.3, 128.4, 126.5 (C-Ar), 112.3, 111.1 (2 $(CH_3)_2C(OR)_2$), 101.4 (*C*HPh), 85.3 (C-3), 85.2 (C-2), 76.7 (C-2′), 74.4 (C-5), 69.2 (C-4′), 68.8 (C-4), 67.1 (C-6), 67.0 (C-3′), 48.2 (C-1), 45.8 (C-1′), 25.7, 25.5, 23.6, 22.5 (4 × *C*H_3). Anal. calcd. for $C_{23}H_{32}O_{10}S_2$: C 51.86, H 6.06; found: C 52.06, H 5.87. HRMS calcd. for $C_{23}H_{33}O_{10}S_2$: 533.1510 (M + H^+); found: 533.1512.

1,4-Anhydro-2,3,5,6-di-O-isopropylidene-1-[(S)-[(2′S,3′S)-2′,4 -benzylidenedioxy-3′-(sulfooxy)butyl]selenonio]-L-allitol inner salt (31)

The reaction of compound **17** (500 mg, 1.63 mmol) with the cyclic sulfate **19** (530 mg, 1.94 mmol) in HFIP (2.0 mL) for 12 h at 65–70 °C gave compound **31** as a colourless, amorphous solid (850 mg, 90% based on **17**). $[\alpha]^{22}_D$ +18° (*c* 1.0, CH_2Cl_2). ^{1}H NMR (CD_2Cl_2) δ: 7.48–7.38 (m, 5H, H-Arom.), 5.61 (s, 1H, C*H*Ph), 5.41 (ddd, 1H, H-2), 5.15 (dd, 1H, $J_{2,3}$ = 5.3 Hz, H-3), 4.81 (ddd, 1H, $J_{4,5}$ = 2.0 Hz, $J_{5,6a}$ = 4.6 Hz, $J_{5,6b}$ = 7.8 Hz, H-5), 4.60 (m, 1H, H-4), 4.55 (ddd, 1H, H-3′), 4.52 (dd, 1H, H-4′b), 4.42 (d, 2H, H-1′b, H-1′a), 4.38–4.32 (m, 1H, H-2′), 4.20 (dd, 1H, $J_{5,6b}$ = 7.8 Hz, $J_{6a,6b}$ = 9.6 Hz, H-6b), 3.95 (dd, 1H, $J_{5,6a}$ = 4.6 Hz, H-6a), 3.85 (dd, 1H, $J_{4'a,4'b}$ = 10.0 Hz, H-4′a), 3.63 (dd, 1H, H-1b), 3.60 (dd, 1H, $J_{1a,2}$ = 5.1 Hz, $J_{1a,1b}$ = 13.9 Hz, H-1a), 1.60, 1.44, 1.36, 1.32 (4 s, 12H, 4 × CH_3). ^{13}C NMR (CD_2Cl_2) δ: 137.0, 129.5, 128.6, 126.3 (C-Ar), 112.1, 111.2 (2 $(CH_3)_2C(OR)_2$), 101.8 (*C*HPh), 87.8 (C-2), 85.7 (C-3), 76.9 (C-3′), 74.7 (C-5), 70.5 (C-4), 69.3 (C-4′), 67.7 (C-2′), 67.2 (C-6), 44.5 (C-1′), 43.2 (C-1), 26.2, 26.0, 23.3, 22.9 (4 × *C*H_3). Anal. calcd. for $C_{23}H_{32}O_{10}SSe$: C 47.67, H 5.57; found: C 47.89, H 5.67.

1,4-Anhydro-2,3,5,6-di-O-isopropylidene-1-[(S)-[(2′S,3′S)-2′,4′-benzylidenedioxy-3′-(sulfooxy)butyl]sulfonio]-L-allitol inner salt (32)

The reaction of compound **18** (500 mg, 1.92 mmol) with the cyclic sulfate **19** (630 mg, 2.31 mmol) in HFIP (2.0 mL) for 12 h at 80–85 °C gave compound **32** as a colourless, amorphous solid (940 mg, 92% based on **18**). $[\alpha]^{22}_D$ +10° (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 7.48–7.39 (m, 5H, H-

Arom.), 5.59 (s, 1H, C*H*Ph), 5.26 (ddd, 1H, H-2), 5.10 (dd, 1H, $J_{2,3}$ = 5.8 Hz, H-3), 4.88 (ddd, 1H, $J_{4,5}$ = 7.6 Hz, H-5), 4.68 (ddd, 1H, H-3′), 4.54 (m, 1H, H-4), 4.50 (dd, 1H, $J_{3',4'}$ = 1.8 Hz, H-4′), 4.40 (d, 2H, H-1′b, H-1′a), 4.34 (m, 1H, H-2′), 4.32 (dd, 1H, $J_{5,6b}$ = 7.9 Hz, $J_{6a,6b}$ = 9.8 Hz, H-6b), 4.01 (dd, 1H, $J_{5,6a}$ = 4.6 Hz, H-6a), 3.82 (dd, 1H, H-4′a), 3.68 (dd, 1H, $J_{1b,2}$ = 5.3 Hz, $J_{1a,1b}$ = 15.0 Hz, H-1b), 3.62 (dd, 1H, H-1a), 1.60, 1.44, 1.36, 1.34 (4 s, 12H, 4 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 136.9, 129.6, 128.6, 126.3 (C-Ar), 112.8, 111.5 (2 $(CH_3)_2C(OR)_2$), 101.9 (*C*HPh), 86.2 (C-2), 84.1 (C-3), 76.9 (C-3′), 74.8 (C-5), 71.4 (C-4), 69.2 (C-2), 67.3 (C-6), 65.7 (C-4′), 47.7 (C-1), 45.9 (C-1′), 26.0, 25.9, 23.3, 22.6 (4 × *C*H_3). HRMS calcd. for $C_{23}H_{33}O_{10}S_2$: 533.1510 ($M + H^+$): found: 533.1515.

1,4-Anhydro-2,3,5,6-di-O-isopropylidene-1-[(S)-[(2′R,3′S,4′R,5′R)-2′,4′-benzylidenedioxy-5′,6′-isopropylidenedioxy-3′-(sulfooxy)hexyl]selenonio]-D-allitol inner salt (33)

The reaction of compound **15** (500 mg, 1.63 mmol) with the cyclic sulfate **20** (730 mg, 1.96 mmol) in HFIP (2.0 mL) for 12 h at 80–85 °C gave compound **33** as a colourless, amorphous solid (770 mg, 70% based on **15**). $[\alpha]^{22}_D$ +8° (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 7.58–7.32 (m, 5H, H-Arom.), 5.90 (s, 1H, C*H*Ph), 5.63 (ddd, 1H, $J_{2,3}$ = 5.4 Hz, H-2), 5.26 (dd, 1H, H-3), 4.92 (m, 1H, H-2′), 4.82 (ddd, 1H, $J_{5,6b}$ = 7.7 Hz, $J_{5,6a}$ = 4.9 Hz, $J_{4,5}$ = 3.2 Hz, H-5), 4.62 (dd, 1H, $J_{1'a,1'b}$ = 12.2 Hz, $J_{1'b,2'}$ = 5.9 Hz, H-1′ b), 4.59–4.57 (m, 2H, H-3′, H-4), 4.46 (ddd, 1H, $J_{4',5'}$ = 2.3 Hz, $J_{5',6'a}$ = 8.1 Hz, $J_{5',6'b}$ = 6.8 Hz, H-5′), 4.40 (m, 1H, H-4′), 4.29 (dd, 1H, $J_{6'a,6'b}$ = 8.5 Hz, H-6′b), 4.28 (dd, 1H, H-6b), 4.18 (dd, 1H, H-1′a), 4.16 (dd, 1H, H-6′a), 4.08 (dd, 1H, $J_{6a,6b}$ = 9.5 Hz, H-6a), 3.76 (dd, 1H, $J_{1a,1b}$ = 14.1 Hz, $J_{1b,2}$ = 5.4 Hz, H-1b), 3.60 (dd, 1H, H-1a), 1.59, 1.43, 1.36, 1.33, 1.31, 1.29, 1.28 (6 s, 18H, 6 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 138.2, 129.1, 128.4 and 126.3 (C-Ar), 111.3, 110.6, 107.5 (3 × $(CH_3)_2C(OR)_2$), 100.6 (*C*HPh), 88.1 (C-2), 85.9 (C-3), 78.9 (C-4′), 76.5 (C-5′), 74.8 (C-5), 74.0 (C-2′), 71.1 (C-3′), 69.1 (C-4), 67.1 (C-6), 64.6 (C-6′), 43.9 (C-1′), 43.6 (C-1), 26.0, 25.7, 25.6, 25.5, 23.4, 22.5 (6 × *C*H_3). Anal. calcd. for $C_{28}H_{40}O_{12}SSe$: C 49.48, H 5.93; found: C 49.16, H 6.09.

1,4-Anhydro-2,3,5,6-di-O-isopropylidene-1-[(S)-[(2′R,3′S,4′R,5′R)-2′,4′-benzylidenedioxy-5′,6′-isopropylidenedioxy-3′-(sulfooxy)hexyl]sulfonio]-D-allitol inner salt (34)

The reaction of compound **16** (500 mg, 1.92 mmol) with the cyclic sulfate **20** (860 mg, 2.30 mmol) in HFIP (2.0 mL) for 12 h at 90–95 °C gave compound **34** as a colourless, amorphous solid (1.0 g, 82% based on **16**). $[\alpha]^{22}_D$ +5.4° (*c* 0.1, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 7.60–7.38 (m, 5H, H-Arom.), 5.89 (s, 1H, C*H*Ph), 5.50 (ddd, 1H, H-2), 5.26 (dd, 1H, $J_{2,3}$ = 5.8 Hz, H-3), 4.88 (ddd, 1H, $J_{2',3'}$ = 5.0 Hz, $J_{1'b,2'}$ = 5.0 Hz, $J_{1'a,2'}$ = 2.1 Hz, H-2′), 4.83 (ddd, 1H, $J_{5,6b}$ = 2.8 Hz, $J_{5,6a}$ = 5.1 Hz, $J_{4,5}$ = 7.6 Hz, H-5), 4.59 (dd, 1H, $J_{3,4}$ = 2.4 Hz, H-4), 4.57–4.52 (m, 2H, H-1′b, H-3′), 4.50 (ddd, 1H, $J_{4',5'}$ = 2.1 Hz, $J_{5',6'a}$ = 9.1 Hz, $J_{5',6'b}$ = 7.1 Hz, H-5′), 4.42 (dd, 1H, $J_{3',4'}$ = 1.8 Hz, H-4′), 4.33 (dd, 1H, H-6′b), 4.30 (dd, 1H, $J_{5,6b}$ = 2.8 Hz, H-6b), 4.28 (m, 1H, H-1′a), 4.18 (dd, 1H, $J_{6'a,6'b}$ = 8.4 Hz, H-6′a), 4.11 (dd, 1H, $J_{6a,6b}$ = 9.6 Hz, H-6a), 3.90 (dd, 1H, $J_{1b,2}$ = 5.4 Hz, H-1b), 3.75 (dd, 1H, $J_{1a,1b}$ = 14.3 Hz, H-1a), 1.61, 1.43, 1.37, 1.30, 1.29, 1.28 (6 s, 18H, 6 × CH_3). ^{13}C NMR ($(CD_3)_2O$) δ: 138.2, 129.1, 128.4, 126.3 (C-Ar), 112.1, 110.9, 107.5 (3 × $(CH_3)_2C(OR)_2$), 100.7 (*C*HPh), 86.2 (C-2), 84.5 (C-3), 79.0 (C-4), 76.7 (C-5′), 74.7 (C-5), 74.1 (C-2′), 70.3 (C-3′), 70.0 (C-4′), 67.1 (C-6), 64.6 (C-6′), 47.9 (C-1), 46.1 (C-1′), 23.9, 25.6, 25.5, 25.4, 23.4, 22.4 (6 × *C*H_3). Anal. calcd. for $C_{28}H_{40}O_{12}S_2$: C 53.15, H 6.37; found: C 52.92, H 6.17.

1,4-Anhydro-2,3,5,6-di-O-isopropylidene-1-[(S)-[(2′R,3′S,4′R,5′R)-2′,4′-benzylidenedioxy-5′,6′-isopropylidenedioxy-3′-(sulfooxy)hexyl]selenonio]-L-allitol inner salt (35)

The reaction of compound **17** (500 mg, 1.63 mmol) with the cyclic sulfate **20** (730 mg, 1.96 mmol) in HFIP (2.0 mL) for 12 h at 80–85 °C gave compound **35** as a colourless, amorphous solid (740 mg, 67% based on **17**). $[\alpha]^{22}_D$ –12 (*c* 1, CH_2Cl_2). ^{1}H NMR ($(CD_3)_2O$) δ: 7.60–7.38 (m, 5H, H-Arom.), 5.92 (s, 1H, C*H*Ph), 5.55 (ddd, 1H, H-2), 5.21 (dd, 1H, $J_{2,3}$ = 5.4 Hz, $J_{3,4}$ = 1.8 Hz, H-3), 4.96–4.92 (m, 1H, H-2′), 4.60 (dd, 1H, H-3′), 4.53 (dd, 1H, $J_{1'b,2'}$ = 6.4 Hz, $J_{1'b,1'a}$ = 12.2 Hz, H-1′ b), 4.45 (ddd, 1H, $J_{4,5}$ = 2.3 Hz, $J_{5,6'a}$ = 9.2 Hz, $J_{5,6'b}$ = 6.9 Hz, H-5′), 4.41 (dd, 1H, H-4′), 4.40–4.36 (m, 1H, H-5), 4.34 (dd, 1H, $J_{6'a,6'b}$ = 8.6 Hz, H-6′b), 4.24–4.18 (m, 3H, H-4, H-1′a, H-6′a), 3.99 (dd, 1H, 1H, $J_{5,6b}$ = 7.3 Hz, $J_{6a,6b}$ = 9.3 Hz, H-6b), 3.96 (dd, 1H, $J_{1b,2}$ = 5.2 Hz, H-1b), 3.90 (dd, 1H, $J_{1a,1b}$ = 14.2 Hz, H-1a), 3.76 (dd, 1H, $J_{5,6a}$ = 5.2 Hz, H-6a), 1.59, 1.39, 1.35, 1.30, 1.29, 1.25 (6 s, 18H, 6 × C*H*$_3$). ^{13}C NMR ($(CD_3)_2O$) δ: 142.9, 133.9, 133.1, 131.0 (C-Ar), 116.1, 115.3, 112.1 (3 × $(CH_3)_2C(OR)_2$), 105.0 (*C*HPh), 91.5 (C-3), 91.0 (C-2), 83.4 (C-4′), 81.2 (C-5′), 78.7 (C-5), 78.5 (C-2′), 75.5 (C-3′), 72.3 (C-4), 71.6 (C-6), 69.3 (C-6′), 49.3 (C-1), 48.0 (C-1′), 30.7, 30.6, 30.3, 30.2, 28.1, 27.5 (6 × *C*H_3). Anal. calcd. for $C_{28}H_{40}O_{12}SSe$: C 49.48, H 5.93; found: C 49.31, H 5.90.

1,4-Anhydro-2,3,5,6-di-O-isopropylidene-1-[(S)-[(2′R,3′S,4′R,5′R)-2′,4′-benzylidenedioxy-5′,6′-isopropylidenedioxy-3′-(sulfooxy)hexyl]sulfonio]-L-allitol inner salt (36)

The reaction of compound **18** (500 mg, 1.92 mmol) with the cyclic sulfate **20** (860 mg, 2.30 mmol) in HFIP (2.0 mL) for 12 h at 90–95 °C gave compound **36** as a colourless, amorphous solid (960 mg, 77% based on **18**). $[\alpha]^{22}_D$ –15° (*c* 0.5, CH_2Cl_2). ^{1}H NMR (CD_2Cl_2) δ: 7.56–7.40 (m, 5H, H-Arom.), 5.76 (s, 1H, C*H*Ph), 5.19 (ddd, 1H, H-2), 4.98 (dd, 1H, $J_{2,3}$ = 5.7 Hz, H-3), 4.68–4.62 (m, 2H, H-2′, H-3′), 4.51 (ddd, 1H, H-5′), 4.42 (dd, 1H, $J_{1'b,2'}$ = 5.7 Hz, $J_{1'b,1'a}$ = 13.5 Hz, H-1′b), 4.28 (dd, 1H, $J_{1'a,2'}$ = 2.3 Hz, H-1′a), 4.28–4.25 (m, 1H, H-5), 4.25–4.18 (m, 3H, H-6′a, H-6′b, H-4′), 4.14 (m, 1H, H-4), 3.90 (dd, 1H, $J_{1a,1b}$ = 15.4 Hz, H-1b), 3.86 (dd, 1H, $J_{1a,2}$ = 4.6 Hz, H-1a), 3.86 (dd, 1H, 1H, $J_{5,6b}$ = 7.8 Hz, H-6b), 3.71 (dd, 1H, $J_{5,6a}$ = 5.1 Hz, $J_{6a,6b}$ = 9.5 Hz, H-6a), 1.62, 1.39, 1.38, 1.37, 1.34, 1.24 (6 s, 18H, 6 × C*H*$_3$). ^{13}C NMR (CD_2Cl_2) δ: 137.4, 129.7, 128.6, 126.3 (C-Ar), 112.7, 111.5, 108.5 (3 × $(CH_3)_2C(OR)_2$), 100.9 (*C*HPh), 85.2 (C-2), 84.8 (C-3), 79.1 (C-4′), 75.5 (C-5′), 74.3 (C-5), 74.0 (C-3′), 70.5 (C-2′), 69.8 (C-4), 67.0 (C-6), 65.0 (C-6′), 47.8 (C-1), 45.9 (C-1′), 26.4, 26.1, 25.9, 25.5, 23.3, 22.8 (6 × *C*H_3). Anal. calcd. for $C_{28}H_{40}O_{12}S_2$: C 53.15, H 6.37; found: C 53.36, H 6.41.

General procedure for the deprotection of the coupled products to yield the final compounds 7–14

The protected coupled products **29–36** were dissolved in CH_2Cl_2 (2 mL), TFA (10 mL) was then added, and the mixture was stirred for 6–8 h at RT. The progress of the reaction was followed by TLC analysis of the aliquots (EtOAc–MeOH–H_2O, 7:3:1). When the starting material had been consumed, the TFA and CH_2Cl_2 were removed under reduced pressure. The residue was rinsed with CH_2Cl_2 (4 × 2 mL) and the CH_2Cl_2 was decanted to remove the cleaved protecting groups. The remaining gum was dissolved in water and purified by column chromatography (EtOAc and EtOAc–MeOH, 2:1) to give the purified compounds **7–10** as colourless, amorphous, and hygroscopic solids. In the cases of **33–36**, the benzylidene groups were not completely cleaved. The residue was then dissolved in 80% AcOH (10 mL) and Pd–C (10%, 200 mg, in two portions) was added and the reaction mixture was subjected to hydrogenolysis for 48 h at RT. After filtering the Pd–C, the filtrate was mixed with water (100 mL) and the solvents were removed under reduced pressure. The remaining gum was dissolved in water and purified by column chromatography (EtOAc and EtOAc–MeOH, 2:1) to give the purified compounds **11–14** as colourless, amorphous, and hygroscopic solids.

1,4-Anhydro-1-[(S)-[(2′S,3′S)-2′,4′*-dihydroxy-3′-(sufooxy)butyl]selenonio]-*D-allitol inner salt (7)

To a solution of **29** (500 mg, 0.86 mmol) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **7** as a colourless, amorphous, and hygroscopic solid (202 mg, 57%). $[\alpha]^{22}_D$ +54° (*c* 2, H_2O). ^{1}H NMR (D_2O) δ: 4.74 (m, 1H, H-2), 4.34 (dd, 1H, $J_{2,3}$ = 9.1 Hz, $J_{3,4}$ = 3.1 Hz, H-3), 4.28 (ddd, 1H, H-3′), 4.25–4.18 (m, 2H, H-2′, H-5), 4.05 (dd, 1H, $J_{4,5}$ = 4.3 Hz, H-4), 3.97 (dd, 1H, $J_{1'b,2'}$ = 3.6 Hz, $J_{1'a,1'b}$ = 12.6 Hz, H-1′b), 3.82 (dd, 1H, $J_{3',4'b}$ = 6.4 Hz, H-4′b), 3.80 (dd, 1H, $J_{1'a,2'}$ = 3.2 Hz, H-1′a), 3.73 (dd, 1H, $J_{3',4'a}$ = 3.3 Hz, 1H, $J_{4'a,4'b}$ = 12.8 Hz, H-4′a), 3.68 (m, 2H, H-6a, H-6b), 3.55 (dd, 1H, $J_{1b,2}$ = 3.7 Hz, H-1b), 3.33 (dd, 1H, $J_{1a,2}$ = 2.1 Hz, $J_{1a,1b}$ = 13.1 Hz, H-1a). ^{13}C NMR (D_2O) δ: 80.8 (C-3′), 76.0 (C-2), 75.9 (C-3), 68.4 (C-5), 66.0 (C-2′), 65.1 (C-4), 63.4 (C-6), 60.1 (C-4′), 48.5 (C-1′), 40.5 (C-1). HRMS calcd. for $C_{10}H_{19}O_{10}SSe$: 410.9859 (M – H); found: 410.9861.

1,4-Anhydro-1-[(S)-[(2′S,3′S)-2′,4′*-dihydroxy-3′-(sufooxy)butyl]sulfonio]-*D-allitol inner salt (8)

To a solution of **30** (500 mg, 0.94 mmol) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **8** as a colourless, amorphous, and hygroscopic solid (240 mg, 69%). $[\alpha]^{22}_D$ +39° (*c* 2, H_2O). ^{1}H NMR (D_2O) δ: 4.63 (m, 1H, H-2), 4.48 (dd, 1H, $J_{2,3}$ = 8.7 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 4.36–4.30 (m, 2H, H-2′, H-5), 4.27 (ddd, 1H, H-3′), 4.12 (dd, 1H, $J_{1'b,2'}$ = 3.4 Hz, $J_{1'a,1'b}$ = 13.6 Hz, H-1′ b), 4.05 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 8.6 Hz, H-4), 3.86 (dd, 1H, $J_{3',4'b}$ = 2.8 Hz, H-4′b), 3.85 (dd, 1H, $J_{1'a,2'}$ = 8.3 Hz, H-1′a), 3.78 (dd, 1H, $J_{3',4'a}$ = 3.2 Hz, 1H, $J_{4'a,4'b}$ = 12.8 Hz, H-4′a), 3.70 (m, 2H, H-6a, H-6b), 3.69 (dd, 1H, $J_{1b,2}$ = 3.3 Hz, H-1b), 3.46 (dd, 1H, $J_{1a,2}$ = 1.6 Hz, $J_{1a,1b}$ = 14.4 Hz, H-1a). ^{13}C NMR (D_2O) δ: 79.8 (C-3′), 74.7 (C-2), 74.4 (C-3), 68.3 (C-2′), 65.6 (C-4), 65.5 (C-5), 63.0 (C-6), 59.9 (C-4′), 51.1 (C-1′), 44.2 (C-1). HRMS calcd. for $C_{10}H_{20}O_{10}S_2Na$: 387.0390 (M + Na); found: 387.0391.

1,4-Anhydro-1-[(S)-[(2′S,3′S)-2′,4′*-dihydroxy-3′-(sufooxy)butyl]selenonio]-*L-allitol inner salt (9)

To a solution of **31** (500 mg, 0.86 mmol) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **9** as a colourless, amorphous, and hygroscopic solid (216 mg, 61%). $[\alpha]^{22}_D$ –17° (*c* 0.5, H_2O). ^{1}H NMR (D_2O) δ: 4.77 (ddd, 1H, H-2), 4.42 (dd, 1H, $J_{2,3}$ = 8.8 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 4.33–4.25 (m, 2H, H-5, H-2′), 4.25–4.30 (ddd, 1H, H-3′), 4.13 (dd, 1H, $J_{4,5}$ = 8.7 Hz, H-4), 3.97 (dd, 1H, $J_{1'b,2'}$ = 4.0 Hz, $J_{1'a,1'b}$ = 12.4 Hz, H-1′b), 3.94 (dd, 1H, $J_{1'a,2'}$= 8.7 Hz, H-1′a), 3.83 (dd, 1H, $J_{3',4'b}$ = 3.2 Hz, H-4′b), 3.75 (dd, 1H, $J_{3',4'a}$ = 3.2 Hz, 1H, $J_{4'a,4'b}$ = 12.8 Hz, H-4′a), 3.68 (d, 2H, H-6a, H-6b), 3.58 (dd, 1H, $J_{1b,2}$ = 8.5 Hz, H-1b), 3.36 (dd, 1H, $J_{1a,2}$ = 2.2 Hz, $J_{1a,1b}$ = 13.3 Hz, H-1a). ^{13}C NMR (D_2O) δ: 81.0 (C-3), 75.8 (C-2), 75.5 (C-3), 68.7 (C-2), 66.5 (C-5), 65.5 (C-4), 63.4 (C-6), 60.0 (C-4), 48.4 (C-1), 40.4 (C-1). HRMS calcd. for $C_{10}H_{19}O_{10}SSe$: 410.9859 (M – H); found: 410.9857.

1,4-Anhydro-1-[(S)-[(2′S,3′S)-2′,4′*-dihydroxy-3′-(sufooxy)butyl]sulfonio]-*L-allitol inner salt (10)

To a solution of **32** (500 mg, 0.94 mmol) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **10** as a colourless, amorphous, and hygroscopic solid (223 mg, 65%). $[\alpha]^{22}_D$ +6° (*c* 0.5, H_2O). ^{1}H NMR (D_2O) δ: 4.60 (m, 1H, H-2), 4.47 (dd, 1H, $J_{2,3}$ = 8.3 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 4.32 (ddd, 1H, H-5), 4.28–4.24 (m, 1H, H-2′), 4.22 (ddd, 1H, H-3′), 4.07 (dd, 1H, $J_{4,5}$ = 8.5 Hz, H-4), 3.98 (dd, 1H, $J_{1'b,2'}$ = 3.5 Hz, H-1′b), 3.92 (dd, 1H, $J_{1'a,2'}$ = 8.8 Hz, $J_{1'a,1'b}$ = 13.6 Hz, H-1′a), 3.86 (dd, 1H, $J_{3',4'b}$ = 9.5 Hz, H-4′b), 3.74 (dd, 1H, $J_{3',4'a}$ = 3.2 Hz, 1H, $J_{4'a,4'b}$ = 12.8 Hz, H-4′a), 3.66 (d, 2H, H-6a, H-6b), 3.64–3.61 (m, 1H, H-1b), 3.44 (dd, 1H, $J_{1a,2}$ = 9.7 Hz, $J_{1a,1b}$ = 14.3 Hz, H-1a). ^{13}C NMR (D_2O) δ: 80.5 (C-3′), 74.6 (C-2), 74.5 (C-3), 68.8 (C-5), 66.6 (C-2′), 66.2 (C-4), 63.1 (C-6), 59.9 (C-4′), 50.9 (C-1′), 44.1 (C-1). HRMS calcd. for $C_{10}H_{20}O_{10}S_2Na$: 387.0390 (M + Na); found: 387.0389.

1,4-Anhydro-1-[(S)-[(2′R,3′S,4′R,5′R)-2′,4′,5′,6′*-tetrahydroxy-3′-(sufooxy)hexyl]selenonio]-*D-allitol inner salt (11)

To a solution of **33** (600 mg, 0.88 mmol) in CH_2Cl_2 (2 mL) was added TFA (10 mL). After removing the cleaved protecting groups, the remaining gum was then dissolved in AcOH (10 mL), Pd–C (10%, 100 mg) was added, and the reaction mixture was subjected to hydrogenolysis to give compound **11** as a colourless, amorphous, and hygroscopic solid (157 mg, 38%). $[\alpha]^{22}_D$ –8° (*c* 0.5, H_2O). ^{1}H NMR (D_2O) δ: 4.80 (m, 1H, H-2), 4.59 (dd, 1H, H-3′), 4.48 (ddd, 1H, H-2′), 4.43 (dd, 1H, $J_{2,3}$ = 8.9 Hz, $J_{3,4}$ = 2.8 Hz, H-3), 4.31 (ddd, 1H, H-5), 4.14 (dd, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 4.08 (dd, 1H, $J_{1'b,2'}$ = 9.9 Hz, $J_{1'a,1'b}$ = 12.2 Hz, H-1′b), 3.95 (dd, 1H, $J_{1'a,2'}$ = 3.5 Hz, H-1′a), 3.84–3.74 (m, 3H, H-4′, H-5′, H-6′b), 3.72 (d, 2H, H-6a, H-6b), 3.62–3.57 (m, 2H, H-6′a, H-1b), 3.38 (dd, 1H, $J_{1a,2}$ = 1.9 Hz, $J_{1a,1b}$ = 13.0 Hz, H-1a). ^{13}C NMR (D_2O) δ: 78.5 (C-3′), 75.8 (C-2), 75.7 (C-3), 70.7 (C-5′), 69.6 (C-4′), 68.8 (C-5), 68.1 (C-2′), 65.5 (C-4), 63.4 (C-

6′), 62.8 (C-6), 47.7 (C-1′), 40.2 (C-1). HRMS calcd. for $C_{12}H_{25}O_9Se$: 393.0658 (M + H – SO_3); found: 393.0656.

1,4-Anhydro-1-[(S)-[(2′R,3′S,4′R,5′R)-2′,4′,5′,6′-tetrahydroxy-3′-(sufooxy)hexyl]sulfonio]-D-allitol inner salt (12)

To a solution of **34** (500 mg, 0.79 mmol) in CH_2Cl_2 (2 mL) was added TFA (10 mL). After removing the cleaved protecting groups, the remaining gum was then dissolved in AcOH (10 mL), Pd–C (10%, 100 mg) was added, and the reaction mixture was subjected to hydrogenolysis to give compound **12** as a colourless, amorphous, and hygroscopic solid (140 mg, 42%). $[\alpha]^{22}_D$ –32° (*c* 2, H_2O). ^1H NMR (D_2O) δ: 4.53 (m, 1H, H-2), 4.51 (dd, 1H, $J_{2',3'}$ = 5.1 Hz, $J_{3',4'}$ = 1.1 Hz, H-3′), 4.44 (ddd, 1H, H-2′), 4.26 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 3.1 Hz, H-3), 4.12 (ddd, 1H, H-5), 3.95 (dd, 1H, $J_{1b,2}$ = 10.8 Hz, $J_{1'a,1'b}$ = 13.4 Hz, H-1′b), 3.88 (dd, 1H, $J_{1'a,2'}$ = 2.8 Hz, H-1′a), 3.86 (dd, 1H, $J_{4,5}$ = 8.2 Hz, H-4), 3.74 (dd, 1H, $J_{4',5'}$ = 9.2 Hz, H-4′), 3.72 (dd, 1H, $J_{5,6b}$ = 3.1 Hz, $J_{6a,6b}$ = 11.9 Hz, H-6b), 3.67 (dd, 1H, $J_{5',6'b}$ = 2.5 Hz, $J_{6'a,6'b}$ = 11.8 Hz, H-6′b), 3.66–3.63 (m, 1H, H-5′), 3.59 (dd, 1H, $J_{5,6a}$ = 3.9 Hz, H-6a), 3.52–3.46 (m, 3H, H-1a, H-1b, H-6′a). ^{13}C NMR (D_2O) δ: 77.7 (C-3′), 76.1 (C-3), 72.8 (C-2), 70.4 (C-5′), 68.9 (C-4′), 67.8 (C-2′), 67.4 (C-5), 64.6 (C-6), 64.3 (C-4), 62.7 (C-6′), 49.3 (C-1′), 44.4 (C-1). HRMS calcd. for $C_{12}H_{25}O_9S$: 345.1214 (M + H – SO_3); found: 345.1214.

1,4-Anhydro-1-[(S)-[(2′R,3′S,4′R,5′R)-2′,4′,5′,6′-tetrahydroxy-3′-(sufooxy)hexyl]selenonio]-L-allitol inner salt (13)

To a solution of **35** (600 mg, 0.88 mmol) in CH_2Cl_2 (2 mL) was added TFA (10 mL). After removing the cleaved protecting groups, the remaining gum was then dissolved in AcOH (10 mL), Pd–C (10%, 100 mg) was added, and the reaction mixture was subjected to hydrogenolysis to give compound **13** as a colourless, amorphous, and hygroscopic solid (197 mg, 47%). $[\alpha]^{22}_D$ –22° (*c* 1, H_2O). ^1H NMR (D_2O) δ: 4.76 (ddd, 1H, H-2), 4.57 (dd, 1H, $J_{2',3'}$ = 5.2 Hz, H-3′), 4.50 (ddd, 1H, H-2′), 4.37 (dd, 1H, $J_{2,3}$ = 9.1 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 4.25 (ddd, 1H, H-5), 4.06 (dd, 1H, $J_{4,5}$ = 7.9 Hz, H-4), 4.00 (dd, 1H, $J_{1'b,2'}$ = 4.0 Hz, $J_{1'a,1'b}$ = 12.4 Hz, H-1′b), 3.89 (dd, 1H, $J_{1'a,2'}$ = 9.0 Hz, H-1′a), 3.84–3.79 (m, 1H, H-5′), 3.72 (d, 2H, H-6a, H-6b), 3.63 (dd, 1H, H-4′), 3.60–3.50 (m, 3H, H-6′b, H-6′a, H-1b), 3.34 (dd, 1H, $J_{1a,2}$ = 2.7 Hz, $J_{1a,1b}$ = 13.0 Hz, H-1a). ^{13}C NMR (D_2O) δ: 78.3 (C-3′), 76.0 (C-3), 75.4 (C-2), 73.1 (C-5′), 69.8 (C-4′), 68.2 (C-5), 67.1 (C-2′), 64.7 (C-4), 62.8 (C-6), 62.6 (C-6′), 47.4 (C-1′), 40.2 (C-1). HRMS calcd. for $C_{12}H_{25}O_9Se$: 393.0658 (M + H – SO_3); found: 393.0656.

1,4-Anhydro-1-[(S)-[(2′R,3′S,4′R,5′R)-2′,4′,5′,6′-tetrahydroxy-3′-(sufooxy)hexyl]sulfonio]-L-allitol inner salt (14)

To a solution of **36** (600 mg, 0.95 mmol) in CH_2Cl_2 (2 mL) was added TFA (10 mL). After removing the cleaved protecting groups, the remaining gum was then dissolved in AcOH (10 mL), Pd–C (10%, 100 mg) was added, and the reaction mixture was subjected to hydrogenolysis to give compound **14** as a colourless, amorphous, and hygroscopic solid (165 mg, 41%). $[\alpha]^{22}_D$ –32° (*c* 1, H_2O). ^1H NMR (D_2O) δ: 4.58 (ddd, 1H, H-2), 4.55 (dd, 1H, $J_{2',3'}$ = 4.6 Hz, $J_{3',4'}$ = 0.7 Hz, H-3′), 4.49 (ddd, 1H, H-2′), 4.42 (dd, 1H, $J_{2,3}$ = 8.7 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 4.25 (ddd, 1H, H-5), 4.03 (dd, 1H, $J_{1'b,2'}$ = 3.8 Hz, H-1′b), 4.04–3.99 (m, 1H, H-4), 3.92 (dd, 1H, $J_{1'a,2'}$ = 9.1 Hz, $J_{1'a,1'b}$ = 13.5 Hz, H-1′a), 3.79 (dd, 1H, $J_{4',5'}$ = 8.0 Hz, H-4′), 3.68 (dd, 1H, $J_{5',6'b}$ = 2.4 Hz, H-6′b), 3.68–3.64 (m, 1H, H-5′), 3.67 (d, 2H, H-6a, H-6b), 3.61 (dd, 1H, $J_{1b,2}$ = 3.2 Hz, $J_{1a,1b}$ = 14.2 Hz, H-1b), 3.52 (dd, 1H, $J_{5',6'a}$ = 5.6 Hz, $J_{6'a,6'b}$ = 11.5 Hz, H-6′a), 3.44 (dd, 1H, $J_{1a,2}$ = 8.0 Hz, H-1a). ^{13}C NMR (D_2O) δ: 77.7 (C-3′), 74.8 (C-3), 74.4 (C-2), 70.5 (C-5′), 69.1 (C-4′), 68.3 (C-5), 67.0 (C-2′), 65.0 (C-4), 62.8 (C-6′), 62.7 (C-6), 49.9 (C-1′), 43.9 (C-1). HRMS calcd. for $C_{12}H_{25}O_9S$: 345.1214 (M + H – SO_3); found: 345.1211.

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Synthesis of an 11-*cis*-locked biotinylated retinoid for sequestering 11-*cis*-retinoid binding proteins[1]

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Abstract: The synthesis of a seven-membered ring locked analogue of 11-*cis*-retinol, tethered to a cross-linking moiety on C-15 and a lysine-extended biotin on the C-3, was accomplished for its utilization as a probe to fish out retinol binding proteins that may be involved in the reisomerization of retinal from all-*trans* to 11-*cis* in the visual cycle.

Key words: retinoids, biotin, 11-*cis*-locked, cross-linking, retinol binding proteins.

Résumé : La synthèse d'un analogue de 11-*cis*-rétinol sous la forme d'un anneau verrouillé, comportant sept membres, attachés en partie, au C-15, avec un groupe ayant la possibilité de se liér aux protéines a été réalisée. En plus, l'analogue est attaché de l'autre côté sur le C-3, avec une lysine biotine étendue. Cette synthèse a été réalisée afin d'utilizer le composé comme agent détecteur des protéines qui portent des rétinols et qui pourraient être impliquées dans la réisomerization du all-*trans* retinal au 11-*cis* dans le cycle de vision.

Mots clés : rétinoides, biotine, 11-*cis*-verrouillé, liés, protéines qui portent des rétinols.

Introduction

The basic process of vision, first elucidated by Wald (1), involves the light-triggered isomerization of retinal (or vitamin A aldehyde) from its 11-*cis* conformation to the all-trans conformation. Retinal, in its 11-*cis* geometry, is bound by the apoprotein opsin, a G-protein coupled receptor, forming a protonated Schiff base with Lys296, present in Helix G of the seven-membered transmembrane protein,which generates rhodopsin, the active photoreceptor unit in the cones and rods of eyes (2, 3). Upon absorption of a photon by 11-*cis*-retinal, the retinoid undergoes an isomerization to the all-trans geometry, resulting in a conformational change in the protein that leads to the activation of the G protein, which ultimately results in vision (4). The all-*trans*-retinal is subsequently hydrolyzed off the lysine residue, freeing the protein for a fresh 11-*cis*-retinal molecule. The completion of the visual cycle is ultimately dependent on the less well-understood proteins that are capable of binding all *trans*-retinoids and converting them to the 11-*cis*-retinal geometry (5). The latter proteins are collectively termed retinol binding proteins (RBPs). Their crucial involvement in the visual cycle warrants the need for the development of tools that enable their isolation and purification for further studies of their detailed function.

We have previously synthesized (6) a biotin-linked 11-*cis*-retinol analogue (structure **1** without the trimethylene bridge linking C-10 and C-13), as well as the all-*trans*-retinol analogue, **1a**. The latter derivative, bearing a biotin moiety and a chloroacetate cross-linking unit, enabled us to successfully isolate and characterize certain retinol binding proteins (7). We attempted to use the biotin-linked 11-*cis* analogue in the isolation of RBPs involved in the isomerization of all-*trans*-retinal to 11-*cis*-retinal. Despite the synthetic accomplishment (6), the retinoid was prone to undergoing an inevitable isomerization from 11-*cis* to all-trans upon incubation in the retinal pigment epithelial (RPE) cells, thus losing its affinity toward the RBPs of interest. To circumvent this problem, we resorted to ret7 (Fig. 1), the first of the 11-*cis*-locked analogues, which is comprised of a seven-membered ring locking the double bond at the C-11 position into a *cis*-conformation (8). This retinoid was particularly useful because it retains the full chromophore properties of native 11-*cis*-retinal and readily forms, with bovine opsin, the nonbleachable pigment, rhodopsin 7 or rh7. Both the UV–vis λ_{max} of 490 nm and the CD maxima at 330 and 488 nm

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Scheme 1. Retrosynthetic analysis for the biotinylated retinoid **1**.

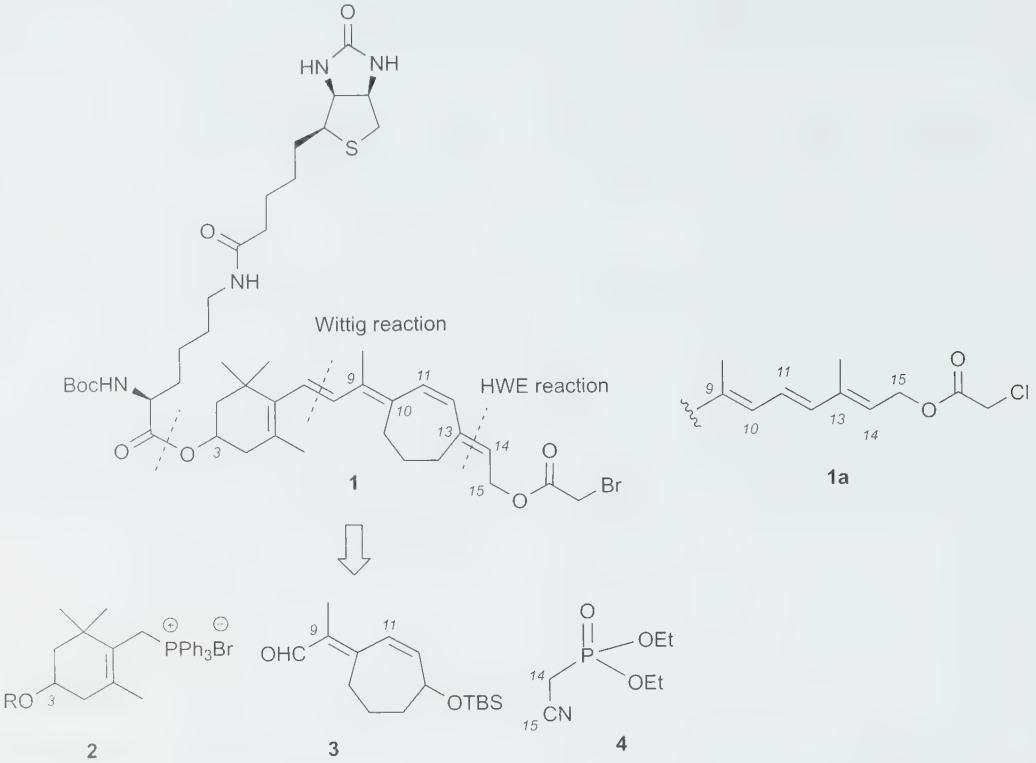
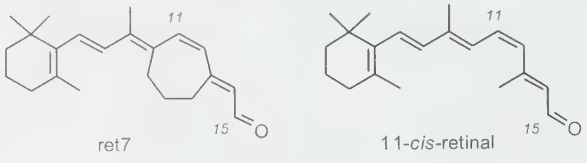


Fig. 1. The structures of ret7 and the native 11-*cis*-retinal.



(digitonin–phosphate buffer, pH 7) are similar to those of the native chromophore (UV–vis λ_{max} at 500 nm and CD maxima at 340 and 490 nm), indicating that the binding sites are the same. These aspects have made this pigment a popular substrate for various spectroscopic measurements (9–11).

We hereby report the synthesis of 11-*cis*-locked retinoid **1** bearing an appropriate functionality for isolation through cross-linking and which possesses the additional advantage of resisting isomerization under light conditions as well as in the media of RPE cells.

The target structure **1** has significant features that merit highlighting. It has the basic 11-*cis*-retinoid structure that can bind selectively to certain RBPs involved in the reisomerization of all-*trans*- to 11-*cis*-retinal. It also harbors an active cross-linking unit, the bromoacetate functionality, which can form a stable covalent bond with the RBPs and it also has the (Boc)Lys-biotinyl linker anchored at C-3, which will facilitate isolation of the covalently linked protein via an avidin affinity chromatography. Moreover, the ret7 moiety in the structure ensures its stability against light and (or) the RPE cell medium. Based on our earlier studies, the presence of the seven-membered ring would not prevent the retinoid from binding into the protein (8, 12, 13).

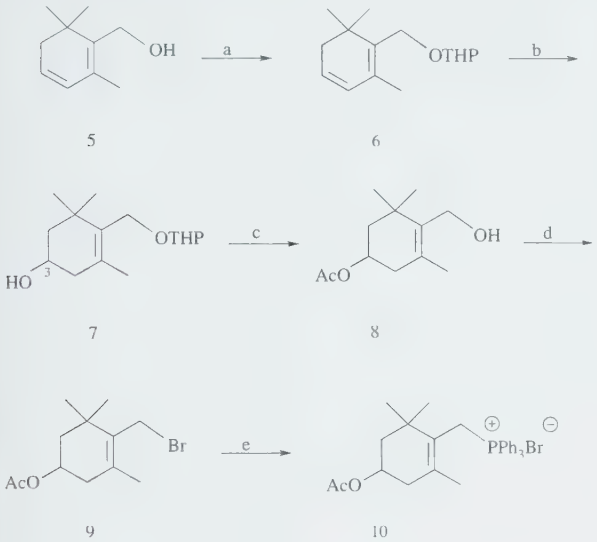
Results and discussion

The retrosynthetic logic for **1** is shown in Scheme 1. It stems from our earlier work conducted on the seven-membered ring unit **3**, synthesized from 2-cyclohepten-1-one in five steps (14). The hydroxylated β-ionone ring structure can be introduced by employing a Wittig reaction between aldehyde **3** and synthon **2**, the latter being prepared from dehydro-β-cyclocitral (also known as safranal) in seven steps as outlined in Scheme 2. The Horner–Wadsworth–Emmons (HWE) reaction can be used to install a nitrile group at the C-14 position with reagent **4**, followed by its reduction to the corresponding aldehyde, which would be subjected to further reduction to the corresponding primary alcohol onto which a bromoester can be esterified in the final stages.

Synthon **3** has been prepared from the commercially available 2-cyclohepten-1-one, according to our earlier report (14). The synthesis featured an allylic oxidation of 2-cyclohepten-1-one, a three-carbon homologation by HWE reaction with the reagent bearing the nitrile functionality, and lastly, a partial reduction of the nitrile to the corresponding aldehyde.

The synthesis of **10** (the synthon **2** unit) is outlined in Scheme 2. Dehydro-β-cyclocitrol (**5**), prepared from dehydro-β-cyclocitral (15), was protected as the tetrahydropyranyl (THP) ether (→**6**, 81%) and subsequently treated

Scheme 2. Reagents and conditions: (*a*) DHP, *p*-TsOH, CH_2Cl_2, 0 °C (81%); (*b*) 9-BBN, THF, Δ, then MeOH, NaOH, H_2O_2, 0 °C → 50 °C (55%); (*c*) (*i*) Ac_2O, pyridine, CH_2Cl_2, rt, (*ii*) *p*-TsOH, MeOH, rt (60%, two steps); (*d*) PPh_3, CBr_4, THF (94%); (*e*) PPh_3, benzene, Δ (quant.).]



with 9-borabicyclo[3.3.1]nonane (9-BBN) to undergo a hydroboration reaction affording the 3-hydroxy **7** in 55% yield. As in the case of the biotinylated all-trans analogue **1a** (6, 7), no attempts were made to resolve the C-3 enantiomers. The 3-hydroxy group was protected as the acetate by treatment with acetic anhydride (Ac_2O) – pyridine. The allylic hydroxy group was then liberated by acidic cleavage of the THP group to give alcohol **8**, which was transformed to the corresponding bromide **9** using triphenylphosphine (PPh_3) and carbon tetrabromide (94% yield). The phosphonium salt **10** was synthesized from **9** by treatment with PPh_3 under reflux conditions.

Scheme 3 shows the critical steps that assemble the retinoid from synthons **3** and **10**. A Wittig reaction between aldehyde **3** and phosphonium salt **10** afforded the desired tetraene **11a** (33%), along with a considerable amount of **11b** (40%). The trans geometry of the olefin thus formed was confirmed from the coupling constant (J = 16 Hz) observed for the H-7 and H-8 protons. The TBS group of **11a** was removed using tetrabutylammonium fluoride (TBAF) to give the free allylic alcohol, which, upon treatment with MnO_2, underwent smooth oxidation to afford the conjugated ketone **12** in 84% yield. A two-carbon extension through HWE reaction was carried out on ketone **12** with cyanomethylphoshonate (**4**) to afford the (*E*)-isomer **13** in 27% yield (the (*Z*)-isomer, 53%). The *E*/*Z* geometry was determined by NOE experiments for the H-12 and H-14 protons. Nitrile **13** was subjected to partial reduction with diisobutylaluminum hydride (DIBAH) to the corresponding aldehyde accompanied by an inevitable reductive cleavage of the acetate group at the C-3 position. After reprotection of the free alcohol with an acetyl group, resulting in **14**, the aldehyde was further reduced to the corresponding primary alcohol by treatment with sodium borohydride and was then protected as a TBS ether to afford **15**. Basic cleavage of the 3-acetyl group gave the corresponding 3-OH followed by esterification with biotinyl-(Boc)Lys-OH to give **16** (78% yield, two steps). The TBS group was deprotected, releasing the primary alcohol, which was eventually subjected to esterification with bromoacetic acid to afford the target structure **1** in 66% yield.

Preliminary studies directed towards isolation and characterization of RBPs employing **1** performed by Rando's group (Harvard Medical School, Boston, Massachusetts) have shown that some RBPs have been sequestered and identified. The results of the isolation and characterization of the RBPs using **1** will be reported in a subsequent manuscript.

Conclusion

The synthesis of biotinylated retinoid **1** was accomplished via a series of Wittig reactions, esterification of a (Boc)Lys-biotin on the 3-hydroxy position of the β-ionone ring, and the final attachment of the active bromoester cross-linking unit. The significance of the seven-membered ring lock is evident as the preliminary biological studies using this molecule have already proven the robust nature of the 11-*cis*-olefin unit. The target structure will be able to cross-link to RBPs that are involved in the crucial isomerization process that regenerates 11-*cis*-retinal. Avidin affinity chromatography will enable facile purification of the sequestered protein, and basic hydrolysis will release the isolated protein from the affinity column by cleaving the ester at the C-15 position. The purified protein can be further studied and characterized for the elucidation of its detailed function.

Experimental section

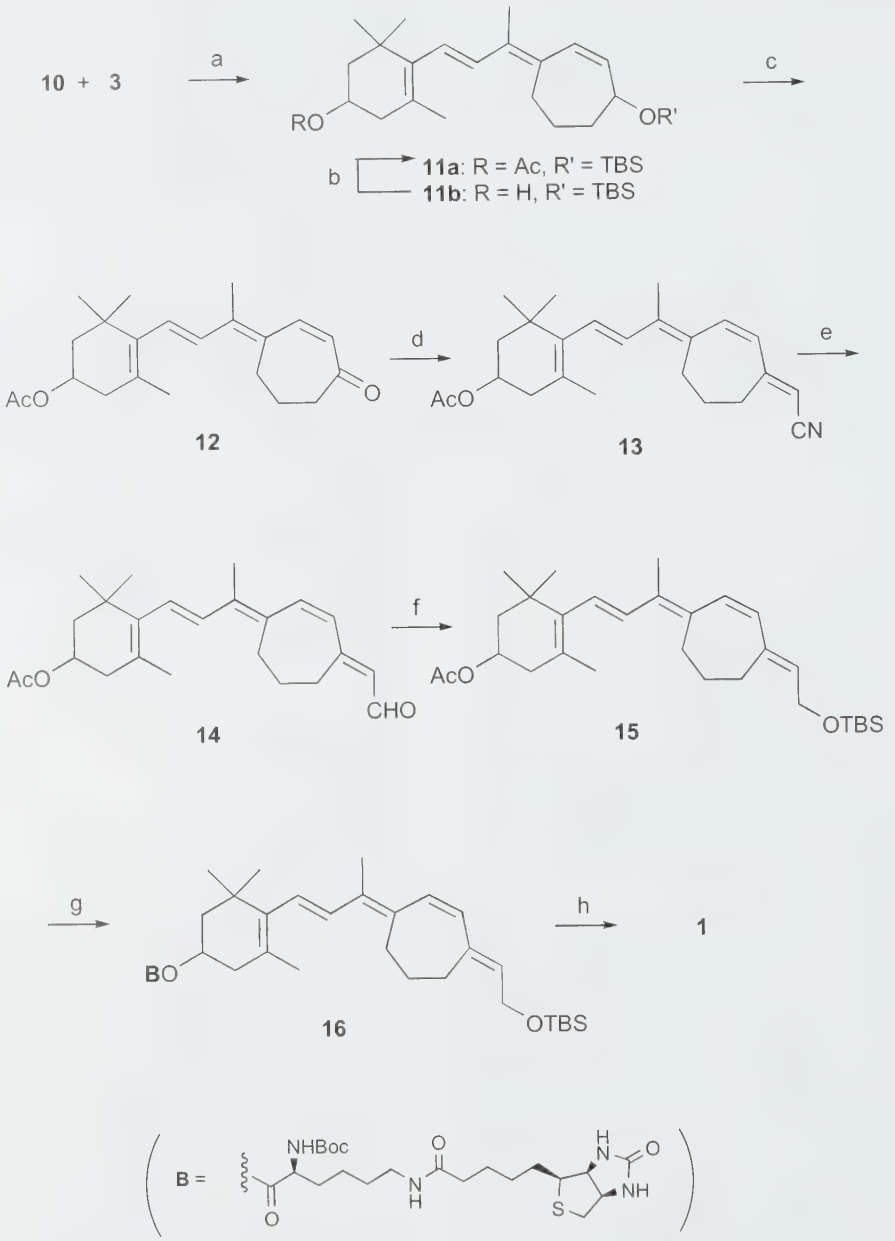
General considerations

^{1}H NMR spectra were measured on a Bruker DMX 400 or Bruker DPX 300 spectrometer (400 or 300 MHz). The chemical shifts are expressed in ppm downfield from the signal of tetramethylsilane, used as an internal standard in the solvent $CDCl_3$. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet), and br (broad). High resolution mass spectrometry (HRMS) were measured on a JEOL (Tokyo) JMS-HX110/110 tandem mass spectrometer equipped with a Xe beam FAB gun (6 kV), using 3-nitrobenzyl alcohol as a matrix. Analytical and preparative thin layer chromatography (TLC) was carried out using precoated silica gel plates (Merck silica gel $60F_{254}$). The silica gel used for column chromatography was 230–400 mesh (Merck). All reactions were carried out under an Ar atmosphere using predried solvents. Anhydrous CH_2Cl_2, Et_2O, and THF were obtained from the solvent purification system via passage through an activated alumina cartridge.

Tetrahydropyranyl safranol (6)

To a solution of safranol **5** (7.67 g, 50.4 mmol) in CH_2Cl_2 (100 mL) was added 3,4-dihydro-2*H*-pyran (DHP, 8.48 g, 101 mmol). The mixture was stirred and cooled to –10 °C and *p*-toluenesulfonic acid monohydrate (*p*-TsOH, 190 mg, 1.00 mmol) was then added. After 10 min of stirring, triethylamine (1.0 mL) was added to quench the reaction.

Scheme 3. Reagents and conditions: (*a*) *n*-BuLi, THF, –78 °C → rt, (for **11a**, 33%; for **11b**, 40%); (*b*) Ac_2O, pyridine, DMAP, rt for **11b** (63%); (*c*) (*i*) TBAF, THF, 0 °C → rt (99%), (*ii*) MnO_2, CH_2Cl_2, 0 °C → rt (84%); (*d*) **4**, NaH, THF, 0 °C → rt (*E*:*Z*, 27%:53%); (*e*) (*i*) DIBAH, Et_2O, –78 °C → 0 °C (82%), (*ii*) Ac_2O, pyridine, CH_2Cl_2, 0 °C → rt (50%); (*f*) (*i*) $NaBH_4$, MeOH–$CHCl_3$ (1:10), 0 °C, (*ii*) TBSCl, imidazole, CH_2Cl_2, 0 °C (70%, two steps); (*g*) (*i*) K_2CO_3, MeOH, 0 °C → rt, (*ii*) biotinyl (Boc)lys-OH (**B**-OH), EDC, DMAP, CH_2Cl_2, 0 °C → rt (78%, two steps); (*h*) (*i*) TBAF, THF, 0 °C → rt (60%), (*ii*) $BrCH_2COOH$, EDC, DMAP, 0 °C → rt (66%).



The mixture was poured into water (150 mL) and extracted with Et_2O (3 × 150 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 10:90) afforded the THP ether **6** (9.60 g, 40.8 mmol, 81%) as a colorless oil. ^{1}H NMR ($CDCl_3$, ppm) δ: 5.75 (2H), 4.61 (1H, brs), 4.31 (1H, d, *J* = 11.2 Hz), 4.07 (1H, d, *J* = 11.2 Hz), 3.91 (1H, m), 3.52 (1H, m), 2.05 (2H, s), 1.81 (3H, s), 1.81–1.69 (6H), 1.04, 1.01 (each 3H, s). ^{13}C NMR ($CDCl_3$, ppm) δ: 134, 129.9, 129.1, 126, 97.7, 63.4, 62.4, 40.3, 33.5, 31.0, 26.7 (2C), 25.9, 19.9, 18.4. FAB-HRMS calcd. for $C_{15}H_{24}O_2$ *m*/*z*: 236.1776 [M^+]; found: 236.1769.

Tetrahydropyranyl 3-hydroxysafranol (7)

To a solution of THP ether **6** (6.66 g, 28.2 mmol) in THF (40.0 mL), 9-BBN (0.5 mol/L solution in THF, 113 mL, 56.4 mmol) was added slowly over 20 min. The reaction

mixture was heated up to 60 °C and was stirred for 4 h. After the reaction mixture was cooled to room temperature, methanol (68.0 mL) and an aq. NaOH solution (3 mol/L, 9.4 mL) were added to it. Subsequently, H_2O_2 (30% solution, 8.0 mL) was added slowly to the stirring reaction mixture using an ice bath. The reaction mixture was heated for 2 h at 55 °C. The mixture was poured into water (100 mL) and extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 30:70) afforded a diastereomeric mixture of **7** (3.94 g, 15.5 mmol, 55%). The ^{1}H NMR spectra indicated that the sample consisted of a mixture of diastereomers (50:50). ^{1}H NMR ($CDCl_3$, ppm) δ: 4.55 (2 × 0.5H, dt, J = 3.2, 8.5 Hz), 4.26, 4.17, 3.80, 3.74 (each 0.5H, d, J = 10.7 Hz), 3.93–3.81 (0.5H × 2 × 2), 3.50 (0.5H × 2, m), 2.37 (0.5H × 2, brs), 2.27 (0.5H × 2, brdt), 2.01 (0.5H × 2, brdd), 1.78 (0.5H × 2, m), 1.69, 1.68 (each 1.5H, s), 1.70–1.62 (0.5H × 2 × 2), 1.56–1.40 (0.5H × 2 × 5), 1.06, 1.02, 1.00, 0.993 (each 1.5H, s). ^{13}C NMR ($CDCl_3$, ppm) δ: 134, 133, 131.5, 131.4, 98.9, 98.6, 64.9 (0.5C × 2), 63.5, 63.4, 62.4, 62.3, 48.2 (0.5C × 2), 42.3 (0.5C × 2), 36.8 (0.5C × 2), 30.7 (0.5C × 2), 29.4, 29.2, 28.7, 28.6, 25.5 (0.5C × 2), 19.7 (0.5C × 2), 19.69, 19.63. FAB-HRMS calcd. for $C_{15}H_{26}O_3$ *m/z*: 254.1882 [M$^+$]; found: 254.1891.

3-*O*-Acetoxysafranol (8)

To a solution of hydroxy **7** (1.00 g, 3.93 mmol) in pyridine (7.0 mL), acetic anhydride (3.5 mL) was added at 0 °C. The resultant mixture was stirred at room temperature. After 12 h of stirring, the mixture was azeotropically concentrated with toluene (×3) in vacuo. The crude sample was subjected to the next step without purification. The acetate was treated with a catalytic amount of *p*-TsOH (10.0 mg) in methanol (60.0 mL). The resultant mixture was allowed to stir for 12 h at room temperature. The mixture was neutralized with Et_3N (1.0 mL) and concentrated under reduced pressure. Silica gel purification of the residue (EtOAc–hexanes, 25:75) gave the 3-*O*-acetyl safranol **8** (576 mg, 2.72 mmol, 70%, in two steps). ^{1}H NMR ($CDCl_3$, ppm) δ: 4.97 (1H, m), 4.13, 4.07 (each 1H, d, J = 11.5 Hz), 2.35 (1H, dd, J = 5.7, 16.9 Hz), 2.04 (1H, dd, J = 9.4, 16.9 Hz), 2.00 (3H, s), 1.71 (1H, m) overlapping with 1.72 (3H, s), 1.52 (1H, t, J = 11.9 Hz), 1.45 (1H, br, CH_2OH), 1.09, 1.05 (each 3H, s). ^{13}C NMR ($CDCl_3$, ppm) δ: 170, 137, 127, 68.2, 58.2, 43.8, 38.2, 36.4, 29.2, 28.5, 21.5, 19.5.

3-*O*-Acetoxysafranyl bromide (9)

To a solution of alcohol **8** (576 mg, 2.72 mmol) in THF (20.0 mL) at 0 °C, PPh_3 (1.07 g, 4.08 mmol) and CBr_4 (1.35 g, 4.08 mmol) were added. The resultant mixture was stirred at room temperature for 1 h. The mixture was poured into water (50 mL) and extracted with Et_2O (3 × 50 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with silica gel chromatography (EtOAc–hexanes, 2:98) to afford the allyl bromide **9** (710 mg, 2.55 mmol, 94%). ^{1}H NMR ($CDCl_3$, ppm) δ: 4.99 (1H, m), 4.07, 3.96 (each 1H, d, J = 8.2 Hz), 2.43 (1H, dd, J = 4.5, 13.8 Hz), 2.11 (1H, dd, J = 7.4, 13.8 Hz), 2.02 (3H, s), 1.72 (1H, m) overlapping with 1.75 (3H, s), 1.58 (1H, t, J = 9.5 Hz), 1.20, 1.12 (each 3H, s). ^{13}C NMR ($CDCl_3$, ppm) δ: 169, 133.4, 144.2, 67.2, 43.5, 38.4, 36.7, 29.0, 28.6, 28.3, 21.1, 19.6. FAB-HRMS calcd. for $C_{12}H_1{}^{8}{}^{79}BrO_2$ *m/z*: 273.0490 [M – H]$^+$; found: 273.0497.

3-*O*-Acetoxysafranyl triphenylphosphonium bromide (10)

To a solution of allyl bromide **9** (710 mg, 2.55 mmol) in benzene (20.0 mL) at room temperature, PPh_3 (670 mg, 2.55 mmol) was added. The resultant mixture was heated up to the reflux temperature (~85 °C bath) for 12 h. After the mixture was cooled to room temperature, the volatiles were evaporated in vacuo. The residue was washed with benzene (×3) and dried under the reduced pressure for 1 day to give **10** (1.37 g, 2.55 mmol, quantitative yield). ^{1}H NMR ($CDCl_3$, ppm) δ: 7.9–7.6 (15H), 4.97 (1H, m), 4.58, 4.42 (each 1H, t, J = 14.0 Hz), 2.26 (1H, m), 2.04 (3H, s), 1.95 (1H, m), 1.71 (1H, dd, J = 2.0, 12.0 Hz), 1.51 (1H, t, J = 12.0 Hz), 1.07 (3H, d, J = 4.0 Hz), 0.88, 0.84 (each 3H, s). FAB-HRMS calcd. for $C_{30}H_{34}O_2P$ *m/z*: 457.2291 [M – Br]$^+$; found: 457.2285.

3-*O*-Acetyl-13-*O*-TBS (11a)

To a solution of the triphenylphosphonium bromide **10** (657 mg, 1.22 mmol) in THF (7.0 mL) at –78 °C, *n*-BuLi (2.5 mol/L solution in hexanes, 1.4 mL, 3.50 mmol) was added, and the resultant mixture was allowed to warm to room temperature and was stirred at this temperature for 1 h to generate the corresponding ylide. To a solution of aldehyde **3** (460 mg, 1.64 mmol) in THF (10.0 mL), the ylide solution was added. After 14 h of stirring at the same temperature, the mixture was poured into water and extracted with Et_2O (3 × 30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 5:95 and 20:80) afforded the acetyl **11a** (245 mg, 534 μmol, 33%) and alcohol **11b** (276 mg, 663 μmol, 40%) as a colorless oil. The ratio of diastereomers was not determined and this sample was used as a mixture.

To a solution of 3-hydroxy **11b** (294 mg, 706 μmol) in pyridine (3.0 mL) at room temperature, Ac_2O (1.5 mL) and *N*,*N*-dimethylaminopyridine (DMAP, 5.0 mg) were added, and the resultant mixture was stirred at the same temperature for 12 h. The mixture was poured into a satd. aq. solution of $NaHCO_3$ (30 mL) and extracted with Et_2O (3 × 30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 2:98) provided the acetyl **11a** (205 mg, 446 μmol, 63%) as a colorless oil. The ratio of diastereomers was not determined, and this sample was used as a diastereomeric mixture. ^{1}H NMR for **11a** ($CDCl_3$, ppm, major signals are only described.) δ: 6.49, 6.09 (each 1H, dd, J = 1.8, 16.0 Hz), 6.45, 5.69 (each 1H, dd, J = 2.2, 11.8 Hz), 5.06 (1H, m), 4.46 (1H, m), 2.67 (1H, dt, J = 5.0, 13.7 Hz), 2.44 (1H, dd, J = 5.8, 17.0 Hz), 2.23 (1H, m), 2.10 (1H, dd, J = 9.4, 16.6 Hz), 2.04 (3H, s), 1.87 (3H, s), 1.83–1.75 (2H), 1.72 (3H, s), 1.8–1.7 (2H), 1.58 (2H, t, J = 12.0 Hz), 1.10, 1.07 (each 3H, s), 0.906 (3H × 3, s), 0.090, 0.081 (each 3H, s). ^{13}C NMR

($CDCl_3$, ppm) δ: 170, 138, 137, 134, 132, 130, 129, 125.8, 125.0, 71.0, 68.4, 43.9, 38.3, 36.6, 35.6, 30.0, 29.8, 28.4, 25.8 (3C), 23.8, 21.4 (2C), 18.2, 14.3, –4.6 (2C). FAB-HRMS calcd for $C_{28}H_{46}O_3Si$ *m/z*: 458.3216 [M^+]; found: 458.3196. ^1H NMR for **11b** ($CDCl_3$, ppm, major signals are only described.) δ: 6.11, 6.49 (each 1H, d, *J* = 16.0 Hz), 5.69, 6.46 (each 1H, d, *J* = 11.9 Hz), 4.46 (1H, m), 4.01 (1H, m), 2.68 (1H, dt, *J* = 5.4, 8.8 Hz), 2.38 (1H, dd, *J* = 5.4, 16.6 Hz), 2.24 (1H, m), 2.04 (1H, m), 1.86 (3H, s), 1.71–1.85 (4H) overlapping with 1.73 (3H, s), 1.65 (1H, brs), 1.48 (1H, t, *J* = 11.9 Hz), 1.07 (3H × 2, s), 0.907 (3H × 3, s), 0.0815, 0.0914 (each 3H, s). ^{13}C NMR ($CDCl_3$, ppm) δ: 138, 136, 134, 132, 130, 130, 125.67, 125.64, 71.0, 64.9, 48.2, 42.4, 37.0, 35.6, 30.2, 29.8, 28.6, 25.8 (3C), 23.8, 21.5, 18.2, 14.4, –4.6 (2C). FAB-MS *m/z* (%, rel. int.): 416 (52, M^+), 398 (25, [M – H_2O]$^+$). FAB-HRMS calcd. for $C_{26}H_{44}O_2Si$ *m/z*: 416.3111 [M^+]; found: 416.3106.

13-Ketone (12)

To a solution of **11a** (205 mg, 446 mmol) in THF (10.0 mL) at 0 °C, tetrabutylammonium fluoride (TBAF, 1.0 mol/L solution in THF, 892 µL, 892 µmol) was added, and the resultant mixture was allowed to warm to room temperature and was continuously stirred at this temperature. After 3 h of stirring, the mixture was poured into water (30 mL) and extracted with Et_2O (3 × 30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 15:85) afforded the 13-hydroxy compound (145 mg, 425 µmol, 99%) as a colorless oil. ^1H NMR ($CDCl_3$, ppm) δ: 6.51, 5.73 (each 1H, d, *J* = 11.8 Hz), 6.47, 6.10 (each 1H, d, *J* = 15.8 Hz), 5.05 (1H, m), 4.47 (1H, m), 2.70 (1H, m), 2.44 (1H, dd, *J* = 5.4, 6.8 Hz), 2.23 (1H, m), 2.12 (1H, m), 2.05 (3H, s), 2.00–1.89 (2H), 1.88 (3H, s), 1.81–1.68 (2H, m), 1.71 (3H, s), 1.58 (2H, t, *J* = 11.9 Hz), 1.10, 1.07 (each 3H, s).

To a solution of the 13-hydroxy (209 mg, 607 µmol) in CH_2Cl_2 (15.0 mL) at 0 °C, MnO_2 (1.60 g, 18.2 mmol) was added, and the resultant mixture was stirred at this temperature. After 40 min of stirring at the same temperature, the mixture was filtered and the volatiles were removed under reduced pressure. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 20:80) afforded ketone **12** (174 mg, 507 µmol, 84%) as a colorless oil. ^1H NMR ($CDCl_3$, ppm) δ: 7.32, 5.92 (each 1H, d, *J* = 12.0 Hz), 6.55, 6.32 (each 1H, d, *J* = 18.0 Hz), 5.03 (1H, m), 2.63 (2H, t, *J* = 6.6 Hz), 2.57 (2H, t, *J* = 6.6 Hz), 2.45 (1H, dd, *J* = 5.4, 16.9 Hz), 2.11 (1H, dd, *J* = 9.6, 16.9 Hz), 2.04, 2.02 (each 3H, s), 1.87 (2H, qn, *J* = 6.6 Hz), 1.79 (1H, brt), 1.72 (3H, s), 1.58 (1H, t, *J* = 12.0 Hz), 1.10, 1.07 (each 3H, s). ^{13}C NMR ($CDCl_3$, ppm) δ: 203, 170, 143, 137.9, 137.0, 134, 132, 130, 129, 126, 68.1, 43.8, 42.9, 38.3, 36.5, 31.2, 29.9, 28.4, 23.1, 21.4, 21.3, 15.0. FAB–HRMS calcd. for $C_{22}H_{31}O_3^+$ *m/z*: 343.2273 [M + H]$^+$; found: 343.2266.

13-Nitrilemethylene (13)

To a solution of NaH (freshly prepared by washing with hexanes and drying under reduced pressure, 140 mg, 5.84 mmol) in THF (15.0 mL) at 0 °C, $(EtO)_2P(O)CH_2CN$ (**4**, 944 µL, 5.84 mmol) was added, and the resultant mixture was allowed to warm to room temperature and was stirred at this temperature for 1 h to generate the corresponding ylide. To a solution of ketone **12** (174 mg, 507 µmol) in THF (25.0 mL), the generated ylide was added. After 12 h of stirring at the same temperature, the mixture was poured into water (30 mL) and extracted with Et_2O (3 × 30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 7:93) afforded the (*E*)-nitrile **13** (47.1 mg, 135 µmol, 27%) and the (*Z*)-nitrile (99.3 mg, 265 µmol, 53%) as yellowish oils, respectively. ^1H NMR for (*E*)-isomer **13** ($CDCl_3$, ppm) δ: 6.82, 6.13 (each 1H, d, *J* = 11.3 Hz), 6.52, 6.25 (each 1H, d, *J* = 15.9 Hz), 5.15 (1H, s), 5.04 (1H, m), 2.67 (2H, t, *J* = 6.7 Hz), 2.52 (2H, t, *J* = 6.7 Hz), 2.46 (1H, dd, *J* = 5.9, 17.2 Hz), 2.12 (1H, dd, *J* = 9.5, 17.2 Hz), 2.05, 1.96 (each 3H, s), 1.87 (2H, qn, *J* = 6.7 Hz), 1.79 (1H, m), 1.73 (3H, s), 1.59 (1H, t, *J* = 12.2 Hz), 1.11, 1.08 (each 3H, s). ^{13}C NMR ($CDCl_3$, ppm) δ: 170, 162, 139, 138, 134 (2C), 132, 129, 128, 126, 117, 96.3, 68.2, 43.9, 38.4, 36.6, 33.0, 31.3, 30.0, 28.5, 26.9, 21.5, 21.4, 14.9. FAB–HRMS calcd. for $C_{24}H_{31}NO_2$ *m/z*: 365.2355 [M^+]; found: 365.2354. ^1H NMR for the (*Z*)-isomer ($CDCl_3$, ppm) δ: 6.94, 6.57 (each 1H, d, *J* = 11.4 Hz), 6.50, 6.25 (each 1H, d, *J* = 16.0 Hz), 5.07 (1H, s), 5.04 (1H, m), 2.51 (2H, t, *J* = 6.7 Hz), 2.46 (1H, m) 2.42 (2H, t, *J* = 6.7 Hz), 2.11 (1H, dd, *J* = 9.5, 17.0 Hz), 2.04, 1.97 (each 3H, s), 1.83 (2H, qn, *J* = 6.7 Hz), 1.72 (3H, s), 1.59 (2H, t, *J* = 11.9 Hz), 1.11, 1.08 (each 3H, s).

14-Aldehyde (14)

To a solution of the (*E*)-nitrile **13** (35.7 mg, 97.7 µmol) in Et_2O (3.0 mL) at –78 °C, DIBAH (1.0 mol/L solution in toluene, 900 µL, 900 µmol) was added, and the resultant mixture was stirred at 0 °C. After 40 min of stirring, methanol (0.63 mL) was carefully added, followed by a 30% aqueous solution of Rochelle salt (potassium sodium tartrate) (1.08 mL), the resultant mixture was then stirred for 40 min. The organic layer was washed with a 30% Rochelle salt aqueous solution (2 × 0.45 mL and 1 × 0.23 mL). The combined aqueous layer was back-extracted with Et_2O (3 × 30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (Et_2O–hexanes, 50:50) afforded the aldehyde without an acetyl group at C-3 (26.1 mg, 80.1 µmol, 82%) as an oil. ^1H NMR ($CDCl_3$, ppm) δ: 10.0 (1H, d, *J* = 8.2 Hz), 6.90, 6.24 (each 1H, d, *J* = 11.3 Hz), 6.53, 6.27 (each 1H, d, *J* = 15.9 Hz), 5.93 (1H, d, *J* = 8.2 Hz), 3.97 (1H, m), 2.85 (2H, t, *J* = 6.7 Hz), 2.56 (2H, t, *J* = 6.7 Hz), 2.40 (1H, dd, *J* = 6.2, 17.0 Hz), 2.05 (1H, dd, *J* = 10.0, 17.0 Hz), 1.98 (3H, s), 1.89 (2H, qn, *J* = 6.7 Hz), 1.83–1.74 (1H, m), 1.74 (3H, s), 1.49 (1H, t, *J* = 11.8 Hz), 1.08 (3H × 2, s).

To a solution of the aldehyde (26.1 mg, 80.0 µmol) in a mixture of CH_2Cl_2 (1.0 mL) and pyridine (0.2 mL) at 0 °C, Ac_2O (0.1 mL) and DMAP (2.0 mg) were added, and the resultant mixture was allowed to warm to room temperature and was stirred at this temperature. After 1 h of stirring, the volatiles were removed in vacuo. Purification of the residue by silica gel column chromatography (Et_2O–hexanes, 15:85) afforded the alcohol (14.5 mg, 39.3 µmol, 50%) as an oil.

^{1}H NMR ($CDCl_3$, ppm) δ: 10.0 (1H, d, J = 8.2 Hz), 6.90, 6.24 (each 1H, d, J = 11.3 Hz), 6.53, 6.25 (each 1H, d, J = 15.9 Hz), 5.93 (1H, d, J = 8.2 Hz), 5.05 (1H, m), 2.85 (2H, t, J = 6.7 Hz), 2.56 (2H, t, J = 6.7 Hz), 2.45 (1H, dd, J = 5.5, 16.4 Hz), 2.12 (1H, dd, J = 9.4, 16.4 Hz), 2.05 (3H, s), 1.98 (3H, s), 1.90 (2H, qn, J = 6.7 Hz), 1.79 (1H, m), 1.74 (3H, s), 1.59 (1H, t, J = 12.0 Hz), 1.11, 1.08 (each 3H, s). ^{13}C NMR ($CDCl_3$, ppm) δ: 190, 170, 160, 139, 138, 135, 134, 132.4, 132.2, 128.8, 128.5, 126, 68.2, 43.8, 38.4, 36.6, 31.2, 29.9, 29.0, 28.4 (2C), 21.4 (2C), 14.9. FAB–HRMS calcd. for $C_{24}H_{31}O_3$: 367.2273 $[M - H]^+$; found: 367.2271.

15-*O*-TBS (15)

To a solution of the aldehyde **14** (14.5 mg, 39.3 μmol) in a mixture of $CHCl_3$ (0.2 mL) and methanol (1.0 mL) at –10 °C, $NaBH_4$ (8.9 mg, 236 μmol) was added. After 2 min of stirring, a satd. aq. solution of NH_4Cl (20 mL) was added and the resultant mixture was extracted with EtOAc (3 × 20 mL). The organic layers were washed with brine, combined, and dried over $MgSO_4$. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.50, 6.10 (each 1H, d, J = 15.9 Hz), 6.47, 6.12 (each 1H, d, J = 11.3 Hz), 5.66 (1H, t, J = 7.0 Hz), 5.04 (1H, m), 4.25 (2H, d, J = 7.0 Hz), 2.52 (2H, t, J = 6.7 Hz), 2.44 (1H, dd, J = 6.0, 17.6 Hz), 2.36 (2H, t, J = 6.7 Hz), 2.11 (1H, dd, J = 8.9, 17.6 Hz), 2.05 (3H, s), 1.92 (3H, s), 1.83–1.70 (3H), 1.72 (3H, s), 1.58 (1H, t, J = 11.9 Hz), 1.10, 1.07 (each 3H, s).

To a solution of the crude alcohol in CH_2Cl_2 (1.0 mL) at room temperature, imidazole (16.0 mg, 197 μmol) was added. The mixture was cooled to 0 °C, and TBSCl (11.8 mg, 78.6 μmol) was added at this temperature. After 2 h of stirring, the mixture was poured into water (20 mL) and the resultant mixture was extracted with Et_2O (3 × 20 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 7:93) afforded **15** (13.4 mg, 27.6 μmol, 70%, in two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.51, 6.08 (each 1H, d, J = 16.0 Hz), 6.42, 6.11 (each 1H, d, J = 11.4 Hz), 5.57 (1H, t, J = 6.4 Hz), 5.05 (1H, m), 4.28 (2H, d, J = 6.4 Hz), 2.52 (2H, t, J = 6.7 Hz), 2.44 (1H, dd, J = 5.5, 17.0 Hz), 2.31 (2H, t, J = 6.7 Hz), 2.10 (1H, dd, J = 9.3, 17.0 Hz), 2.05, 1.91 (each 3H, s), 1.82–1.73 (3H), 1.72 (3H, s), 1.58 (1H, t, J = 12.0 Hz), 1.10, 1.07 (each 3H, s), 0.906 (3H × 3, s), 0.0813 (3H × 2, s). ^{13}C NMR ($CDCl_3$, ppm) δ: 170, 139, 138, 135, 134, 132, 131, 130.4, 130.3, 125.7, 125.0, 68.4, 59.9, 44.0, 38.5, 36.7, 31.3, 30.4, 30.1, 28.9, 28.6, 27.9, 26.1 (3C), 21.6, 18.5, 14.7, –4.80 (2C). FAB-HRMS calcd. for $C_{30}H_{48}O_3Si$ *m/z*: 484.3373 $[M^+]$; found: 484.3366.

3-*O*-Biotinyl (Boc)Lys-15-*O*-TBS (16)

To a solution of **15** (5.4 mg, 11.1 μmol) in methanol (1.0 mL) at 0 °C, K_2CO_3 (2.0 mg, 14.5 μmol) was added. The mixture was stirred and allowed to warm to room temperature. After 12 h of stirring, the mixture was poured into a satd. aq. solution of NH_4Cl (20 mL) and the resultant mixture was extracted with EtOAc (3 × 20 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, and concentrated under reduced pressure. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.51, 6.11 (each 1H, d, J = 15.9 Hz), 6.43, 6.11 (each 1H, d, J = 11.4 Hz), 5.57 (1H, t, J = 6.3 Hz), 4.28 (2H, d, J = 6.3 Hz), 4.00 (1H, m), 2.52 (2H, t, J = 6.6 Hz), 2.38 (1H, dd, J = 5.0, 16.7 Hz), 2.31 (2H, t, J = 6.6 Hz), 2.04 (1H, dd, J = 9.7, 16.7 Hz), 1.91 (3H, s), 1.77 (1H, m), 1.73 (2H, qn, J = 6.7 Hz), 1.73 (3H, s), 1.47 (2H, t, J = 11.9 Hz), 1.07 (3H × 2, s), 0.906 (3H × 3, s), 0.0807 (3H × 2, s).

To a mixture of the crude 3-OH compound, biotinyl (Boc)Lys-OH (7.9 mg, 16.7 μmol),1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 6.4 mg, 33.3 μmol) at 0 °C, and CH_2Cl_2 (0.7 mL) were added. DMAP (2.0 mg) was also added at this temperature. The mixture was warmed to room temperature and stirred. After 3 h of stirring, the mixture was poured into a satd. aq. solution of $NaHCO_3$ (20 mL) and the resultant mixture was extracted with $CHCl_3$ (20 mL). The organic layer was washed with a satd. aq. NH_4Cl solution, water, and brine, followed by drying over $MgSO_4$. Purification of the residue by silica gel column chromatography (methanol–$CHCl_3$, 7:93) afforded **16** (7.8 mg, 8.69 μmol, 78%, in two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.52, 6.11 (each 1H, d, J = 16.1 Hz), 6.44, 6.13 (each 1H, d, J = 11.3 Hz), 6.24 (1H, brs), 6.18 (1H, brs), 5.59 (1H, t, J = 6.5 Hz), 5.45–5.38 (1H, m), 5.37 (1H,brs), 5.20 (1H, d, J = 6.5 Hz), 5.10 (1H, m), 4.53 (1H, dd, J = 4.8, 7.5 Hz), 4.37–4.28 (1H, m), 4.29 (2H, d, J = 6.5), 4.23 (1H, m), 3.23 (2H, qn, J = 5.9 Hz), 3.16 (1H, m), 2.92 (1H, dd, J = 4.8, 12.6 Hz), 2.75 (1H, d, J = 12.6 Hz), 2.52 (2H, t, J = 6.4 Hz), 2.44 (1H, m), 2.32 (2H, t, J = 7.4 Hz), 2.20 (2H, t, J = 7.4 Hz), 2.13 (1H, m), 1.91 (3H, s), 1.85–1.50 (15H), 1.73 (3H, s), 1.45 (3H × 3, s), 1.10, 1.08 (each 3H, s), 0.908 (3H × 3, s), 0.0813 (3H × 2, s). FAB-HRMS calcd. for $C_{49}H_{81}N_4O_7SSi^+$ *m/z*: 897.5590 $[M + H]^+$; found: 897.5574. FAB-HRMS calcd. for $C_{49}H_{81}N_4NaO_7SSi$: 920.5493 $[M + H + Na]^+$; found: 920.5489.

3-*O*-Biotinyl (Boc)Lys 15-*O*-bromoacetate (1)

To a solution of **16** (4.1 mg, 4.57 μmol) in THF (1.0 mL) at 0 °C, TBAF (1.0 mol/L solution in THF, 9.2 μL, 9.2 μmol) was added. The mixture was warmed to room temperature and stirred. After 2 h of stirring, the mixture was poured into water (20 mL) and the resultant mixture was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine, combined, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (methanol–$CHCl_3$, 10:90) afforded the biotinylated alcohol (2.1 mg, 2.68 μmol, 60%) as a colorless oil. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.52, 6.13 (each 1H, d, J = 15.3 Hz), 6.49, 6.15 (each 1H, d, J = 11.1 Hz), 5.90 (1H, brs), 5.68 (1H, t, J = 6.8 Hz), 5.56 (1H, brs), 5.17 (1H, d, J = 7.9 Hz), 5.10 (1H, m), 4.90 (1H, brs), 4.52 (1H, m), 4.33 (1H, m), 4.26 (2H, d, J = 6.8 Hz), 4.25 (1H, brs), 3.23 (2H, brs), 3.17 (1H, q, J = 4.4 Hz), 2.93 (1H, dd, J = 4.8, 12.9 Hz), 2.74 (1H, d, J = 12.9 Hz), 2.53 (2H), 2.44 (1H, m), 2.37 (2H, t, J = 6.6 Hz), 2.28–2.18 (2H), 2.18–2.10 (1H, m), 1.92 (3H, s), 1.85–1.48 (16H), 1.73 (3H, s), 1.45 (3H × 3, s), 1.10, 1.08 (each 3H, s).

To a solution of the biotinylated alcohol (2.1 mg, 2.68 μmol) in CH_2Cl_2 (0.7 mL) at room temperature, $BrCH_2COOH$ (2.0 mg, 14.4 μmol) was added. The mixture was cooled to –10 °C and EDC (3.1 mg, 16.1 μmol) and DMAP (1.0 mg) were added. After 15 min of stirring at the

same temperature, the mixture was poured into a satd aq. solution of $NaHCO_3$ (20 mL) and the resultant mixture was extracted with $CHCl_3$ (20 mL). The organic layer was washed with a satd aq. NH_4Cl solution, water and brine, followed by drying over $MgSO_4$. After concentration in vacuo, purification of the residue by silica gel column chromatography (methanol–$CHCl_3$, 7:93) afforded the biotinylated bromoacetate **1** (1.6 mg, 1.77 μmol, 66%) as a colorless oil. ^1H NMR ($CDCl_3$, ppm) δ: 6.53, 6.13 (each 1H, d, J = 11.4 Hz), 6.50, 6.12 (each 1H, d, J = 15.7 Hz), 5.86 (1H, t, J = 5.0 Hz), 5.58 (1H, t, J = 7.3 Hz), 5.51 (1H, brs), 5.16 (1H, d, J = 8.6 Hz), 5.10 (1H, m), 4.87 (1H, brs), 4.77 (2H, d, J = 7.3 Hz), 4.51 (1H, dd, J = 4.7, 7.8 Hz), 4.32 (1H, dd, J = 4.7, 7.6 Hz), 4.23 (1H, m), 3.83 (2H, s), 3.23 (2H, qn, J = 6.1 Hz), 3.16 (1H, m), 2.92 (1H, dd, J = 4.7, 12.6 Hz), 2.73 (1H, d, J = 12.6 Hz), 2.51 (2H, t, J = 7.0 Hz), 2.39 (2H, t, J = 6.5 Hz), 2.10 (1H, m), 2.14 (2H, t, J = 6.5 Hz), 2.10 (1H, m), 1.92 (3H, s), 1.88–1.30 (16H), 1.72 (3H, s), 1.45 (3H × 3, s), 1.10, 1.08 (each 3H, s).

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A theoretical and experimental investigation of some unusual intermolecular hydrogen-bond IR bands — Appearances can be deceptive[1]

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Abstract: The IR spectra of the O-H stretch for hydrogen bonds (HBs) arising from complex formation between the HB donor (HBD), 4-fluorophenol, and the HB acceptors, peroxides and ethers, frequently show asymmetry that appears to arise from two incompletely resolved bands from two different complexes, but the O-H HB bands with the HBD methanol are symmetric (M. Berthelot, F. Bessau, and C. Laurence. Eur. J. Org. Chem. 925 (1998)). The present studies show that this difference in O-H HB band shapes also is true for other phenols and alcohols. However with ethylene oxide, 4-fluorophenol gives an almost symmetric O-H HB band with a very broad maximum, while alcohols give symmetric O-H HB bands with well-defined maxima. It is shown by experiment that the unusual O-H HB band shapes for the phenols are not due to Fermi resonance and are unrelated to the enthalpies of HB complex formation. Theoretical exploration of the potential energy (PE) surfaces for complexes of 4-fluorophenol and methanol with *tert*-butyl methyl ether and ethylene oxide reveals that O-H HB band asymmetry or broadness cannot be ascribed to the presence of two different HB complexes. For this ether, the PE surfaces for rotation about the HB and for up-and-down motion of the HBD with respect to the COC plane of the ether are relatively symmetric for methanol, but are strongly asymmetric for 4-fluorophenol, hence the differences in the O-H HB band shapes. The PE surfaces for the epoxide are effectively symmetric, but the PE for rotation about the HB has a single broad minimum for methanol, whereas with 4-fluorophenol there are two minima owing to attractive interactions between the phenyl group and the CH_2 groups of the epoxide. The previously unknown β_2^H values for ethylene oxide and tetramethylethylene oxide are 0.36 and 0.58, respectively.

Key words: asymmetric IR O-H bands, asymmetric potential energy surfaces, hydrogen-bonded complexes, hydrogen bond enthalpy, O-H frequency shift.

Résumé : Les spectres IR de l'élongation O-H des liaisons hydrogènes (LH) découlant de la formation de complexes entre le donneur de liaison hydrogène (DLH), 4-fluorophénol, et des accepteurs de LH, tels les peroxydes et les éthers, présentent fréquemment une asymétrie qui semble découler de la présence de deux bandes pas complètement résolues provenant de deux complexes différents, mais les bandes de LH O-H avec le DLH méthanol sont symétriques (M. Berthlot, F. Bessau, et C. Laurence. Eur J. Chem. 925 (1998)). La présente étude montre que cette différence dans les formes de la bande de LH O-H est aussi vraie pour d'autres phénols et d'autres alcools. Toutefois, avec l'oxyde d'éthylène, le 4-fluorophénol donne lieu à une bande de LH O-H qui est pratiquement symétrique avec un maximum très large alors que les alcools donnent lieu à des bandes de LH OH symétriques avec des maxima bien définis. On a montré sur la base d'expériences que les formes inhabituelles de la bande de LH OH des phénols ne sont pas causées par une résonance de Fermi et qu'elles ne sont pas associées aux enthalpies de formation du complexe de LH. Une étude théorique des surfaces d'énergie potentielle (EP) des complexes du 4-fluorophénol et du méthanol avec l'oxyde de *tert*-butyle et de méthyle et l'oxyde d'éthylène montre que l'asymétrie ou la largeur de la bande de LH O-H ne peut pas être attribuée à la présence de deux complexes différents de LH. Pour cet éther, les surfaces d'EP pour la rotation autour de la LH et pour les mouvements ascendant et descendant du DLH par rapport au plan COC de l'éther sont relativement symétriques pour le méthanol, mais fortement asymétriques pour le 4-fluorophénol; d'où les différences dans les formes des bandes des LH O-H. Les surfaces d'EP pour l'époxyde sont effectivement symétriques, mais l'EP pour la rotation autour de la LH ne présente qu'un seul minimum élargi pour le méthanol alors que pour le 4-fluorophénol on observe deux minima qui résultent d'interactions d'attraction entre le groupe phényle et les groupes CH_2 de l'époxyde. Les valeurs β_2^H qui n'était pas connues antérieurement pour l'oxyde d'éthylène et l'oxyde de

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tétraméthyléthylène sont respectivement égales à 0,36 et 0,58.

Mots clés : bandes O-H IR asymétriques, surfaces d'énergie potentielle asymétriques, complexes à liaisons hydrogènes, enthalpie d'une liaison hydrogène, déplacement d'une fréquence O-H.

[Traduit par la Rédaction]

Introduction

During a critical reevaluation of the O—H bond dissociation enthalpy of phenol (1), the relative hydrogen bond acceptor (HBA) activity of di-*tert*-butyl peroxide was required. This is best quantified using the β_2^H scale of HBA relative activities developed by Abraham et al. (2). This is a general, thermodynamically related scale of solute hydrogen bond basicities in CCl_4. Values of β_2^H are calculated from the equilibrium constants for 1:1 complex formation between the HBA and a "calibrated" hydrogen bond donor (HBD), XOH, measured by IR spectroscopy in CCl_4 at room temperature (2)

[1] $$XOH + HBA \rightleftharpoons XOH\cdots HBA$$

[2] $$K_{eq} = \frac{[XOH\cdots HBA]}{([XOH]_0 - [XOH\cdots HBA])([HBA]_0 - ([XOH\cdots HBA])}$$

where the subscript 0 refers to the concentrations of XOH and the HBA in the absence of complex formation. Phenol and 4-fluorophenol (4-F-phenol) are often used as the calibrated HBA, the latter being particularly popular because, for 4-F-phenol only, there is a very simple relation between β_2^H and K_{eq} (β_2^H = (log K_{eq} + 1.1)/4.636) (2).[4] Values of β_2^H range from 0.00 for saturated hydrocarbons to 1.00 for hexamethylphosphortriamide, the strongest organic base.

Berthelot et al. (3) had reported a β_2^H value of 0.33 for di-*tert*-butyl peroxide, which we confirmed (1). We also confirmed their report that hydrogen-bond (HB) formation between 4-F-phenol and di-*tert*-butyl peroxide gives an asymmetric O-H HB stretching band in the IR that appears to arise from two incompletely resolved bands. Very reasonably, Berthelot et al. assigned this asymmetry and the asymmetry they found in the O-H HB bands for HB complexes of 4-F-phenol with some, but not all, ethers to the existence of two stereoisomeric hydrogen bonded species. These were suggested to have structures **A** and **B** (Fig. 1).

The asymmetric ether (peroxide)···HOC_6H_4F O-H HB bands discovered by Berthelot et al. (3) are intriguing. Herein, an experimental study of some asymmetric (and symmetric) O-H HB bands, which confirms and extends the earlier report (3), is combined with theoretical calculations on the structures of the species responsible for them.

Experimental

Materials

With one exception, all compounds were purchased from Sigma-Aldrich. Anhydrous solvents and the phenols were of highest purity available (usually 99%+) and were used as received except as noted. Prior to their use, the phenols were kept in a desiccator over P_2O_5 and di-*tert*-butyl peroxide was passed over basic alumina. Gaseous ethylene oxide was dissolved in CCl_4 to obtain a stock solution. The ethylene oxide concentration in the stock solution was determined by ^1H NMR using a sample to which CH_3CN had been added as an internal standard. 1,1,2,2-Tetramethylethylene oxide (purity 98%) was purchased from ChemSampCo Inc., Trenton, New Jersey.

IR spectra

Spectra were measured in CCl_4 at ambient temperatures. Each spectrum was collected on a Shimadzu FTIR 8201PC apparatus using a 1.03 mm CaF_2 cell (20 scans with a resolution of 1 cm^{-1}), and the baseline was corrected using solutions having the same concentration of the HBA as in the HBD–HBA solution. For all HBD–HBA measurements, the HBD concentrations were kept below a level that would lead to HBD self-association.

Theoretical calculations

All calculations were performed using the Gaussian 03 program package (4). Structures, vibration frequencies, and hydrogen bond strengths were computed using B971/6-31+G**(5). This level of theory was shown to predict reasonable hydrogen-bond strengths (6). Hydrogen-bond strengths were corrected for basis set superposition error via the counterpoise technique (7). Additional calculations to generate approximate potential energy surfaces (PESs) were performed with MP2/6-31+G**. This level of theory was used to avoid any uncertainties associated with the use of a density functional theory method to describe effects owing to steric repulsion at the extrema of the PESs.

Results

IR spectra

Figure 2A shows the O-H stretching region with 4-F-phenol (11.5 mmol/L) and concentrations of di-*tert*-butyl peroxide ranging from 109 to 561 mmol/L. The asymmetry of the O-H HB band is very apparent at all HBA concentrations. Deconvolution of this O-H HB band by Berthelot et al. (3) yielded wavenumber differences from the band maximum for the non-hydrogen bonded (i.e., "free") 4-F-phenol (3614 cm^{-1}), $\Delta\nu$(OH) = 145 and 220 cm^{-1}. Additional support for the assignment of this asymmetric band entirely to hydrogen bonding was obtained by measurements using *O*-deuterio-4-F-phenol. The addition of a very small quantity of D_2O to CCl_4 containing 4-F-phenol (16.5 mmol/L) followed by the addition of di-*tert*-butyl peroxide produced the spectra shown in Fig. 2B. The O-H HB band in Fig. 2B has shifted roughly 900 cm^{-1} from that shown in Fig. 2A, but the two bands have the same asymmetric shape. This "makes

[4] From ref. 2, a solute hydrogen bond basicity scale against reference acids is established through the relationship log $K_{eq} = L_A$ log $K_B^H + D_A$. For the reference acid (4-F-phenol), L_A = 1.000 and D_A = 0.000 giving log K_B^H = log K_{eq}.

Table 1. Infrared spectral data for five phenols and three alcohols in CCl_4 and for their 1:1 hydrogen-bonded complexes with *tert*-butyl methyl ether, and the enthalpies of formation of these complexes.

			ν(OH) (cm^{-1})[b]				
HBD	$\Sigma\sigma^a$	α_2^H	Free	HB	Δν	A ($(mol/L)^{-1}/cm^{-2}$) Free	$-\Delta H$ (kcal/mol)[c]
Phenols							
3,5-Cl_2	0.74	0.728[d]	3604	3224, **3253**	380, **351** (419)	6750	6.80 (7.69)
4-CF_3	0.54	0.680[d]	3607	3250, **3260**	357, **347** (392)	6430	6.32 (7.36)
4-F	0.06	0.629[e]	3615	3303, **3317**	312, **298** (341)	5090	5.80 (6.66)
C_6H_5OH	0.00	0.590[d]	3613	3315, **3319**	298, **294** (328)	4900	5.40 (6.16)
4-MeO	–0.27	0.550[d]	3618	3333, **3355**	285, **263** (307)	4200	5.00 (5.96)
Alcohols							
CF_3CH_2OH		0.567[e]	3622	3367	255 (306)	3340	5.17 (6.27)
MeOH		0.367[e]	3645	3482	163 (219)	2360	3.14 (4.44)
Me_3COH		0.320[e]	3618	3484	134 (177)	1870	2.66 (4.10)

Note: See text for the meaning of the column headers.

[a]From C. Hansch, A. Leo, and R.W. Taft. Chem. Rev. **91**, 165 (1991).

[b]Numbers in regular type refer to band maxima and numbers in boldface refer to the center of asymmetric O-H HB bands (defined as the frequencies at which 50% of the overall band is at higher, and 50% at lower, frequencies). Numbers in parentheses are values calculated using the B971 functional.

[c]Calculated using eq. [3] with β_2^H = 0.494 for *tert* butyl methyl ether (3) and the values in parentheses were calculated using the B971 functional.

[d]From D.W. Snelgrove, J. Lusztyk, J.T. Banks, P. Mulder, and K.U. Ingold. J. Am. Chem. Soc. **123**, 469 (2001).

[e]From ref. 8.

Fig. 1. The two possible structures of the 1:1 comlex of an ether (or peroxide) with a hydrogen bond donor as proposed in ref. 3.

A **B**

improbable the attribution of the doublet to a Fermi resonance" (3).

Next we demonstrated that asymmetric O-H HB bands are not specific to 4-F-phenol, and furthermore that their shape is more or less independent of the HBD activity of the phenol. Relative HBD activities are best quantified using the α_2^H scale developed by Abraham et al. (8). Like his β_2^H scale, the α_2^H scale is a general, thermodynamically related scale of solute hydrogen bond acidities in CCl_4. Values of α_2^H are also calculated from the equilibrium constants for 1:1 complex formation between the HBD and a calibrated HBA and are measured by IR spectroscopy in CCl_4 at room temperature. Values of α_2^H range from 0.00 for saturated hydrocarbons to nearly 1 for strong organic acids, e.g., 0.951 for CF_3COOH (8). As the HBDs, we chose five phenols covering a range of α_2^H values (Table 1.) As the HBA, we chose *tert*-butyl methyl ether (β_2^H = 0.494), which had been shown to give an asymmetric O-H HB band with 4-F-phenol that was deconvoluted into two bands with Δν(OH) = 186 and 315 cm^{-1}(3). Our results are presented in Fig. 3 and Table 1. Both the free O-H and O-H HB band maxima shift to higher wavenumbers as the electron-withdrawing ability of the substituents on the phenols decrease, i.e., on going down the list of phenols in Table 1. It has been shown (9) that for phenol

Fig. 2. OH stretching region of the IR spectrum of (A) 4-F-phenol (11.5 mmol/L) and (B) OD stretching region of *O*-deuterio-4-F-phenol (16.5 mmol/L) in CCl_4 containing mmol/L concentrations of di-*tert*-butyl perioxide as indicated.

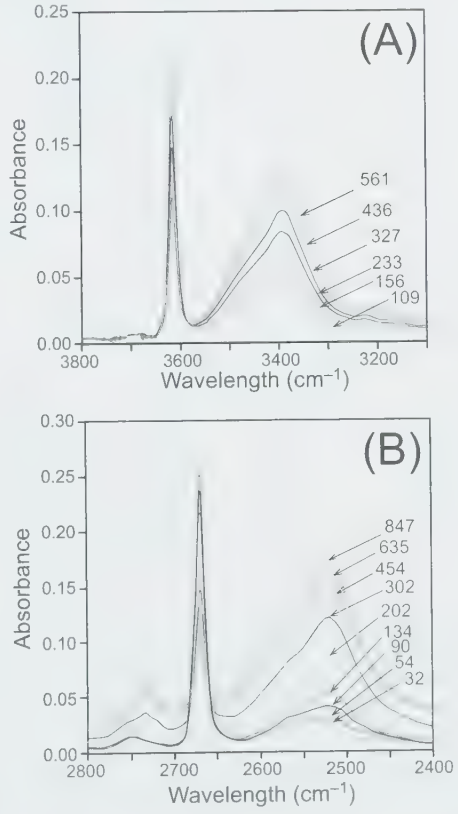
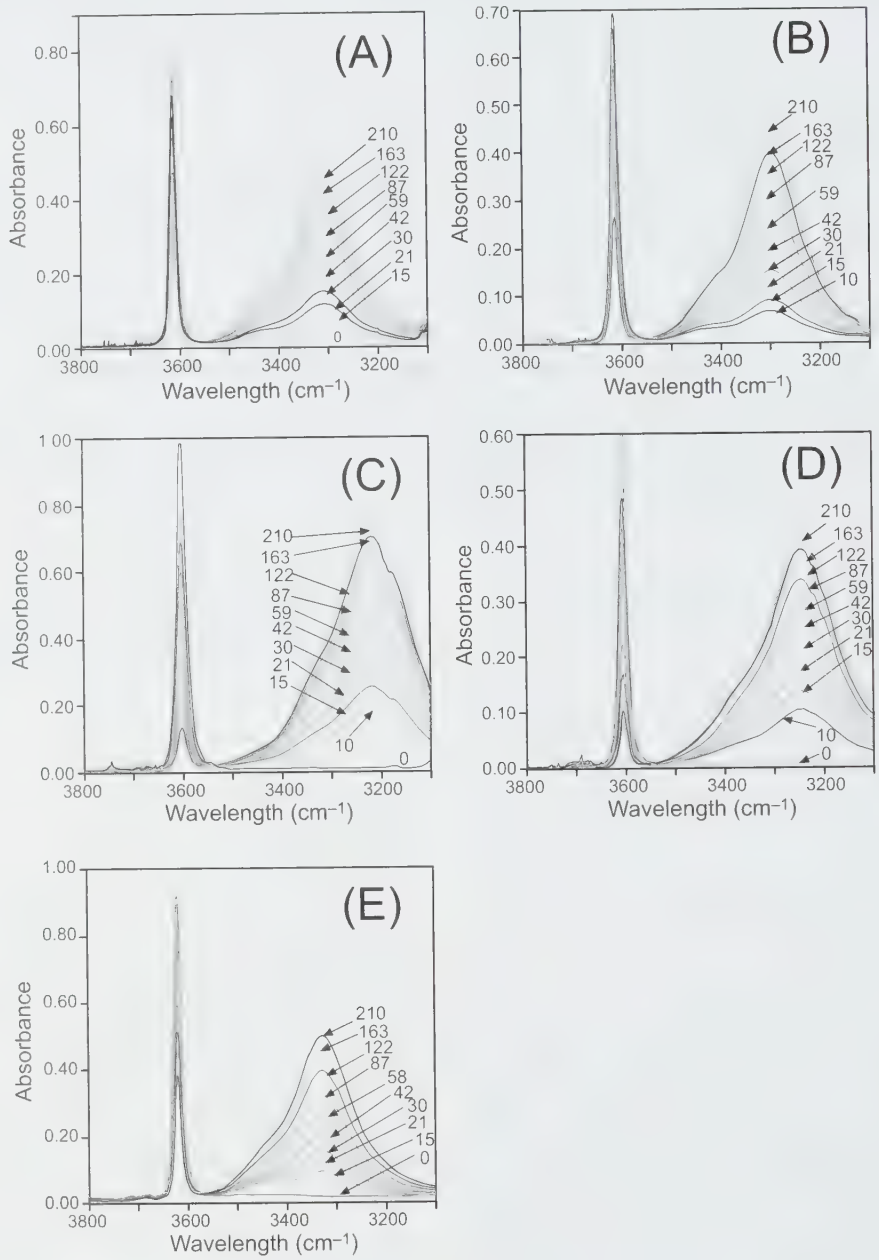


Fig. 3. OH stretching region of the IR spectrum of (A) PhOH (13.6 mmol/L), (B) 4-F-phenol (12.5 mmol/L), (C) 3,5-Cl_2-phenol (15.8 mmol/L), (D) 4-CF_3-phenol (9.2 mmol/L), and (E) 4-MeO-phenol (20.1 mmol/L) in $CC1_4$ containing mmol/L concentrations of *tert*-butyl methyl ether as indicated.



and 17 meta- and para-substituted phenols in CCl_4, the free OH band maximum frequencies (ν(OH)) and the integrated intensities of their bands (*A*) correlate with $\Sigma\sigma$ where σ is the Hammett substituent constant. In Hammett plots, the frequencies decrease ($\rho = -13.9$ cm^{-1}) and the intensities increase ($\rho = 1930$ (mol/L)$^{-1}$ cm^{-2}) as σ increases (9). The present results on the free O-H stretching band (Table 1) are consistent with this earlier report. The magnitudes of the shifts in the O-H stretching frequencies upon H-bonding to *tert*-butyl methyl ether, $\Delta\nu$ = ν(OH free) – ν(OH HB), are also given in Table 1 using both the O-H HB band maximum and the "center" of those O-H HB bands that are asymmetric. The center is the frequency at which 50% of the area of the O-H HB band is at higher, and 50% at lower, frequencies. B971 calculated values of $\Delta\nu$ have also been included.

In earlier work (1), an empirical equation was derived that relates ΔH_1 for 1:1 hydrogen bond complex formation (rxn.

[1]) between an HBD and an HBA to their α_2^H and β_2^H values, respectively. This equation (which is accurate to ±0.4 kcal/mol, 1 cal = 4.184 J) is

[3] $\Delta H_1 = -20.56\alpha_2^H\beta_2^H + 0.59$ kcal/mol

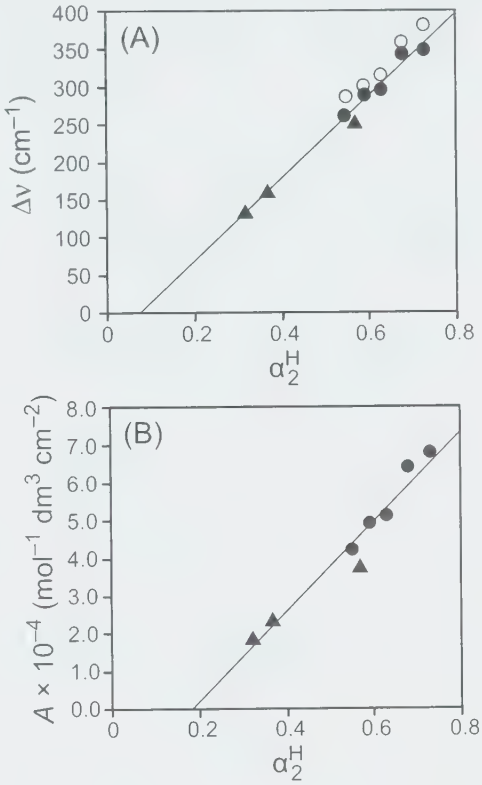
Values of ΔH_1 evaluated using eq. [3] and calculated using the B971 functional are included in Table 1.

The three quantities ($\Delta\nu$(OH), α_2^H, and ΔH_1) for each HBD – *tert*-butyl methyl ether combination (Table 1) are obviously interrelated. For example, a plot of experimental $\Delta\nu$(OH) vs. α_2^H yields an excellent straight line for the five phenol and three alcohol HBDs studied in the present work provided that the centers of the ν(OH HB) bands of the phenols are used rather than the band maxima (Fig. 4A). Such linear correlations are not surprising because the O-H and H···O moieties in hydrogen-bonded complexes are coupled oscillators (10). The integrated OH band areas for the free phenols (*A*) also correlate with α_2^H (Fig. 4B).

Asymmetric O-H HB bands have been observed for 4-F-phenol complexes with a number of ethers and peroxides (3) (Figs. 2 and 3). In contrast, methanol has been reported to give a single O-H HB band maximum with all but one of the same substrates (3).[5] Reported differences between the frequencies of the free OH band maxima for methanol and 4-F-phenol and their O-H HB band maxima for their 1:1 complexes with 40 ethers and 3 peroxides (3) reveal that $\Delta\nu$(OH) MeOH]/[$\Delta\nu$(OH) 4-F-phenol ~ 0.5 with all 43 bases. Obviously, methanol forms a weaker hydrogen bond to a particular base than does 4-F-phenol, as is fully consistent with their α_2^H values (0.367 and 0.629, respectively, Table 1). This suggested that HB bond asymmetry might only become obvious for strong HBDs.[6] To check this possibility we again chose *tert*-butyl methyl ether as the HBA and used three alcohols as HBDs: (*i*) methanol, (*ii*) the weaker HBD, *tert*-butanol, and (*iii*) the much stronger HBD, 2,2,2-trifluoroethanol (see α_2^H values in Table 1). The resulting IR spectra are shown in Fig. 5 and the spectral data together with the calculated values of ΔH_1 are collected in Table 1. None of these alcohols give rise to an asymmetric O-H HB band. This allows us to rule out a simple thermodynamic cause (i.e., the magnitude of ΔH_1) for O-H HB band asymmetry.

It was by now clear that an explanation for O-H HB band asymmetry would not come from experiment alone, it would require examination of some of the HBA···HBD complexes that gave asymmetric O-H HB bands by theory, and a simple, preferably fairly rigid, HBA would make high level calculations more practical. We therefore reexamined the data from Berthelot et al. These contain one epoxide[7] in which the epoxide ring plane was also a plane of symmetry for the whole molecule. This was 2,3-diadamant-2-yl oxirane.[8] With 4-F-phenol this epoxide gave an asymmetric O-H HB band

Fig. 4. Values of (A) $\Delta\nu$ = ν(OH free) – ν(OH HB) and (B) *A* as functions of the α_2^H parameter of HBD. Alcohols (▲), phenols using ν(OH HB) band maxima (○), phenols using the center of the ν(OH HB) band (●). Note: There is, of course, only a single *A* value for each alcohol and phenol.



that was deconvoluted into two bands ($\Delta\nu$ = 234 and 338 cm^{-1}). Unfortunately, this is too large a molecule for high-level calculations to be carried out in any reasonable time. However, this result of Berthelot et al. did encourage us to examine ethylene oxide and tetramethylethylene oxide, neither of which has previously been used in IR studies of hydrogen bonding. In the presence of 4-F-phenol, the spectra (Figs. 6A and 7A) showed O-H HB bands that were almost symmetric, but were very broad with maxima that are wide plateaus rather than the fairly sharp maxima seen for all the other O-H HB bands (Figs. 2, 3, and 5). In contrast, the O-H HB bands formed between alcohols and these two epoxides are not only symmetric, but also show distinct maxima (Figs. 6B, 6C, and 7B).

Deconvolution of the O-H HB bands shown in Figs. 6A and 7A using two Lorentzian functions yields two band

[5] The exception was 2,3-diadamant-2-yl oxirane. Deconvolution of the HB band yielded two band maxima ($\Delta\nu$(OH) = 129 and 180 cm^{-1}, ref. 3).

[6] However, this would not explain why 4-F-phenol does not give asymmetric HB bands with all ethers. That is, if chloroethers and dibenzyl ether are excluded because they contain two HBA moieties (chlorine and an aromatic ring) that could give rise to separate HB bands and hence to asymmetry, only 12 out of 36 ether–4-F-phenol HB bands were deconvoluted into two bands (3).

[7] Four epoxides were employed, but three of them (propylene oxide, cyclohexene oxide, and epichlorhydrin) lack the single plane of symmetry for the epoxide ring and the whole molecule desired to simplify the theoretical calculations.

[8] This is also the only HBA that gave an asymmetric HB band with methanol that was deconvoluted into two bands ($\Delta\nu$ = 129 and 180 cm^{-1}, ref. 3).

Fig. 5. OH stretching region of the IR spectrum of (A) MeOH (10.9 mmol/L), (B) *t*-BuOH (13.9 mmol/L), and (C) CF_3CH_2OH (15.1 mmol/L) in CCl_4 containing mmol/L concentrations of *tert*-butyl methyl ether as indicated.

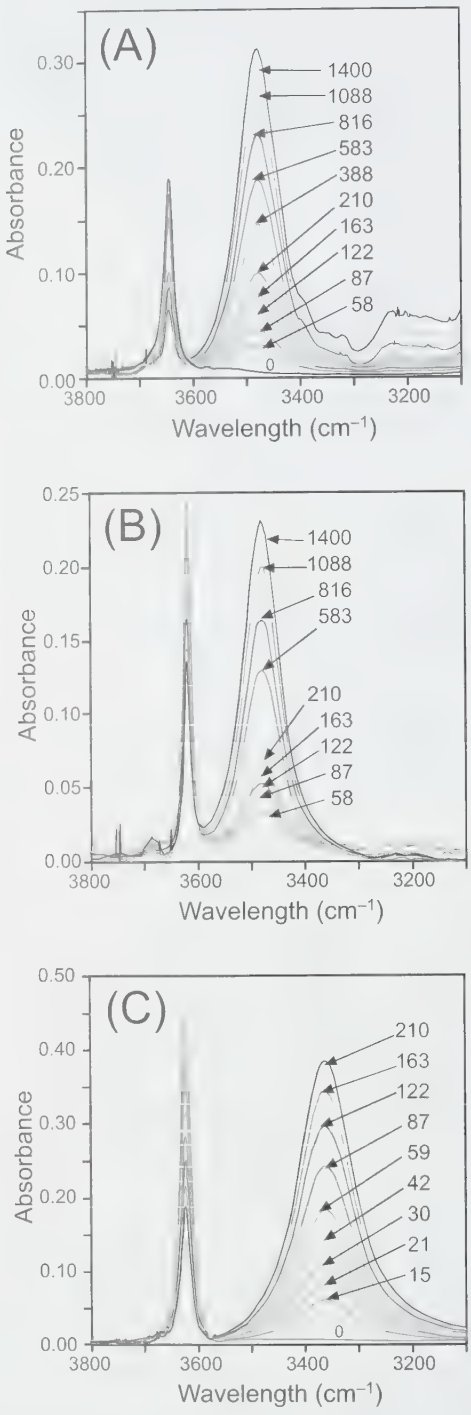
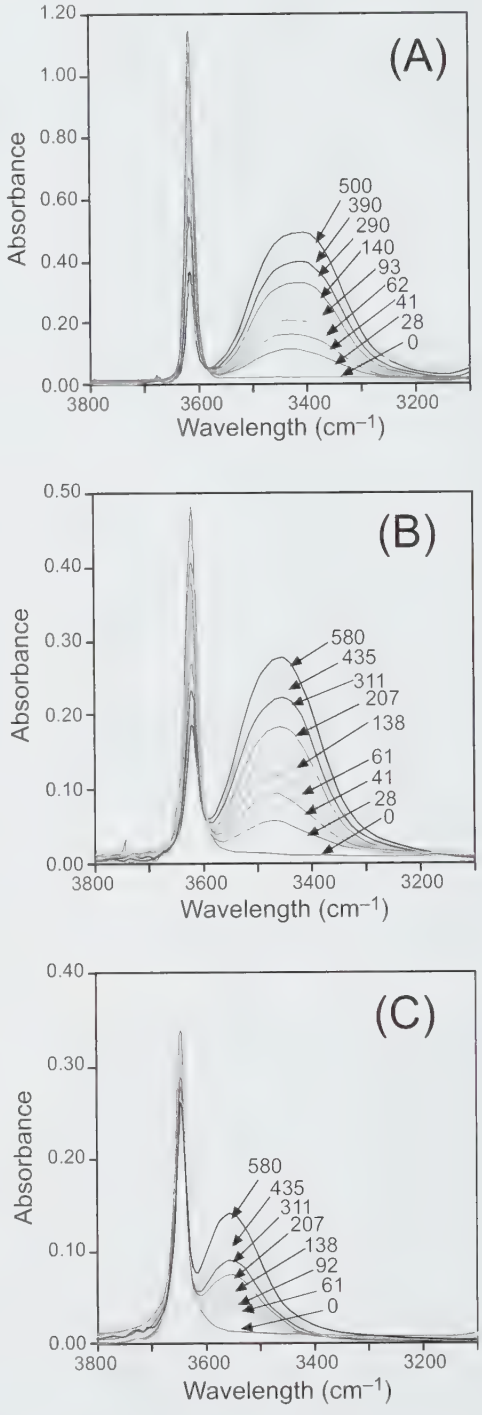
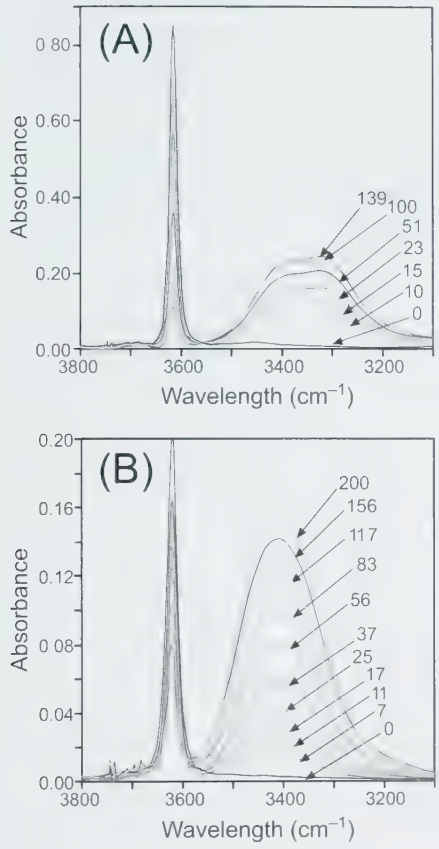


Fig. 6. OH stretching region of the IR spectrum of (A) 4-F-phenol (20.0 mmol/L), (B) CF_3CH_2OH (15.2 mmol/L), and (C) MeOH (15.4 mmol/L) in CCl_4 containing mmol/L concentrations of ethylene oxide as indicated.



maxima. However, not only would the implied existence of two HB complexes with different structures be inconsistent with theory (vide infra), but also the two deconvoluted band maximum frequencies vary with the concentration of the epoxide. For example, band maxima are found at 3382 and 3456 cm^{-1} with 41 mmol/L ethylene oxide and at 3392 and

Fig. 7. OH stretching region of the IR spectrum of (A) 4-F-phenol (14.6 mmol/L) and (B) CF_3CH_2OH (16.2 mmol/L) in CCl_4 containing mmol/L concentrations of 1,1,2,2-tetramethylethylene oxide as indicated.



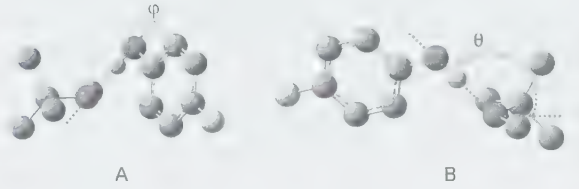
3471 cm^{-1} with 435 mmol/L ethylene oxide (see Supplementary data),[9] a result that can be attributed to differences in the permittivity (dielectric constant) of the two solvent mixtures.

The traces shown in Figs. 6 and 7 can be used to calculate the previously unknown β_2^H values for ethylene oxide (0.36) and tetramethylethylene oxide (0.58) (see Supplementary data).[9] The much larger β_2^H value for tetramethylethylene oxide compared with ethylene oxide is congruent with the β_2^H values for *tert*-butyl alcohol (0.49) vs. methanol (0.41) (2) and is undoubtedly due to the greater inductive electron-donating ability of $(CH_3)_nC$- groups compared with a CH_3 group.

Theoretical calculations

The changes in the potential energy as a function of the dihedral angle defined by R-O-H···O-C(methyl), i.e., as a function of rigid rotations of the molecules about their common hydrogen bond (structure **A**, Fig. 8), are shown in Figs. 9A and 10A, respectively. The results of relaxed

Fig. 8. The rotational potential energy surfaces (shown in Figs. 9A and 10A) were generated by rotation of the dihedral angle (φ) defined by R-O-H···O-C(methyl), as illustrated in structure **A** for the 4-F-phenol – *tert*-butyl methyl ether HB complex. The bending potentials shown in Figs. 9B and 10B were generated by changing the angle (θ) defined by the O—H bond of the HBD and the COC plane of the HBA, as illustrated in structure **B** for the same HB complex. Hydrogen atoms have been removed for clarity.



MP2/6-31+G** potential energy (PE) surface scans as a function of the bending angle (θ) defined by the O-H bond of the HBD and the COC plane of the HBA (structure **B**, Fig. 8) for the same two complexes are shown in Figs. 9B and 10B. This bending motion connects structures **A** and **B** in Fig. 1. These calculations reveal that structure **B** in Fig. 1 (with $\theta = 180°$) is not even a metastable energy minimum. For methanol, but not for 4-F-phenol, the $\theta = 180°$ structure is close to the transition state for the shift of the HBD from the "upper" lone pair of electrons on the oxygen atom (structure **A** in Fig. 1) to the equivalent lower lone pair. These PE surfaces demonstrate that these H-bonded complexes must sample a large range of configurations at room temperature.

Discussion

The structures of the HB complexes of 4-F-phenol and methanol with *tert*-butyl methyl ether are similar. In both complexes, the HBDs are aligned so that the plane defined by their COH atoms is roughly perpendicular to and roughly bifurcates the plane defined by the COC atoms of the ether (see structure **A** in Fig. 1). The PE surfaces generated by changes in φ (structure **A**, Fig. 8), i.e., by rigid rotation about the HB in both HB complexes, are fairly similar (see Fig. 9A). They reflect repulsive steric interactions between the hydrocarbon moieties of the HBDs and the HBA at rotation angles that substantially deviate from those of the minimum energy structures. The differences in steric bulk of the HBD and HBA hydrocarbon groups (HBD: *tert*-butyl > methyl; HBA: phenyl > methyl) are evident in Fig. 9A.

In contrast, the PE surfaces associated with changes in θ, i.e., with the bending motion of the HBD up and down with respect to the COC plane of the ether (structure **B**, Fig. 8), are very different for the methanol – *tert*-butyl methyl ether and 4-F-phenol – *tert*-butyl methyl ether complexes (see Fig. 9B). For methanol, this PE surface has two degenerate minima that correspond to HB formation to each of the lone pairs of the oxygen atom of the HBA. Note that in the second minimum, the HBA is reoriented to the "trans" position by a 180° rotation about the HB. This reorientation is possi-

[9] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5071. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Fig. 9. Potential energy surface (PES) scans at the MP2/6-31+G** level of theory for 4-F-phenol – methyl *tert*-butyl ether (solid line, ■) and for methanol – methyl *tert*-butyl ether (dotted line, ▲). (A) Rigid PE surface associated with changes in φ, i.e., associated with rotation about the hydrogen bond, as illustrated in structure **A** of Fig. 8. The asymmetries of these PE surfaces are due to the different sizes of the methyl and *tert*-butyl groups. (B) Relaxed PE surface associated with changes in θ, the bend angle defined as illustrated in structure **B** of Fig. 8. This second PE surface connects structures **A** and **B** of Fig. 1. The dashed horizontal lines in the plots indicate the value of *RT* at 298.15 K. The arrows indicate that the potential anergies rise steeply toward the HB strength of the complex.

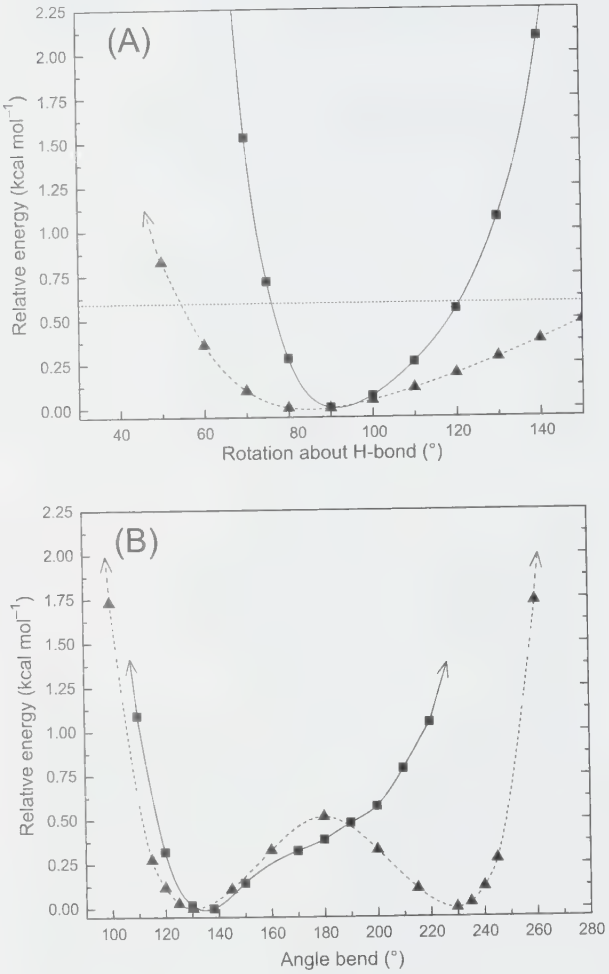
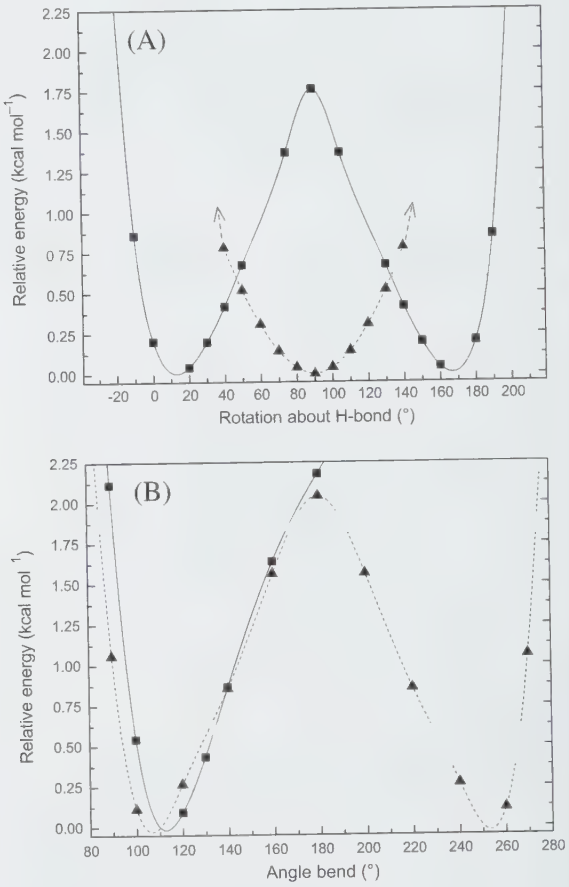


Fig. 10. Potential energy surface (PES) scans at the MP2/6-31+G** level of theory for 4-F-phenol – ethylene oxide (solid line, ■) and for methanol – ethylene oxide (dotted line, ▲). (A) Rigid PE surface associated with changes in φ, i.e., associated with rotation about the hydrogen bond, as illustrated in structure **A** of Fig. 8 for 4-F-phenol – methyl *tert*-butyl ether. (B) Relaxed PE surface associated with changes in θ, the bend angle defined as illustrated in structure **B** of Fig. 8 for 4-F-phenol – methyl *tert*-butyl ether. For methanol, this second PE surface connects structures **A** and **B** in Fig. 1, but for 4-F-phenol the PE continues to increase as θ increases above 180°. The dashed horizontal lines in the plots indicate the value of *RT* at 298.15 K. The arrows indicate that the potential energies rise steeply toward the HB strength of the complex.



ble because of the small size of the methyl group. However, the larger steric bulk of the phenyl ring in the 4-F-phenol complex prevents the facile reorientation of this HBD. Thus, the PE associated with changes in θ in the 4-F-phenol – *tert*-butyl methyl ether HB complex increases continuously from the minimum rather than reaching a local maximum at 180° as is the case for the methanol complex (Fig. 9B). This increase in PE is slow at first, but as the HB approaches the second lone-pair of the oxygen atom of the ether, steric repulsion becomes large and the PE increases more rapidly. A large portion of this asymmetric PE surface can be sampled at room temperature (RT = 0.59 kcal/mol at 298 K), and because the coupling between the O-H oscillator of the HBD and the O···H oscillator of the HB changes over this configuration sampling, an asymmetric O-H HB band is produced.

The situation is different for the ethylene oxide HB complexes. Figure 10A shows the PE surface associated with changes in φ, i.e., associated with rotation about the HB, in the methanol – ethylene oxide and the 4-F-phenol – ethylene oxide complexes. For the former complex, the COH plane of

the methanol bifurcates and is perpendicular to the plane of the ethylene oxide ring. Rotation about this HB produces a broader, single minimum PE surface analogous to that found for the similar motion in the methanol – *tert*-butyl methyl ether complex (Fig. 9A). In contrast, with 4-F-phenol the PE surface has two minima that are due to attractive interactions between the π electron cloud of the phenyl group and the CH_2 groups of the ethylene oxide.

The θ angle bend PE surface for the methanol – ethylene oxide HB complex has a similar shape to that found for the methanol – *tert*-butyl methyl ether complex (Fig. 10B). That is, two identical HB complexes of equal energy are formed in which the OH group of the HBD interacts with each lone pair on the oxygen atom of the epoxide. The minimum energy structures are transoid with the methyl group pointing away from the epoxide ring and are rather easily interconverted at room temperature. The methanol – ethylene oxide complex therefore yields a symmetric O-H HB band. For the 4-F-phenol – ethylene oxide HB complex, the strong secondary interactions that produce the double minimum shown in Fig. 10A prevent facile changes in the θ angle, i.e., the PE surface for this motion is quite steep. Both of the PE surfaces for the 4-F-phenol – ethylene oxide HB complex are effectively symmetric, which accounts for this complex having a symmetric O-H HB band. In this complex, the broadness of the O-H HB band results from the changes in coupling upon the interconversion of the two structures whose energy minima are shown in Fig. 10A.

Further evidence that two different HB complexes are not formed between *tert*-butyl methyl ether and 4-F-phenol comes from the plots in Fig. 4. The plots of Δν against α_2^H (Fig. 4A) for the phenols, with their asymmetric O-H HB bands, and for the alcohols, with their symmetric O-H HB bands, yield a single straight line.[10] A least-squares fitting of the data presented in Table 1 gives $\Delta\nu(OH) = 54(-\Delta H) - 9$ cm^{-1} ($R^2 = 0.98$, SD = 11 cm^{-1}). If we now use the two Δν values given by Berthelot et al. (3) for the deconvoluted 4-F-phenol – methyl *tert*-butyl ether O-H HB band (vide supra), we obtain $-\Delta H$ values of 3.6 (Δν = 186 cm^{-1}) and 6.0 (Δν = 315 cm^{-1}) kcal/mol. These HB enthalpies imply that if there really were two different complexes, the ratio of the weaker to the stronger would be ca. 2:98. Such a small population of the weaker HB complex would be unlikely to make an observable contribution to the O-H HB band and hence be the reason for the observed asymmetry.

In conclusion, although the asymmetries of the O-H HB bands for many phenol–ether complexes appear at first sight to be due to two (deconvolutable) overlapping bands that reflect the presence of two distinct HB complex configurations, this is not the true situation. In these cases, as in so many other aspects of science and life, appearances can be deceptive.

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[10]The point for CF_3CH_2OH deviates from the linear fit because this HBD undergoes a reorientation in the HB complex. This reorientation allows for a more favourable alignment of the H···O and C–F local dipoles than would be achieved if the HBD had an anti conformation.

Syntheses and characterization of phthalonitriles and phthalocyanines substituted with adamantane moieties[1]

Patrick W. Causey, Igor Dubovyk, and Clifford C. Leznoff

Abstract: The reaction of 3,4,5,6-tetrafluorophthalonitrile with 1-adamantanol, 1-adamantylamine, 1-adamantanemethanol, and 1-adamantaneethanol gave 4,5-di-(1-adamantyloxy)-3,6-difluorophthalonitrile, 4,5-di-(1-adamantylamino)-3,6-difluorophthalonitrile, 4-(1-adamantylamino)-3,5,6-trifluorophthalonitrile, 3,4,5,6-tetra-(1-adamantylmethoxy)phthalonitrile, and 3,4,5,6-tetra-(1-adamantylethoxy)phthalonitrile, respectively. The conversion of these tetrasubstituted phthalonitriles to magnesium, nickel, and metal-free phthalocyanines was demonstrated. These highly hindered phthalocyanines exhibited interesting red shifts in their UV–vis spectra.

Key words: highly hindered adamantane phthalocyanines, adamantylphthalonitriles.

Résumé : La réaction du 3,4,5,6-tétrafluorophtalonitrile avec l'adamantan-1-ol, l'adamantyl-1-amine, l'adamantane-1-méthanol et l'adamantane-1-éthanol conduit à la formation des 4,5-di-(adamantanyl-1-oxy)-3,6-difluorophtalonitrile, 4,5-di-(adamantanyl-1-amino)-3,6-difluorophtalonitrile, 4-(adamantanyl-1-amino)-3,5,6-trifluorophtalonitrile, 3,4,5,6-tétra-(adamantanyl-1-méthoxy)phtalonitrile, 3,4,5,6-tétra-(adamantanyl-1-éthoxy)phtalonitrile respectivement. On a démontré qu'il est possible de transformer ces phtalonitriles tétrasusbstitués en phtalocyanines libre ou complexées avec du nickel ou du magnésium. Les spectres UV–visible de ces phtalocyanines fortement empêchées présentent des déplacements intéressants vers le rouge.

Mots clés : phtalocyanines de l'adamantane fortement empêchées, adamantylphtalonitriles.

[Traduit par la Rédaction]

Introduction

Phthalocyanines (Pcs) are brilliantly coloured purple, blue, or green macrocyclic compounds that have been extensively studied, initially because of their extensive use as dyes (1), but more recently because of their interesting photochemistry (2), potential applications as chemical sensors (3), nonlinear optics (4), and as medicinal agents in photodynamic therapy (PDT) (5). Recently, red-coloured manganese Pcs for analogs, substituted with highly hindered, bulky hexadecaalkoxyl functional groups, have been reported (6, 7), while other red phthalocyanines bearing alkylthio (8) and phenyl groups (9) have been described. These analogs represent Pcs exhibiting pronounced red shifts. Previously, some highly red-shifted analogs of some Pcs had been prepared with some difficulty owing to insolubility (10) and decomposition problems (11).

A significant bathochromic red shift of the Pc chromophore has long been associated with analogs bearing electron-donating substituents at the 1, 4, 8, 11, 15, 18, 22, and 25 positions (nonperipheral), while less pronounced red shifts of the Q band are associated with substitution on the 2, 3, 9, 10, 16, 17, 23, and 24 positions (peripheral) (12, 13). For analogs fully substituted at both the peripheral and nonperipheral positions with alkoxy moieties, enhanced red shifts of the Q band have also been reported (14). It has been postulated that sterically bulky substituents at the peripheral positions around the Pc exert influence upon the nonperipheral positions, thereby effectively increasing the steric bulk of the nonperipheral substituents and further promoting a shifting of the Q band. Various metallated and nonmetallated Pcs bearing sterically bulky alkoxy moieties have been reported, including both neopentoxy and cyclohexylmethoxy groups (6, 7). In addition to the effect that these substitutions appear to have on the absorption spectra of the resulting Pcs, a disruption of the π stacking among the aromatic macrocycles increases the solubility of the molecule, even in nonpolar solvents.

One particular bulky alkyl moiety that has interested our research group is adamantane. In particular, amine-substituted adamantanes have been approved for treatment as an antiviral agent against influenza A (15) and adamantyl moieties have been investigated for their potential use as carrier groups for anticonvulsant (16) and anticancer drugs

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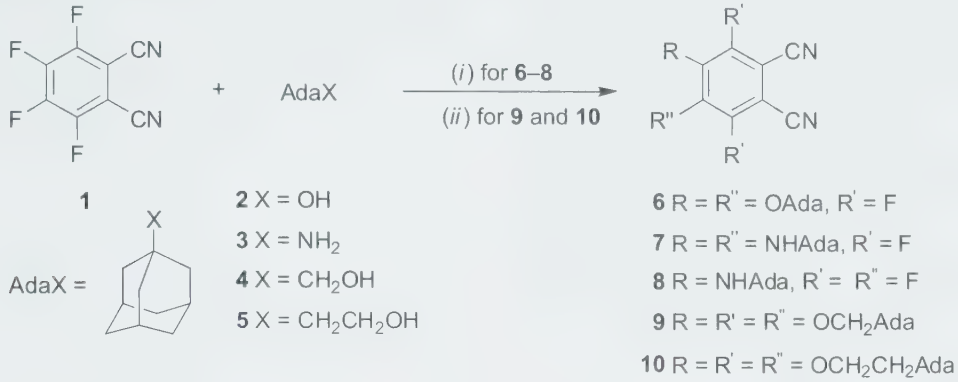
Scheme 1. Reagents and conditions: (*i*) *n*-BuLi, THF, 25 °C, 1 h; (*ii*) K_2CO_3, DMF, 140 °C, 4 days.



(17). However, it is their more general physicochemical characteristics associated with large steric bulk and their close steric relationship to our favorite bulky group, the neopentoxy group, that have piqued our interest as related to the potential for substitution onto the Pc framework.

The synthesis of substituted Pcs can be accomplished through two distinct approaches, each involving nucleophilic aromatic substitution. A recent approach employed in our research group has focused upon directly reacting metallated hexadecafluorophthalocyanines with various heteroatom nucleophiles (18). A limit to this synthetic approach is the distribution of substituents replacing the fluorine atoms resulting in a range of products that are difficult to separate by flash chromatography. Furthermore, complete replacement of all 16 fluorine atoms is limited to sterically small, strong nucleophiles Alternatively, tetrasubstituted phthalonitriles bearing functionalities, such as the neopentoxy group, can be readily produced by nucleophilic aromatic substitution reactions on 3,4,5,6-tetrafluorophthalonitrile (**1**) despite the steric bulk of the substituents (19).

The general synthetic strategy employed for the synthesis of adamantyl-substituted Pcs follows the production and isolation of substituted phthalonitriles. Subsequent condensation of the adamantyl-substituted phthalonitriles gives the required phthalocyanines. In this research we were interested in systematically varying the bulk of the substitiuents so as to produce a series of hexadecasubstituted phthalocyanines and examining their spectroscopic properties.

Results and discussion

A novel series of phthalocyanine compounds were designed and synthesized bearing bulky adamantane-based substituents. Commercially available 3,4,5,6-tetrafluorophthalonitrile (**1**) was reacted with 1-adamantanol (**2**), 1-adamantylamine (**3**), 1-adamantanemethanol (**4**), or 2-(1-adamantanyl)ethanol (**5**) in the presence of a base to generate 4,5-di-(1-adamantyloxy)-3,6-difluorophthalonitrile (**6**), 4,5-di-(1-adamantylamino)-3,6-difluorophthalonitrile (**7**), 4-(1-adamantylamino)-3,5,6-trifluorophthalonitrile (**8**), 3,4,5,6-tetra-(1-adamantylmethoxy)phthalonitrile (**9**), or 3,4,5,6-tetra-[2-(1-adamantyl)ethoxy]phthalonitrile (**10**). For the synthesis of fully substituted adamantylmethoxyl and adamantylethoxyl (Scheme 1) derivatives, a previously reported synthetic approach was followed in which an excess of alkyl alcohol was combined with 3,4,5,6-tetrafluorophthalonitrile (**1**) in *N*,*N*-dimethylformamide (DMF) at 140 °C in the presence of potassium carbonate (19). Both tetrasubstituted crude products, purified by flash silica gel column chromatography, were eluted with dichloromethane–methanol and reduced to an amber-coloured oil under reduced pressure. These oils solidified under a stream of air yielding the desired final products, which were confirmed by EI mass spectra NMR and IR spectroscopic analysis and microanalyses.

Despite repeated attempts to synthesize the tetrasubstituted analog from 1-adamantanol and **1** using this synthetic approach, the reaction was not successful. Therefore, an alternative synthetic approach for the aromatic nucleophilic substitution of the phthalonitrile fluorine was implemented, in which *n*-butyllithium in tetrahydrofuran (THF) was used to deprotonate **2** (or **3**) to create the desired nucleophile. Although this modified approach did result in fluorine substitution, complete tetrasubstitution was not achieved, presumably because of the high degree of steric bulk associated with the adamantanyl cage. This steric hindrance is not so severe in the adamantanemethanol and adamantaneethanol homologs, thereby enabling complete substitution. An obvious colour change was noted immediately upon addition of 3,4,5,6-tetrafluorophthalonitrile to the activated adamantyloxide nucleophile, and despite allowing the reaction to continue for up to 72 h, substitution of more than two fluorine moieties was not observed (Scheme 1). TLC of the reaction mixture did reveal an additional spot that was presumed to be the monosubstituted analog, although isolation of this species was not achieved. As usual, a sharp intense absorbance at 2239 cm^{-1} was observed in the IR spectra and was attributed to CN stretching. Furthermore, EI mass spectroscopy and microanalysis confirmed that the product from this reaction is a disubstituted phthalonitrile. The ^1H NMR spectra for this compound revealed the expected resonances for the adamantyl protons between δ 1.68 and 2.24 ppm, while the ^{19}F NMR exhibited a singlet at δ –114.9 ppm. The singlet suggests that the two adamantyloxy substituents are positioned at the peripheral position.

The synthesis of derivatives substituted with nitrogen-containing adamantane analogs was accomplished through an approach similar to adamantanol involving the in situ

generation of an adamantamide anion from **3**, followed by subsequent addition of **1**. The desired disubstituted product was separated by flash silica gel column chromatography, yielding an amber-coloured oil that solidified under air. EI mass spectroscopy and elemental analysis confirmed the product, while fluorine NMR spectra for the species showed a singlet at $\delta \sim -119$ ppm.

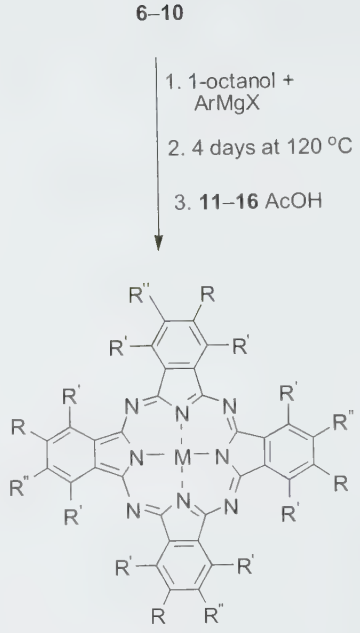
Subsequently, the reaction was repeated with 1 equiv. of adamantylamine (**3**) and **1** to generate the monosubstituted analog, **8**. Three distinct resonances (δ –118.7, –129.7, and –136.8) were identified in the ^{19}F NMR, corresponding to the three inequivalent fluorines from the monosubstituted phthalonitrile. Further characterization by EI mass spectroscopy, FT-IR spectroscopy, and elemental analysis confirm the synthesis of the monosubstituted adamantylamine-substituted analog.

Each of the above phthalonitriles (**6–10**) was condensed with 1-octanol and phenyl or 4-methoxyphenylmagnesium bromide to yield the corresponding magnesium phthalocyanine, as outlined in Scheme 2. The formed Pcs were all purified by flash silica gel column chromatography, eluting with a solvent mixture of hexane – ethyl acetate, and subsequently characterized by MALDI mass spectroscopy (MALDI-MS), elemental analyses, UV–vis spectrophotometry, and NMR analyses. The mass spectra of all magnesium phthalocyanines gave the expected parent ion clusters. In addition, daughter ion clusters corresponding to the loss of the adamantanyl fragments cleaved at the alkyl–heteroatom bond were also detected.

The ^1H NMR spectra for all magnesium phthalocyanines exhibited resonances for the adamantanyl protons between 1.6 and 2.3 ppm. In the OCH_2 region for the hexadeca-adamantylmethoxysubstituted analog **14**, a broad singlet was observed. A similar nickel phthalocyanine bearing hexadeca-cyclohexylmethoxyl moieties revealed temperature-dependant separation of the peripherally and nonperipherally substituted methylene protons and that at room temperature the two chemically different proton pairs appeared as a broad singlet (19) The peripheral and nonperipheral OCH_2 protons for the hexadecaadamantylethoxyphthalocyanine **15** are chemically inequivalent and appeared as distinct triplets at 4.27 and 4.16 ppm, respectively. As expected, the ^{19}F NMR for the hexadecasubstituted analogs showed no fluorine resonances, while the octaadamantyloctafluoro Pcs **11** and **12** exhibited singlets at approximately –120 ppm. However, the ^{19}F NMR for the tetrasubstituted analog **13**, which consists of a mixture of isomers, revealed multiple fluorine resonances corresponding to the multitude of inequivalent fluorines formed during the phthalocyanine condensation reaction.

A comparison of the UV–vis spectra for the Mg Pcs exhibits the expected red shifts owing to the substitution onto the macrocyclic aromatic ring, as shown in Table 1. Each of the hexadecasubstituted compounds exhibited a pronounced red shift of the Q band, with λ_{max} values similar to those reported in the literature for magnesium hexadecaneopentoxyphthalocyanine (754 nm) (6, 7). The tetrasubstituted derivative **13** was not red-shifted as greatly as the octaadamantylamine derivative, further supporting the association between large, sterically bulky substituents and the red shift of the corresponding UV–vis spectra. As compared

Scheme 2.



11 R = R" = OAda, R' = F, M = Mg
12 R = R" = NHAda, R' = F, M = Mg
13 R = NHAda, R' = R" = F, M = Mg
14 R = R' = R" = OCH_2Ada, M = Mg
15 R = R' = R" = OCH_2CH_2Ada, M = Mg
16 R = R" = OAda, R' = F, M = H_2

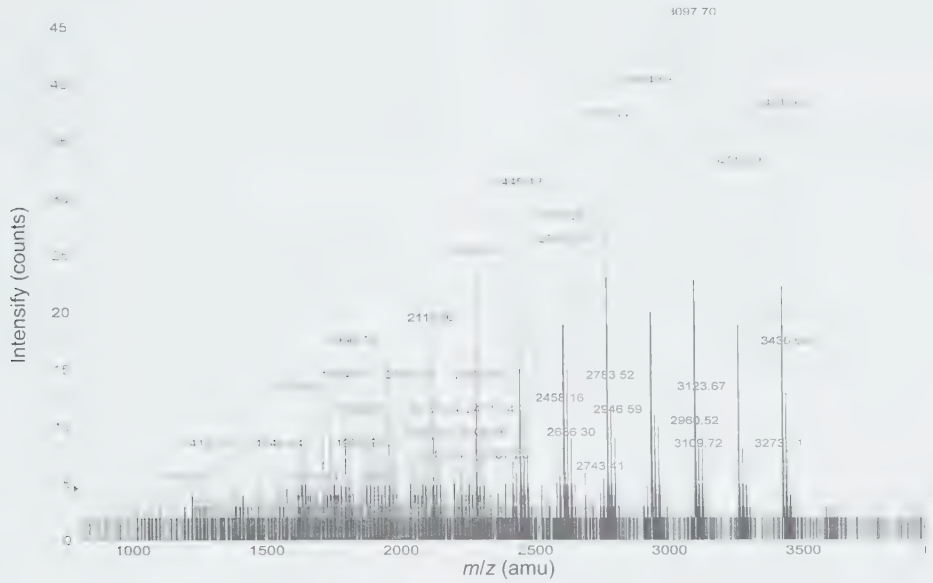
Table 1. Summary of the UV–vis spectra for the adamantane-substituted magnesium phthalocyanines.

Mg Pc	λ_{max} (log ε)
11	708 (4.83)
12	794 (4.57)
13	714 (4.63)
14	752 (4.91)
15	744 (4.93)

with the tetrasubstituted analog, the octaadamantylamine-substituted derivative exhibited a red shift of 80 nm. It is possible that these bulky adamantylamino groups, even at the peripheral positions, distort the planar Pc ring, causing this red shift. Not surprisingly, a small decrease in the λ_{max} was detected upon insertion of a methylene unit for the hexadecasubstituted analogs **15**, as compared with **14**, as the extra methylene group in **15** will position the bulky adamantyl group further from the core of the Pc.

Metal-free Pcs are useful intermediates for transmetallating synthetically challenging complexes. A metal-free phthalocyanine analog **16** was synthesized after refluxing the magnesium derivative **11** in acetic acid. Purification was achieved by flash silica gel column chromatogra-

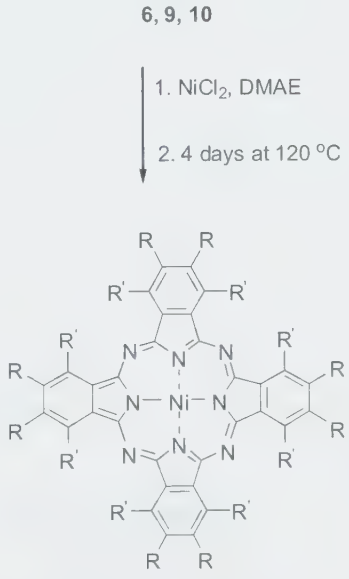
Fig. 1. MALDI-MS spectra for **19** showing parent ion cluster $[M + H]^+$ at 3418, along with daughter ion clusters separated by 163 amu ($C_{12}H_{19}$).



phy with hexane – ethyl acetate used as the mobile phase. This compound was characterized by MALDI-MS and again revealed the expected parent ion cluster at 1883 amu. A series of daughter ion clusters were observed separated by 135 amu, corresponding to the loss of an adamantanyl unit ($C_{10}H_{15}$). The complex was further characterized by NMR spectroscopy, elemental analysis, and UV–vis spectrophotometry, with the λ_{max} of the Q band red-shifted by 26–764 nm with respect to the magnesium derivative. Following the isolation and characterization of the metal-free derivative, repeated attempts to introduce manganese into the core of the phthalocyanine were unsuccessful.

Due to the difficulty associated with forming the metal-free phthalocyanines incorporating adamantane-based substituents, a multistep synthesis for transmetalating Pcs was not viable. Therefore, direct condensation of precursor phthalonitriles with nickel as the core metal ion was pursued. As previously described (19), the general synthetic approach is outlined in Scheme 3 in which **6**, **9**, or **10** was heated with $NiCl_2$ in *N,N*-dimethylaminoethanol (DMAE) for 4 days at 120 °C to give the nickel phthalocyanines **17**–**19**, respectively. Again, MALDI-MS revealed the expected parent ion clusters, in addition to daughter ion clusters corresponding to fragmentation between the alkyl substituents and oxygen. For the octaadamantyloctafluoro-nickel Pc **17**, the daughter ions were separated by 135 amu, while the daughter ion clusters for the hexadecaadamantylmethoxy-nickel Pc **18** were separated by 149 amu and the daughter ion peaks corresponding to hexadecaadamantylethoxy-substituted analog were separated by 163 amu, as shown in Fig. 1. Similar to the magnesium Pc analogs, the OCH_2 resonances for the adamantylmethoxyphthalocyanine **18** appeared as a broad signal at 4.21 ppm representing both the peripheral and nonperipheral substituents, while two clearly distinct triplet resonances at 4.78 and 4.53 ppm were observed for the peripheral and nonperipheral OCH_2 protons, respectively, of the adamantylethoxyl Pc **19**. UV–vis spectra were recorded for the three nickel phthalocyanines (summarized in Table 2), although the Q bands are not as red-shifted as the corresponding magnesium phthalocyanines. The most sterically congested nickel Pc (**18**) exhibited the greatest red

Scheme 3.



17 R = OAda, R' = F

18 R = R' = OCH_2Ada

19 R = R' = OCH_2CH_2Ada

Table 2. Summary of the UV–vis spectra for the adamantane-substituted nickel phthalocyanines.

Ni Pc	λ_{max} (log ε)
17	708 (4.91), 636 (4.23)
18	750 (4.93), 672 (4.43)
19	736 (4.88), 660 (4.25)

shift, while the octaadamantyloxy-octafluorophthalocyanine **17** was the least red-shifted nickel complex. Perhaps some aggregation in **17**–**19** resulted in somewhat lower log ε values than usual. This reinforces the association between large sterically hindered substitutions onto the aromatic macrocycle and the red shifting of the Q band for phthalocyanines, although the λ_{max} for **18** was slightly less red-shifted as compared with hexadecaneopentoxyphthalocynaninato nickel (750 vs. 758 nm) (19).

Experimental

General methods

Inert atmosphere conditions were maintained using Air Liquide prepurified argon. Magnetic stirring methods were utilized during all reactions. Flash chromatography was performed using silica gel of particle size 40–63 μm, with eluting solvents mixtures as described. Nuclear magnetic resonance (NMR) spectroscopy for proton and fluorine was performed using a Bruker 300 spectrometer at room temperature and was processed using XWIN-NMR 3.5 software. Chemical shifts are reported in parts per million (δ). Infrared (IR) spectra were recorded on a Mattson 3000 FT-IR spectrometer using KBr discs. UV–vis were recorded on a Hewlett-Packard HP8452A diode array spectrophotometer. For all phthalonitriles, low-resolution mass spectra (MS) were recorded in electron ionization (70 eV) mode on a Micromass/Waters GCT time-of-flight instrument. For all phthalocyanines, low-resolution MS were recorded using laser desorption ionization (LDI) on a PE Sciex Q-STAR XL or PerSeptive Biosystems Voyager – DE STR spectrometer. Microanalyses were performed by Guelph Chemical Laboratory Ltd., Guelph, Ontario.

Synthesis of 4,5-di-(1-adamantyloxy)-3,6-difluorophthalonitrile (6)

1-Adamantanol (**2**, 1.50 g, 9.85 mmol, 2 equiv.) was dissolved in 10 mL of THF and the solution was stirred under an argon atmosphere at room temperature. To this solution was added *n*-butyllithium in hexanes (4.94 mL, 2 mol/L, 2 equiv.). The reaction mixture initially turned cloudy and a fine white precipitate was observed. The mixture was stirred for 1 h before a solution of 3,4,5,6-tetrafluorophthalonitrile (**1**, 0.986 g, 4.93 mmol, 1 equiv.) in THF was added dropwise under argon. The reaction mixture turned reddish-purple and was stirred at room temperature for 4 h. After this period, 100 mL of water was added to the reaction mixture and the mixture was extracted with diethyl ether (3 × 50 mL). After drying over sodium sulfate, the solvent was removed under reduced pressure, resulting in an amber-coloured oil. The oil was then dissolved in a minimum of toluene and was passed through a flash silica gel column using toluene as eluant. The first fraction was collected and the solvent was removed under reduced pressure, yielding an oil that solidified upon sitting under a stream of air overnight. Yield: 76% (1.74 g); mp 196–198 °C. TLC (toluene): R_f 0.63. IR (KBr, cm^{-1}) ν: 2911, 2846, 2239 (CN), 1454, 1354, 1295, 1113, 1042. ^{1}H NMR ($CDCl_3$) δ :2.24 (br m, 6H, bridgehead C-H), 1.93 (m, 12H, CH_2), 1.68 (br m, 12H, CH_2). ^{19}F NMR ($CDCl_3$) δ: –114.9 (s). EI-MS *m/z* (rel. intensity): M^+ 464 (64). Anal. calcd. for $C_{28}H_{30}O_2N_2F_2$: C 72.39, H 6.51, N 6.03; found: C 72.42, H 6.34, N, 6.11.

Synthesis of 4,5-di-(1-adamantylamino)-3,6-difluorophthalonitrile (7)

1-Adamantylamine (**3**, 1.52 g, 10.1 mmol, 2 equiv.) was dissolved in 15 mL of THF and the solution was stirred under an argon atmosphere at room temperature. To this was added *n*-butyllithium in hexanes (4.0 mL, 2.5 mol/L, 2 equiv.). The reaction mixture initially turned cloudy and a fine white precipitate was observed. The mixture was stirred for 1 h before a solution of 3,4,5,6-tetrafluorophthalonitrile (**1**, 0.986 g, 4.93 mmol, 1 equiv.) in THF was added dropwise under argon. The reaction mixture turned dark red and was stirred at room temperature for 4 h. After this period, 100 mL of water was added to the reaction mixture and was extracted with diethyl ether (3 × 50 mL). After drying over sodium sulfate, the solvent was removed under reduced pressure, resulting in an amber-coloured oil. The oil was then dissolved in a minimum of toluene and was passed through a flash silica gel column using toluene for elution. The first fraction was collected and the solvent was removed under reduced pressure, yielding an oil that solidified upon sitting under a stream of air overnight. Yield: 52% (1.12 g); mp 184–186 °C. TLC (toluene): R_f 0.61. IR (KBr, cm^{-1}) ν: 3377, 2910, 2850, 2225 (CN), 1594, 1515, 1453, 1384, 1359, 1306. ^{1}H NMR ($CDCl_3$) δ: 4.05 (br s, 2H, N-H), 2.20 (br s, 6H, bridgehead C-H), 1.94 (m, 6H, CH_2), 1.85 (m, 6H, CH_2), 1.70(m, 12H, CH_2). ^{19}F NMR ($CDCl_3$) δ: –119.6. EI-MS *m/z* (rel. intensity): M^+ 462 (100). Anal. calcd. for $C_{28}H_{32}N_4F_2$: C 72.70, H 6.97, N 12.11; found: C 72.89, H 7.20, N 12.16.

Synthesis of 4-(1-adamantylamino)-3,5,6-trifluorophthalonitrile (8)

1-Adamantylamine (**3**, 0.76 g, 5.0 mmol, 1 equiv.) was dissolved in 15 mL of THF and the solution was stirred under an argon atmosphere at room temperature. To this solution was added *n*-butyllithium in hexanes (2.0 mL, 2.5 mol/L, 1 equiv.). The reaction mixture initially turned cloudy and a fine white precipitate was observed. The reaction was stirred for 1 h before a solution of 3,4,5,6-tetrafluorophthalonitrile (**1**, 0.986 g, 4.93 mmol, 1 equiv.) in THF was added dropwise under argon. It was then stirred at room temperature for 4 h and worked up as for **7**. IR (KBr, cm^{-1}) ν: 3418, 3382, 2912, 2854, 2231 (CN), 1566, 1452, 1382, 1108. Yield: 58% (0.95 g); mp 135–137 °C. TLC (toluene): R_f 0.65. ^{1}H NMR ($CDCl_3$) δ: 3.42 (br s, 1H, N-H), 2.19 (br s, 3H, bridgehead C-H), 1.93 (br s, 6H, CH_2), 1.71 (br s, 6H, CH_2). ^{19}F NMR ($CDCl_3$) δ: –118.7 (m), –129.7 (m), –136.8 (m). EI-MS *m/z* (rel. intensity): M^+ 331 (47). Anal. calcd. for $C_{18}H_{16}N_3F_3$: C 65.25, H 4.87, N 12.68; found: C 65.03, H 4.85, N 12.78.

Synthesis of 3,4,5,6-tetra-(1-adamantylmethoxy)phthalonitrile (9)

1-Adamantanemethanol (**4**, 5.0 g, 30.1 mmol, 24 equiv.), potassium carbonate (5 g, 36 mmol, 30 equiv.), and 3,4,5,6-tetrafluorophthalonitrile (**1**, 1.0 g, 5 mmol, 1 eq.) were dissolved in 12 mL DMF and the reaction mixture was heated to 120 °C for 4 days. After this period, 100 mL of water was added to the reaction mixture, which was subsequently extracted with diethyl ether (3 × 75 mL). After drying over sodium sulfate, the solvent was removed under reduced pressure, yielding an amber-coloured oil. The oil was dissolved in a minimum of dichloromethane and was passed through a flash silica gel column using dichloromethane–methanol (20:1) as eluant. The first fraction was collected and the solvent was removed under reduced pressure, yielding an amber oil that solidified to an off-white solid under a stream of air overnight. Yield: 78% (3.07 g); mp 173–176 °C. TLC (toluene): R_f 0.66. IR (KBr, cm^{-1}) ν: 2943, 2917, 2230 (CN), 1558, 1489, 1358, 1101. ^{1}H NMR ($CDCl_3$) δ: 3.69 (s, 4H, CH_2), 3.68 (s, 4H, CH_2), 2.04 (m, 12H, bridgehead C-H), 1.71 (m, 24H, CH_2), 1.67 (m, 24H, CH_2). EI-MS *m/z* (rel. intensity): M^+ 784 (41). Anal. calcd. for $C_{52}H_{68}O_4N_2$: C 79.55, H 8.73, N 3.57; found: C 79.14, H 9.07, N 3.59.

Synthesis of 3,4,5,6-tetra-(1-adamantylethoxy)phthalonitrile (10)

1-Adamantaneethanol (**5**, 5.0 g, 27.8 mmol, 8 equiv.), potassium carbonate (4.3 g, 32 mmol, 8 equiv.), and 3,4,5,6-tetrafluorophthalonitrile (**1**, 0.7 g, 3.5 mmol, 1 equiv.) were added to 12 mL of DMF and the reaction mixture was heated to 120 °C for 4 days. The work-up proceeded as for **9**, but dichloromethane–methanol (10:1) was used as eluant. Yield: 81% (2.39 g); mp 166–168 °C. TLC (toluene): R_f 0.68. IR (KBr, cm^{-1}) ν: 2935, 2846, 2231 (CN), 1559, 1448, 1382, 1371, 1244, 1106. ^{1}H NMR ($CDCl_3$) δ: 4.19 (m, 8H, OCH_2), 1.98 (br s, 12H, bridgehead C-*H*), 1.67 (m, 24H, CH_2), 1.56 (m, 32H, OCH_2CH_2 and adamantyl CH_2). EI-MS *m/z* (rel. intensity): M^+ 840 (51). Anal. calcd. for $C_{56}H_{76}O_4N_2$: C 79.96, H 9.11, N 3.33; found: C 79.60, H 9.35, N 3.32.

Synthesis of magnesium 2,3,9,10,16,17,23,24-octa-(1-adamantyloxy)-1,4,8,11,15,18,22,25-octafluorophthalocyanine (11)

4-Methoxyphenylmagnesium bromide (2 mL, 0.5 mol/L in THF) was added to 3 mL of 1-octanol and the mixture was stirred for 0.5 h under argon at room temperature. To this was added 4,5-di-(1-adamantyloxy)-3,6-difluorophthalonitrile (**6**) (0.250 g, 0.53 mmol) and the mixture was heated under argon to 120 °C. Upon heating, the clear, colourless mixture turned green. After heating for 24 h, 50 mL of methanol was added and a green solid precipitated out of solution. The solid was collected by centrifugation and was washed with water and methanol. The crude product was then passed through a flash silica gel column eluting with hexane – ethyl acetate (9:1). The first fraction was collected and the solvent was removed under reduced pressure, yielding a dark green solid. Yield: 34% (0.085 g); mp >300 °C. TLC (hexane – ethyl acetate, 5:1): R_f 0.72. UV–vis (dichloromethane) λ_{max} (log ε) (nm): 708 (4.83), 636 (4.06), 364 (4.43), 318 (4.37). ^{1}H NMR ($CDCl_3$) δ: 2.50 (br s, 24H, bridgehead C-H), 2.31 (m, 48H, CH_2), 2.22 (m, 48H, CH_2). ^{19}F NMR ($CDCl_3$) δ: –119.2. MALDI-MS *m/z* (rel. intensity): 1883 $[M]^+$ (10), 1748 $[M - C_{10}H_{15}]^+$ (21), 1613 $[M - 2(C_{10}H_{15})]^+$ (25), 1478 $[M - 3(C_{10}H_{15})]^+$. Anal. calcd. for $C_{112}H_{120}O_8N_8F_8Mg$: C 71.46, H 6.43, N 5.95; found: C 71.48, H 6.44, N, 6.11

Synthesis of magnesium 2,3,9,10,16,17,23,24-octa-(1-adamantylamino)-1,4,8,11,15,18,22,25-octafluorophthalocyanine (12)

4-Methoxyphenylmagnesium bromide (2 mL, 0.5 mol/L in THF) was added to 3 mL of 1-octanol and the mixture was stirred for 0.5 h under argon at room temperature. To this was added 4,5-di-(1-adamantylamino)-3,6-difluorophthalonitrile (**7**, 0.250 g, 0.53 mmol) and the mixture was heated under argon to 120 °C. Upon heating, the clear, colourless mixture turned red and was worked up as for **11**, yielding a dark green solid. Yield: 17% (0.042 g); mp >300 °C. TLC (hexane – ethyl acetate, 5:1): R_f 0.72. UV–vis (dichloromethane) λ_{max} (log ε) (nm): 794 (4.57), 708 (4.09), 478 (4.04), 358 (4.34), 322 (4.34). ^{1}H NMR ($CDCl_3$) δ: 2.11 (m, 24H, bridgehead C-H), 1.87 (m, 48H, CH_2), 1.68 (m, 48H, CH_2). MALDI-MS *m/z* (rel. intensity): 1872 $[M]^+$ 100. Anal. calcd. for $C_{112}H_{128}N_{16}F_8Mg$: C 71.76, H 6.88, N 11.95; found: C 71.87, H 7.27, N 11.24.

Synthesis of magnesium 2,9,16,23-tetra-(1-adamantylamino)-1,3,4,8,10,11,15,17,18,22,24,25-dodecafluorophthalocyanine (13)

4-Methoxyphenylmagnesium bromide (2 mL, 0.5 mol/L in THF) was added to 3 mL of 1-octanol and the mixture was stirred for 0.5 h under argon at room temperature. To this was added 4-(1-adamantylamino)-3,5,6-trifluorophthalonitrile (**8**, 0.250 g, 0.75 mmol) and the mixture was heated under argon to 120 °C. Upon heating, the clear, colourless mixture turned green. After heating for 24 h, 50 mL of methanol was added and a green solid precipitated out of solution and was worked up as for **11**, yielding a dark green solid. Yield: 21% (0.053 g); mp >300 °C. TLC (hexane – ethyl acetate, 9:1): R_f 0.62. UV–vis (dichloromethane) λ_{max} (log ε) (nm): 714 (4.63), 646 (4.07), 362 (4.37). ^{1}H NMR ($CDCl_3$) δ: 3.82 (br s, 4H, NH), 2.18 (m, 12H, bridgehead C-H), 1.71–1.96 (m, 24H, CH_2), 1.58 (br s, 24H, CH_2). ^{19}F NMR ($CDCl_3$) δ: –128 (m), –138 (m). MALDI-MS *m/z* (rel. intensity): 1348 $[M]^+$ (100), 1213 $[M - C_{10}H_{15}]^+$ (63), 1078 $[M - 2(C_{10}H_{15})]^+$ (53), 943 $[M - 4(C_{10}H_{15})]^+$ (24). Anal. calcd. for $C_{72}H_{64}N_{12}F_{12}Mg$: C 64.07, H 4.78, N 12.45; found: C 64.44, H 4.94, N 12.78

Synthesis of magnesium 1,2,3,4,8,9,10,11,15,16,17,18,22,23,24,25-hexadeca-(1-adamantylmethoxy)phthalocyanine (14)

4-Methoxyphenylmagnesium bromide was added (2 mL, 0.5 mol/L in THF) to 3 mL of 1-octanol and the mixture was stirred for 0.5 h under argon at room temperature. To this was added 3,4,5,6-tetraadamantylmethoxyphthalonitrile (**9**, 0.250 g, 0.32 mmol) and the mixture was heated under argon to 120 °C. Upon heating, the clear, colourless mixture turned green. After heating for 24 h, 50 mL of methanol was added and a green solid precipitated out of solution and was worked up as for **11**, yielding a dark green solid. Yield: 15%

(0.039 g); mp >300 °C. TLC (hexane – ethyl acetate, 15:1): R_f 0.52. UV–vis (dichloromethane) λ_{max} (log ε) (nm): 752 (4.91), 672 (4.12), 364 (4.19). ^{1}H NMR ($CDCl_3$) δ: 3.49 (br s, 32H, OCH_2), 2.00 (m, 48H, bridgehead C-H), 1.70–1.90 (m, 192H, CH_2). MALDI-MS *m/z* (rel. intensity): 3160 $[M]^+$ (49), 3011 $[M - C_{11}H_{17}]^+$ (57), 2862 [M – 2(C11H17)]$^+$ (100), 2713 $[M - 3(C_{11}H_{17})]^+$ (96). Anal. calcd. for $C_{208}H_{272}O_{16}N_8Mg$: C 78.94, H 8.66, N 3.54; found: C 78.50, H 8.47, N, 3.28.

Synthesis of magnesium 1,2,3,4,8,9,10,11,15,16,17,18, 22,23,24,25-hexadeca-(1-adamantaneethoxy)phthalocyanine (15)

4-Methoxyphenylmagnesium bromide (2 mL, 0.5 mol/L in THF) was added to 3 mL of 1-octanol and the mixture was stirred for 0.5 h under argon at room temperature. To this was added 3,4,5,6-tetra-(1-adamantylethoxy)phthalonitrile (**10**, 0.250 g, 0.30 mmol) and the mixture was heated under argon to 120 °C. Upon heating, the clear, colourless mixture turned green. After heating for 24 h, 50 mL of methanol was added and a green solid precipitated out of solution. The solid was collected by centrifugation and was washed with water and methanol. The crude product was then passed through a flash silica gel column eluting with hexane – ethyl acetate (9:1). The first fraction was collected and the solvent was removed under reduced pressure, yielding a dark green solid. Yield: 20% (0.051 g); mp >300 °C. TLC (hexane – ethyl acetate, 15:1): R_f 0.49. UV–vis (dichloromethane) λ_{max} (log ε) (nm): 744 (4.93), 668 (4.09), 328 (4.10). ^{1}H NMR ($CDCl_3$) δ: 4.27 (t, 16H, J = 9.0 Hz, OCH_2), 4.16 (t, 16H, J = 9.0 Hz, OCH_2), 1.99 (br s, 48H, bridgehead C-*H*), 1.76 (m, 96H, CH_2), 1.61 (m, 128H, OCH_2OCH_2- and CH_2). MALDI-MS *m/z* (rel. intensity): 3384 $[M]^+$ (68), 3221 $[M - C_{12}H_{19}]^+$ (71), 3058 $[M - 2(C_{12}H_{19})]^+$ (95), 2895 $[M - 3(C_{12}H_{19})]^+$ (89), 2732 $[M - 4(C_{12}H_{19})]^+$ (83), 2569 $[M - 5(C_{12}H_{19})]^+$ (83), 2406 $[M - 6(C_{12}H_{19})]^+$ (100). Anal. calcd. for $C_{224}H_{304}O_{16}N_8Mg$: C 79.38, H 9.04, N 3.31; found: C 78.77, H 9.41, N 3.78

Synthesis of metal-free 2,3,9,10,16,17,23,24-octa-(1-adamantyloxy)-1,4,8,11,15,18,22,25-octafluorophthalocyanine (16)

Magnesium 2,3,9,10,16,17,23,24-octa-(1-adamantyloxy)-1,4,8,11,15,18,22,25-octafluorophthalocyanine (**11**, 0.502 g, 0.27 mmol) was dissolved in glacial acetic acid (5 mL) and the mixture was refluxed under air. After 4 days, the crude product was precipitated out of solution following the addition of absolute ethanol (50 mL). The dark green precipitate was washed with ethanol (2 × 30 mL) and methanol (1 × 30 mL). The crude product was purified by flash silica gel column chromatography using hexane – ethyl acetate (4:1) as eluant. The first fraction was collected and the solvent was removed under reduced pressure. Yield: 11% (55 mg); mp >300 °C. TLC (hexane – ethyl acetate, 4:1): R_f 0.80. UV–vis (dichloromethane) λ_{max} (log ε) (nm): 734 (4.02), 704 (4.01), 670 (3.51), 636 (3.40), 358 (3.63). ^{1}H NMR ($CDCl_3$) δ: 2.25 (m, 24H, bridgehead C-H), 1.52–1.98 (m, 96H, CH_2). ^{19}F ($CDCl_3$) δ: –119.2. IR (KBr, cm^{-1}) ν: 3275, 2915, 2853, 1732, 1653, 1456, 1300, 1281, 1048, 967. MALDI-MS *m/z* (rel. intensity): 1858 $[M]^+$ (28), 1723 $[M - C_{10}H_{15}]^+$ (51), 1588 $[M - 2(C_{10}H_{15})]^+$ (87), 1453 $[M - 3(C_{10}H_{15})]^+$ (100). Anal. calcd. for $C_{112}H_{122}O_8N_8F_8$: C 72.31, H 6.61, N 6.02; found: C 71.90, H 6.75, N 5.96.

Synthesis of nickel 2,3,9,10,16,17,23,24-octa-(1-adamantyloxy)-1,4,8,11,15,18,22,25-octafluorophthalocyanine (17)

4,5-Di-(1-adamantyloxy)-3,6-difluorophthalonitrile (**6**, 0.306 g, 0.65 mmol) and nickel(II) chloride (90 mg, 0.7 mmol) were added to 4 mL of *N,N*-dimethylaminoethanol (DMEA). The mixture was heated to 145 °C and stirred under argon. After stirring for 24 h, a green solid was precipitated following the addition of 40 mL of water. The precipitate was collected by centrifugation. The crude product was purified by flash silica gel column chromatography with hexane – ethyl acetate (4:1) as eluant. The first fraction was collected and the solvent was removed under reduced pressure. Yield: 24% (0.076 g); mp >300 °C. TLC (hexane – ethyl acetate, 2:1): R_f 0.81. UV–vis (dichloromethane) λ_{max} (log ε) (nm): 708 (4.91), 636 (4.23), 342 (4.34), 304 (4.47). ^{1}H NMR ($CDCl_3$) δ: 2.41 (br s, 24H, bridgehead C-H), 2.36 (br m, 48H, CH_2), 1.74 (m, 48H, CH_2). ^{19}F NMR ($CDCl_3$) δ: –126.1. MALDI-MS *m/z* (rel. intensity): 1914 $[M]^+$ (10), 1779 $[M - C_{10}H_{15}]^+$ (23), 1644 $[M - 2(C_{10}H_{15})]^+$ (42), 1509 $[M - 2(C_{10}H_{15})]^+$ (67), 1374 $[M - 4(C_{10}H_{15})]^+$ (91). Anal. calcd. for $C_{112}H_{120}O_8N_8F_8Ni$: C 70.18, H 6.31, N 5.85; found: C 69.91, H 6.78, N 5.74.

Synthesis of nickel 1,2,3,4,8,9,10,11,15,16,17,18, 22,23,24,25-hexadeca-(1-adamantylmethoxy)phthalocyanine (18)

3,4,5,6-Tetra-(1-adamantylmethoxy)phthalonitrile (**9**, 0.202 g, 0.26 mmol) and nickel(II) chloride (36 mg, 0.28 mmol) were added to 4 mL of DMEA. The mixture was heated to 145 °C and allowed to stir under argon. After stirring for 24 h, a green solid was precipitated following the addition of 40 mL of water and was worked up as for **17**. Yield: 14% (29 mg); mp >300 °C. TLC (hexane – ethyl acetate, 9:1): R_f 0.71. UV–vis (dichloromethane) λ_{max} (log ε) (nm): 750 (4.93), 672 (4.43), 386 (4.55), 314 (4.77). ^{1}H NMR ($CDCl_3$) δ: 4.21 (br m, 32H, OCH_2), 2.10 (br m, 24H, bridgehead CH), 1.98 (br m, 24H, bridgehead CH), 1.61–1.88 (m, 192H, CH_2). MALDI-MS *m/z* (rel. intensity): 3214 $[M + H_2O]^+$ (38), 3065 $[M + H_2O - C_{11}H_{17}]^+$ (52), 2916 $[M + H_2O - 2(C_{11}H_{17})]^+$ (53), 2769 $[M + H_2O - 3(C_{11}H_{17})]^+$ (94). Anal. calcd. for $C_{208}H_{272}O_{16}N_8Ni$: C 77.65, H 8.58, N 3.48; found: C 77.48, H 9.03 N, 3.61.

Synthesis of nickel 1,2,3,4,8,9,10,11,15,16,17,18, 22,23,24,25-hexadeca-(1-adamantaneethoxy)phthalocyanine (19)

3,4,5,6-Tetra-(1-adamantaneethoxy)phthalonitrile (**10**, 0.260 g, 0.31 mmol) and nickel(II) chloride (40 mg, 0.31 mmol) were added to 4 mL of DMEA. The mixture was heated to 145 °C and allowed to stir under argon. After stirring for 24 h, a green solid was precipitated following the addition of 40 mL of water and was worked up as for **17**. Yield: 32% (85 mg); mp >300 °C. TLC (hexane – ethyl acetate, 9:1): R_f 0.73. UV–vis (dichloromethane) λ_{max} (log ε) (nm): 736 (4.85), 660 (4.25), 372 (4.40), 340 (4.48), 312 (4.61). ^{1}H NMR ($CDCl_3$) δ: 4.78 (t, 16H, J = 7.1 Hz, OCH_2CH_2), 4.53 (t, 16H, J = 7.1 Hz, OCH_2CH_2), 2.12 (t, 16H, J = 7.1 Hz,

OCH_2CH_2), 2.05 (two br m, 48H, bridgehead CH), 1.94 (t, 16H, J = 7.1 Hz, OCH_2CH_2), 1.62–1.85 (m, 192H, adamantyl-CH_2). MALDI-MS m/z (rel. intensity): 3418 $[M + H]^+$ (83), 3256 $[M + H - C_{12}H_{19}]^+$ (72), 3094 $[M + H - 2(C_{12}H_{19})]^+$ (100), 2930 $[M + H - 3(C_{12}H_{19})]^+$ (85). Anal. calcd. for $C_{224}H_{304}O_{16}N_8Ni$: C 78.59, H 8.95, N 3.27; found: C 78.07, H 9.29, N 3.64.

Conclusions

Phthalocyanines bearing large bulky substituents have previously shown interesting physicochemical properties, including a red shifting of the Q band. A series of metallated and nonmetallated Pcs have been synthesized incorporating large bulky substituents based upon analogs of adamantane. These complexes exhibit interesting characteristics, notably pronounced red shifting of the Q band.

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Synthesis and Lewis acid induced isomerization of mono-, di-, and tri-spiro α-keto tetrahydro-furans and -pyrans[1]

David G. Hilmey, Peter R. Selvaraj, and Leo A. Paquette

Abstract: The stereoselectivity of the acid-catalyzed ring expansion of dihydrofuranyl and dihydropyranyl 1,2-adducts to spirocyclic ketones 8 and **9** has been examined. These substrates have become readily available by the utilization of 1,3-dichloroacetone as a synthetic equivalent of cyclopropanone. The kinetically controlled isomerizations result in ring expansion to dispirocyclopentanones. Third-stage conversion to trispirocyclohexanones was shown to be possible in select examples. On a different front, the syn and anti pairs proved capable of interconversion by heating in the presence of boron trifluoride etherate. A push–pull fragmentation of the ketone ring is proposed to account for these epimerizations. Calculations have been performed to simulate transition state energies in the oxonium ion intermediates and to gain some idea of the preferred ground-state geometries of the final products.

Key words: oxonium ion rearrangements, ring expansions, acid-catalyzed epimerizations, cyclopropanone equivalent, spirocyclic ethers.

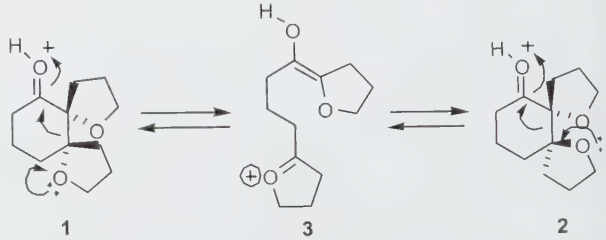
Résumé : On a étudié la stéréosélectivité de l'expansion de cycle acidocatalysée de 1,2-adduits dihydrofuranyles et dihydropyranyles en cétones spirocycliques **8** et **9**. Ces substrats sont facilement disponibles à partir de la 1,3-dichloroacétone utilisée comme équivalent de synthèse de la cyclopropanone. Les isomérisations sous contrôle cinétique conduisent à une expansion de cycle qui fournit des dispirocyclopentanones. On a démontré la possibilité de réaliser le troisième stade de conversion en trispirocyclopentanones en utilisant des exemples choisis. On a par ailleurs démontré que les paires syn et anti peuvent subir des interconversions par chauffage en présence d'éthérate de trifluorure de bore. On propose une fragmentation de type « push–pull » du cycle cétonique pour expliquer ces épimérisations. Des calculs ont été effectués pour simuler les énergies de l'état de transition dans les ions oxonium intermédiaires et pour mieux comprendre les géométries de l'état fondamental privilégié des produits finaux.

Mots clés : réarrangement d'ion oxonium, expansion de cycle, épimérisation acidocatalysée, équivalent de cyclopropanone, éthers spirocycliques.

[Traduit par la Rédaction]

Introduction

The feasibility of inducing epimerization in molecules constructed of two neighbouring quaternary carbon centers is seldom encountered. One way to drive this process is to suitably position a heteroatom such as an ether oxygen or a divalent sulfur β to a carbonyl group (1, 2). This structural arrangement allows for the operation under acidic conditions of a push–pull fragmentation of the cycloalkanone, with subsequent reconstitution of the original but now stereochemically scrambled substrate (3). The interconversion of **1** with **2** via **3** is illustrative of the process. Since **1** and **2** are chiral and amenable to resolution while **3** is not, the cyclization of this tethered oxonium ion – enol intermediate results in racemization as has been observed experimentally (3). Rotation of either terminus of the chain relative to the other prior to ring closure provides the enabling means for losing stereochemical "memory".



1 **3** **2**

Studies involving such molecular frameworks have previously been limited to di- and tri-spirocyclic cyclohexanone systems because of synthetic constraints. To explore a more representative array of congeners, it became imperative that cyclopropanone replace cyclobutanone as the key building

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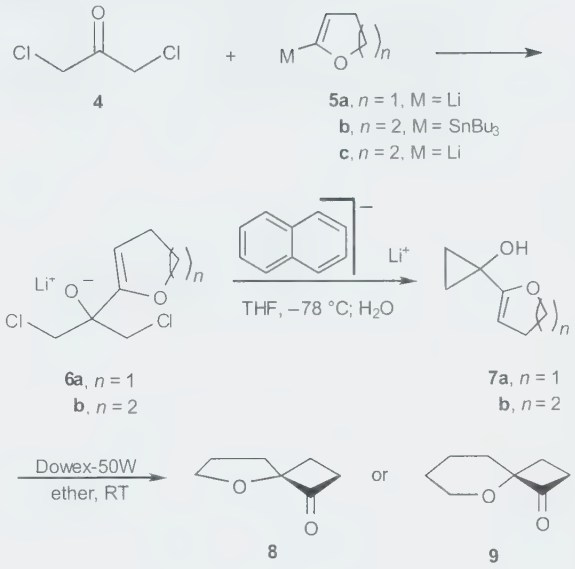
block. However, the highly reactive nature of this compound does not lend itself to being accessible in preparative quantities in a standard laboratory setting (4, 5). Most often, recourse has been made to release of the three-membered cyclic ketone from its ethyl hemiketal (6), 1-acetoxycyclopropanol (7), or a select carbinolamine (8). None of these alternatives was considered to be particularly desirable in the present context.

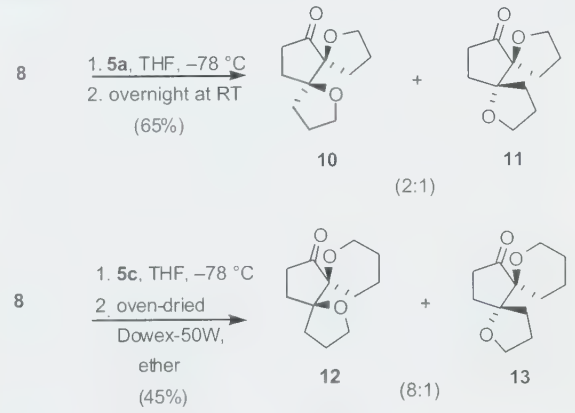
A more promising alternative originated from reports that appeared several decades ago indicating that 1,3-dichloroacetone **4** (Scheme 1) undergoes a straightforward 1,2-addition in the presence of Grignard reagents. Subsequent exposure of these adducts to ethylmagnesium bromide and iron(III) chloride then furnished 1-substituted cyclopropanols (9, 10). At a later date, Barluenga et al. (11) discovered that the initial Grignard adducts are amenable to reductive cyclization when admixed with $MgBr_2$ and lithium powder, or more conveniently with lithium naphthalenide in THF. We have come to favour the latter approach to reactive three-membered carbinols and detail here the advantages that materialize when this chemistry precedes application of the oxonium ion initiated pinacolic ring expansion (12). The use of 1,3-dichloroacetone in this manner offers an experimentally simple and versatile means for varying not only the dimensions of the central ring, but the number of spirocycles attached thereto as well as their individual size (13).

Also addressed herein is the extent to which the end products are subject to solution-phase epimerization in the presence of boron trifluoride etherate. MM3 calculations have also been performed to gauge the relative stabilities of the isomer pairs in the gas phase, and in combination with AM1 semiempirical calculations, the thermodynamically preferred geometry of the putative oxonium ion intermediates.

Scheme 1.



Scheme 2.



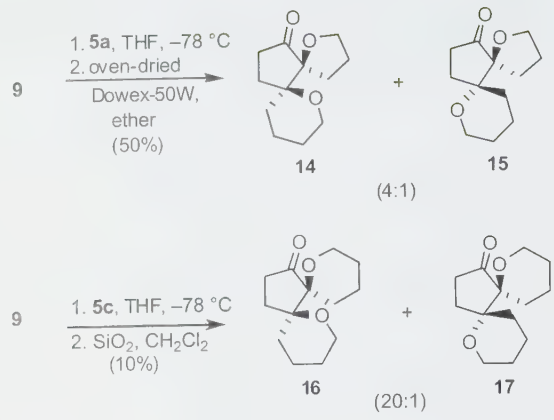
Synthetic efforts

The deprotonation of 2,3-dihydrofuran with *tert*-butyllithium (14) proceeds efficiently to produce **5a** whose condensation with **4** gives rise to alkoxide **6a** (Scheme 1). Direct reductive dechlorination of **6a** with a solution of lithium naphthalenide in THF at –78 to 20 °C promoted conversion to cyclopropanol **7a** after workup. Overnight stirring of **7a** with a small quantity of Dowex-50W resin at room temperature resulted in smooth isomerization to the volatile spiro ketone **8**, which was isolated in 65% overall yield from **4**. When comparable direct use was made of 3,4-dihydropyran as the anticipated precursor to organometallic **5c**, a diverse array of products was formed in low yield following exposure to **4**. This situation was remedied by effecting transmetalation instead via stannane **5b** (15). This alternative means for the generation of **5c** and its further processing as in Scheme 1 furnished **9** with an overall efficiency of 75%.

In the case of **8**, second-stage coupling to **5a** led to a diastereomeric mixture of two tertiary carbinols intended to serve as precursors to **10** and **11** (Scheme 2). Fortunately, the pinacol rearrangement of these adducts occurred spontaneously on standing in neat condition at room temperature. Attempts to bring about this isomerization with acid promoters under more customary conditions (3, 16) resulted instead in hydrolysis of the enol ether functionality. Consequently, cyclopentanones **10** and **11** were formed as a chromatographically separable 2:1 mixture in a single laboratory manipulation (65%). The second example, involving the combination of **5c** with **8**, produced carbinols that proved amenable to ring expansion in the presence of oven-dried Dowex-50W resin. The dominance of the more polar syn isomer **12** by the margin of 8:1 is noteworthy.

Our attention was next directed to the acquisition of analogs characterized by the presence of a spirotetrahydropyranyl unit β to the ketone carbonyl. The response of **9** to the action of **5a** and subsequent ring expansion proceeded in a manner closely comparable to the precedent set by **8**. Once again, the syn isomer **14** was more prevalent in the product mixture than **15** (4:1, Scheme 3). A striking difference in behaviour was encountered following preparation of the tertiary carbinol from 1,2-addition of **5c** to **9**. In contrast to its congeners, this intermediate proved to be unusually sensitive to the presence of Dowex-50W. When the targeted ring enlargement could not be brought about in this manner, other promoters were sought and silica gel slurried in CH_2Cl_2

Scheme 3.



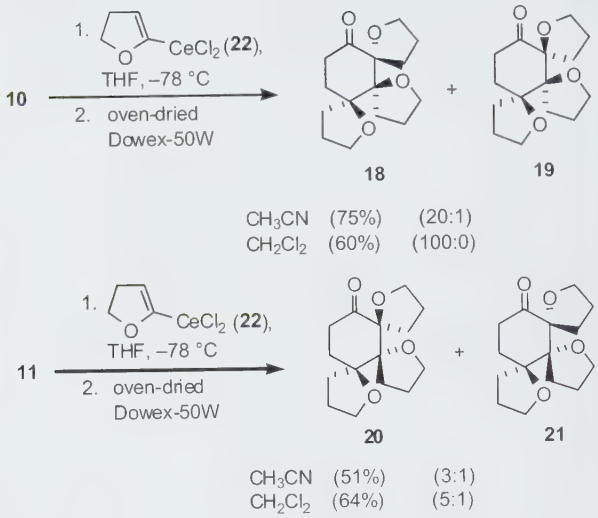
proved to be workable. With this catalyst, isomerization proceeded slowly. After 3 days, a mixture of **16** and **17** richer in the syn isomer was generated and chromatographically separated. The diminished efficiencies of the ring expansions involving **9** are a likely reflection of enhanced steric congestion in the vicinity of the reaction centers. The stereochemical assignments to all of the di- and tri-spiro ketones have been documented elsewhere (13), based on distinctive ^{1}H NMR spectral features and polarity considerations.

Compounds **10** and **11** proved amenable to a third-stage enhancement of the core ring size to the cyclohexanone level provided that the cerate reagent **22** was used to curtail the significant tendency of these cyclopentanones to experience competitive enolization (17, 18). Two important issues emerge from the data compiled in Scheme 4. The more obvious finding is the preference exhibited for introducing the third spirotetrahydrofuran anti to that positioned at the adjacent β-carbon. For **20** and **21**, the stereoselectivity gap is modest (3–5:1) and of comparable magnitude in the two solvents. Where **18** and **19** are concerned, the bias for producing **18** is quite substantial and is particularly dominant when the reaction is performed in CH_2Cl_2. Under the latter conditions, no **19** was observed. In these examples, the trispiro product ratios are reversed relative to those witnessed for the dispiro analogs such as **10/11**, **12/13**, **14/15**, and the like. We also call attention to the brevity with which **18–21** can be prepared from 1,3-dichoroacetone, thus doing away with issues surrounding their availability.

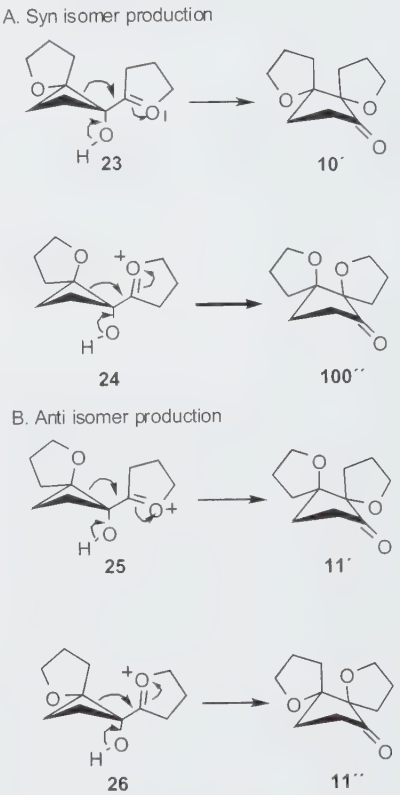
Stereoselectivity considerations

In line with ample precedent, the migratory aptitudes associated with 1,2-shifting to the oxonium ion center strongly favour translocation of the more electron-rich neighbouring carbon atom (1, 12, 19, 20). The end result is therefore a preferred migration of that adjacent carbon atom, which is the more highly alkylated. The only restriction is the requirement that the migrating bond be capable of being properly aligned with the pπ orbital, resident at the electrophilic center. In the present examples, the degrees of freedom are such that two modes of structural staging are possible for each product isomer. The conformational facets of the conversion of **8** to **10** and **11** are exemplified in Scheme 5. At issue is the diastereoselectivity of oxonium ion capture, a

Scheme 4.



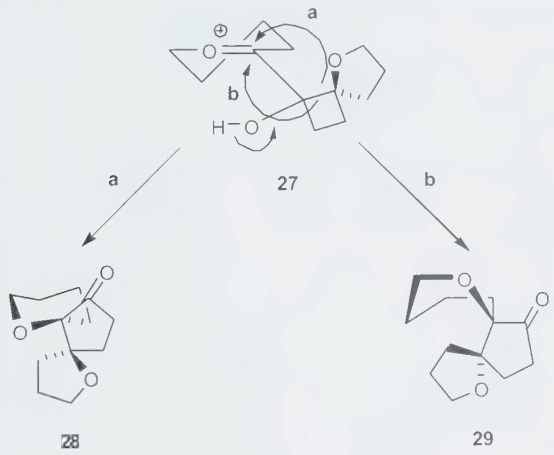
Scheme 5.



phenomenon that holds considerable fascination (21). One sees that **23** and **24** are capable of arriving at **10′** and **10″**, while **25** and **26** lead instead to **11′** and **11″**, respectively. The possibility exists, of course, that the relative magnitude and direction of stereoselectivity is founded only on steric grounds, an analysis made acceptable by the kinetically irreversible nature of the conversion to products. In this con-

nection, it is perhaps insignificant that the ratio of diastereomeric tertiary carbinols (e.g., the precursors to **23/26** and **24/25**) is not known with precision. The key outcome is the favoured proximal placement of the methylene groups, as in **10′**, or of the ether oxygen atoms, as in **10″**, relative to the pair of alternatives **11′** and **11″** where nonbonded CH_2–O interaction develops.

The change from a flexible envelope arrangement having pseudorotational capability as in tetrahydrofurans to a well-defined axial–equatorial status in tetrahydropyrans, because of the adoption of chairlike arrangements, is a dramatic one. As a result, the diastereoselectivity associated with migrations involving six-membered oxonium ions can be projected to be more pronounced. Thus, the conversion of **27** to **28** should occur more readily and its formation not deterred as in **29** because of the development of boatlike features.

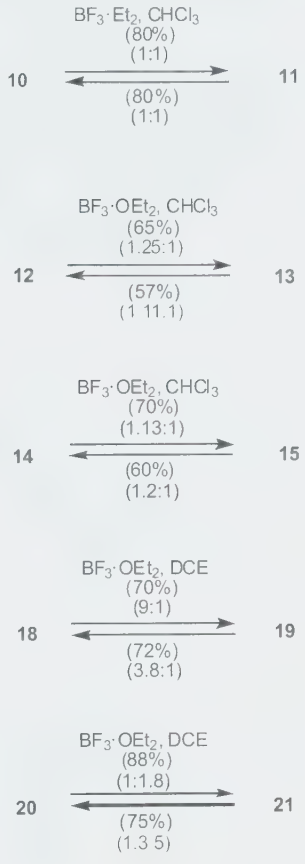


Calculations show that the oxonium functionality preferentially orients its oxygen antiperiplanar to the hydroxyl substituent (22) , as seen in **24**. This conformer will then rearrange to syn isomer **10″**, which would explain, in part, the overall preference for more prevalent formation of dispirocyclopentanones **10**, **12**, **14**, and **16**. On the other hand, the enhanced ability of the oxonium intermediate derived from the chelation-controlled adduct of **10** to adopt a synperiplanar relationship with the hydroxyl group explains the preferences for the formation of **18**. Relevantly, when the addition to **10** is nonchelation-controlled, the preferred conformation of the oxonium unit reverts back to antiperiplanar with respect to the hydroxyl, again giving **18** after ring expansion. These conformational preferences, regardless of the facial selectivity of the addition process, concisely account for the very high selectivity noted in the formation of **18** over **19**.

Lewis acid induced isomerizations

On an allied front, the ability of the various syn–anti isomer pairs to interconvert when heated in the presence of boron trifluoride etherate has been examined. An important distinction to be made regarding isomerizations of the type **1** ⇄ **2** is that kinetic control is not operative. All of the ketones prepared in the course of this investigation were treated in a comparable manner involving either chloroform or 1,2-dichloroethane as solvent. The results are compiled in Table 1. Chlorinated solvents proved most well-suited to these processes, with interconversion being optimal in the indicated medium. Except perhaps for the **10** ⇄ **11** example, complete equilibration was not reached for the majority of the isomerizations. Higher temperatures and longer reaction times only enhanced the extent of the accompanying decomposition. Under no circumstances did **16** and **17** interconvert.

Table 1. BF_3·OEt_2-induced equilibrations.



Molecular mechanics (MM3) calculations were performed on seven sets of isomers, including the **30/31** pair for the sake of completeness. The conformational searching was performed with recourse to the Monto Carlo simulation capability in MacroModel version 5.0 (23). A minimum of 1000 simulations were determined per structure and involved operations featuring one bond closure (1.0–3.0 Å) in all rings. The minimum energy diagrams were visualized with Chem 3D Ultra (24).

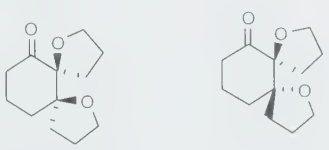
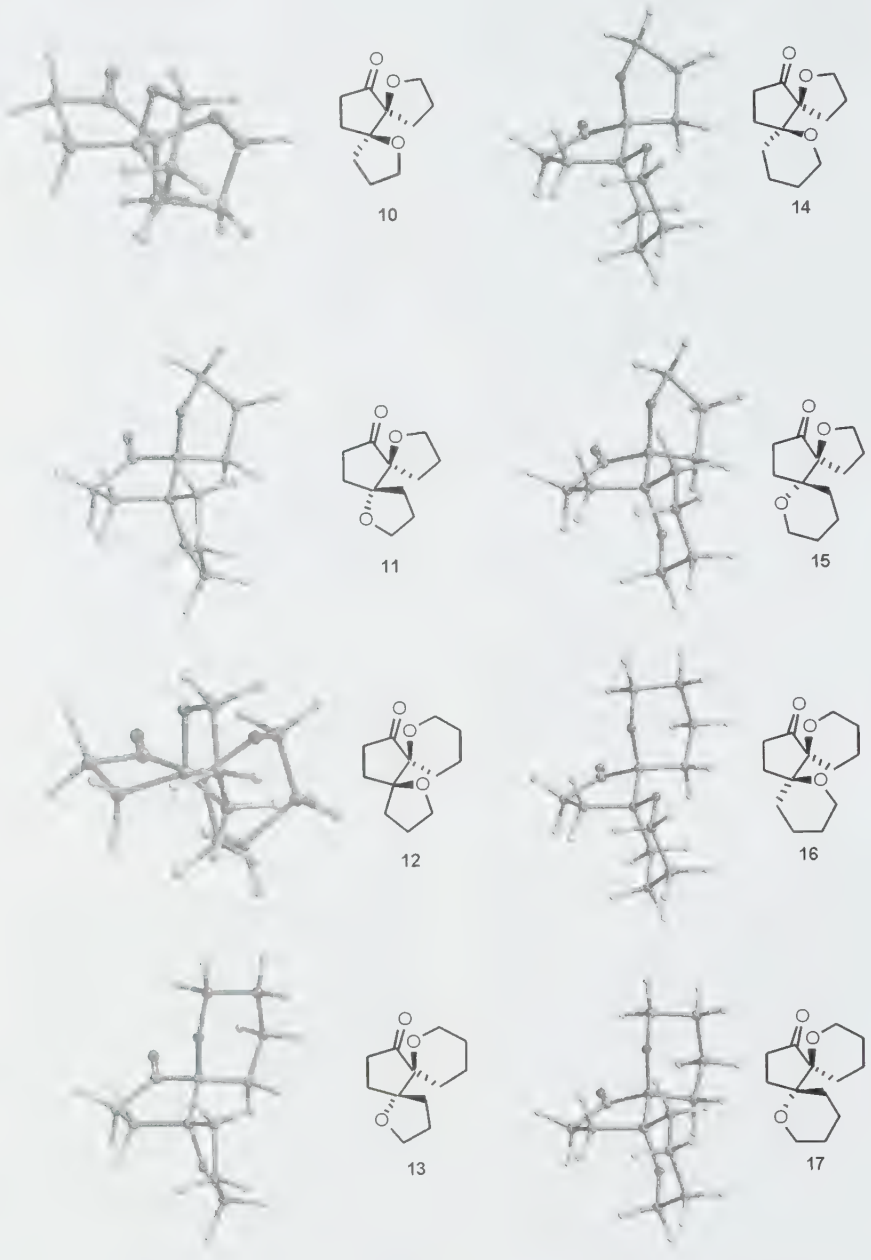


Fig. 1. Perspective drawings of the minimal energy conformations of **10–31**. Note that the representations for **18–21** are enantiomeric to those depicted in the text.



A conformational model of the lowest energy conformation of each of the 14 structures is illustrated in Fig. 1, and the associated steric energy values are compiled in Table 2. These data reveal the cyclopentanone systems **10–17** to have rather similar strain energy differences ranging from 2.6–2.8 kcal/mol (1 cal = 4.184 J). These values indicate the anti isomers to be thermodynamically advantaged to the extent of 95:5 at RT. For the cyclohexanone systems, the energy differences between pairs is considerably smaller (ca. 1 kcal/mol), thus reducing the energy gaps to a factor of only three- to six-fold. In addition, the **20/21** pair alone exhibits greater stability for its syn diastereomer.

Whereas **11** has both of its heteroatoms oriented pseudoaxially, isomer **10** projects its α C—O bond in a pseudoequatorial fashion. The latter preference persists when the α-spirocycle is expanded to the tetrahydropyranyl level as seen in **12**. We conclude that the [4.4] and [4.5] dispiro systems, including **14/15** and **16/17**, have lower energy when the capability exists to orient the α- and β-heteroatoms pseudoaxially. In the mixed systems, the

Fig. 1 (*concluded*).

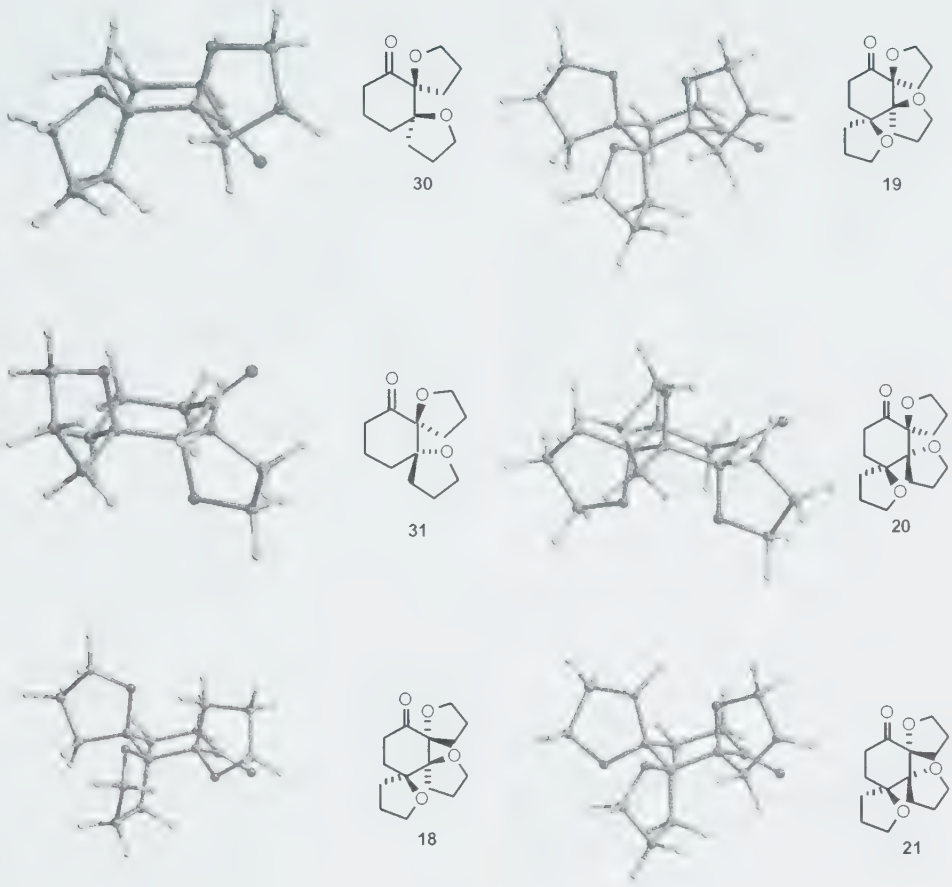


Table 2. MM3-derived steric energies.

Compound	E_{steric} (kcal/mol)	ΔE (kcal/mol)
10	57.5	
11	54.8	–2.7
12	52.1	
13	49.3	–2.8
14	46.7	
15	44.1	–2.6
16	51.9	
17	49.3	–2.6
30	52.6	
31	51.9	–0.7
19	74.1	
18	72.9	–1.2
21	72.8	
20	73.8	+1.0

Note: The syn isomer is cited first.

tetrahydropyranyl ring, whether situated α or β to the ketone as in **12** and **14**, likewise prefers to adopt a pseudoaxial orientation placing the tetrahydrofuranyl ring in a seemingly less favourable equatorial position. This conformational dominance by the six-membered heteroring is noteworthy.

The anti isomer of the **30/31** pair is modestly lower in energy (0.7 kcal/mol). This small but significant difference can be traced back to the axial character of the C—O bonds that is adopted twice in **31** and only once in **30**. Finally, in the remaining cyclohexanones **18–21**, the spiroannulated tetrahydrofuran rings orient themselves in a fashion opposite to that reflected in the cyclopentanone systems. In these trispirocyclic examples, increased equatorial placement of the C—O bonds serves to lower the level of steric strain in the system, as noted in other contexts (25–27).

At the experimental level, the acid-catalyzed equilibrations of pure samples of **10–14** gave rise to product mixtures approximating 1:1. In light of the energy differences determined in the gas phase for these syn–anti isomer pairs, these distributions appear not to be controlled by ground state energetics. We can hypothesize, though, that the final distribution is influenced by solvent effects and more strongly by coordination with the one equivalent of $BF_3{\cdot}OEt_2$. This latter association is likely leveling the energetic differences seen between syn and anti isomers, either through altered conformation or steric and electronic factors. On the other hand, the epimerizations have proven quite utilitarian as a means for funneling one stereoisomer into another. The initial experiments, which were performed with catalytic levels of $BF_3{\cdot}OEt_2$, fared poorly. Subsequently, the use of catalytic

quantities was abandoned in favor of a full equivalent of Lewis acid, despite the possibility that such high levels of promoter could play a role in leveling the relative amounts of isomers in each subset.

For **18**–**21**, it proved possible to make use of 0.3 equiv. of catalyst. This reduced loading resulted in the generation of isomer ratios more reflective of the theoretical equilibrium values. The discrepancies that remain might stem from the tight binding of boron trifluoride to one-third of the respective starting cyclohexanone.

In conclusion, the isomerization of **10**–**15** with stoichiometric amounts of Lewis acid does not adhere to thermodynamic control largely through acid coordination and solvent effects. Ketones **18**–**21** perform better at approaching equilibrium, although very slowly, while **16** and **17** are unresponsive to these conditions. The energetic preference is biased in favour of the anti relationship of the C—O bonds with one exception. The THF and THP spirocycles favour axial oxygen orientations in the dispiro examples regardless of ring size, while an equatorial preference is seen in the trispirocycles.

Experimental

1-Oxaspiro[3.4]octan-6-one (8)

Dry tetrahydrofuran (100 mL) and freshly distilled 2,3-dihydrofuran (7.15 mL, 94.5 mmol) were placed in a 500 mL flame-dried flask, purged with N_2, and cooled to –78 °C. After 15 min, *tert*-butyllithium (55.6 mL of 1.7 mol/L in pentane, 94.5 mmol) was introduced via cannula. After 30 min, the solution was brought to 0 °C (ice bath) and after an additional 30 min introduced into a solution of 1,3-dichloroacetone (10.0 g, 78.8 mmol) in anhydrous ether (200 mL) at –78 °C. The yellow reaction mixture was stirred in the cold for 2 h before a solution of lithium naphthalenide (197 mL of 1 mol/L in THF) was added via cannula. After 4 h, the green solution was allowed to warm to rt and then cooled to 0 °C before being quenched with sat. $NaHCO_3$ solution. The separated aqueous phase was extracted with ether (3 × 150 mL) and the combined organic phases were dried and filtered. The filtrate was admixed with Dowex-50W resin (8 g), stirred overnight, and filtered again. The solvent was removed by bulb-to-bulb distillation to a volume of about 150 mL, followed by rotatory evaporation (no heat) until a solid–oil mixture was seen. Addition of toluene (25 mL), column chromatography on silica gel (elution with 5%–20% ether in petroleum ether), and subsequent fractional distillation to remove solvent afforded **8** as a pale yellow oil (6.4 g, 65%). IR (neat, cm^{-1}): 1790, 1058. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.93 (t, J = 6.6 Hz, 2H), 2.79–2.70 (m, 2H), 2.22–2.05 (m, 3H), 2.02–1.90 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 211.7, 96.8, 70.1, 39.7, 33.8, 26.6, 25.6. EI-MS *m/z* calcd.: 144.07 [$M^+ - H_2O$]; found: 144.05. Anal. calcd. for $C_7H_{10}O_2$: C 66.64, H 7.99; found: C 66.52, H 8.23.

1-Oxaspiro[3.5]nonan-7-one (9)

A solution of **5b** (14.93 g, 40.0 mmol) in dry THF (150 mL) was blanketed with N_2, cooled to –78 °C, and treated dropwise with *n*-butyllithium (29.2 mL of 1.3 mol/L in pentane, 0.038 mol). Upon completion of the addition, the reaction mixture was stirred in the cold for 30 min prior to being added to a solution of 1,3-dichloroacetone (5.08 g, 0.040 mol) in dry THF (100 mL) at –78 °C. After 1 h at this temperature, a solution of lithium naphthalenide (from lithium (0.69 g, 0.10 mol) and naphthalene (19.22 g, 0.15 mol)) in THF (200 mL) was added. The reaction mixture was maintained at –78 °C for 2 h, quenched with water, diluted with petroleum ether (200 mL), and extracted with ether (3 × 300 mL). The organic extracts were washed with brine, treated with Dowex-50W (3 g), and stirred for 3 h. The resin was separated by filtration, the solvent removed by bulb-to-bulb distillation, and the residue purified by chromatography on silica gel (elution with 4:1 petroleum ether – ether) to furnish 4.0 g (75%) of **9** as a colourless, volatile oil. IR (neat, cm^{-1}): 1732, 1464, 1282. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.18–4.10 (m, 1H), 3.65–3.59 (m, 1H), 2.56–2.32 (m, 2H), 1.90–1.80 (m, 1H), 1.44–1.28 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.3, 87.5, 64.9, 39.1, 34.2, 30.1, 29.8, 25.8, 25.4, 20.2. ES-HRMS *m/z* calcd.: 163.0735 [M + Na]$^+$; found: 163.0735.

Dispirocyclopentanones 10 and 11

A solution of 2,3-dihydrofuran (5.2 mL, 69.0 mmol) in dry THF (75 mL) was cooled to –78 °C under N_2, treated with *tert*-butyllithium (46 mL of 1.5 mol/L in pentane), and stirred for 0.5 h at –78 °C followed by 0.5 h at 0 °C. A solution of **8** (5.8 g, 46.0 mmol) in THF (25 mL) was introduced dropwise at this temperature and the reaction mixture was allowed to warm to rt after 2 h. While being cooled in an ice bath, the mixture was quenched with sat. $NaHCO_3$ solution and diluted with ether. The separated aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried and evaporated. After 2 days, chromatography on silica gel (elution with 25%–50% ethyl acetate in hexanes) afforded 4.17 g of the polar **10** and 2.0 g of **11**, both as colourless oils.

10

IR (neat, cm^{-1}): 1751, 1078. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.10 (m, 1H), 3.95–3.80 (m, 3H), 2.38 (q, J = 9.7 Hz, 1H), 2.23 (ddd, J = 2.8, 9.3, 19.2 Hz, 1H), 2.10–1.65 (series of m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 216.5, 90.7, 88.6, 70.1, 68.4, 32.2, 31.0, 30.4, 29.9, 25.8, 25.3. ES-HRMS *m/z* calcd.: 219.0992 [M + Na]$^+$; found: 219.0998.

11

IR (neat, cm^{-1}): 1750, 1067. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.95–3.79 (m, 4H), 2.48–2.23 (m, 2H), 2.20–1.80 (series of m, 9H), 1.70–1.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 216.4, 89.7, 88.4, 69.5, 68.5, 33.4, 31.7, 30.8, 27.1, 26.3, 26.1. ES-HRMS *m/z* [M + Na]$^+$ calcd.: 219.0992; found: 219.0990.

Dispirocyclopentanones 12 and 13

n-Butyllithium (29 mL of 1.54 mol/L, 45 mmol) was added to a solution of **5b** (18.65 g, 50 mmol) in anhydr. THF (100 mL) at –78 °C. After 30 min, the mixture was added to a solution of **8** (5.0 g, 39.7 mmol) in THF (50 mL) and stirring was maintained in the cold for 2 h. Water was slowly added, the products were extracted into ether, and the combined organic layers were washed with brine and dried.

Oven-dried Dowex-50W resin (2 g) was added and ultimately filtered off when isomerization was complete (TLC analysis). The filtrate was evaporated and the residue chromatographed on silica gel (gradient elution with hexanes – ethyl acetate). Ketone **12** eluted with a 2:1 solvent mixture while **13** eluted with a 10:1 solvent system. **12** (3.33 g, 40%) and **13** (0.42 g, 5%) were isolated as colourless oils.

12

IR (neat, cm^{-1}): 1743, 1450. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.33–4.24 (m, 1H), 3.90–3.79 (m, 3H), 2.45–2.32 (m, 1H), 2.22–2.05 (m, 2H), 1.96–1.46 (series of m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 216.4, 89.9, 81.4, 68.6, 64.2, 33.5, 30.3, 30.1, 26.2, 25.7, 25.3, 18.6. ES-HRMS *m/z* calcd.: 233.1148 $[M + Na]^+$; found: 233.1148.

13

IR (neat, cm^{-1}): 1741, 1443. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.80–3.56 (m, 4H), 2.30–1.99 (m, 5H), 1.94–1.83 (m, 3H), 1.77–1.61 (m, 3H), 1.54–1.34 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 215.9, 90.4, 79.8, 68.3, 64.1, 34.1, 31.4, 28.9, 26.1, 25.8, 23.0, 18.3. ES-HRMS *m/z* calcd.: 233.1148 $[M + Na]^+$; found: 233.1158.

Dispirocyclopentanones 14 and 15

A solution of 2,3-dihydrofuran (2.64 mL, 35 mmol) in anhydr. THF (100 mL) was cooled to –78 °C, treated with *tert*-butyllithium (17.6 mL of 1.7 mol/L, 30 mmol), stirred in the cold for 1 h, and allowed to warm to rt for 30 min. The reaction mixture was returned to –78 °C at which point it was added to a solution of **9** (4.0 g, 28.5 mmol) in dry THF (50 mL). Once TLC analysis indicated the ketone to be consumed, water was slowly introduced and the product was extracted into ether (3 × 100 mL). The combined organic layer was washed with brine and dried. Oven-dried Dowex-50W resin (2.5 g) was added to the filtrate. When the reaction was complete (TLC analysis), the resin was filtered off, the filtrate was concentrated, and the residue was chromatographed on silica gel (gradient elution from hexane to ethyl acetate – hexane) to afford **14** (2.40 g, 40%) and **15** (0.59 g, 10%), both as colourless oils.

14

IR (neat, cm^{-1}): 1752, 1448. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.13–3.92 (m, 2H), 3.82–3.77 (dd, J = 10.5, 3.5 Hz, 1H), 3.60–3.52 (dt, J = 11, 3.0 Hz, 1H), 2.53–2.44 (ddd, J = 3.3, 9.0, 10.3 Hz, 1H), 2.33–2.11 (m, 2H), 2.02–1.54 (series of m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 216.7, 92.0, 80.3, 70.1, 62.1, 30.8, 29.0, 27.2, 25.5, 25.1, 24.0, 19.2. ES-HRS *m/z* calcd.: 233.1154 $[M + Na]^+$; found: 233.1143.

15

IR (neat, cm^{-1}): 1750, 1446. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.88–3.54 (m, 4H), 2.45–2.11 (m, 3H), 2.04–1.72 (m, 6H), 1.62–1.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 216.1, 89.8, 80.5, 77.5, 77.0, 69.0, 61.6, 32.0, 27.2, 26.5, 26.1, 24.8, 18.9. ES-HRMS *m/z* calcd.: 233.1154 $[M + Na]^+$; found: 233.1156.

Reaction of 5c with 9

n-Butyllithium (20.1 mL of 1.54 mol/L in hexane, 31 mmol) was added to a solution of **5b** (11.94 g, 32 mmol) in anhydr. THF (100 mL) at –78 °C. After being stirred for 30 min, this solution was added to a solution of **9** (2.8 g, 20 mmol) in the same medium (50 mL) and at the same temperature. After the disappearance of **9** (TLC), water was slowly introduced, the products were extracted into ethyl acetate (3 × 200 mL), and the combined organic layers were washed with brine and dried. The residue remaining after solvent evaporation was dissolved in dry CH_2Cl_2 (250 mL). Silica gel (4 g) was added and stirring was maintained at rt for 3 days. After filtration, solvent removal, and chromatographic separation on silica gel (hexane – ethyl acetate, 25–5:1), less polar **17** (20 mg, 0.5%) and more polar **16** (400 mg, 9%) were isolated.

16

Colourless solid, mp 70–72 °C. IR (neat, cm^{-1}): 1745, 1443, 1219. ^1H NMR (300 MHz, C_6D_6) δ: 4.57–4.48 (dt, J = 2.8, 11.4 Hz, 1H), 3.83–3.71 (m, 2H), 3.40–3.31 (dt, J = 2.7, 8.5 Hz, 1H), 2.29–2.17 (m, 1H), 2.12–2.03 (m, 1H), 1.87–1.76 (m, 2H), 1.63–1.53 (dt, J = 4.2, 12.5 H, 1H), 1.49–1.12 (m, 10H), 1.03–0.97 (m, 1H). ^{13}C NMR (75 MHz, C_6D_6) δ: 214.9, 82.6, 80.8, 63.4, 61.8, 32.4, 27.2, 25.8, 25.7,24.8, 23.8, 19.1, 18.8. ES-HRMS *m/z* calcd.: 247.1310 $[M + Na]^+$; found: 247.1308.

17

Colourless oil. IR (neat, cm^{-1}): 1743, 1441, 1094. ^1H NMR (300 MHz, C_6D_6) δ: 3.69–3.64 (m, 2H), 3.50–3.44 (m, 1H), 3.30–3.21 (dt, J = 11.6, 2.8 Hz, 1H), 2.56–2.40 (m, 1H), 2.27–2.00 (m, 4H), 1.77–1.21 (m, 11H). ^{13}C NMR (75 MHz, C_6D_6) δ: 214.4, 82.3, 80.3, 63.9, 61.0, 32.6, 27.2, 26.4, 26.2, 23.7, 22.5, 19.1, 18.8. ES-HRMS *m/z* calcd.: 247.1310 $[M+Na]^+$; found: 247.1310.

Ring expansion of 10 with 2,3-dihydrofuran

Cerium trichloride heptahydrate (31.3 g, 41.8 mmol) was dried overnight under high vacuum at 140 °C, admixed with dry THF (125 mL), and stirred at rt for 2 h. The resulting slurry was cooled to –78 °C and *tert*-butyllithium (1.6 mol/L in pentane) was added until a pink color persisted at which point a solution of **5a** (from 2,3-dihydrofuran (4.8 mL, 63.4 mmol)) in THF (75 mL) was introduced. Stirring was maintained at –78 °C for 2 h prior to the addition of **10** (8.2 g, 41.8 mmol) dissolved in THF (50 mL) via syringe pump over 45 min. After 2 h of stirring in the cold, the reaction mixture was warmed to 0 °C, quenched with sat. $NaHCO_3$ solution, and filtered through Celite after 30 min. The separated aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic phases were dried and evaporated. The resulting oil was dissolved in acetonitrile (200 mL), admixed with oven-dried Dowex-50W resin (8 g), and stirred overnight. The mixture was filtered through Celite and freed of solvent to leave a residue that was chromatographed on silica gel (elution with 30% ethyl acetate in hexane) to give 8.0 g of **18** and 0.35 g of **19** (total 75%), both of which were spectroscopically identical with earlier recorded data. When the last step was performed in CH_2Cl_2, a 60% yield of **18**, exclusively, was isolated.

Ring expansion of 11 with 2,3-dihydrofuran

Reaction of cerium trichloride heptahydrate (14.0 g, 37.4 mmol), 2,3-dihydrofuran (1.8 mL, 23.8 mmol), *tert*-butyllithium in pentane (14 mL, 1.6 mol/L), and **11** (2.2 g, 11.2 mmol) in the predescribed manner, and performance of the final step in acetonitrile gave rise to the isolation of 1.5 g of **20** and 0.5 g of **21** for a combined yield of 51% in a ratio of 3:1. Use of CH_2Cl_2 as solvent led to the isolation of **20** and **21** in 64% combined yield in a ratio of 5:1. The spectral features of these products proved identical to those previously reported.

Isomerization of 10 and 11 — Prototypical procedure

Ketone **10** (4.5 g, 22.9 mmol) dissolved in $CHCl_3$ (100 mL) was treated with boron trifluoride etherate (2.9 mL, 23 mmol), refluxed for 6 h, cooled to 0 °C, and quenched with water. The separated organic phase was dried and freed of solvent to leave a residue that was chromatographed on silica gel. Elution with 25%–50% ethyl acetate in hexane furnished 1.7 g of **10** and 1.9 g (80% total) of **11**.

An identical procedure was adopted starting from **11** (500 mg, 2.65 mmol) in $CHCl_3$ (10 mL) and the subsequent introduction of boron trifluoride etherate (0.37 mL, 2.91 mmol). A parallel workup protocol furnished 206 mg of **10** and 1.93 mg of **11** (total of 80%).

Acknowledgment

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Deprotonation of β,β-disubstituted α,β-unsaturated amides — Mechanism and stereochemical consequences[1]

James R. Green, Marek Majewski, and Victor Snieckus

Abstract: A detailed study of the lithium dialkylamide induced deprotonation of β,β-disubstituted α,β-unsaturated amides is presented. The preferential γ-*Z*-deprotonation and stereochemical outcome of substituents on the γ-*Z* carbon atom are rationalized in terms of a cyclic eight-membered transition state, which is supported by DFT calculations. Analogous deprotonations on cyclohexylidenecarboxamides reveal a delicate balance of the preference for the eight-membered cyclic transition state with the effects of existing substituents on the ring and the intervention of a twist-boat transition state.

Key words: dienolate, amide, deprotonation mechanism, transition state, enolization, regioselectivity, stereoselectivity.

Résumé : On a effectué une étude détaillée de la déprotonation induite par les dialkylamides de lithium d'amides α,β-insaturés et β,β-disubstitués. La déprotonation préférentielle en γ-*Z*- et le résultat stéréochimique des substitutions sur l'atome de carbone γ-*Z* sont rationalisés en termes d'un état de transition cyclique à huit chaînons qui est supporté par des calculs de la théorie de la densité fonctionnelle. Des déprotonations analogues sur les cyclohexylidènecarboxamides mettent en évidence la délicate balance de la préférence en faveur de l'état de transition cyclique à huit chaînons avec les effets des substituants déjà présents sur le cycle et l'intervention d'un état de transition en forme de bateau croisé.

Mots clés : diénolate, amide, déprotonation, mécanisme, état de transition, énolisation, régiosélectivité, stéréosélectivité.

[Traduit par la Rédaction]

Introduction

The prediction of the stereochemistry of enolate formation is of fundamental significance to the large number of valuable C—C bond-forming synthetic strategies of which the aldol condensation is arguably the most prominent (1). A body of data (2) on the stereoselection of enolization has been rationalized by the pericyclic chairlike transition state model (structure 1 in Fig. 1) originally proposed by Ireland et al. (3) in which deprotonation occurs perpendicular to the plane of the carbonyl coordinated to the lithium dialkylamide (4). This model is based on allylic strain (5) and stereoelectronic (4, 6) considerations. Compelling kinetic (7, 8) and spectroscopic (9) evidence for lithium base carbonyl complexation associated with proton abstractions has been advanced (10), although the strict cyclohexane-like chair nature of the transition state has required revision in light of computational analysis (11).

In spite of the extensive synthetic use of β,β-disubstituted, α,β-unsaturated carbonyl compounds (**2**) and related derivatives (12, 13), the stereoselectivity aspects of dienolate formation (γ-*Z* or γ-*E* proton abstraction) have not been systematically addressed (14–17). Although the preferential deprotonation of γ-*Z* over equivalently substituted γ-*E* protons has been established (12*a*, 14*a*–14*c*, 18, 19), the scope and limitations of this feature as it pertains to differential substitution at the γ-*Z* and γ-*E* sites, a systematic study of the stereochemical fate of γ-*Z* substituents, and the stereochemical disposition of the proton undergoing abstraction have not been dealt with in depth. Originating with our interest in the synthetic utility of α,β-unsaturated amides (16*k*), we addressed this question (18, 19) and herein present extended detailed studies, which significantly amplify our preliminary results, may have broader application to other α,β-unsaturated functionalized systems (20), and thereby may shed further light on this interesting question, which has considerable synthetic and mechanistic interest.

Concerning the site of deprotonation of senecioamides

Previous work using unsaturated esters does not allow unambiguous generalization concerning the *syn* vs. *anti* γ-H site of deprotonation to analogous systems (14*r*, 14*m*, 14*q*,

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Dedicated to Alfred Bader, for the chemistry he created amongst all chemists and in appreciation of his tenacious support of Canadian chemistry.

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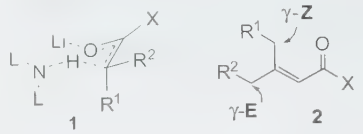
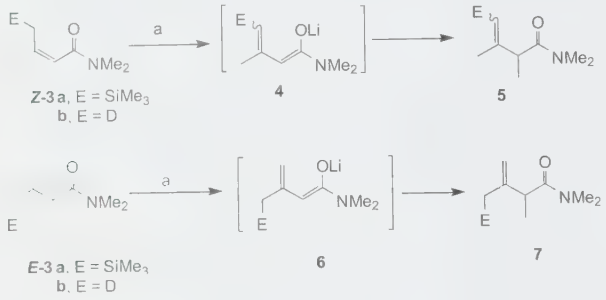
Fig. 1. Deprotonation in carbonyls and unsaturated carbonyls.



Scheme 1. Reagents and conditions: (*a*) (*i*) LDA, THF; (*ii*) MeI, 0 °C to room temperature.



14*n*, 14*k*, 14*a*–14*d*, 19). We decided to approach this question for unsaturated amides in conjunction with ongoing studies. γ-Silylated carboxamides ***Z*-3a** and ***E*-3b** (Scheme 1), available as a result of our work on amide dienolate reactivity (13*c*, 21), were subjected to LDA deprotonation at room temperature (RT) and the resulting dienolates **4a** and **6a** were quenched with methyl iodide to give products **5a** (*Z*, *E*) and **7a** in 90% and 84% yields, respectively. The products were readily distinguished by ^{1}H NMR spectroscopy (see the Experimental section), which showed that compounds ***Z*-3a** and ***E*-3a** gave exclusively compounds **5a** and **7a**, respectively. The issues of acidifying and steric effects led us to consider replacement of silicon by deuterium as a positional γ marker that would minimally perturb the system under study.

Using conditions previously developed in our laboratories for regio- and stereo-selective introduction of electrophiles into γ-*cis* methyl positions of senecioamdies (16*k*), the dimethyl amide **8** (Scheme 2) was subjected to LDA deprotonation at –78 °C followed by treatment with CuI, according to the protocol of Katzenellenbogen for favoring γ-functionalization, and D_2O in sequence to give a mixture of γ- and α-deuterated products ***Z*-3b** and **9** in a 57:43 ratio. Exclusion of CuI in this sequence led to lower γ:α product ratios. The corresponding ***E*-3b** isomer was prepared according to the excellent and dependable Sum and Weiler procedure (22) involving γ-deuteration of **10** to give **11** followed by stereoselective β-methylation via the enol phosphonate **12**. The location and content of deuterium in the products depicted in Scheme 2 were determined by MS and ^{2}H NMR (see the Experimental section). For compound ***E*-3b**, ^{2}H NMR analysis showed approximately 5% contamination with the ***Z*-3b** isomer.

Deprotonation of ***Z*-3b** and ***E*-3b** under identical conditions (LDA, THF, 0 °C, 0.5 h) and subsequent methylation of the resulting dienolates gave **5b** (78%) and **7b** (68%), respectively. The ^{1}H NMR spectrum of ***Z*-5b** showed significant deuteration in the vinyl site but not in the allylic methyl group, while the corresponding spectrum of ***E*-5b** indicated

Scheme 2. Reagents and conditions: (*a*) (*i*) LDA, THF, –78 °C; (*ii*) CuI; (*iii*) MeOD, –78 °C. (*b*) (*i*) NaH; (*ii*) *n*-BuLi; (*iii*) $F_3CCO_2D + D_2O$; (*iv*) NH_4Cl. (*c*) (*i*) NaH; (*ii*) $ClP(O)(OEt)_2$. (*d*) (*i*) Me_2CuLi, –78 to –40 °C; (*ii*) NH_4Cl.

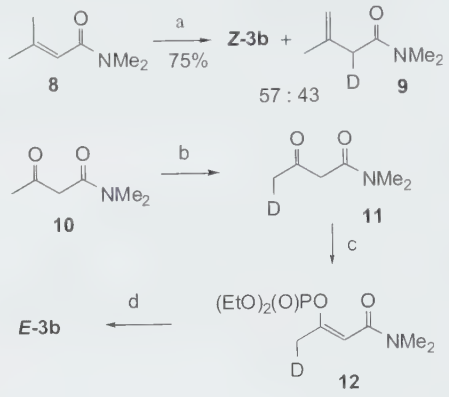
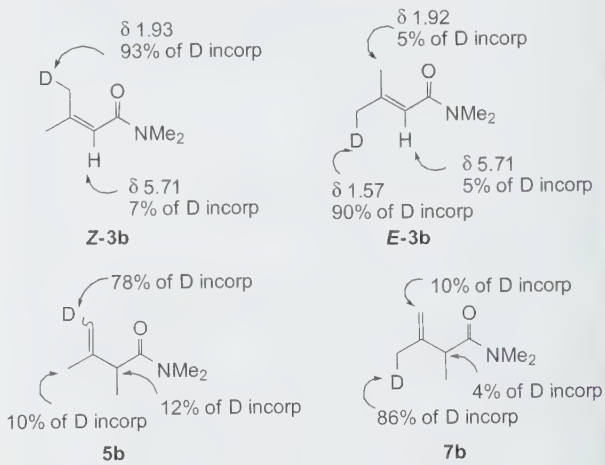


Fig. 2. ^{2}H NMR based relative deuterium incorporation levels.



essentially no deuteration in the vinyl group but significant deuterium incorporation in the allylic methyl group (see the Experimental section and Fig. 2). More conclusive data was obtained from the ^{2}H NMR spectra (Fig. 2), which showed relative deuterium incorporation at the vinyl, α-carbon, and allylic methyl in a ratio of 78:12:10 for **5b** and 10:4:86 for **7b**. These results indicate that γ-*Z* over γ-*E* deprotonation has occurred to the extent of 89% and 96% in the two substrates ***Z*-3b** and ***E*-3b**, respectively, and therefore implicate the intermediacy of the dienolates **4b** and **6b**, respectively. Thermodynamic deprotonation of these systems is ruled out by the observation that ***E*-3a** did not proceed via dienolate **4a**. The results of our studies with ***Z*-3b** and ***E*-3b** mirror the observations of Harris and Weiler (19) on the corresponding carboxylic acids and esters.

Substituent effects on γ-deprotonation

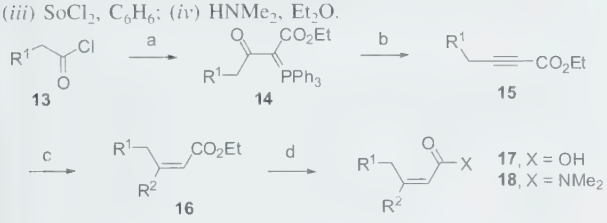
In seeking a more detailed understanding of the factors affecting the geometry of dienolate formation, we investigated

Table 1. Stereoselectivity in deprotonations of **Z-3a** and **18**.

Entry	Amide	R^1	R^2	Product[a]	trans:cis Ratio
1	**18g**	Me	Et	**19g** (80)	79:21
2[b]	**18g**	Me	Et	**19g** (71)	92:8
3	**18a**	Me	*n*-Bu	**19a** (54)	79:21
4	**18b**	Me	*s*-Bu	**19b** (89)	41:59
5	**18c**	Me	*t*-Bu	**19c** (75)	<3:>97
6	**18d**	*i*-Pr	*s*-Bu	**19d** (54)	8:92
7	**18f**	OMe	*n*-Bu	**19e** (84)	<3:>97
8	***Z*-3a**	$SiMe_3$	Me	**5a** (90)	79:21

[a] Yields in parentheses
[b] Reaction conducted at 78 °C.

Scheme 3. Reagents and conditions: (*a*) $2Ph_3P{=}CHCO_2Et$. (*b*) 270 °C, ~0.4 Torr. (*c*) (*i*) R^2R^3CuLi, THF, 78 °C; (*ii*) H_3O^+; (*iii*) $SoCl_2$, C_6H_6; (*iv*) $HNMe_2$, Et_2O.

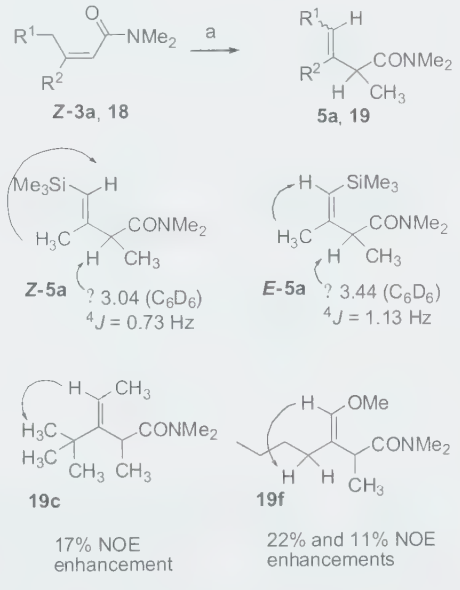


For **13**–**15** **a**, $R^1 = CH_3$; **b**, $R^1 = {}^iPr$; **c**, $R^1 = {}^tBu$; **d**, $R^1 = OMe$
For **16**–**18** **a**, $R^1 = CH_3$, $R^2 = R^3 = {}^nBu$; **b**, $R^1 = CH_3$, $R^2 = R^3 = {}^sBu$; **c**, $R^1 = CH_3$, $R^2 = {}^tBu$, $R^3 = Me$; **d**, $R^1 = {}^iPr$, $R^2 = R^3 = {}^sBu$; **e**, $R^1 = {}^tBu$, $R^2 = R^3 = {}^sBu$; **f**, $R^1 = OMe$, $R^2 = R^3 = {}^nBu$

the deprotonation chemistry of a variety of β,γ-disubstituted acrylamides. In particular, we were interested in the effect of substituents anchored at the site of deprotonation. For this purpose, a series of stereochemically homogeneous β,β-disubstituted acrylamides **18** were prepared by adapting cuprate-addition chemistry to ethyl-2-alkynoates (Scheme 3) (23). Condensation of acyl halides **13a**–**13d** with carboethoxymethylene triphenylphosphorane using the procedure described by Hanack et al. (24) as modified by Markl (25) afforded the acyl phosphoranes **14a**–**14d**, which normally were not isolated but directly pyrolyzed to give the 2-alkynoate esters **15a**–**15d**. Treatment of esters **15a**–**15d** with lithium dialkyl cuprates furnished the stereochemically pure α,β-unsaturated esters **16a**–**16f** in variable yields (37%–81%). The conversion of esters **16a**–**16f** into the requisite dimethyl amides **18a**–**18f** was carried out under standard conditions via the intermediate carboxylic acids **17a**–**17f**. Amide **18g** (R^1 = Me, R^2 = Et) was prepared using a Horner–Wadsworth–Emmons procedure (see the Experimental section). The structures and stereochemistry of all amides **18** were assigned by ^1H NMR spectroscopy: with one exception (**18f**), the CH_2 group cis to the amide carbonyl appears as expected downfield (δ 2.3) from the one located trans to the carbonyl (δ 2.15). Furthermore, the *cis*-CH_2 resonances experienced an aromatic solvent-induced shift to lower field (δ 2.47) upon replacement of $CDCl_3$ with C_6D_6 as solvent (26).

Compounds **18a**–**18g** were deprotonated with LDA in THF at room temperature, except for entry 2, and quenched with methyl iodide to give mixtures of products *trans*-**19a**–**19d**, **19f**, and **19g** and *cis*-**19a**–**19d**, **19f**, and **19g**[4] (Scheme 4, Table 1). Attempted deprotonation of **18e** resulted in extensive decomposition and thus was not pursued further. For the sake of completeness, the deprotonation of ***Z*-3a** is included (Table 1, entry 8). The trans to cis ratio was established by integration of the ^1H NMR methine resonance of the two isomers with chemical shifts δ separated by a consistent value of approximately 0.3 ppm (3.3 ppm for trans and 3.6 ppm for cis isomers). Stereochemical assignments at the newly formed double bond were determined by the four-bond vinyl-to-methyl coupling constant in accordance with the literature (Scheme 4) (27). In addition, the stereochemistry of compounds *trans*-**19c** and *trans*-**19f** was confirmed by NOE difference experiments.

Scheme 4. Reagents and conditions: (*a*) (*i*) LDA, THF; (*ii*) MeI, 0 °C to room temperature.

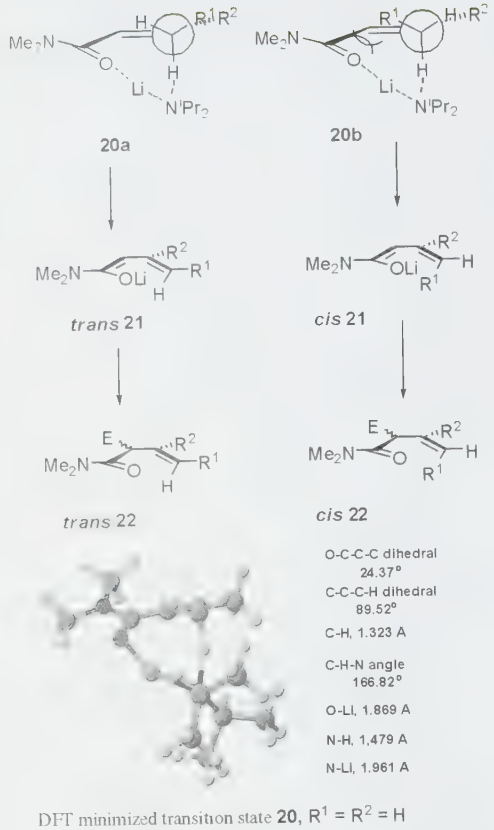


The mechanism of γ-deprotonation

On the basis of the above results, we propose that deprotonation of β,β-disubstitued α,β-unsaturated amides oc-

[4] *Z/E* nomenclature is not used because of priority changes in R^2 in the progression of the series.

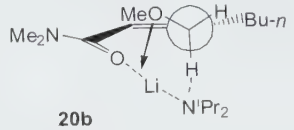
Scheme 5.



DFT minimized transition state **20**, $R^1 = R^2 = H$

curs through a cyclic eight-membered ring transition state (**20a** and **20b**), which highlights lithium carboxamide oxygen coordination according to the established complex-induced proximity effect (CIPE) (7) (Scheme 5). Since the γ-*Z* carbon is in closer proximity to the amide carbonyl than the γ-*E* carbon atom, deprotonation occurs preferentially from the former leading to dienolates *cis*-**21** and *trans*-**21**, which undergo reaction with the electrophile at the α site to give products *cis*-**22** and *trans*-**22**. To rationalize substitutent effects, we begin with the assumption that deprotonation occurs perpendicular to the plane of the unsaturated amide (3). While semiempirical calculations (MNDO) have indicated a H-C-C-O torsion angle for ketone deprotonation of only about 60° (11), DFT[5] calculations on **20** reveal that the eight-membered ring transition state incorporates an optimal H-C-C-C torsion angle (89.5°) for senecioamide deprotonation, with a minimal twist (24.4°) from coplanarity of the unsaturated carbonyl. With small R^2 substituents, the γ-R^1 group prefers to be oriented away from the carboxamide in transition state **20a**, leading preferentially to dienolate *trans*-**21** and ultimately to alkylated product *trans*-**22**. As the size of the R^2 group is increased (Et < *s*-Bu < *t*-Bu), the steric repulsion between R^1 and R^2 increases, giving rise to greater amounts of deprotonation from transition state **20b**, which cascades to dienolate *cis*-**21** and product *cis*-**22**. Comparison

Fig. 3. Deprotonation transition state for **18f**.



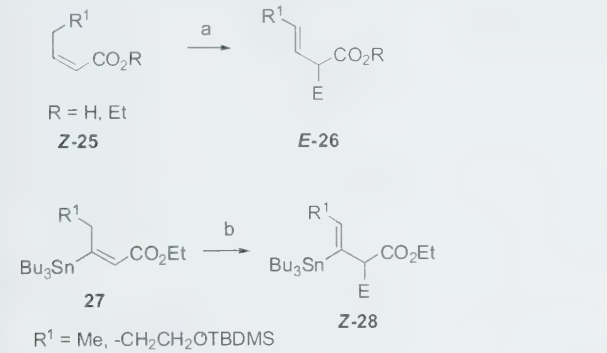
Scheme 6. Reagents and conditions: (*a*) (*i*) LDA, THF, RT; (*ii*) MeI, 0 °C to room temperature.

of entries 4 and 6 (Table 1) suggests that an increase in the size of R^1 enhances the energy difference between transition states **20a** and **20b**. In this context, the result obtained with the TMS (entry 8) shows no size effect in spite of the fact that this group has an A value similar to *i*-Pr (28). The case of the OMe substituent (Table 1, entry 7) is striking in that, on the basis of steric arguments, preferential formation of *trans*-**19f** was expected. The exclusive formation of *cis*-**19f** strongly suggests that lithium–OMe coordination (Fig. 3) in the transition state is significant although the tentative nature of this proposal is recognized in view of reports on the dimeric (29) and tetrameric (30) nature of dienolates in the solid state. Finally, a comparison of the results of deprotonation of **19g** at –78 °C and room temperature (Table 1, entries 1 and 2) shows the expected enhancement in selectivity with decreased temperature consistent with a 0.8–0.95 kcal/mol (1 kcal = 4184 J) difference in activation energy for the respective dienolate isomer formation. To confirm that the products result from kinetic deprotonation and that double bond isomerization about Cβ—Cγ does not occur in the dienolate, the β,γ-unsaturated amide **Z-23** was prepared according to Baldwin and co-workers (16*j*) and subjected to the standard LDA deprotonation conditions. The product **Z-24** showed retention of double bond geometry, which must stem from the thermodynamically less stable dienolate, thereby providing confirmation of kinetic deprotonation (Scheme 6). Because of the lack of proximity of the carbonyl oxygen and the deprotonation site, our model clearly does not contribute to an understanding of the mechanism of deprotonation of *E*-α,β-unsaturated esters and acids (16*a*, 16*f*, 16*j*).

The earlier observations of Pfeffer and Silbert (16*u*), Krebs (16*r*), and Kende and Toder (16*p*) on the deprotonation of *Z*-unsaturated esters and acids (**Z-25** to ***E*-26** in Scheme 7) are in agreement with our proposed model of deprotonation (Scheme 5). In all these earlier investigations, compounds with no β-*E* substitutents were employed (Scheme 5, R^2 = H). As a consequence, the R^1 – carbonyl oxygen interaction constitutes the only significant repulsive interaction. A transition state analogous to **20a** is therefore expected, which ultimately leads to the corresponding

[5] DFT calculations were carried out using the B88-PW91 method, and a DZVP basis set, using CAChe® version 6.1.12.33 (see Supporting information). All stationary points were confirmed via frequency calculations.

Scheme 7. Reagents and conditions: (*a*) (*i*) LDA, HMPA, THF, –78 °C; (*ii*) E^+. (*b*) (*i*) LDA, THF; (*ii*) H^+, –98 °C. (*c*) (*i*) base, THF, –78 °C; (*ii*) Me_3SiCl.

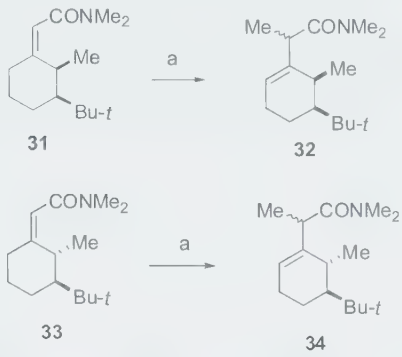


dienolate *trans*-**21** and product *trans*-**22**. In addition, Piers and Gavai (16*l*) and Schlessinger and co-workers (15*d*) have reported on the low-temperature deprotonation of β-stannyl (**27**) and β-pyrrolidino (**29**) substituted unsaturated esters. Piers and Gavai found that LDA deprotonation of **27** followed by proton quench produced only the ***Z*-28** isomer, which is consistent with the relatively small conformational *A* value of tin (either 0.94 (31)) or 1.06 (32)). Piers and Gavai also observed that the presence of an oxygen function in **27**, R = $CH_2CH_2OTBDMS$, does not alter the stereochemical outcome of deprotonation. This may be due to the oxygen function being too distant to participate in coordination to lithium or the inhibition of coordination by the bulky TBDMS group. In the Schlessinger study, deprotonation of the β-pyrrolidino system **29** with LDA gave exclusively the *cis*-enolate as reflected in the formation of the *O*-silyl dienolate product ***E*-30**, a result in qualitative agreement with our results (Table 1) if one considers the large *A* value (2.1) of a dialkylamino group (33). The lack of selectivity shown by KDA in the deprotonation of **29** to give ***E*-30** and ***Z*-30** may reflect an earlier transition state and weaker metal-to-carbonyl coordination. Our study of the effect of base on the deprotonation of **18g** led to inconclusive results (13*c*).

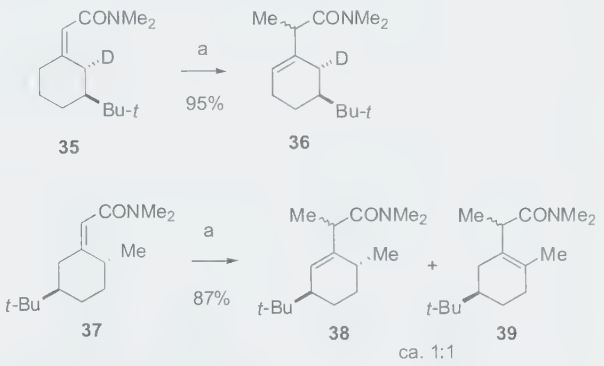
These arguments concerned with substituent effects on γ-deprotonation appear to be applicable and lead to similar conclusions for α,β-unsaturated systems with other carbonyl acidifying functionality (20), such as phosphonates and phosphine oxides (34) and sulfones (35).

At this point in the study, we were interested in determining whether the requirement for perpendicular C-H orientation would manifest itself in axial proton abstraction in cyclohexylidene carboxamides. For this purpose, we prepared diastereomers **31** and **33** using cuprate conjugate addition and Peterson olefination chemistry (see Supplementary material)[6] and subjected them to the standard LDA deprotonation – methyl iodide quench conditions to give the deconjugated amides **32** and **34**, respectively (Scheme 8). Disappointingly, deprotonation had occurred at the γ-*E* methylene to the exclusion of γ-*Z* methine proton. We considered that the factor responsible for the unwanted γ-*E* deprotonation is the presence of the equatorial γ-methyl or the δ-*t*-Bu groups. Therefore, we prepared (see Supplementary material)[6] γ-deuterated (**35**) and the *t*-Bu γ-methyl (**37**) derivatives and treated these under the normal deprotonation–methylation conditions. Unfortunately, compound **35** also underwent deprotonation at the γ-*E*-methylene site to give deconjugated product **36** (Scheme 9). Furthermore, compound **37** gave a mixture of compounds **38** and **39** (approx. 1:1) indicating γ-*E*-methylene and γ-*Z*-methine deprotonation, respectively. We surmise that the presence of the γ-methyl function in the cyclohexylidene amides either causes the six-membered ring to adopt a twist-boat conformation or prevents the proper orientation of the

Scheme 8. Reagents and conditions: (*a*) (*i*) LDA, THF, RT; (*ii*) MeI, 0 °C to room temperature.

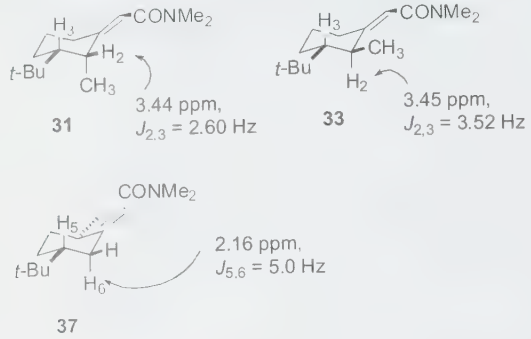


Scheme 9. Reagents and conditions: (*a*) (*i*) LDA, THF, RT; (*ii*) MeI, 0 °C to room temperature.

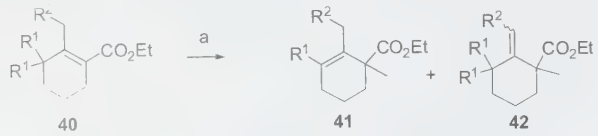


[6] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5078. For more information on obtaining material, refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Fig. 4. Selected ^{1}H NMR spectral data of cyclohexylidene amides.



Scheme 10. Reagents and conditions: (*a*) (*i*) base, THF, –78 °C; (*ii*) MeI.

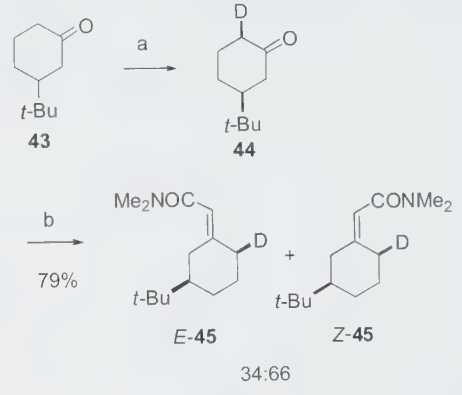


Entry		Base	41:42 Ratio	
1.	R^1 = H, R^2 = H	LilCA	0	100
2.	R^1 = H, R^2 = Me	LDA/HMPA	100	0
3.	R^1 = D, R^2 = Me	LDA/HMPA	40	60
4.	R^1 = H, R^2 = Me	LDA	0	100

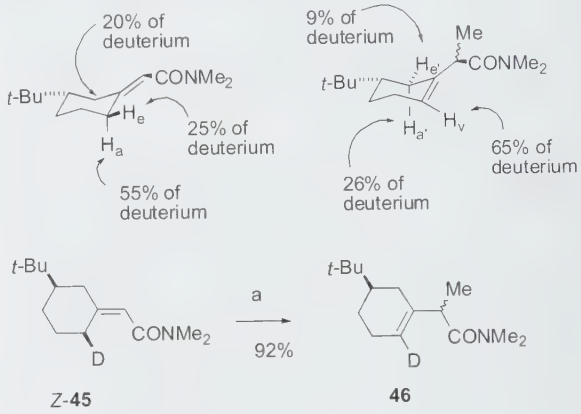
amide carbonyl for formation of the required transition state **20** (Scheme 5). In the ^{1}H NMR of cyclohexanones, axial hydrogens resonate at lower fields than the corresponding equatorial hydrogen (36). This is clearly not the case for the corresponding hydrogens H_2 in the cyclohexylidene amides **31** and **33** (Fig. 4). Similarly, the axial hydrogen H_6 in **37** resonates at δ 2.16, but more importantly shows coupling with the adjacent methine hydrogen with J = normal practice 5 Hz. Spectroscopic characterization of **35** does not allow the identification of the conformation of the cyclohexane ring. It appears, however, that the *tert*-butyl function at the position γ to the carbonyl is sufficient to block deprotonation at the γ-*Z* site.

Our difficulties in deprotonating cyclohexylidene amide systems are reminiscent of the results observed by White (14*t*), Gesson (14*o*), and Weiler (14*h*) and their co-workers on cyclohexene carboxylate esters **40** (Scheme 10). Examination of the entries shows that the seemingly trivial modification of substituents of the base (compare entries 2 and 3 or 2 and 4 in Table 1) leads to dramatic changes in ratios of deconjugated products **41** and **42**. Considering that the γ-*Z* deprotonation in the unperturbed cases has been demonstrated by our previous results (Table 1 and Scheme 1), we chose to prepare compound **43** (Scheme 11), which incorporates a *t*-Bu group in a location remote from the site of deprotonation. Treatment of 3-*tert*-butylcyclohexanone **43** with LDA followed by deuteration afforded **44**, albeit with modest incorporation of deuterium (d_1 = 40%, d_2 = 10%) (37). Peterson olefination of **44** with the lithio enolate of α-silyl acetamide gave a mixture of ***Z*-45** and ***E*-45** in a ratio of

Scheme 11. Reagents and conditions: (*a*) (*i*) LDA, THF, –78 °C; (*ii*) $CF_3CO_2D + D_2O$. (*b*) (*i*) $Me_3SiCH_2CONMe_2$, LDA, THF, –78 °C; (*ii*) **44**, –78 °C to room temperature.



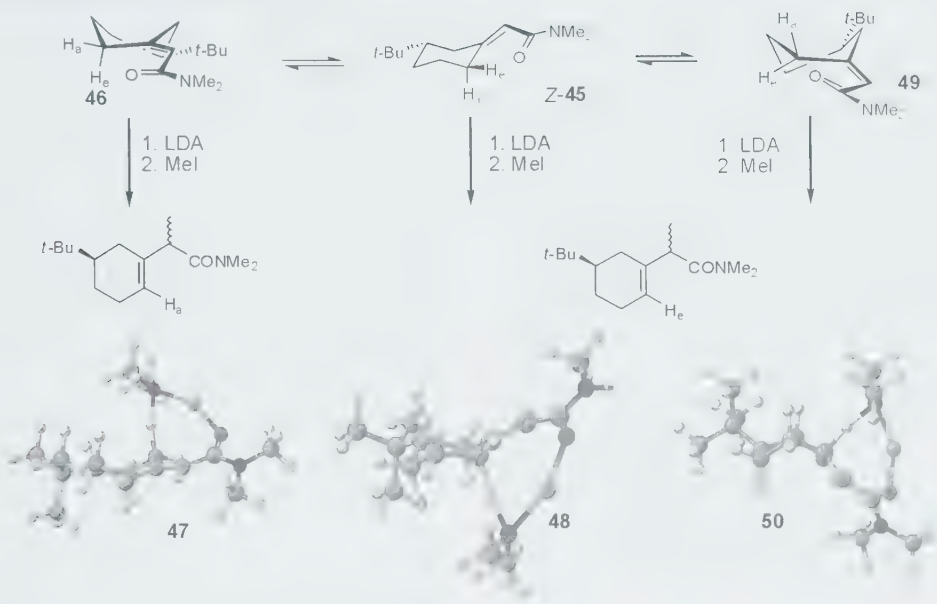
Scheme 12. Reagents and conditions: (*a*) (*i*) LDA, THF; (*ii*) MeI, 0 °C to room temperature.



66:34, which were separated by column chromatography to give pure ***Z*-45**. The mass spectrum of ***Z*-45** indicated 37% d_1 and 9% d_2 incorporation, while the ^{2}H NMR showed approximately 55%, 25%, and 20% relative deuteration at H_a, H_e, and γ-*E* sites, respectively. When ***Z*-45** was subjected to deprotonation and methylation under normal conditions, compound **46** was obtained in high yield and its ^{2}H NMR spectrum showed relative deuterium incorporation of 65%, 26%, and 9% at H_γ, H_a, and H_e, respectively (Scheme 12). This corresponds to an approximately 20:80 ratio favoring equatorial deprotonation. The mass spectrum of **46** showed 27% d_1 and 8% d_2 content, which is consistent with predominant equatorial deprotonation.

We believe that the explanation of these results lies in the classic work of Fraser and Champagne (4) who demonstrated that protonation or deprotonation in conformationally locked systems can occur via perpendicular attack by base through a twist-boat transition state, and in the proposal that these transition states are responsible for equatorial protonation or deprotonation in cyclohexanones (38). The predominant equatorial deprotonation of ***Z*-45** is due to an analogous twist-boat cyclohexylidene conformation **46** (Scheme 13) in which the axial hydrogen H_e is suitably ori-

Scheme 13. Twist-boat deprotonation model of **Z-45**.



ented. DFT calculations[5] on the transition state for the deprotonation of protio-**Z-45**, employing lithium dimethylamide for simplification of the calculations, support the assertion that H_e deprotonation occurs through a twist-boat transition state (**47**). As the transition state for H_a deprotonation through the chair (**48**) is 2.2 kcal/mol lower in energy relative to **47** according to DFT calculations (again employing lithium dimethylamide), it is entirely possible that the observed results are due to a primary deuterium isotope effect in **Z-45** impeding axial H_a deprotonation via **48**; the degree of the contribution of this isotope effect, however, is unknown at this time. Deprotonation of H_a through a complementary twist-boat conformation (**49**) may also be deduced computationally (**50**), with approximately the same energy as **47** (within 0.1 kcal/mol).

Conclusions

We believe that the results reported herein advance our understanding of vinylogous deprotonation reactions in α,β-unsaturated carbonyl systems. The conditions for regio- and stereoselective γ-deprotonation of systems **2** (X = NR_2) followed by simple electrophile quench may be usefully extended to functionalized, and therefore more useful, electrophiles and thereby lead to γ-chain extended intermediates of synthetic value. As one illustration, the construction of terpenoid frameworks could be achieved in a direct manner rather than in several steps. Finally, in view of the progress in the area of enantioselective deprotonation chemistry (39), potentially important results for construction of chiral building blocks may be anticipated.

Experimental section

General methods

Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. Melting points were determined on a Büchi SMP-20 instrument and are uncorrected. Infrared spectra were determined on a PerkinElmer 983 spectrophotometer. ^{1}H NMR spectra were determined with Bruker WP-80 and Bruker AM-250 spectrometers. The spectra were recorded at 80 or 250 MHz in $CDCl_3$ with tetramethylsilane as an internal standard unless otherwise stated. ^{2}H NMR spectra were determined using a Bruker AM-250 spectrometer in C_6H_6 or $CHCl_3$, with C_6D_6 or $CDCl_3$, respectively, as internal standards. Spectral features are tabulated in the following order: chemical shift (δ, ppm); multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), broad (br)), coupling constant (*J*, Hz); number of protons; assignment. Low-resolution mass spectra were determined on a VG 7070F instrument at 20 eV (1 eV = 1.602 19 × 10^{-19} J) unless otherwise stated. High-resolution mass spectra were determined on a VG ZAB-E spectrometer. Analytical gas chromatography (GC) was performed on either a Hewlett Packard 5840 A instrument or a Varian 6500 instrument using commercially available 10% SE-30 packed and capillary columns, respectively. Preparative HPLC was done on a Waters PREP-500 with an SiO_2 column. Analytical thin layer chromatography (TLC) was performed using Merck precoated silica gel 60F-254 or aluminum oxide 150F-254 neutral (type T) sheets. Preparative TLC was performed using Merck silica gel 60GF-254 with a plate thickness of 1 mm. Column chromatography was carried out using silica gel 60 (0.063–0.20 mm and 0.04–0.063 mm). Flash chromatography refers to the method reported by Still et al. (40).

All dry solvents were employed after distillation from the appropriate drying agent (41). Diethyl ether (Et_2O), benzene, and tetrahydrofuran (THF) were distilled from benzophenone-ketyl immediately prior to use. Solutions of *n*-BuLi, *s*-BuLi, and *t*-BuLi were titrated with 2,5-dimethoxybenzyl alcohol (42) as a standard. Diisopropylamine was dried and distilled over CaH_2 and stored in brown bottles over 4 Å mo-

lecular sieves in a dessicator containing $CaCl_2$. All other reagents were purified according to literature procedures (41). All lithiation reactions were carried out under high purity nitrogen or argon.

The term "–78 °C" refers to the temperature of a CO_2–acetone bath (normally –75° to –78 °C). The phrase "workup in the usual manner" or "standard workup" refers to the addition of satd. aq. NH_4Cl to the reaction mixture, followed by evaporation of the organic solvent under reduced pressure, extraction of the residue with CH_2Cl_2 or diethyl ether (Et_2O), drying of the organic extract over $MgSO_4$, filtration, and then evaporation to dryness under reduced pressure to afford the crude product. Subsequent chromatography and (or) recrystallization and (or) distillation of the crude material afforded pure products.

Cuprate reactions were worked up in the following manner. The organic solvent was evaporated under reduced pressure, diethyl ether was added, and the mixture was filtered. The ethereal layer was separated and the remaining aqueous layer was further extracted with diethyl ether. The combined ether layers were then back-extracted with aq. NH_4OH and satd. NaCl, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

General procedure for the formation of lithium dienolates

Preparation of LDA

Diisopropylamine (5 mmol, 0.70 mL) was dissolved in THF (25 mL), and cooled to 0 °C. *n*-BuLi (5 mmol) was added by syringe injection over a period of about 30 s. The solution was then stirred for a further 0.5 h at 0 °C.

Lithiation with LDA — Procedure A

The amide in question was added by syringe to 1.05 equiv. of LDA in THF at –78 °C so that the concentration in solution was roughly 0.2 mol/L. This solution was stirred at –78 °C for 1 h prior to electrophile addition.

Lithiation with LDA — Procedure B

The amide in question was added by syringe to 1.05 equiv. of LDA in THF at 0 °C so that the concentration in solution was roughly 0.2 mol/L. This solution was stirred at 0 °C for 0.5 h prior to electrophile addition.

Lithiation with LDA — Procedure C

The amide in question was added by syringe to 1.05 equiv. of LDA in THF at room temperature (RT) so that the concentration of the amide or amide dienolate in solution was roughly 0.2 mol/L. This solution was stirred at RT for 1 h prior to electrophile addition.

Alkylation of lithium dienolates

The temperature of the solution of the lithium dienolate was adjusted to 0 °C at which time an excess of the electrophile was added by syringe. The resulting mixture was allowed to stir for 0.5 h at 0 °C before the ice bath was removed. The mixture was allowed to come to room temperature, after which a standard workup was performed.

Z- and *E*-*N*,*N*,2,3-Tetramethyl-4-trimethylsilyl-3-butenamide (*Z*- and *E*-5a)

Compound **Z-3a** (0.9212 g, 4.62 mmol) was lithiated according to procedure C and alkylated with iodomethane (0.4 mL) in the normal manner. After a standard workup, the crude product was subjected to column chromatography (ethyl acetate – hexane, 1:1–2:1) to give a mixture of **Z-** and ***E*-5a** (0.8860 g, 90%); bp 40–43 °C at 0.005 Torr (1 Torr = 133.322 4 Pa). IR (neat, cm^{-1}) ν_{max}: 1649, 1611. ^1H NMR (C_6D_6) δ: 0.10 and 0.07 (2s, 9H, $3SiCH_3$), 1.35, 1.38 (2d, J = 7 Hz, 3H, CH_3), 1.75, 1.79 (2d, J = 0.73, 1.17 Hz, 3H, CH_3), 2.40, 2.67 (2s, 6H, $2NCH_3$), 3.04, 3.41 (2q, J = 7 Hz, 1H, CH), 5.26, 5.36 (2m, 1H, vinyl CH). MS *m/e* (rel. intensity): 213 (M^+, 9), 199(33), 198(100), 140(24), 101(36), 73(43). Anal. calcd. for $C_{11}H_{23}NOSi$: C 61.91, H 10.86, N 6.56; found: C 62.10, H 11.05, N 6.73.

Preparative HPLC (hexane – ethyl acetate, 3:1) successfully separated small amounts of **Z-5a** and ***E*-5a**. The following peaks in the ^1H NMR spectrum were assigned to represent the *E* isomer: 0.10, 1.35, 1.75 (J = 0.73 Hz), 3.04, 5.36. The following peaks in the ^1H NMR spectrum were assigned to represent the *Z* isomer: 0.079, 1.38, 1.79 (J = 1.17 Hz), 3.41, 5.26. By peak heights of the various distinguishable signals and the integrated areas under the δ 3.04 and δ 3.41 peaks, the ratio of ***E*-5a** to **Z-5a** in the unseparated mixture was established to be 79:21.

N,*N*,2-Trimethyl-3-trimethylsilylmethyl-3-butenamide (7a)

Compound ***E*-3a** (0.7191 g, 3.61 mmol) was lithiated according to procedure B and alkylated with iodomethane (0.4 mL) in the normal manner. After a standard workup, the crude product was subjected to flash chromatography (CH_2Cl_2–acetone,15:1) to give 0.6993 g (84%) of **7a**; bp 60–62 °C at 0.01 Torr (lit. value (15*k*) bp 65–70 °C at 0.015 Torr).

4-Deuterio-*N*,*N*,3-trimethyl-2-butenanide (*Z*-3b)

N,*N*-Dimethylsenecioamide (1.34 mL, 9.8 mmol) was lithiated according to procedure A. To the resulting dienolate at –78 °C was added CuI (1.822 g, 9.6 mmol). The mixture was stirred for a further 1 h at –78 °C and 1.7 mL (excess) MeOD was added. The reaction was allowed to warm to RT over 6 h, before 2.0 mL of D_2O was added. After a standard workup, the crude product was subjected to column chromatography (ethyl acetate – hexane, 3:2) to give 0.9562 g (75%) of a 57:43 mixture of **Z-3b** and its double bond isomer **9**, as determined by the relative areas of vinyl resonances in the ^1H NMR spectrum. Preparative HPLC (CH_2Cl_2–acetone, 10:1) enabled the separation of a small amount of pure **Z-3b**; bp 35–40 °C at 0.004 Torr (lit. value (43) bp 62–64 °C at 3.0 Torr). ^1H NMR (C_6D_6) δ: 1.55 (s, 3H, CH_3), 1.96 (s, 2.45H, CH_2D). ^2H NMR (C_6H_6, decoupled) δ: 1.93 (86% of D, CH_2D), 2.84 (7% of D, CHD from **9**), 5.71 (7% of D, CD). MS *m/e* (rel. intensity): 129, 128, 127 (M^+, d_2:d_1:d_0, corrected, 1:75:24).

N,*N*-Dimethyl-3-oxobutanamide (10)

Compound **10** was prepared by literature methods (44) in 67% yield; bp 80–83 °C at 0.9 Torr (lit. value (44) bp 109° at 10 Torr).

4-Deuterio-*N*,*N*-dimethyl-3-oxobutanamide (11)

To a suspension of NaH (1.6917 g, 66 mmol) in THF (125 mL) was slowly added **10** (4.2925 g, 33.2 mmol). After stirring for 20 min, the resulting white gel was cooled to 0 °C and *n*-BuLi (36.5 mmol) added. The resulting mixture was stirred for 20 min at 0 °C. In a separate flask, D_2O (3 mL) was added to trifluoroacetic anhydride (7 mL) at 0 °C and the resulting solution was rapidly added to the first flask. After stirring for 15 min at 0 °C, the reaction was worked up in the following manner. Saturated aqueous ammonium chloride was added and the mixture was concentrated under reduced pressure. The resulting mixture was extracted several times with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with saturated aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude product was distilled to give **11** (2.8935, g, 67%); bp 95 to 96 °C at 1.9 Torr. ^{1}H NMR δ: 1.91, 2.24 (2m, 2H, CH_2D), 2.98, 3.00 (2s, 6H, $2NCH_3$), 3.54 (s, 1.15H, CH_2), 4.14 (s, 0.43H, vinyl CH). MS *m/e* (rel. intensity): 131, 130, 129 (M^+, d_2:d_1:d_0, corrected, 9:72:19).

Z-4-Deuterio-3-[(diethylphosphoryl)oxy]-*N*,*N*-dimethyl-2-butenamide (12) and *E*-4-deuterio-*N*,*N*,3-trimethyl-2-butenamide (*E*-3b)

To a suspension of NaH (0.5780 g, 26.1 mmol) in THF (125 mL) was slowly added **11** (2.8363 g, 21.8 mmol). After stirring for 20 min, diethyl chlorophosphate (3.40 mL, 22.9 mmol) was added. The resulting yellow suspension was stirred for 0.5 h. A standard workup gave **12**. IR (neat, cm^{-1}) ν_{max}: 1679, 1631, 1275. ^{1}H NMR δ: 1.35 (td, J = 7, 1.0 Hz, 6H, $2CH_3$), 2.11 (br s, 2H, CH_2D), 2.96, 3.05 (2s, 6H, $2NCH_3$), 4.18 (dq, J = 7, 7 Hz, 4H, $2OCH_2$), 5.42 (s, 1H, CH). MS *m/e* (rel. intensity): 267, 266, 265 (M^+, d_2:d_1:d_0, corrected, 14:68:17), 266 (M^+, 20), 222(29), 194(22), 166(44), 156(36), 155(100), 127(72). The crude **12** was not purified, but was carried on directly to the next step.

To a solution of lithium dimethylcuprate (46.4 mmol) in Et_2O (125 mL) at –78 °C was added **12** (6.5361 g). The suspension was stirred for 2 h at –78 °C, then for 1 h at –45 °C and finally warmed to 0 °C for 15 min. After a standard workup, column chromatography of the crude reaction product gave ***E*-3b** (1.8574 g, 67%); bp 45–50 °C at 0.05 Torr. ^{1}H NMR (C_6D_6) δ: 1.54 (br s, 2H, CH_2D), 1.97 (d, J = 1.2 Hz, 3H, CH_3), 2.39, 2.70 (2br s, 6H, $2NCH_3$), 5.65 (br s, 1H, CH). ^{2}H NMR (C_6H_6, decoupled) δ: 1.57 (90% of D, CH_2D), 1.92 (5% of D, CH_2D), 5.72 (5% of D, CD). MS *m/e* (rel. intensity): 129, 128, 127 (M^+, d_2:d_1:d_0, corrected, 10:71:19), 85, 84, 83 (M^+ – 44, d_2:d_1:d_0, corrected, 8:70:22).

4-Deuterio-*N*,*N*,2,3-tetramethyl-3-butenanide (*E*-5b)

Compound ***Z*-3b** (0.10 mL, 0.72 mmol) was lithiated according to procedure B and the resulting dienolate was alkylated in the normal manner with iodomethane (0.08 mL). After a standard workup, distillation of the crude product gave ***E*-5b** (0.0803 g, 78%); bp 40–50 °C at 0.004 Torr. ^{1}H NMR δ: 1.26 (d, J = 7 Hz, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.93, 2.98 (2s, 6H, $2NCH_3$), 3.34 (q, J = 7 Hz, 1H, CH), 4.79, 4.86 (2m, 1.3H, CHD). ^{2}H NMR (C_6H_6) δ: 1.60 (t, J = 2.2 Hz, 10% of D), 2.93 (s, 12% of D, CD), 4.72 (s, 78% of D, CHD). MS *m/e* (rel. intensity): 128, 127, 126 (M^+ – 15, d_2:d_1:d_0, corrected, 4:65:31).

3-Deuteriomethyl-*N*,*N*,2-trimethyl-3-butenanide (7b)

Compound ***E*-3b** (0.4149 g, 3.24 mmol) was lithiated according to procedure B and the resulting dienolate was alkylated with iodomethane (0.30 mL) in the normal manner. Following a standard workup, the crude product was subjected to column chromatography (ethyl acetate – hexane, 4:1) to give **7b** (0.3124 g, 68%); bp 30–35 °C at 0.08 Torr (Kugelrohr). ^{1}H NMR (C_6D_6) δ: 1.26 (d, J = 7 Hz, 3H, CH_3), 1.62 (m, 2H, CH_2D), 2.42, 2.67 (2br s, 6H, $2NCH_3$), 3.03 (q, J = 7 Hz, 1H, CH), 4.72 (s, 2H, CH_2). ^{2}H NMR (C_6H_6, decoupled) δ: 1.60 (87% of D, CH_2D), 2.97 (4% of D, CD), 4.72 (10% of D, CHD). MS *m/e* (rel. intensity): 85, 84, 83 (M^+ – 59, d_2:d_1:d_0, corrected, 11:65:24).

Ethyl 3-oxo-2-triphenylphosphoranylidenepentanoate (14a) and ethyl 2-pentynoate (15a)

Ethyl 3-oxo-2-triphenylphosphoranylidenepentanoate(**14a**) was prepared from the reaction of ethyl phosphoranylidene acetate and propanoyl chloride as described by Hanack et al. (24). Compound **14a** was identified by ^{1}H NMR only. ^{1}H NMR δ: 0.85 (t, J = 7 Hz, 3H, CH_3), 1.40 (t, J = 8 Hz, 3H, CH_3), 3.17 (q, J = 8 Hz, 2H, CH_2), 3.81 (q, J = 7 Hz, 2H, OCH_2), 7.71 (m, J = 15 Hz, 3H, C_6H_5). The crude **14a** was heated in a flask fitted with a Vigreux column at 260–280 °C and 0.4 Torr for 4 h and the distillate was collected in a flask at –78 °C. The distillate was redistilled under reduced pressure to give **15a** (2.7577 g, 71% based on propanoyl chloride); bp 64–66 °C at 9 Torr (lit. value (45) bp 178.5 °C).

Ethyl *E*-3-ethyl-2-heptenoate (16a)

To a solution of lithium di-*n*-butylcuprate (5.5 mmol) in THF (25 mL) at –78 °C was added **15a** (0.6341 g, 5.03 mmol) in a minimum amount of THF (~2 mL). The mixture was stirred at –78 °C for 1.5 h, after which ethanol and then satd. aq. NH_4Cl were added dropwise. The mixture was then allowed to warm to room temperature overnight. After the normal workup for cuprate reactions, the crude product was purified by distillation under reduced pressure to give **16a** (0.6843 g, 75%); bp 96–98 °C at 8 Torr. IR (neat, cm^{-1}) ν_{max}:1715, 1642. ^{1}H NMR δ: 0.8–1.6 (m, 13H, $3CH_3$ + $2CH_2$), 2.16 (br m, 2H, CH_2), 2.61 (q, J = 8 Hz, 2H, CH_2), 4.15 (q, J = 7 Hz, 2H, OCH_2), 5.61 (br s, 1H, CH). MS *m/e* (rel. intensity): 184 (M^+, 35), 155(59), 142(75), 139(100), 127(23), 114(51). Anal. calcd. for $C_{11}H_{20}O_2$: C 71.70, H 10.94; found: C 71.68, H 11.01.

***E*-3-Ethyl-2-heptenoic acid (17a) and *E*-3-ethyl-*N*,*N*-dimethyl-2-heptenamide (18a)**

To a solution of KOH (0.8695 g) in methanol–water (15 mL, H_2O–MeOH, 10:1) was added ester **16a** (0.6563 g, 3.56 mmol). The reaction mixture was heated under reflux for 5 h, extracted with diethyl ether (50 mL), acidified with HCl, and extracted with CH_2Cl_2 (4 × 25 mL). The combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **17a** (0.5091 g, 92%). Compound **17a** was identified spectroscopically by IR ((neat, cm^{-1}) ν_{max}: 1690, 1636 (lit. value (46) ν_{max} 1690, 1640)), then dissolved in benzene (25 mL) and treated with

thionyl chloride (0.9 mL) for 40 h. The excess thionyl chloride and benzene were removed under reduced pressure, the residue dissolved in diethyl ether (25 mL), and dimethylamine bubbled through the solution for 0.5 h at 0 °C. The mixture was made basic with 10% aq. NaOH, the organic layer separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Distillation of the crude product gave **18a** (0.5028 g, 84%); bp 78–80 °C at 0.3 Torr. IR (neat, cm^{-1}) ν_{max}: 1628. ^1H NMR δ: 0.8–1.2 (m, 6H, $2CH_3$), 1.3–1.6 (m, 4H, $2CH_2$), 2.12 (m, 2H, CH_2), 2.31 (q, J = 7 Hz, 2H, CH_2), 2.97, 3.01 (2s, 6H, $2NCH_3$), 5.74 (br s, 1H, CH). MS *m/e* (rel. intensity): 183 (M^+, 51), 153(32), 139(100), 72(83). Anal. calcd. for $C_{11}H_{21}NO$: C 72.08, H 11.55, N 7.64; found: C 71.94, H 11.33, N, 7.66.

3-Ethyl-*N*,*N*-dimethyl-2-pentenamide (18g)

To a suspension of NaH (0.6032 g, 25.1 mmol) in benzene (125 mL) was added diethyl 2- (dimethylamino)-2-oxoethylphosphonate (4.92 mL, 25.0 mmol). The mixture was stirred for 45 min and then 3-pentanone (28 mL, 26 mmol) was added. The reaction mixture was heated under reflux for 21 h and the reaction worked up in the normal manner. The crude product was subjected to flash chromatography (ethyl acetate – hexane, 4:1) to give one fraction, which was shown to be **18g** (1.7642 g, 46%); bp 64 to 65 °C at 0.6 Torr. IR (neat, cm^{-1}) ν_{max}: 1630. ^1H NMR δ: 1.05 (m, 6H, $2CH_3$), 2.15 (q, J = 8 Hz, 2H, CH_2), 2.32 (q, J = 8 Hz, 2H, CH_2), 2.98, 3.00 (2s, 6H, $2NCH_3$), 5.73 (br s, 1H, CH). MS *m/e* (rel. intensity): 155 (M^+, 57), 111(100), 72(27). Anal. calcd.for $C_9H_{17}NO$: C 69.63,H 11.04, N 9.02; found: C 69.59, H 11.13, N 9.01.

Z- and *E*-3-(1-Butyl)-*N*,*N*,2-trimethyl-3-pentenamide (19a)

Compound **18a** (0.5028 g, 2.743 mmol) was lithiated according to procedure C and the resulting dienolate was alkylated with iodomethane (0.35 mL) in the normal manner. Following a standard workup, the crude reaction product was subjected to preparative TLC (ethyl acetate – hexane, 95:2) to afford two fractions. The first fraction was shown to be **19a** (0.2925 g, 54%); bp 60–65 °C at 0.2 Torr. IR (neat, cm^{-1}) ν_{max}: 1645. ^1H NMR (250 MHz) δ: 0.85–1.05 (m, 3H, CH_3), 1.21 (d, J = 7 Hz, 3H, CH_3), 1.32 (m, 2H, CH_2), 1.61, 1.66 (2d, J = 7 Hz, 2H, CH_2 from ***E***- and ***Z*-19a**, respectively), 2.06 (m, 2H, CH_2), 2.90, 2.91, 2.94, 2.97 (2 × 2s, 6H, $2NCH_3$ from ***Z***- and ***E*-19a**, respectively), 3.28, 3.62 (2q, J = 7 Hz, 1H, CH from ***E***- and ***Z*-19a**, respectively, relative area 79:21), 5.29 (q, J = 7 Hz, 2H, vinyl CH). MS *m/e* (rel. intensity): 197 (M^+, 5), 182(94), 72(100), 59(100). Anal. calcd. for $C_{12}H_{23}NO$: C 73.04, H 11.75, N 7.10; found: C 72.83, H 11.77, N 7.36. The second fraction proved to be starting **18a** (0.1276 g, 25%).

Z- and *E*-3-(2-Butyl)-*N*,*N*,-2-trimethyl-3-pentenamide (19b)

Compound **18b** (0.1260 g, 0.6784 mmol) was lithiated according to procedure C and the resulting dienolate was alkylated with iodomethane (0.15 mL) in the normal manner. Following a standard workup, the crude reaction product was subjected to column chromatography (hexane – ethyl acetate, 3:1). After a small forerun containing dialkylated material, the one significant fraction proved to be **19b** (0.1212 g, 89%); bp 65–70 °C at 0.2 Torr. IR (neat, cm^{-1}) ν_{max}: 1646. ^1H NMR (250 MHz) δ: 0.7–1.5 (m, 11H, $3CH_3$ + CH_2), 1.66, 1.69 (2d, J = 7 Hz, 3H, CH_3 for ***E***- and ***Z*-19b**, respectively), 2.06, 2.46 (2m, 1H,CH for ***Z***- and ***E*-19b**, respectively), 2.92, 2.93 and 2.94, 3.02 (2× 2s, 6H, $2NCH_3$, for ***Z***- and ***E*-19b**, respectively). MS *m/e* (rel. intensity): 197(M^+, 4), 182(100), 72(45). Anal. calcd. for $C_{12}H_{23}NO$: C 73.04, H 11.75, N 7.10; found: C 73.23, H 11.73, N 6.93.

***E*-3-(1,1-Dimethylethyl)-*N*,*N*-2-trimethyl-3-pentenamide (19c)**

Compound **18c** (0.1160 g, 0.6328 mmol) was lithiated according to procedure C and the resulting dienolate alkylated with iodomethane (0.20 mL) in the normal manner. Following a standard workup, the crude reaction mixture was subjected to column chromatography (hexane – ethyl acetate, 3:1) to give only one fraction, which was shown to be **19c** (0.0940 g, 75%); bp 60–65 °C at 0.05 Torr. IR (neat, cm^{-1}) ν_{max}: 1648. NMR (250 MHz) δ: 1.09 (s, 9H, $3CH_3$), 1.32 (d, J = 7 Hz, 3H, CH_3), 1.66 (d, J = 7 Hz, 3H, CH_3), 2.93 (s, 6H, $2NCH_3$), 3.56 (q, J = 7 Hz, 1H, CH), 5.54 (q, J = 7 Hz, 1H, CH). MS *m/e* (rel. intensity): 197 (M^+, 2), 182(100), 72(83). Anal. calcd. for $C_{12}H_{23}NO$: C 73.04, H 11.75, N 7.10; found: C 72.89, H 11.51, N, 7.28.

Z- and *E*-3-(2-Butyl)-*N*,*N*,2,5-tetramethyl-3-hexenamide (19d)

Compound **18d** (0.4405 g, 2.084 mmol) was lithiated according to procedure C and the resulting dienolate alkylated with iodomethane (0.30 mL) in the normal manner. Following a standard workup, the crude reaction product was subjected to preparative TLC (ethyl acetate – hexane, 1:1) to give two fractions. The first fraction was shown to be **19d** (0.2254 g, 54%); bp 60–64 °C at 0.02 Torr. IR (neat, cm^{-1}) ν_{max}: 1643. ^1H NMR (250 MHz) δ: 7.15 (m, 17H, $5CH_3$ + CH_2), 2.03 (m, 1H, CH), 2.65 (m, 1H, CH), 2.94 (m, 6H, $2NCH_3$), 3.25, 3.71 (m, 1H, CH). MS *m/e* (rel. intensity): 225 (M^+, 3), 210(100), 100(23), 72(66). Anal. calcd. for $C_{14}H_{27}NO$: C 74.61, H 12.08, N 6.21; found: C 74.61, H 11.88, N 6.01. The second fraction was found to contain starting material **18d** (0.1657 g, 38%).

***Z*-3-(1-Butyl)-4-methoxy-*N*,*N*,2-trimethyl-3-butenanide (19f)**

Compound **18f** (0.1365 g, 0.6849 mmol) was lithiated according to procedure C and the resulting dienolate alkylated with iodomethane (0.15 mL) in the normal manner. Following a standard workup, the crude reaction product was subjected to flash chromatography (fine silica, ethyl acetate – hexane, 1:1) to afford **19f** (0.1234 g, 84%); bp 59–62 °C at 0.007 Torr. IR (neat, cm^{-1}) ν_{max}: 1647. ^1H NMR (250 MHz) δ: 0.87 (m, 3H, CH_3), 1.17 (d, J = 7 Hz, 3H, CH_3), 1.29 (m, 4H, $2CH_2$), 1.82 (m, 2H, CH_2), 2.91, 2.94 (2s, 6H, $2NCH_3$), 3.58 (s, 3H, OCH3), 3.90 (q, J = 7 Hz, 1H, CH), 5.76 (m, 1H, CH). Irradiation of the δ 5.76 resonance resulted in a 22% integrated enhancement of the δ 1.82 resonance; irradiation of the δ 1.82 resonance resulted in an 11% integrated enhancement in the δ 5.76 signal. MS *m/e* (rel. intensity):

213 (M^+, 26), 198(27), 141(100), 99(62). Anal. calcd. for $C_{13}H_{23}NO$: C 67.57, H 10.87, N 6.57; found: C 67.68, H 10.76, N 6.63.

Z- and E-3-Ethyl-*N*,*N*,3-trimethyl-3-pentenamide (19g)

Compound **18g** (0.1220 g, 0.7858 mmol) was lithiated according to procedure C and the resulting dienolate alkylated with iodomethane (0.20 mL) in the normal manner. Following standard workup, column chromatography (hexane – ethyl acetate, 5:2) afforded one fraction, which was shown to be **19g** (0.1057 g, 80%); bp 58–62 °C at 0.2 Torr. IR (neat, cm^{-1}) ν_{max}: 1645. ^1H NMR (250 MHz) δ: 0.96 (t, J = 8 Hz, 3H, CH_3), 1.18, 1.21 (2d, J = 7 Hz, 3H, CH_3 for **Z-** and ***E*-19g**, respectively), 1.62, 1.67 (2d, J = 7, 3H, CH_3 for ***E*-** and **Z-19g**, respectively), 2.10 (q, J = 8 Hz, 2H, CH_2), 2.96 (m, 6H, $2NCH_3$), 3.29, 3.64 (2q, J = 7 Hz, 1H, CH for ***E*-** and **Z-19g**, respectively, relative area 79:21), 5.27 (q, J = 7 Hz, 1H, CH). MS *m/e* (rel. intensity): 169 (M^+, 4), 154(100), 74(69), 72(89). Anal. calcd. for $C_{10}H_{19}NO$: C 70.96, H 11.31, H 8.28; found: C 70.86, H 10.89, N 8.63.

Compound **18g** (0.4156 g, 268 mmol) was lithiated according to procedure C and alkylated at –78 °C with iodomethane (0.4 mL). After allowing the reaction to warm overnight to RT, a standard workup was performed and the crude reaction product was subjected to preparative TLC (ethyl acetate – hexane, 5:2) to yield **19g** (0.3213 g, 71%) as the only isolated fraction. Integration of the δ 3.29 and δ 3.64 resonances in the ^1H NMR spectrum established the ratio of ***E*-19g**:**Z-19g** as 92:8.

Z-*N*,*N*-Dimethyl-3-hexenamide (23)

Compound **23** was prepared by the method reported by Baldwin and co-workers (16*j*) in 35% yield based on methyl sorbate; bp 46–48 °C at 2 Torr.

Z-*N*,*N*,-2-Trimethyl-3-hexenamide (24)

Compound **23** (0.1394 g, 0.987 mmol) was lithiated according to procedure A and the resulting dienolate alkylated with iodomethane (0.20 mL) in the normal manner. Following a standard workup, column chromatography (hexane – ethyl acetate, 5:2) of the crude product gave, after a forerun that contained a trace amount of dialkylated material, compound **24** (0.1281 g, 84%); bp 75–80 °C at 2.0 Torr. IR (neat, cm^{-1}) ν_{max}: 1643. ^1H NMR (250 MHz) δ: 1.00 (t, J = 8 Hz, 3H, CH_3), 1.81 (d, J = 7 Hz, 3H, CH_3), 2.10 (m, 2H, CH_2), 2.94, 3.01 (2s, 6H, $2NCH_3$), 3.61 (qd, J = 7, 7 Hz, 1H, CH), 5.04 (m, 2H, $2CH_2$); a signal at δ 3.33 (qd, m, CH for ***E*-24**) was barely perceptible and ***E*-24** was therefore estimated to be present to the extent of 5%. MS *m/e* (rel. intensity): 155 (M^+, 16), 140(22), 83(100). Anal. calcd. for $C_9H_{17}NO$: C 69.63, H 11.04, N 9.02; found: C 69.63, H 11.16, N 9.08.

N,N-Dimethyl-2-[*cis*-5-(1,1-dimethylethyl)-6-methyl-1-cyclohexenyl]propanamide (32)

Compound **31** (0.2468 g, 1.04 mmol) was lithiated according to procedure C and the resulting dienolate alkylated with iodomethane (0.18 mL) in the normal manner. Following a standard workup, the crude product was subjected to column chromatography (hexane – ethyl acetate, 4:1) to give one fraction, which was shown to contain **32** as a pair of diastereomers (0.2480 g, 95%); bp 89–94° at 0.02 Torr. IR (neat, cm^{-1}) ν_{max}: 1646. ^1H NMR (250 MHz) δ: 0.87, 0.89 (2s, 9H, $3CH_3$), 1.03, 1.15 (2d, J = 7 Hz, 3H, CH_3), 1.26 (d, J = 7 Hz, 3H, CH_3), 1.4–2.1 (m, 5H, $2CH_2$ + CH), 2.23 (q, J = 7 Hz, 1H, CH), 2.93, 3.06 and 2.95, 2.97 (4s, 6H, $2NCH_3$), 3.32, 3.37 (2q, J = 7 Hz, 1H, CH), 5.45, 5.73 (2dd, J = 7, 7 Hz, 1H, CH). MS *m/e* (rel. intensity): 251 (M^+, 9), 236(33), 194(100), 101(25), 72(136). Anal. calcd. for $C_{16}H_{29}NO$: C 76.44, H 11.63, N 5.57; found: C 76.36, H 11.72, N 5.48.

N,N-Dimethyl-2-[*trans*-5-(1,1-dimethylethyl)-6-methyl-1-cyclohexenyl]propanamide (34)

Compound **33** (0.198 g, 0.808 mmol) was lithiated according to procedure C and the resulting dienolate alkylated with iodomethane (0.10 mL) in the normal manner. Following a standard workup, the crude reaction product was subjected to flash chromatography (fine silica, hexane – ethyl acetate, 9:2) to give one major fraction, which contained **34** as a pair of diastereomers (0.1670 g, 82%); bp 90–95 °C at 0.02 Torr. IR (neat, cm^{-1}) ν_{max}: 1646. ^1H NMR δ: 0.84 (s, 9H, $3CH_3$), 0.9–2.3 (m, 12H, $2CH_3$ + $2CH_2$ + 2CH), 2.93, 2.97 (2s, 6H, $2NCH_3$), 3.1–3.6 (m, 1H, CH), 5.34, 5.58 (2br s, 1H, CH). MS *m/e* (rel. intensity): 251 (M^+, 12), 236(39), 194(100), 101(38), 72(147). Anal. calcd. for $C_{16}H_{29}NO$: C 76.44, H 11.63, N, 5.57; found: C 76.21, H 11.50, N 5.64.

***trans*-6-Deuterio-5-(1,1-dimethylethyl)-1-cyclohexenyl-*N*,*N*-dimethylpropanamide (36)**

Compound **Z-35** (0.1666 g, 0.743 mmol) was lithiated according to procedure C and the resulting dienolate alkylated with iodomethane (0.15 mL) in the normal manner. Following standard workup, the crude product was subjected to flash chromatography (fine silica, hexane – ethyl acetate, 4:1) to afford one fraction, which contained **36** as a pair of diastereomers (0.1667 g, 95%); bp 90–95 °C at 2 Torr. IR (neat, cm^{-1}) ν_{max}: 1646. ^1H NMR (250 MHz) δ: 0.87 (s, 9H, $3CH_3$), 1.22 (d, J = 7 Hz, 3H, CH_3), 1.0–1.35 (partially obscured m, 1H, CH), 1.65–2.2 (m, 5H, CH_2 + 3CH), 2.95, 2.96, 2.97, 2.98 (4s, 6H, $2NCH_3$), 3.18 (m, 1H, CH), 5.47 (m, 1H, CH). ^2H NMR δ: 1.92 (s, approx. 89% of D), 3.07 (s, approx. 8% of D), 5.49 (s, approx. 3% of D). MS *m/e* (rel. intensity): 239, 238, 237 (M^+, d_2:d_1:d_0, corrected, 5:93:22), 238 (M^+, 36), 223(38), 181(100), 167(35), 100(40), 72(173).

N,N-Dimethyl-2-[*trans*-3-(1,1-dimethylethyl)-6-methyl-1-cyclohexenyl]propanamide (38) and *N*,*N*-dimethyl-2-[5-(1,1-dimethylethyl)-2-inethyl-1-cyclohexenyl]propanamide (39)

Compound **Z-37** (0.1442 g, 0.607 mmol) was lithiated according to procedure C and the resulting dienolate alkylated with iodomethane (0.15 mL) in the normal manner. Following a standard workup, the reaction product was subjected to column chromatography (hexane – ethyl acetate, 5:1) to give one fraction. The contents of this fraction were shown by GC and ^1H NMR spectroscopy to be a roughly 1:1 mixture of **38** and **39** (0.1328 g, 87%); bp 89–94 °C at 0.05 Torr. IR (neat, cm^{-1}) ν_{max}: 1648. ^1H NMR (250 MHz) δ: 0.83, 0.83 (2s, 9H, $3CH_3$), 1.0–2.3 (m, 12 protons of **38** and 13 protons of **39**, $2CH_3$ + $2CH_2$ + 2CH of **38** and $2CH_3$ + $3CH_2$ + CH

of 39), includes 1.65 (s, CH_3 of **39**), 2.9–3.0 (m, 6H, $2NCH_3$), 3.17, 3.3, 3.57 (q, J = 7 Hz, q, J = 7 Hz and m, 1H, CH), 5.33, 5.57 (2s, 1 proton of **38**, CH). MS *m/e* (rel. intensity): 251 (M^+, 12), 236(52), 194(100), 180(52), 101(36), 84(20), 72(171). Anal. calcd. for $C_{16}H_{29}NO$: C 76.44, H 11.63, N 5.57; found: C 76.56, H 11.75, N 5.56.

cis-2-Deuterio-5-(1,1-dimethylethyl)cyclohexanone (44)

To a solution of LDA (13 mmol) in THF (65 mL) at –78 °C was added 3-(1,1-dimethylethyl)cyclohexanone (0.9988 g, 6.48 mmol) in a minimum amount of THF (~5 mL). The solution was stirred for 1 h at –78 °C. In a separate flask, D_2O (0.25 mL) was added to a stirred solution of trifluoroacetic anhydride (0.92 mL, 13 mmol) at –78 °C and the solution allowed to warm to RT. The contents of the latter flask were then added to the former flask, the mixture was stirred at –78 °C for 10 min, and $MgSO_4$ added. After warming to RT, the mixture was filtered through Celite and concentrated under reduced pressure. Distillation of the crude reaction product gave **44** (0.4614 g, 46%); bp 96–98 °C at 10 Torr. MS *m/e* (rel. intensity): 155, 154, 153 (M^+, d_2:d_1:d_0 = 10:40:50).

***Z*- and *E*-(*cis*-2-Deuterio-5-(1,1-dimethylethyl)cyclohexylidene]-*N*,*N*-dimethylacetamide (*Z*- and *E*-45)**

N,*N*-Dimethyltrimethylsilylacetamide (0.9543 g, 5.99 mmol) was lithiated according to procedure A. To a –78 °C solution of the resulting enolate was added **44** (0.9301 g, 5.99 mmol) in a minimum amount of THF (~3 mL). The reaction mixture was stirred for 3 h at –78 °C, warmed to RT, and two drops of water and $MgSO_4$ were added. After filtration through Celite and concentration of the filtrate under reduced pressure, the crude reaction product was subjected to flash chromatography (fine silica, hexane–Et_2O, 2:1). Four fractions were isolated. The first fraction contained starting material **44** (0.0530 g, 6%). The second fraction proved to be ***E*-45** (6.2084 g, 27% including fraction No. 3, see compound ***Z*-35**) contaminated with a small amount (4%) of ***Z*-45**. The third fraction was a 34:66 mixture of ***E*-45** and ***Z*-45** (0.2084 g). The final fraction was shown to contain ***Z*-45** (0.3805 g, 52% including fraction Nos. 2 and 3); bp 85–90 °C at 0.1 Torr. IR (neat, cm^{-1}) ν_{max}: 1628. ^1H NMR (250 MHz) δ: 0.87 (s, 9H, $3CH_3$), 1.0–1.3 (m, 2H, CH_2), 1.65–2.1 (m, 4.5H, CH_2 + 2CH + CD), 2.30 (d, J = 13 Hz, 1H, CH), 2.93 (obscured d, 1H, CH), 5.71 (s, 1H, CH). ^1H NMR (250 MHz, C_6D_6) δ: 0.79 (s, 9H, $3CH_3$), 0.8–1.8 (m, 6H, $2CH_2$ + 2CH + CD), 2.21 (br d, J = 13 Hz, 1H, CH), 2.24, 2.72 (2s, 6H, $2NCH_3$), 3.57 (br d, J = 11 Hz, 1H, CH), 5.68 (s, 1H, CH). ^2H NMR (C_6D_6, decoupled) δ: 1.60 (55% of D), 2.16 (20% of D), 3.48 (25% of D). MS *m/e* (rel. intensity): 225, 224, 223 (M^+, d_2:d_1:d_0, corrected, 9:37:54), 223 (M^+, 100), 180(69), 166(86), 121(46), 95(87), 81(49), 72(115). Anal. calcd. for $C_{14}H_{25}NO$: C 75.28, H 11.28, N 6.27; found: C 74.98, H 11.24, N 6.25.

2-Deuterio-5-(1,1-dimethyl ethyl)-1-cyclohexenyl-*N*,*N*-2-trimethylacetamide (46)

Compound ***Z*-45** (0.1601 g, 0.714 mmol) was lithiated according to procedure C and the resulting dienolate alkylated with iodomethane (0.15 mL) in the usual manner. Following a standard workup, the crude reaction product was subjected to column chromatography (hexane – ethyl acetate, 1:1) to afford one fraction, which contained **46** as a pair of diastereomers (0.1562 g, 92%); bp 85–90 °C at 0.2 Torr. IR (neat, cm^{-1}) ν_{max}: 1644. ^1H NMR δ: 0.87 (s, 9H, $3CH_3$), 1.0–1.35 (partially obscured m, 1H, CH), 1.6–2.2 (m, 6H, $2CH_2$ + 2CH), 2.95, 2.96, 2.97, 2.98 (4s, 6H, $2NCH_3$), 3.18 (m, 1H, CH), 5.47 (m, 0.65H, CD). ^2H NMR (decoupled) δ: 1.72 (9% of D), 2.28 (26% of D), 3.60 (65% of D). MS *m/e* (rel. intensity): 239, 238, 237 (M^+, d_2:d_1:d_0, corrected, 8:27:65), 237 (M^+, 27), 222(26), 181(100), 166(31), 101(50), 72(38). Anal. calcd. for $C_{15}H_{27}NO$: C 75.90, H 11.46, N 5.90; found: C 76.02, H 11.72, N 6.38.

Material on deposit

The experimental procedures and spectral data for the preparation of **14b–14d**, **15b–15d**, **16b–16f**, **17b–17f**, **18b–18f**, (diethylamino)-2-oxoethylphosphonate, the precursors to **31**, **33**, **35**, and **37**, and the minimized structures, final Cartesian coordinates, and energies for the calculated transition states for senecioamide deprotonation (**47**, **49**, and **50**) have been deposited as Supplementary material.[6]

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Synthesis and characterization of a series of novel phenol- and polyphenol-based glycerolipids[1]

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Abstract: A building block approach was used to design a modular synthetic route for the preparation of novel glycerolipids with phenolic and polyphenolic headgroups. Based on this scheme, it is possible to vary the substitution pattern of the headgroup, the stereochemistry of the backbone, and the length of the sidechains. Five glycerolipids with different headgroups and identical backbone stereochemistry and chain length have been prepared.

Key words: glycerolipid, polyphenol, hydrogen bonding, lipid-protein interaction, self-adhering.

Résumé : On a développé une méthode modulaire de synthèse de nouveaux glycérolipides comportant des têtes phénoliques et polyphénoliques. En se basant sur ce schéma, il est possible de faire varier la nature du groupe de tête, la stéréochimie du squelette et la longueur des chaînes latérales. On a préparé cinq glycérolipides dont la stéréochimie du squelette et la longueur de la chaîne sont les mêmes, mais qui diffèrent par la nature de leur groupe de tête.

Mots clés : glycérolipide, polyphénol, liaison hydrogène, interaction lipide-protéine, autoadhérente.

[Traduit par la Rédaction]

Introduction

It is well-known that polyphenols bind and precipitate proteins and (or) peptides and can act as antioxidants (Handique and Baruah (1) provide a comprehensive review of natural and synthetic polyphenols). Furthermore, poly(phenol) films have been used as protective coatings for proteins immobilized onto electrodes (2). A novel synthetic lipid, 1,2-dipalmitoylgalloylglycerol (DPGG), has been prepared (3) that incorporates a polyphenol as the headgroup. The authors suggest that this lipid has the potential to exhibit comparable protein-binding properties (4) so that Langmuir–Blodgett films of such lipids could prove useful as biocompatible coatings. Pollastri et al. (3) demonstrated the self-adhesive nature of DPGG bilayers and proposed both strong inter- and intra-bilayer hydrogen bonding between gallic acid headgroups. We have recently shown that DPGG monolayers exhibit strong lateral cohesion and high rigidity, which can also be attributed to lateral hydrogen bonding (5). The influence of hydrogen bonding on monolayer and bilayer phase behaviour has been previously documented for lipids such as phosphatidylethanolamines and cerebrosides (3, 6, 7). To probe and understand the lateral cohesion in monolayers due to a hydrogen bonding network requires systematic chemical modification with respect to hydrogen bonding sites. In contrast to phosphatidylethanolamines and cerebrosides, DPGG provides an ideal template for a library of analogous lipids. We have employed a building block approach to design a modular synthetic route for the preparation of this library of novel glycerolipids with phenolic and polyphenolic headgroups. We report here the preparation of DPGG analogues with headgroups varying in number and position of hydroxyl groups (Fig. 1).

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Results and discussion

The preparation of DPGG in two steps from tri-O-benzylgalloyl chloride and dipalmitoylglycerol has been described in the literature (3). The key features of this synthesis are the use of the benzyl protecting group and the introduction of a side chain bearing glycerol moiety. We report a more modular synthetic route to DPGG and some of its analogues, which allows for easy variation not only of the headgroup (number and position of hydroxyl groups) but also the stereochemistry of the backbone (R or S) and the chemical character of the side chains (chain length, units of unsaturation, functionalization, etc.) (Scheme 1). All of these parameters are known to influence monolayer phase behaviour and more generally, lipid self-assembly properties.

Compounds **3a**, **3c**, and **3e** are commercially available in gram quantities. Compounds **3b** and **3d** were prepared by well-known methods from 3-hydroxybenzoic acid methyl ester and 3,4-dihydroxybenzoic acid, respectively. Therefore, it is easy to alter the headgroup structure of the title compounds by varying the substitution pattern of the starting material. In the first step of the synthesis of the title compounds, phenol-bearing benzoic acids **3** are reacted with a racemic mixture of 2,2-dimethyl-1,3-dioxolane-4-methanol (solketal, a protected glycerol) to give compounds **4**. Importantly, the same procedure could be used to prepare the enantiomerically pure analogues starting from commercially

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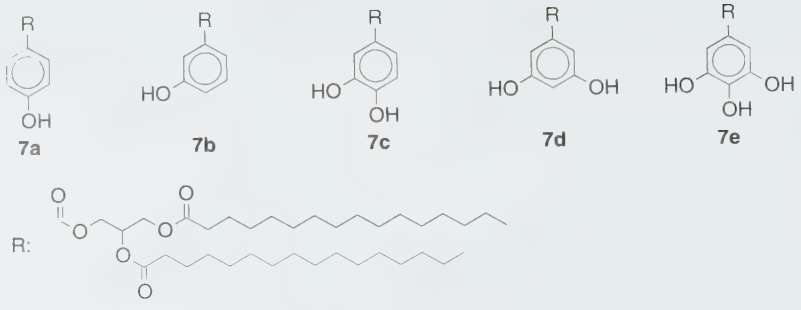
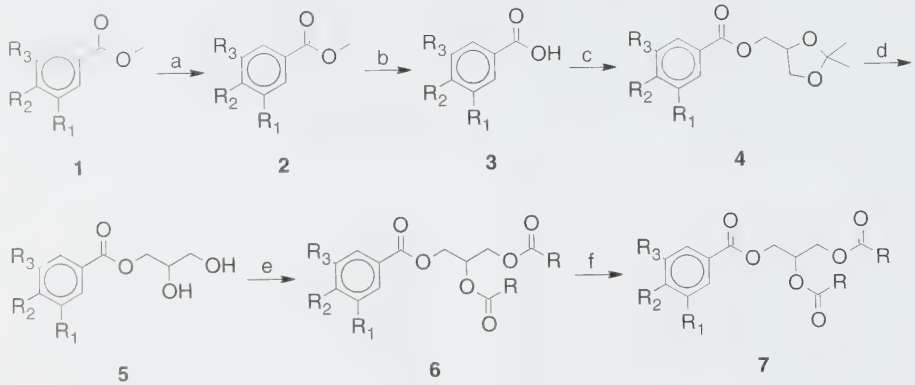
Fig. 1. Chemical structure of DPGG (**7e**) and prepared analogues.



Scheme 1. Reagents: (*a*) BnBr, K_2CO_3, CH_2Cl_2–MeOH, (*b*) KOH, THF–H_2O, (*c*) solketal, 1-methylimidazole, *p*-TsCl, MeCN, (*d*) Amberlyst® 15, MeOH–H_2O, (*e*) hexadecanoic acid, DMAP, EDCI, CH_2Cl_2, (*f*) H_2, 10% Pd–C.



1, 7	R_1	R_2	R_3
a	H	OH	H
b	OH	H	H
c	OH	H	OH
d	OH	OH	H
e	OH	OH	OH

2–6	R_1	R_2	R_3
a	H	OBn	H
b	OBn	H	H
c	OBn	H	OBn
d	OBn	OBn	H
e	OBn	OBn	OBn

available (*R*)-(-)- or (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol instead of the racemic mixture, provided that the pH is held between 7 to 8 to retain optical purity (8). The isopropylidene and benzyl protecting groups were chosen from orthogonal sets to provide selective deprotection of the isopropylidene in step d (Fig. 1). The protected benzoates **4** were not isolated, but the glycerol moiety was deprotected by treatment with wet Amberlyst® 15, a strongly acidic resin that allows for easy removal from the reaction mixture by gravity filtration. The advantage of Amberlyst® 15, aside from easy removal, is the fact that the sulfonic residues bound to the resin beads provide significant steric hindrance to prevent ester cleavage (9). Cleavage of the isopropylidene protecting group with I_2 in methanol (10) or under acidic conditions using aqueous acetic acid (11) was not successful. It has to be noted that a similar approach has previously been employed by Schmidt and Blank (12) for the preparation of compounds **4e** and **5e**. However, reaction times are generally much shorter and workup much simpler for our synthetic scheme with similar yields. In the next step, the palmitoyl side chains were introduced by coupling **5** with palmitic acid in the presence of *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP) (13, 14). This acylation method was shown to be superior to the coupling of acid chlorides or anhydrides with the corresponding aliphatic acids (15). Furthermore, excess EDCI and the 1-(3-dimethylamino-propyl)-3-ethyl-urea formed during the reaction can easily be removed from the reaction mixture by liquid–liquid extraction because of their good solubility in water. The reaction has also been successfully carried out with the corresponding myristoyl and stearoyl side chains (data not shown). In addition, it is possible to selectively introduce two dissimilar side chains (e.g., palmitoyl and stearoyl) by successive coupling with the respective acids (15, 16).

Diacetylation in the first step as well as 1,2-acyl migration in the second step can be avoided by maintaining the reaction temperature between 0 and 20 °C (15). The benzyl protecting group is removed by catalytic hydrogenation under moderate pressure in the final step. The reaction time in-

creases with the number of benzyl groups to be removed. DPGG and its benzyl-protected precursor were also prepared by this method with comparable yields to the literature (3).

Conclusion

We have prepared a library of phenolic and polyphenolic glycerolipids according to a relatively simple modular reaction scheme. Moreover, the same scheme can be used to prepare glycerolipids that are enantiomerically pure and (or) have dissimilar side chains.

Experimental

All chemicals were purchased from commercial suppliers and used without further purification. 4-Benzyloxybenzoic acid, 3,5-di-benzyloxybenzoic acid, and 3,4,5-tris-benzyloxybenzoic acid were obtained from Tokyo Chemical Industry Co., Ltd. (TCI, Tokyo, Japan). ^{1}H spectra were obtained at 300 MHz and ^{13}C NMR spectra were obtained at 75 MHz in $CDCl_3$ unless otherwise noted using the NMR solvent as an internal reference. Abbreviations used in the descriptions of NMR spectra are singlet (s), doublet (d), triplet (t), multiplet (m), broad signal (br). The coupling constants (J) are given in Hertz. Mass spectrometry measurements were carried out on a MALDI mass spectrometer using dithranol as a matrix. IR measurements were carried out using a liquid cell equipped with KBr windows and in $CDCl_3$ unless otherwise noted. All melting points are uncorrected. Silica gel for flash chromatography was acquired from Life Force Inc. (Flushing, New York).

3,4-Dihydroxybenzoic acid methyl ester (1d)

3,4-Dihydroxybenzoic acid (1 g, 6.49 mmol) was dissolved in 40 mL of MeOH. After the addition of 2 drops of concd. H_2SO_4, the solution was refluxed for 7 days. The reaction was stopped by the addition of 300 mL of distilled H_2O. The mixture was extracted with ethyl acetate – hexanes (60:40). The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure to give 0.8 g of a light-brown solid in 73% yield.

3-Benzyloxybenzoic acid methyl ester (2b)

Compound **2b** was prepared according to the literature (17) with a reaction time of 6 h. The product was purified by flash chromatography on SiO_2 (hexanes – ethyl acetate, 80:20) to give 0.98 g of a white solid in 61% yield.

3,4-Bis-benzyloxybenzoic acid methyl ester (2d)

Compound **2d** was prepared in a manner analogous to **2b**. However, 2.3 equiv. of benzyl bromide were used and gave 1.19 g of a white solid in 77% yield.

3-Benzyloxybenzoic acid (3b)

Compound **2b** (0.75 g, 3.1 mmol) was dissolved in 35 mL of THF. A solution of KOH (1.04 g, 18.6 mmol, 6 equiv.) in 50 mL of distilled H_2O was added and the reaction was stirred for 24 h. The reaction mixture was added to 250 mL of distilled H_2O and acidified to pH 5 with 2N HCl. The mixture was extracted with diethylether. The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure to yield 0.67 g of a white solid in 95% yield.

3,4-Bis-benzyloxy-benzoic acid (3d)

Compound **3d** was prepared in a manner analogous to **3b** with a reaction time of 48 h. The reaction gave 0.67 g of a white solid in 70% yield.

Synthesis of the benzyloxybenzoic acid 2,3-dihydroxypropyl esters (5a–5d)

Typical procedure

Compound **3a** (1.0 g, 4.38 mmol), 1-methyl-imidazole (1.08 g, 13.14 mmol, 3 equiv.), and *p*-toluenesulfonyl chloride (1.17 g, 6.13 mmol, 1.4 equiv.) were dissolved in 45 mL of CH_3CN and stirred for 30 min. After the addition of racemic 2,2-dimethyl-1,3-dioxolane-4-methanol (0.58 g, 4.38 mmol, 1 equiv.), the solution was stirred under inert atmosphere for 3 h. The volume of the solution was reduced to approximately 4 mL under reduced pressure and the solution filtered through Al_2O_3 with 40 mL of CH_2Cl_2. The solvent was removed under reduced pressure to give 1.0 g of a white solid which was used without further purification. Compound **4a** (0.15 g, 0.438 mmol) was suspended in 40 mL of EtOH–H_2O (95:5). Wet Amberlyst® 15 (0.180 g, 1 equiv.) was added to the suspension and the suspension was refluxed for 24 h. The solution was allowed to cool to room temperature and 40 mL of CH_2Cl_2 and 300 mL of brine were added. The mixture was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure. The crude was purified by flash chromatography on SiO_2 (ethyl acetate – hexanes, 70:30) to give 0.105 g of a white solid in 80% yield.

Data for 5a

Melting point 77–79 °C. IR (cm^{-1}) ν: 3614, 3036, 2952, 2886, 1713, 1606. ^{1}H NMR δ: 8.01 (m, 2H), 7.40 (m, 5H), 7.01 (m, 2H), 5.13 (s, 2H, ArCH_2), 4.42 (m, 2H), 4.00 (m, 1H), 3.71 (m, 2H). ^{13}C NMR δ: 166.7, 162.8, 136.1, 131.8, 128.7, 128.2, 127.5, 122.1, 114.6, 70.45, 70.13, 65.5, 63.4. MS *m/z*: 325.3 [M + Na]$^+$

Data for 5b

Yield 80%, mp 76–78 °C. IR (cm^{-1}) ν: 3618, 3036, 2952, 2884, 1719, 1586. ^{1}H NMR δ: 7.68 (m, 2H), 7.40 (m, 6H), 7.19 (m, 1H), 5.11 (s, 2H, ArCH_2), 4.42 (m, 2H), 4.06 (m, 1H), 3.72 (m, 2H). ^{13}C NMR δ: 166.8, 158.7, 136.4, 130.9, 129.6, 128.6, 128.1, 127.5, 122.4, 120.5, 115.4, 70.3, 70.2, 65.8, 63.4. MS *m/z*: 325.3 [M + Na]$^+$.

Data for 5c

Yield 85%, mp 94 to 95 °C. IR (cm^{-1}) ν: 3618, 3035, 2952, 2884, 1717, 1596. ^{1}H NMR δ: 7.38 (m,10H), 7.28 (d, 2H, J = 2.33 Hz), 6.82 (t, 1H, J = 2.34 Hz), 5.07 (s, 4H, ArCH_2), 4.52 (m, 2H), 4.05 (m, 1H), 3.71 (m, 2H). ^{13}C NMR δ: 166.6, 159.8, 136.4, 131.4, 128.6, 128.2, 127.6, 108.6, 107.4, 70.4, 70.3, 65.9, 63.4. MS *m/z*: 431.4 [M + Na]$^+$.

Data for 5d

Yield 83%, mp 80 to 81 °C. IR (cm^{-1}) ν: 3613, 3034, 2951, 2885, 1712, 1601. ^1H NMR δ: 7.63 (m, 2H), 7.39 (m, 10H), 6.93 (m, 1H), 5.23 (s, 2H, ArCH_2), 5.20 (s, 2H, ArCH_2), 4.37 (m, 2H), 4.02 (m, 1H), 3.68 (m, 2H). ^{13}C NMR δ: 166.7, 153.3, 148.3, 136.7, 136.4, 128.6, 128.5, 128.0, 127.9, 127.4, 127.1, 124.3, 122.3, 115.7, 113.2, 71.3, 70.8, 70.4, 65.6, 63.3. MS *m/z*: 431.4 $[M + Na]^+$.

Data for 5e

Yield 57%.

Synthesis of benzyloxybenzoic acid 2,3-bis-hexadecanoyloxypropyl esters (6a–6e)

Typical procedure

Compound **5a** (0.38 g, 1.25 mmol) and hexadecanoic acid (0.73 g, 2.825 mmol, 2.26 equiv.) were dissolved in 20 mL of CH_2Cl_2. A suspension of DMAP (0.35 g, 2.825 mmol, 2.26 equiv.) and EDCI (0.58 g, 3 mmol, 2.4 equiv.) in 10 mL of CH_2Cl_2 was added to the reaction mixture and the mixture was stirred for 4 h. Brine (300 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure. The product was purified by flash chromatography on SiO_2 (hexanes – ethyl acetate, 80:20) to give 0.80 g of a white solid in 82% yield.

Data for 6a

Melting point 64–66 °C. IR (cm^{-1}) ν: 2927, 2855, 1736, 1606. ^1H NMR δ: 7.98 (m, 2H), 7.39 (m, 5H), 7.01 (m, 2H), 5.41 (m, 1H), 5.12 (s, 2H, ArCH_2), 4.41 (m, 3H), 4.24 (m, 1H), 2.33 (t, 2H, *J* = 7.5 Hz, CH_2COO), 2.32 (t, 2H, *J* = 7.6 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.70 Hz, CH_3). ^{13}C NMR δ: 173.3, 172.9, 165.7, 162.8, 136.2, 131.8, 128.7, 128.2, 127.4, 122.1, 114.6, 70.1, 68.9, 62.6, 62.3, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 802.1 $[M + Na]^+$.

Data for 6b

Reaction time 6 h, yield 44%, mp 51 to 52 °C. IR (cm^{-1}) ν: 2927, 2855, 1735, 1586. ^1H NMR δ: 7.64 (m, 2H), 7.39 (m, 6H), 7.18 (m, 1H), 5.42 (m, 1H), 5.11 (s, 2H, ArCH_2), 4.43 (m, 3H), 4.24 (m, 1H), 2.33 (t, 2H, *J* = 7.5 Hz, CH_2COO), 2.32 (t, 2H, *J* = 7.6 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.3, 172.9, 165.8, 158.8, 136.5, 130.8, 129.5, 128.6, 128.1, 127.5, 122.3, 120.5, 115.3, 70.2, 68.9, 63.0, 62.2, 34.3, 34.1, 31.9, 29.8, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 802.1 $[M + Na]^+$.

Data for 6c

Reaction time 12 h, yield 94%, mp 66–68 °C. IR (cm^{-1}) ν: 2927, 2855, 1736, 1596. ^1H NMR δ 7.38 (m, 10H), 7.26 (d, 2H, *J* = 2.3 Hz), 6.81 (t, 1H, *J* = 2.3 Hz), 5.41 (m, 1H), 5.07 (s, 4H, ArCH_2), 4.45 (m, 3H), 4.22 (m, 1H), 2.33 (t, 4H, *J* = 7.5 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ 173.3, 172.9, 165.7, 159.8, 136.4, 131.4, 128.6, 128.1, 127.6, 108.5, 107.5, 70.3, 68.8, 63.0, 62.1, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 908.3 $[M + Na]^+$.

Data for 6d

Reaction time 12 h, yield 63%, mp 45–47 °C. IR (cm^{-1}) ν: 2927, 2855, 1736, 1601. ^1H NMR δ: 7.62 (m, 1H), 7.58 (d, 1H, *J* = 2.1 Hz), 7.42 (m, 10H), 6.93 (d, 1H, *J* = 8.5 Hz), 5.41 (m, 1H), 5.23 (s, 2H, ArCH_2), 5.20 (s, 2H, ArCH_2), 4.40 (m, 3H), 4.17 (m, 1H), 2.33 (t, 4H, *J* = 7.5 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.3, 172.9, 165.6, 153.2, 148.4, 136.8, 136.5, 128.6, 128.5, 128.0, 127.9, 127.4, 127.1, 124.1, 122.3, 115.5, 113.2, 71.6, 70.8, 68.9, 62.7, 62.2, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 908.3 $[M + Na]^+$.

Data for 6e

Reaction time 15 h, yield 70%.

Synthesis of hydroxybenzoic acid 2,3-bis-hexadecanoyloxypropyl esters (7a–7e)

Typical procedure

Compound **6a** (0.2 g, 0.257 mmol) was dissolved in 20 mL of dry THF. 10% Pd–C (0.07 g, 30 wt%) was added and the reaction mixture was placed in a pressure reactor and stirred under 3.5 atm (1 atm = 101.325 kPa) of hydrogen gas for 4 h. The mixture was filtered through Celite 545 and the solvent removed under reduced pressure to give 0.14 g of a white solid in 80% yield.

Data for 7a

Melting point 69–71 °C. IR (cm^{-1}) ν: 3587, 2927, 2855, 1736, 1610. ^1H NMR δ: 7.94 (m, 2H), 6.86 (m, 2H), 5.42 (m, 1H), 5.33 (br, 1H, *OH*), 4.44 (m, 3H), 4.24 (m, 1H), 2.33 (t, 2H, *J* = 7.5 Hz, CH_2COO), 2.32 (t, 2H, *J* = 7.5 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.5, 173.1, 165.7, 160.0, 132.1, 122.1, 115.3, 69.0, 62.7, 62.3, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 712.0 $[M + Na]^+$.

Data for 7b

Reaction time 6 h, 61% yield, mp 64 to 65 °C. IR (cm^{-1}) ν: 3594, 2927, 2855, 1734, 1593. ^1H NMR δ: 7.61 (m, 1H), 7.48 (m, 1H), 7.32 (m, 1H), 7.06 (m, 1H), 5.43 (m, 1H), 5.20 (br, 1H, *OH*), 4.43 (m, 3H), 4.24 (m, 1H), 2.33 (t, 2H, *J* = 7.4 Hz, CH_2COO), 2.32 (t, 2H, *J* = 7.5 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.4, 173.1, 165.7, 155.8, 130.1, 129.8, 122.1, 120.5, 116.3, 68.9, 63.0, 62.2, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 712.0 $[M + Na]^+$.

Data for 7c

Reaction time 7 h, 53% yield, mp 78 to 79 °C. IR (cm^{-1}) ν: 3594, 2927, 2855, 1733, 1605. ^1H NMR δ: 7.07 (d, 2H, *J* = 2.2 Hz), 6.59 (t, 1H, *J* = 2.3 Hz), 5.45 (m, 3H), 4.41 (m, 3H), 4.24 (m, 1H), 2.33 (t, 6H, *J* = 7.6 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.6, 173.3, 165.4, 157.1, 131.6, 109.2, 107.8, 68.5, 63.1, 62.2, 34.3, 34.1, 31.9, 29.7, 29.6,

29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 728.0 $[M + Na]^+$.

Data for 7d

Reaction time 7 h, 50% yield, mp 92 to 93 °C. IR (cm^{-1}) ν: 3566, 2927, 2855, 1734, 1616. ^1H NMR δ: 7.07 (d, 2H, J = 2.2 Hz), 6.59 (t, 1H, J = 2.3 Hz), 5.45 (m, 3H), 4.41 (m, 3H), 4.24 (m, 1H), 2.33 (t, 6H, J = 7.6 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, J = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.7, 173.4, 166.3, 149.8, 146.8, 123.1, 120.9, 115.9, 114.6, 68.9, 62.5, 62.2, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 728.0 $[M + Na]^+$.

Data for 7e

Reaction time 8 h. The product was then adsorbed to silica in the presence of 1 mL of acetic acid and purified by flash chromatography on SiO_2 using a solvent gradient of hexanes – ethyl acetate from 90:10 to 30:70. The product was then extracted from 200mL of brine with $CHCl_3$ (5 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure to give 0.050 g of a white solid in 70% yield.

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Hydrosilylation of ketones catalyzed by C_2-symmetric proline-derived complexes[1]

Li Gan and Michael A. Brook

Abstract: Extracoordinate chiral hydrosilanes were generated in situ from triethoxysilane and a C_2-symmetric ligand derived from bisproline 7. In the presence of a catalytic amount of ligand **7**, prochiral ketones were reduced in moderate yield with moderate enantioselectivity (up to 64% ee). Alternatively, TiF_4 complexes of **7** were used to provide higher enantioselectivity and with improved yields. The copper complex of ligand **7** and ^{29}Si NMR data provide some guidance as to the key factors responsible for the observed reactivity at the silicon and at the ligand centre.

Key words: extracoordinate chiral silane, C_2-symmetry, enantioselectivity, Lewis acid titanium catalysis.

Résumé : On a effectué une génération *in situ* d'hydrosilanes chiraux extracoordinés à partir du triéthoxysilane et d'un ligand de symétrie C_2 dérivé de la bisproline **7**. En présence d'une quantité catalytique du ligand **7**, les cétones prochirales sont réduites avec des rendements moyens et un énantiosélectivité modérée, allant jusqu'à 64 % d'excès énantiomère. D'une façon alternative, on a utilisé des complexes du tétrafluorure de titane du ligand **7** qui ont fourni une énantiosélectivité supérieure et de meilleurs rendements. Le complexe de cuivre du ligand **7** et les données de la RMN du ^{29}Si donnent des indications sur les facteurs clés responsables au niveau de l'atome de silicium et du centre du ligand pour la réactivité observée.

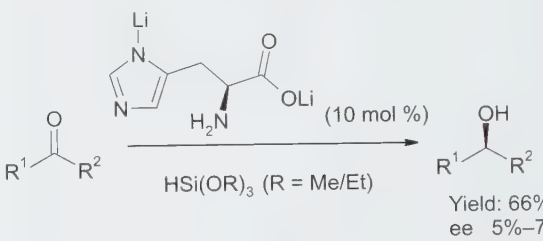
Mots clés : silane chiral extracoordiné, symétrie C_2, énantiosélectivité, catalyseur de titane agissant comme acide de Lewis.

[Traduit par la Rédaction]

Introduction

The enantioselective reduction of carbonyl groups remains one of the fundamental operations in organic synthesis (1). Typical catalytic systems utilize a chiral ligand complexed with a transition metal (2). With the exception of boron, such as the well-developed chiral boron catalyst (CBS) (3), the use of chiral catalytic motifs based on main group elements is uncommon (4). However, in a process related to that reported by Shiffers and Kagan (5) and Hosomi and coworkers (6), we previously demonstrated that the complex derived from hydrosilanes and a catalytic amount of amino acids can reduce ketones enantioselectively (Scheme 1) (7).

Scheme 1. Histidine-catalyzed ketone reduction.



These reactions with hydrosilanes occur via extracoordinate silicon in the presence of anionic catalysts. Sakurai and co-workers (8a, 8b) has demonstrated that diastereoselective allylation of carbonyl groups in the presence of pentacoordinate silicon hydrides, for example, can best be explained by invoking six-membered ring transition states (Scheme 2). Coordination of the nucleophile, the carbonyl group, to the extracoordinate silicon is followed by allyl group transfer. As a departure point, we proposed that a related assembly of ketone and carboxylate on an extracoordinate silicon 1 could be used to explain the observed stereoselectivity in the hydrosilane reduction of acetophenone, although related bidentate structures could also be envisaged. While the mechanisms of these reactions have not yet been clearly established, the presence of extracoordinate

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It is a great pleasure to dedicate this paper to the superb career of Alfred Bader. I learned about his passion for chemistry and chemists when we met several times when I was a graduate student and postdoctoral fellow. It meant a great deal to me then, and now, that "Please Bother Us" meant anyone interested in chemistry, not just the professors. I thank him for sharing his vision and enthusiasm for chemistry with me then and many times since. The example he set has profoundly affected the way my career has evolved.

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[1]This article is part of a Special Issue dedicated to Dr. Alfred Bader.

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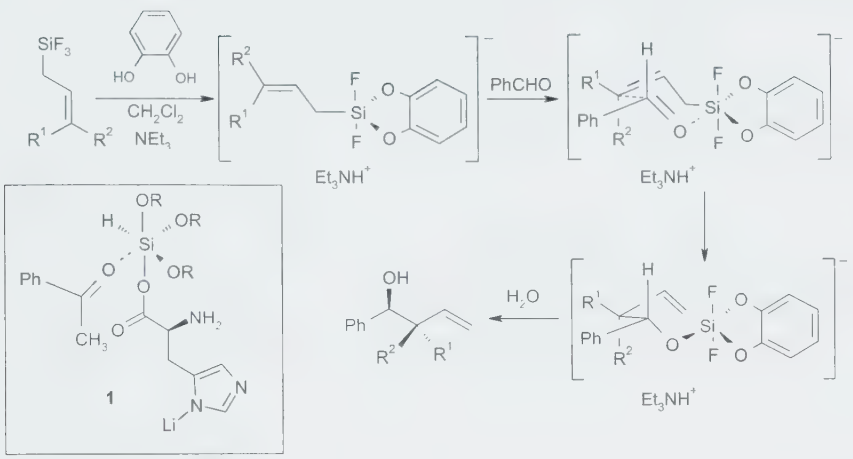
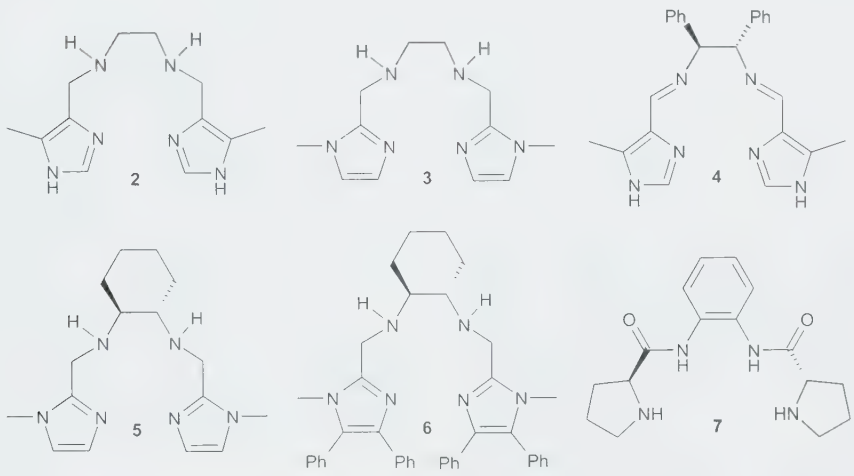
Scheme 2.



Scheme 3.



silicon, particularly the pentacoordinate species, is evident from Si NMR.

In an attempt to better understand the processes involved in the reduction, recent research has turned to the utilization of multidentate ligands that, on binding, would have fewer degrees of freedom and, additionally, would be more amenable to structural characterization. The use of C_2-symmetry, in particular, provides a more highly structured environment for enantioselective reactions (9), a strategy we recently utilized with silane-medicated reductions (**2**–**6**, Scheme 3) (10). Unfortunately, only moderate ee were observed in these reactions.

In this study, we developed a C_2-symmetric multidentate ligand that utilizes proline, perhaps the most widely utilized amino acid chiral template (11). We report the synthesis of the C_2-symmetric compound **7** (Scheme 3), the formation of pentacoordinate silicon complexes on reaction of **7** with $HSi(OEt)_3$, as shown by ^{29}Si NMR, the ability of this complex to reduce ketones, and the characterization of its copper complex **13** by an X-ray structure. In addition, the behaviour of the Lewis acidic derivative formed from the reaction of **7** with TiF_4 is described in the same carbonyl reduction process.[3]

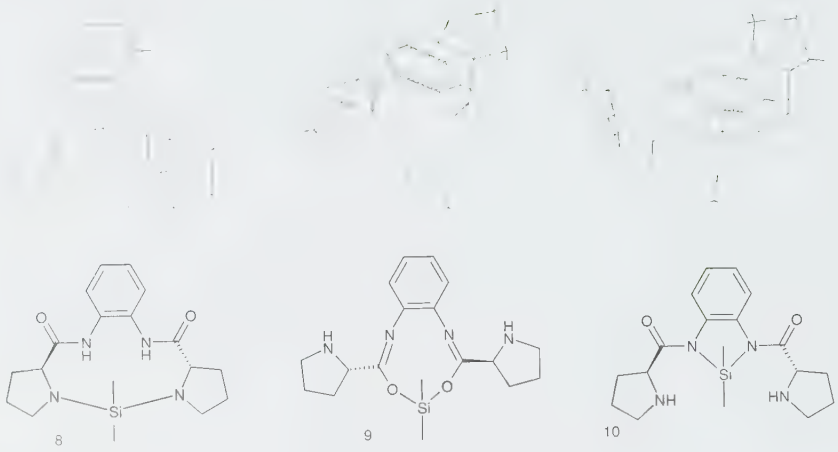
Results and discussion

Preparation and characterization of the ligands

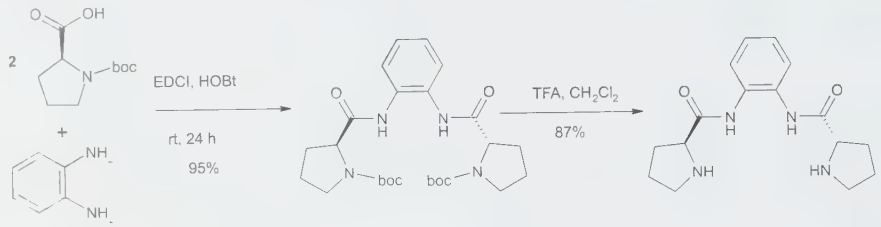
A series of molecular modeling experiments were undertaken with C_2-symmetric diamino acid derivatives. Preliminary studies compared the geometries of bidentate

[3] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5079. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 601366 and 601367 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Fig. 1. Molecular models of dimethylsilyl derivatives of **7**.



Scheme 4. Preparation of bisproline **7**.



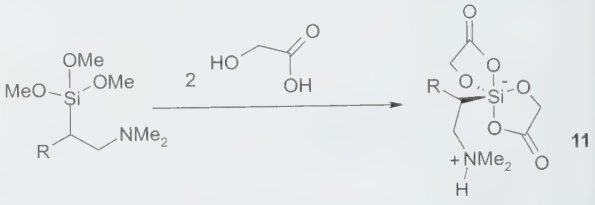
dimethylsilicon complexes based on various amino acid complexes of 1,2-diaminobenzene. Among the amino acids examined (phenylalanine, histidine, alanine, and proline), the latter had a more tightly constrained structure, irrespective of whether the linkages occurred through the proline nitrogen **8**, amide oxygen **9**, or amide nitrogen **10** (Fig. 1). All of the derivatives had more rigid and compact chiral environments than structures based on the structural motifs found in **4** or **5** (Scheme 3). Therefore, the bisproline ligand **7** was prepared by coupling 1,2-diaminobenzene with commercially available N-protected L-proline (Scheme 4). The optically pure ligand was obtained, after deprotection by trifluoroacetic acid, by recrystallization from methanol in an overall yield of 83% and structurally characterized by NMR (^{1}H, ^{13}C), HRMS, and IR.

Mechanistic study

Silicon compounds undergo extracoordination in the presence of silaphilic nucleophiles, particularly oxygen, fluoride, and aromatic amines (12). Coordination expansion is facilitated by electron-withdrawing groups on silicon, especially fluoride and oxygen ligands. Thus, the facility of trialkoxysilanes to undergo extracoordination lies between that of trialkyl- and trihalo-silanes (12). Tacke and co-workers (13), in a beautiful series of papers, demonstrated that bidentate nucleophiles are particularly efficacious in inducing coordination expansion. A broad variety of pentacoordinate amino and hydroxy acid derivatives, exemplified by **11**, have been isolated in crystalline form (Scheme 5) (13, 14).

Complexes of **7** and $HSi(OEt)_3$ were characterized by ^{29}Si NMR. The ^{29}Si NMR of the neutral mixture gave a singlet at

Scheme 5. Formation of extracoordinate silicon with α-hydroxy acids.



–58.68 ppm, consistent with reported data for triethoxysilane (15). Thus, the amine groups are insufficiently basic to engender extracoordination at silicon. By contrast, when the bisproline tetraanion of **7** was mixed with triethoxysilane in a ratio of 1:2 (sensitivity of the NMR precluded lower concentrations of the silicon compound and higher concentration of the bisproline tetraanion led to precipitates) ^{29}Si NMR showed two singlets at –84.27 and –98.83 ppm, respectively.

It is challenging to assign putative structures to compounds with these chemical shifts. Each exchange at silicon of H by O or N leads to an upfield shift, as does each exchange of N by O. For example, the addition of the anionic ligand of **7** to $HSi(OEt)_3$ to give a pentacoordinate species $(HSi(OEt)_3\text{-}N7)^-$ would lead to an upfield shift of about 20 ppm. However, displacement of the EtO^- by the same nitrogen to give a tetracoordinate species $(HSi(OEt)_2\text{-}N7)$ would lead to a downfield shift of about 15 ppm (16). The observed peaks are consistent with a pentacoordinate species ($HSiX_4^-$, –84.27 ppm) and an oxidized pentacoordinate species (SiX_5^-) or a hydrido hexacoordinate species ($HSiX_5^{2-}$,

Fig. 2. ORTEP drawing of the structure of **12**, a copper complex **13**, and a possible structure of the hydridosiliconate **14**.

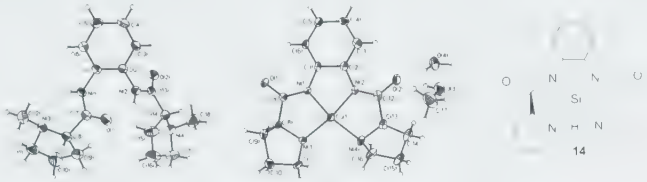


Table 1. Selected crystallographic data for ligand **7**.

Identification code	CCDC 601366
Empirical formula	$C_{18}H_{26}N_4O_2$
Formula weight (g mol^{-1})	330.43
Crystal system	Monoclinic
Space group	*C*2
a (Å)	20.259(8)
b (Å)	8.751(3)
c (Å)	10.929(4)
α (°)	90
β (°)	113.066(6)
γ (°)	90
Volume (Å^3)	1782.6(12)
Z	4
Density$_{calcd.}$ (Mg/m^3)	1.231
Absorption coefficient (mm^{-1})	0.082
F(000)	712
Crystal size (mm^3)	0.38 × 0.18 × 0.08
θ range for data collection (°)	2.03–26.48
Reflections collected	7556
Independent reflections	3346
R_{int}	0.0346
Data, restraints, parameters	3346, 1, 218
Goodness-of-fit on F^2	1.009
Final *R* indices [$I > \sigma(I)$]	$R_1 = 0.0419$, $wR_2 = 0.0898$
R indices (all data)	$R_1 = 0.0702$, $wR_2 = 0.0993$
Largest diff. peak and hole (e Å^{-3})	0.116 and –0.118

Table 2. Selected crystallographic data for **13**.

Identification code	CCDC 601367
Empirical formula	$C_{17}H_{24}CuN_2O_4$
Formula weight	411.94
Space group	*P*2(1)2(1)2(1)
Crystal system	Orthorhombic
Crystal size (mm^3)	0.20 × 0.18 × 0.06
a (Å)	8.3234(4)
b (Å)	11.7554(5)
c (Å)	18.5682(8)
α (°)	90
β (°)	90
γ (°)	90
Volume (Å^3)	1816.80(14)
Z	4
Density$_{calcd.}$ (Mg/m^3)	1.506
Absorption coefficient (mm^{-1})	1.233
F(000)	860
θ range for data collection (°)	2.05–28.31
Reflections collected	16 688
Independent reflections	4359
R_{int}	0.0891
Completeness to θ = 28.31° (%)	98.00
Data, restraints, parameters	4359, 0, 248
Goodness-of-fit on F^2	1.042
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0593$, $wR_2 = 0.1036$
R indices (all data)	$R_1 = 0.1041$, $wR_2 = 0.1152$
Largest diff. peak and hole (e Å^{-3})	0.526 and –0.555

–98.83 ppm), respectively. Since extracoordinate hydridosiliconates are required to reduce ketones (see later), it is anticipated that these peaks represent penta- and hexacoordinate silicon hydrides; after the ketone reduction, ^{29}Si NMR showed only one peak at –82.39 ppm.

It did not prove possible to prepare crystals of sufficient quality for an X-ray analysis. By contrast, the *N*,*N*-dimethyl derivative **12** gave suitable crystals (Fig. 2, for crystallographic parameters and typical bond lengths and angles see Table 1). To explore complexed ligand structures that would be related to the reduction process, the copper complex **13** of ligand **7** was prepared by the reaction of the ligand with copper(II) chloride in methanol in the presence of excess potassium carbonate (Fig. 2). An X-ray crystal structure of the compound showed a nearly square planar arrangement of the C_2-symmetric nitrogen ligands around copper (Tables 2 and 3). The ligand in **13** forms a compact complex with short Cu—N bond lengths that brings the stereodirecting chiral centres in closer proximity to the metal centre. This structure was very encouraging as it suggests that analogous C_2-symmetric structures, such as **14**, may be formed. Extensive attempts to isolate various silicon complexes of **7** in crystalline form were unsuccessful.

Reductions of acetophenone

Previous work demonstrated that ketone reduction with hydrosilanes could be initiated with carboxylate or other anions to activate the silicon (7). A series of reductions of acetophenone was undertaken to establish the key factors required for efficacy in the presence of **7** (Table 4). Negative controls included a set of reactions in which each of the key ingredients was selectively absent. Notable among the results is the reduction of acetophenone with the proline anion, which resulted in 50% yield and 15% ee (Table 4, entry 3). This is a result that is related to, but less efficient than, reductions in the presence of anions of histidine and particularly phenylalanine that occurred in yields typically of 80% and ee up to 70% (7). A series of experiments demonstrated that the best compromise for yield and ee occurred at 55 °C, higher than would be expected for a reaction run under ki-

Table 3. Selected bond lengths (Å) and angles (°) for **13** (esds in parentheses).

Bond lengths (Å)	
Cu(1)—N(1)	1.924(4)
Cu(1)—N(4)	2.006(4)
C(12)—C(13)	1.526(7)
C(7)—C(8)	1.517(7)
N(3)—C(8)	1.525(6)
Cu(1)—N(2)	1.925(4)
N(1)—C(7)	1.342(6)
N(2)—C(2)	1.413(6)
N(2)—C(12)	1.305(6)
Cu(1)—N(3)	1.997(4)
N(1)—C(1)	1.410(6)
C(1)—C(2)	1.426(6)
N(4)—C(13)	1.511(6)
Bond angles (°)	
N(1)-Cu(1)-N(2)	83.38(16)
N(1)-Cu(1)-N(4)	168.95(17)
C(7)-N(1)-C(1)	127.5(4)
C(6)-C(1)-N(1)	127.5(4)
C(12)-N(2)-Cu(1)	116.8(3)
N(2)-C(2)-C(1)	114.4(4)
C(8)-N(3)-Cu(1)	106.5(3)
C(13)-N(4)-Cu(1)	107.2(3)
N(1)-C(7)-C(8)	113.5(4)
C(9)-C(8)-N(3)	103.8(4)
N(2)-C(12)-C(13)	115.2(4)
C(15)-C(14)-C(13)	103.8(5)
N(1)-Cu(1)-N(3)	85.66(17)
N(2)-Cu(1)-N(4)	85.60(16)
C(7)-N(1)-Cu(1)	116.7(3)
N(1)-C(1)-C(2)	113.0(4)
C(2)-N(2)-Cu(1)	114.2(3)
C(11)-N(3)-C(8)	106.4(4)
C(16)-N(4)-C(13)	105.5(4)
O(1)-C(7)-N(1)	128.0(4)
C(7)-C(8)-C(9)	114.1(4)
O(2)-C(12)-N(2)	127.3(5)
N(4)-C(13)-C(12)	112.3(4)
N(2)-Cu(1)-N(3)	166.91(16)
N(3)-Cu(1)-N(4)	105.17(17)
C(1)-N(1)-Cu(1)	115.1(3)
C(12)-N(2)-C(2)	127.9(4)
C(3)-C(2)-N(2)	125.8(4)
C(11)-N(3)-Cu(1)	118.2(3)
C(16)-N(4)-Cu(1)	117.7(3)
O(1)-C(7)-C(8)	118.5(4)
C(7)-C(8)-N(3)	113.0(4)
O(2)-C(12)-C(13)	117.5(4)
C(12)-C(13)-C(14)	114.3(4)

netic control. The reactions further confirmed that extracoordinate hydrosilanes are more reactive towards a variety of electrophiles than their four-coordinate counterparts (12). For example, neutral $HSi(OEt)_3$ is not able to reduce acetophenone in the absence of nucleophilic activation (Table 4, entry 1). Neutral bisproline **7** is similarly unable to activate triethoxysilane to undergo the reduction (Table 4, entry 2) as was also shown by ^{29}Si NMR experiments (see earlier). By contrast, the most effective reduction took place with the tetraanion of **7** (Table 3, entry 4). While the tetraanion of **7** can make a tight complex with silicon, it can do so with loss of chirality because of amino acid epimerization.

While the yields of these reactions were acceptable, the ee were marginal. Although the crystal structure of the copper complex **13** shows that the stereochemistry of the amino acids are maintained in the complex, it is also conceivable that α-amido epimerization occurs under the more basic conditions used for these reductions. To reduce this possibility, the efficacy of the reaction was tested as a function of the equivalents of base added (from 1 to 4 equiv.). The most interesting results came with 2 equiv. of base, which should deprotonate the amide NHs, possibly leading to bidentate complexes **15** (Table 4) and **16** (analogous to **9** and **10**, Fig. 3) without affecting the chiral centres. The reaction was more sluggish and it can be seen that, in one case, the ee improved, but at the expense of reaction yield (Table 4, entries 5–7).

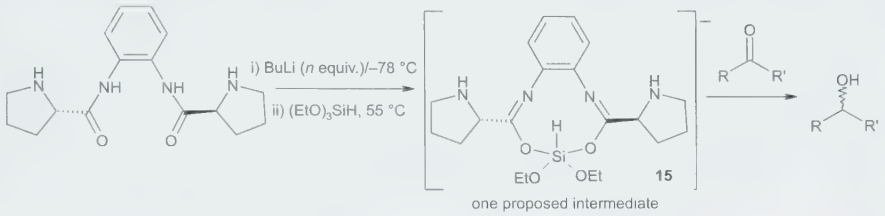
Hydrosilanes are very stable at neutral conditions, but significantly less so away from neutrality, particularly under basic conditions. Exchangeable hydrogens under these conditions serve as excellent electrophiles, with the result that H_2 is normally released (e.g., $R_3SiH + HY \rightarrow R_3SiY + H_2$) (17). This process is particularly favoured when multidentate ligands are utilized (14) and can be exploited as a method for generating H_2 in situ on demand (18).

In the current case, the design of the ligand is challenged by this reactivity. Tetradentate complexation giving compounds such as **14** could also result in loss of chirality through epimerization **17**. By contrast, a bidentate chiral C_2-symmetric complex such as **16** is subject to loss of hydride through the processes just described (**16** → **18**, Fig. 3).

Si-H groups are significantly less reactive to acidic than basic conditions (19). It was reasoned that these problems could be mitigated or avoided by changing from basic to acidic conditions. That is, the same ligand could be complexed by a Lewis acid that would fit into the chiral pocket of the ligand and direct reduction. An important precedent for this approach is the observation by Cozzi and coworkers (20) that Lewis acidic titanium fluoride complexes **19**, based on readily accessible chiral bisoxazoline complexes of Evans, will catalyze carbonyl reductions (Scheme 6). The titanium complex of ligand **7** is expected to be tetradentate (Table 5) based on the structure of the copper complex **13**. Carbonyl complexation will preferentially occur at the more Lewis acidic site (titanium) and the locus of the reduction reaction will be taken away from silicon. These proposals were tested by complexing ligand **7** with titanium-based Lewis acids and examining the reduction reaction in the absence and presence of base (Table 5) in the presence of 5 mol% of the chiral catalyst.

The relative Lewis acidity of simple titanium catalysts follows the order $Ti(OiPr)_4 < TiCl_4 < TiF_4$. Replacement of halides or alkoxy groups with amines will further moderate Lewis acidity. No reduction was observed under any conditions when the first two less acidic compounds were employed as catalysts (Table 5). When 2 equiv. of BuLi were

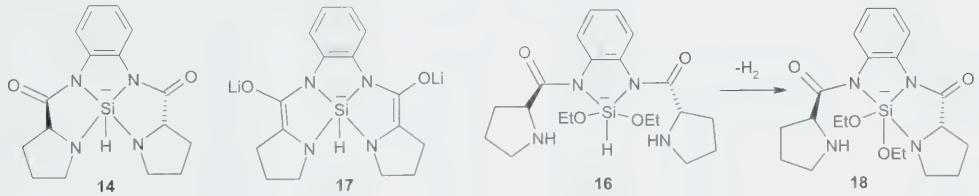
Table 4. Basic reduction of acetophenone by $(EtO)_3SiH$ in the presence of **7**.



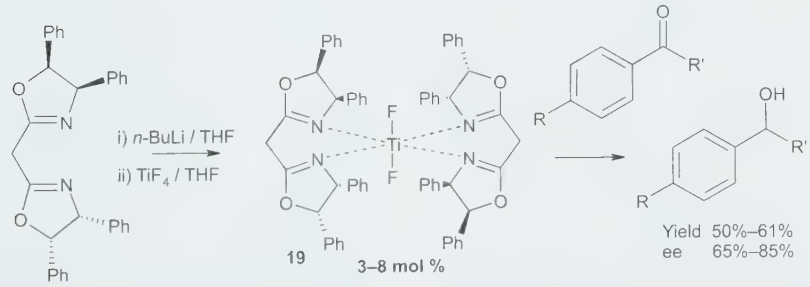
Entry	A	Conditions	*n* (equiv. base)	Yield (%)	ee (%)
1	Acetophenone	55 °C, 72 h	0	NR[a]	—
2	Acetophenone	**7**, 55 °C, 12 h	0	NR	—
3	Acetophenone	proline, BuLi, 55 °C, 24 h	2	50	15
4	Acetophenone	**7**, BuLi, rt, 12 h	4	85	5
5	Acetophenone	**7**, BuLi, rt, 72 h	2	35	64
6	2-Bromoacetophenone	**7**, BuLi, rt, 72 h	2	20	20
7	4-Methoxyacetophenone	**7**, BuLi, rt, 72 h	2	48	5

[a]NR = No reaction.

Fig. 3. Possible pentacoordinate intermediates prior to and following reduction.



Scheme 6.

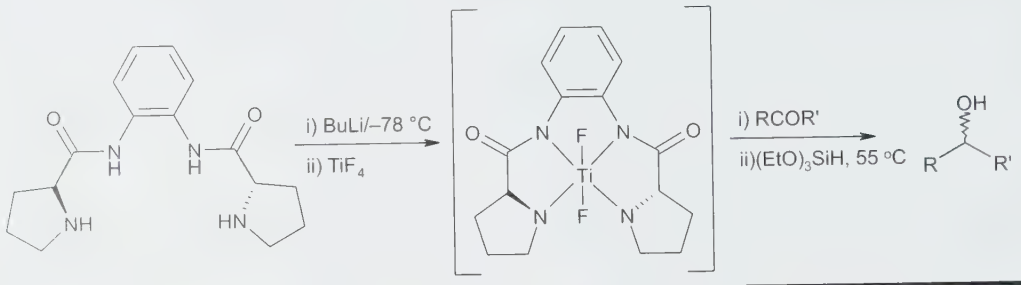


used to facilitate formation of the titanium–**7** complex, only marginal reduction yields were observed, in general worse than in the absence of the titanium compound (Table 4). Of the three reducing agents H_2, Ph_2SiH_2, and $HSi(OEt)_3$, only the last was somewhat efficient. H_2 was used as a negative control. Of the two silanes, $HSi(OEt)_3$ is generally more reactive than Ph_2SiH_2. It has a greater facility for coordination expansion, and as discussed earlier, silylhydrides are more reactive as five- rather than four-coordinate silicon. Improved results were obtained when 4 equiv. of base was used to create the titanium–**7** complex. Yields increased as did enantioselectivity as determined using Mosher ester synthesis (21), although not to levels sufficient for practical application.

A bidentate adduct could form from addition of the dianion **20** to TiF_4 (Scheme 7), which will be a less rigid structure than a tridentate complex such as **21** or the C_2-symmetric catalyst tetradentate titanium complex **22** that should form when 4 equiv. of base are added (Scheme 7). The more rigid structures with proximal chiral groups should have improved enantioselectivity, as was observed with the system derived from the tetraanion.

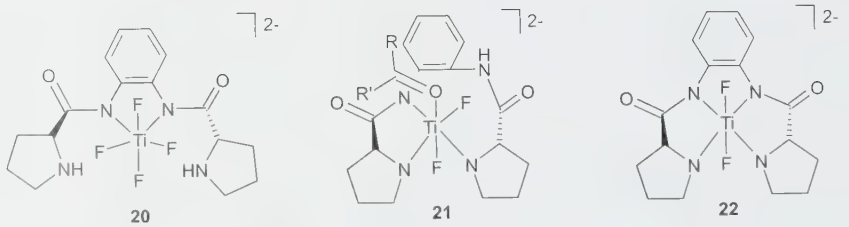
Several observations provide guidance about the role of the titanium complex **20**. Oxophilic titanium will preferentially jettison nitrogen groups to form a complex with the carbonyl oxygen to give a motif such as **21**, which is widely exploited in titanium-catalyzed aldol and related reactions (22), but in doing so will lose C_2-symmetry. The attempt to crystallize **20** or carbonyl complexes of it were unfortunately unfruitful. Hydrosilanes are normally insufficiently reactive

Table 5. Enantioselective reduction of ketones using a bisproline-Ti catalytic system.



Entry	Ketone	7 (mol%)	Metal catalyst (equiv.)	Reaction time (h)	Temp. (°C)	Reducing agent	*n* (equiv. BuLi)	Yield	ee
1	Acetophenone	5	None	12	25	$HSi(OEt)_3$	4	85	5
2	Acetophenone	0	TiF_4 (5)	24	55	$HSi(OEt)_3$	0	NR	—
3	Acetophenone	5	$TiCl_4$ (10)	24	55	$HSi(OEt)_3$	2	NR	—
4	Acetophenone	10	TiF_4 (10)	24	25	H_2	2	NR	—
5	Acetophenone	5	None	24	55	Ph_2SiH_2	2	NR	—
6	Acetophenone	5	TiF_4 (5)	24	55	Ph_2SiH_2	2	17	—
7	Acetophenone	5	TiF_4 (5)	24	55	$(EtO)_3SiH$	2	10	—
8	Acetophenone	5	$TiCl_4$ (5)	24	55	$(EtO)_3SiH$	4	NR	—
9	Acetophenone	5	$RhCl_3$ (5)	24	55	$HSi(OEt)_3$	4	20	—
10	Acetophenone	5	TiF_4 (5)	12	25	$HSi(OEt)_3$	4	80	2
11	Acetophenone	5	TiF_4 (5)	24	55	$HSi(OEt)_3$	4	80	20
12	Acetophenone	5	TiF_4 (5)	12	55	$(EtO)_3SiH$	4	80	20
13	2-Bromoacetophenone	5	TiF_4 (5)	12	55	$(EtO)_3SiH$	4	60	20
14	2-Methoxyacetophenone	5	TiF_4 (5)	12	55	$(EtO)_3SiH$	4	40	2
15	*trans*-4-Phenyl-3-buten-2-one	5	TiF_4 (5)	12	55	$(EtO)_3SiH$	4	90	2

Scheme 7.



to reduce such titanium carbonyl complexes. By contrast, carbocations can be trapped to give C—H bonds (23).

While the specific role of the hydrosilane has not yet been established in the Ti-catalyzed reductions, it seems likely, as with the basic conditions, that extracoordinate silicon is responsible for reduction. The inability of the $TiCl_4$ complex of **7** to catalyze reduction is instructive in this context. The formation of a Lewis acidic chiral complex will liberate the halide Cl^-, which is normally not able to facilitate extracoordination at silicon (12). Thus, while a chiral carbonyl–Ti complex may form, the only reducing agent present is $HSi(OEt)_3$, which is a not viable reducing agent for ketones.

As reported by many researchers, fluoride activates silicon hydrides to reduce carbonyls (24). Formation of compounds such as **22** with TiF_4 serves two purposes. It first provides a chiral Lewis acidic pocket that serves as the locus of reduction and further liberates 2 equiv. of F^-. Fluoride is key, as it can convert the hydrosilane into an active reducing agent, $HSi(OEt)_3F^-$. The obvious disadvantage of this process is that the activated fluoride complex $HSi(OEt)_3F^-$ can directly reduce the ketone outside the sphere of the chiral ligand, leading to a reduction in the overall enantioselectivity of the process.

Of the two very mild approaches examined, the Lewis acidic approach was more efficacious than the extracoordinate hydrosiliconate, with respect to both yields and enantioselectivity. Our current focus is to develop ligands that provide chirality and intramolecular activation to the silicon. Such a system will constrain all reactions to the proximity of the chiral environment.

Conclusion

A C_2-symmetric bisproline ligand can be used as a cata-

lyst to induce enantioselective induction as an anionic extracoordinate silicon complex or after complexation with TiF_4. The Lewis acid catalyzed route led to high yields because side reactions are reduced and showed higher ee.

Experimental section

Reagents and physical methods

The following materials were obtained from Sigma-Aldrich and were used without further purification: acetophenone, *n*-butyllithium (1.6 mol/L solution in cyclohexane), (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl (+)), 2-methoxyacetophenone, *trans*-4-phenyl-3-buten-2-one, sodium sulfate, triethoxysilane, 1,2-diaminobenzene, *N*-BOC-(*S*)-proline, hydroxybenztriazole (HOBt), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), rhodium(III) chloride, titanium(IV) fluoride, and titanium(IV) chloride.

All solvents were thoroughly dried before use; THF was dried from Na/benzophenone. All reactions were carried out in flame-dried apparatus under an argon atmosphere with the use of septa and syringes for the transfer of reagents.

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (at 200 MHz for protons, 50.32 MHz for ^{13}C) Fourier transform spectrometer. ^{29}Si NMR was performed on a Bruker DRX-300 (at 75.44 and 59.60 MHz for carbon and silicon, respectively). ^1H-NMR was also performed on a Bruker DRX-500 (at 500 MHz for hydrogen). ^1H chemical shifts are reported either with respect to tetramethylsilane as an external standard set to 0 ppm or $CDCl_3$ as an internal standard set to 7.26 ppm. ^{13}C NMR chemical shifts are reported either with respect to $CDCl_3$ as an internal standard set to 77.26 or THF-d_8 as an internal standard set to 67.57 ppm. Coupling constants (*J*) are recorded in Hertz (Hz). The abbreviations singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), multiplet (m) are used to report spectra.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a Micromass GCT (Waters Corporation, Milford, Massachusetts) mass spectrometer using a heated probe. High-resolution mass spectral (HRMS) data were obtained using the EI method calibrant with perfluorotributyl amine. Molecular modeling calculations were undertaken using the MM2 molecular mechanics parameter set, using Hyperchem 5.01 from Hypercube Inc. (Gainesville, Florida).

X-ray crystallographic data for **7** and **13** were collected from suitable samples mounted with epoxy on the end of thin glass fibers. Data collections were performed at 273 K.

Data for **7** were collected on a Bruker P4 diffractometer equipped with a Bruker SMART 1K CCD area detector (using the program SMART (25)) and a rotating anode utilizing graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). Data processing was carried out by use of the program SAINT (26), while the program SADABS (27) was utilized for the scaling of diffraction data, the application of a decay correction, and an empirical absorption correction based on redundant reflections. The structures were solved by using the direct methods procedure in the Bruker SHELXTL (28) program library and refined by full-matrix least-squares methods on F^2. All non-hydrogen atoms were refined using anisotropic thermal parameters and hydrogen atoms were added as fixed contributors at calculated positions, with isotropic thermal parameters based on the atom to which they are bonded.

Data for **13** were collected on a three-circle D8 Bruker diffractometer equipped with a Bruker SMART 6000 CCD area detector (using the program SMART (25)) and a rotating anode utilizing cross-coupled parallel focusing mirrors to provide monochromated Cu Kα radiation (λ = 1.541 78 Å). Data processing and structure solving were carried out as noted previously.

Preparation of the bis(L)prolinyl amide of 1,2-diaminobenzene

A solution of 1,2-diaminobenzene (0.36 g, 3.3 mmol) and *N*-(*tert*-butoxycarbonyl)-L-proline (1.5 g, 6.9 mmol) in CH_2Cl_2–DMF (10:1, 30 mL) was treated at 0 °C with HOBt (0.93 g, 6.9 mmol) and EDC (1.35 g, 6.9 mmol). The reaction mixture was stirred at 0 °C for 2 h and allowed to warm up to room temperature (rt) overnight. Solvents were removed under reduced pressure. CH_2Cl_2 (20 mL) was added to the yellow residue and stirred for 2 h. TFA (10 mL) was added dropwise at rt to the solution, which was stirred for another 2 h. Saturated K_2CO_3 solution (20 mL) neutralized the solution (pH 9). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over anhydr. Na_2SO_4. After removing the solvents under reduced pressure, the product was recrystallized from methanol and dichloromethane (20:1). The product, a colourless crystal, was formed in 83% yield. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.73–1.80 (m, 4H, R_1-C*H*-R_2), 2.02–2.13 (m, 2H, NH), 2.18–2.24 (m, 4H, R_2-C*H*-R_3), 2.95–3.10 (m, 4H, CH_2-NH), 3.86–3.93 (q, 2H, *CH*-NH), 7.13–7.19 (m, 2H, Ph-*H*), 7.65–7.70 (m, 2H, Ph-*H*). ^{13}C NMR (d_6-DMSO, 200 MHz) δ: 33.27, 37.76, 54.07, 67.92, 131.03, 132.11, 137.72, 181.25. LRMS (EI) *m/z* (%): 302 (M^+, 13), 232 (62), 205 (53), 188 (100), 91 (92), 70 (83), 45 (87). HRMS (ES) *m/z* calcd. for $(C_{16}H_{23}N_4O_2)^+$: 303.1808; found: 303.1821.

Preparation of the *N*,*N*′-dimethyl bis(L)prolinyl amide of 1,2-diaminobenzene (12)

To a stirred solution of **7** (1 g, 3.3 mmol) and 37% aqueous formaldehyde (2 mL, 25 mmol) in 20 mL acetonitrile was added sodium cyanoborohydride (0.8 g, 10 mmol). Glacial acetic acid was added until the solution reached neutrality. The reaction was stirred at ambient temperature for 3 h. The reaction mixture was poured into 50 mL of ether and washed with 3 × 30 mL portions of 1 N KOH and one 30 mL portion of brine. The ether solution was dried (Na_2SO_4) and evaporated under reduced pressure. The desired product was recrystallized from MeOH and ether (1:10). The product, a colourless crystal, was formed in 80% yield, mp 206 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.77–1.80 (m, 4H, R_1-C*H*$_2$-R_2), 1.82–1.99 (m, 2H, CH-C*H*$_2$-CH$_2$), 2.25–2.42 (m, 4H, CH-C*H*$_2$-CH$_2$), 2.46 (s, 6H, C*H*$_3$-N), 3.02 (q, 2H, *J* = 5.1, 10.2 Hz, C*H*$_2$-NHCH$_3$), 3.14–3.19 (m, 2H, C*H*$_2$-NHCH$_3$), 3.29–3.32 (m, 2H, C*H*-NCH$_3$), 7.20–7.25 (m, 2H, Ph-*H*), 7.62–7.67 (m, 2H, Ph-*H*), 9.38 (s, 2H, CONH). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 24.38, 31.15, 41.79, 56.67, 69.23, 124.25, 125.80, 129.77, 173.43. LRMS (ES) *m/z* (%): 331.6 (M^+, 100), 147.0 (5), 65 (10). HRMS (ES) *m/z* calcd.

for $(C_{18}H_{27}N_4O_2)^+$: 331.2134; found: 331.2139. For X-ray data, see Table 1.

Preparation of the copper complex of the bis(L)prolinyl amide of 1,2-diaminobenzene (13)

Ligand **7** (0.03 g, 0.1 mmol) was dissolved in methanol (5 mL) before the addition of anhydr. K_2CO_3 (0.055 g, 0.4 mmol) and $CuCl_2{\cdot}2H_2O$ (0.017 g, 0.1 mmol). The resulting system was stirred overnight, then the solid was filtered off and the clear blue solution was layered with ether. After 2 weeks, purple crystals were isolated, mp 295 °C (dec.). HRMS (ES) *m/z* calcd. for $(C_{16}H_{21}N_4O_2Cu)^+$: 364.0961; found: 364.0957. For X-ray data, see Tables 2 and 3.

General procedure for the ^{29}Si NMR experiment (example ligand 7–triethoxysilane, 1:2)

To a dry NMR tube was added **7** (0.039 g, 0.13 mmol) and d_8-THF (0.3 mL). This solution was cooled to –78 °C and *n*-butyllithium (0.16 mL, 1.6 mol/L solution in hexanes, 0.26 mmol) was added dropwise. The resulting yellowish solution was warmed to 0 °C for 15 min. To this yellow solution was added triethoxysilane (0.05 mL, 0.26 mmol). The solution was allowed to stand at 0 °C then warmed up to rt for 30 min. ^{29}Si NMR was examined in proton decoupled mode using the Bruker DRX-500.

General procedure for basic reduction of ketone in the presence of 7 (example acetophenone) (Table 4)

To a dry 10 mL round-bottomed flame-dried flask protected by argon was added **7** (0.016 g, 0.05 mmol) and THF (5 mL). This solution was cooled to –78 °C and *n*-butyllithium (0.13 mL, 1.6 mol/L solution in hexanes, 0.2 mmol) was added dropwise. The resulting yellowish solution was stirred for 5 min at –78 °C and then warmed to 0 °C for 15 min at which point $(EtO)_3SiH$ (0.38 mL, 2.06 mmol) was added. The resulting clear solution was stirred for 1 h at rt, then acetophenone (0.12 mL, 1.02 mmol) was added. The solution was stirred at rt and product development was monitored by TLC. The reaction mixture was acidified by adding 1 N HCl at 0 °C and carefully made to pH 6 (29). The organic phase collected. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers weree combined, dried over sodium sulfate, and then concentrated to give the crude product, which was purified by column chromatography eluting with hexanes – ethyl acetate (5:1). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.56 (d, 3H, *J* = 6.5 Hz, PhCH(OH)CH_3), 2.76 (bs, 1H, PhCH(OH)CH_3), 4.94 (q, 1H, *J* = 6.5 Hz, PhCH(OH)CH_3), 7.32–7.45 (m, $5H_{arom}$). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 24.97, 69.99, 125.24, 127.14, 128.24, 145.75. MS (EI) *m/z* (%): 122 (M^+, 10), 121 (40), 104 (68), 79 (28), 57 (7), 43 (100). MS (CI) *m/z* (%): 140 ($(M + 18)^+$, 17), 122 (100), 105 (41), 78 (2), 52 (1), 44(1).

General procedure for Lewis acid catalyzed reduction of ketone (example acetophenone) (Table 5)

To a dry 10 mL round-bottomed flame-dried flask protected by argon was added **7** (0.016 g, 0.05 mmol) and THF (5 mL). This solution was cooled to –78 °C and *n*-butyllithium (0.13 mL, 1.6 mol/L solution in hexanes, 0.2 mmol) was added dropwise. The resulting yellowish solution was stirred for 5 min at –78 °C and warmed to 0 °C for 15 min. To this yellow solution was added TiF_4 (6 mg, 0.05 mmol) and the mixture was vigorously stirred until the salt was completely dissolved. The resulting yellow mixture was stirred for 1 h at rt and triethoxysilane (0.38 mL, 2.06 mmol) and acetophenone (0.12 mL, 1.02 mmol) were added. The solution was stirred at 55 °C and product development was monitored by TLC. The reaction mixture was diluted with ethyl acetate (5 mL) and carefully made basic (pH 9) with 1 mol/L of sodium hydroxide (30). The solid was separated by filtration and the organic phase was collected. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, dried over sodium sulfate, and then concentrated to give the crude product which was purified by column chromatography eluting with hexanes – ethyl acetate (5:1).

2-Bromophenethyl alcohol

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.69 (bs, 1H, OH), 3.69–3.45 (m, 2H, CH_2Br), 4.90 (dd, *J* = 3.5, 8.6 Hz, 1H, PhCH(OH)), 7.36 (s, $5H_{arom}$). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 40.12, 73.78, 125.95, 128.43, 128.65, 140.31. MS (EI) *m/z* (%): 202 ($(M + 2)^+$, 2), 200 (M^+, 2), 185 (5), 183 (5), 121 (5), 107 (100), 91 (10), 79 (78), 51 (29).

***trans*-4-Phenyl-3-buten-2-ol**

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.38 (d, 3H, *J* = 6.4 Hz, PhCH=CHCH(OH)CH_3), 2.26 (bs, 1H, PhCH=CHCH(OH)CH_3), 4.48 (dp, 1H, *J* = 0.9, 6.3 Hz, PhCH=CHCH(OH)CH_3), 6.26 (dd, 1H, *J* = 6.3, 16.0 Hz, PhCH=CHCH(OH)CH_3), 6.56 (d, 1H, *J* = 16.0 Hz, PhCH=CHCH(OH)CH_3), 7.20–7.41 (m, $5H_{arom}$). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 23.27, 68.68, 126.34, 127.47, 128.44, 129.16, 133.51, 136.61. MS (EI) *m/z* (%): 148 (M^+, 63), 131 (66), 115 (26), 105 (100), 91 (49), 77 (37), 55 (15), 43 (71).

4-Methoxyphenethyl alcohol

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.41 (d, 3H, *J* = 6.4 Hz, CH_3O-C_6H_4CH(OH)CH_3), 2.64 (bs, 1H, $CH_3OC_6H_4$CH(OH)CH_3), 3.74 (s, 3H, $CH_3OC_6H_4$-CH(OH)CH_3), 4.76 (q, 1H, *J* = 6.4 Hz, $CH_3OC_6H_4CH$(OH)CH_3), 6.85 (d, 2H, *J* = 8.0 Hz, 2 × CH_3OC-CH-CH), 7.25 (d, 2H, *J* = 8.0 Hz, 2 × CH_3OC-CH-CH). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 24.88, 55.09, 69.61, 113.62, 126.53, 138.00, 158.70. MS (EI) *m/z* (%): 152 (M^+, 6), 135 (37), 109 (78), 105 (50), 84 (17), 77 (74), 51 (42), 43 (100).

2-Methoxyphenethyl alcohol

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.81 (s, 1H, OH), 3.43 (s, 3H, CH_3O), 3.53 (dd, 2H, *J* = 1.2, 4.1 Hz, CH_3O-CH_2-CH(OH)), 4.88 (dd, 1H, *J* = 1.2, 1.7 Hz, CH(OH)), 7.30–7.40 (m, $5H_{arom}$). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 24.12, 26.89, 57.69, 115.62, 129.53, 139.00. MS (EI) *m/z* (%): 144 (M^+, 9), 113 (31), 96 (68), 77 (78), 67 (70), 31 (100).

General procedure for reduction of ketone using rhodium chloride and titanium chloride

The general procedure for Table 5 was followed except that $RhCl_3$ (10 mg, 0.05 mmol) or $TiCl_4$ (9.5 mg, 0.05 mmol) were used, respectively.

General experimental procedure for preparation of Mosher esters (example (*S*)-1-phenylethanol)

(*S*)-1-Phenylethanol (2 mg, 0.02 mmol) and MTPA-Cl (+) (4 μL, 0.02 mmol) were mixed with carbon tetrachloride (3 drops) and dry pyridine (3 drops). The reaction mixture was allowed to stand in a stoppered flask for 12 h at ambient temperature. Water (1 mL) was added and the reaction mixture transferred to a separatory funnel and extracted with ether (20 mL). The ether solution, after washing successively with HCl (1 mol/L, 20 mL), saturated sodium carbonate solution (20 mL), and water (20 mL), was dried with sodium sulfate, filtered, and the solvent was removed in vacuo. The residue was dissolved in deuterated chloroform for NMR analysis. The integration of the hydrogen on the carbon bearing the hydroxyl group was used as a measure to assess the enantioselection.

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Hydrogen-bonded networks in crystals built from bis(biguanides) and their salts[1]

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Abstract: Biguanide groups and biguanidinium cations incorporate multiple sites that can donate or accept hydrogen bonds. To assess their ability to associate and to direct the formation of extended hydrogen-bonded networks, we examined the structure of crystals of four compounds in which two neutral biguanide groups or the corresponding cations are attached to the 1,4- and 1,3-positions of phenylene spacers. As expected, all four structures incorporate extensive networks of hydrogen bonds and reveal other reliable features. In particular, (1) neutral biguanide groups favor a roughly planar conformation with an intramolecular hydrogen bond, and they associate as hydrogen-bonded pairs, (2) despite coulombic repulsion, biguanidinium cations can also associate as hydrogen-bonded pairs, and (3) the 1,3-phenylenebis(biguanidinium) dication favors a pincerlike conformation that allows chelation of suitable counterions. However, the precise patterns of hydrogen bonding in the structures vary substantially, limiting the usefulness of biguanide and biguanidinium as groups for directing supramolecular assembly.

Key words: bis(biguanide), bis(biguanidinium), structure, hydrogen-bonded network, noncovalent interaction, supramolecular chemistry, crystal engineering.

Résumé : Des groupes biguanide et des cations biguanidinium incorporent de multiples sites qui peuvent donner ou accepter des liaisons hydrogène. Dans le but d'évaluer la capacité d'associer et de diriger la formation de réseaux étendus de liaisons hydrogène, on a étudié la structure cristalline de quatre composés dans lesquels deux groupes biguanide neutres, ou les cations correspondants, sont attachés aux positions 1,4- et 1,3- de groupes phénylènes. Comme prévu, les quatre structures permettent d'incorporer des réseaux de liaisons hydrogène et mettent en évidence d'autres caractéristiques fiables. En particulier, 1) les groupes biguanide neutres favorisent une conformation pratiquement plane avec une liaison hydrogène intramoléculaire et s'associent sous la forme de paires réunies par des liaisons hydrogène, 2) malgré une répulsion coulombique, les cations biguanidinium peuvent aussi former des paires associées par des liaisons hydrogène et 3) le dication phénylène-1,3-bis(biguanidinium) favorise une conformation en forme de pince qui permet d'effectuer une chélation avec des contre-ions appropriés. Toutefois, les régimes précis des liaisons hydrogène varient d'une façon substantielle, ce qui limite l'utilité des groupes biguanide et biguanidinium comme unités pouvant orienter un assemblage supramoléculaire.

Mots clés : bis(biguanide), bis(biguanidinium), structure, réseau à liaisons hydrogène, interaction non covalente, chimie supramoléculaire, génie cristallin.

[Traduit par la Rédaction]

Introduction

The general family of compounds that includes biguanide (**1**) has been known for over 100 years (1–3).[3] Members of the family have important applications as medicines, as ligands in coordination chemistry, as bases, and as precursors for the synthesis of various heterocyclic compounds (4). In addition, biguanide groups and biguanidinium cations incorporate characteristic patterns of sites that can donate or accept hydrogen bonds, thereby allowing them to associate and engage in supramolecular assembly (4).

A productive strategy for engineering predictably ordered supramolecular materials is to build them from compounds incorporating multiple sticky sites that participate in directional intermolecular interactions (5). These interactions tend to place adjacent molecules in specific positions, leading to the formation of extensive networks with predetermined architectures. In this paper, we assess the potential of multiple biguanide and biguanidinium groups to serve in this way as sticky sites, and we describe the hydrogen-bonded networks present in crystals of bis(biguanide) **2**, its dihydrochloride, and the dihydrochloride and carbonate of isomeric bis(biguanide) **3**. Previous use of such compounds in supramolecular chemistry has been limited to the chelation of metals by ethylenebis(biguanide) (6, 7).

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Dedicated with respect and affection to Dr. Alfred Bader for his friendship, encouragement, generosity, entreprenurial spirit, love of art, and enduring service to chemistry.

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[1]This article is part of a Special Issue dedicated to Dr. Alfred Bader.

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[3]For the sake of simplicity, biguanides and their salts are normally represented in this paper as single tautomers.

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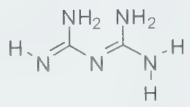
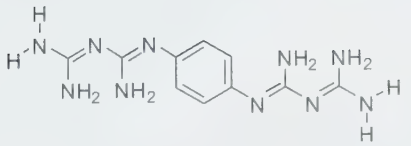
Table 1. Crystallographic data for bis(biguanide) **2**, its dihydrochloride, and the dihydrochloride and carbonate of isomeric bis(biguanide) **3**.

Compound	**2**·H_2O	**2**·2HCl·H_2O	**3**·2HCl·3H_2O	**3**·H_2CO_3·H_2O·0.5 dioxane
Temperature (K)	100	293	100	100
λ (Å)	1.54178	1.54178	1.54178	1.54178
Formula	$C_{10}H_{18}N_{10}O$	$C_{10}H_{20}Cl_2N_{10}O$	$C_{10}H_{24}Cl_2N_{10}O_3$	$C_{13}H_{24}N_{10}O_5$
Fw	294.34	367.26	403.29	400.42
F(000)	936	384	424	424
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic
Z	6	2	2	2
d (g cm^{-3})	1.432	1.420	1.435	1.420
μ (mm^{-1})	0.863	3.591	3.437	0.947
Space group	*P*-1	*P*-1	*P*-1	*P*-1
a (Å)	10.0311(16)	5.8749(8)	9.3537(3)	9.9072(3)
b (Å)	10.8820(18)	12.036(5)	9.6015(3)	10.1769(3)
c (Å)	21.127(3)	13.084(5)	11.4402(4)	11.0195(5)
α (°)	88.090(7)	105.66(3)	82.983(2)	77.297(2)
β (°)	87.280(7)	95.65(3)	71.193(2)	67.906(2)
γ (°)	62.735(6)	102.12(2)	73.759(2)	65.826(2)
Volume ($Å^3$)	2047.5(6)	859.1(5)	933.19(5)	936.32(6)
θ max (°)	58.01	70.01	70.01	72.03
h, *k*, *l* max	10, 11, 23	7, 14, 15	11, 11, 14	12, 12, 13
Unique reflections	6951	3241	3545	3557
Observed reflections ($I > 2\sigma(I)$)	3715	2766	2583	2403
*R*1	0.0600	0.0456	0.0745	0.0487
*wR*2	0.0903	0.1109	0.2142	0.1277
*R*1 (all data)	0.1294	0.0463	0.0818	0.0699
*wR*2 (all data)	0.1012	0.1110	0.2351	0.1357
Diff. peak and hole (e, $Å^3$)	0.318, –0.360	0.323, –0.396	0.913, –0.626	0.397, –0.479
GoF	1.012	1.105	1.058	0.942



1



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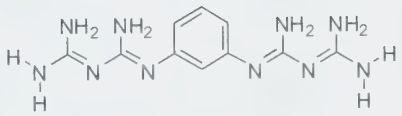


3

Results and discussion

Crystal structure of bis(biguanide) 2

Bis(biguanide) **2** was prepared by a published method (4) and was crystallized from hot water. X-ray diffraction established that the crystals belong to the triclinic space group *P*-1 and exist as a pair of nonmerohedral twins (8). The crystals have the composition **2**·H_2O and each unit cell contains six molecules of bis(biguanide) **2** and six molecules of H_2O. Crystallographic parameters are given in Table 1, views of the structure appear in Figs. 1 and 2, and additional information is provided as Supplementary data.[4] Multiple symmetry-independent biguanide groups are present in the unit cell, but all correspond to tautomeric form **I** (Scheme 1) and have a roughly planar geometry with internal torsion angles in the range 2.5(3)°–29.8(3)°. This geometry is enforced by an intramolecular NH···N hydrogen bond, with N···H distances of normal values (1.993(5)–2.263(5) Å). Similar features appear in all previous structural studies of neutral biguanides (4, 9–11), so a nearly planar geometry and an intramolecular hydrogen bond appear to be structural features of biguanides that can be used reliably by crystal engineers. The average

[4] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Directory of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. DUD 3662. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 291494–291497 contain the crystallographic data for this manuscript. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Fig. 1. View of the crstal structure of neutral bis(biguanide) **2** grown from water. The view reveals that each biguanide group incorporates an internal NH···N hydrogen bond and favors tautomeric form **1** (Scheme 1). In addition, the view shows bifurcated intermolecular hydrogen bonds that link compound **2** into continuous ribbons, as well as additional hydrogen bonds involving water. Hydrogen bonds are represented by broken lines. Hydrogen atoms appear in white, carbon in light gray, nitrogen in black, and oxygen in dark gray.

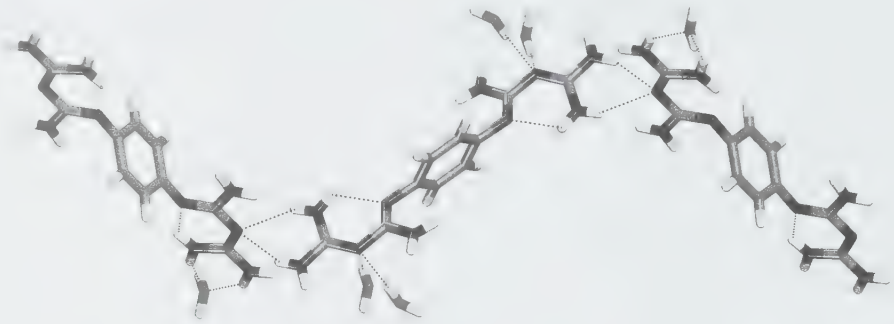
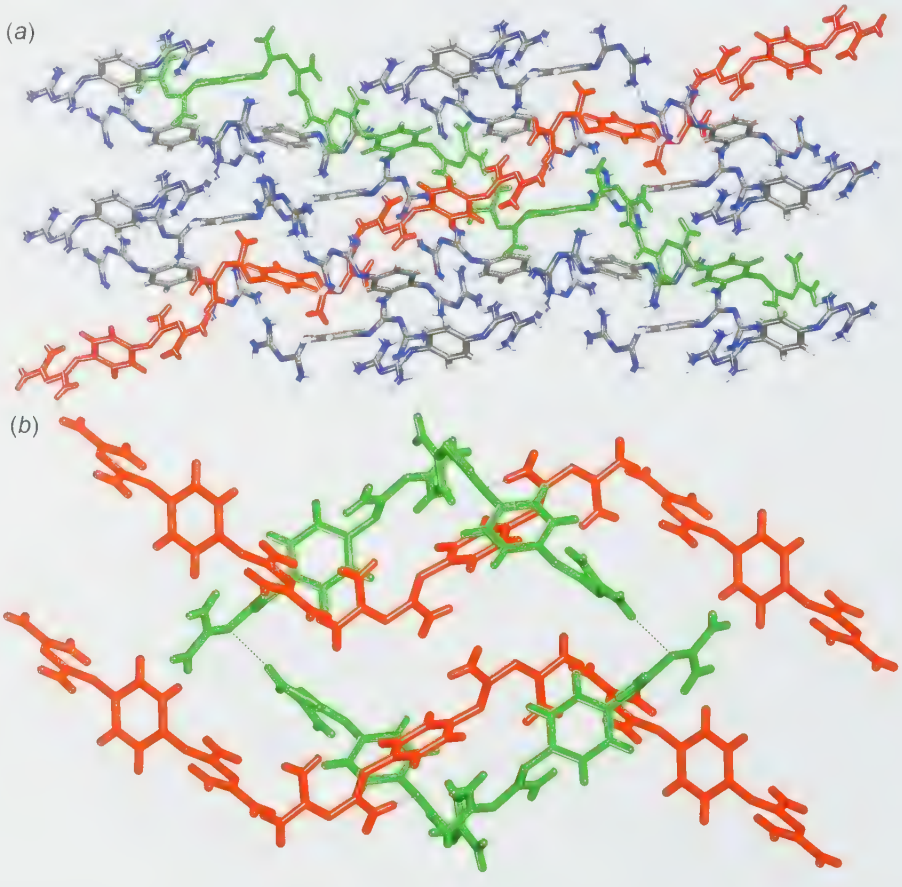


Fig. 2. (*a*) View along the *b* axis of the structure of crystals of neutral bis(biguanide) **2**, with hydrogen atoms shown in white, carbon in gray, and nitrogen in blue. Two hydrogen-bonded ribbons are highlighted in red and green. The two highlighted ribbons run in opposite directions along the *ac* diagonal. (*b*) View along the *a* axis showing secondary hydrogen bonds (represented by broken lines) between the characteristic ribbons. In both views, water molecules are omitted for clarity.



planes defined by the biguanide groups form dihedral angles in the range 67.6(1)°–88.7(1)° with respect to the plane of the central aromatic ring.

Intermolecular hydrogen bonds involving bis(biguanide) **2** and water create a complex network (Figs. 1 and 2), with over 40 hydrogen bonds per unit cell. A primary motif in

Scheme 1.

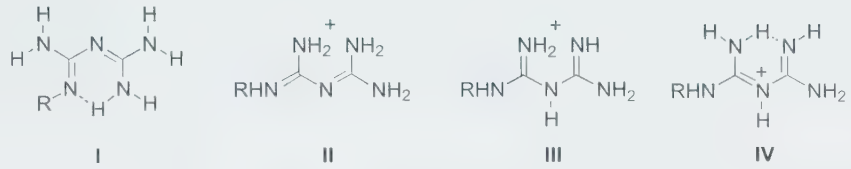
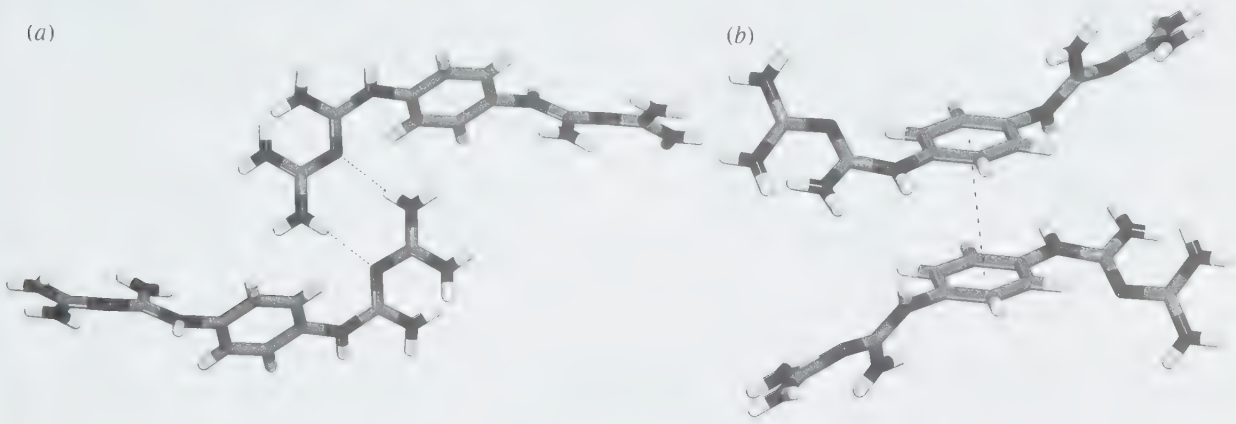


Fig. 3. Views of the crystal structure of the dihydrochloride salt of bis(biguanide) **2** grown from acetone–water. (*a*) The biguanidinium cations favour structure **II** (Scheme 1) and form hydrogen-bonded pairs. (*b*) Additional cohesion is contributed by slightly offset face-to-face aromatic interactions. Hydrogen bonds and the aromatic interaction are represented by broken lines and included water molecules are omitted for simplicity. Hydrogen atoms appear in white, carbon in gray, and nitrogen in black.



this network is the ribbon shown in Fig. 1, which links molecules of bis(biguanide) **2** end-to-end by novel bifurcated hydrogen bonds. Each molecule in the ribbon serves either as a double acceptor or a double donor of these bifurcated bonds. The resulting ribbons are aligned with the *ac* diagonal and linked by additional hydrogen bonds between biguanide groups, as well as by bridging molecules of water (Fig. 2).

Crystal structure of the dihydrochloride salt of bis(biguanide) 2

Crystals were grown by allowing acetone to diffuse slowly into an aqueous solution of bis(biguanidinium) dichloride (**2**·2HCl), which was prepared by a known method (4). X-ray diffraction demonstrated that the crystals belong to the triclinic space group *P*-1 and have the composition **2**·2HCl·H_2O. Each unit cell contains two symmetry-equivalent molecules of bis(biguanidium) dichloride and two molecules of H_2O. There are four potential sites for H_2O, associated in pairs within van der Waals distances, but only half are occupied. Crystallographic parameters appear in Table 1, views of the structure are shown in Figs. 3 and 4, and additional information is given as Supplementary data.[4] The biguanidinium groups are extensively delocalized, as demonstrated by the similarity of the C-N distances (1.310(3)–1.366(2) Å). Each biguanidinium group can be represented by structure **II** (Scheme 1) and its resonance hybrids, and alternatives in which the central atom of nitrogen is protonated (structure **III**) or in which an intramolecular hydrogen bond is present (structure **IV**) are not favoured in the solid state. Similar conclusions have been reached in all previous structural analyses of biguanidinium cations (4, 10–21), so protonation of biguanides to give structure **II** (Scheme 1) appears to be a fundamental preference, both in solution (2) and in the solid state. Although the biguanidium groups in the dihydrochloride salt of compound **2** can be represented by structure **II**, they are not planar. The two guanidinium subunits that can be considered to be present in each biguanidinium group are individually planar, but their planes define dihedral angles of 39.2(1)° and 45.5(1)° in the two arms of each dication.

The structure of the dihydrochloride salt of bis(biguanide) **2** can be described as a complex network held together in part by hydrogen-bonded pairing of biguanidinium cations (Fig. 3*a*). The N··N distance in these cationic pairs is 3.033(3) Å. Intercationic hydrogen bonding is inhibited by coulombic repulsion and is absent in most biguanidinium salts (4, 11, 14, 15, 17, 19–21), although it has previously been observed in a few cases (12, 13, 18). Slightly offset face-to-face aromatic interactions are also observed in the structure of salt **2**·2HCl (Fig. 3*b*), with a center-to-center separation of 3.879(2) Å. In addition, the structure of the salt reveals multiple ionic hydrogen bonds between biguanidium cations and chloride (Fig. 4). There are two distinct types of chloride ion in the structure, each of which accepts hydrogen bonds from N-H groups provided by neighbouring bis(biguanidium) dications. One type (Cl1) accepts five hydrogen bonds from four dications (Fig. 4*a*) and the other type (Cl2) accepts six hydrogen bonds from four dications, two of which are involved in chelation of chloride (Fig. 4*b*). Each bis(biguanidinium) dication is linked by hydrogen bonding to eight chloride ions, two molecules of water, and one other bis(biguanidinium) dication. The resulting network

Fig. 4. Views of the crystal structure of the dihydrochloride salt of bis(biguanide) **2** showing ionic hydrogen bonds involving chloride. (*a*) One type of chloride ions (Cl1) accepts hydrogen bonds donated by five N-H groups in four different bis(biguanidinium) dications. (*b*) The other type of chloride (Cl2) accepts six hydrogen bonds (four involving chelation), again contributed by N-H groups in four different bis(biguanidinium) dications. In both views, hydrogen bonds are represented by broken lines. Chloride ions are represented by small circles, with hydrogen atoms shown in white, carbon in gray, and nitrogen in black.

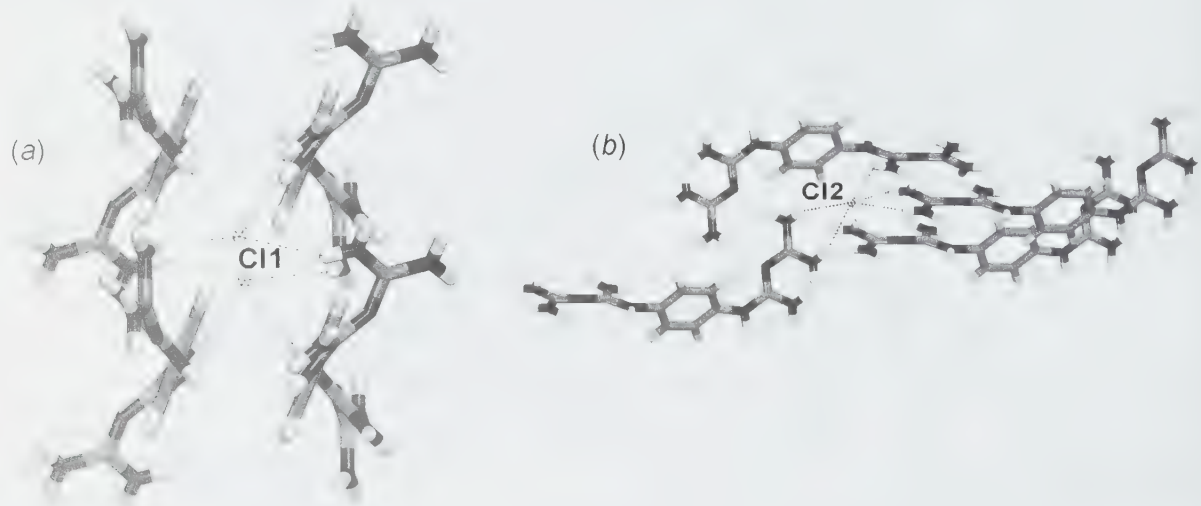
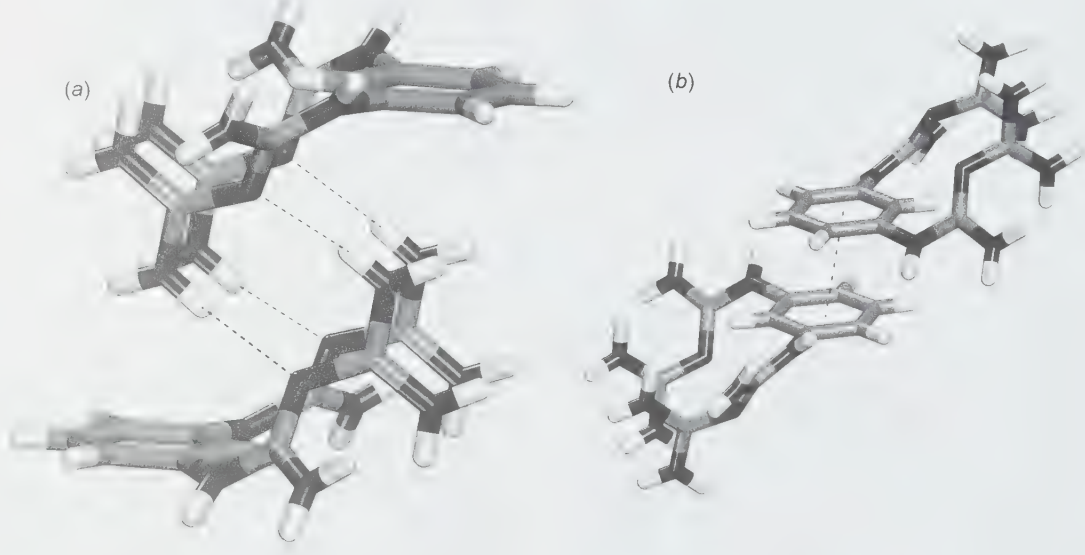


Fig. 5. Views of the crystal structure of the dihydrochloride salt of bis(biguanide) **3** grown from acetone–water. (*a*) The biguanidinium cations favor structure **II** (Scheme 1) and form hydrogen-bonded pairs. (*b*) Additional cohesion is contributed by face-to-face aromatic interactions. Hydrogen bonds and the aromatic interaction are represented by broken lines, and included water molecules are omitted for simplicity. Hydrogen atoms appear in white, carbon in gray, and nitrogen in black.

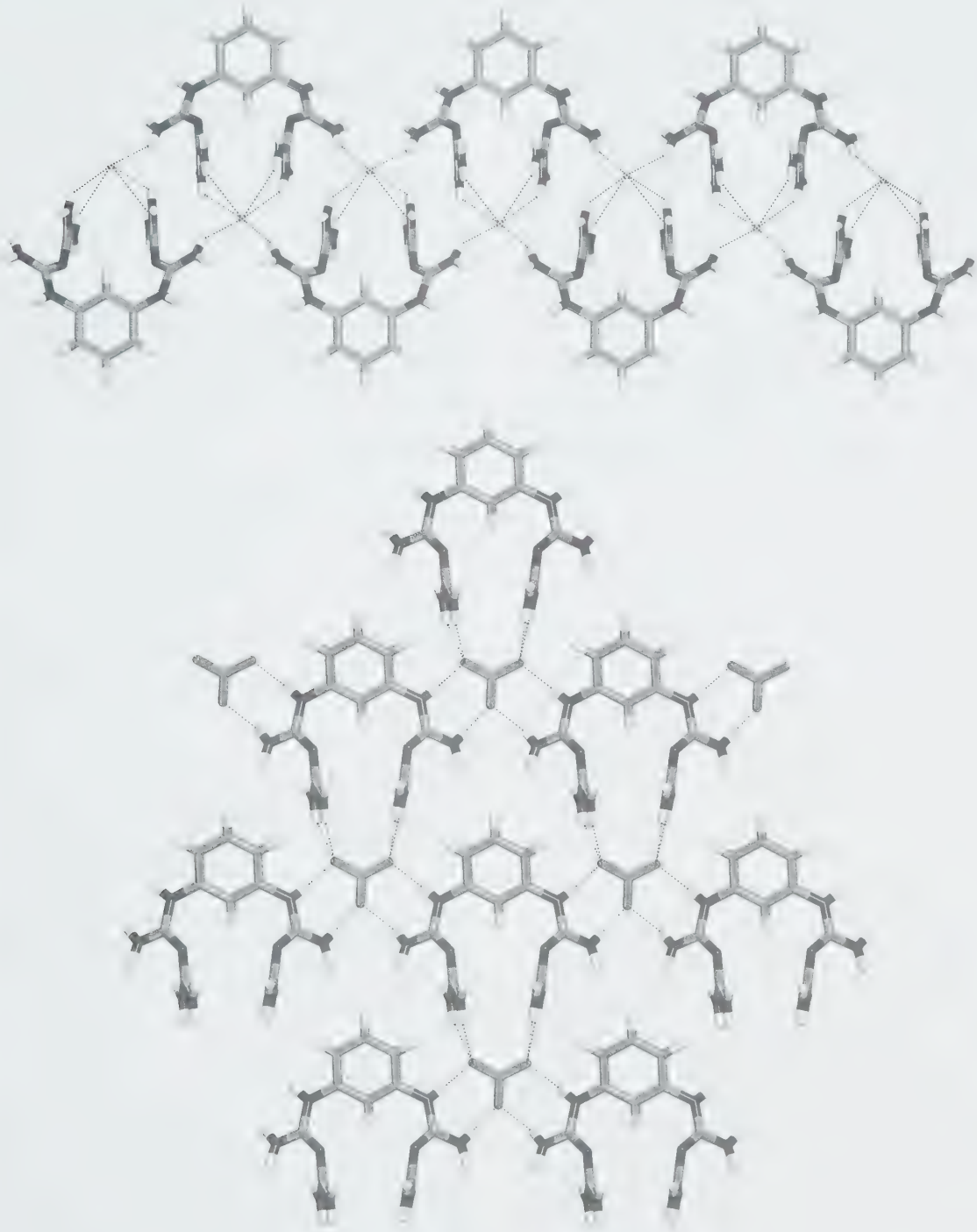


defines small channels along the *a* axis that are occupied by included molecules of water.

Crystal structure of the dihydrochloride salt of bis(biguanide) 3

Bis(biguanidinium) dichloride **3**·2HCl was prepared by a known method (4) and was crystallized from acetone–water. X-ray diffraction revealed that (*i*) the crystals belong to the triclinic space group *P*-1, (*ii*) their composition corresponds to **3**·2HCl·3H_2O, and (*iii*) each unit cell contains two equivalent molecules of bis(biguanidium) dichloride and six molecules of H_2O. Crystallographic parameters are given in Table 1, views of the structure appear in Figs. 5 and 6*a*, and additional information is provided in the Supplementary data.[4] As noted in other biguanidinium salts, the cations are extensively delocalized, and the C-N distances have similar

Fig. 6. (*a*) View along the *c* axis of the crystal structure of the dihydrochloride salt of bis(biguanide) **3** grown from acetone–water. The view shows a tape constructed by ionic hydrogen bonding involving one of the two types of chloride ions in the structure. Each bis(biguanidinium) dication adopts a pincerlike conformation that permits chelation of chloride by the simultaneous donation of four hydrogen bonds. (*b*) View along the *c* axis of the closely related structure of crystals of the carbonate salt of bis(biguanide) **3** grown from dioxane–water. In both views, hydrogen bonds are represented by broken lines. Chloride ions are represented by small circles, with hydrogen atoms shown in white, carbon in light gray, nitrogen in black, and oxygen in dark gray.



values (1.320(5)–1.353(5) Å). Again, each biguanidinium group can be represented by structure **II** (Scheme 1). This further reinforces the conclusion, drawn previously from analysis of salt **2**·2HCl and related compounds (4), that structure **II** is a fundamental preference of biguanidinium cations and can be used dependably by crystal engineers. As in the case of analogue **2**·2HCl, the two biguanidinium groups in each bis(biguanidinium) dication are distinctly nonplanar, and the planes of the guanidinium subunits that can be considered to be present define dihedral angles of 52.6(2)° and 54.8(2)°.

Various important interactions can be identified in the structure of the dihydrochloride salt of bis(biguanide) **3**. As in the structure of the analogous salt **2**·2HCl, a network is formed by hydrogen-bonded pairing of biguanidinium cations (Fig. 5*a*), with N···N distances similar to those observed previously (2.979(4) and 3.028(4) Å). It is noteworthy that this uncommon hydrogen-bonded dimeric motif is observed in the structures of both bis(biguanidinium) salts, despite its coulombic disadvantage. Nevertheless, its absence in the structures of most other biguanidinium salts (4, 11, 14, 15, 17, 19–21) suggests that it does not define a motif that can be used reliably in supramolecular construction.

Additional cohesive forces in the structure of salt **3**·2HCl, also observed in that of analogue **2**·2HCl, are contributed by face-to-face aromatic interactions with a center-to-center separation of 3.687(2) Å (Fig. 5*b*). The structure of salt **3**·2HCl, like that of analogue **2**·2HCl, reveals multiple ionic hydrogen bonds between biguanidium cations and chloride (Fig. 6*a*). Again, there are two distinct types of chloride ion in the structure. One accepts a total of six hydrogen bonds from N-H groups provided by three neighbouring bis(biguanidium) dications (Fig. 6*a*). This type of chloride accepts an additional hydrogen bond from one of the included molecules of water. The dications adopt a pincerlike conformation that favors the binding of chloride by allowing each biguanidinium group to donate two hydrogen bonds to a single chloride, resulting in a characteristic chelation (Fig. 6*a*). Binding of chloride in this way generates tapes that run along the *ab* diagonal. The second type of chloride forms additional ionic hydrogen bonds that help bridge the tapes, and further links between the tapes are created by the hydrogen-bonded pairing of biguanidinium cations (Fig. 5*a*).

Crystal structure of the carbonate salt of bis(biguanide) 3

In contact with air, solutions of bis(biguanide) **3** in dioxane–water yielded crystals of the corresponding carbonate. X-ray diffraction established that (*i*) the crystals belong to the triclinic space group *P*-1, (*ii*) their composition corresponds to **3**·H_2CO_3·H_2O·0.5 dioxane, and (*iii*) each unit cell contains two equivalent molecules of bis(biguanidium) carbonate. Crystallographic parameters are provided in Table 1, a view of the structure appears in Fig. 6*b*, and additional information is given in the Supplementary data.[4] The bis(biguanidinium) dications adopt essentially the same pincerlike conformation observed in dichloride **3**·2HCl, and the two structures are strikingly similar. Chelation of carbonate leads to the assembly of sheets rather than tapes (Fig. 6*b*). Hydrogen-bonded pairing of biguanidinium cations, also observed in the other salts of bis(biguanides) **2** and **3**, then joins the sheets in a three-dimensional network. Each carbonate also accepts an additional hydrogen bond from an adjacent sheet, and molecules of dioxane are held between the sheets by multiple hydrogen bonds.

Conclusions

Biguanides are an intrinsically interesting class of compounds with many known or potential applications. Because biguanides and biguanidinium salts incorporate multiple sites that can donate or accept hydrogen bonds, they are inherently disposed to associate, making them attractive candidates for applications in crystal engineering and other areas of supramolecular chemistry. To evaluate their potential, we have linked two biguanide or biguanidinium groups to rigid aromatic spacers, and we have determined how the resulting bis(biguanides) and bis(biguanidinium) dications interact in the crystalline state. These studies, along with previous structural analyses, have confirmed that the biguanide and biguanidinium groups can be counted on to engage in multiple hydrogen bonds, leading to the formation of extended networks. However, the precise patterns of hydrogen bonding vary significantly, suggesting that other groups are inherently more suitable for fully controlling molecular aggregation.

Experimental

Crystallization of bis(biguanide) 2

Bis(biguanide) **2** was prepared according to a published procedure (4) and crystallized from hot water.

Crystallization of the dihydrochloride salt of bis(biguanide) 2

The dihydrochloride salt of bis(biguanide) **2** was prepared according to a published procedure (4). Single crystals suitable for X-ray diffraction were grown by allowing acetone to diffuse slowly into an aqueous solution of the salt.

Crystallization of the dihydrochloride salt of bis(biguanide) 3

The dihydrochloride salt of bis(biguanide) **3** was prepared according to a published procedure (4). Single crystals suitable for X-ray diffraction were grown by allowing acetone to diffuse slowly into an aqueous solution of the salt.

Crystallization of the carbonate salt of bis(biguanide) 3

Bis(biguanide) **3** was prepared according to a published procedure (4). Single crystals of the carbonate salt suitable for X-ray diffraction were grown by allowing dioxane to diffuse slowly into an aqueous solution of compound **3** in contact with air.

X-ray crystallographic studies

The structures were solved by direct methods using SHELXS-97 (22) and refined with SHELXL-97 (23). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms bonded to nitrogen atoms were located from difference Fourier maps, whereas hydrogen atoms bonded to the carbon atoms of aryl groups were placed in idealized positions. All hydrogen atoms were refined as riding atoms. The structure of bis(biguanide) **2** was refined as a two-

component twin with twin element scale factors of 0.512(1) and 0.488(1) (24).

Acknowledgements

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Triazene derivatives of (1,*x*)-diazacycloalkanes. Part VII. Synthesis of a series of 1-aryl-2-[3-(3-[2-aryl-1-diazenyl]-1,3-diazepan-1-ylmethyl)-1,3-diazepan-1-yl]-1-diazenes from the reaction of diazonium salts with mixtures of formaldehyde and 1,4-diaminobutane[1,2]

Reid Tingley and Keith Vaughan

Abstract: A new series of bistriazenes, the 1-aryl-2-[3-(3-[2-aryl-1-diazenyl]-1,3-diazepan-1-ylmethyl)-1,3-diazepan-1-yl]-1-diazenes (**8**), has been synthesized from the reaction of diazonium salts with a mixture of 1,4-diaminobutane and formaldehyde. All new compounds of series **8** have been characterized by IR and NMR spectroscopy, and the elemental composition of selected examples has been verified by elemental analysis. The connectivity of the series has been unequivocally determined by X-ray crystallography. The new bistriazenes are important because the structure contains the novel saturated heterocycle, 1,3-diazepane. The general conclusion of this study is that alkanediamines with three or four carbon atoms in the spacer link between the nitrogen atoms give rise to the linear bicyclic molecules of type **2**, in contrast to the case of ethylenediamine (two carbon atoms in spacer link), which affords molecules of type **3**, which exemplify the cage structure of type **1**.

Key words: diazonium salt, triazene, bistriazene, diazepane, formaldehyde, nuclear magnetic resonance.

Résumé : On a réalisé la synthèse d'une nouvelle série de bistriazènes, les 1-aryl-2-[3-(3-[2-aryldiazén-1-yl]-1,3-diazépan-1-ylméthyl)-1,3-diazépan-1-yl]diaz-1-ènes (**8**) en faisant réagir les sels de diazonium avec un mélange de 1,4-diaminobutane et de formaldéhyde. On a caractérisé tous les nouveaux composés de la série **8** par spectroscopies IR et RMN et on a vérifié la composition élémentaire d'exemples choisis par le biais d'analyses élémentaires. La connectivité dans les produits de la série a été déterminée sans équivoque par diffraction des rayons X. Les nouveaux bistriazènes sont importants puisque leur structure comporte le nouvel hétérocycle saturé, 1,3-diazépane. La conclusion générale de cette étude est que les alcanediamines comportant 3 ou 4 atomes de carbones entre les atomes d'azote conduisent à des molécules bicycliques linéaires de type **2** alors que l'éthylènediamine, qui ne comporte que deux atomes de carbone entre les atomes d'azote, conduit à la formation de molécules de type **3** tel qu'on l'observe dans la structure en cage de type **1**.

Mots clés : sel de diazonium, triazène, bistriazène, diazépane, formaldéhyde, résonance magnétique nucléaire.

[Traduit par la Rédaction]

Introduction

The term "bistriazene" has been coined to describe any molecule that contains two triazene units in the same molecule with a link or spacer in between the triazene moieties. Recent progress in the synthesis of bistriazenes has been reviewed (1). One of the conclusions of recent work is that there are two distinct types of oligomer produced by the interaction of a diazonium salt with a mixture of formaldehyde and a bis-primary amine. The cage-type of bistriazene is exemplified by the general structure **1** (Chart 1) . Examples of this structural type are the bistriazenes (**3**), which arise from ethylene diamine (2) and the 3,7-di-[2-aryl-1-diazenyl]-1,3,5,7-tetraazabicyclo[3.3.1]nonanes (**4**), which are formed by the reaction of a diazonium ion with ammonia/formaldehyde mixtures (3). The alternate type of molecular geometry is the linear bicyclic structure (**2**).

The molecule of type **2** is exemplified by the structure **5a**, which describes the series of products that were obtained from the diazonium coupling reaction with a mixture of formaldehyde and 1,3-propanediamine. The description of the synthesis and characterization of the series **5a** was published in Part IV of this series (4) and the connectivity of one member of series **5a** (with X = *p*-CN) was established

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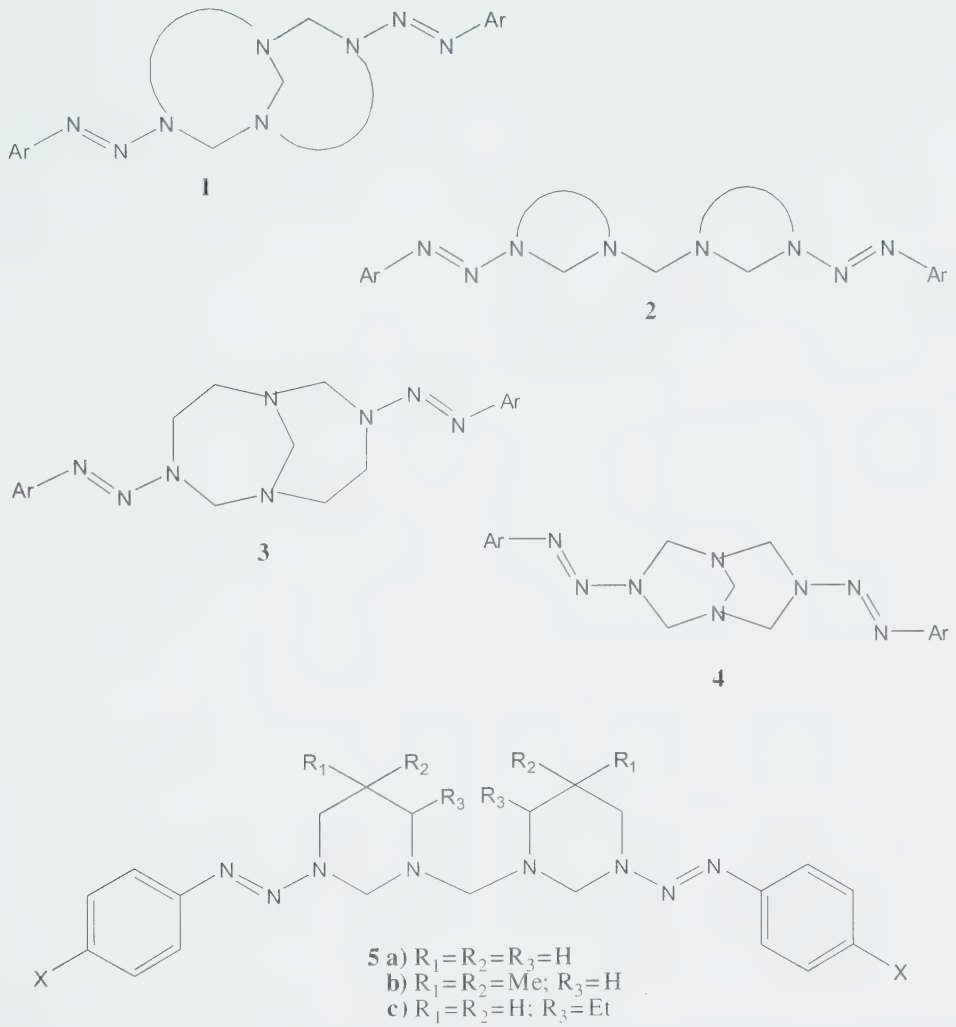
Chart 1.



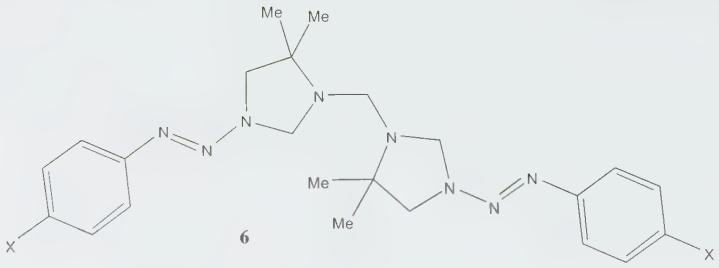
unequivocally by an X-ray structure determination (5). This work was extended to the dimethyl-substituted series **5b** by the analogous reaction with 2,2-dimethyl-1,3-propanediamine. This work was included in Part IV and an X-ray structure of the methyl benzoate analogue (**5b**, X = CO_2Me) was completed and published (6). The compounds of series **5a** and **5b** are important as new derivatives of the saturated heterocyclic hexahydropyrimidine system, in addition to being illustrations of the linear bicyclic genereal structure **2**.

The linear bicyclic bistriazenes (**5c**) were obtained from the analogous reaction of diazonium salts with formaldehyde and 1,3-pentanediamine, which affords the 6-ethylhexahydropyrimidin-1-yl system. These results have been reported in Part V of this series (7) and an X-ray crystal structure of the *p*-bromo derivative of series **5c** has been published (8). Examples of the linear bicycles of type **2** are not restricted to the six membered ring pyrimidines (**5**). The bistriazene series (**6**) (Chart 2) , which are important and novel derivatives of the rare imidazolidine system, have been obtained from the reaction of diazonium salts with a mixture of formaldehyde and 2-methyl-1,2-propanediamine. The synthesis, characterization and X-ray crystal structure (of **6**, X = CO_2Me) have been published as Part VI of this series (9).

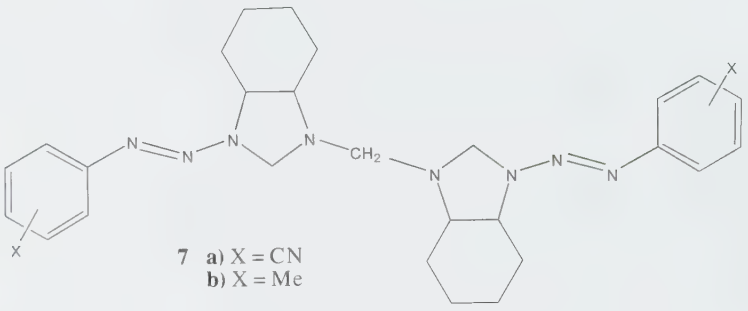
Further examples of imidazolidine-containing molecules of type **2** were found as products of the reaction of diazonium salts with a mixture of formaldehyde and 1,2-cyclohexanediamine. These products have been assigned the structure **7** (Chart 2). The synthesis and characterization of the series **7** has been published (10), and the X-ray structure of the *p*-cyano derivative (**7a**) has been reported (11). The X-ray structure of the second example of this series (**7b**, X = Me) has been published recently (12).

Thus, there seems to be a crossover in behaviour of the alkanediamine going from ethylenediamine to propanediamine and also in the introduction of a branching chain in the ethylenediamine. In the present study, we have extended these reactions with the next further homologue in the diamine series, specifically 1,4-butanediamine, and it is clear that the linear bicyclic molecule of type **2** is formed in preference to the cage structures of type **1**. The products of these

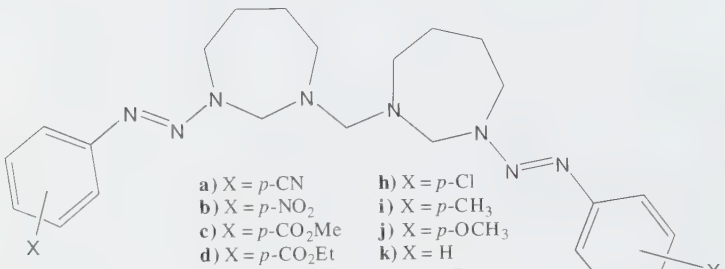
Chart 2.



6



7 **a)** X = CN
b) X = Me



8

a) X = *p*-CN
b) X = *p*-NO_2
c) X = *p*-CO_2Me
d) X = *p*-CO_2Et
e) X = *p*-$COCH_3$
f) X = *p*-$CONH_2$
g) X = *p*-Br
h) X = *p*-Cl
i) X = *p*-CH_3
j) X = *p*-OCH_3
k) X = H
l) X = *o*-Br
m) X = *o*-CN
n) X = *o*-CO_2Me

reactions are seen in Chart 2 (**8a–8n**). In this paper, we report the details of the synthesis of series **8** and their characterization by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Experimental

All reagents were reagent grade materials purchased from the Sigma-Aldrich Chemical Co. Ltd. (Oakville, Ontario) and were used without further purification. Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected. IR spectra were obtained using Nujol mulls, unless otherwise stated, on a PerkinElmer 299 spectrophotometer or with a Brucker Vector 22 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained using either the Anasazi Instruments 60 MHz EFT spectrometer at Saint Mary's University, or the Bruker 250 MHz spectrophotometer at the Atlantic Regional Magnetic Resonance Centre at Dalhousie University in Halifax, Nova Scotia. Chemical shifts were recorded in $CDCl_3$ or d_6-DMSO solutions at 20 °C, and are relative to TMS as internal standard. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu-intet), multiplet (m), and broad (br).

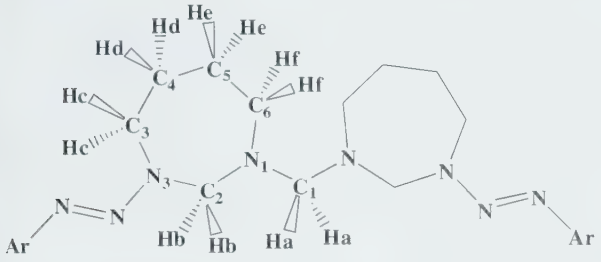
1-Aryl-2-[3-(3-[2-aryl-1-diazenyl]-1,3-diazepan-1-ylmethyl)-1,3-diazepan-1-yl]-1-diazenes (8a–8n)

General procedure

Method A

The appropriate arylamine (0.010 mol) was dissolved in hydrochloric acid (3 mol/L, 40 ml) with heating if necessary to obtain a clear solution. This solution was then cooled in an ice/salt bath. The arylamine hydrochloride solution was diazotized at 0–5 °C with a solution of sodium nitrite (0.011 mol) in water and the resulting mixture was stirred in the cold for 0.5 h. Any insoluble impurities were removed by vacuum filtration. The mixture was brought to pH 7 using a saturated solution of sodium bicarbonate, at which point 37% aqueous formaldehyde solution (5 mL) was added. 1,4-Diaminobutane (0.010 mol) was slowly added to the solution, which was allowed to stir in the cold for a further 0.5 h. Occasionally, a slight precipitate was evident during the period of the addition, but was not removed. The mixture was then adjusted to alkaline pH with additional saturated sodium bicarbonate solution, whereupon the product precipi-

Fig. 1. Proton and carbon labels in **8** for the discussion of NMR assignments.



tated out of solution. Solid precipitates were isolated by vacuum filtration and purified by recrystallization from an appropriate solvent. The oil **8n** was recovered by extraction into dichloromethane (three 20 mL aliquots), dried over anhyd $MgSO_4$, and rotoevaporated under vacuum.

Method B

The procedure of Method A was followed exactly with the exception of the amount of formaldehyde used. A 40:1 molar ratio of formaldehyde–arylamine was used, i.e., approx. 32 mL of 37% aqueous formaldehyde was added at the appropriate time. Application of these procedures afforded compounds **8a–8n**.

1-(*p*-Cyanophenyl)-2-[3-{3-[2-(*p*-cyanophenyl)-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (8a)

Method B: yield 100%; lustrous pale yellow prisms; from ethanol – ethyl acetate; mp 191–193 °C. IR (cm^{-1}) ν_{max}: 2220 (CN), 843 (OOP). ^1H NMR (250 MHz, $CDCl_3$, ppm): 1.64 (4H, br m, H_e), 1.96 (4H, br m, H_d), 2.93 (4H, t, J = 5.2 Hz, H_f), 3.25 (2H, s, H_a), 3.75 (4H, t, J = 6.0 Hz, H_c), 4.98 (4H, s, H_b), 7.42 (4H, d, J = 8.9 Hz, arom.), 7.56 (4H, d, J = 8.9 Hz, arom.) (See Fig. 1 for the key to the proton and carbon labels in the NMR spectra). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): 24.7 (C-5), 28.0 (C-4), 49.9 (C-6), 53.2 (C-3), 64.7 (C-1), 69.9 (C-2), 107.9 (CN),119.6, 121.0, 133.1, 154.5 (arom.). Anal. calcd. for $C_{25}H_{30}N_{10}$: C 63.8, H 6.4, N 29.8; found: C 64.1, H 6.3, N 29.0%.

1-(*p*-Nitrophenyl)-2-[3-{3-[2-(*p*-nitrophenyl)-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (8b)

Method A: 100%. Method B: 86%. Reddish brown prisms; from ethanol – ethyl acetate; mp 165–167 °C. IR (cm^{-1}) ν_{max}: 1507 and 1328 (NO_2), 855 (OOP). ^1H NMR (250 MHz, $CDCl_3$, ppm): 1.64–1.80 (4H, br m, H_e), 2.02 (4H, br m, H_d), 2.95 (4H, t, J = 5.3 Hz, H_f), 3.27 (2H, s, H_a), 3.80 (4H, t, J = 7.2 Hz, H_c), 5.00 (4H, s, H_b), 7.45 (4H, d, J = 9.2 Hz, arom.), 8.15 (4H, d, J = 9.2 Hz, arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): 24.7 (C-5), 28.1 (C-4), 49.8 (C-6), 53.4 (C-3), 64 (w) (C-1), 69.8 (C-2), 120.6, 129.7, 155.0 (arom.). Anal. calcd. for $C_{23}H_{30}N_{10}O_4$: C 54.1, H 5.9; found: C 55.5, H 6.0%.

Methyl-4-(2-{3-[(3-{2-[4-(methoxycarbonyl)phenyl]-1-diazenyl}-1,3-diazepan-1-yl)methyl]-1,3-diazepan-1-yl}-1-diazenyl)benzoate (8c)

Method B: 86%; off-white powder; from ethanol – ethyl acetate; mp 184–187 °C. IR (cm^{-1}) ν_{max}: 1715 (C=O), 859 (OOP). ^1H NMR (250 MHz, $CDCl_3$, ppm): 1.61 (4H, br m, H_e), 1.97 (4H, br m, H_d), 2.91 (4H, t, J = 4.9 Hz, H_f), 3.26 (2H, s, H_a), 3.73 (4H, t, J = 5.8 Hz, H_c), 3.89 (6H, s, O–Me), 4.98 (4H, s, H_b), 7.41 (4H, d, J = 8.5 Hz, arom.), 7.96 (4H, d, J = 8.5 Hz, arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): 24.8 (C-5), 28.1 (C-4), 49.7 (C-6), 52.0 (O–Me) 53.4 (C-3), 64.8 (C-1), 69.6 (C-2), 120.3, 126.5, 130.7, 154.9 (arom.), 167.2 (C=O). Anal. calcd. for $C_{27}H_{36}N_8O_4$: C 60.43 H 6.76, N 20.88 ; found: C 60.4, H 6.75, N 20.4%.

Ethyl 4-(2-{3-[(3-{2-[4-(ethoxycarbonyl)phenyl]-1-diazenyl}-1,3-diazepan-1-yl)methyl]-1,3-diazepan-1-yl}-1-diazenyl)benzoate (8d)

Method B: 99%; white needles; from ethanol – ethyl acetate; mp 152–154 °C. IR (cm^{-1}) ν_{max}: 1712 (C=O), 1266 and 1143 (CO), 863 (OOP). ^1H NMR (250 MHz, $CDCl_3$, ppm): 1.39 (6H, t, J = 7.2 Hz, C–CH_3), 1.61 (4H, br m, H_e), 2.01 (4H, br m, H_d), 2.93 (4H, t, J = 5.0 Hz, H_f), 3.26 (2H, s, H_a), 3.75 (4H, t, J = 6.0 Hz, H_c), 4.36 (4H, q, J = 7.1 Hz, O–CH_2), 4.98 (4H, s, H_b), 7.42 (4H, d, J = 8.5 Hz, arom.), 7.98 (4H, d, J = 8.5 Hz, arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): 14.5 (CH_3), 24.8 (C-5), 28.2 (C-4), 49.7 (C-6), 53.5 (C-3), 60.8 (O–CH_2), 64.8 (C-1), 69.6 (C-2), 120.3, 126.9, 130.7, 154.8 (arom.), 166.8 (C=O). Anal. calcd. for $C_{29}H_{40}N_8O_4$: C 61.7, H 7.1, N 19.9 ; found: C 61.6, H 7.2, N 19.8%.

1-(4-{2-[3-({3-[2-(4-Acetylphenyl)-1-diazenyl]-1,3-diazepan-1-yl}methyl)-1,3-diazepan-1-yl]-1-diazenyl}phenyl)-1-ethanone (8e)

Method A: 94%; off-white prisms; from ethanol; mp 175–177 °C. IR (cm^{-1}) ν_{max}: 1676 (C=O), 850 (OOP). ^1H NMR (60 MHz, $CDCl_3$, ppm): 1.82 (8H, br m, H_d and H_e), 2.56 (6H, s, acetyl Me), 2.95 (4H, br t, J = 4.7 Hz, H_f), 3.30 (2H, s, H_a), 3.77 (4H, br t, J = 5.3 Hz, H_c), 5.00 (4H, s, H_b), 7.42 (4H, d, J = 8.5 Hz, arom.), 7.90 (4H, d, J = 8.7 Hz, arom.). ^{13}C NMR (15.1 MHz, $CDCl_3$, ppm): 24.1 (C-5), 25.9 (acetyl Me), 27.4 (C-4), 49.0 (C-6), 52.6 (C-3), 64.3 (C-1), 69.2 (C-2), 119.9, 129.0, 133.3, 154.4 (arom.), 196.8 (C=O). Anal. calcd. for $C_{27}H_{36}N_8O_2$: C 64.28, H 7.14; found: C 63.7, H 6.8%.

4-(2-{3-[(3-{2-[4-(Aminocarbonyl)phenyl]-1-diazenyl}-1,3-diazepan-1-yl)methyl]-1,3-diazepan-1-yl}-1-diazenyl)benzamide (8f)

Method A: 100%; method B: 96%; pale yellow powder; from ethanol – ethyl acetate/toluene; mp 212–215 °C. IR (cm^{-1}) ν_{max}: 3388 (NH), 1655 (C=O), 856 (OOP). ^1H NMR (60 MHz, $CDCl_3$, ppm): 1.68 (8H, br m, H_d and H_e), 2.87 (4H, br, H_f), 3.35 (2H, s, H_a), 3.65 (4H, br m, H_c), 4.97 (4H, br s, H_b), 7.31 (4H, d, J = 8.2 Hz, arom.), 7.85 (4H, d, J = 8.9 Hz, arom.).

1-(*p*-Bromophenyl)-2-[3-{3-[2-(*p*-bromophenyl)-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (8g)

Method B: 95%; off-white needles; from ethanol – ethyl acetate; mp 183–184 °C. IR (cm^{-1}) ν_{max}: 829 (OOP). ^1H NMR (400 MHz, $CDCl_3$, ppm): 1.63 (4H, br m, H_e), 1.90 (4H, br m, H_d), 2.91 (4H, br t, J = 6.0 Hz, H_f), 3.25 (2H, s, H_a), 3.70 (4H, quintet, J = 6.1 Hz, H_c), 4.93 (4H, s, H_b),

7.25 (4H, d, J = 9.8 Hz, arom.), 7.39 (4H, d, J = 8.6 Hz, arom.). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): 25.0 (C-5), 29.9 (C-4), 49.5 (C-6), 53.6 (C-3), 64.8 (C-1), 69.6 (C-2), 122.3, 132.0, 150.3 (arom.). Anal. calcd. for $C_{23}H_{30}N_8Br_2$: C 47.77, H 5.19, N 19.38 ; found: C 46.9, H 5.2, N 19.3%.

1-(*p*-Chlorophenyl)-2-[3-{3-[2-(*p*-chlorophenyl)-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (8h)

Method A: 90%; off-white needles; from ethanol – ethyl acetate; mp 163–167 °C. IR (cm^{-1}) ν_{max}: 839 (OOP). ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 1.78 (8H, br m, H_d and H_e), 2.94 (4H, br t, J = 4.8 Hz, H_f), 3.34 (2H, br s, H_a), 3.75 (4H, br t, J = 5.4 Hz, H_c), 4.94 (4H, s, H_b), 7.26 (8H, m, arom.). Anal. calcd. for $C_{23}H_{30}N_8Cl_2$: C 56.5, H 6.1, N 22.9; found: C 56.4, H 6.3, N 22.5%.

1-(*p*-Tolyl)-2-[3-{3-[2-(*p*-tolyl)-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (8i)

Method B: 68%; pale yellow prisms; from ethanol – ethyl acetate; mp 177–179 °C. IR (cm^{-1}) ν_{max}: 824 (OOP). ^{1}H NMR (250 MHz, $CDCl_3$, ppm): 1.60 (4H, br m, H_e), 1.93 (4H, br m, H_d), 2.32 (6H, s, tolyl Me), 2.92 (4H, t, J = 5.0 Hz, H_f), 3.29 (2H, br s, H_a), 3.71 (4H, br, H_c), 4.94(4H, s, H_b), 7.10 (4H, d, J = 8.2 Hz, arom.), 7.30 (4H, d, J = 8.2 Hz, arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): 21.1 (tolyl Me), 25.0 (C-5), 28.1 (C-4), 49.2 (C-6), 53.5 (C-3), 65 (w) (C-1), 69.3 (C-2),120.4, 129.5, 134.9, 149.0 (arom.). Anal. calcd. for $C_{25}H_{36}N_8$: C 67.0, H 8.0, N 25.0; found: C 67.1, H 8.1, N 24.7%.

1-(*p*-Methoxyphenyl)-2-[3-{3-[2-(*p*-methoxyphenyl)-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (8j)

Method B: 48%; golden yellow plates; from ethanol – ethyl acetate; mp 183–184 °C. IR (cm^{-1}) ν_{max}: 1239 (C O), 833 (OOP). ^{1}H NMR (250 MHz, $CDCl_3$, ppm): 1.63 (4H, br m, H_e), 1.93 (4H, br m, H_d), 2.92 (4H, t, J = 5.2 Hz, H_f), 3.31 (2H, br s, H_a), 3.70 (4H, t, J = 7.0 Hz, H_c), 3.79 (6H, s, O–Me), 4.92 (4H, s, H_b), 6.87 (4H, d, J = 8.9 Hz, arom.), 7.36 (4H, d, J = 9.2 Hz, arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): 25.0 (C-5), 29.0 (C-4), 53.4 (C-3), 55.6 (O–Me), 114.1, 121.5, 145.2, 157.6 (arom.). Anal. calcd. for $C_{25}H_{36}N_8O_2$: C 62.5, H 7.5; found: C 61.9, H 7.5%.

1-Phenyl-2-[3-{3-[2-phenyl-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (8k)

Method A: 58%; brown powder; mp 99–102 °C. IR (cm^{-1}) ν_{max}: 761 (OOP). ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 1.74 (8H, br m, H_d and H_e), 2.92 (4H, t, J = 4.9 Hz, H_f), 3.35 (2H, s, H_a), 3.75 (4H, t, J = 5.6 Hz, H_c), 4.93 (4H, s, H_b), 7.06–7.60 (8H, m, arom.). ^{13}C NMR (15.1 MHz, $CDCl_3$, ppm): 24.6 (C-5), 27.7 (C-4), 48.8 (C-6), 53.0 (C-3), 64.9 (C-1), 69.1 (C-2), 1120.4, 125.1, 128.6, 151.0 (arom.).

1-(*o*-Bromophenyl)-2-[3-{3-[2-(*o*-bromophenyl)-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (8l)

Method B: 96%; white needles; from ethanol – ethyl acetate; mp 117–120 °C. IR (cm^{-1}) ν_{max}: 754 (OOP). ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 1.77 (8H, br m, H_d and H_e), 2.94 (4H, t, J = 4.8 Hz, H_f), 3.30 (2H, s, H_a), 3.78 (4H, t, J = 6.0 Hz, H_c), 4.96 (4H, s, H_b), 6.78–7.63 (8H, m, arom.).

1-(*o*-Cyanophenyl)-2-[3-{3-[2-(*o*-cyanophenyl)-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (8m)

Method B: 67%; beige powder; from ethanol – ethyl acetate; mp 132–135 °C. IR (cm^{-1}) ν_{max}: 2226 (CN), 764 (OOP). ^{1}H NMR (250 MHz, $CDCl_3$, ppm): 1.25–1.78 (4H, br m, H_e), 2.01 (4H, br m, H_d), 2.95 (4H, t, J = 5.0 Hz, H_f), 3.27 (2H, s, H_a), 3.80 (4H, br, H_c), 4.97 (4H, s, H_b), 7.6–8.1 (8H, m, arom.).

Methyl 2-(2-{3-[(3-{2-[2-(methoxycarbonyl)phenyl]-1-diazenyl}-1,3-diazepan-1-yl) methyl]-1,3-diazepan-1-yl}-1-diazenyl)benzoate (8n)

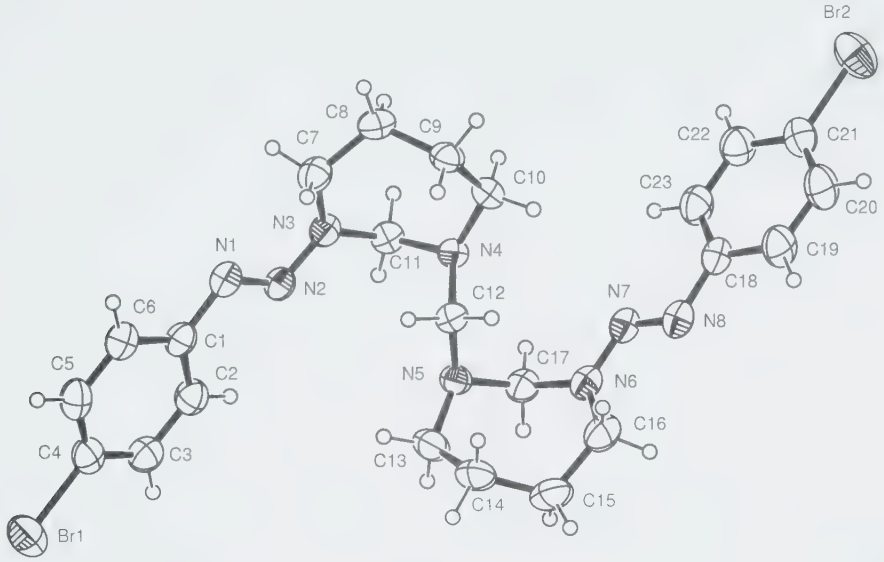
Method A: 18%; oil. IR (cm ^{1}) ν_{max}: 1731 (C=O), 721 (OOP). ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 1.76 (8H, br m, H_d and H_e), 2.90 (4H, br t, J = 4.7 Hz, H_f), 3.32 (2H, br s, H_a), 3.75 (4H, br t, J = 7.5 Hz, H_c), 4.91 (4H, s, H_b), 7.03–7.68 (8H, m, arom.).

Results and discussion

The required diazonium salt, ArN_2^+, was prepared by diazotization of the appropriate arylamine. The diazonium salt solution was then treated with a mixture of formaldehyde and 1,4-diaminobutane ($NH_2(CH_2)_4NH_2$). On the basis of IR and NMR spectroscopic analysis, together with elemental analysis whenever possible, the products of this reaction have been identified unequivocally as the 1-aryl-2-[3-(3-[2-aryl-1-diazenyl]-1,3-diazepan-1-ylmethyl)-1,3-diazepan-1-yl]-1-diazenes (**8a–8n**). The connectivity in structure **8** has been established by X-ray crystyallography. The yields of the products are excellent, often in excess of 90%, and the solid products recrystallize in most cases from a mixture of ethanol and ethyl acetate. The pure compounds are generally colourless or pale in colour, crystallizing as needles, prisms, or plates. The IR spectra were recorded mainly to confirm the presence of the particular aryl substituent (X), such as the presence of a carbonyl band in **8c–8f** and **8n**, and also to confirm the substitution pattern as ortho or para from the measurements of the OOP bending vibrations.

The ^{1}H NMR spectra of the new bistriazenes are very informative about the structures of these molecules, in particular the presence of two identical 1,3-diazepanyl groups attached to a central methylene group. The detailed structure in Fig. 1 shows the proton labels from H_a to H_e, which is useful to interpret the following discussion. The central methylene group between the heterocyclic rings (H_a) appears universally as a two-proton singlet at ~3.30 ppm, sometimes broadened. The protons (H_b) of the two equivalent methylene groups situated between the N1 and N3 nitrogen atoms of the diazepane rings appear as a four-proton singlet at ~5.0 ppm. The protons (H_c) of the two equivalent *N*-methylene groups of the heterocyclic rings appear at ~3.70–3.80 ppm as a four-proton triplet with coupling constant J_{cd} in the range 5–7 Hz because of the anticipated coupling to the protons of the adjacent methylene group (H_d). Likewise, the protons (H_f) of the other equivalent *N*-methylene groups appear as a four-proton triplet with J_{ef} = ~5.0 Hz because of

Fig. 2. ORTEP view of 1-(*p*-bromophenyl)-2-[3-{3-[2-(*p*-bromophenyl)-1-diazenyl]-1,3-diazepan-1-ylmethyl}-1,3-diazepan-1-yl]-1-diazene (**8g**) showing the thermal ellipsoids at 40% probability level.



the coupling to H_e. However, the chemical shift of H_f is at a higher field (~2.90 ppm). The proximity of the triazene group to the H_c protons is presumably responsible for this difference. The protons of the other methylene groups of the diazepane rings appear as four-proton multiplets at ~1.6 ppm and 2.0 ppm. Other features of the NMR spectra, such as the AA′BB′ aromatic protons and the proton signals of the aryl substituent (X), are clearly evident.

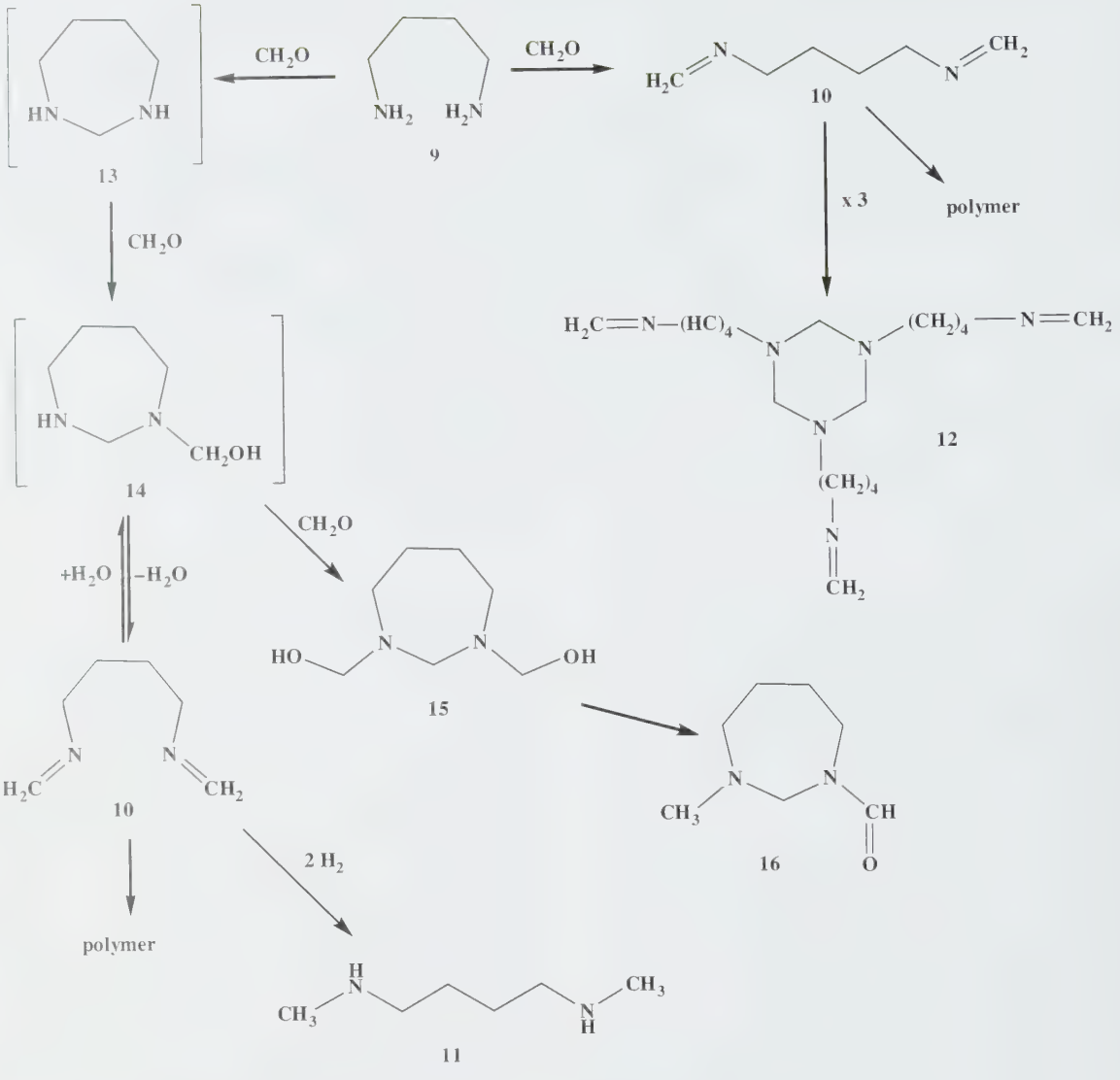
^{13}C NMR analysis of the series **8a**–**8n** was not possible for all compounds because of the combination of limited solubility and the extreme broadening of carbon signals ubiquitous in triazenes of this type (4). Nevertheless, complete ^{13}C NMR spectral data was acquired for a significant number of these compounds. The assignment of carbon signals is based on the numbering scheme shown in Fig. 1. The carbon of the central methylene group (C1) in **8** is observed at ~64–65 ppm and C2 of the diazepane ring is observed in the narrow range 69.1–69.9 ppm. The assignments of C3, C4, C5, and C6 to the signals at ~53, 28, 25, and 49,respectively, is based on the proximity to the nitrogen atoms N1 and N3, and to the triazene moiety. The ^{13}C NMR data is a strong supporting evidence for the structure **8** assigned to these products.

It should be noted that there is a wide range of stability for the compounds in the series **8a**–**8n**. These stability problems are not new to our experience with similar bistriazenes, such as those of type **5a**–**5c** (4, 7). Several products displayed a limited shelf-life when stored for a couple of years. Samples that were fine powders when fresh are now glass, such as **8d**, **8l**, and **8m**. Others like **8a**–**8c** and **8g** show little if any sign of decay. Compound **8j**, which afforded an X-ray crystallographic structure, is somewhat fickle in this regard. A crude sample that was stored for over two years showed definite signs of decomposition, whereas a purified sample of the same compound showed no sign of decomposition. It is possible that the stability of these bis(aryldiazenyl-1,3-diazepanyl)methanes is prolonged in the crystalline state compared with the amorphous state; however, we have not undertaken a systematic study of this question. This stability problem had a detrimental effect on the results of elemental analysis of several new compounds, which were not universally successful. There is an approximate correlation of the stability of the compounds in this series and either the success or lack of success of elemental analysis. However, elemental analysis of selected compounds in the series **8** did provide further evidence of the assigned structures. Unequivocal evidence of the connectivity of the compounds in series **8** has been obtained from the X-ray crystal structures of three compounds **8a**, **8g**, and **8j**. Full details of the X-ray analysis will be published elsewhere (13)and an ORTEP diagram of the *p*-bromo derivative (**8g**) is shown in Fig. 2.

In consideration of the possible reaction pathways that could be involved in the formation of molecules of type **8**, it is essential to examine the reported work on the reaction of 1,4-diaminobutane with formaldehyde. The earliest work of any consequence is that of Krassig (14), who concluded that the reaction of diaminobutane (**9**) with formaldehyde afforded viscose polymers, described as "poly-bismethylenetetramethylenediamines". He suggested that the initial condensation product (Scheme 1) has structure **10**, which can trimerise to the novel 1,3,5-triazine derivative (**12**). An evidence for the existence of **10** is the isolation and characterization of *N*,*N*′-dimethyl-1,4-diaminobutane (**11**) from the reductive amination of formaldehyde by **9**. Subsequent to Krassig's work, Evans and co-workers (15) investigated the reaction of 1,4-diaminobutane with acetamidine, which resulted in a synthetic method for a variety of substituted diazepines.

However, the most significant and enlightening work with relevance to the present study is the paper by Dale and Sigvartsen (16). The surprising result in their paper is that the final product after prolonged standing of the reactants is

Scheme 1.



the formamide (**16**), together with the initial polymer. They suggest that the formamide (**16**) is produced by the sequence of reactions starting with condensation to give the diazepane (**13**), which can hydroxymethylate to give **14**. This carbinolamine can either: (*i*) dehydrate reversibly to give Krassig's di-imine (**10**), which could be the source of the polymer, or (*ii*) condense further with formaldehyde to give the diol **15**. Cannizzaro-like redox disproportionation of **15** produces the final product **16**.

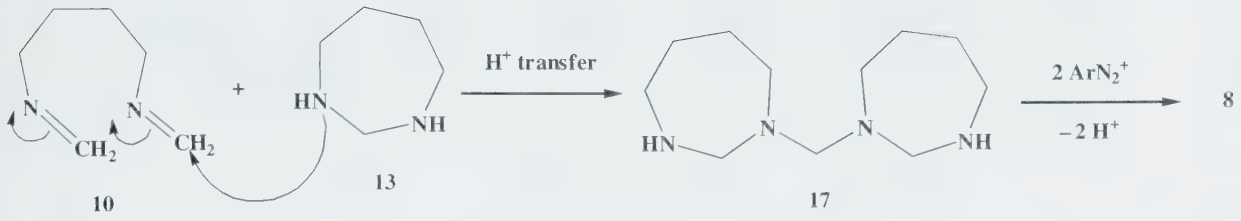
The work of Dale and Sigvartsen leads to a logical hypothesis (Scheme 2) for the formation of the novel bistriazenes (**8**). Reaction of a molecule of Krassig's diimine (**10**) with a molecule of the diazepane (**13**) affords the bis(1,3-diazepanyl)methane (**17**) by ring-closure dimerization. Reaction of **17** with two equivalents of the diazonium ion followed by deprotonation affords the observed product (**8**).

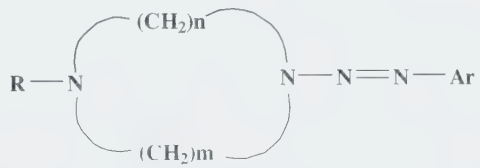
Conclusion

It appears, from our on-going studies, that the interaction of a diazonium salt with a mixture of formaldehyde and an alkanediamine $[NH_2(CH_2)_nNH_2]$ gives rise to two distinct types of oligomer. Bistriazenes of types **3** (2) and **4** (3) are examples of the bridged bicyclic bistriazene, whereas the compounds of series **5** (5, 7) exemplify the linear bicyclic bistriazene. The new compounds of series **8**, reported here, clearly belong to the linear bicyclic class, providing further evidence that there is a crossover in the molecular architecture going from the two-carbon spacer of ethylenediamine to the three- or four-carbon spacer.

This paper is part VII in a series that describes the synthesis of a variety of triazenes and bistriazenes that fit the general classification of 1-aryldiazenyl-(1,x)-diazacycloalkanes described by the general structure **18**, where m = 1 or 2 and

Scheme 2.





18

n = 2, 3, 4 or 5. Previously, we reported new triazenes derived from imidazolidine (m = 1, n = 2) (9, 10), hexahydropyrimidine (m = 1, n = 3) (4), piperazine (m = n = 2) (17, 18), and homopiperazine (m = 2, n = 3) (19). The new diazepanes of series **8** fit to the general structure **18**, where m = 1 and n = 4. Future work in this field of chemistry will endeavour to further extend the family of (1,x)-diazacycloalkanes.

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In situ nitrosonium ion generation — α-Oximinylation of enol ethers from steroidal spiroketals: Introduction of C23 (*R*)-OH in cephalostatin intermediates[1]

Seongmin Lee and Philip L. Fuchs

Abstract: Nitrosonium ion generated in situ from the reaction of *t*-$BuNO_2$ and $BF_3{\cdot}Et_2$ is an effective oximinylating agent for enol ethers derived from steroidal spiroketals. The scope and limitations of this method has been studied. The difficult reduction of C23 ketone to C23 (*R*)-alcohol has now been selectively achieved via L-Selectride® reduction. Application to cephalostatin intermediates is discussed.

Key words: oximinylation, nitrosonium ion, steroid spiroketal, cephalostatins.

Résumé : L'ion nitrosonium généré in situ par réaction du *t*-$BuNO_2$ avec le $BF_3{\cdot}OEt_2$ est un agent d'oximinylation efficace pour les éthers énoliques dérivés de spirocétals stéroïdaux. On a étudié la portée et les limitations de cette méthode. Faisant appel à une réduction à l'aide de L-Selectride®, on a maintenant réalisé la difficile réduction stéréosélective de la cétone C23 en alcool-(*R*) C23. On discute de l'application à des intermédiaires de la céphalostatine.

Mots clés : oximinylation, ion nitrosonium, spirocétal stéroïdal, céphalostatines.

[Traduit par la Rédaction]

Introduction

The 45 members of the cephalostatin and ritterazine family, along with analogs, afford the basis for elucidating some of the structure–activity relationships (SAR) of these potent cytotoxins (1). All members of the cephalostatin family possess two steroidal spiroketals connected by a pyrazine. The most active compounds bear a highly oxygenated north unit and a substantially less polar south unit. In terms of bioactivity, cephalostatin **1** (Fig. 1) shows average 1 nmol/L GI_{50}s in 2 day tests in the NCI 60-line screen and 10^{-14} mol/L GI_{50}s in 6day tests in the Purdue 6 line mini-panel (2). Cephalostatin **1**, cephalostatin **7**, ritterazine **M**, and ritterazine **K** have been synthesized by our group (3), while we and others (4) have also been active in the synthesis and testing of analogs.

The mechanism of action of the cephalostatins and ritterazines is currently unknown, although recent data indicates that ritterazine **B** is an apoptotic agent like OSW-1 (5) and cephalostatin **7** (6). The role of spiroketals and sugars as hydrogen bond donors and (or) acceptors has been suggested (7). Although it is evident from the NIH 60-cell line COMPARE studies that cephalostatin 1 and OSW-1 are related, significant biological differences[3] and recent bioactivity data of C22 deoxy OSW-**1** analogs (8) suggest that they may have a modified mechanism of action. Correlation of cytotoxicity with energy for E-ring oxacarbenium ion access in cephalostatins and ritterazines has been proposed (9). SAR studies indicate that the hydroxyl groups of both north and south units of the cephalostatin family play an essential role in tumor eradication. Hydroxyl groups provide "polarity match" (10), a requirement for the exhibition of bioactivity, and affect the heat of formation of the E-ring oxacarbenium ion,[4] thus adjusting bioactivity. When the C17 alcohol, for instance, in the north unit of cephalostatin **1** was replaced by a hydrogen, the antitumor activity dropped dramatically.[5] The presence of the C23 hydroxyl group also contributes to the anticancer activity. The recently synthesized C23′-deoxy cephalostatin **1**(11) is about 10 times less potent than cephalostatin **1**.

Our second generation synthesis of cephalostatin **1** (**4**) uses a "redox" strategy(12), requiring a scalable protocol ca-

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[2]Corresponding author (e-mail: pfuchs@purdue.edu).
[3]P. Huang. Unpublished results.
[4]T.G. LaCour and P.L. Fuchs. Unpublished results.
[5]Compare, for example, ritterazine **A** (17 -OH, 24 nmol/L) and ritterazine **T** (17 -H, 590 nmol/L).

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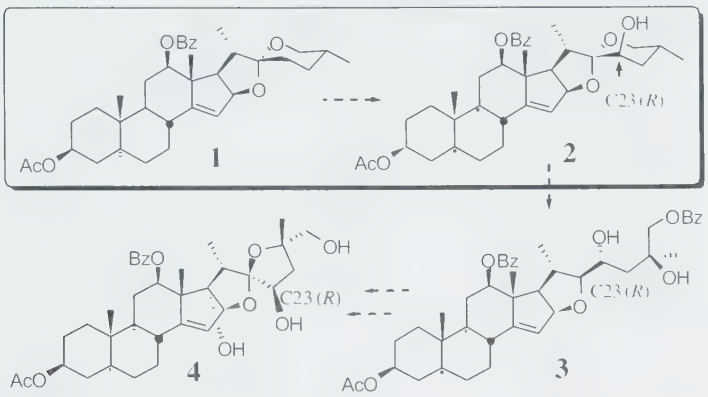
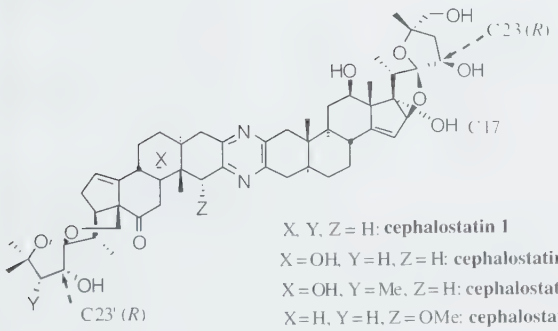
Scheme 1.



North unit of cephalosatin 1

Fig. 1.



X, Y, Z = H: **cephalostatin 1**
X = OH, Y = H, Z = H: **cephalostatin 2**
X = OH, Y = Me, Z = H: **cephalostatin 3**
X = H, Y = H, Z = OMe: **cephalostatin 19**

pable of efficient introduction of the C23 (*R*)-alcohol (Scheme 1). Eighteen of nineteen known cephalostatins possess the north C23 (*R*)-alcohol and seventeen of those bear the south C23 (*R*)-alcohol (Fig. 1).

Many efforts have been made to introduce the C23 (*R*)-alcohol (13), such as the reduction of the C23 carbonyl group (14), sulfinylation of a C22,C23 enol ether with TFAA-activated DMSO followed by allylic rearrangement (15), and addition of allyl stannane to an aldehyde (16). However, none of these methods provided the requisite C23 (*R*)-alcohol in workable excess (de < 30%). At present, the only acceptable method is the dimethyldioxirane (DMDO) oxidation of an enone – vinyl ether to quantitatively achieve stereospecific cyclization to the prized (*R*)-alcohol. However, this method employs 750 mL of DMDO for the production of 15.7 g of C23 alcohol (17) and also requires the use of stoichiometric amounts of toxic selenium and stannyl reagents to prepare **2**. Herein, we describe a scalable pathway leading to C23 (*R*)-OH.

Results and discussion

The known methods for α-oxidation of ketones, enols, and spiroketals (Scheme 2) were initially surveyed to access the desired C23 ketone **7**. We first attempted the synthesis of a masked C23 ketone, such as nitroimine 5 or oxime 6. Although Suàrez and co-workers (18) recently demonstrated that the C14,C15-saturated spiroketal forms the nitroimine in acceptable yield, our attempts to use this procedure on substrate **1** only afforded the C23 nitroimine **5** in very low yield. We also investigated S_N2 chemistry with equatorial C23 bromide **8** and iodide **9**, prepared from **1** with phenyltrimethylammonium bromide (PTAB) or iodine monochloride, respectively. Unfortunately, numerous reagents that convert alkyl halides to alkoxy groups, including superoxide (19), KNO_2 (20), O_2–Bu_3SnH (21), $AgBF_4$–glyme–H_2O (22), AgOAc (23), and CsF–BzOH (24), were either unreactive or severely destructive.

The known methods for α-oximinylation of ketones were not applicable to our substrate (25). Thus, we were delighted that the formation of the desired oxime spiroketal **12** took place smoothly from the reaction of rockogenin diacetate **11** with *t*-$BuNO_2$ and $BF_3{\cdot}Et_2$. Optimization of this new procedure is summarized in Table 1. The choice of Lewis acid is critical for this event, as $BF_3{\cdot}Et_2$ gave the best yields while $FeCl_3$, $TiCl_4$, $SnCl_4$, $ZnBr_2$, $Sc(OTf)_3$, and TMSOTf failed to give reasonable conversions, probably because of their decreased oxophilic character relative to $BF_3{\cdot}OEt_2$.

Minimization of undesired lactone **13**, which comes from oxime spiroketal **12**, requires using excess *t*-BuONO (5 equiv.) and catalytic $BF_3{\cdot}OEt_2$ (0.5 equiv.) in acetic acid at ambient temperature for the minimum time. The use of less *t*-BuONO (Table 1, entries 1–5 and 7) and $BF_3{\cdot}Et_2$ (Table 1, entry 11), solvents other than AcOH (Table 1, entries 1, 3, and 4), lower temperature (Table 1, entry 2), or prolonged reaction time (Table 1, entry 10) results in the formation of significant amounts of lactone **13**.

The proposed mechanism of oximinylation involves nitrosonium ion (26) mediated nitrosylation of the enol ether **11a** formed via Lewis acid opening of the steroid spiroketal (Scheme 3). First, nitrosonium ion ($NO^+BF_4^-$) is generated in situ from a reaction of *t*-$BuNO_2$ and $BF_3{\cdot}OEt_2$. Then, the attack of enol ether **11a** on the nitrogen atom of nitrosonium ion takes place to produce nitroso spiroketal **12a**. Finally, the nitroso spiroketal **12a** is rapidly isomerized to give oxime spiroketal **12**. The presence of a $NOBF_4$ (–141.6 ppm, CD_3CN) peak in the ^{19}F NMR supports this mechanism. The reaction of spiroketal **11** with 3 equiv. of commercial $NOBF_4$ (Table 1, entry 19) in acetic acid affords the same

Scheme 2.

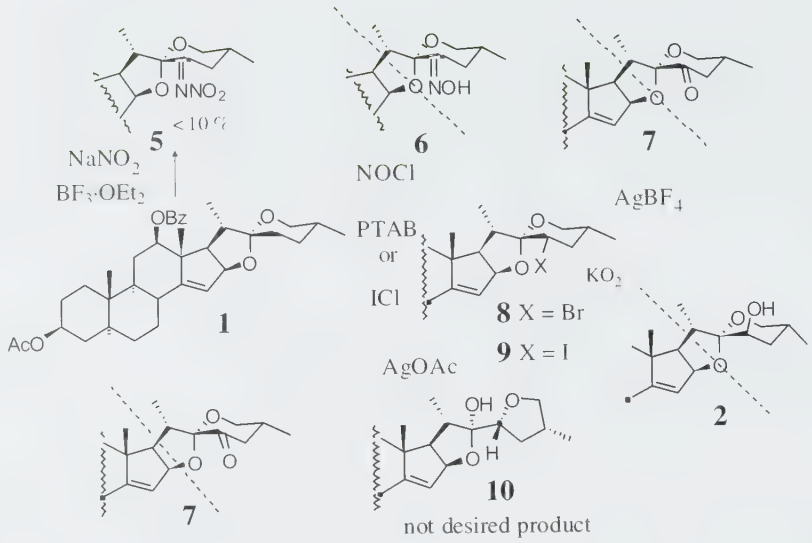
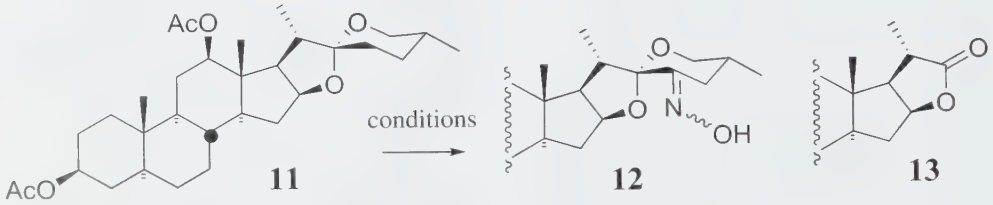


Table 1. Optimization of α-oximinylation.



Entry	Lewis acid (equiv.)	*t*-$BuNO_2$ (equiv.)	Solvent	*T* (°C)	Time (h)	Yields of **12** and **13** (%)
1	$BF_3{\cdot}OEt_2$ (1)	3	CH_2Cl_2	25	3	45, 31
2	$BF_3{\cdot}OEt_2$ (1)	3	CH_2Cl_2	0	3	NR
3	$BF_3{\cdot}OEt_2$ (1)	3	Toluene	25	3	40, 23
4	$BF_3{\cdot}OEt_2$ (1)	3	MeCN	25	3	35, 48
5	$BF_3{\cdot}OEt_2$ (1)	3	AcOH	25	0.5	62, 17
6	—	3	AcOH	25	1	NR
7	$BF_3{\cdot}OEt_2$ (2)	2	AcOH	25	1	37, 45
8	$BF_3{\cdot}OEt_2$ (0.5)	3	AcOH	25	1	32, 52
9	$BF_3{\cdot}OEt_2$ (0.5)	5	AcOH	25	0.2	92, 0
10	$BF_3{\cdot}OEt_2$ (0.5)	5	AcOH	25	2	50, 36
11	$BF_3{\cdot}OEt_2$ (0.2)	5	AcOH	25	2	41, 44
12	$NOBF_4$ (3)		AcOH	25	0.2	82, 0

Note: NR = No reation.

oxime spiroketal **12** in 82% yield after 10 min, thus exhibiting similar reactivity and product distribution pattern to that observed in the reaction of spiroketal **11** with $BF_3{\cdot}Et_2$ and *t*-BuONO (Table 1, entry 16). The Lewis acid promoted second-order Beckmann fragmentation (27) of α-oxygenated oxime spiroketal **12** appears to account for the formation of lactone **13**. The scope and limitation of the oximinylation of steroid spiroketals was then explored.[6] The results in Table 2 reveal some interesting features. First, C23 oximinylation works for only 5/6 spiroketals, not for 5/5 and 6/5 spiro systems, such as **21** and **22**. Hecogenin acetate (starting material for **15**) containing a C12 ketone, which is diffi-

[6] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5081. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Scheme 3.

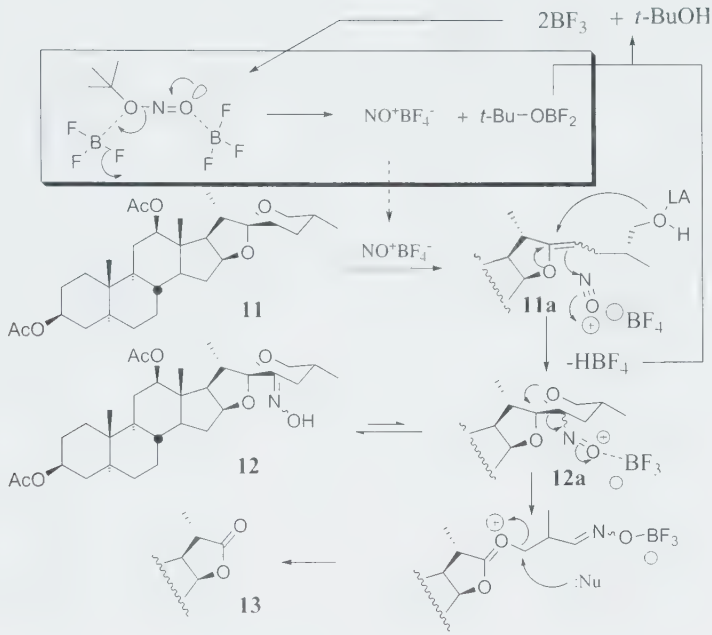
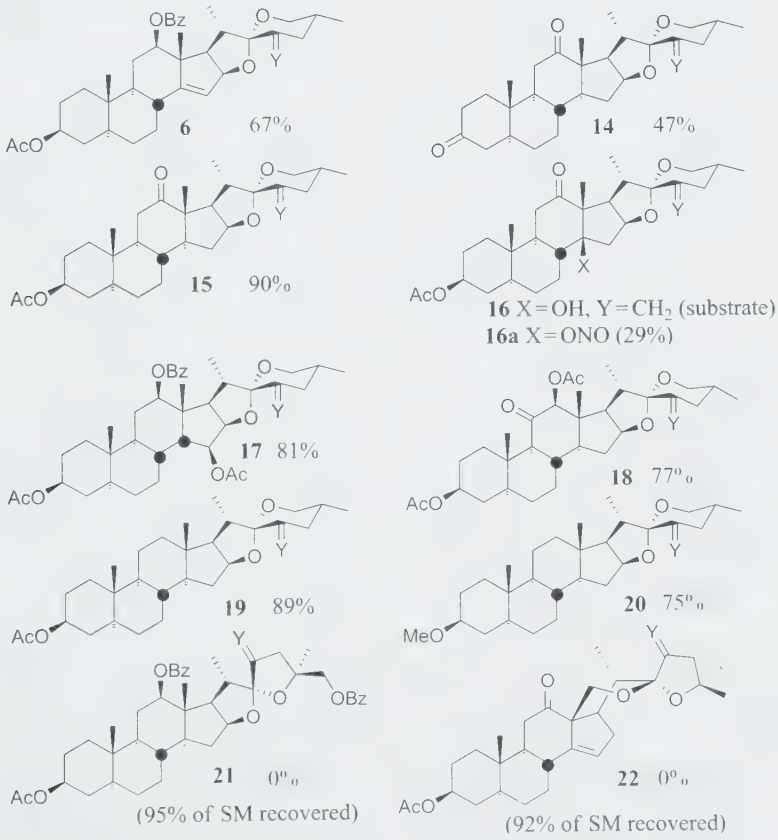
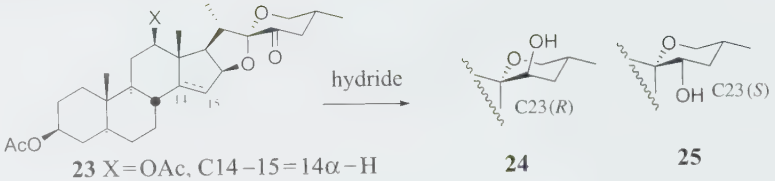


Table 2. α-Oximinylation of steroid spiroketals.



Note: isolated yields. Y = H_2 (substrates) or Y = NOH (products).

Table 3. Reduction of the C23 ketone.



23 X=OAc, C14–15=14α–H **24** **25**

7 X=OBz, C14–15=Δ^{14} **2** **26**

Entry	Substrate	Hydride	Conditions	Products	Yield (%)	C23 (*R*):C23 (*S*)
1	23	$LiAl(OtBu)_3H$	0 °C, THF	**24**, **25**	93	1:20
2	23	$NaBH_4$	25 °C, MeOH	**24**, **25**	97	1:19
3	23	(*R*)-CBS/BH_3	25 °C, THF	**24**, **25**	85	1:11
4	23	$CeCl_3/NABH_4$	–78 °C, 2 h	**24**, **25**	94	1:4.2
5	23	LS-Selectride®	–78 °C, THF	**24**, **25**	81	1:1.4
6	23	L-Selectride®	–78 °C, THF	**24**, **25**	89	2.5:1
7	23	K-Selectride®	–78 °C, THF	**24**, **25**	83	4.6:1
8	23	(*S*)-CBS/BH_3	25 °C, 0.5 h, THF	**24**, **25**	91	6.2:1
9	7	L-Selectride®	–78 °C, 3 h, THF	**2**, **26**	87	10.3:1
10	7	(*S*)-CBS/BH_3	25 °C, 0.5 h, THF	**2**, **26**	92	7.3:1
11	7	L-Selectride®	–78 °C, 3 h, PhMe	**2**, **26**	85	5.5:1

cult to enolize, smoothly gave oxime spiroketal **15**. The presence of more readily enolized C3 ketone resulted in low yield of **14** because of the formation of by-products. It is notable that olefin moieties (**6** and **22**) are intact under the reaction conditions. Alcohol functionality was converted to nitrite **16a**. Most importantly, employing the new protocol, we were able to obtain a key intermediate (5/6 spiroketal **6**) in reasonable yield.

C23 ketones **23** and **7** were readily prepared by *p*-toluenesulfonic acid catalyzed deoximinylation. We next turned our attention to establishing the requisite C23 (*R*) stereochemistry (Table 3). In the case of C14,C15-saturated C23 ketone **23**, (*S*)-CBS best effected the desired reduction to afford C23 (*R*) and C23 (*S*) in a reproducible ratio of 6.2:1[7] (Table 3, entry 8, C23 (*R*) (78%) and C23 (*S*) (13%), isolated yield, 50 mmol scale; previous results (28) show formation of C23 (*R*) and C23 (*S*) in a ratio of 1.7:1 (72%)). We were pleased that the L-Selectride® reduction of C14,C15-unsaturated ketone **7** (Table 3, entry 9) delivered C23 axial alcohol **2** in a highly stereoselective fashion.

In conclusion, an efficient and economical in situ method to generate nitrosonium fluoroborate is presented. This chemistry provides a large-scale pathway for the establishment of the C23 (*R*) stereochemistry of steroidal sapogenins. Further research is ongoing regarding the application of this method for the synthesis of the north unit of cephalostatin **1**.

Acknowledgments

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[7] Preincubation (~30 min) of (*S*)-CBS and BH_3 Me_2 in THF before the addition of **23** is critical to obtain good stereoselectivity.

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Preparation of enantiopure long chain *threo*-2-amino-3-hydroxyesters via chiral morpholinone-derived azomethine ylids[1]

Victoria A. Brome, Laurence M. Harwood, and Helen M.I. Osborn

Abstract:

Résumé :

Introduction

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This article is part of a Special Issue dedicated to Dr. Arthur Birch.

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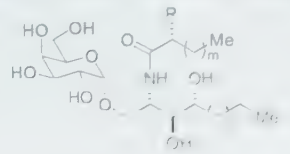
Fig. 1. Representative structure for a galactosylsphingolipid.



Scheme 1. Reagents and conditions: *(i)* RCHO (excess), reflux; *(ii)* 1 mol/L HCl, MeOH, reflux; *(iii)* H_2 (5 atm), $Pd(OH)_2/C$, TFA (1 equiv.), aq. MeOH; *(iv)* basic ion-exchange resin

R = H (**3a**)
R = Phenyl, (**3b**)
R = *p*-OMe Phenyl, (**3c**)
R = Furyl, (**3d**)
R = Propyl, (**3e**)
R = Butyl, (**3f**)
R = Cyclohexyl, (**3g**)

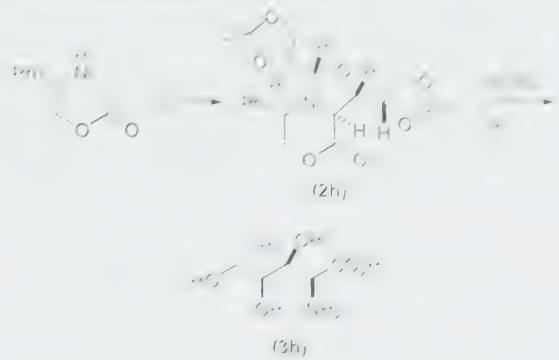
R = H, (**2a**)
R = Phenyl, (**2b**)
R = *p*-OMe Phenyl, (**2c**)
R = Furyl, (**2d**)
R = Propyl, (**2e**)
R = Butyl, (**2f**)
R = Cyclohexyl, (**2g**)

amino acids (**3b–3g**) (Scheme 1) in good yields (11). The value of this route was subsequently illustrated by a concise synthesis of (+)-polyoxamic acid (**3h**) (Scheme 2) (12).

Results and discussion

To extend this methodology to allow preparation of long chain hydroxyamino acids, which could act as precursors to sphingosine analogues, preliminary investigations focused on hexadecanal as a representative substrate, in terms of alkyl chain length. Following our previous protocol, 3 equiv. of the aldehyde were added to (5*R*)-5-phenylmorpholin-2-one ((*R*)-(**1**)) (i.e., 6 mmol aldehyde : 1 mmol (*R*)-(**1**)) in toluene and the mixture was heated to reflux for 48 h, after which time, TLC analysis indicated that all of the morpholinone had been consumed. As the hexadecanal proved to be far less polar than previous aldehydes employed in this reaction, the eluent chosen for chromatographic purification had to reflect this; a system of 19:1 petroleum – diethyl ether proving the most efficient. Unfortunately, only low yields (18%) of pure cycloadduct (**4a**) were isolated under these conditions, with much of the remaining product being contaminated with residual hexadecanal. NOE investigations of cycloadduct **4a** failed to determine conclusively the stereochemistry of the adduct, the very large signal representing the aliphatic protons masking important regions in the ^{1}H NMR spectrum. Additionally, the pure product was isolated as a waxy solid, which was unsuitable for X-ray analysis. However, as ^{1}H

Scheme 2. Reagents and conditions: *(i)* [illegible] glyceraldehyde acetonide, 55% [illegible] *(iii)* H_2 (5 atm), $Pd(OH)_2/C$, TFA (1 equiv.), aq. MeOH [illegible] basic ion-exchange resin, 65% [illegible]



(2h)

(3h)

Scheme 3. R[illegible]

R-(1) R = $C_{15}H_{31}$- (4a)

Table 1. [illegible]

[illegible]	Reaction time	Isolated yield of **4a**
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]

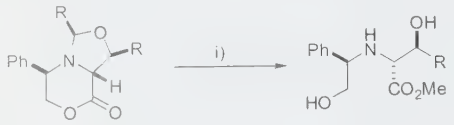
NMR data were in agreement with those of cycloadducts **2e–2f**, derived from lower homologue [illegible] (12), the hexadecanal-derived cycloadduct was tentatively assigned as **4a** (Scheme 2). It was clear that an excess of aldehyde in the cycloaddition reaction was not only required but was also hampering isolation and purification of the desired product. The reaction conditions were therefore examined with the objective of achieving higher yields of the pure hexadecanal-derived cycloadduct. The effect of the number of equivalents of [illegible] phenylmorpholin-2-one was reduced from 10 to 1.5, the rationale being that reduced chromatographic contamination of the crude product could simplify isolation of the cycloadduct. TLC analysis of the reaction mixture after 72 h indicated that the starting material had been almost completely consumed and the crude reaction mixture [illegible] resulting in the isolation of [illegible] pure cycloadduct. Further reduction to 1.1 equiv. of aldehyde required a reaction time of 5 days before all starting morpholinone had been consumed, but this resulted in a greatly improved yield of 65% of pure cycloadduct (**4a**) after a single purification (Table 1).

Thus, although reducing the number of equivalents of aldehyde in the reaction mixture necessitated an increase in

Table 2. Optimized yields of the cycloadducts of (**4b**–**4e**).

Aldehyde	Yield of (**cycloadduct**) (%)
Tetradecanal	58 (**4b**)
Pentadecanal	68 (**4c**)
Heptadecanal	56 (**4d**)
Octadecanal	62 (**4e**)

Scheme 4. Reagents and conditions: (*i*) MeOH, 5 mol/L HCl, reflux 1 h



R = $C_{15}H_{31}$ (**4a**)
R = $C_{13}H_{27}$ (**4b**)
R = $C_{14}H_{29}$ (**4c**)
R = $C_{16}H_{33}$ (**4d**)
R = $C_{17}H_{35}$ (**4e**)

R = $C_{15}H_{31}$ (**5a**)
R = $C_{13}H_{27}$ (**5b**)
R = $C_{14}H_{29}$ (**5c**)
R = $C_{16}H_{33}$ (**5d**)
R = $C_{17}H_{35}$ (**5e**)

reaction time, it resulted in a greater than three-fold increase in yield and involved less wastage of aldehyde.

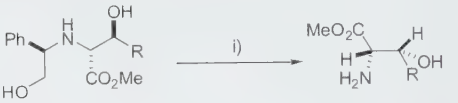
With the procedure for preparing the hexadecanal-derived cycloadduct optimized, a range of analogues derived from aldehydes with chain lengths between 14 and 18 carbon atoms was synthesized, utilizing 1.1 equiv. of aldehyde. In each case a single cycloadduct (**4b**–**4e**) was isolated in an acceptable yield after purification by column chromatography (Table 2).

The subsequent step of the synthesis was the opening of the cycloadduct to afford the corresponding amino esters (**5a**–**5e**). The two-step hydrolysis and hydrogenolysis sequence, previously shown to be the optimal procedure for aliphatic aldehyde-derived cycloadducts, was adopted. Previously, the hydrolysis had been carried out in methanol at reflux using 1 mol/L hydrochloric acid to release the amino ester, but when applied to the hexadecanal-derived cycloadduct (**4a**), the conditions failed to effect hydrolysis, leaving the starting material intact. It was observed that the starting material was only sparingly soluble in aqueous methanol at room temperature but was more soluble in hot methanol. Thus, the effect of the addition of 5 mol/L hydrochloric acid to a hot methanolic solution of the cycloadduct was investigated, and this furnished the corresponding methyl ester in 1 h. In the first instance, the lactone-opened products **5a**–**5e** were isolated for characterization purposes and were obtained in moderate to good yield (Scheme 4, Table 3). These derivatives were solids, as opposed to the oils obtained when using the lower homologue aldehydes. The proposed structure for the hexadecanal-derived methyl ester **5a**, (a representative example) was supported by characteristic ^{1}H NMR data, which displayed a multiplet at 7.30 ppm representing the five aromatic protons; a one proton doublet at 3.17 ppm corresponding to the proton α to the amino group and a one proton multiplet at 3.75–3.68 ppm for the methane proton α to the hydroxyl functionality. A set of overlapping multiplets, integrating to 30 protons, due to the aliphatic hydrogens of the long alkyl chain, dominated the spectrum.

Table 3. Methanolysis of the cyloadducts (**4a**–**4e**)

Cycloadduct	Yield of (**methyl ester**) %
4a	81 (**5a**)
4b	79 (**5b**)
4c	82 (**5c**)
4d	68 (**5d**)
4e	56 (**5e**)

Scheme 5. Reagents and conditions: (*i*) H_2 (5 atm), Pearlman's catalyst, TFA, MeOH (aq), 48 h.



R = $C_{15}H_{31}$ (**5a**)
R = $C_{13}H_{27}$ (**5b**)
R = $C_{14}H_{29}$ (**5c**)
R = $C_{16}H_{33}$ (**5d**)
R = $C_{17}H_{35}$ (**5e**)

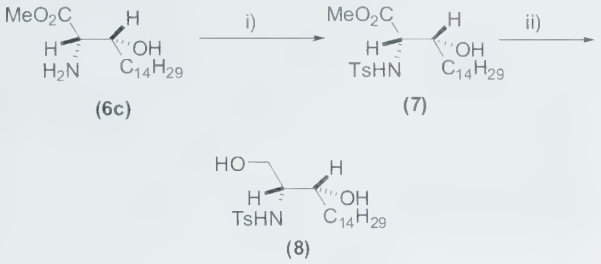
R = $C_{15}H_{31}$ (**6a**)
R = $C_{13}H_{27}$ (**6b**)
R = $C_{14}H_{29}$ (**6c**)
R = $C_{16}H_{33}$ (**6d**)
R = $C_{17}H_{35}$ (**6e**)

Table 4. Hydrogenolysis of the methyl esters (**5a**–**5e**).

Methyl ester precursor (**5**)	Yield of (**hydroxyamino ester**) (**6**) %
5a	53 (**6a**)
5b	60 (**6b**)
5c	54 (**6c**)
5d	66 (**6d**)
5e	69 (**6e**)

Following the previously developed reaction protocol (11*b*), it was envisaged that the crude hydrolysis reaction mixture would be concentrated and subjected directly to hydrogenolysis at 5 bar (1 bar = 100 kPa) using Pearlman's catalyst and TFA in methanol. The first complication encountered was the insolubility of the crude reaction mixture in methanol. Therefore, to aid solubility, a 10:1 ratio of methanol to ethyl acetate was used. Continuing with the standardized conditions, the amino ester was subjected to hydrogenolysis, but after 48 h there was no evidence of reaction. Gratifyingly, when the hydrolysis products (**5a**–**5e**) were purified by column chromatography prior to hydrogenation, the reactions proceeded efficiently. Presumably, components of the crude reaction mixtures were poisoning the catalyst. A further deviation from the original method when applied to the longer aliphatic chain analogues was the final purification procedure. The original method (11*b*) used ion exchange chromatography to afford the free amino acids as colourless solids in near quantitative yields, but the hexadecanal analogue could not be treated in the same way, as the hydrogenolysis product was insoluble in water, and so more conventional silica gel chromatography was implemented. As a result, the final product was isolated as the methyl ester **6a** (Scheme 5), as opposed to the free β-hydroxy-α-amino acid. In this way, all the long chain hydroxyamino esters (**6a**–**6e**) could be isolated in pure form and in acceptable yields (Table 4). In all cases, detailed

Scheme 6. Reagents and conditions: (*i*) *p*-TsCl, imidazole, DMAP, DCM, 43%; (*ii*) $LiBH_4$, THF, rt, 74%.



spectroscopic analysis showed these final products to be homogeneous with a resonance for the proton α- to the amino group, appearing as a doublet between 3.52 and 3.45 ppm, corresponding to the equivalent proton in the pentanal-derived material (3.45 ppm).

In a further illustrative extension of how these long chain hydroxyamino esters could be converted into *N*-protected sphingosine analogues, **6c** was *N*-tosylated to yield **7** in 43% isolated yield, and this was subsequently reduced to diol **8** in 74% yield using lithium borohydride in THF (Scheme 6).

Conclusions

In conclusion, we have developed protocols in which long chain aliphatic aldehydes will undergo 1,3-dipolar cycloadditions with (5*R*)-5-phenyl-morpholin-2-one to furnish cycloadducts containing three newly defined stereocentres in good yield. Degradation of these cycloadducts affords diastereomerically and enantiomerically pure β-substituted-α-amino acid derivatives, and further modification can furnish sphingosine analogues suitable for coupling to appropriate carbohydrate donors.

Experimental section

General techniques

^{1}H NMR spectra were recorded on either a Bruker AMX 400 NMR (400 MHz) or a Bruker DPX 250 (250 MHz) spectrometer in chloroform-*d* or dimethyl sulfoxide-*d* and referenced to the residual solvent residual proton. Signal positions were recorded in δ ppm with the abbreviations s, d, t, q, quint., br, and m denoting singlet, doublet, triplet, quartet, quintet, broad, and multiplet, respectively. ^{13}C NMR spectra were recorded on the same spectrometers listed above at either 100 or 62.5 MHz, respectively, and were referenced to chloroform-*d* or dimethyl sulfoxide-*d*. All NMR chemical shifts are quoted in ppm.

Infrared spectra were recorded on a PerkinElmer 1720-X. Spectra were analysed as either thin films between sodium chloride plates or as potassium bromide disks.

Mass spectra (*m/z*) and accurate mass (HR-MS) were recorded under conditions of electron impact (EI) or chemical ionization using ammonia as the ionizing source (CI). The instrument used was a Fisons VG Autospec mass spectrometer.

Specific rotations ($[\alpha]^{20}_D$) were recorded using the sodium D line (589.3 nm) in the appropriate solvent and are quoted in 10^{-1} deg cm^2 g^{-1}. Solution conentrations are given in the units g 100 mL^{-1}. Readings were measured using a PerkinElmer 341 polarimeter.

Melting points were obtained using a Reichert Kofler heated-stage microscope and are uncorrected. Flash column chromatography was performed according to the method of Still (13) with silica gel 60 (Merck 9385) using head pressure by the means of hand bellows. TLC analyses were carried out using 0.25 mm silica gel precoated aluminium or glass-backed plates with fluorescent indicator UV_{254}. Spots were visualized either by the quenching of UV fluorescence or by staining with an acidic ammonium heptamolydate solution.

Reagents obtained from Acros Organics (Loughborough, UK), Aldrich (Gillingham, UK), Avocado (Heysham, UK), Fluka (Gillingham, UK), and Lancaster fine chemicals (Morecombe, UK) suppliers were used directly as supplied or following purification according to standard procedures. Acetonitrile and dichloromethane were dried by distillation from calcium hydride under nitrogen. Tetrahydrofuran was dried by distillation from sodium-benzophenone ketyl under nitrogen. Petrol refers to light petroleum ether in the boiling point range 30–40 °C, which was fractionally distilled through a Vigreux column prior to use. (5*R*)-5-Phenylmorpholin-2-one was synthesized according to the literature procedure (9). The long chain aldehydes were obtained in quantitative yield from the corresponding commercially available alcohols by oxidation using 4-methylmorpholine-*N*-oxide (1.5 equiv.) and tetra-*n*-propylammonium perruthenate (5 mol%) in dichlorormethane at room temperature in the presence of 4A molecular sieves (14).

General method for preparation of cycloadducts (4a–4e)

The requisite aldehyde (2.2 mmol, 1.1 equiv.) was added to a solution of (5*R*)-5-phenylmorpholin-2-one ((*R*)-(**1**), 1.0 mmol, 1 equiv.) in anhydrous toluene (40 cm^3). The flask was fitted with a magnetic stir.bar, a Soxhlet extractor containing 4A molecular sieves, and a condenser. The reaction mixture was heated to reflux under nitrogen for 5 d. The solvent was removed in *vacuo*, and the resulting pale yellow oil was subjected to column chromatography (diethyl ether – petroleum ether, 1:19) to yield the corresponding cycloadduct.

(2R,6R,7S,9R)-2-Phenyl-7,9-dipentadecyl-1-aza-4,8-dioxabicyclo[4.3.0^{1,6}]nonan-5-one (4a)

Yield 65%; colourless needles; mp 53 to 54 °C. $[\alpha]^{20}_D$ – 4.8 (*c* 1.0, $CHCl_3$). IR (KBr disc, cm^{-1}) ν_{max}: 2920, 1730 (lactone C=O). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.94 (6H, t, J = 6.5, alkyl CH_3), 1.00–1.20 (60H, m, alkyl CH_2), 3.73 (1H, d, J = 8.2, H-6), 3.84 (1H, dd, J = 3.6, J' = 10.5, H-3_{eq}), 4.10 (1H, dt, J = 3.3, J' = 9.6, H-7), 4.18 (1H, dd, J = 3.5, J' = 10.3, H-2), 4.23 (1H, t, J = 10.3, J' = 10.5, H-3_{ax}), 4.32–4.26 (1H, m, H-9), 7.37–7.33 (5H, m, Ph-H). ^{13}C NMR (60 MHz, $CDCl_3$) δ: 14.5 (alkyl CH_3), 23.1, 24.8, 26.6, 29.6, 29.7, 29.8, 29.9, 30.1, 32.3, 35.3, 35.9 (alkyl CH_2), 60.1 (C-3), 63.7 (C-6), 72.9 (C-2), 79.2 (C-7), 97.3 (C-9), 128.5, 129.1, 129.2, 137.4 (Ar–*C*), 169.8 (C=O). CI-MS *m/z* (%): 640 ([M + NH_4]$^+$, 8), 400 (74), 252 (39), 216 (70), 104 (100). HR-MS calcd. for $C_{42}H_{77}O_3N_2$ ([M + NH_4]$^+$): 640.5669; found: 640.5665.

(2*R*,4*R*,5*S*,6*R*)-2-Phenyl-7-thiabicyclo[4.1.0]heptane-4,5-diyl diacetate (3*R*,4*S*)-3-acetoxy-5-oxo-4-phenylpentyl ester (4a)

[illegible] IR (KBr) [illegible] cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ [illegible] (m, Ph–H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ [illegible] (CH$_3$), [illegible] (CH$_2$), [illegible] (CH), [illegible] (Ph–H), [illegible] (C=O); CI-MS *m/z* (rel. int.) [illegible] (M^+ + 1, 100), [illegible] (20); HR-MS calcd. for $C_{26}H_{28}O_6S$ [illegible], found: [illegible].

(2*R*,4*R*,5*S*,6*R*)-2-Phenyl-7-thiabicyclo[4.1.0]heptane-4,5-diyl diacetate (3*R*,4*S*)-3-acetoxy-5-oxo-4-phenylhexyl ester (4b)

[illegible] IR (KBr) [illegible] cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ [illegible] (m, Ph–H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ [illegible] (CH$_3$), [illegible] (CH$_2$), [illegible] (CH), [illegible] (Ph–H), [illegible] (C=O); CI-MS *m/z* (rel. int.) [illegible] (M^+ + 1, 100), [illegible] (20); HR-MS calcd. for $C_{27}H_{30}O_6S$ [illegible], found: [illegible].

(2*R*,4*R*,5*S*,6*R*)-2-Phenyl-7-thiabicyclo[4.1.0]heptane-4,5-diyl diacetate (3*R*,4*S*)-3-acetoxy-5-oxo-4-phenylheptyl ester (4c)

[illegible] IR (KBr) [illegible] cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ [illegible] (m, Ph–H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ [illegible] (CH$_3$), [illegible] (CH$_2$), [illegible] (CH), [illegible] (Ph–H), [illegible] (C=O); CI-MS *m/z* (rel. int.) [illegible] (M^+ + 1, 100), [illegible] (20); HR-MS calcd. for $C_{28}H_{32}O_6S$ [illegible], found: [illegible].

(2*R*,4*R*,5*S*,6*R*)-2-Phenyl-7-thiabicyclo[4.1.0]heptane-4,5-diyl diacetate (3*R*,4*S*)-3-acetoxy-5-oxo-4-phenylnonyl ester (4d)

[illegible] IR (KBr) [illegible] cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ [illegible] (m, Ph–H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ [illegible] (CH$_3$), [illegible] (CH$_2$), [illegible] (CH), [illegible] (Ph–H), [illegible] (C=O); CI-MS *m/z* (rel. int.) [illegible] (M^+ + 1, 100), [illegible] (20); HR-MS calcd. for $C_{30}H_{36}O_6S$ [illegible], found: [illegible].

General procedure for the preparation of amino esters (5a–5e)

Cycloadduct **4** (100 mg) was dissolved in methanol (1 cm^3) and 5 mL of hydrochloric acid (1 cm^3) was added. The reaction mixture was heated to reflux and left at this under nitrogen for 2 h. Saturated sodium carbonate solution (5 cm^3) was added and the aqueous layer separated and extracted with ethyl acetate (3 × 5 cm^3). The organic phases were combined, washed with brine, dried ($MgSO_4$), filtered and the excess solvent removed in vacuo to give a yellow oil which was subjected to column chromatography (silica gel – diethyl ether) to afford the corresponding amino ester.

Methyl (2*R*,3*S*,3′*R*)-2*N*-2-hydroxy-3-phenylethylamino-3-hydroxy-3-phenylpropionate (5a)

Yield 85%, colourless solid, mp 61 to 62 °C; $[\alpha]_D^{20}$ −26.5 (c 1.0, MeOH); IR (KBr) [illegible] cm^{-1}; 3336 (O–H, N–H), 2926 (Ar–H), 2850 (C–H), 1740 (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ [illegible] (m, Ar–H), [illegible] (m, CH$_2$), [illegible] (m, CH$_2$), 2.90 (2H, m, NH and OH), 3.17 (1H, d, J = 5.3 Hz, CHCO$_2$CH$_3$), 3.45 (3H, s, CO$_2$CH$_3$), 3.60–3.84 (3H, m, CH–OH and PhCH$_2$), 3.75–3.88 (1H, m, CHOH), 7.17–7.29 (5H, m, Ph–H); ^{13}C NMR (62 MHz, $CDCl_3$) δ [illegible] (CH$_2$), 24.2, 27.1, 30.4, 31.1, 31.2, 33.5, 35.2, 35.2 (CH$_2$), 52.5 (CO$_2$CH$_3$), 67.2, 67.3 (CHCO$_2$CH$_3$ and CHOH), [illegible] (CH), 72.0 (Ph–CH$_2$), 126.1, 129.4, 129.8, 142.2 (Ar–C), 174.1 (C=O); CI-MS *m/z* (rel. int.) 450 (M^+ + 1, 20), 179 (100); HR-MS calcd. for $C_{27}H_{32}O_6N$ (M^+ + 1) 450.2230, found: 450.2240.

Methyl (2*R*,3*S*,3′*R*)-2*N*-2-hydroxy-3-phenylpropylamino-3-hydroxy-3-phenylpropionate (5b)

Yield 82%, colourless solid, mp 52 to 53 °C; $[\alpha]_D^{20}$ −24.5 (c 1.0, MeOH); IR (KBr) [illegible] cm^{-1}; 3336 (O–H, N–H), 2926 (Ar–H), 2850 (C–H), 1740 (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ [illegible] (m, Ar–H), [illegible] (m, CH$_2$), [illegible] (m, CH$_2$), 2.90 (2H, m, NH and OH), 3.17 (1H, d, J = 5.3 Hz, CHCO$_2$CH$_3$), 3.45 (3H, s, CO$_2$CH$_3$), 3.60–3.84 (3H, m, CH–OH and PhCH$_2$), 3.75–3.88 (1H, m, CHOH), 7.17–7.29 (5H, m, Ph–H); ^{13}C NMR (62 MHz, $CDCl_3$) δ [illegible] (CH$_2$), 24.2, 27.1, 30.4, 31.1, 31.2, 33.5, 35.2, 35.2 (CH$_2$), 52.5 (CO$_2$CH$_3$), 67.2, 67.3 (CHCO$_2$CH$_3$ and CHOH), [illegible] (CH), 72.0 (Ph–CH$_2$), 126.1, 129.4, 129.8, 142.2 (Ar–C), 174.1 (C=O); CI-MS *m/z* (rel. int.) 450 (M^+ + 1, 20), 179 (100); HR-MS calcd. for $C_{27}H_{32}O_6N$ (M^+ + 1) 450.2230, found: 450.2240.

Methyl (2*R*,3*S*,3′*R*)-2*N*-2-hydroxy-3-phenylpentylamino-3-hydroxy-3-phenylpropionate (5c)

Yield 82%, colourless solid, mp 56 to 57.5 °C; $[\alpha]_D^{20}$ −23.6 (c 1.0, MeOH); IR (KBr) [illegible] cm^{-1}; 3336 (O–H,

3025 (Ar–H), 2870 (C–H), 1735 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.86 (3H, t, J = 7.0, CH_2CH_3), 1.25 1.41 (6H, m, alkyl CH_2), 3.12 (1H, d, J = 6.0, $CHCO_2CH_3$), 3.29 (3H, s, CO_2CH_3), 3.51–3.69 (4H, m, CH_2OH, PhC*H*, C*H*OH), 7.13–7.39 (5H, m, Ph–H). ^{13}C NMR (60 MHz, $CDCl_3$) δ: 14.8 (alkyl CH_3), 24.0, 29.4, 34.9 (alkyl CH_2), 52.5 (CO_2CH_3), 67.3, 67.4 (*C*HCO$_2$CH$_3$ and *C*HOH), 68.1 (*C*H$_2$OH), 73.9 (PhCH), 129.1, 129.4, 129.8, 142.2 (Ar–C), 176.1 (C=O). CI-MS *m/z* (%): 296 ([MH]$^+$, 75), 264 (47), 210 (38), 178 (100), 118 (35). HR-MS calcd. for $C_{16}H_{26}O_4N$ ([MH]$^+$): 296.1862; found: 296.1864.

Methyl (2R,3S,1′R)-(2N-2′-hydroxy-1′-phenylethylamino)-3-hydroxynonadecanoate (5d)

Yield 68%; colourless solid; mp 64–65.5 °C. $[\alpha]^{20}_D$ –21.7 (*c* 1.0, $CHCl_3$). IR (KBr disc, cm^{-1}) ν_{max}: 3351 (O–H), 2920 (Ar–H), 2855 (C–H), 1740 (C=O). ^{1}H NMR (250 MHz, MeOD) δ: 0.80 (3H, t, J = 6.2 alkyl CH_3), 1.36–1.19 (28H, m, alkyl CH_2), 3.07 (1H, d, J = 5.9, $CHCO_2CH_3$), 3.25 (3H, s, CO_2CH_3), 3.48–3.51 (3H, m, CH_2OH and PhC*H*), 3.56–3.64 (1H, m, C*H*OH), 7.12–7.20 (5H, m, Ph-H). ^{13}C NMR (60 MHz, MeOD) δ: 14.9 (alkyl *C*H$_3$), 24.2, 27.1, 30.9, 31.0, 31.1, 31.2, 33.5, 35.2 (alkyl *C*H$_2$), 52.5 (CO_2CH_3), 67.2, 67.3 (*C*HCO$_2$CH$_3$ and *C*HOH), 68.1 (*C*H$_2$OH), 74.0 (PhCH), 129.1, 129.4, 129.8, 142.4 (Ar–C), 176.1 (C=O). CI-MS *m/z* (%): 446 ([MH]$^+$-H$_2$O, 9), 414 (19), 210 (10), 178 (100), 118 (15). HR-MS calcd. for $C_{28}H_{49}O_3N$ ([MH]$^+$-H$_2$O): 446.3634; found: 446.3448.

Methyl (2R,3S,1′R)-(2N-2′-hydroxy-1′-phenylethylamino)-3-hydroxyicosanoate (5e)

Yield 56%; colourless solid; mp 59–61 °C. $[\alpha]^{20}_D$ –23.8 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3315 (O-H), 2920 (Ar–H), 2850 (C–H), 1740 (C=O). ^{1}H NMR (250 MHz, MeOD) δ: 0.80 (3H, t, J = 6.2, alkyl CH_3), 1.19–1.36 (30H, m, alkyl CH_2), 3.07 (1H, d, J = 5.9, $CHCO_2CH_3$), 3.26 (3H, s, CO_2CH_3), 3.48–3.51 (3H, m, CH_2OH and PhC*H*), 3.56–3.62 (1H, m, C*H*OH), 7.13–7.20 (5H, m, Ph-H). ^{13}C NMR (60 MHz, MeOD) δ: 14.9 (alkyl *C*H$_3$), 24.2, 27.1, 30.9, 31.0, 31.1, 31.2, 33.5, 35.2 (alkyl *C*H$_2$), 52.5 (CO_2CH_3), 67.2, 67.3 (*C*HCO$_2$CH$_3$ and *C*HOH), 68.1 (*C*H$_2$OH), 74.0 (PhCH), 129.1, 129.4, 129.8, 142.4 (Ar–C), 176.1 (C=O). CI-MS *m/z* (%): 460 ([MH]$^+$-H$_2$O, 12), 428 (76), 268 (16), 216 (25), 178 (100), 104 (37). HR-MS calcd. for $C_{29}H_{50}O_3N$ ([MH]$^+$-H$_2$O): 460.3790; found: 460.3799.

General method for the preparation of long chain amino acid methyl esters (6a–6e)

Amino ester (1 equiv.) was dissolved in methanol, and water (10:1) and Pearlman's catalyst were added (weight for weight of amino ester) followed by the addition of trifluoroacetic acid (1 equiv.). The system was degassed and hydrogen introduced. The system was once again degassed and hydrogen re-introduced. The reaction mixture was warmed to 50 °C and left to stir for 16 h. The hydrogen was released, and the reaction mixture filtered through Celite® and the filtrate concentrated in *vacuo*. The residue was subjected to column chromatography (eluent petrol – diethyl ether, 1:1, then 10% methanol) to afford the amino acid methyl ester.

Methyl (2R,3S)-2-amino-3-hydroxyoctadecanoate (6a)

Yield 53%; colourless solid; mp 74–76.5 °C. $[\alpha]^{20}_D$ –10.5 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3355 (N–H), 3130 (O–H), 2915, 2840 (C–H), 1720 (C=O). ^{1}H NMR (250 MHz, D_6 acetone) δ: 0.82 (3H, t, J = 6.4 alkyl CH_3), 1.19–1.38 (28H, m, alkyl CH_2), 3.45 (1H, d, J = *CH*NH$_2$), 3.53 (3H, s, $COOCH_3$), 3.62–3.74 (1H, m, C*H*OH). ^{13}C NMR (60 MHz, D_6 acetone) δ: 14.8 (alkyl CH_3), 23.7, 27.3, 29.3, 33.0, 36.2 (alkyl CH_2), 52.9 ($COOCH_3$), 66.2 (*C*HNH$_2$), 81.5 (*C*HOH), 173.7 (C=O).

Methyl (2R,3S)-2-amino-3-hydroxyhexadecanoate (6b)

Yield 60%; colourless solid; mp 61–63 °C. $[\alpha]^{20}_D$ –14.3 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3345 (O–H), 2920, 2850 (C–H), 1680 (C=O). ^{13}C NMR (250 MHz, D_6 acetone) δ: 0.75 (3H, t, J = 6.5, alkyl CH_3, 1.16–1.40 (24H, m, alkyl CH_2), 3.52 (1H, d, J = 7.7, $CHNH_2$), 3.60 (3H, s, CO_2CH_3), 3.64–3.72 (1H, m, C*H*OH). ^{13}C NMR (60 MHz, D_6 acetone) δ: 14.8 (alkyl CH_3), 23.7, 27.3, 29.3, 31.1, 33.0, 36.2 (alkyl *C*H$_2$),52.9 ($COOCH_3$), 66.1 (*C*HNH$_2$), 81.5 (*C*HOH), 173.5 (C=O). CI-MS *m/z* (%): 302 ([MH]$^+$, 89), 242 (10), 89 (100). HR-MS calcd. for $C_{17}H_{36}O_3N$ ([MH]$^+$): 302.2695; found: 302.2708.

Methyl (2R,3S)-2-amino-3-hydroxyheptadecanoate (6c)

Yield 54%; colourless solid; mp 75–77.5 °C. $[\alpha]^{20}_D$ –16.8 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3135 (O–H), 2915, 2845 (C–H), 1735 (C=O). ^{1}H NMR (250 MHz, D_6 acetone) δ: 0.75 (3H, t, J = 6.4, alkyl CH_3), 1.25–1.45 (26H, m, alkyl CH_2), 3.48 (1H, d, J = 7.7, $CHNH_2$), 3.57 (3H, s, $COOCH_3$), 3.59–3.70 (1H, m, C*H*OH). ^{13}C NMR (60 MHz, D_6 acetone) δ: 14.8 (alkyl *C*H$_3$), 23.7, 27.3, 28.2, 33.0, 36.3 (alkyl *C*H), 52.8 ($COOCH_3$), 66.4 (*C*HNH$_2$), 81.7 (*C*HOH), 173.6 (C=O). CI-MS *m/z* (%): 316 ([MH]$^+$, 100), 256 (10), 89 (50). HR-MS calcd. for $C_{18}H_{38}O_3N$ ([MH]$^+$): 316.2852; found: 316.2847.

Methyl (2R,3S)-2-amino-3-hydroxynonadecanoate (6d)

Yield 66%; colourless solid; mp 84–86.5 °C. $[\alpha]^{20}_D$ –6.1 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3130 (O–H), 1720 (C=O). ^{1}H NMR (250 MHz, acetone) δ: 0.75 (3H, t, J = 6.2, alkyl CH_3), 1.24–1.53 (30H, m, alkyl CH_2), 2.76 (3H, br s, NH_2 and O*H*), 3.47 (1H, d, J = 7.7, $CHNH_2$), 3.62 (3H, s, $COOCH_3$), 3.63–3.67 (1H, m, C*H*OH). ^{13}C NMR (60 MHz, D_6 acetone) δ: 14.7 (alkyl *C*H$_3$), 23.7, 27.3, 33.0, 36.3 (alkyl *C*H$_2$), 52.8 ($COOCH_3$), 66.3 (*C*HNH$_2$), 81.6 (*C*HOH), 173.6 (C=O). CI-MS *m/z* (%): 326 ([MH]$^+$-H$_2$O, 69), 266 (18), 115 (100), 82 (13), 56 (25). HR-MS calcd. for $C_{20}H_{39}O_2N$ ([MH]$^+$-H$_2$O): 326.3059; found: 326.3043.

Methyl (2R,3S)-2-amino-3-hydroxyicosanoate (6e)

Yield 69%; colourless solid; mp 86 to 87 °C. $[\alpha]^{20}_D$ –7.1 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3140 (O–H), 2915, 2845 (C–H), 1720 (C=O). ^{1}H NMR (250 MHz, D_6 acetone) δ: 0.75 (3H, t, J = 6.2, alkyl CH_3), 1.28–1.54 (32H, m, alkyl CH_2), 2.76 (3H, br s, NH_2 and O*H*), 3.47 (1H, d, J = 7.7, $CHNH_2$), 3.59 (3H, s, $COOCH_3$), 3.62–3.65 (1H, m, C*H*OH). ^{13}C NMR (60 MHz, D_6 acetone) δ: 14.8 (alkyl *C*H$_3$), 23.7, 27.3, 33.0, 36.3 (alkyl *C*H$_2$), 52.8 ($COOCH_3$), 66.3 (*C*HNH$_2$), 81.6 (*C*HOH), 173.6 (C=O). CI-MS *m/z* (%): 358 ([MH]$^+$, 26), 90 (100). HR-MS calcd. for $C_{21}H_{44}NO_3$ ([MH]$^+$): 358.3321; found: 358.3313.

Methyl (2*R*,3*S*)-3-hydroxy-2-(toluenesulfonylamino)heptadecanoate (7)

Amino ester **6c** (74 mg, 0.0.23 mmol) was dissolved in anhydrous dichloromethane (5 cm^3), and freshly recrystallized *p*-toluenesulfonyl chloride (45 mg, 0.23 mmol, 1 equiv.) was added followed by dimethylaminopyridine (2 drops). The reaction mixture was left to stir under an atmosphere of nitrogen for 16 h. Water was added (5 cm^3), the organic layer was separated, and the aqueous phase extracted with dichloromethane (5 × 10 cm^3). The organic fractions were combined, dried ($MgSO_4$), filtered, and the solvent removed in *vacuo*. The residue was purified by column chromatography, eluting with dichloromethane–acetone (10:1), to afford the title compound as a colourless solid (47 mg, 43%), mp 85 to 86 °C. $[\alpha]^{20}_D$ –15.3 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3400 (O–H), 2910, 2840 (C–H), 1710 (C=O), 1165 (SO_2). ^1H NMR (250 MHz, $CDCl_3$) δ: 0.81 (3H, t, *J* = 6.4, alkyl CH_3), 1.19–1.47 (26H, m, alkyl CH_2), 2.22 (1H, br s, O–H), 2.34 (3H, s, Ph–CH_3), 3.45 (3H, s, $COOCH_3$), 3.80–3.85 (2H, m, C*H*OH, C*H*NHTs), 5.58 (1H, d, *J* = 9.6, N*H*PhCH$_3$), 7.21 (2H, d, *J* = 8.4, *m*-Ph–H), 7.65 (2H, d, *J* = 8.4, *o*-Ph–H). ^{13}C NMR (60 MHz, $CDCl_3$) δ: 14.5 (alkyl CH_3), 21.9 (Ph–CH_3), 23.1, 25.8, 29.8, 29.9, 30.0, 30.1, 30.1, 32.3, 34.0 (alkyl CH_2), 53.0 ($COOCH_3$), 59.9 (*C*HNHTs), 72.8 (*C*HOH), 127.6 (*m*-Ar–C), 129.9 (*o*-Ar–C), 137.3 (*p*-Ar–C), 144.0 (*i*-Ar–C), 171.5 (C=O).

(2*S*,3*R*)-2-(Toluenesulfonylamino)heptadecan-1,3-diol (8)

The *N*-protected amino ester **7** (49 mg, 0.098 mmol) was dissolved in anhydrous THF (5 cm^3), and lithium borohydride (2 mg, 0.36 mmol) was added. The reaction mixture was left to stir under nitrogen for 16 h. Water (5 cm^3) was added, the organic phase separated, and the aqueous phase extracted with ethyl acetate (5 × 5 cm^3). The organic fractions were combined, dried ($MgSO_4$), filtered, and the solvent removed in *vacuo*, to afford the title compound as a colourless solid (32 mg, 74%), mp 80 to 81 °C. $[\alpha]^{20}_D$ +10.6 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) ν_{max}: 3415 (O–H), 2910, 2840 (C–H), 1160 (SO_2). ^1H NMR (250 MHz, $CDCl_3$) δ: 0.81 (3H, t, *J* = 6.3, alkyl CH_3), 1.04–1.27 (26H, m, alkyl CH_2), 2.35 (3H, s, Ph–CH_3), 2.87 (1H, br s, O–H), 3.09–3.16 (1H, m, C*H*NHTs), 3.64 (2H, d, *J* = 3.7, CH_2OH), 3.71–3.79 (1H, m, C*H*OH), 5.57 (1H, d, *J* = 7.9, N*H*Ts), 7.22 (2H, d, *J* = 8.2, *m*-Ph–H), 7.71 (2H, d, *J* = 8.2, *o*-Ph–H). ^{13}C NMR (60 MHz, $CDCl_3$) δ: 13.1 (alkyl CH_3), 20.5 (Ph–CH_3), 21.7, 24.4, 28.4, 28.5, 28.7, 28.7, 30.9, 32.8 (alkyl CH_2), 55.7 (*C*HNHTs), 64.4 (CH_2OH), 72.2 (*C*HOH), 126.1 (*o*-Ph–H), 128.7 (*m*-Ph–H), 136.6 (*p*-Ph–H), 142.5 (*i*-Ph–H). CI-MS *m/z* (%): 442 ([MH]$^+$, 100), 410 (15), 213 (15), 91 (7), 60 (10). HR-MS calcd. for $C_{24}H_{44}O_4SN$ ([MH]$^+$): 442.2991; found: 442.2979.

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Intramolecular [4 + 3] cycloadditions — Stereochemical issues in the cycloaddition reactions of cyclopentenyl cations — A synthesis of (+)-dactylol[1]

Michael Harmata, Paitoon Rashatasakhon, and Charles L. Barnes

Abstract: Five cyclopentanones were prepared for the purpose of examining the effects of stereogenic centers on the course of the intramolecular [4 + 3] cycloaddition reactions of cyclopentenyl cations. One substrate reacted with very high levels of diastereoselectivity and was converted to (+)-dactylol. The cyclopentenone without stereogenic centers on the tether or the five-membered ring gave two cycloadducts, the endo isomer being only slightly favored over the exo. Other substrates reacted with generally good to poor stereoselectivity. An epimer of the substrate leading to (+)-dactylol afforded all possible isomers of the cycloadduct with relatively poor stereoselectivity.

Key words: cycloaddition, total synthesis, dactylol.

Résumé : On a préparé cinq cyclopentanones dans le but d'examiner les effets des centres stéréogènes sur le cours des réactions de cycloaddition [4 + 3] intramoléculaires des cations cyclopentényles. Un substrat réagit avec des degrés élevés de diastéréosélectivité et conduit à la formation du (+)-dactylol. La cyclopenténone sans centres stéréogènes sur la chaîne latérale ou sur le cycle à cinq chaînons conduit à la formation de deux cycloadduits dans lesquels l'isomère endo est légèrement favorisé par rapport à l'isomère exo. D'autres substrats réagissent avec des stéréosélectivités qui vont généralement de bonnes à mauvaises. Un épimère du substrat qui conduit au (+)-dactylol a permis d'isoler tous les isomères possibles du cycloadduit avec une stéréosélectivité relativement faible.

Mots clés : cycloaddition, synthèse totale, dactylol.

[Traduit par la Rédaction]

Introduction

The intramolecular [4 + 3] cycloaddition reaction of allylic cations and dienes has been shown to be a powerful route to polycyclic compounds (1). One variation on this theme involves the use of cyclic cations in the cycloaddition reaction. Appropriate modifications of the cycloadducts from such reactions can then provide useful routes to natural products (2). We and others realized the potential for this process in the context of the synthesis of cyclooctanoids (3). We recently reported a total synthesis of (+)-dactylol based on this chemistry (2*c*). This report is a more detailed description of that work, including studies to evaluate the effects of various stereocenters on the course of the cycloaddition reaction.

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Results and discussion

Diene synthesis

The basic approach for the preparation of substrates for this study consisted of the alkylation of cyclopentanone enolates with diene-containing electrophiles. The synthesis of the dienes used is shown in Scheme 1. Treatment of **1a**–**1c** with $TMSCH_2MgCl$–$CeCl_3$ followed by iodide formation afforded **3a**–**3c** in excellent yields (4, 5).

Ester **1a** was prepared by a literature procedure (6). Esters **1b** and **1c** were prepared as shown in Scheme 2. Protection of 1,4-butanediol with allyl bromide followed by oxidation gave the acid **5** in 69% yield from **4**. Oxazolidinones were formed from **5** in standard fashion and alkylated with high stereoselectivity and in good yields to afford **6b** and **6c**. Reduction with LAH gave the alcohols **7b** and **7c** in excellent yields. Swern oxidation, Wittig homologation, and deprotection (7) afforded esters **1b** and **1c** in 81% and 77% yields, respectively.

Preparation of cycloaddition substrates

Cycloaddition substrates were easily prepared by alkylation. For example, the reaction of **8** with potassium carbonate in the presence of **3a** afforded the alkylation product **9** in good yield. This was converted to the ketone **11** in 66% yield via reaction with potassium cyanide in hot DMSO

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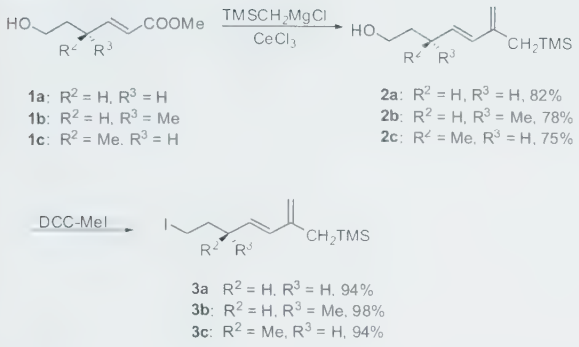
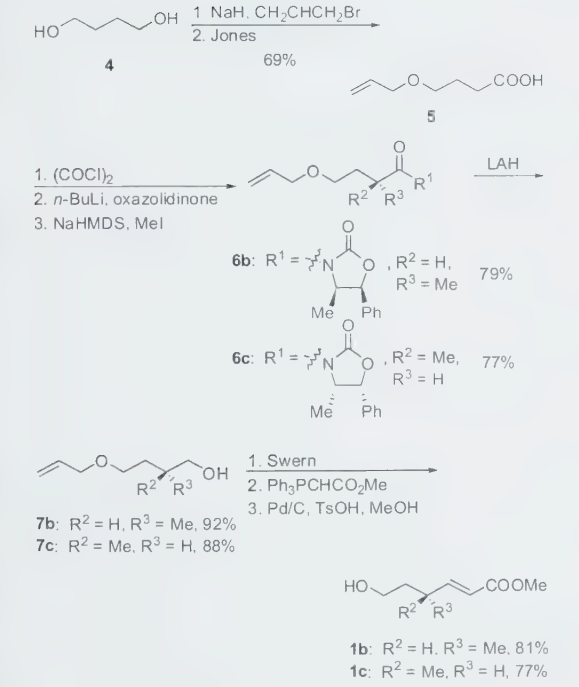
Scheme 1.



Scheme 2.



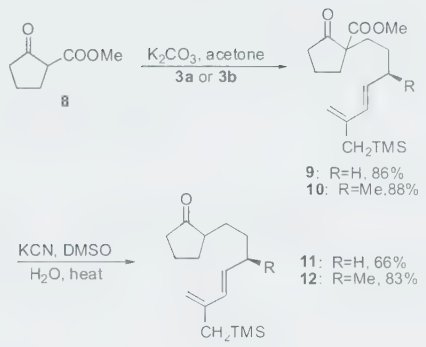
(8). Ketone **12** was prepared in a similar fashion in 73% overall yield (Scheme 3).

The ketoester **13** was readily prepared from (*R*)-pulegone by a known procedure (9). Dianion formation followed by alkylation and decarboalkoxylation afforded cycloaddition substrates **17**–**19**, as shown in Scheme 4.

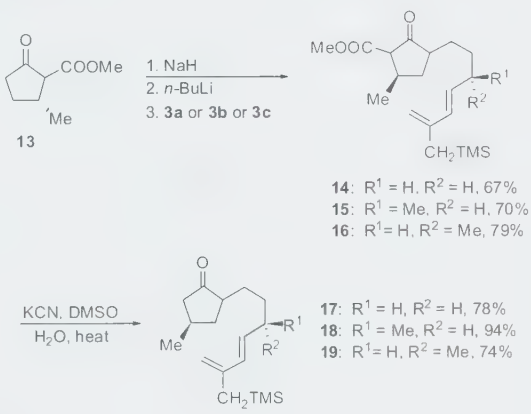
The synthesis of (+)-dactylol

We begin with the synthesis of dactylol, since that was indeed the first cycloaddition in this series that we examined. Treatment of **18** with Lithium diisopropylamide (LDA) and reacting the resultant enolate with triflyl chloride gave an α-chloroketone. This was not characterized but immediately subjected to typical cycloaddition conditions: stirring at –78 °C to room temperature in a 1:1 mixture of ether and trifluoroethanol in the presence of 3 equiv. of triethylamine (Scheme 5). Even though the purification of the cycloadduct

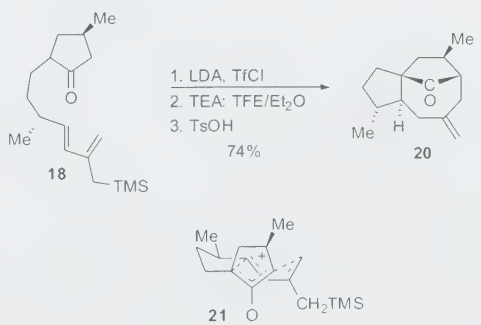
Scheme 3.



Scheme 4.



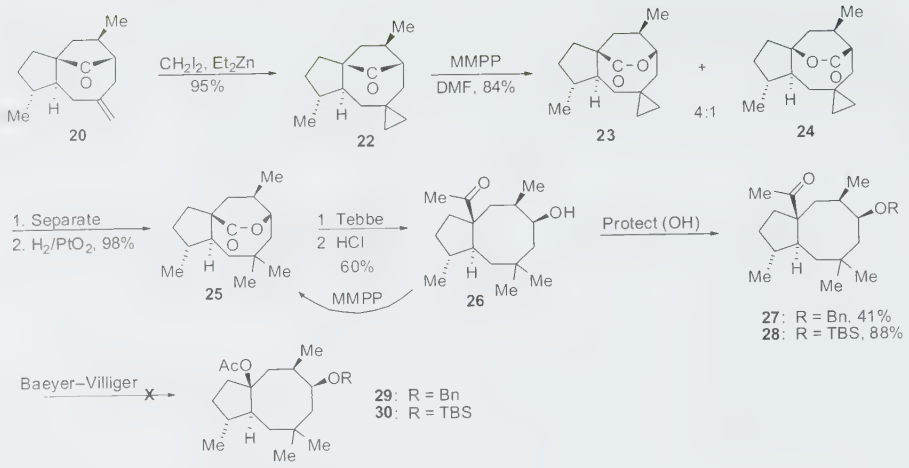
Scheme 5.



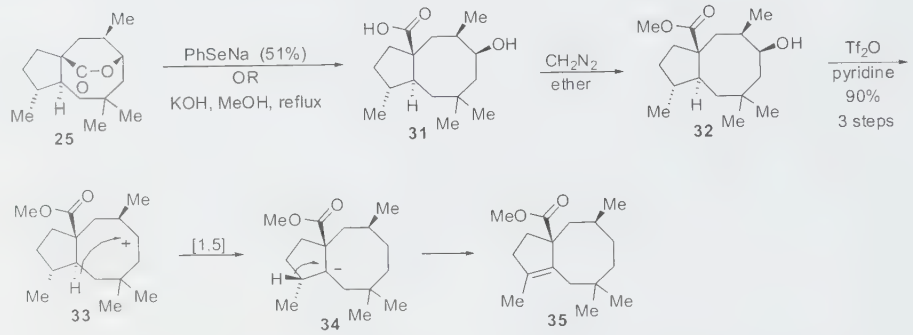
could be carried out at this stage, we found that some desilylation and double bond migration occurred during the chromatography on silica gel.

Therefore, the crude product was subsequently treated with tosic acid to give rise to alkene **20** as a 25:1 mixture of isomers in 74% yield for the three steps. The diastereomeric ratio was determined by GC and integration of the olefinic region of the ^{1}H NMR of a crude product mixture. The minor isomer has not been characterized. The rationalization for the favorable stereochemical outcome is depicted in structure **21**. We anticipated that the diene would approach the dienophile in an endo fashion on the less-hindered face of the dienophile. In addition, the methyl group on the tether

Scheme 6.



Scheme 7.



would occupy a pseudoequatorial orientation on the puckered, incipient five-membered ring with the diene oriented so as to minimize gauche interactions.

The next stage of the synthesis is shown in Scheme 6. Simmons–Smith cyclopropanation of **20** produced **22** in 95% yield. The Baeyer–Villiger reaction of **22** with MMPP in DMF afforded a 4:1 mixture of two regioisomers after purification. Surprisingly, the major product was that resulting from the migration of the less substituted carbon atom. Attempts to alter the regioselectivity using a variety of reaction conditions were unsuccessful, as some reagents gave higher regioselectivity but lower yields of the products.[3] Studies we have conducted suggest that the methyl substituent on the five-membered ring has a major, but not exclusive, influence on the regiochemistry of the reaction (10). The major isomer **23** was separated, and the cyclopropane ring was cleaved by hydrogenolysis to afford **25** in 98% yield. The structure and relative stereochemistry were established by X-ray crystallography.

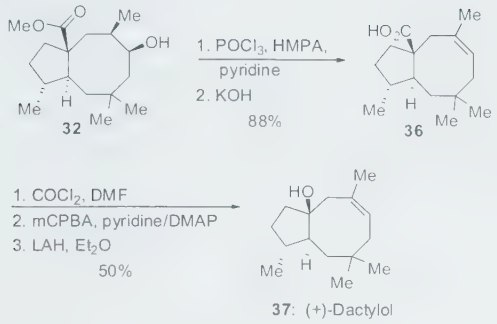
Our first attempt to convert **25** into dactylol began with a methylenation reaction using Tebbe's reagent (11). Hydrolysis of the resultant enol ether afforded the ketone **26**, whose hydroxy group could be protected with either a benzyl or TBS group. We anticipated that a Baeyer–Villiger oxidation of either of these species would afford the corresponding acetate **29** or **30**.[4] Unfortunately, no reaction occurred between either **27** or **28** and MMPP, *m*-CPBA, or TFAA-H_2O_2 after a 24 h period at room temperature. Treatment of **26** with MMPP afforded lactone **25** (10). We also attempted a reaction between lactone **25** and sodium phenylselenide and expected to obtain a system suitable for further elaboration to (+)-dactylol. However, the hydroxy acid **31** was obtained as the sole product in 51% yield, via an apparent hydrolysis reaction. Even though this result was not satisfactory, it proved the existence and stability of the hydroxycarboxylic acid **31**, which became significant.

Thus, the next sequence to (+)-dactylol began with a hydrolysis of lactone **25** using KOH in refluxing aqueous methanol and esterification of the corresponding hydroxy acid with diazomethane (Scheme 7). The next challenging step was the introduction of the double bond in dactylol by dehydration of **32**. Regioselectivity was a problem, as were side reactions. For example, treatment of **32** with $POCl_3$ in pyridine, Tf_2O in pyridine, or Martin's sulfurane resulted in

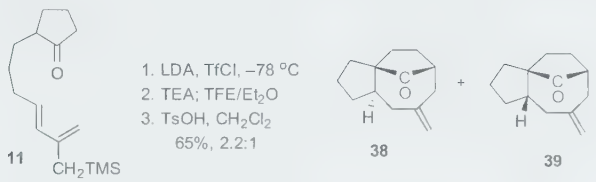
[3] Reagent, ratio **23**:**24**, solvent, temperature, time, yield: (*a*) *m*-CPBA–$NaHCO_3$, 6:1, CH_2Cl_2, RT, 5 d, 67%; (*b*) TFAA–H_2O_2, 5:1, CH_2Cl_2, 0 C – RT, 3 d, 36%; (*c*) *m*-CPBA–TFA, 4:1, CH_2Cl_2, 0 °C–rt, 48 h, 53%; (*d*) peracetic acid – NaOAc, 9:1, AcOH, RT, 48 h, 31%; (*e*) MMPP, 4:1, DMF, RT, 48 h, 84%.

[4] Without protection of the alcohol group, the Baeyer–Villiger reaction proceeded by an unexpected course. See ref. 10.

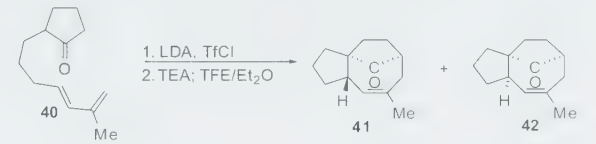
Scheme 8.



Scheme 9.



Scheme 10.



the formation of a compound identified as **35**. Presumably, these reagents induced cation formation, which was followed by a 1,5-transannular hydride shift to form **34**, and subsequent elimination to give tetra-substituted alkene **35**, whose structure was determined based on spectroscopic and analytical data. The ^{1}H NMR spectrum showed no signal for olefinic protons. The most downfield peak appeared at 3.59 ppm as a singlet, which corresponded to the methyl ester. There was also a singlet peak that integrated for three protons at 1.65 ppm, suggesting the presence of a methyl substituent on an olefin. The ^{13}C NMR spectrum confirmed the existence of ester and alkene (δ: 177.3, 136.9, 134.7).

By taking advantage of the dehydration procedure developed by Trost and Jungheim (12), we were able to overcome this problem (Scheme 8). Phosphorus oxychloride ($POCl_3$) was added to a solution of **32** in HMPA with slow heating from room temperature to 50 °C. After the white precipitate that formed dissolved, pyridine was added and heating was continued to 100 °C at which point the dehydration was complete. Subsequent hydrolysis of the sterically hindered methyl ester group using KOH in DMSO provided **36** as a single product (based on crude ^{1}H NMR) in 84% yield. At this point, we found that typical acid chloride formation procedures failed to give the acid chloride of the hindered acid **36**.[5] However, upon treatment with DMF and phosgene in refluxing toluene, **36** was cleanly converted to the corresponding acid chloride (13). In a benzene solution containing pyridine and DMAP, this acid chloride reacted with mCPBA to form a mixed anhydride, which rearranged upon stirring for 24 h at room temperature to a mixed carbonate with retention of configuration (14). Reduction of the mixed carbonate with LAH then afforded (+)-dactylol in 50% overall yield from **36**. The spectral, analytical, and optical rotation data were consistent with those reported in the literature (15).

Simple diastereoselectivity

After the successful synthesis of (+)-dactylol, we decided to examine the influence of all stereocenters on the course of the reaction. First, however, we looked at simple diastereoselectivity. Past experience suggested that the intramolecular [4 + 3] cycloaddition reaction of cyclopentenyl cations with tethered butadienes would proceed with only a slight simple diastereoselectivity in favor of the endo product (*3b*). This was indeed the case.

The ketone **11** was treated with LDA and TfCl to furnish the corresponding α-chloroketone, which was subjected to the [4 + 3] cycloaddition and desilylation reactions (Scheme 9). Two diastereomeric cycloadducts (**38** and **39**) were obtained in 65% yield in a ratio of 2.2:1. The product ratio was determined by gas chromatographic analysis and integration of the crude product ^{1}H NMR spectrum. After purification by flash chromatography on silica gel, the major product was treated with excess NH_2OH·HCl and KOH in refluxing ethanol to form an oxime derivative. Recrystallization of this oxime from hexane and EtOAc afforded crystals of suitable quality for single crystal X-ray crystallographic analysis. Thus, the major product was assigned as the endo isomer **38**. It should be noted that cycloadditions of this type appear to take place under kinetic control.

We have examined simple diastereoselectivity computationally for the conversion of **40** to **41** and **42**. We found that while the lowest energy transition state corresponds to the endo product **41**, other transition state structures that lead to the exo product are close in energy, and thus, for unsubstituted systems at least, simple diastereoselectivity should not ever be expected to be substantial (Scheme 10) (16).

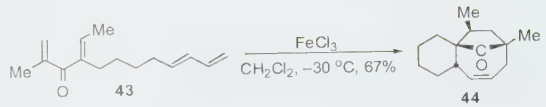
It is interesting to note that West and co-workers (*3a*) have reported very high simple diastereoselectivity in the formation of **44** via a domino Nazarov – [4 + 3] cycloaddition process as shown in Scheme 11. It is clear that many new features of this aspect of the intramolecular [4 + 3] cycloaddition reaction of cyclopentenyl cations remain to be uncovered.

Relative stereoselection I — Cycloaddition of 12

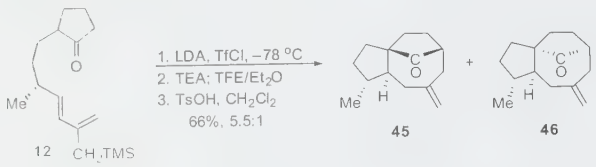
The introduction of a stereogenic center in the tether joining the diene and dienophile in these reactions introduces a new complication. Our goal in pursuing the cycloaddition of **12** was essentially to discover the impact of the stereocenter on the course of the reaction in an effort to elucidate which of the stereocenters in **18** had a more profound impact on the stereochemical outcome on that compound's cycloaddition.

[5] For example, stirring the solution of **36** in hexane with 3 equiv. of oxalyl chloride or heating a hexane solution of **36** with excess thionyl chloride resulted in no change.

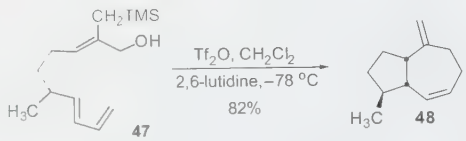
Scheme 11.



Scheme 12.



Scheme 13.



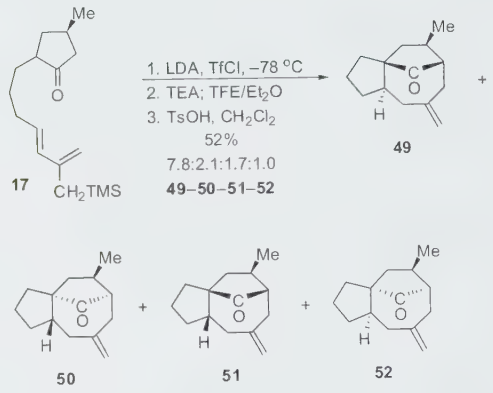
Cycloaddition of **12** afforded four products, only two of which, **45** and **46**, could be cleanly isolated (Scheme 12). Gas chromatographic analysis of the crude reaction mixture indicated a product ratio of 47.2(**45**):8.1(**46**):1:2.3. The major product of the reaction was **45**, as expected on the basis of the small but real endo preference observed in these systems and a report by Giguere and co-workers (17) on relative diastereoselection in intramolecular [4 + 3] cycloadditions. In that paper, Giguere and co-workers (17) reported that treatment of **47** with triflic anhydride afforded cycloadduct **48** as the major product of the reaction (Scheme 13). Regardless of the mechanistic basis for the outcome, one could assume that stereogenic centers adjacent to dienes would produce similar stereochemical outcomes in other intramolecular [4 + 3] cycloaddition reactions. This is what is observed in the formation of **45** and **46**. The structure of both compounds was established by X-ray analysis of the corresponding oximes.[6]

Relative stereoselection II — Cycloaddition of 17

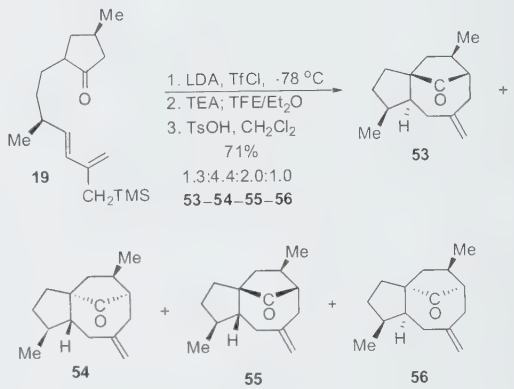
The cycloaddition reaction of **17** was anticipated to be reasonably selective. Endo–exo selectivity was not expected to be high but facial selectivity was expected to be reasonable, the diene approaching the less hindered face of the dienophile (i.e., on the face opposite the methyl substituent). There is a reasonable amount of precedent for this in the literature (18).

Surprisingly, the reaction produced all four possible isomeric products (**49–52**) in 52% yield overall from ketone **17** (Scheme 14). Gas chromatographic analysis of the crude product mixture suggested that the products were formed in a ratio of 7.8:2.1:1.7:1.0. They were separated by flash chromatography on silica gel and individually transformed into their oxime derivatives. Consistent with other data, the major

Scheme 14.



Scheme 15.



products were those derived from the transition states having the diene approaching from the opposite side of the methyl group on the stereogenic center. However, the level of facial selectivity in this reaction was approximately 3:1, while the endo–exo ratio was 3.4:1. The low level of facial selectivity is surprising, but larger substituents at the stereogenic centers should produce a better result.

Cycloaddition of 19 — The mismatched case

The last [4 + 3] cycloaddition in this study was the reaction of ketone **19**. Since the stereogenic center on the cyclopentanone remained the same (*R*) while the one on diene was switched from (*R*) to (*S*) compared with ketone **18**, we expected to see the diastereomer of **20** formed as the major isomer. In fact, the reaction produced all four isomers of cycloadduct (**53–56**) in 71% yield in a ratio of 1.3:4.4:2.0:1.0 (Scheme 15). Each product was purified, characterized, and converted into an oxime derivative, and the stereochemical assignment was made using X-ray crystallography. The major isomer (**54**) derived from a transition state having an endo approach of the diene with a tether conformation that minimized gauche interactions. However, at-

[6]The oxime derived from **46** gave poor quality X-ray data. Finding a suitable crystal was problematic and the one found turned out to be racemic, in spite of the fact that the bulk sample was clearly enantiomerically enriched based on optical rotation data. However, the data were sufficient to establish the relative stereochemistry.

tack occurred on what appears to be the more sterically hindered face of the oxyallylic cation intermediate.

Surprisingly, the overall facial selectivity in this case, (**53** + **55**):(**54** + **56**), was 1:1.6 in favor of the products derived from the approach of the diene to the more hindered face of the cyclopentanone. The endo–exo ratio, (**53** + **54**):(**55** + **56**) was 1.9:1 in favor of endo products. The relative stereoselectivity (**53** + **56**):(**54** + **55**) was 1:2.8 in favor of the products having a cis relationship between the angular hydrogen and the methyl group on the newly formed five-membered ring.

Conclusion

The intramolecular [4 + 3] cycloaddition of cyclopentenyl cations to dienes is a useful route to cyclooctanoids. High levels of stereocontrol in this reaction are possible, but it is clear that effects that might appear to be cooperative need not be and that further studies of these cycloadditions will be necessary to achieve results that are more generally suitable for applications in synthesis. This conclusion is true for acyclic dienes tethered to cyclopentenyl cations. High levels of simple diastereoselection are possible with tethered furans (3). Whether this inherent selectivity can be used to produce high levels of relative stereocontrol remains to be seen. We plan to perform further work to solve the problems that exist and continue to apply the methodology to the synthesis of cyclooctanoids. Further results will be reported in due course.[7]

Experimental

General procedure for Peterson olefination: synthesis of 2a–2c

A 500 mL round-bottomed flask was charged with powdered cerium(III) chloride heptahydrate ($CeCl_3$-$7H_2O$, 13.02 g, 34.96 mmol). The flask was immersed in an oil bath and evacuated to a full vacuum (about 0.1 mmHg (1 mmHg = 133.322 4)). The solid was magnetically stirred as the flask was heated at 150 °C for 2 h. After the flask was cooled to room temperature, it was vented to the atmosphere and quickly purged with a steam of argon for 30 s. The flask was capped with a rubber septum and 60 mL of THF was added. The white suspension was stirred at room temperature for 1 h, cooled to –78 °C in a dry ice – 2-propanol bath, and a 1 mol/L solution of trimethylsilylmethylmagnesium chloride (35 mL, 35 mmol) was added over a period of 15 min. After the cold mixture was stirred for an additional 15 min, 9.99 mmol of **1a**, **1b**, or **1c** was added dropwise and the mixture was allowed to warm slowly to room temperature over a period of 3 h. The reaction was quenched with ice-cold 1 mol/L HCl (60 mL) and stirred for 5 min. The layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution (100 mL), dried over magnesium sulfate, filtered, and the solvents were removed by rotavap. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1).

6-Trimethylsilylmethyl-hepta-4,6-dien-1-ol (2a)

Yield: 82%, colorless oil. IR (neat, cm^{-1}): 3353 (ms), 2947 (s), 1252 (s), 859 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.09 (d, J = 15.6 Hz, 1H), 5.58 (dt, J = 7.0, 15.6 Hz, 1H), 4.78 (d, J = 1.5 Hz, 1H), 4.66 (s, 1H), 3.68–3.61 (m, 2H), 2.18 (q, J = 7.3 Hz, 1H), 1.77 (br t, J = 4.5 Hz, 1H), 1.72–1.61 (m, 2H), 1.69 (s, 2H), 0.00 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 143.7, 133.6, 129.7, 112.0, 62.3, 32.3, 29.0, 22.1, –1.2. HR-MS (EI) calcd. for $C_{11}H_{20}OSi$ (M^+): 198.1440; found: 198.1438.

(3R)-Methyl-6-trimethylsilylmethyl-hepta-4,6-dien-1-ol (2b)

Yield: 78%, colorless oil. $[\alpha]^{20}_D$ –24.42 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3334 (m), 2957 (s), 2929 (m), 2898 (m), 1596 (w), 1422 (w), 1250 (m), 1157 (m), 1054 (m), 967 (m), 853 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.07 (d, J = 15.7 Hz, 1H), 5.45 (dd, J = 8.3, 11.3 Hz, 1H), 4.80 (d, J = 1.9, 1H), 4.68 (s, 1H), 3.66 (br s, 1H), 2.37 (sept, J = 7.1 Hz, 1H), 1.70 (s, 2H), 1.66–1.35 (m, 2H), 1.35 (br s, 1H), 1.05 (d, J = 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.7, 135.7, 132.0, 112.3, 61.2, 39.8, 34.0, 22.1, 21.0, –1.2. Anal. calcd. for $C_{12}H_{24}O_3Si$: C 67.86, H 11.39; found: C 67.92, H 11.47.

(3S)-Methyl-6-trimethylsilylmethyl-hepta-4,6-dien-1-ol (2c)

Yield: 75%, colorless oil. $[\alpha]^{20}_D$ +26.67 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3378 (s), 2957 (s), 2877 (s), 1459 (m), 1420 (m), 1380 (m), 1254 (s), 1055 (s), 853 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.07 (d, J = 15.7 Hz, 1H), 5.45 (dd, J = 8.3, 11.3 Hz, 1H), 4.80 (d, J = 1.9, 1H), 4.68 (s, 1H), 3.66 (br s, 1H), 2.37 (sept, J = 7.1 Hz, 1H), 1.70 (s, 2H), 1.66–1.35 (m, 2H), 1.35 (br s, 1H), 1.05 (d, J = 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.7, 135.7, 132.0, 112.3, 61.2, 39.8, 34.0, 22.1, 21.0, –1.2. HR-MS (EI) calcd. for $C_{12}H_{24}OSi$ (M^+): 212.1596; found: 212.1610.

General procedure for conversion of alcohols to iodides: synthesis of 3a–3c

To a solution of **2a**, **2b**, or **2c** (4.70 mmol) in THF (47 mL) was added 9.42 mmol of DCC-MeI salt. The mixture was stirred in an oil bath at 35 °C for 6 h. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (100% hexane). Due to the instability of the products, the characterizations were performed by NMR and IR only.

(7-Iodo-2-methylene-hept-3-enyl)-trimethylsilane (3a)

Yield: 94%, colorless oil. IR (neat, cm^{-1}): 3078 (w), 2945 (s), 2896 (s), 1597 (m), 1423 (m), 1241 (m), 1155 (s), 967 (m), 846 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.12 (d, J = 15.7 Hz, 1H), 5.51 (dt, J = 7.0, 15.6 Hz, 1H), 4.81 (d, J =

[7] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5104. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 282839–282845 and 282856 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

2.0 Hz, 1H), 4.69 (s, 1H), 3.19 (t, J = 6.9 Hz, 2H), 2.21 (q, J = 7.0 Hz, 2H), 1.92 (quint, J = 7.0 Hz, 2H), 1.69 (d, J = 0.7 Hz, 2H), –0.48 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 143.6, 134.6, 128.0, 112.5, 33.3, 33.1, 22.1, 6.3, –1.2.

(7-Iodo-(5R)-methyl-2-methylene-hept-3-enyl)-trimethyl-silane (3b)

Yield: 98%, colorless oil. $[\alpha]^{20}_D$ –43.94 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3078 (w), 2955 (s), 2927 (m), 2897 (m), 1597 (m), 1422 (m), 1249 (s), 1158 (m), 969 (m), 851 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.12 (d, J = 15.7 Hz, 1H), 5.35 (dd, J = 8.4, 15.6 Hz, 1H), 4.84 (d, J = 1.9 Hz, 1H), 4.71 (s, 1H), 3.23–3.09 (m, 2H), 2.35 (sept, J = 6.8 Hz, 1H), 1.90–1.80 (m, 2H), 1.70 (s, 2H), 1.05 (d, J = 6.7 Hz, 3H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.5, 134.0, 132.9, 112.7, 40.6, 38.0, 22.1, 20.3, 4.9, –1.2.

(7-Iodo-(5R)-methyl-2-methylene-hept-3-enyl)-trimethyl silane (3c)

Yield: 94%, colorless oil. $[\alpha]^{20}_D$ +39.71 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3079 (w), 2952 (s), 2927 (m), 2887 (m), 1594 (m), 1421 (m), 1252 (s), 1160 (m), 970 (m), 853 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.12 (d, J = 15.7 Hz, 1H), 5.35 (dd, J = 8.4, 15.6 Hz, 1H), 4.84 (d, J = 1.9 Hz, 1H), 4.71 (s, 1H), 3.23–3.09 (m, 2H), 2.35 (sept, J = 6.8 Hz, 1H), 1.90–1.80 (m, 2H), 1.70 (s, 2H), 1.05 (d, J = 6.7 Hz, 3H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.6, 134.0, 132.9, 112.7, 40.6, 38.0, 22.1, 20.3, 4.9, –1.2.

4-(2-Propenyloxy)-butanoic acid (5)

To a solution of 1,4-butanediol (54.0 g, 600 mmol) in dry DMF (400 mL) was added 60% NaH (5.76 g, 240 mmol) portionwise while the solution was stirred in an ice-water bath. After the addition of NaH, the reaction flask was removed from the bath. The mixture was stirred at room temperature for 30 min and cooled in the ice-water bath again. Allyl bromide (17.3 mL, 200 mmol) was added dropwise, and the mixture stirred for 1 h. The reaction was quenched with water (500 mL) and extracted with EtOAc. The organic phase was concentrated on a rotatory evaporator, and the residue dissolved in acetone (400 mL). The solution was cooled in the ice bath and Jones reagent (prepared from 133.6 g of CrO_3, 115 mL of H_2SO_4, and 350 mL of H_2O) was added dropwise with stirring until a red color persisted (approximately 70 mL of Jones reagent was used). Volatile solvents were removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$ solution (300 mL × 2), and the organic layer was discarded. The aqueous phase was acidified by addition of 6 mol/L HCl until pH ≤ 4, and extracted with ether (100 mL × 3). The combined organic phase was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the product was obtained as a colorless liquid (19.9 g, 69%). NMR and IR data were consistent with those published in literature (19).

(4*R*)-Methyl-(5*S*)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one and (4*S*)-methyl-(5*R*)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one

Oxalyl chloride (30 mL, 343.34 mmol) was added to a solution of acid **5** (16.5 g, 114.45 mmol) in hexane (220 mL) and the mixture was stirred at room temperature for 3 h. Volatile compounds were removed under reduced pressure, and the crude product was used in the next step without further purification. A solution of (4*R*)-methyl-(5*S*)-phenyl-oxazolidin-2-one or (4*S*)-methyl-(5*R*)-phenyl-oxazolidin-2-one (16.89 g, 95.31 mmol) in dried THF (320 mL) was cooled to –78 °C and 2.2 mol/L *n*-BuLi (43.3 mL, 95.31 mmol) was added dropwise. After the addition of *n*-BuLi, 4-(2-propenyloxy)butanoyl chloride (18.6 g, 114.38 mmol) was added in one portion. The reaction flask was moved into an ice-water bath and stirred for 30 min. The reaction was quenched with 1 mol/L K_2CO_3 (200 mL) and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1) on silica gel.

(4R)-Methyl-(5S)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one

Yield: 94%, colorless oil. $[\alpha]^{20}_D$ +41.72 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3072 (w), 2932 (m), 2860 (m), 1783 (s), 1702 (s), 1455 (m), 1349 (s), 1198 (s), 1120 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.29 (m, 5H), 5.98–5.85 (m, 1H), 5.66 (d, J = 7.30 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.17 (dq, J = 10.4, 1.5 Hz, 1H), 4.76 (quint, J = 6.8 Hz, 1H), 3.97 (dm, J = 5.5 Hz, 2H), 3.52 (t, J = 6.3 Hz, 2H), 3.14–2.97 (m, 2H), 1.99 (sept, J = 7.1 Hz, 2H), 0.89 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.7, 153.0, 134.8, 133.3, 128.7, 128.6, 125.6, 116.8, 78.9, 71.7, 69.1, 54.7, 32.5, 24.4, 14.5. Anal. calcd. for $C_{17}H_{21}NO_4$: C 67.31, H 6.98; found: C 67.55, H 6.81.

(4S)-Methyl-(5R)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one

Yield: 95%, colorless oil. $[\alpha]^{20}_D$ –40.00 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3074 (w), 2935 (m), 2861 (m), 1784 (s), 1708 (s), 1350 (s), 1198 (s), 1120 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.29 (m, 5H), 5.98–5.85 (m, 1H), 5.66 (d, J = 7.30 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.17 (dq, J = 10.4, 1.5 Hz, 1H), 4.76 (quint, J = 6.8 Hz, 1H), 3.97 (dm, J = 5.5 Hz, 2H), 3.52 (t, J = 6.3 Hz, 2H), 3.14–2.97 (m, 2H), 1.99 (sept, J = 7.1 Hz, 2H), 0.89 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.7, 153.0, 134.9, 133.3, 128.7, 128.6, 125.6, 116.7, 78.9, 71.7, 69.1, 54.7, 32.5, 24.4, 14.5. Anal. calcd. for $C_{17}H_{21}NO_4$: C 67.31, H 6.98; found: C 67.42, H 6.79.

(4*R*)-Methyl-(5*S*)-phenyl-3-(4-propenyloxy-2(*R*)-methyl-butanoyl)-oxazolidine-2-one (6b) and (4*S*)-methyl-(5*R*)-phenyl-3-(4-propenyloxy-(2*S*)-methyl-butanoyl)-oxazolidine-2-one (6c)

To a flame-dried, 1 L, round-bottomed flask was placed 27.1 g (89.33 mmol) of (4*R*)-methyl-(5*S*)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one or (4*S*)-methyl-(5*R*)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one and freshly distilled THF (350 mL). The solution was cooled to –78 °C, and 2.0 mol/L NaHMDS in THF (53.6 mL, 107.2 mmol) was added dropwise over 20 min. The mixture was stirred at –78 °C for 30 min and MeI (38.0 mL, 268.0 mmol) was added. After stirring at –78 °C for an additional 4 h, the reaction was quenched with half-saturated NH_4Cl solution (300 mL). The organic phase was separated, and the aqueous

phase was extracted with EtOAc (200 mL × 3). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 10:1) on silica gel.

6b

Yield: 84%, colorless oil. $[\alpha]^{20}_D$ +9.59 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2980 (m), 2937 (m), 2872 (m), 1782 (s), 1700 (s), 1457 (m), 1347 (s), 1242 (s), 1197 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.42–7.29 (m, 5H), 5.99–5.84 (m, 1H), 5.63 (d, *J* = 7.1 Hz, 1H), 5.28 (dq, *J* = 1.7, 17.2 Hz, 1H), 5.17 (dq, *J* = 1.7, 8.9 Hz, 1H), 4.74 (quint, *J* = 6.9 Hz, 1H), 3.95–3.89 (m, 3H), 3.53–3.48 (m, 2H), 2.18–2.03 (m, 1H), 1.79–1.67 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.5, 152.6, 134.8, 133.4, 128.5, 125.5, 116.3, 78.6, 71.5, 68.1, 54.7, 35.1, 33.4, 17.5, 14.4. Anal. calcd. for $C_{18}H_{23}NO_4$: C 68.12, H 7.30; found: C 68.28, H 7.16.

6c

Yield: 81%, colorless oil. $[\alpha]^{20}_D$ –9.44 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2980 (m), 2932 (m), 2871 (m), 1784 (s), 1698 (s), 1459 (m), 1342 (s), 1244 (m), 1196 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 7.45–7.27 (m, 5H), 5.99–5.84 (m, 1H), 5.63 (d, *J* = 7.1 Hz, 1H), 5.28 (dq, *J* = 1.7, 17.2 Hz, 1H), 5.17 (dq, *J* = 1.7, 10.4 Hz, 1H), 4.74 (quint, *J* = 6.7 Hz, 1H), 3.95–3.87 (m, 3H), 3.53–3.46 (m, 2H), 2.18–2.04 (m, 1H), 1.79–1.67 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.6, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 176.7, 152.7, 134.9, 133.5, 128.6, 125.6, 116.5, 78.7, 71.6, 68.2, 54.8, 35.2, 33.5, 17.6, 14.5. Anal. calcd. for $C_{18}H_{23}NO_4$: C 68.12, H 7.30; found: C 67.81, H 7.51.

4-Allyloxy-(2*R*)-methyl-butan-1-ol (7b) and 4-allyloxy-(2*S*)-methyl-butan-1-ol (7c)

To a cooled solution (0 °C) **6b** or **6c** (25.27 g, 79.61 mmol) in diethyl ether (320 mL) was added 6.05 g (159.23 mmol) of $LiAlH_4$ portionwise over 40 min and stirred for 2 h. The reaction was quenched by a slow addition of water and 1 N NaOH (20 mL). The mixture was filtered, and the white precipitate was washed with ether (300 mL × 2). The combined ether solution was concentrated, and crude product was purified by vacuum distillation (bp = 60–65 °C, 0.1 mmHg).

7b

Yield: 92%, colorless oil. $[\alpha]^{20}_D$ +14.16 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3397 (s), 3081 (w), 2930 (s), 2870 (s), 1458 (m), 1097 (s), 1044 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 5.99–5.83 (m, 1H), 5.27 (dq, *J* = 1.6, 17.3 Hz, 1H), 5.18 (dq, *J* = 1.2, 10.4 Hz, 1H), 3.98 (d, *J* = 5.6 Hz, 2H), 3.60–3.40 (m, 4H), 2.87 (br t, *J* = 5.7 Hz, 1H), 1.83–1.50 (m, 3H), 0.93 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.4, 117.1, 71.8, 68.6, 68.0, 34.1, 34.0, 17.1. Anal. calcd. for $C_8H_{16}O_2$: C 66.63, H 11.18; found: C 66.73, H 11.31.

7c

Yield: 88%, colorless oil. $[\alpha]^{20}_D$ –12.53 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3413 (s), 2957 (s), 2926 (s), 2870 (s), 1459 (m), 1099 (s), 1047 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 5.99–5.83 (m, 1H), 5.27 (dq, *J* = 1.6, 17.3 Hz, 1H), 5.18 (dq, *J* = 1.2, 10.4 Hz, 1H), 3.98 (d, *J* = 5.6 Hz, 2H), 3.60–3.40 (m, 4H), 2.87 (br t, *J* = 5.7 Hz, 1H), 1.83–1.50 (m, 3H), 0.93 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.4, 117.1, 71.8, 68.6, 68.0, 34.1, 34.0, 17.1. Anal. calcd. for $C_8H_{16}O_2$: C 66.63, H 11.18; found: C 66.73, H 11.28.

Synthesis of 6-allyloxy-(4*R*)-methyl-hex-2-enoic acid methyl ester and 6-allyloxy-(4*S*)-methyl-hex-2-enoic acid methyl ester

DMSO (9.4 mL, 132.41 mmol) was added to a cooled solution (–78 °C) of oxalyl chloride (5.8 mL, 66.20 mmol) in methylene chloride (460 mL). After 5 min, a solution of **7b** or **7c** (6.80 g, 47.29 mmol) in 10 mL of methylene chloride was added. The mixture was stirred for 30 min at –78 °C, and triethylamine (29.0 mL, 208.08 mmol) was added. After stirring for an additional 1 h at –30 °C, the reaction was quenched and washed with water (200 mL × 2). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude product was dissolved in 1,2-dichloroethane (50 mL), $Ph_3PCHCOOMe$ (16.56 g, 47.26 mmol) was added, and it was refluxed for 6 h. Volatile solvents were removed under reduced pressure, and the crude product was purified by flash chromatography (hexane–EtOAc, 4:1) on silica gel.

6-Allyloxy-(4R)-methyl-hex-2-enoic acid methyl ester

Yield: 88%, colorless oil. $[\alpha]^{20}_D$ –43.85 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2956 (s), 2867 (s), 1726 (s), 1658 (m), 1436 (m), 1273 (s), 1180 (m), 1103 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.87 (dd, *J* = 8.0, 15.7 Hz, 1H), 5.95–5.82 (m, 1H), 5.80 (dd, *J* = 1.0, 15.8 Hz, 1H), 5.26 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.16 (dq, *J* = 1.6, 9.9 Hz, 1H), 3.93 (m, 2H), 3.73 (s, 3H), 3.45–3.39 (m, 2H), 2.52 (sept, *J* = 7.0 Hz, 1H), 1.65 (q, *J* = 6.7 Hz, 2H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.1, 154.0, 134.7, 119.5, 116.7, 71.7, 67.7, 51.3, 35.7, 33.3, 19.3. Anal. calcd. for $C_{11}H_{18}O_3$: C 66.64, H 9.15; found: C 66.47, H 8.98.

6-Allyloxy-(4S)-methyl-hex-2-enoic acid methyl ester

Yield: 85%, colorless oil. $[\alpha]^{20}_D$ +45.35 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2957 (m), 2873 (m), 1730 (s), 1660 (m), 1435 (m), 1274 (m), 1183 (m), 1104 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.87 (dd, *J* = 8.0, 15.7 Hz, 1H), 5.95–5.82 (m, 1H), 5.80 (dd, *J* = 1.0, 15.8 Hz, 1H), 5.26 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.16 (dq, *J* = 1.6, 9.9 Hz, 1H), 3.93 (m, 2H), 3.73 (s, 3H), 3.45–3.39 (m, 2H), 2.52 (sept, *J* = 7.0 Hz, 1H), 1.65 (q, *J* = 6.7 Hz, 2H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.1, 154.0, 134.7, 119.5, 116.7, 71.7, 67.7, 51.3, 35.7, 33.3, 19.3. Anal. calcd. for $C_{11}H_{18}O_3$: C 66.64, H 9.15; found: C 66.81, H 9.36.

6-Hydroxy-(4*R*)-methyl-hex-2-enoic acid methyl ester (1b) and 6-hydroxy-(4*R*)-methyl-hex-2-enoic acid methyl ester (1c)

To a solution of 6-allyloxy-(4*R*)-methyl-hex-2-enoic acid methyl ester or 6-allyloxy-(4*S*)-methyl-hex-2-enoic acid methyl ester (8.25 g, 41.60 mmol) in anhydrous methanol (150 mL) was added 10% Pd–C (4.16 g) and *p*-toluenesulfonic acid (2.08 g). The mixture was stirred and heated under a reflux condition for 24 h, then filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 2:1).

1b

$[\alpha]^{20}_D$ –40.73 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3437 (m), 2958 (s), 2879 (m), 1725 (s), 1657 (s), 1437 (m), 1275 (s), 1210 (s), 1175 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.88 (dd, *J* = 8.0, 15.7 Hz, 1H), 5.83 (dd, *J* = 1.0, 15.7 Hz, 1H), 3.73 (s, 3H), 3.68–3.61 (m, 2H), 2.53 (m, 1H), 2.24 (s, 1H), 1.064 (q, *J* = 6.78 Hz, 2H), 1.08 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.2, 154.1, 119.5, 60.2, 51.4, 38.5, 33.0, 19.3. Anal. calcd. for $C_8H_{14}O_3$: C 60.74, H 8.92; found: C 60.91, H 8.77.

1c

$[\alpha]^{20}_D$ +44.08 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3429 (s), 2956 (s), 2879 (s), 1726 (s), 1658 (s), 1439 (s), 1276 (s), 1210 (s), 1175 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.88 (dd, *J* = 8.0, 15.7 Hz, 1H), 5.83 (dd, *J* = 1.0, 15.7 Hz, 1H), 3.73 (s, 3H), 3.68–3.61 (m, 2H), 2.53 (m, 1H), 2.24 (s, 1H), 1.064 (q, *J* = 6.78 Hz, 2H), 1.08 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 167.2, 154.1, 119.6, 60.4, 51.4, 38.6, 33.1, 19.3. Anal. calcd. for $C_8H_{14}O_3$: C 60.74, H 8.92; found: C 60.60, H 8.96.

General procedure for the alkylation of ketoester 8: synthesis of 9 and 10

To a solution of **8** (5 mmol) in acetone (25 mL) was added alkyl iodide **3a** or **3b** (2.5 mmol) and K_2CO_3 (7.5 mmol). The mixture was heated under a reflux condition under N_2 for 12 h. After the mixture was cooled to room temperature, water (30 mL) was added and the mixture was extracted with Et_2O (30 mL × 3). Combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane–ether, 20:1).

9

Yield: 86%, colorless oil. IR (neat, cm^{-1}): 3079 (w), 2956 (s), 2896 (s), 1751 (s), 1730 (s), 1436 (m), 1251 (m), 1159 (m), 855 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.06 (d, *J* = 15.6 Hz, 1H), 5.54 (dt, *J* = 7.0, 15.6 Hz, 1H), 4.78 (d, *J* = 2.0 Hz, 1H), 4.66 (s, 1H), 3.71 (s, 3H), 2.57–1.86 (m, 8H), 1.68 (s, 2H), 1.64–1.32 (m, 4H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.7, 171.5, 143.7, 133.7, 128.6, 112.0, 60.4, 52.5, 37.9, 33.6, 32.9, 32.8, 24.7, 22.1, 19.6, –1.2. Anal. calcd. for $C_{18}H_{30}O_3Si$: C 67.03, H 9.38; found: C 66.88, H 9.12.

10

Yield: 88%, colorless oil. IR (neat, cm^{-1}): 3080 (w), 2957 (s), 2928 (s), 1754 (s), 1729 (s), 1600 (m), 1460 (m), 1250 (s), 1157 (m), 856 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.05 and 6.01 (d, *J* = 15.7 and 15.7 Hz, 1H), 5.44–5.32 (m, 1H), 4.79 (d, *J* = 2.0 Hz, 1H), 4.66 (d, *J* = 2.0 Hz, 1H), 3.70 and 3.69 (s, 3H), 2.63–1.77 (m, 8H), 1.68 (s, 2H), 1.67–1.12 (m, 3H), 1.00 and 0.99 (d, *J* = 6.7 and 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.71, 214.65, 171.6, 171.4, 143.74, 143.69, 135.5, 132.1, 132.0, 112.13, 112.08, 60.4, 60.3, 52.4, 38.0, 37.8, 37.5, 37.4, 32.9, 32.7, 32.0, 31.9, 31.8, 22.1, 22.0, 20.8, 20.7, 19.5, –1.2. HR-MS (EI) calcd. for $C_{19}H_{31}O_3Si$ (M^+): 336.2121; found: 336.2121.

General procedure for the alkylation of ketoester 13: synthesis of 14–16

To a flame-dried, 50 mL, round-bottomed flask equipped with a magnetic bar was placed 0.65 g (17 mmol) of 60% NaH in mineral oil and 27 mL of freshly distilled THF. The mixture was stirred in an ice bath, and a solution of **13** (15 mmol) in 3 mL of THF was added slowly. The mixture was stirred for 5 min, and 2.5 mol/L solution of *n*-BuLi (15 mmol) was added. After stirring for an additional 5 min, a solution of alkyl iodide **3a**, **3b**, or **3c** (10 mmol) in 3 mL of THF was added into the orange-yellow solution. The mixture was stirred and allowed to warm to room temperature overnight. The reaction was quenched with water (25 mL) and extracted with ether (30 mL × 3). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated with a rotatory evaporator. The crude product was purified by column chromatography (silica gel, pentane–ether, 20:1) to give a mixture of diastereomers.

14

Yield: 67%, yellow oil. $[\alpha]^{20}_D$ +49.70 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3083 (w), 2957 (s), 2967 (s), 1753 (s), 1730 (s), 1436 (m), 1250 (m), 857 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.05 (d, *J* = 15.6 Hz, 1H), 5.55 (dt, *J* = 7.0, 15.6 Hz, 1H), 4.78 (d, *J* = 2.2 Hz, 1H), 4.66 (s, 1H), 3.75 and 3.74 (s, 3H), 2.86 and 2.74 (d, *J* = 10.0 and 11.44 Hz, 1H), 2.70–2.40 (m, 1H), 2.39–2.21 (m, 1H), 2.14–2.07 (m, 2H), 2.03–1.74 (m, 1H), 1.72–1.59 (m, 1H), 1.68 (s, 2H), 1.50–1.34 (m, 4H), 1.18 and 1.16 (d, *J* = 6.34 and 6.45 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 212.5, 169.63, 169.59, 143.8, 133.6, 129.8, 111.9, 111.2, 62.9, 62.8, 52.3, 50.5, 47.9, 36.2, 35.0, 34.1, 33.6, 32.6, 32.5, 30.4, 29.3, 27.8, 27.4, 27.3, 22.1, 19.7, 19.1, 15.8, –1.2. Anal. calcd. for $C_{19}H_{32}O_3Si$: C 67.81, H 9.58; found: C 67.66, H 9.52.

15

Yield: 70%, yellow oil. $[\alpha]^{20}_D$ +37.22 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2955 (s), 2874 (m), 1756 (s), 1731 (s), 1250 (m), 853 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.02 (d, *J* = 15.7 Hz, 1H), 5.47–5.35 (m, 1H), 4.78 (d, *J* = 1.7 Hz, 1H), 4.66 (s, 1H), 3.75 and 3.74 (s, 3H), 2.95 and 2.85 (d, *J* = 10.3 and 9.5 Hz, 1H), 2.75–2.42 (m, 1H), 2.35–2.13 (m, 2H), 1.99–1.59 (m, 2H), 1.68 (s, 2H), 1.39–1.23 (m, 3H), 1.18–1.06 (m, 4H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 212.6, 169.6, 169.6, 143.8, 143.8, 135.9, 135.8, 131.9, 131.8, 112.1, 112.0, 63.0, 62.8, 52.3, 50.5, 48.2, 37.2, 37.1, 36.2, 35.1, 35.1, 34.6, 34.1, 33.6, 28.8, 27.5, 22.1, 22.1, 20.9, 20.5, 19.2, –1.2. Anal. calcd. for $C_{20}H_{34}O_3Si$: C 68.52, H 9.78; found: C 68.70, H 9.85.

16

Yield: 79%, yellow oil. $[\alpha]^{20}_D$ +45.50 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3084 (w), 2956 (s), 2867 (s), 1759 (s), 1729 (s), 1444 (m), 1250 (s), 1158 (m), 849 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 5.97 (d, *J* = 15.7 Hz, 1H), 5.42–5.30 (m, 1H), 4.74 (d, *J* = 2.0 Hz, 1H), 4.61 (br s, 2H), 3.70 and 3.69 (s, 3H), 2.81 and 2.69 (d, *J* = 9.6 and 11.6 Hz, 1H), 2.65–2.10 (m, 4H), 1.97–1.53 (m, 2H), 1.64 (s, 2H), 1.40–1.19 (m, 3H), 1.12 and 1.11 (d, *J* = 6.3 and 6.4 Hz, 3H),

1.05–1.00 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), –0.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.3, 212.3, 169.5, 169.4, 143.6, 143.5, 135.7, 135.6, 131.8, 131.7, 111.93, 111.87, 62.8, 62.7, 52.1, 50.5, 47.8, 37.1, 36.8, 36.1, 35.0, 34.7, 34.6, 34.0, 33.4, 28.4, 27.6, 21.98, 21.96, 20.7, 20.5, 19.6, 19.0, –1.3. HR-MS (EI) calcd. for $C_{20}H_{34}O_3Si$ (M^+): 350.2277; found: 350.2241.

General procedure for decarbomethoxylation: synthesis of 11–12 and 17–19

To a solution of β-keto ester (3.0 mmol) in DMSO (6.0 mL) was added potassium cyanide (6.0 mmol) and water (6.0 mmol). The mixture was heated under reflux for 30 min, allowed to cool to room temperature, diluted with water (20 mL), and extracted with ether (20 mL × 3). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, pentane–ether, 20:1).

11

Yield: 66%, colorless oil. IR (neat, cm^{-1}): 3079 (w), 2956 (s), 1740 (s), 1250 (s), 1157 (m), 856 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.06 (d, J = 15.6 Hz, 1H), 5.57 (dt, J = 7.06, 15.6 Hz, 1H), 4.78 (d, J = 2.01, 1H), 4.66 (s, 1H), 2.36–1.93 (m, 7H), 1.88–1.72 (m, 2H), 1.69 (s, 2H), 1.62–1.21 (m, 4H), 0.39 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.3, 143.8, 133.5, 130.1, 111.8, 49.1, 38.1, 32.8, 29.6, 29.4, 27.5, 22.2, 20.7, –1.2. Anal. calcd. for $C_{16}H_{28}OSi$: C 72.66, H 10.67; found: C 72.50, H 10.49.

12

Yield: 83%, colorless oil. $[\alpha]^{20}_D$ –10.13 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3080 (w), 2956 (s), 2870 (s), 1738 (s), 1249 (s), 1160 (m), 857 (s). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.02 (d, J = 15.7 Hz, 1H), 5.48–5.36 (m, 1H), 4.79 (d, J = 2.2 Hz, 1H), 4.66 (br s, 1H), 2.35–1.93 (m, 6H), 1.87–1.65 (m, 2H), 1.69 (s, 2H), 1.60–1.15 (m, 4H), 1.02 and 1.01 (d, J = 6.7 and 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.3, 143.9, 143.8, 136.1, 136.0, 131.8, 131.6, 111.94, 111.89, 49.3, 49.1, 38.14, 38.11, 37.4, 37.1, 35.2, 34.8, 29.63, 29.59, 27.8, 27.5, 22.14, 22.12, 20.9, 20.7, 20.5, –1.2. HR-MS (EI) calcd. for $C_{17}H_{30}OSi$ (M^+): 278.2066; found: 278.2079.

17

Yield: 78%, colorless oil. $[\alpha]^{20}_D$ +71.31 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3081 (w), 2954 (s), 2862 (s), 1743 (s), 1459 (w), 1250 (s), 1158 (m), 857 (s). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.06 (d, J = 15.3 Hz, 1H), 5.63–5.54 (m, 1H), 4.78 (d, J = 2.2 Hz, 1H), 4.66 (s, 1H), 2.52–2.03 (m, 6H), 1.97–1.62 (m, 2H), 1.69 (s, 2H), 1.51–1.20 (m, 3H), 1.18–1.05 (m, 1H), 1.14 and 1.09 (d, J = 6.4 and 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.6, 220.7, 143.8, 133.5, 133.4, 130.1, 130.1, 111.8, 50.8, 47.0, 46.8, 46.4, 35.6, 36.9, 32.8, 32.7, 30.2, 29.7, 29.4, 28.3, 27.5, 22.2, 20.8, 20.3, –1.2. Anal. calcd. for $C_{17}H_{30}OSi$: C 73.31, H 10.86; found: C 73.41, H 10.68.

18

Yield: 94%, colorless oil. $[\alpha]^{20}_D$ +41.65 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3079 (w), 2955 (s), 2870 (s), 1740 (s), 1593 (m), 1458 (m), 1249 (s), 1158 (m), 968 (m), 854 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.02 (d, J = 15.6 Hz, 1H), 5.50–5.35 (m, 1H), 4.79 (d, J = 2.0 Hz, 1H), 4.66 (s, 1H), 2.50–2.05 (m, 4H), 1.95–1.60 (m, 2H), 1.69 (s, 2H), 1.40–1.18 (m, 5H), 1.13 and 1.09 (d, J = 6.4 and 6.5 Hz, 3H), 1.01 and 1.00 (d, J = 6.7 and 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 221.7, 220.7, 143.9, 143.8, 136.2, 136.0, 131.8, 131.6, 112.0, 111.9, 50.9, 47.3, 46.9, 46.4, 38.5, 37.4, 37.1, 36.9, 35.2, 34.8, 29.7, 28.6, 28.3, 27.4, 22.2, 22.1, 20.9, 20.8, 20.5, 20.3, –1.2. Anal. calcd. for $C_{18}H_{32}OSi$: C 73.90, H 11.03; found: C 73.85, H 10.95.

19

Yield: 74%, colorless oil. $[\alpha]^{20}_D$ +66.45 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3081 (w), 2956 (s), 2923 (s), 2865 (m), 1744 (s), 1250 (s), 1158 (m), 850 (s). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.02 (d, J = 15.7 Hz, 1H), 5.47–5.36 (m, 1H), 4.78 (d, J = 2.1 Hz, 1H), 4.65 (d, J = 1.4 Hz, 1H), 2.50–2.06 (m, 5H), 1.91–1.62 (m, 3H), 1.69 (s, 2H), 1.43–1.21 (m, 2H), 1.13 and 1.08 (d, J = 6.4 and 6.6 Hz, 3H), 1.17–1.06 (m, 1H), 1.02 and 1.00 (d, J = 6.7 and 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 221.6, 220.6, 143.8, 136.1, 136.0, 131.8, 131.7, 111.9, 51.0, 47.0, 46.8, 46.4, 38.6, 37.4, 37.1, 37.0, 35.1, 34.8, 29.7, 28.4, 28.3, 27.8, 22.1, 20.84, 20.76, 20.6, 20.3, –1.2. HR-MS (EI) calcd. for $C_{18}H_{32}OSi$ (M^+): 292.2222; found: 292.2241.

α-Chlorination of cyclopentanone, intramolecular [4 + 3] cycloaddition, and desilylation of allylsilane: synthesis of 20

To a cooled solution (–78 °C) of ketone **18** (2.0 mmol) in THF (15 mL) was slowly added a solution of LDA (prepared by adding a 2.5 mol/L solution of *n*-BuLi (2.5 mmol) into a solution of diisopropylamine (3.0 mmol) in THF (5 mL) at 0 °C). The mixture was stirred at –78 °C for 30 min and trifluoromethanesulfonyl chloride (2.5 mmol) was added dropwise. After stirring for 5 min, the reaction was quenched with water (20 mL) and extracted with ether (15 mL × 3). The combined organic phases were washed with water (20 mL), dried over magnesium sulfate, filtered, and concentrated. Volatile solvents were removed under high vacuum. The resulting colorless oil was dissolved in freshly distilled ether (10 mL), cooled to –78 °C, and diluted with trifluoroethanol (10 mL). The mixture was stirred for a few minutes and triethylamine (6.0 mmol) was added dropwise. The reaction was allowed to warm to room temperature overnight, quenched with water (20 mL), and extracted with ether (15 mL × 3). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated. The crude product was dried under high vacuum. The resulting yellow oil was dissolved in methylene chloride (20 mL), and $TsOH{\cdot}H_2O$ (0.2 mmol) was added. The mixture was stirred at room temperature for 6 h and washed with water (20 mL). The organic phase was separated and dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using hexane–EtOAc (30:1) as the eluent. Ketone **20** was obtained as a colorless oil in 74% yield. $[\alpha]^{20}_D$ +44.60 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3073 (w), 2952 (s), 2867 (s), 1735 (s), 1643 (w), 1455 (m), 1154 (w). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.83 (d, J = 13.5 Hz, 2H), 2.46–1.68 (m, 8H), 1.58–0.92 (m,

6H), 1.04 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 220.8, 146.5, 115.0, 61.1, 58.6, 52.7, 46.9, 43.2, 39.9, 39.4, 35.1, 31.7, 28.0, 21.0, 18.3. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.25, H 10.20.

Simmons–Smith cyclopropanation: synthesis of 22

To a cooled solution (0 °C) of **20** (2.29 mmol) in methylene chloride (5 mL) was added methylene iodide (5.4 mL, 5.8 mmol) and 1.0 mol/L solution of diethylzinc in hexane (23 mL, 23 mmol). The mixture was stirred vigorously for 12 h while it was allowed to warm to room temperature. The reaction was quenched with water (20 mL), 1 N HCl (5 mL) was added, and it was extracted with ether (20 mL × 3). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated using a rotatory evaporator. The crude product was purified by flash chromatography (3:1, hexane–CH_2Cl_2). Ketone **22** was obtained in 95% yield as a colorless oil. $[\alpha]^{20}_D$ +12.63 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2956 (s), 2869 (s), 1728 (s), 1457 (m), 1390 (m), 1164 (m), 1114 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.63–2.51 (m, 1H), 2.28–2.11 (m, 3H), 1.99–1.94 (m, 4H), 1.84–1.77 (m, 1H), 1.56–1.43 (m, 1H), 1.36–1.13 (m, 5H), 1.03 (d, J = 6.88 Hz, 3H), 0.99–0.95 (m, 1H), 0.91 (d, J = 5.33 Hz, 3H), 0.83–0.75 (m, 1H), 0.51–0.39 (m, 2H), 0.31–0.15 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 220.1, 61.6, 55.0, 41.2, 42.8, 39.1, 35.1, 31.6, 27.3, 21.1, 18.4, 17.0, 14.7, 12.3. Anal. calcd. for $C_{16}H_{24}O$: C 80.70, H 10.41; found: C 82.60, H 10.30.

Baeyer–Villiger oxidation: synthesis of 23 and 24

To a solution of ketone **22** (2.15 mmol) in DMF (4 mL) was added MMPP (10.63 g, 21.50 mmol), and the resulted suspension was stirred at room temperature for 24 h. The mixture was diluted with water (20 mL) and extracted with ether (20 mL × 3). The combined ether solutions were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 10:1).

23

Yield: 68%, white solid (recrystallized from hexane–EtOAc), mp 52–54 °C. $[\alpha]^{20}_D$ +26.46 (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): 2956 (d), 2869 (d), 1728 (d), 1457 (m), 1390 (m), 1164 (m), 1114 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.36–4.31 (m, 1H), 2.70–2.46 (m, 3H), 2.03 (dd, J = 7.4, 13.5 Hz, 1H), 1.94–1.83 (m, 1H), 1.78–1.65 (m, 2H), 1.61–1.33 (m, 3H), 1.25–1.03 (m, 2H), 1.10 (d, J = 6.9 Hz, 3 H), 0.92 (br s, 1H), 0.88 (d, J = 6.0 Hz, 3H), 0.53–0.42 (m, 2H), 0.38–0.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.3, 85.4, 57.7, 51.1, 44.5, 42.0, 41.4, 38.0, 36.0, 33.0, 26.6, 22.2, 18.0, 16.7, 14.9, 14.7. Anal. calcd. for $C_{16}H_{24}O_2$: C 77.38, H 9.74; found: C 77.23, H 9.89.

24

Yield: 16%, white solid (recrystallized from hexane–EtOAc), mp 65–67 °C. $[\alpha]^{20}_D$ –103.65 (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): 2956 (s), 2917 (s), 2871 (s), 1722 (s), 1452 (w), 1374 (w), 1266 (w), 1098 (s). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.66–2.38 (m, 3H), 2.21–1.79 (m, 5H), 1.67–1.53 (m, 2H), 1.39–1.21 (m, 2H), 1.13–0.96 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.79–0.73 (m, 1H), 0.55–0.28 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 178.0, 90.6, 56.8, 46.8, 43.5, 42.6, 41.7, 41.1, 35.6, 32.1, 25.4, 23.0, 18.6, 17.5, 15.1, 14.3. Anal. calcd. for $C_{16}H_{24}O_2$: C 77.38, H 9.74; found: C 77.50, H 9.71.

Hydrogenolysis of a cyclopropane: synthesis of 25

To a 20 mL hydrogenation vessel was placed 0.90 mmol of cyclopropane **23**, 9.0 mL of glacial acetic acid, PtO_2 (4 equiv.), and NaOAc (4 equiv.). The vessel was connected to a hydrogenation apparatus, and the system was flushed with H_2 gas for a few minutes. The hydrogen pressure was adjusted to 100 psi (1 psi = 6.894 757 kPa), and the mixture was stirred under hydrogen for 12 h. The vessel was vented, and the catalyst was filtered off. The filtrate was partitioned between ether (20 mL) and water (20 mL). The organic phase was separated, and the aqueous phase was extracted with ether (20 mL × 2). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 10:1). Lactone **25** was synthesized in 98% yield as a white crystalline solid, mp 91 to 92 °C. $[\alpha]^{20}_D$ +15.23 (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): 2955 (s), 2872 (s), 1720 (s), 1455 (m), 1113 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.36 (q, J = 3.5 Hz, 1H), 2.73–2.60 (m, 1H), 2.43–2.34 (m, 1H), 2.07 (dd, J = 8.3, 13.8 Hz, 1H), 1.93–1.82 (m, 2H), 1.75–1.16 (m, 8H), 1.12 (s, 3H), 1.09 (d, J = 6.9 Hz, 3H), 0.98–0.96 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.3, 85.3, 54.0, 51.3, 46.3, 43.0, 42.6, 42.0, 36.5, 36.4, 32.9, 32.5, 29.5, 27.3, 23.2, 18.3. Anal. calcd. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.80, H 10.56.

Hydrolysis of lactone 25 and esterification of carboxylic acid 31: synthesis of 32

To a 10 mL round-bottomed flask equipped with a reflux condenser was placed **25** (0.05 g, 0.20 mmol), MeOH (2.0 mL), water (1.0 mL), and KOH (0.5 g). The mixture was heated and stirred under a reflux condition for 12 h. The mixture was allowed to cool to room temperature, was diluted with 2 N HCl (5 mL), and extracted with ether (10 mL × 3). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude product was dissolved in 5 mL of ether; a solution of diazomethane in ether was added until a yellow color persisted. The mixture was stirred for 5 min, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1). Ester **32** was obtained as a colorless oil (0.053 g, 95%). $[\alpha]^{20}_D$ –27.08 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3424 (m), 2960 (s), 2872 (s), 1720 (s), 1466 (m), 1175 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.80–3.74 (m, 1H), 3.67 (s, 3H), 2.26 (dd, J = 9.3, 15.0 Hz, 1H), 2.04–1.83 (m, 4H), 1.73–1.35 (m, 6H), 1.26–1.15 (m, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.96–0.93 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.6, 72.4, 55.4, 51.4, 49.7, 46.9, 41.4, 39.4, 37.7, 36.8, 35.9, 32.0, 31.9, 31.2, 24.1, 20.2, 19.3. Anal. calcd. for $C_{17}H_{30}O_3$: C 72.30, H 10.71; found: C 72.42, H 10.61.

Dehydration of alcohol 32 using Tf_2O–pyridine: synthesis of 35

To a solution of **32** (0.01 g, 0.04 mmol) in pyridine (1.0 mL) was added Tf_2O (0.013 mL, 0.08 mmol), and it

was stirred for 12 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ether (5 mL × 3). Combined organic phases were washed with 0.5 N HCl (5 mL) and brine, dried over magnesium sulfate, filtered, and concentrated. After a chromatographic purification (silica gel, hexane–EtOAc, 10:1), **35** was obtained in 90% yield as a colorless oil. $[\alpha]^{20}_D$ +94.86 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2949 (s), 2918 (s), 1730 (s), 1467 (m), 1220 (m), 1158 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 3.59 (s, 3H), 2.50–2.30 (m, 1H), 2.25–1.59 (m, 8H), 1.65 (s, 3H), 1.44–1.35 (m, 2H), 1.20–1.10 (m, 2H), 0.97 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 177.3, 136.9, 134.7, 61.7, 51.5, 38.1, 36.4, 35.7, 35.1, 34.43, 34.35, 29.6, 27.6, 26.2, 25.7, 22.1, 16.3. Anal. calcd. for $C_{17}H_{28}O_2$: C 77.22, H 10.67; found: C 77.34, H 10.44.

Dehydration of alcohol 32 using $POCl_3$–HMPA–pyridine and hydrolysis of ester: synthesis of 36

A 10 mL round-bottomed flask was charged with 0.053 g (0.19 mmol) of **32**, 2.0 mL of HMPA, and 0.2 mL of $POCl_3$. The resulting white suspension was stirred for 1 h at room temperature and for another 1 h in an oil bath at 50 °C. Pyridine (0.2 mL) was added, and the mixture was stirred at 50 °C for 1 h, at 75 °C for 45 min, and at 100 °C for 30 min. The mixture was allowed to cool to room temperature and was quenched by the dropwise addition of water (2 mL). The mixture was extracted with ether (5 mL × 3). The combined organic phases were washed with water (5 mL), dried over magnesium sulfate, filtered, and concentrated. The volatile compounds were removed under high vacuum, and the residue was dissolved in DMSO (2 mL). A few drops of water and 0.1 g of KOH were added, and the mixture was heated under reflux for 1 h. The reaction was allowed to cool to room temperature, 2 N HCl (5 mL) was added, and the mixture was extracted with ether (10 mL × 3). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 10:1). Acid **36** was obtained as a white solid (0.04 g, 88%). mp 133–135 °C. $[\alpha]^{20}_D$ +17.78 (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): 3435–2372 (s), 2952 (s), 1697 (s), 1466 (m), 1249 (m), 1205 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 12.00 (br, 1H), 5.50 (t, *J* = 8.4 Hz, 1H), 2.55 (d, *J* = 13.4 Hz, 1H), 2.31 (d, *J* = 13.5 Hz, 1H), 2.15–1.81 (m, 5H), 1.77 (s, 3H), 1.72–1.60 (m, 2H), 1.25–1.10 (m, 2H), 1.02 (d, *J* = 15.0 Hz, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.5, 135.4, 125.9, 58.2, 52.0, 40.7, 39.1, 38.9, 38.2, 34.7, 29.7, 28.1, 26.4, 20.1. Anal. calcd. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.94, H 10.40.

Carboxy inversion: synthesis of (+)-dactylol (37)

A dried, 10 mL, round-bottomed flask was charged with 0.03 g (0.11 mmol) of acid **36**, 2.0 mL of 20% solution of $COCl_2$ in toluene, and four drops of DMF. The mixture was stirred at room temperature for 1 h, and then heated under reflux for 30 min. The mixture was allowed to cool to room temperature and was diluted with pentane (5 mL), filtered, and concentrated. The resulting colorless oil was dissolved in benzene (2.0 mL). *m*-CPBA (0.019 g, 0.11 mmol), pyridine (0.1 mL, 0.12 mmol), and DMAP (0.005 g) were added. The mixture was stirred at room temperature for 24 h, filtered, and concentrated. The volatile compounds were removed under high vacuum, and the residue was dissolved in ether (2 mL). The solution was cooled in an ice-water bath and 0.013 g (0.33 mmol) of $LiAlH_4$ was added. The suspension was stirred at 0 °C for 2 h and slowly quenched with water, filtered, and the white precipitate washed thoroughly with ether (5 mL × 3). The combined organic phases were concentrated, and the crude product was purified by flash chromatography (hexane–EtOAc, 10:1). (+)-Dactylol (**37**) was obtained as a white solid (0.012 g, 50%). mp 49 to 50 °C (lit. value (15e), mp 50.3–51.5 °C). $[\alpha]^{20}_D$ +21.38 (*c* 1.0, $CHCl_3$) (lit. value (15e)) $[\alpha]^{20}_D$ +22.5). IR (neat, cm^{-1}): 3500 (w), 2955 (s), 2872 (s), 1465 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 5.49 (t, *J* = 8.4 Hz, 1H), 2.21 (d, *J* = 13.4 Hz, 1H), 2.07 (d, *J* = 13.4 Hz, 1H), 1.95–1.85 (m, 2H), 1.82 (s, 3H), 1.80–1.71 (m, 1H), 1.70–1.60 (m, 1H), 1.57–1.49 (m, 2H), 1.46 (dd, *J* = 15.0, 7.9 Hz, 1H), 1.33 (br s, 1H), 1.09–0.95 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 3H), 0.85 (s, 3H), 0.71 (d, *J* = 114.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.9, 124.6, 82.8, 52.9, 43.1, 40.4, 39.4, 39.3, 36.5, 35.2, 29.5, 29.3, 28.9, 27.9, 19.2. Anal. calcd. for $C_{15}H_{26}O$: C 81.02, H 11.78; found: C 81.27, H 12.00.

[4 + 3] Cycloaddition of 11: synthesis of 38 and 39

Ketone **11** was subjected to an α-chlorination, [4 + 3] cycloaddition, and desilylation conditions using the procedure described in the synthesis of ketone **20**. Cycloadduct **38** and **39** were obtained and separated by hexane–EtOAC (20:1).

38

Yield: 47%, colorless oil. IR (neat, cm^{-1}): 3069 (m), 2950 (s), 2872 (s), 1730 (s), 1454 (m). ^1H NMR (250 MHz, $CDCl_3$) δ: 4.84 (s, 1H), 4.80–4.73 (m, 1H), 2.45–2.30 (m, 3H), 2.26–2.09 (m, 2H), 2.00–1.80 (m 3H), 1.79–1.40 (m, 6H), 1.39–1.29 (m, 1H), 1.21–1.09 (m, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.3, 146.0, 115.4, 58.2, 51.7, 43.7, 41.5, 40.0, 36.7, 36.3, 33.8, 26.3, 19.8. Anal. calcd. for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 81.92, H 9.65.

39

Yield: 18%, colorless oil. IR (neat, cm^{-1}): 3071 (w), 2957 (s), 2870 (m), 1737 (s), 1451 (m). ^1H NMR (250 MHz, $CDCl_3$) δ: 4.80–4.65 (m, 2H), 2.70 (dd, *J* = 7.1, 15.0 Hz, 1H), 2.26–2.54 (m, 1H), 2.38 (dd, *J* = 3.2, 13.6 Hz, 1H), 2.30–2.07 (m, 5H), 1.91–1.27 (m, 8H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.4, 145.8, 114.6, 58.5, 51.6, 44.8, 38.9, 36.1, 33.2, 30.0, 27.8, 26.2, 21.6. Anal. calcd. for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 81.95, H 9.33.

[4 + 3] Cycloaddition of 12: synthesis of 45 and 46

Ketone **12** was subjected to an α-chlorination, [4 + 3] cycloaddition, and desilylation conditions using the procedure described in the synthesis of ketone **20**. Cycloadducts **45** and **46** were obtained and separated by pentane–Et_2O (20:1).

45

Yield: 57%, colorless oil. $[\alpha]^{20}_D$ +41.46 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3070 (w), 2950 (s), 2863 (m), 1733 (s), 1456 (m). ^1H NMR (250 MHz, $CDCl_3$) δ: 4.87 (br s, 1H), 4.80 (t,

J = 2.0 Hz, 1H), 2.49–2.36 (m, 3H), 2.30–2.13 (m, 2H), 2.09–1.62 (m, 5H), 1.55–1.22 (m, 4H), 1.16–1.05 (m, 1H), 0.98 (d, J = 6.2 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.8, 145.8, 115.3, 59.1, 59.0, 43.7, 43.1, 40.3, 39.5, 37.4, 35.1, 33.9, 29.7, 18.2. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1499.

46

Yield: 9%, colorless oil. $[\alpha]^{20}_D$ –108.75 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3070 (w), 2951 (s), 2866 (m), 1733 (s), 1449 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.80–4.73 (m, 2H), 2.72 (dd, J = 5.9, 12.5 Hz, 1H), 2.62–2.50 (m, 1H), 2.38 (dd, J = 2.0, 11.5 Hz, 1H), 2.27–1.61 (m, 8H), 1.40–1.22 (m, 2H), 1.06–0.95 (m, 2H), 1.00 (d, J = 5.4 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.4, 145.7, 114.7, 59.3, 58.3, 44.8, 43.1, 37.1, 34.4, 31.3, 31.2, 29.2, 26.2, 18.6. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1517.

[4 + 3] Cycloaddition of 17: synthesis of 49–52

Ketone **17** was subjected to an α-chlorination, [4 + 3] cycloaddition and desilylation conditions using the procedure described in the synthesis of ketone **20**. Cycloadducts **49–52** were obtained and separated by pentane–Et_2O (20:1 to 10:1). Ketone **49** and **50** were not completely separable. The mixture was obtained as slightly yellow oil (41%). Further chromatographic purification on silica gel (pentane–Et_2O 30:1) afforded a sufficient amount of each isomer for characterization of the two isomers.

49

$[\alpha]^{20}_D$ +62.08 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3072 (w), 2949 (s), 2866 (s), 1731 (s), 1642 (m), 1452 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.83 (s, 1H), 4.77 (t, J = 2.0 Hz, 1H), 2.46–2.33 (m, 2H), 2.31–2.15 (m, 2H), 2.13–2.00 (m, 2H), 1.99–1.84 (m, 2H), 1.81–1.61 (m, 3H), 1.59–1.24 (m, 3H), 1.22–1.08 (m, 1H), 1.04 (d, J = 6.6 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 220.8, 146.6, 115.1, 60.2, 52.7, 51.3, 46.1, 41.8, 39.2, 36.4, 33.6, 28.0, 26.3, 21.0. HR-MS (EI) calcd. for $C_{15}H_{24}O$ (M^+): 204.1514; found: 204.1510.

50

$[\alpha]^{20}_D$ +13.24 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3069 (w), 2934 (s), 2869 (m), 1733 (s), 1643 (m), 1456 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.91–4.88 (m, 1H), 4.85 (br s, 1H), 2.64 (dd, J = 4.7, 12.6 Hz, 1H), 2.54 (d, J = 13.6 Hz, 1H), 2.38–2.12 (m, 5H), 1.99–1.41 (m, 7H), 1.28–1.17 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 223.5, 146.3, 114.2, 57.9, 55.0, 51.6, 47.3, 40.1, 36.9, 34.3, 34.2, 30.7, 25.8, 15.1. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1520.

51

Yield: 7%, colorless oil. $[\alpha]^{20}_D$ +32.17 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3072 (w), 2953 (s), 2871 (s), 1737 (s), 1637 (w), 1457 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.78–4.71 (m, 2H), 2.75–2.63 (m, 1H), 2.48–2.34 (m, 2H), 2.29–2.04 (m, 5H), 1.89–1.26 (m, 6H), 1.13 (dd, J = 6.7, 20.7 Hz, 1H), 1.04 (d, J = 7.0 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.0, 145.8, 114.8, 59.8, 54.2, 51.5, 38.3, 37.5, 36.5, 34.7, 33.9, 30.1, 23.9, 21.6. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1503.

52

Yield: 4%, colorless oil. IR (neat, cm^{-1}): 3072 (w), 2948 (s), 2872 (s), 1738 (s), 1635 (w), 1455 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.79–4.74 (m, 2H), 2.52–1.52 (m, 13H), 1.44–1.19 (m, 2H), 1.13 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 220.4, 145.6, 115.3, 59.6, 52.3, 50.8, 37.5, 35.7, 34.3, 30.7, 29.9, 29.6, 21.8, 15.6. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1524.

[4 + 3] Cycloaddition of 19: synthesis of 53–56

Ketone **19** was subjected to an α-chlorination, [4 + 3] cycloaddition, and desilylation conditions using the procedure described in the synthesis of ketone **20**. Cycloadducts **53–56** were obtained and separated by pentane–Et_2O (30:1 to 10:1).

53

Yield: 10%, colorless oil. $[\alpha]^{20}_D$ +67.40 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2950 (s), 2927 (s), 2867 (m), 1732 (s), 1455 (m), 1379 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.85 (br s, 1H), 4.80–4.78 (m, 1H), 2.45–2.36 (m, 1H), 2.30–1.90 (m, 7H), 1.80–1.57 (m, 3H), 1.50–1.40 (m, 1H), 1.38–1.23 (m, 2H), 1.04 (d, J = 6.3 Hz, 3H), 0.83 (d, J = 7.2Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.6, 147.6, 115.2, 60.8, 53.4, 52.9, 46.6, 39.5, 39.3, 37.5, 34.1, 31.7, 28.1, 21.0, 15.1. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.67, H 10.33.

54

Yield: 41%, colorless oil. $[\alpha]^{20}_D$ +34.55 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2950 (s), 2933 (s), 2868 (m), 1731 (s), 1452 (m), 1165 (w). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.92–4.88 (m, 1H), 4.85 (br s, 1H), 2.64–2.53 (m, 2H), 2.35–2.12 (m, 5H), 1.94–1.81 (m, 2H), 1.60–1.18 (m, 5H), 1.12 (d, J = 6.2 Hz, 3H), 0.93 (d, J = 6.3 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 223.6, 146.1, 114.2, 61.2, 58.7, 51.5, 48.0, 40.8, 28.3, 34.9, 34.8, 34.5, 30.7, 17.3, 15.1. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.36, H 9.97.

55

Yield 12%, colorless oil. $[\alpha]^{20}_D$ +75.05 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2950 (s), 2932 (s), 2863 (m), 1732 (s), 1456 (m), 1375 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.77 (br s, 1H), 4.75–4.72 (m, 1H), 2.71 (dd, J = 7.6, 14.9 Hz, 1H), 2.50–1.60 (m, 10H), 1.43–1.07 (m, 3H), 1.02 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 220.8, 145.7, 114.8, 60.5, 58.1, 54.1, 38.7, 38.4, 37.2, 34.8, 34.6, 32.0, 31.3, 23.8, 18.6. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.39, H 10.19.

56

Yield 7%, colorless oil. $[\alpha]^{20}_D$ +25.40 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2956 (s), 2868 (s), 1737 (s), 1460 (m), 1169 (m), 1121 (w). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.82–4.76 (m, 2H), 2.53–1.61 (m, 12H), 1.50–1.18 (m, 2H), 1.11 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 220.5, 146.0, 115.7, 59.4, 54.3, 51.3, 36.9, 35.2, 35.0, 34.4, 33.4, 31.9, 29.4, 18.4, 15.4. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.51, H 9.99.

Acknowledgment

This paper is dedicated to Dr. Alfred R. Bader on the occasion of his 80th birthday and as a tribute to his many contributions to organic chemistry, art, scholarship, and humanity. This work was supported by the National Science Foundation, to whom we are grateful.

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Polycyclic oxonium ylides — Use of cyclic acetals as convenient scaffolds in the construction of fused bicyclic compounds containing a medium ring[1]

Graham K. Murphy, Fredrik P. Marmsäter, and F.G. West

Abstract: Cyclic mixed acetals with pendant diazoketone side chains undergo efficient rearrangement to ether-bridged cyclooctanoid and cycloheptanoid systems upon treatment with $Cu(hfacac)_2$. Stevens [1,2]-shift of an oxonium ylide furnishes the major product, in some cases accompanied by minor amounts of a product resulting from [1,2]-shift of a sulfonium ylide. These results demonstrate that hetero-substituted carbons are suitable migrating groups for the Stevens [1,2]-shift of oxonium ylides. In cases employing a mixed thioacetal, the resulting sulfide served as a trigger for cleavage of the bridging ether through one of two complementary strategies. In the hydrazulene series, the desired bicyclo[5.3.0]heptene was accompanied by the product of novel transannular S_N2' attack on the resulting allylic ketal.

Key words: [1,2]-shift, diazo, medium-sized ring, oxonium ylide, ring expansion.

Résumé : Les acétals cycliques mixtes portant des chaînes latérales diazocétones soumis à un traitement avec du $Cu(hfacac)_2$ subissent un réarrangement efficace en systèmes cyclooctanoïdes et cycloheptanoïdes à pont éther. Un déplacement [1,2] de Stevens d'un ylure d'oxonium conduit à la formation du produit principal qui est dans quelques cas accompagné de quantités mineures d'un produit qui résulte d'un déplacement [1,2] d'un ylure de sulfonium. Ces résultats démontrent que les carbones substitués par des hétéroatomes sont des groupes migratoires appropriés pour le déplacement [1,2] de Stevens d'ylures d'oxonium. Dans les cas où on fait appel à un acétal mixte, le sulfure qui en résulte sert à déclencher le clivage de l'éther de pont par le biais d'une des deux stratégies complémentaires. Dans la série de l'hydroazulène, le bicyclo[5.3.0]heptène est accompagné par le produit d'une nouvelle attaque transannulaire S_N2' sur le cétal allylique qui en résulte.

Mots clés : déplacement [1,2], diazo, cycle de taille moyenne, ylure d'oxonium, expansion de cycle.

[Traduit par la Rédaction]

Introduction

Stereocontrolled synthesis of medium-sized carbocycles is an important challenge in synthetic organic chemistry. We have had a long-standing interest in the chemical synthesis of natural products such as dactylol, traversianal, and phorbol (Fig. 1). Common structural features among these compounds include the presence of a functionalized medium-sized ring fused to one or more smaller rings, along with bridgehead oxygenation. Efforts towards the chemical synthesis of these compounds have resulted in many new methods (1). For example, use of a preexisting carbocyclic or heterocyclic ring as a scaffold could allow the formation of an intermediate bridged bicyclic compound by closure of a smaller second ring. Fragmentation of the bridge would then reveal a medium-ring skeleton and install a bridgehead hydroxyl group (2), although attempted cleavage of bridging ethers (3) or their carbon analogues (4) is not always a straightforward process.

The Stevens [1,2]-shift of fused bicyclic oxonium ylides can furnish medium-ring ethers or carbocycles with bridging ethers (5). Early examples typically involved the migration of aryl-substituted carbons, and the products were not well suited to synthetic manipulation. In an effort to broaden the synthetic potential of this approach, we have examined various hetero-substituted examples of the oxonium ylide ring expansion (6, 7). By this approach, bicyclic acetals with bridgehead diazoketone side chains could be used as convenient scaffolds for the construction of seven- and eight-membered carbocycles (Scheme 1). The key [1,2]-shift step is believed to involve a stepwise homolytic mechanism, with subsequent recombination of the intermediate biradical (8).

Here we present a full account of this work, an oxonium ylide-based method that permits the concise synthesis of

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Dedicated to Dr. Alfred Bader in recognition of his immense impact on the field of organic chemistry and his lasting legacy to Canadian science.

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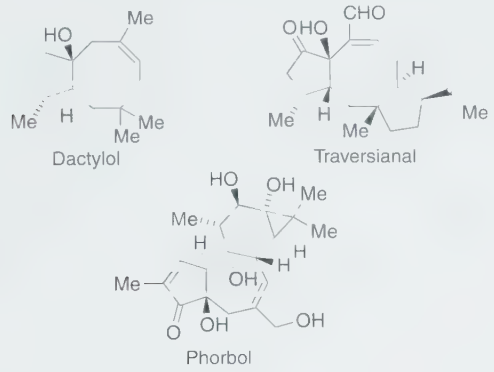
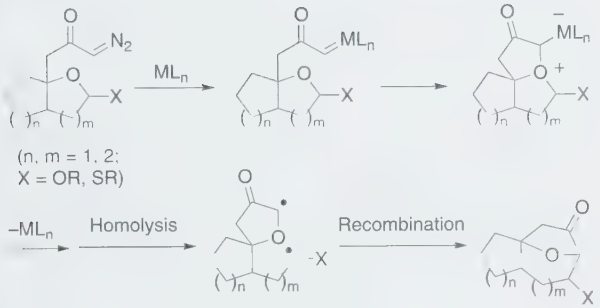
Fig. 1. Medium ring containing natural products possessing angular hydroxyls.



Scheme 1.



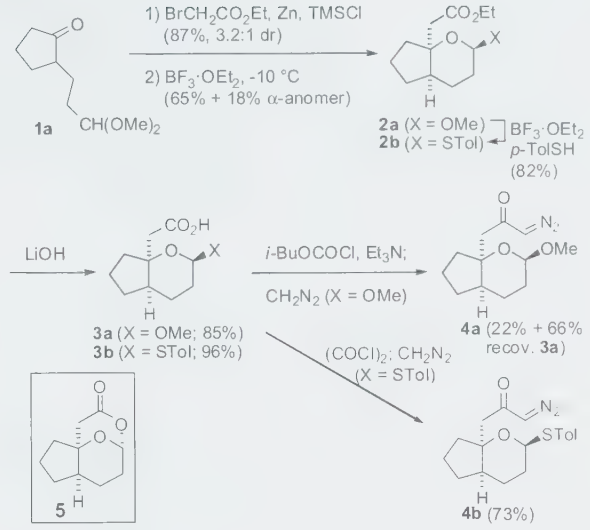
functionalized fused 5–8 and 5–7 bicyclic ring systems using a novel sulfur- or oxygen-directed Stevens rearrangement of oxonium ylides. In addition, convenient methodology is described for subsequent sulfur-mediated cleavage of the ether bridge to introduce a bridgehead alcohol.

Results and discussion

Substrate synthesis

Substrates were prepared in a straightforward fashion via cyclopentanone precursors **1** (Scheme 2). Reformatsky addition of ethyl bromoacetate to the known 2-(3,3)-dimethoxypropyl)-cyclopentanone **1a** (9) was followed by conversion to cyclic acetal **2a** with $BF_3{\cdot}OEt_2$. The methoxy group of the acetal could be exchanged for STol with careful control of temperature and stoichiometry to give mixed thioacetal **2b**. Both **2a** and **2b** were formed as the expected β anomers. Saponification to the acids **3a** and **3b** was uneventful and these intermediates were then converted to the desired diazoketones **4a** and **4b**. Diazoketone **4a** was formed via activation of **3a** as the mixed anhydride, followed by treatment with diazomethane. This method was not suitable in the case of **3b**, as the mixed anhydride was found to be insufficiently reactive. The corresponding acid chloride did furnish some of **4b**, but the process was complicated by the formation of lactone-bridged side product **5**. This material presumably results from acid-catalyzed decomposition of the

Scheme 2.



thioacetal with subsequent trapping by the carboxyl group. We eventually found that careful control of reaction temperature minimized the formation of **5**, allowing access to **4b** in 73% yield.

The lower homologue **1b** (10) was treated with the lithium enolate of ethyl acetate and the diastereomeric adducts were treated with $BF_3{\cdot}OEt_2$ (Scheme 3).[3] This effected cyclization of the cis isomer to the fused bicyclic mixed acetals **2c** and **2d** (4.4:1 mixture of anomers), while leaving the trans diastereomer unchanged. Thio exchange (HSTol, $BF_3{\cdot}OEt_2$) furnished the corresponding mixed thioacetals **2e** and **2f** in good yield. The esters **2c**–**2f** were subjected to saponification to give acids **3c**–**3f**, then converted to diazoketones **4c**–**4f**. As before, the methoxy acetals could be activated via the mixed anhydrides, but the thioacetals required the more reactive acid chlorides. In these cases, the presence of 2,6-lutidine was found to suppress acid-catalyzed decomposition, allowing the formation of **4e** and **4f** in 60% yield.

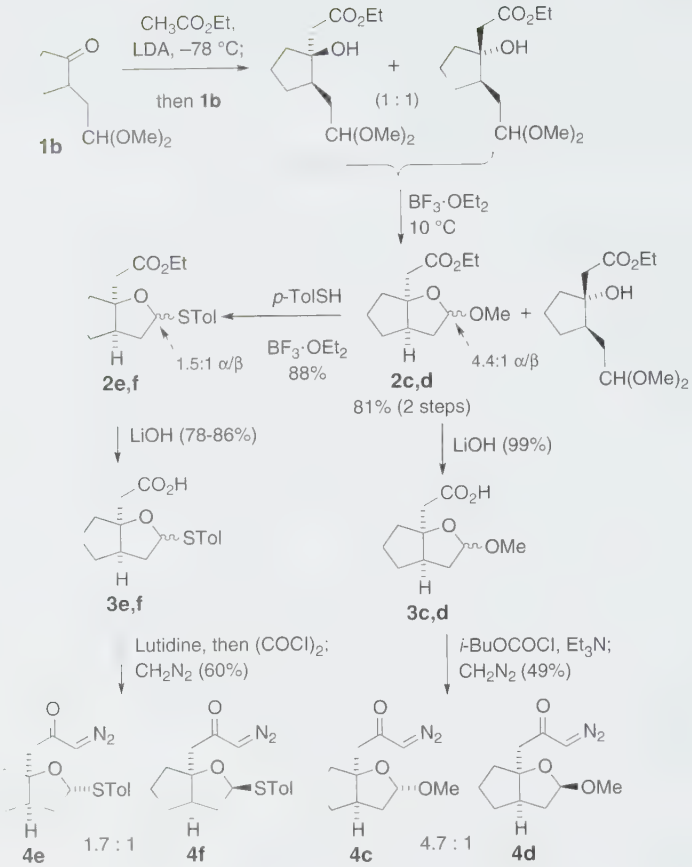
Finally, two substrates possessing additional carbonyl stabilization at the incipient ylide centre were prepared (Scheme 4). Mixed thioacetals **2b**, **2e**, and **2f** were condensed with ethyl acetate to furnish the corresponding keto esters **6a**–**6c**. Attempts to form **6a** more directly by the addition of the dianion of ethyl acetoacetate to **1a** and **1b**, cyclization to the mixed acetal, and thio exchange encountered a variety of undesired side reactions, so the crossed Claisen approach was followed in all three cases. Standard diazotransfer conditions with *p*-toluenesulfonyl azide (11) were then carried out on **6a** and the major five-membered anomer **6b** to yield the diazoketones **4g** and **4h**.

Oxonium ylide generation and rearrangement — Formation of bicyclo[6.3.0]undecanones and bicyclo[5.3.0]decanones

Substrates **4a**–**4h** were subjected to catalytic carbene transfer conditions to effect generation of the desired

[3] Use of Reformatsky conditions resulted in similar diastereomer ratios and lower yields.

Scheme 3.



oxonium ylide intermediates. Initial trials with thioacetal **4b** (Scheme 5) were conducted using several transition metal catalysts known to effect oxonium ylide formation (8, 12). Rhodium(II) catalysts were found to be ineffective: both rhodium(II) acetate dimer and the bulkier rhodium(II) triphenylacetate (13) gave a side product tentatively assigned as **8** and only minor amounts of the desired [1,2]-shift product **7b**.[4] There is considerable precedent for poor selectivity for oxonium ylide formation vs. C–H insertion with rhodium carbenoids (5*b*, 8, 12). The optimal conditions ($Cu(tfacac)_2$, CH_2Cl_2, reflux) for the generation and [2,3]-shift of allyl-substituted oxonium ylides (12, 14) gave only low yields of several unidentified products, consistent with the observation that this catalyst is not effective for 1,2]-shift processes (14). In contrast to the above, $Cu(hfacac)_2$ provided **7b** in high yield and with excellent diastereoselectvity. The major diastereomer of **7b** was the result of a [1,2]-shift with retention of configuration at the migrating anomeric centre.[5] Mixed acetal **4a** was also subjected to the optimized conditions found for **4b** and furnished the analogous [1,2]-shift product **7a** in good yield as a single diastereomer, again the result of migration with retention.

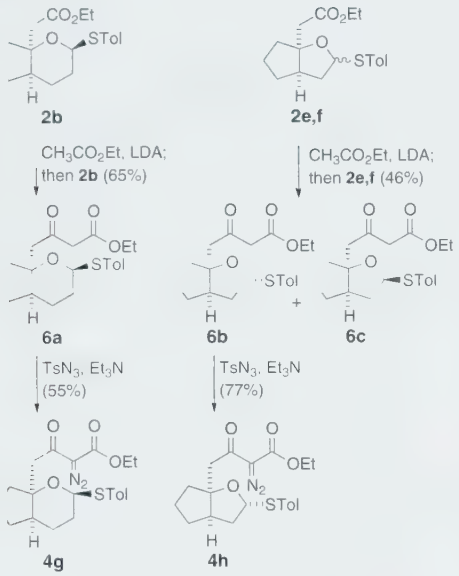
The five-membered acetal substrates **4c–4f** were next examined (Scheme 6). In each case, the desired ether-bridged bicyclo[5.3.0]octanone system was formed, although the degree of stereochemical retention observed was substantially lower than with **4a** and **4b**. Thus, either the α anomer (**4c**) or the β anomer (**4d**) of the methoxy mixed acetal provided a mixture of **7c** and **7d** in moderate yield, in each case with a small preference for the product of retention. In the case of **4c**, an additional very minor product was isolated and tentatively assigned as structure **9**.[6] Mixed thioacetal **4f** underwent conversion to **7e** and **7f** in excellent yield and with relatively good diastereoselectivity. The corresponding α anomer (**4e**) provided the same products in somewhat lower yield, but in this case a side product, **10e**, was isolated in significant quantities. This compound apparently results from formation of the alternative sulfonium ylide **A**, fol-

[1] Spectral data indicated a newly formed ketone and an intact thioacetal. Evidence for the proposed structure includes the apparent presence of an anomeric acetal-type proton in the ^1H NMR spectrum and a ^{13}C NMR carbonyl chemical shift consistent with a cyclopentanone.

[5] X-ray data confirming the structures of compounds **7b** and **12** can be found in CIF format in the Supporting Information of ref. 7*a*.

[6] Compound **9** may arise from competing formation of the oxonium ylide derived from the OMe group, followed by a 1,4-shift of the methyl substituent. Evidence for the proposed structure of this acid-labile substance includes the presence of both an enol ether and an anomeric carbon, and its silica gel-mediated conversion to an apparent α-methoxy aldehyde.

Scheme 4.



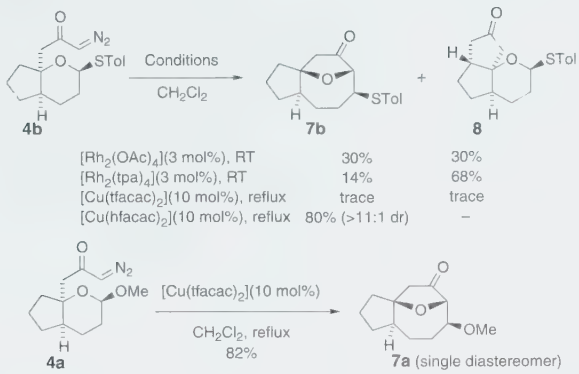
lowed by [1,2]-shift of the anomeric carbon with concomitant ring contraction.

Finally, the doubly stabilized diazoketoester substrates **4g** and **4h** were subjected to $Cu(hfacac)_2$ in refluxing toluene (Scheme 7). Six-membered thioacetal **4g** underwent conversion to **7g** (4.5:1 mixture of diastereomers) in moderate yield. The five-membered thioacetal **4h** gave dramatically different results: only minor amounts of the oxonium ylide-derived products **7h** and **7i** (8:1 dr) were obtained. Instead, the major product was **10h** (ca. 7:1 dr), resulting from selective formation and rearrangement of the sulfonium ylide.

In the key rearrangement steps, it appears that in most cases the oxonium ylide was formed efficiently with $Cu(hfacac)_2$ catalysis and underwent smooth a [1,2]-shift to give the ether-bridged medium-ring products. The exceptions are the doubly stabilized substrates **4g** and **4h**, which did not react in refluxing CH_2Cl_2 and required extended stirring in refluxing toluene to consume starting material. Carbene transfer from diazo compounds substituted with two electron-withdrawing groups is known to be relatively slow.[7] Although the diastereoselectivity varied substantially, in all cases the major product resulted from migration with retention of configuration. Most mechanistic evidence related to ylide [1,2]-shifts points to stepwise rearrangement via radical pair intermediates (8). However, rearrangement with moderate to high degrees of retention in the Stevens rearrangement of both oxonium (5) and ammonium (15) ylides has been observed. One possible explanation for migration with retention is rapid radical recombination as compared with bond rotation (16). However, direct involvement by the transition metal catalyst in the rearrangement step cannot be ruled out (8*b*, 17).

The origin of the lower levels of retention seen for the five-membered acetals **4c**–**4f** as compared with the six-membered substrates **4a**, **4b**, and **4g**, is unclear. Assuming a

Scheme 5.



stepwise mechanism via a radical pair intermediate, this result suggests that the relative rate for recombination vs. bond rotation is greater for six-membered rings despite the presence of an additional freely rotating C–C bond in the side chain. A possible explanation may derive from the relative strain of the angularly fused tricyclic ylide precursors. Homolysis of the more strained 5-5-5 tricyclic ylide **B** could involve greater ring strain release, which might permit a higher amount of randomization by the biradical **C** prior to recombination than in the case of the higher homologues **D** and **E** (Scheme 8; shown for β anomers but also applicable to α anomers **4c**, **4e**, and **4h**). Recombination of **C** may also be slowed relative to that of **E** as a result of increased strain in the cyclization transition state due to the shorter tether. However, since involvement of the catalyst in the [1,2]-shift is also possible (8*b*, 14), this explanation must be viewed as tentative.

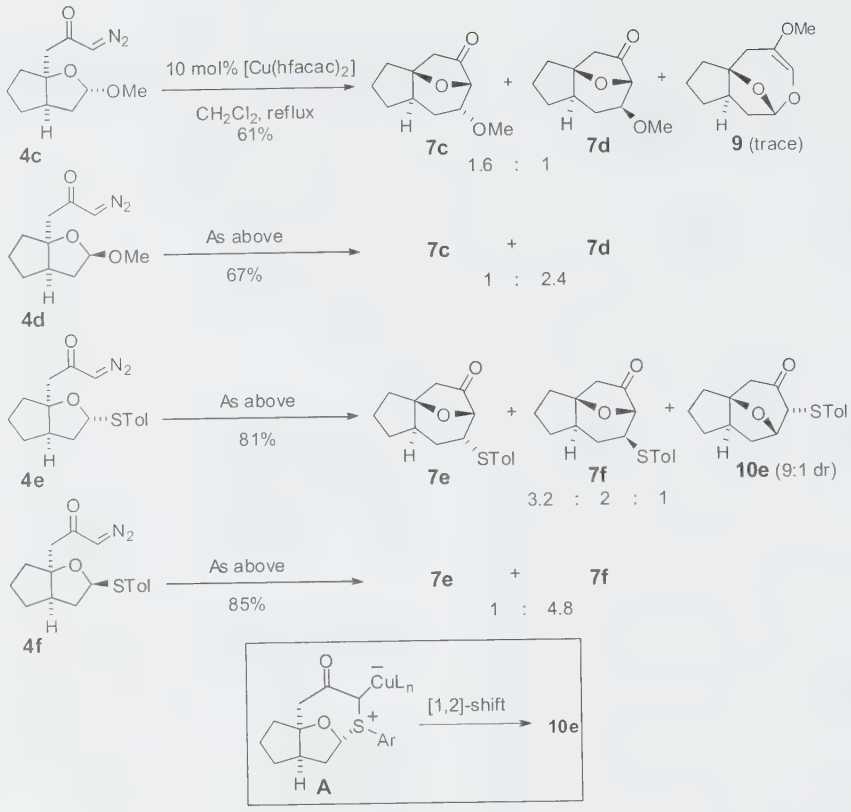
Competing formation of the ylide derived from the exocyclic XR group was observed in several cases. This was not seen for six-membered acetal substrates **4a**, **4b**, and **4g** due to the predominant or exclusive formation of the β anomers, with the XR group disposed trans to the diazoketone side chain. On the other hand, the five-membered acetals were formed as anomeric mixtures, and products apparently resulting from the alternative ylides were seen in each case with the α anomers (**4c**, **4e**,and **4h**). Notably, **4h** reacted mainly via the 7-membered sulfonium ylide, possibly as a result of the greater electrophilicity and (or) selectivity of the metallocarbene precursor. Equilibration between the two possible ylides may be possible, based on related competition experiments (4).

Cleavage of the ether bridge

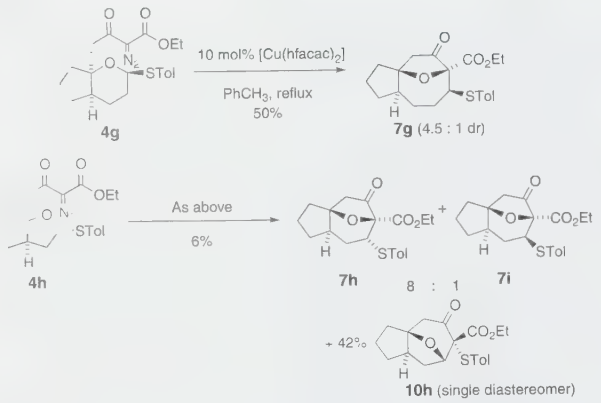
The methodology described above allows for quick entry into a series of ether-bridged fused bicyclic skeletons containing a medium-sized ring. For application to natural product targets, an effective method for cleavage of the bridging ether is needed. We felt that the thioacetal-derived products **7b** and **7e** were well suited to this goal: the thioaryl group, which had effectively mediated the [1,2]-shift of the former anomeric carbon, could now be used as an anionic trigger for eliminative opening of the ether. First, the keto group of

[7] See ref. 11, pp. 64–65.

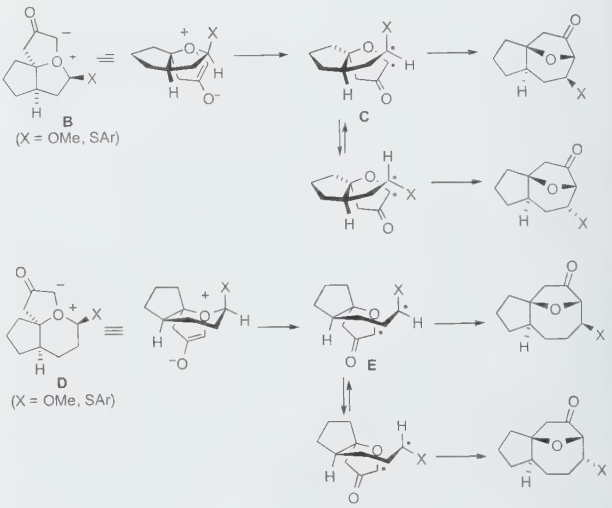
Scheme 6.



Scheme 7.

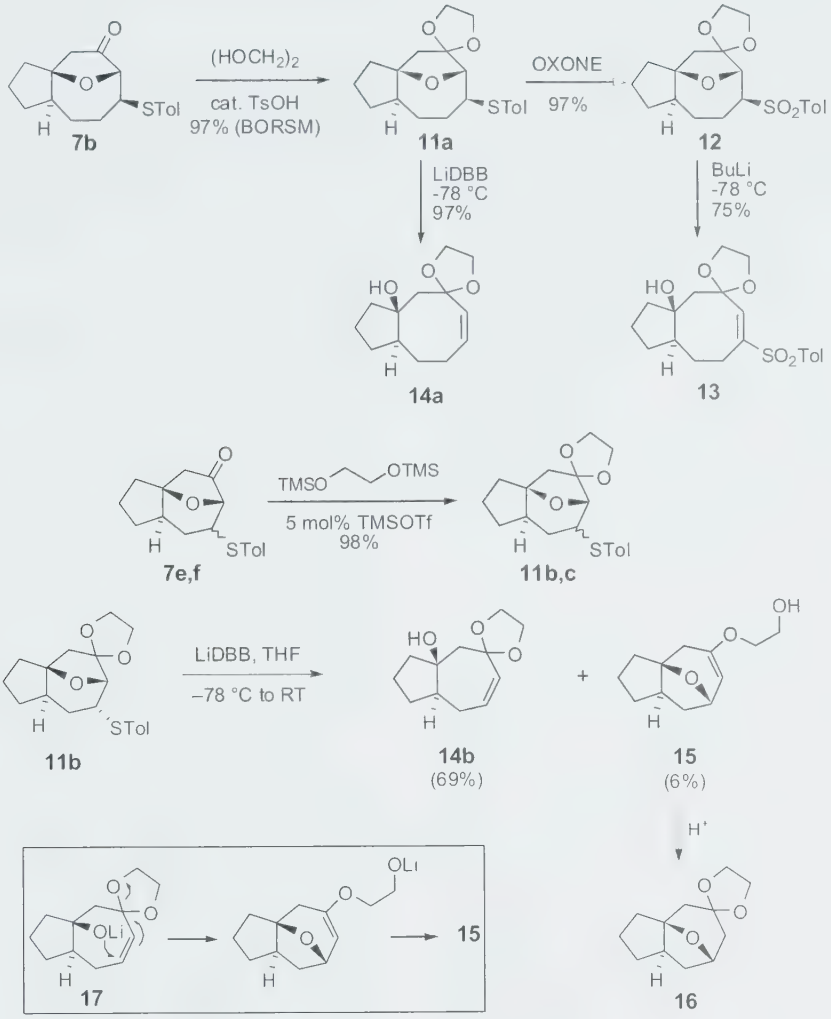


Scheme 8.



7b was protected as the ethylene ketal to give **11a**, and the thioaryl group oxidized to the corresponding sulfone **12** (18) (Scheme 9). Treatment of this compound with *n*-BuLi at low temperature effected the elimination of the ether to give unsaturated sulfone **13**. Alternatively, **11a** could be subjected to reductive desulfurization with LiDBB (19) to provide cyclooctene **14a** in excellent yield. A mixture of hydrazulenes **7e** and **7f** was converted to ketals **11b** and **11c**, and **11b** was also subjected to the reductive conditions. In this case, cycloheptene **14b** was obtained in good yield, accompanied by minor amounts of enol ether **15**, which underwent slow, acid-catalyzed conversion to ketal **16**. This compound is believed to arise from in situ transannular S_N2' attack by the initially formed lithium alkoxide **17** on the unsaturated ketal. Paquette et al. (20) reported a related case involving

Scheme 9.



transannular cyclization of a medium-ring enolate with concomitant with S_N2' displacement of a methoxy leaving group.

The methodology described here allows for the expeditious construction of fused bicyclic skeletons containing a medium-sized ring, starting with readily available mixed acetals. In cases involving mixed thioacetals, two convenient methods are available for cleavage of the bridging ethers found in the rearrangement products. Interesting reactivity differences are seen, depending upon ring size and anomeric configuration. Application of this chemistry to natural product targets is currently underway and will be reported in due course.

Experimental[8]

General information

Reactions were conducted in oven-dried (120 °C) or flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: dichloromethane from calcium hydride; diethyl ether and tetrahydrofuran from sodium benzophenone ketyl. Thin layer chromatography (TLC) was performed on plates of silica precoated with 0.25 mm Kieselgel 60 F_{254}. Flash chro-

[8] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5103. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 227793 and 227794 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

matography columns were packed with 230–400 mesh silica gel. Where given, column dimensions include outer diameters. Radial chromatography was performed on plates of silica precoated with 1, 2, or 4 mm silica gel 60 PF_{254} containing gypsum.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300, 400, or 500 MHz on Varian Inova 300, 400, and 500, Mercury 400, or Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Coupling constants (*J*) are reported in Hz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Infrared spectra (IR) were measured with a Nicolet Magna 750 FT-IR infrared spectrophotometer. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Elemental analyses were obtained at the University of Alberta on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer.

Substrate syntheses

Ethyl 2-(2-(3,3-dimethoxypropyl)-1-hydroxycyclopent-1-yl)acetate

To a two-necked flask equipped with a large stir bar and condenser, charged with a mixture of Zn (400 mg, 6.1 mmol) in Et_2O (6 mL), TMSCl (47 µL, 0.36 mmol) was added via syringe (21). The mixture was heated to reflux for 15 min and then stirred at RT for an additional 15 min. Freshly distilled ethyl bromoacetate (0.68 mL, 6.1 mmol) was added dropwise via syringe. The mixture was heated to reflux for 45 min and then stirred at RT for an additional 1 h. During this time, the mixture turned to a yellow tint and most of the solid Zn was consumed. The solution of Reformatsky reagent thus prepared was then transferred via cannula to a second flask, leaving behind any remaining solid Zn. The flask was then cooled to –10 °C (acetone – ice bath) and 2-((3,3)-methoxypropyl)cyclopentanone **1a** (8) (677 mg, 3.61 mmol) was slowly added as a solution in Et_2O (3 mL) via cannula. The reaction was stirred at –10 °C for 1 h and then for an additional 2 h at RT at which time the reaction had consumed the starting material as ascertained by TLC. The reaction was diluted with Et_2O (30 mL) and quenched by addition of satd. NH_4Cl solution (30 mL). The aqueous phase was extracted with Et_2O (3 × 30 mL) and the combined organic phase was dried with $MgSO_4$, filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 3 cm × 24 cm column, solvent ramp: 200 mL each of 20%, 30%, and 40% EtOAc–hexanes) to yield the desired alcohol (856 mg, 87%) as a 3.2:1 cis/trans mixture of diastereomers. R_f = 0.17 (30% EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3516, 2951, 2872, 1731, 1189, 1053. ^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer) δ: 4.35 (t, *J* = 5.7 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.32 (s, 3H), 3.30 (s, 3H), 2.71 (d, J_{AB} = 15.7 Hz, 1H), 2.33 (d, J_{AB} = 15.4 Hz, 1H), 1.90–1.44 (m, 11H), 1.38–1.31 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer) δ: 173.6, 105.1, 79.7, 60.9, 53.3, 52.7, 49.5, 40.0, 31.9, 29.9, 23.9, 21.3, 14.4. HR-MS (ESI) calcd. for $C_{13}H_{22}O_4$ ($M - MeOH^+$): 242.1518; found: 242.1521.

Mixed acetal 2a

To a solution of ethyl 2-(2-(3,3-dimethoxypropyl)-1-hydroxycyclopent-1-yl)acetate (812 mg, 2.96 mmol, 3.2:1 mixture of diastereomers) in CH_2Cl_2 (150 mL) cooled to –10 °C (acetone – ice bath), $BF_3{\cdot}OEt_2$ (376 µL, 2.96 mmol) was added via syringe. The reaction was stirred for 15 min at which time the reaction had consumed the starting material as ascertained by TLC. The reaction was quenched by addition of Et_3N (~1 mL) followed by H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL) and the combined organic phase was washed with brine (200 mL), dried with Na_2SO_4, filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 3 cm × 24 cm column, solvent ramp: 200 mL each of 2.5%, 5%, 10%, and 20% EtOAc–hexanes) to yield the minor (α) anomer of **2a** (99 mg, 18% based on 3.2:1 diastereomer ratio of starting material), major (β) anomer of **2a** (354 mg, 65% based on 3.2:1 diastereomer ratio of starting material), and a mixture of anomers derived from the minor trans diastereomer (131 mg, 77% based on 1:3.2 diastereomer ratio of starting material). Major anomer of **2a**: R_f = 0.49 (30% EtOAc – hexanes). IR (neat, cm^{-1}): 2953, 2870, 1734, 1368, 1225, 1150, 1016. ^{1}H NMR (500 MHz, $CDCl_3$, major anomer) δ: 4.62 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.21 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.09 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.42 (s, 3H), 2.97 (d, J_{AB} = 13.4 Hz, 1H), 2.31 (d, J_{AB} = 13.3 Hz, 1H), 2.10–2.05 (m, 1H), 1.92–1.84 (m, 2H), 1.82–1.65 (m, 5H), 1.63–1.54 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, major anomer) δ: 171.1, 98.6, 83.8, 60.5, 56.1, 41.1, 40.9, 39.9, 27.9, 25.9, 21.9, 21.8, 14.5. HR-MS (ESI) calcd. for $C_{13}H_{22}O_4$ (M^+): 242.1518; found: 242.1516.

Thioglycoside 2b

A solution of **2a** (275 mg, 1.14 mmol) and thiocresol (141 mg, 1.14 mmol) in CH_2Cl_2 (114 mL) was stirred for 10 min to ensure that the thiocresol was completely dissolved. The solution was cooled to –10 °C (acetone – ice bath) and $BF_3{\cdot}OEt_2$ (144 µL, 1.14 mmol) was added dropwise via syringe. The reaction was stirred for 10 min at which time the reaction had consumed the starting material as ascertained by TLC. The reaction was quenched by addition of Et_3N (~1 mL) followed by H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL) and the combined organic phase was washed with brine (200 mL), dried with Na_2SO_4, filtered, and concentrated. The resulting oil was purified by radial chromatography (4 mm plate, solvent ramp: 100 mL each of 2.5%, 5%, and 10% EtOAc–hexanes) to yield **2b** as a single anomer (313 mg, 82%). R_f = 0.53 (30% EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2951, 2869, 1733, 1221, 1044. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 4.90 (dd, *J* = 10.6, 3.6 Hz, 1H), 4.05 (dq, *J* = 11.1, 7.3 Hz, 1H), 3.95 (dq, *J* = 10.9, 7.3 Hz, 1H), 2.88 (d, J_{AB} = 13.6 Hz, 1H), 2.45 (d, J_{AB} = 13.5 Hz, 1H), 2.31 (s, 3H), 2.10–2.05 (m, 1H), 1.92–1.55 (m, 10H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.9, 137.6, 133.4, 130.1, 129.5, 84.6, 79.8, 60.5, 40.1, 39.9, 39.4, 27.7, 25.9, 22.7, 22.0,

21.3, 14.4. HR-MS (ESI) calcd. for $C_{12}H_{19}O_3$ (M – $CH_3C_6H_4S^+$): 211.1334; found: 211.1336.

Acid 3a

To a solution of hemiacetal **2a** (410 mg, 1.69 mmol) in THF (3.0 mL) and methanol (3.0 mL), a 2 mol/L solution of LiOH (1.7 mL) was added. The reaction was stirred for 16 h at RT, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (15 mL) and Et_2O (15 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with ether (15 mL). The aqueous layer was then acidified with 0.5 mol/L HCl to pH ~3, resulting in a cloudy suspension. Ethyl acetate (20 mL) was added to this and the resulting layers separated. The aqueous layer was washed with 3 portions of ethyl acetate (20 mL) and the combined organic extracts were washed with water and then brine, dried over magnesium sulfate, filtered, and concentrated to yield the acid, as a yellow oil (307 mg, 85%). IR (CH_2Cl_2 cast, cm^{-1}): 3500–2400, 2946, 2891, 2680, 1704, 1451, 1408, 1391, 1363, 1335, 1322, 1307. ^1H NMR (500 MHz, $CDCl_3$) δ: 10.90 (br s, 1H), 4.66–4.64 (m, 1H), 3.41 (s, 3H), 2.94 (d, J_{AB} = 14.1 Hz, 1H), 2.35 (d, J_{AB} = 14.1 Hz, 1H), 2.16 (m, 1H), 1.91–1.80 (m, 3H), 1.78–1.72 (m, 4H), 1.66–1.58 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.9, 98.9, 83.8, 56.0, 41.2, 41.0, 38.9, 28.1, 26.2, 21.7, 21.5. HR-MS (EI) calcd. for $C_{11}H_{18}O_4$ (M^+): 214.1205; found 214.1192. Anal. calcd. for $C_{11}H_{18}O_4$: C 61.66, H 8.73; found: C 61.31, H 8.47.

(1S*,3S*,6R*)-3-Methoxy-2-oxabicycl[4.3.0]nonane-1-acetic acid isobutyrylcarbonic mixed anhydride

To a solution of the acid (100 mg, 0.47 mmol) in Et_2O (2 mL) at 0 °C was added Et_3N (68 μL, 0.49 mmol) followed by isobutyl chloroformate (65 μL, 0.49 mmol). The reaction was stirred for 4 h, resulting in an off-white precipitate. The reaction mixture was filtered through a fritted filter (D), the residue was rinsed with Et_2O (20 mL), and the combined filtrates were concentrated to give the anydride as a yellow oil (149 mg, 100%) used directly in the next step. R_f = 0.66 (30% EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2956, 2874, 1819, 1735, 1457, 1392, 1369, 1336, 1307, 1230, 1207. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.60 (dd, J = 8.8, 3.0 Hz, 1H), 4.04 (d, J = 6.7 Hz, 2H), 3.42 (s, 3H), 3.08 (d, J_{AB} = 13.6 Hz, 1H), 2.42 (d, J_{AB} = 13.6 Hz, 1H), 2.16 (m, 1H), 2.01 (sept, J = 6.7 Hz, 1H), 1.94–1.83 (m, 2H), 1.82–1.68 (m, 5H), 1.64–1.53 (m, 3H), 0.97 (d, J = 6.7 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.4, 149.3, 98.7, 83.5, 75.7, 56.2, 41.2, 40.9, 39.7, 28.0, 27.8, 25.9, 21.9, 21.8, 19.0. HR-MS (EI) calcd. for $C_{16}H_{26}O_6$ (M^+): 314.1729; found: 314.1721.

Diazoketone 4a

Into a solution of freshly prepared diazomethane (12 mmol) in Et_2O (40 mL) at –15 °C was added a solution of the mixed anhydride (250 mg, 0.80 mmol) in Et_2O (10 mL), and the resulting mixture was allowed to stir overnight as the cold bath expired. A stream of N_2 was applied to the system to allow for slow evaporation of both excess diazomethane and solvent, and the resulting yellow oil was diluted in ether and passed through a short pad of silica gel in a fritted filter, eluting with ether. This was then concentrated and the resulting oil purified by radial chromatography (2 mm plate, solvent ramp: 100 mL each of 5%, 10% then 15% EtOAc–hexanes until the product was recovered) to yield starting material (152 mg) as well as **4a** (51 mg, 22%; 70% BRSM) as a yellow oil. R_f = 0.33 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3082, 2953, 2869, 2101, 1733, 1637, 1457, 1364, 1226, 1187. ^1H NMR (500 MHz, –20 °C, $CDCl_3$) δ: 5.50 (s, 1H), 4.64 (dd, J = 8.4, 3.1 Hz, 1H), 3.46 (s, 3H), 2.96 (d, J_{AB} = 13.7 Hz, 1H), 2.33 (d, J_{AB} = 13.7 Hz, 1H), 2.09 (ddd, J = 12.8, 8.2, 4.0 Hz, 1H), 1.86 (m, 2H), 1.82–1.66 (m, 5H), 1.66–1.54 (m, 3H). ^{13}C NMR (125 MHz, –60 °C, $CDCl_3$,) δ: 193.0, 98.2, 83.8, 56.7, 56.6, 46.0, 41.1, 39.2, 26.8, 25.2, 21.4, 21.0. HR-MS (EI) calcd. for $C_{12}H_{17}N_2O_3$ (M – H^+): 237.1239; found: 237.1225.

Acid 3b

To a solution of **2b** (850 mg, 2.54 mmol) in THF (2 mL) and MeOH (4 mL) was added a 2 N solution of LiOH (2.54 mL). The reaction was stirred for about 12 h during which time the reaction turned slightly yellow and the starting material was consumed as ascertained by TLC. The reaction was diluted by addition of Et_2O (50 mL) and H_2O (50 mL). The aqueous phase was washed with Et_2O (50 mL). After the layers were separated, EtOAc (50 mL) was added to the aqueous phase followed by the dropwise addition of 3 N HCl until the pH reached ~2. The cloudy aqueous phase was then extracted with EtOAc (3 × 30 mL), the combined organic phase was dried with Na_2SO_4, filtered, and concentrated to yield the desired acid as a white solid (743 mg, 96%), mp 122–124 °C. IR (CH_2Cl_2 cast, cm^{-1}): 3220, 3030, 2948, 1707, 1042, 979. ^1H NMR (500 MHz, $CDCl_3$) δ: 10.88 (br s, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 4.89–4.86 (m, 1H), 2.98 (d, J_{AB} = 14.6 Hz, 1H), 2.39 (dd, J = 14.5, 1.9 Hz, 1H), 2.32 (s, 3H), 2.13–2.08 (m, 1H), 1.91–1.59 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.7, 138.1, 133.6, 129.6, 129.4, 84.6, 80.3, 40.4, 39.8, 38.9, 27.7, 25.8, 22.7, 21.9, 21.4. HR-MS (ESI) calcd. for $C_{17}H_{22}O_3S$ (M^+): 306.1289; found: 306.1284.

Diazoketone 4b

To a solution of oxalyl chloride (38 μL, 0.44 mmol) and the acid in CH_2Cl_2 (2.4 mL) cooled to –45 °C (acetonitrile – dry ice bath) was added 1 drop of DMF. The reaction was stirred at this temperature for 1 h then allowed to warm to –10 °C (acetone – ice bath; gas evolution was observed during the warming of the reaction) and stirred an additional 1 h at that temperature. The reaction was then directly transferred via cannula to a freshly prepared solution of diazomethane (~4 mmol) in Et_2O (~12 mL) and cooled to –45 °C (acetonitrile – dry ice bath). The bath was allowed to expire, and a stream of N_2 was introduced once the reaction reached RT The crude yellow oil thus obtained was passed through a short pad of silica gel (1 cm in a disposable pipette), eluting with 10 mL of 50% EtOAc–hexanes. The solvents were removed under reduced pressure and the resulting yellow oil was purified by radial chromatography (2 mm plate, solvent ramp: 100 mL each of 10%, 20%, and 30% EtOAc–hexanes) to yield **4b** as a yellow solid (88 mg, 73%), mp 93 to 94 °C. R_f = 0.30 (30% EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2949, 2868, 2100, 1635, 1363, 1044. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H),

4.84–4.81 (m, 1H), 4.78 (br s, 1H), 2.97 (d, J_{AB} = 14.6 Hz, 1H), 2.31 (s, 3H), 2.09 (br app d, J_{AB} = 14.6 Hz, 1H), 1.95–1.54 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.0, 138.7, 135.1, 129.7, 129.5, 84.6, 80.6, 55.2, 45.7, 42.0, 39.0, 27.8, 25.8, 22.8, 21.9, 21.3. HR-MS (ESI) calcd. for $C_{18}H_{22}N_2O_2NaS$ (M + Na^+): 353.1300; found: 353.1295.

Ethyl acetate adducts of 1b

Into a stirring solution of diisopropyl amine (3.66 mL, 26.1 mmol) in THF (30 mL) at –78 °C, *n*-BuLi (10.9 mL of 2.4 mol/L solution, 26.1 mmol) was added and the resulting mixture was stirred at –78 °C for 30 min. This was then warmed to 0 °C over several minutes and stirred for another 30 min before being cooled once again to –78 °C. Ethyl acetate (2.44 mL, 25 mmol) was added dropwise, and the mixture was stirred for 1 h. A solution of 2-[(2,2-dimethoxy)ethyl]cyclopentanone **1b** (9) (4.0 g, 22.7 mmol) in THF (10 mL) was added dropwise to the above mixture and the reaction mixture was stirred at –78 °C until the reaction was complete by TLC analysis (4 h). The reaction mixture was quenched with saturated ammonium chloride (25 mL). After separation of the phases, the aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic extracts were washed with water (50mL) and brine (50mL), dried ($MgSO_4$), filtered, and concentrated. The crude product (5.64 g, 95.3%), a 1.7:1 mixture of inseparable cis and trans isomers (ratio determined by ^{1}H NMR integration of methoxy singlets), was carried on without further purification.

Cis isomer

R_f = 0.23 (3:7 EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3513, 2953, 2830, 1731, 1447, 1371, 1334, 1190, 1125, 1057, 964. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.37 (dd, J = 7.8, 3.5 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 3.28 (s, 6H), 3.23 (br s, 1H), 2.66 (d, J_{AB} = 15.5 Hz, 1H), 2.33 (d, J_{AB} = 15.5 Hz, 1H), 1.88–1.65 (m, 5H), 1.60–1.50 (m, 4H), 1.25 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 220.7, 103.3, 53.4, 52.8, 45.7, 37.9, 32.7, 30.4, 21.0. LR-MS (ESI) calcd. for $C_{13}H_{24}O_5Na$ (M + Na^+): 283.1; found: 283.1. Anal. calcd. for $C_{13}H_{24}O_5$: C 59.98, H 9.29; found: C 59.58, H 10.01. (Data obtained from the inseparable mixture of diastereomers).

Trans isomer

R_f = 0.23 (3:7 EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3511, 2953, 2830, 1724, 1447, 1371, 1332, 1199, 1124, 1058, 966. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.42 (dd, J = 7.1, 4.4 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.81 (br s, 1H), 3.30 and 3.26 (2s, 6H), 2.47 (d, J_{AB} = 15.6 Hz, 1H), 2.38 (d, J_{AB} = 15.6 Hz, 1H), 2.03–1.94 (m, 2H), 1.82–1.76 (ddd, J = 13.9, 7.1, 4.2 Hz, 1H), 1.75–1.65 (m, 3H), 1.61–1.51 (m, 2H), 1.29–1.20 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.7, 103.8, 80.7, 61.0, 53.5, 52.2, 45.6, 39.7, 38.4, 33.2, 29.3, 20.8, 14.4. LR-MS (ESI) calcd. for $C_{13}H_{24}O_5Na$ (M + Na^+): 283.1; found: 283.1. Anal. calcd. for $C_{13}H_{24}O_5$: C 59.98, H 9.29; found: C 59.85, H 9.29. (Data obtained from a pure sample of the trans isomer recovered after the formation of **2c** and **2d** from the inseparable mixture of cis and trans isomers).

Mixed acetals 2c and 2d

To a solution of the cis and trans ethyl acetate adducts (11.2 g, 43.3 mmol) in CH_2Cl_2 (1.0 L) at –15 °C (acetone – ice bath), $BF_3{\cdot}OEt_2$ (5.50 mL, 43.3 mmol) was added and the reaction was stirred for 20 min, at which time TLC showed consumption of the cis isomer and a mixture of **2c** and **2d**, together with unreacted trans isomer. The reaction was quenched with Et_3N (6 mL) and water (500 mL) and the resulting phases were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (silica gel; 3:7, EtOAc–hexanes) to afford recovered trans adduct and **2c** and **2d** (3.85 g, 62%; 4.4:1 mixture of α and β anomers; ratio based on integration of OMe singlets) as a yellow oil. R_f = 0.53 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2950, 2868, 2829, 1735, 1467, 1447, 1369, 1342, 1300, 1208, 1103, 1049. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.97 (d, J = 5.2 Hz, 0.8H) overlapping with 4.96 (m, 0.2H), 4.11 (q, J = 7.1 Hz, 2H), 3.30 (s, 2.4H), 3.28 (s, 0.6H), 2.85 (d, J_{AB} = 14.4 Hz, 0.8H), 2.67–2.61 (m, 0.8H), 2.64 (d, J_{AB} = 14.4 Hz, 0.2H), 2.63 (d, J_{AB} = 14.4 Hz, 0.8H), 2.56 (m, 0.2H), 2.52 (d, J_{AB} = 14.4 Hz, 0.2H), 2.27 (ddd, J = 13.3, 9.5, 5.7 Hz, 0.2H), 2.20 (dd, J = 13.3, 9.3 Hz, 0.8H), 1.96–1.87 (m, 1H), 1.73–1.56 (m, 4.8H), 1.46–1.41 (m, 1.2H), 1.24 (t, J = 7.2 Hz, 2.4H), 1.23 (t, J = 7.2 Hz, 0.6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: major anomer: 171.4, 106.7, 93.8, 60.4, 54.7, 46.2, 46.0, 41.4, 38.9, 33.6, 24.0, 14.5; minor anomer: 171.2, 107.0, 94.9, 60.5, 54.9, 45.4, 44.9, 40.5, 40.4, 34.2, 24.5, 14.5. HR-MS (EI) calcd. for $C_{12}H_{20}O_4$ (M^+): 228.1362; found: 228.1359. Anal. calcd. for $C_{12}H_{20}O_4$: C 63.14, H 8.83; found: C 62.90, H 9.43.

Mixed thioacetals 2e and 2f

To a solution of **2c** and **2d** (50 mg, 0.22 mmol) and *p*-thiocresol (27 mg, 0.22 mmol) in CH_2Cl_2 (22 mL) at –45 °C, $BF_3{\cdot}OEt_2$ (28 μL, 0.22 mmol) was added and the reaction was stirred until deemed complete by TLC. After 2 h only a trace of starting acetals was observed; the reaction was quenched with Et_3N (0.5 mL) and water (15 mL) and the resulting bi-layer was separated. The aqueous phase was extracted with CH_2Cl_2 (15 mL) and the combined organic extracts were washed with water (30 mL), brine (30 mL), dried with magnesium sulfate, filtered, and concentrated. The crude product was first passed through a pad of silica gel in a fritted filter, eluting with Et_2O, and then purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 100 mL each of 3%, 6%, and then 9% EtOAc–hexanes until the product was recovered) to afford the product, a yellow oil, as a 1:5:1 mixture of partially separable anomers (**2e** and **2f**) in 88% yield (57 mg) based on recovered **2c** and **2d** (4 mg).

Major anomer 2e (α)

R_f = 0.63 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2954, 2867, 1731, 1493, 1446, 1369, 1340, 1300, 1195, 1094, 1054, 1034. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.2 Hz, 2H), 5.51 (dd, J = 6.9, 5.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 2.94 (d, J_{AB} = 14.6 Hz, 1H), 2.85 (d, J_{AB} = 14.6 Hz, 1H), 2.74 (ddd, J =

8.4, 5.2, 3.2 Hz, 1H), 2.29–2.24 (m, 1H), 2.28 (s, 3H), 2.08 (ddd, J = 13.6, 6.8, 5.2 Hz, 1H), 1.97–1.92 (m, 1H), 1.84–1.76 (m, 1H), 1.73–1.58 (m, 3H), 1.49–1.44 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.2, 137.2, 132.2, 131.8, 129.8, 95.0, 88.3, 60.5, 46.9, 44.8, 41.0, 39.2, 33.3, 24.5, 21.3, 14.4. HR-MS (EI) calcd. for $C_{15}H_{24}O_3S$ (M^+): 320.1446; found: 320.1419. Anal. calcd. for $C_{18}H_{24}O_3S$: C 67.47, H 7.55; found: C 67.24, H 7.57.

Minor anomer 2f (β)

R_f = 0.63 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3511, 2953, 2830, 1724, 1447, 1371, 1332, 1199, 1124, 1058, 966. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 5.25 (dd, J = 8.2, 6.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 2.61 (s, 2H), 2.66–2.53 (m, 3H), 2.29 (s, 3H), 2.04 (m, 1H), 1.78–1.50 (m, 6H), 1.22 (t, J = 8.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.1, 137.0, 131.7, 131.6, 129.7, 94.7, 86.2, 60.6, 46.8, 43.9, 41.0, 39.4, 33.8, 24.2, 21.3, 14.5. HR-MS (EI) calcd. for $C_{18}H_{24}O_3S$ (M^+): 320.1446; found: 320.1428.

Diazoketones 4c and 4d

To a solution of mixed acetals **2c** and **2d** (1.00 g, 4.38 mmol) in THF (8 mL) and methanol (8 mL) was added a 2.0 mol/L solution of LiOH (4.38 mL). The reaction was stirred for 16 h at RT, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (20 mL) and Et_2O (20 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with ether (20 mL). The aqueous layer was then acidified with 0.5 mol/L HCl to pH ~3, resulting in a cloudy suspension. This was then diluted with ethyl acetate (30 mL) and the resulting layers separated. The aqueous layer was washed with three portions of ethyl acetate (20 mL) and the combined organic extracts were washed with water then brine, dried over magnesium sulfate, filtered, and concentrated to give the acids **3c** and **3d** (mixture of anomers) as a yellow oil (870 mg, 99%). IR (CH_2Cl_2 cast, cm^{-1}): 3600–2500, 2949, 1708, 1468, 1440, 1409, 1339, 1300, 1218. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.8 (br s, 1H), 4.99 (d, J = 5.2 Hz, 1.0H), 3.30 (s, 2.4H), 3.28 (s, 0.6H), 2.90 (d, J_{AB} = 14.9 Hz, 0.8H), 2.64 (d, J_{AB} = 14.6 Hz, 0.2H), 2.63 (d, J_{AB} = 14.9 Hz, 0.8H), 2.56 (d, J_{AB} = 14.6 Hz, 0.2H), 2.49 (ddd, J = 4.6, 1.2 Hz, 0.2H), 2.27 (ddd, J = 13.6, 9.8, 5.7 Hz, 0.2H), 2.20 (dd, J = 13.3, 9.2 Hz, 0.8H), 1.98–1.80 (m, 1.6H), 1.75–1.55 (m, 5.2H), 1.43 (m, 1.0H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: major anomer: 176.0, 107.1, 93.5, 55.0, 46.5, 46.0, 41.1, 38.9, 33.7, 24.0; minor anomer: 176.0, 107.2, 94.7, 55.1, 44.8, 40.2, 40.1, 34.0, 24.6. HR-MS (EI) calcd. for $C_{10}H_{16}O_4$ (M^+): 200.1049; found: 200.1051.

To a solution of the anomeric acids **3c** and **3d** (800 mg, 4.0 mmol) in Et_2O (50 mL) at 0 °C was added Et_3N (585 μL, 4.4 mmol) followed by isobutyl chloroformate (574 μL, 4.4 mmol) and the reaction was stirred for 2.5 h, resulting in the formation of an off-white precipitate. The reaction mixture was filtered through a fritted filter (D), rinsed with Et_2O (50 mL), and concentrated to give the mixed anhydrides (1.09 g, 91%) as a yellow oil. R_f = 0.62 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2958, 2784, 2831, 1804, 1760, 1470, 1452, 1396, 1370. ^{1}H NMR (500 MHz, $CDCl_3$, major anomer) δ: 5.00 (d, J = 5.3 Hz, 1H), 4.03 (d, J = 7.1 Hz, 2H), 3.31 (s, 3H), 3.03 (d, J_{AB} = 15.3 Hz, 1H), 2.80 (d, J_{AB} = 15.3 Hz, 1H), 2.66 (m, 1H), 2.23 (dd, J = 13.3, 9.2 Hz, 1H), 2.01 (sept, J = 6.8 Hz, 1H), 2.00 (m, 1H), 1.76 (m, 1H), 1.68 (ddd, J = 12.0, 7.5, 5.3 Hz, 1H), 1.63 (m, 2H), 1.46 (m, 1H), 0.95 (d, J = 6.8 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: major anomer: 165.8, 149.4, 106.9, 93.1, 75.7, 54.8, 46.4, 45.7, 41.3, 38.8, 33.5, 27.8, 24.0, 19.0; minor anomer: 165.6, 149.4, 106.7, 94.4, 75.5, 54.8, 45.6, 44.6, 41.4, 38.9, 34.3, 33.6, 24.5, 19.0. HR-MS (EI) calcd. for $C_{15}H_{23}O_6$ ($M - H^+$): 299.1495; found: 299.1499.

A solution of anomeric mixed anhydrides (624 mg, 2.2 mmol) in Et_2O (10 mL) was added via cannula to a solution of freshly prepared diazomethane (20 mmol) in Et_2O (60 mL) at –15 °C, and the resulting mixture was stirred for 16 h as the cooling bath expired. A gentle stream of N_2 was applied to the system to allow for slow evaporation of both excess diazomethane and solvent, and the resulting yellow oil was diluted in ether (20 mL), passed through a short pad of silica gel in a fritted filter, eluting with copious ether. This was then concentrated and the resulting oil purified by radial chromatography (silica gel, 4 mm plate, solvent ramp: 100 mL each of 3%, 6%, 9%, and then 12% EtOAc–hexanes until the products were recovered) to yield **4c** and **4d**, an inseparable 4.7:1 mixture of anomers (228 mg, 49%) as a bright yellow oil, as well as a trace of starting material (not quantified). R_f = 0.23 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3087, 2949, 2868, 2829, 2102, 1817, 1735, 1637, 1440, 1361. ^{1}H NMR (500 MHz, –40 °C, $CDCl_3$) δ: 5.67 (s, 0.8H), 5.52 (s, 0.2H), 5.01 (m, J = 5.1 Hz, 1H), 3.36 (s, 2.4H), 3.30 (s, 0.6H), 2.94 (d, J_{AB} = 14.3 Hz, 0.8H), 2.69 (d, J_{AB} = 13.5 Hz, 0.2H), 2.60 (m, 1H), 2.55 (d, J_{AB} = 14.3 Hz, 0.8H), 2.47 (d, J_{AB} = 13.5 Hz, 0.2H), 2.20 (dd, J = 13.5, 9.5 Hz, 1H), 1.90 (m, 1H), 1.70–1.45 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, –60 °C) δ: major anomer: 194.1, 106.4, 93.4, 56.0, 54.9, 52.8, 46.4, 40.3, 38.1, 32.5, 23.4; minor anomer: 194.1, 106.5, 95.4, 56.8, 54.7, 50.8, 44.2, 40.3, 39.9, 33.6, 24.2; HR-MS (ESI) calcd. for $C_{11}H_{16}N_2O_3Na$ ($M + Na^+$): 247.1059; found: 247.1060.

Diazoketones 4e and 4f

Preparation and characterization of individual acid anomers is given below. For convenience, they were usually prepared as a mixture of anomers and converted into the separable diazoketones.

To a solution of mixed acetal **2e** (423 mg, 1.3 mmol) in THF (5 mL) and methanol (5 mL) was added a 2.0 mol/L solution of LiOH (1.3 mL). The reaction was stirred for 16 h at RT, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (20 mL) and Et_2O (20 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with ether (15 mL). The aqueous layer was then acidified with 0.5 mol/L HCl to pH ~3, resulting in a cloudy suspension. This was then diluted with ethyl acetate (40 mL) and the resulting layers separated. The aqueous layer was washed with three portions of ethyl acetate (20 mL) and the combined organic extracts were washed with water (50 mL) and then brine (50 mL), dried over magnesium sulfate, filtered, and concentrated to yield **3e** as a yellow oil (333 mg, 86%). IR (CH_2Cl_2 cast, cm^{-1}): 3500–2400, 2953, 2867,

1708, 1597, 1493, 1443, 1408, 1300, 1231, 1133, 1093. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 5.56 (dd, J = 6.0, 6.0 Hz, 1H), 3.03 (d, J_{AB} = 14.8 Hz, 1H), 2.74 (d, J_{AB} = 14.8 Hz, 1H), 2.63 (m, 1H), 2.32–2.25 (m, 1H), 2.29 (s, 3H), 2.14 (ddd, J = 13.4, 6.8, 5.0 Hz, 1H), 1.98–1.92 (m, 1H), 1.88–1.79 (m, 1H), 1.70–1.58 (m, 3H), 1.52–1.46 (m, 1H), (COO*H* peak not measured). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.8, 137.9, 132.5, 130.8, 130.0, 94.7, 88.7, 47.5, 44.9, 40.5, 39.0, 33.0, 24.5, 21.3. HR-MS (EI) calcd. for $C_{16}H_{20}SO_3$ (M^+): 292.1133; found: 292.1135.

Following the same procedure as the previous section, **2f** (142 mg, 0.44 mmol) was converted into the corresponding acid **3f** (100 mg, 78%) as a white solid, mp 115 to 116 °C. IR (CH_2Cl_2 cast, cm^{-1}): 3500–2500, 2949, 2865, 1707, 1493, 1439, 1411, 1299, 1232, 1146, 1093. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.4 (br s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 5.28 (dd, J = 8.2, 5.6 Hz, 1H), 2.69 (d, J_{AB} = 14.8 Hz, 1H), 2.57 (d, J_{AB} = 14.8 Hz, 1H), 2.60–2.51 (m, 2H), 2.29 (s, 3H), 2.10 (m, 1H), 1.78–1.54 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.8, 137.7, 132.4, 130.7, 129.9, 94.4, 86.5, 47.6, 43.6, 40.6, 39.0, 33.6, 24.3, 21.3; HR-MS (EI) calcd. for $C_{16}H_{20}SO_3$ (M^+): 292.1133; found: 292.1141. Anal. calcd. for $C_{16}H_{20}O_3S$: C 65.72, H 6.89; found: C 65.21, H 7.07.

To a solution of both anomeric acids (**3e** and **3f**) (1.0 g, 3.42 mmol) in CH_2Cl_2 (140 mL) at –15 °C was added 2,6-lutidine (478 μL, 4.1 mmol) followed by oxalyl chloride (36 μL, 4.1 mmol) and DMF (2 drops, ~10 μL), resulting in the evolution of copious amounts of gas. The reaction was stirred for 4 h, and solvent was removed by rotary evaporation to give a yellow oil entrained in a white precipitate. This material was redissolved in ether (50 mL) and the suspension filtered through a fritted filter (D) and was then washed several times with ether (50 mL). The ethereal solution of the acid chloride was condensed to a lesser volume (~50 mL) and added via cannula to a solution of freshly prepared diazomethane (60 mmol) in Et_2O (200 mL) at –15 °C, and the resulting mixture stirred for 16 h as the cooling bath expired. A gentle stream of N_2 was applied to the system to allow for slow evaporation of both excess diazomethane and solvent, and the resulting yellow oil was diluted in ether (40 mL), passed through a short pad of silica gel in a fritted filter, eluting with copious ether. The filtrate was concentrated and the resulting oil purified by radial chromatography (silica gel, 4 mm plate, solvent ramp: 100 mL each of 3%, 6%, 9%, and then 12% EtOAc–hexanes until the products were recovered) to yield **4e** (410 mg) and **4f** (240 mg), as yellow oils in a combined overall yield of 60%.

Major anomer 4e (α)

R_f = 0.32 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3105, 2953, 2866, 2100, 1636, 1492, 1450, 1358, 1241, 1162, 1093, 1061, 1017. ^{1}H NMR (500 MHz, –60 °C, $CDCl_3$) δ: 7.36 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.81 (dd, J = 6.2, 2.7 Hz, 1H), 5.12 (s, 1H), 3.23 (d, J_{AB} = 13.2 Hz, 1H), 2.66 (approx. q, J = 7.3 Hz, 1H), 2.49 (d, J_{AB} = 13.2 Hz, 1H), 2.37–2.30 (m, 1H), 2.32 (s, 3H), 2.17–2.11 (m, 1H), 1.84–1.52 (m, 6H). ^{13}C NMR (125 MHz, –60 °C, $CDCl_3$) δ: 194.3, 136.5, 131.3, 129.8, 129.8, 95.0, 87.0, 56.2, 52.1, 47.4, 29.8, 98.0, 32.2, 23.5, 21.1. HR-MS (ESI) calcd. for $C_{17}H_{20}N_2O_2SNa$ ($M + Na^+$): 339.1143; found: 339.1147. Anal. calcd. for $C_{17}H_{20}N_2O_2S$: C 64.53, H 6.37, N 8.85; found: C 64.92, H 6.13, N 8.66.

Minor anomer 4f (β)

R_f = 0.26 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3081, 2952, 2865, 2100, 1636, 1492, 1449, 1358, 1161, 1093, 1051, 1016. ^{1}H NMR (500 MHz, –60 °C, $CDCl_3$) δ: 7.39 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.53 (s, 1H), 5.14 (dd, J = 9.7, 5.4 Hz, 1H), 2.66 (d, J_{AB} = 13.6 Hz, 1H), 2.60 (approx. q, J = 7.6 Hz, 1H), 2.53 (d, J_{AB} = 13.6 Hz, 1H), 2.48 (ddd, J = 13.0, 9.0, 5.5 Hz, 1H), 2.34 (s, 3H), 2.04–1.98 (br m, 1H), 1.66–1.46 (m, 6H). ^{13}C NMR (125 MHz, –60 °C $CDCl_3$) δ: 193.8, 137.5, 131.8, 129.7, 129.5, 94.0, 84.9, 56.7, 50.0, 46.8, 39.6, 38.5, 32.7, 23.4, 21.2. HR-MS (ESI) calcd. for $C_{17}H_{20}N_2O_2SNa$ ($M + Na^+$): 339.1143; found: 339.1143. Anal. calcd. for $C_{17}H_{20}N_2O_2S$: C 64.53, H 6.37, N 8.85; found: C 64.40, H 6.58, N 8.52.

Ethyl acetate adduct 6a

Into a stirring solution of diisopropyl amine (1.44 μL, 10.31 mmol) in THF (7 mL) at –78 °C, *n*-BuLi (4.37 mL of 2.36 mol/L solution, 10.31 mmol) was added, and the resulting mixture was stirred at –78 °C for 30 min. This was then warmed to 0 °C over several minutes and stirred for another 30 min before being cooled once again to –78 °C. Ethyl acetate (968 μL, 9.9 mmol) was added dropwise, and the mixture was stirred for 1 h. A solution of anomer **2b** (662 mg, 1.98 mmol, 1 equiv.) in THF (1 mL) was added dropwise to the mixture and the reaction mixture was stirred overnight, allowing the cooling bath to expire. The reaction was then diluted with ethyl ether (10 mL) and quenched by the addition of saturated ammonium chloride solution (10 mL). After separation of the phases, the aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. The crude β-ketoester product was then purified by radial chromatography (4 mm plate, solvent ramp: 100 mL each of 2%, 4%, 8%, and then 15% EtOAc–hexanes until the product was recovered) to afford 424 mg of the product **6a** as a yellow oil in 65% yield, based on recovered **2b** (77 mg). R_f = 0.65 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2952, 2870, 1743, 1712, 1492, 1449, 1366, 1318, 1236, 1152, 1096, 1041. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 4.86 (dd, J = 8.0, 5.6 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.26 (d, J_{AB} = 14.0 Hz, 1H), 3.19 (d, J_{AB} = 15.8 Hz, 1H), 3.05 (d, J_{AB} = 15.8 Hz, 1H), 2.32 (s, 3H), 2.29 (d, J_{AB} = 14.0 Hz, 1H), 1.92–1.52 (m, 11H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.8, 167.3, 138.3, 134.5, 129.5, 129.1, 84.5, 80.2, 61.1, 49.8, 46.4, 41.4, 39.0, 27.4, 25.7, 22.6, 21.8, 21.1, 14.1. HR-MS (EI) calcd. for $C_{21}H_{28}O_4S$ ($M - EtOH^+$): 330.1290; found: 330.12943.

Diazoketoester 4g

To a stirred solution of **6a** (91 mg, 0.24 mmol, 1 equiv.) and TEA (34 μL, 0.24 mmol, 1 equiv.) in CH_3CN (2 mL), *p*-TsN_3 (48 mg, 0.24 mmol, 1 equiv.) was added, and the mixture was vigorously stirred at RT for 2.5 h. The CH_3CN was then removed by rotary evaporation and the resulting oil dissolved in 10 mL ether. This solution was washed with 5 mL of 25% aq. KOH, 5 mL of 6% aq. KOH, and then 10 mL

water. The organic layer was then dried over sodium sulfate and concentrated by rotary evaporation. The product was purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 1%, 2%, 5%, and then 10% EtOAc–hexanes until the product was recovered) to afford 54 mg (55%) of **4g** as a pale yellow oil. R_f = 0.62 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2948, 2869, 2133, 1712, 1652, 1492, 1371, 1300, 1220, 1145, 1040. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.42 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 4.93 (dd, J = 8.0, 5.2 Hz, 1H), 4.21 (q, J = 7.2 Hz, 1H), 4.18 (q, J = 7.2 Hz, 1H), 4.01 (d, J_{AB} = 14.4 Hz, 1H), 2.52 (d, J_{AB} = 14.4 Hz, 1H), 2.31 (s, 3H), 2.13 (m, J = 8.5, 4.7 Hz, 1H), 1.98–1.84 (m, 3H), 1.80–1.54 (m, 7H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.7, 161.2, 137.5, 133.8, 130.0, 129.1, 85.5, 80.2, 61.3, 41.3, 40.8, 40.0, 27.4, 25.7, 22.8, 22.0, 21.0, 14.1, (diazo carbon was not detected for this compound). HR-MS (EI) calcd. for $C_{21}H_{26}O_4S$ ($M - N_2^+$): 374.1552; found: 374.1548.

Ethyl acetate adducts 6b (α) and 6c (β)

Into a stirring solution of diisopropyl amine (409 μL, 2.92 mmol) in THF (1 mL) at –78 °C, *n*-BuLi (1.24 mL of 2.36M solution, 2.92 mmol) was added, and the resulting mixture was stirred at –78 °C for 30 min. This was then warmed to 0 °C over several minutes and stirred for another 30 min before being cooled once again to –78 °C. Ethyl acetate (280 μL, 2.86 mmol) was added dropwise, and the mixture was stirred for 1 h. A solution of anomers **2e** and **2f** (183 mg, 0.57 mmol, 1 equiv.) in THF (1 mL) was added dropwise to the mixture and the reaction mixture was stirred overnight, allowing the cooling bath to expire. The reaction was then diluted with ethyl ether (10 mL) and quenched by the addition of saturated ammonium chloride solution (5 mL). After separation of the phases, the aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. The crude β-ketoester product was then purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 2%, 4%, 8%, and then 15% EtOAc–hexanes until the product was recovered) to afford the products as yellow oils and as a mixture of separable anomers **6b** (α) and **6c** (β) in 46% yield (51 and 38 mg, respectively), based on recovered **2** (13 mg).

Major anomer 6b (α)

R_f = 0.69 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2955, 2867, 1744, 1713, 1493, 1446, 1366, 1313, 1235 1153, 1094, 1031. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.36 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 5.62 (dd, J = 6.2, 6.2 Hz, 1H), 4.16 (q, J = 7.1 Hz, 1H), 4.15 (q, J = 7.1 Hz, 1H), 3.51 (s, 2H), 3.26 (d, J_{AB} = 14.7 Hz, 1H), 2.87 (d, J_{AB} = 14.8 Hz, 1H), 2.62 (m, 1H), 2.32 (s, 3H), 2.27 (ddd, J = 12.7, 8.6, 5.6 Hz, 1H), 1.92–1.84 (m, 2H), 1.70–1.60 (m, 3H), 1.48 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.1, 167.4, 136.8, 131.9, 130.8, 129.7, 95.0, 87.8, 61.1, 52.7, 50.5, 47.4, 40.5, 38.7, 32.7, 24.3, 21.0, 14.1. HR-MS (EI) calcd. for $C_{20}H_{26}O_4S$ (M^+): 362.1552; found: 362.1554.

Minor anomer 6c (β)

R_f = 0.62 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2955, 2867, 1742, 1717, 1493, 1446, 1367, 1305, 1236 1152, 1094, 1026. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.39 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 5.30 (dd, J = 6.2, 6.3 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.52 (d, J_{AB} = 15.7 Hz, 1H), 3.46 (d, J_{AB} = 15.7 Hz, 1H), 2.89 (d, J_{AB} = 14.5 Hz, 1H), 2.74 (d, J_{AB} = 14.5 Hz, 1H), 2.62–2.50 (m, 2H), 2.32 (s, 3H), 2.00 (m, 1H), 1.80–1.52 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.8, 167.2, 137.3, 132.3, 130.8, 129.5, 94.6, 86.4, 61.2, 51.4, 50.5, 47.5, 40.5, 39.0, 33.3, 24.0, 21.1, 14.1. HR-MS (EI) calcd. for $C_{20}H_{26}O_4S$ (M^+): 362.1552; found: 362.1554.

Diazoketone 4h

Ketoester **6b** (50 mg, 0.14 mmol) was subjected to the procedure as described previously for **4g**, to afford 41 mg (77%) of **4h** as a pale yellow oil. R_f 0.73 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2954, 2867, 2131, 1717, 1652, 1493, 1446, 1370, 1297, 1210, 1057. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 5.51 (dd, J = 6.5, 6.3 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.48 (d, J_{AB} = 16.3 Hz, 1H), 3.44 (d, J_{AB} = 15.9 Hz, 1H), 2.76 (dddd, J = 12.6, 8.3, 4.0, 4.0 Hz, 1H), 2.30 (s, 3H), 2.25 (ddd, J = 14.6, 8.6, 6.1 Hz, 1H), 2.10 (ddd, J = 13.4, 6.6, 4.6 Hz, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.72–1.56 (m, 3H), 1.47 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 190.6, 161.3, 136.7, 132.0, 131.5, 129.5, 95.6, 87.8, 61.3, 48.3, 46.7, 40.8, 39.7, 32.9, 24.4, 21.1, 14.3, (diazo carbon was not detected for this compound). HR-MS (EI) calcd. for $C_{20}H_{24}O_4S$ ($M - N_2^+$): 360.13953; found: 360.13900.

Carbene transfer reactions of diazo compounds 4a–4h

Catalytic decomposition of diazoketone 4b with Cu(hfacac)$_2$; 8-(p-tolylthio)-12-oxatricyclo[7.2.1.0^{1,5}]undecan-10-one (7b)

To a solution of $Cu(hfacac)_2$ (11 mg, 0.017 mmol, 10 mol%) in CH_2Cl_2 (22 mL, 0.01 mol/L) heated to reflux, was added dropwise via cannula, a solution of diazoketone **4b** (56 mg, 0.17 mmol) in 2 mL of CH_2Cl_2. Following completion of addition, the reaction was stirred at reflux until complete consumption (ca. 30 min) of **4b** (TLC monitoring), after which the reaction was cooled to RT and a solution of 0.5 mol/L K_2CO_3 was added. The aqueous phase was then extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic phase was dried with $MgSO_4$, filtered, condensed, and purified by radial chromatography to yield 41 mg (80%) of **7b** as a white crystalline solid, mp 75 to 76 °C. R_f = 0.53 (30% EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2934, 2866, 1753, 1492, 1081, 809. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.35 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 4.27 (approx. br s, 1H), 3.59 (ddd, J = 6.6, 4.7, 1.4 Hz, 1H), 2.74 (dd, J = 17.5, 1.1 Hz, 1H), 2.38 (dd, J = 17.3, 1.1 Hz, 1H), 2.31 (s, 3H), 2.15–2.10 (m, 1H), 2.02–1.96 (m, 2H), 1.92–1.83 (m, 2H), 1.80–1.64 (m, 4H), 1.60–1.53 (m, 1H), 1.49–1.43 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.7, 137.6, 132.5, 130.1, 130.0, 91.1, 83.5, 51.7, 51.2, 49.1, 40.3, 32.1, 27.5, 26.3, 23.4, 21.3. HR-MS (EI) calcd. for $C_{18}H_{22}O_2S$ (M^+): 302.1341; found: 302.1342.

8-Methoxy-12-oxatricyclo[7.2.1.0^{1,5}]undecan-10-one (7a)

To a refluxing solution of $Cu(hfacac)_2$ (9.4 mg, 0.02 mmol, 10 mol%) in CH_2Cl_2 (15 mL) was added a solution of **4a** (46.9 mg, 0.20 mmol) in CH_2Cl_2 (5 mL), and the

resulting mixture was stirred at reflux until consumption of **4a** (~30 min), after which the reaction mixture was cooled to RT and quenched with 0.5 mol/L K_2CO_3 (10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined and washed with water and brine, dried with magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (30% EtOAc–hexanes) to give **7a**, a yellow solid (34 mg), in 82% yield, m.p. 41 to 43 °C. R_f = 0.44 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2937, 2867, 2823, 1755, 1450, 1403, 1366, 1342, 1299, 1235. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.05 (s, 1H), 3.50 (ddd, J = 6.2, 4.2, 1.2 Hz, 1H), 3.35 (s, 3H), 2.73 (d, J_{AB} = 17.7 Hz, 1H), 2.37 (d, J_{AB} = 17.7 Hz, 1H), 2.09 (m, 1H), 2.02–1.92 (m, 2H), 1.89–1.81 (m, 2H), 1.79–1.71 (m, 2H), 1.66 (m, 1H), 1.56 (m, 1H), 1.48 (ddd, J= 14.5, 10.2, 4.2 Hz, 1H), 1.37 (ddd, J = 13.7, 10.0, 3.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.5, 90.9, 83.1, 81.6, 56.6, 51.3, 49.0, 40.4, 32.1, 27.0, 23.9, 23.5. HR-MS (EI) calcd. for $C_{12}H_{18}O_3$ (M^+): 210.1256; found: 210.1249. Anal. calcd. for $C_{12}H_{18}O_3$: C 68.60, H 8.60; found: C 68.20, H 9.06.

Carbene transfer reactions of 4c and 4d

Preparation of 7c and 7d

To a refluxing solution of Cu(hfacac)$_2$ (37 mg, 0.08 mmol, 10 mol%) in CH_2Cl_2 (55 mL) was added a solution of **4c** and **4d** (168 mg, 0.75 mmol, 4.4:1 mixture of anomers) in CH_2Cl_2 (25 mL), and the resulting mixture was monitored by TLC. Upon consumption of diazoketone **4a** (45 min), the reaction mixture was cooled to RT and quenched with 0.5 mol/L K_2CO_3 (25 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined and washed with water (20 mL), pre-dried with brine (20 mL), dried with magnesium sulfate, filtered, and concentrated. The resulting pale oil was purified by gradient column chromatograhy (silica gel; 5%, 10%, 15%, and then 20% EtOAc–hexanes until the products were recovered) to yield **7c** (68 mg) and **7d** (25 mg) as pale yellow oils, in an overall yield of 67%. (This reaction was also carried out on a small scale with pure samples of **4c** and **4d**. **4c** also furnished trace amounts of product **9**.).

Major diastereomer 7c (α)

R_f = 0.40 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2938, 2871, 2825, 1760, 1456, 1403, 1370, 1347, 1312. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.04 (d, J = 4.9 Hz, 1H), 3.61 (ddd, J = 10.6, 5.3, 5.3 Hz, 1H), 3.34 (s, 3H), 2.54 (d, J_{AB} = 17.6 Hz, 1H), 2.19 (d, J_{AB} = 17.6 Hz, 1H), 2.06 (dd, J = 13.9, 5.7 Hz, 1H), 1.92–1.76 (m, 5H), 1.76–1.69 (m, 1H), 1.68–1.62 (m, 1H), 1.56 (ddd, J = 13.9, 9.1, 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 214.4, 88.7, 78.3, 74.7, 56.8, 44.6, 44.4, 34.1, 28.9, 27.5, 21.3. HR-MS (ESI) calcd. for $C_{11}H_{16}O_3$ (M^+): 196.1099; found: 196.1097.

Minor anomer 7d (β)

R_f = 0.46 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2938, 2872, 2824, 1761, 1436, 1405, 1368, 1347, 1312. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.19 (s, 1H), 3.28 (s, 3H), 3.23 (m, 1H), 2.60 (d, J_{AB} = 17.3 Hz, 1H), 2.22 (d, J_{AB} = 17.3 Hz, 1H), 2.03–1.74 (m, 7H), 1.66–1.54 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.8, 88.7, 80.3, 75.3, 56.4, 45.3, 41.9, 34.9, 30.9, 26.4, 21.8. HR-MS (ESI) calcd. for $C_{11}H_{16}O_3$ (M^+): 196.1099; found: 196.1092.

Side product 9 (partial data)

^1H NMR (500 MHz, $CDCl_3$) δ: 6.03 (d, J = 2.3 Hz, 1H), 5.56 (d, J = 4.5 Hz, 1H), 3.49 (s, 3H), 2.54 (dd, J = 14.1, 2.3 Hz, 1H), 2.42 (d, J = 14.1 Hz, 1H), 2.33 (dd, J = 13.2, 8.9 Hz, 1H), 2.24 (dddd, J = 9.8, 8.7, 6.4, 4.0 Hz, 1H), 2.01–1.83 (m, 3H), 1.74 (approx. dt, J = 13.2, 4.3 Hz, 1H), 1.70–1.56 (m, 2H), 1.35–1.27 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.2, 134.0, 102.9, 93.2, 60.1, 44.1, 40.9, 36.0, 34.2, 33.1, 25.7.

Carbene transfer reaction of 4e

Preparation of 7e, 7f, and 10e

To a refluxing solution of Cu(hfacac)$_2$ (16 mg, 0.03 mmol, 10 mol%) in CH_2Cl_2 (33 mL) was added a solution of **4e** (105 mg, 0.33 mmol) in CH_2Cl_2 (8 mL), and the resulting mixture was monitored by TLC. Upon consumption of diazoketone **4e** (30 min), the reaction mixture was cooled to RT and quenched with 0.5 mol/L K_2CO_3 (25 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined and washed with water (25 mL), pre-dried with brine (25 mL), dried with magnesium sulfate, filtered, and concentrated. The resulting pale yellow oil was diluted in ether (20 mL), and passed through a short pad of silica gel in a fritted filter while rinsing with excess ether. This was then concentrated and the resulting oil purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 100 mL each of 2%, 5%, 7%, and then 10% EtOAc–hexanes until the products were recovered) to yield a mixture of **7e** and **7f** (59 mg, 68%, ca. 2:1 ratio) as pale yellow oils, as well as **10e** (11 mg, 13%) as a white solid, in an overall yield of 80%. Minor diastereomer **7f** could be obtained as a white solid, mp 64–65 °C.

Diastereomers 7e and 7f

R_f = 0.41 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3019, 2955, 2869, 1785, 1711, 1492, 1447, 1401, 1343. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.35 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.1 Hz, 2H), 4.01 (s, 0.5H), 3.86 (d, J = 3.9 Hz, 1H), 3.50 (ddd, J = 13.2, 5.4, 4.2 Hz, 1H), 3.27 (ddd, J = 6.9, 13.5, 1.7 Hz, 0.5H), 2.60 (d, J_{AB} = 17.3 Hz, 0.5H), 2.57 (d, J_{AB} = 17.6 Hz, 1H), 2.29 (s, 4.5H), 2.24 (d, J_{AB} = 17.3 Hz, 0.5H), 2.23 (d, J_{AB} = 17.6 Hz, 1H), 2.16–2.06 (m, 2H), 1.96–1.77 (m, 7.5H), 1.75–1.62 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: major diastereomer: 213.5, 138.0, 133.3, 130.1, 129.9, 88.5, 79.8, 44.8, 44.5, 44.2, 34.5, 28.1, 27.5, 21.3; minor diastereomer: 216.2, 137.8, 132.5, 131.4, 130.2, 89.1, 81.3, 45.8, 45.5, 43.0, 35.5, 31.4, 26.8, 22.3. HR-MS (EI) calcd. for $C_{17}H_{20}O_2S$ (M^+): 288.1184; found 283.1180. Anal. calcd. for $C_{17}H_{20}O_2S$: C 70.80, H 6.99; found: C 70.36, H 7.05.

Isomer 10e

Melting point 95 °C. R_f = 0.44 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2953, 2866, 1711, 1493, 1448, 1404,

1345, 1301. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.75 (d, J = 7.3 Hz, 1H), 3.43 (d, J_{AB} = 14.8 Hz, 1H), 3.32 (s, 1H), 2.32 (s, 3H), 2.26–2.21 (m, 1H), 2.24 (d, J_{AB} = 14.8 Hz, 1H), 2.16 (m, 1H), 2.13 (dd, J = 12.4, 9.1 Hz, 1H), 1.93–1.84 (m, 3H), 1.67 (m, 1H), 1.51 (ddd, J = 13.4, 9.8, 7.5 Hz, 1H), 1.40 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.4, 138.4, 132.9, 130.1, 93.9, 60.9, 48.9, 45.3, 39.9, 37.1, 34.8, 25.4, 21.4. HR-MS (EI) calcd. for $C_{17}H_{20}O_2S$ (M^+): 288.1184; found: 283.1183. Anal. calcd. for $C_{17}H_{20}O_2S$: C 70.80, H 6.99; found: C 70.90, H 6.68.

Carbene transfer reaction of 4f — Preparation of 7e and 7f

Diazoketone **4f** was subjected to the procedure given previously for **4e**, to yield 85% of **7e** and **7f** in a 1:4.8 ratio. None of the isomeric product **10e** was isolated.

Carbene transfer reaction of 4g — Preparation of 7g

To a solution of **4g** (43 mg, 0.11 mmol) in toluene (9 mL) was added Cu(hfacac)$_2$ (9 mg, 0.01 mmol, 10 mol%), and the resulting mixture was heated to reflux. Upon consumption of diazoketone **4g** (14 h at reflux) the reaction mixture was cooled to RT and quenched with 0.5 mol/L K_2CO_3 (15 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined and washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting pale oil was diluted in ether (20 mL), and passed through a short pad of silica gel in a fritted filter while rinsing with excess ether. This was then concentrated and the resulting oil purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 2%, 5%, 7%, and then 10% EtOAc–hexanes until the products were recovered) to yield 20 mg (50%) of **7g** as a pale oil, and as a 4.5:1 mixture of isomers by GC. This pale oil crystallized upon standing into a white solid. R_f = 0.42 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2952, 2934, 2867, 1769, 1746, 1492, 1443, 1400, 1269, 1254, 1143. ^{1}H NMR (500 MHz, $CDCl_3$; major diastereomer) δ: 7.34 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 4.19 (dq, J = 16.4, 7.1 Hz, 1H), 4.15 (dq, J = 16.4, 7.1 Hz, 1H), 4.04 (dd, J = 3.5, 3.5 Hz, 1H), 2.81 (d, J_{AB} = 17.0 Hz, 1H), 2.54 (d, J_{AB} = 17.0 Hz, 1H), 2.35 (m, 3H), 2.32 (s, 3H), 2.18 (dd, J = 11.5, 11.5 Hz, 1H), 2.03 (m, 1H), 1.97–1.84 (m, 3H), 1.80 (m, 1H), 1.63–1.46 (m, 3H), (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$; major diastereomer) δ: 209.1, 166.1, 137.4, 132.4, 131.5, 129.7, 62.3, 55.8, 52.7, 50.8, 41.6, 35.2, 30.1, 26.7, 24.8, 21.1, 13.9. HR-MS (EI) calcd. for $C_{21}H_{26}O_4S$ (M^+): 374.1552; found: 374.1554.

Carbene transfer reaction of 4h — Preparation of 7h, 7i, and 10h

To a solution of **4h** (122 mg, 0.314 mmol) in toluene (31 mL) was added Cu(hfacac)$_2$ (16 mg, 0.03 mmol, 10 mol%), and the resulting mixture was heated to reflux. Upon consumption of diazoketone **4h** (14 h at reflux) the reaction mixture was cooled to RT and quenched with 0.5 mol/L K_2CO_3 (25 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined and washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting pale oil was diluted in ether (20 mL), and passed through a short pad of silica gel in a fritted filter while rinsing with excess ether. This was then concentrated and the resulting oil purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 2%, 5%, 7%, and then 10% EtOAc–hexanes until the products were recovered) to yield 7 mg of a mixture of **7h** and **7i** (8:1 diastereomers by GC) and 48 mg of **10h** (single diastereomer by GC and NMR) as pale oils (49% combined yield).

7h

R_f = 0.57 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2941, 2871, 1774, 1743, 1493, 1448, 1401, 1342, 1277. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 4.11 (m, 2H), 3.72 (dd, J = 11.4, 6.0 Hz, 1H), 2.78 (d, J_{AB} = 17.4 Hz, 1H), 2.36 (d, J_{AB} = 17.4 Hz, 1H), 2.31 (s, 3H), 2.17 (dd, J = 13.0, 5.9 Hz, 1H), 2.02–1.83 (m, 6H), 1.76–1.64 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.4, 165.6, 137.7, 133.0, 130.4, 129.7, 87.8, 85.6, 62.1, 46.4, 45.5, 44.1, 34.3, 30.1, 28.5, 21.4, 21.1, 13.8. HR-MS (EI) calcd. for $C_{20}H_{24}O_4S$ (M^+): 360.1395; found: 360.1403.

10h

R_f = 0.52 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2955, 2869, 1750, 1717, 1492, 1448, 1402, 1346, 1241. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 4.75 (d, J = 7.0 Hz, 1H), 4.11 (m, 1H), 3.47 (d, J_{AB} = 15.7 Hz, 1H), 2.33 (s, 3H), 2.32–2.27 (m, 3H), 2.16 (m, J = 6.0, 2.6 Hz, 1H), 1.93–1.82 (m, 3H), 1.68 (m, 1H), 1.52 (ddd, J = 16.9, 9.9, 7.7 Hz, 1H), 1.43 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.3, 166.8, 140.3, 136.3, 129.7, 126.4, 93.9, 81.2, 67.3, 61.6, 48.3, 45.3, 38.6, 36.7, 34.4, 24.9, 21.3, 14.0. HR-MS (EI) calcd. for $C_{20}H_{24}O_4S$ (M^+): 360.1395; found: 360.1397.

Modification of rearrangement products

Ketal 11a

A flask containing a solution of **7b** (67 mg, 0.22 mmol), ethylene glycol (144 µL, 3.32 mmol), and TsOH (2 mg, 0.01 mmol) in toluene (5 mL) was equipped with a condenser and Dean-Stark trap (pre-filled with toluene), and then heated to reflux for 12 h. The reaction was cooled to RT and the solution was transferred to a separatory funnel and washed with satd. $NaHCO_3$ (10 mL). The organic phase was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude white solid thus obtained was passed through a short pad of silica gel (1 cm in a disposable pipette) while eluting with 10 mL of 30% EtOAc–hexanes. The solvents were removed under reduced pressure and the resulting white solid was purified by radial chromatography (2 mm plate, solvent ramp: 100 mL of hexanes, 2.5%, 5%, and 10% EtOAc–hexanes) to yield recovered **7b** (16 mg, 25%) and **11a** (55 mg, 73%) as a white solid. R_f = 0.18 (5% EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2946, 2868, 1319, 1092. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 4.11 (approx. br s, 1H), 3.93 (ddd, J = 8.0, 6.6, 4.9 Hz, 1H), 3.85 (approx. q, J = 7.3 Hz, 1H), 3.77 (ddd, J = 6.9, 6.9, 4.9 Hz, 1H), 3.62 (ddd, J = 7.9, 7.1, 7.1 Hz, 1H), 3.62–3.48 (m, 1H),

2.35 (d, J_{AB} = 14.2 Hz, 1H), 2.32 (s, 3H), 2.27 (d, J_{AB} = 14.2 Hz, 1H), 2.05–1.99 (m, 1H), 1.96–1.89 (m, 3H), 1.83–1.70 (m, 4H), 1.65–1.47 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.3, 132.9, 132.1, 129.9, 117.1, 92.0, 86.5, 65.4, 64.2, 50.9, 50.8, 48.0, 41.9, 32.4, 27.8, 26.6, 23.5, 21.3. HR-MS (EI) calcd. for $C_{20}H_{26}O_3S$ (M^+): 346.1603; found: 346.1600.

Tricyclic sulfone 12

To a mixture of **11a** (83 mg, 0.24 mmol) in MeOH (1 mL) cooled to 0 °C was added a mixture of OXONE® (295 mg) in a pH 4 buffer (1 mL) (18). After the addition, the cooling bath was removed and the slurry was stirred at RT for 10 h. The mixture was diluted with water (5 mL) and $CHCl_3$ (5 mL). The biphasic mixture was transferred to a separatory funnel, separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 5 mL). The combined organic phase was washed with brine, dried with $MgSO_4$, and the solvents were removed under reduced pressure. Sulfone **12** was obtained as a white crystalline solid (88 mg, 97%) (homogenous by TLC and ^{1}H NMR analysis), and was used without further purification; mp 191–194 °C. R_f = 0.25 (30% EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2956, 1299, 1145, 1085. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 4.46 (approx. d, J = 2.9 Hz, 1H), 4.01 (ddd, J = 8.0, 6.5, 4.4 Hz, 1H), 3.95–3.90 (m, 1H), 3.85 (approx. q, J = 7.0 Hz, 1H), 3.78 (approx. q, J = 7.4 Hz, 1H), 3.51 (dddd, J = 11.6, 3.3, 3.3, 3.3 Hz, 1H), 2.44 (s, 3H), 2.27 (dd, J = 14.3, 0.9 Hz, 1H), 2.10 (d, J_{AB} = 14.3 Hz, 1H), 1.98–1.90 (m, 2H), 1.80–1.50 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.7, 135.2, 129.9, 129.4, 117.3, 92.7, 79.5, 67.1, 65.4, 64.8, 47.2, 42.6, 39.7, 28.5, 25.2, 21.8, 20.9, 20.5.

Vinyl sulfone 13

To a solution of **12** (22 mg, 0.058 mmol) in THF (1.16 mL) cooled to –78 °C (isopropanol/dry ice bath) was added dropwise via syringe *n*-BuLi (35 µL, 2.52 mol/L in hexanes). The solution initially turned pale yellow, then dark yellow-orange. The starting material was consumed after 20 min as ascertained by TLC, and the reaction was stirred an additional 30 min. The cooling bath was removed and the reaction was immediately quenched by the addition of satd. NH_4Cl solution (4 mL) and Et_2O (5 mL). The biphasic mixture was transferred to a separatory funnel, separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phase was then washed with brine (10 mL), dried with $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resulting crude material was purified by radial chromatography (2 mm plate, solvent ramp: 100 mL each of 20%, 30%, and 40% EtOAc–hexanes) to yield **13** (16 mg, 75%) as a white solid; mp 120–122 °C. R_f = 0.11 (30% EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3534, 2948, 1301, 1143, 1086. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 6.92 (approx. br s, 1H), 4.02–3.92 (m, 3H), 3.87–3.83 (m, 1H), 3.30 (br s, 1H), 3.16 (ddd, J = 14.2, 12.3, 6.7 Hz, 1H), 2.44 (s, 3H), 2.31 (ddd, J = 14.8, 7.3, 1.5 Hz, 1H), 2.26 (d, J_{AB} = 14.6 Hz, 1H), 2.06 (d, J_{AB} = 14.6 Hz, 1H), 1.76–1.73 (m, 2H), 1.67–1.57 (m, 3H), 1.51–1.46 (m, 1H), 1.35–1.19 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.9, 144.8, 140.1, 136.1, 130.1, 128.7, 108.8, 79.8, 65.5, 63.7, 50.2, 47.1, 44.0, 34.5, 28.8, 23.4, 23.2, 21.9. HR-MS (EI) *m/z* calcd. for $C_{20}H_{26}O_5S$: 378.1501; found: 378.1495.

Cyclooctenone ketal 14a

This procedure was carried out under an argon atmosphere. A large excess of LiDBB solution was prepared according to Cohen's procedure (Li (10 mg), di-*tert*-butylbiphenyl (DBB) (358 mg), THF (4.5 mL)) (19*b*). To a solution of **11a** (14 mg, 0.04 mmol) and a crystal of phenanthroline in THF (0.17 mL) cooled to –78 °C (isopropanol/dry ice bath) *n*-BuLi (~10 µL, 2.52 mol/L in hexanes) was added dropwise until the solution turned a red color (19*c*). LiDBB was then added dropwise via cannula to this solution until a persistent dark green color was observed, indicating an excess of LiDBB (exact volume of LiDBB added not measured). Starting material was consumed within 30 min (TLC). The reaction was allowed to stir for an additional 1 h at –78 °C, the cooling bath was then removed followed by the immediate addition of satd. NH_4Cl solution (5 mL) and Et_2O (5 mL). The mixture was then transferred to a separatory funnel, the aqueous phase was back extracted with Et_2O (5 mL), the combined organic phase was washed with brine (10 mL) and dried with $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resulting crude material was purified by radial chromatography (2 mm plate, solvent ramp: 100 mL each of hexanes, 5%, 15%, and 30% EtOAc–hexanes) to yield **14a** (9 mg, 97%) as a colorless oil. R_f = 0.32 (30% EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3542, 3018, 2948, 1061, 757. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.78 (ddd, J = 11.5, 9.7, 7.6 Hz, 1H), 5.58 (dd, J = 11.5, 1.2 Hz, 1H), 4.00–3.98 (m, 1H), 3.94–3.90 (m, 3H), 3.39 (br s, 1H), 2.94–2.85 (m, 1H), 2.26 (d, J_{AB} = 14.4 Hz, 1H), 2.08–2.01 (m, 2H), 1.99 (d, J_{AB} = 14.4 Hz, 1H), 1.80–1.56 (m, 6H), 1.49–1.41 (m, 1H), 1.41–1.34 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 133.2, 132.8, 109.6, 80.3, 64.8, 63.4, 50.3, 46.9, 43.9, 34.8, 29.4, 24.3, 23.3. HR-MS (EI) calcd. for $C_{13}H_{20}O_3$ (M^+): 224.1413; found: 224.1412.

Ketalization of 7e and 7f

Formation of 11b and 11c

To a mixture of diastereomers **7e** and **7f** (340 mg, 1.2 mmol, ca. 2.5:1) in CH_2Cl_2 (6 mL) at 0 °C was added 1,2-bis(trimethylsiloxy)ethane (580 µL, 2.4 mmol) followed by TMSOTf (12 µL, 5 mol%), and the resulting mixture was warmed to RT over several hours. This was then heated to reflux for ca. 12 h, after which TLC showed consumption of starting materials. The reaction was quenched with pyridine (1 mL) and saturated aqueous $NaHCO_3$ (5 mL), diluted with Et_2O (10 mL), and the resulting layers were separated. The aqueous layer was washed with three portions of Et_2O (10 mL) and the combined organic extracts were washed with water (30 mL) and then brine (30 mL), dried over magnesium sulfate, filtered, and concentrated, giving the crude product as a yellow oil. This oil was diluted in ether (20 mL) and passed through a short pad of silica gel in a fritted filter while eluting with ether. This was then concentrated and the resulting oil purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 100 mL each of 3%, 6%, and then 10% EtOAc–hexanes until the products are recovered) to

yield **11b** (283 mg, 72%) as a pale oil and **11c** (102 mg, 26%) as a crystalline solid.

Ketal 11b

R_f = 0.63 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2945, 2869, 1492, 1434, 1398, 1344, 1323, 1291. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.23 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 4.11 (m, 1H), 4.06 (m, 1H), 3.87, (d, J = 2.6 Hz, 1H), 3.84 (m, 1H), 3.76 (m, 1H), 3.31 (ddd, J = 12.7, 5.8, 3.5 Hz, 1H), 2.37 (d, J_{AB} = 13.7 Hz, 1H), 2.42–2.34 (m, 1H), 2.32 (s, 3H), 2.10 (d, J_{AB} = 13.7 Hz, 1H), 2.04 (dd, J = 14.0, 5.7 Hz, 1H), 1.80–1.74 (m, 5H), 1.65–1.57 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.8, 134.1, 131.1, 130.3, 116.9, 88.5, 83.1, 65.5, 64.6, 45.7, 45.3, 44.9, 34.6, 28.5, 28.4, 21.4, 21.2. HR-MS (EI) calcd. for $C_{19}H_{24}O_3S$ (M^+): 332.1146; found: 332.1438. Anal. calcd. for $C_{19}H_{24}O_3S$: C 68.64, H 7.28, S 9.60; found: C 68.78, H 7.05, S 9.79.

Ketal 11c

Melting point 78 to 79 °C. R_f = 0.54 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2951, 2871, 1492, 1445, 1433, 1398. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.29 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 3.92–3.87 (m, 2H), 3.78 (approx. q, J = 7.2 Hz, 1H), 3.63 (ddd, J = 11.5, 7.0, 4.5 Hz, 1H), 3.53 (approx. q, J = 7.4 Hz, 1H), 3.38 (ddd, J = 7.8, 6.1, 1.7 Hz, 1H), 2.29 (s, 3H), 2.24 (d, J_{AB} = 13.4 Hz, 1H), 2.22 (m, 1H), 1.96 (d, J_{AB} = 13.4 Hz, 1H), 1.92–1.74 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.2, 132.5, 132.4, 129.9, 116.7, 89.0, 83.4, 65.4, 64.3, 46.1, 44.1,43.4, 36.5, 32.1, 27.4, 22.9, 21.3. HR-MS (EI) calcd. for $C_{19}H_{24}O_3S$ (M^+): 332.1446; found: 332.1445. Anal. calcd. for $C_{19}H_{24}O_3S$: C 68.64, H 7.28, S 9.60; found: C 68.61, H 7.01, S 9.76.

LDBB reduction of 11b

Formation of 14b and 15

A large excess of LDBB was prepared according to Cohen's procedure, using Li (8 mg, 6 equiv.) and di-*tert*-butylbiphenyl (300 mg) in THF (3.2 mL). To a solution of **11b** (57 mg, 0.19 mmol) and a crystal of phenanthroline in THF (0.7 mL) cooled to –78 °C was added *n*-BuLi until the color turned deep red. LDBB was then added dropwise (without quantification) to the reaction mixture until an intense green color persisted, indicating the presence of excess LDBB. The reaction was stirred until consumption of starting material was observed by TLC (ca. 2 h). The reaction was then quenched by addition of saturated aqueous ammonium chloride (5 mL), further diluted in Et_2O (15 mL), and the resulting bilayer was separated. The aqueous layer was back extracted once with Et_2O (10 mL) and the combined organic extracts were pre-dried with brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by gradient column chromatography (silica gel, 0%, 20%, and 60% EtOAc–hexanes) to give **14a** (25 mg, 69%) as a pale yellow oil, as well as a trace of isomer **15** (2 mg, 5.5%), in an overall yield of 75%. The ratio of product isomers depended on the time allowed for the reaction: if the reaction was quenched after 30 min, the ratio of the products is **14a** (19%) and isomer **15** (45%).

Alcohol 14b

R_f = 0.36 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3513, 3025, 2959, 1653, 1445, 1425, 1397, 1344, 1316, 1281. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.89 (ddd, J = 12.2, 8.9, 3.5 Hz, 1H), 5.65 (ddd, J = 12.0, 3.1, 1.3 Hz, 1H), 4.19 (s, 1H) 3.93 (s, 4H), 2.29 (dddd, J = 16.1, 11.8, 3.1, 3.1 Hz, 1H), 2.21 (d, J_{AB} = 14.1 Hz, 1H), 2.04 (ddd, J = 16.0, 8.8, 2.3 Hz, 1H), 1.86 (d, J_{AB} = 14.1 Hz, 1H), 1.80–1.66 (m, 3H), 1.65–1.50 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 133.9, 133.6, 108.6, 78.6, 64.6, 63.9, 47.2, 44.9, 41.9, 30.9, 26.6, 19.8. HR-MS (ESI) calcd. for $C_{12}H_{18}O_3Na$ ($M + Na^+$): 233.1148; found: 233.1149.

Isomer 15

R_f = 0.09 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 3428 (br), 2946, 2865, 1651, 1446, 1433, 1360, 1327. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.89 (ddd, J = 12.2, 8.8, 3.5 Hz, 1H), 5.64 (d, J = 12.2 Hz, 1H), 4.18 (s, 1H), 3.94 (s, 4H), 2.29 (approx. ddt, J = 14.5, 11.3, 3.3, 3.3 Hz, 1H), 2.21 (d, J_{AB} = 14.1 Hz, 1H), 2.04 (ddd, J = 16.0, 8.8, 2.2 Hz, 1H), 1.86 (d, J_{AB} = 14.1 Hz, 1H), 1.80–1.48 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.2, 99.4, 90.8, 74.1, 67.8, 61.3, 46.0, 46.9, 39.9, 37.1, 33.0, 24.8. HR-MS (EI) calcd. for $C_{12}H_{18}O_3$ (M^+): 210.1256; found: 210.1253.

Isomer **15** was found to reketalize upon standing in $CDCl_3$ to give compound **16**. R_f = 0.40 (3:7, EtOAc–hexanes). IR (CH_2Cl_2 cast, cm^{-1}): 2951, 2869, 1350. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.43 (dd, J = 7.6, 4.3 Hz, 1H), 3.92 (approx. t, J = 6.3 Hz, 2H), 3.81 (approx. t, J = 6.3 Hz, 2H), 2.67 (approx. tt, J = 9.2, 4.7 Hz, 1H), 2.31 (dd, J = 12.2, 9.0 Hz, 1H), 2.08 (d, J_{AB} = 13.5 Hz, 1H), 1.96–1.86 (m, 2H), 1.86–1.78 (m, 2H), 1.72 (dd, J = 13.5, 2.0 Hz, 1H), 1.65–1.61 (m, 1H), 1.64 (ddd, J = 13.8, 1.8, 1.8 Hz, 1H), 1.56–1.51 (m, 1H), 1.45–1.40 (m, 1H), 1.35–1.30 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 107.6, 91.5, 76.0, 64.3, 63.2, 44.5, 44.2, 40.7, 39.0, 37.4, 34.9, 25.1. HR-MS (EI) calcd. for $C_{12}H_{18}O_3$ (M^+): 210.1256; found: 210.1253.

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An examination of VANOL, VAPOL, and VAPOL derivatives as ligands for asymmetric catalytic Diels–Alder reactions[1]

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Abstract: Several derivatives of the vaulted biaryl ligand VAPOL were prepared and evaluated as chiral ligands for aluminum Lewis acids in the catalytic asymmetric Diels–Alder reactions of methyl acrylate and methacrolein with cyclopentadiene. The substituents on VAPOL were introduced into the 6- and 6′-positions in an effort to further extend the chiral pocket of the major groove, which contains the phenol functions at the 4- and 4′-positions. The set of four new ligands that have been prepared have the following groups introduced into the 6- and 6′-positions of VAPOL: bromide, methyl, phenyl and 3,5-di-*t*-butylphenyl. All of these ligands give lower asymmetric inductions than the unsubstituted VAPOL for the Diels–Alder reactions of both methyl acrylate and methacrolein. The positive cooperativity of added carbonyl compounds on the autoinduction in the Diels–Alder reaction of methyl acrylate and cyclopentadiene were also investigated with the VANOL and VAPOL ligands as well as the 6,6′-dibromo and 6,6′-diphenyl derivatives of VAPOL. Only the reaction with VAPOL showed any significant positive cooperativity. The reaction with VANOL was sluggish at –78 °C, but at higher temperatures, the reaction did exhibit positive cooperativity that was similar to that of VAPOL. Finally, no positive cooperativity was observed with the VAPOL ligand for the reaction of methacrolein and cyclopentadiene.

Key words: Diels–Alder, asymmetric catalysis, vaulted biaryl ligands, VANOL, VAPOL.

Résumé : On a préparé plusieurs dérivés du ligand voûté VAPOL et on les a évalués comme ligands chiraux pour des acides de Lewis dérivés de l'aluminium à utiliser dans des réactions de Diels–Alder asymétrique catalytique de l'acrylate de méthyle et de la méthacroléine avec le cyclopentadiène. On a introduit des substituants sur les positions 6 et 6′ du VAPOL dans le but d'agrandir la poche chirale de la cannelure principale qui comporte les fonctions phénols dans les positions 4 et 4′. Dans l'ensemble des quatre nouveaux ligands qui ont été préparés, on a introduit les groupes suivants dans les positions 6 et 6′ du VAPOL: bromure; méthyle; phényle et 3,5-di-tert-butylphényle. Chacun de ces ligands conduit à des inductions asymétriques inférieures à celle observé avec le VAPOL non substitué, tant pour les réactions de Diels-Alder de l'acrylate de méthyle que celles de la méthacroléine. On a aussi étudié la coopération positive des composés carbonyles ajoutés sur l'autoinduction de la réaction de l'acrylate de méthyle et du cyclopentadiène à l'aide de ligands VANOL et VAPOL ainsi qu'avec les dérivés 6,6′-dibromo et 6,6′-diphényl du VAPOL. Seule la réaction avec le VAPOL a montré une coopération positive significative. La réaction avec le VANOL était lente à –78°C, mais à des températures plus élevées, la réaction présente une coopération positive semblable à celle du VAPOL. Enfin, on n'a observé aucune coopération positive avec le ligand VAPOL pour la réaction de la méthacroléine avec le cyclopentadiène.

Mots clés : Diels–Alder, catalyse asymétrique, ligands biaryles voûtés, VANOL, VAPOL.

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This manuscript is dedicated to Dr. Alfred Bader. Dr. Bader is many things to many people and included among them he is an entrepreneur, a lover of the arts, a champion of young scientists, and above all, a generous and gracious human being. When I was a beginning assistant professor in the early 1980s, he awarded me one of his young chemist awards. This was a greatly appreciated and needed boast to my program. A gift of $5000 was a significant sum in those days considering my start-up package was $25 000. His call came out of the blue one day when I was home in bed with a nasty fever. Having failed to reach me at work, he tracked me down at home and what I remember from my delirious state is my wife saying someone named Alfred Bader was on the phone. I think that I thanked him at the time, and if I didn't, I would certainly like to thank him now.

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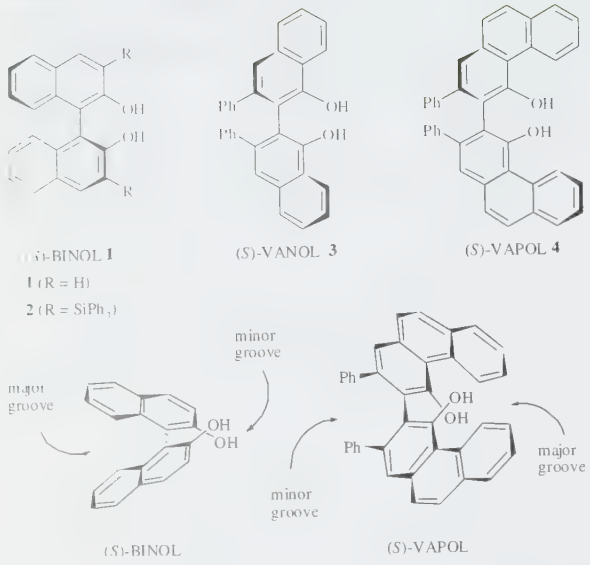
Scheme 1.



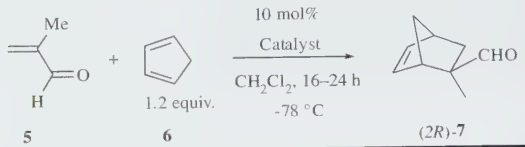
Introduction

One of the most widely used and successful ligands in asymmetric catalysis is 1,1′-binaphth-2,2′-ol, or BINOL 1 (1). In most applications, catalysts are generated from BINOL by the formation of covalent bonds to the two phenol functions with either a transition metal or a main group atom. In many applications it has been found that improved induction results from these catalysts if substituents are introduced in the 3- and 3′-positions of BINOL (such as **2**) (2). This is particularly true for catalysts that have only one BINOL ligand bound to the metal center (2). In the absence of substituents at the 3- and 3′-positions, the BINOL ligand provides a much smaller chiral pocket for the metal center since the phenol functions project into the minor groove of BINOL rather than the major groove (Scheme 1). Our approach to this problem is to design biaryls in which the phenol functions are projected into the major groove of the ligand (Scheme 1). To this end, we simply envisioned an extension of the aromatic system of BINOL out into the region of the phenol functions and as a result ultimately synthesized the vaulted biaryl ligands VANOL **3** and VAPOL **4** (3). These ligands have been demonstrated to be particularly successful in catalytic asymmetric Diels–Alder (4), aziridination (5), Mannich (6) reactions, as well as in Baeyer–Villiger oxidations (7) and imine amination reactions (8).

We have reported that a catalyst prepared from VAPOL and diethylaluminum chloride is effective in providing high asymmetric inductions in the reactions of methacrolein and methyl acrylate with cyclopentadiene (Table 1) (4). A comparison of a series of catalysts prepared from diethyl aluminum chloride and ligands **1**–**4** reveals that only the VAPOL-derived catalyst offers significant asymmetric induction in the reaction with methacrolein (Table 1) (4*a*). The data from a corresponding set of boron catalysts prepared from bromoborane dimethyl sulfide complex revealed that these catalysts are slower and that VANOL gave the catalyst with the superior enantioselectivities (4*b*). Based on the data in Table 1, we set out to prepare and evaluate the set of 6,6′-disubstituted VAPOL ligands **8**–**11** (Scheme 2) as precursors to aluminum catalysts in the asymmetric catalytic Diels–Alder reaction and to compare their selectivity profile with that of the unsubstituted VAPOL ligand **4**. Substituents in the 6- and 6′-positions would be expected to increase the size of the major groove of the VAPOL ligand (Scheme 1) and as a result, the asymmetric induction observed in reactions mediated by catalysts generated from these ligands. In addition, catalysts generated from the VANOL ligand **3** will be evaluated for the Diels–Alder reactions, given the recent findings that the VANOL ligand is equally as effective as the VAPOL ligand in asymmetric catalytic aziridination reactions and superior to the VAPOL ligand in Baeyer–Villiger reactions (7).

The retrosynthesis of the VAPOL derivatives **8**–**11** was envisioned to involve, first, the initial preparation of the 6,6′-dibromoVAPOL **8** and then after subsequent resolution, the utilization of this dibromo derivative as the intermediate through which the other derivatives will be prepared. The synthesis of the 6,6′-dibromo-VAPOL **8** was modeled after the original method that we developed for the synthesis of the VAPOL ligand (3) and involves the oxidative phenol coupling of the phenanthrol **21** (Scheme 3), whose synthesis in turn would involve the benzannulation reaction of the carbene complex **17** with phenylacetylene as the key step (Scheme 4). The synthesis of the alkenyl bromide **16** neces-

Table 1. Diels–Alder reaction of methacrolein and cyclopentadiene.



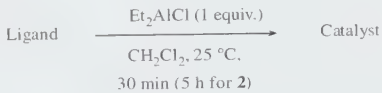
5 6 (2*R*)-**7**

Ligand	Yield **7** (%)	exo–endo	ee% **7** (exo)[a]
(*S*)-BINOL	99	97:3	23
(*S*)-**2**	69	92:8	20
(*S*)-VANOL	84	93:7	5
(*S*)-VAPOL	100	98:2	91.4 (93.6)[b]

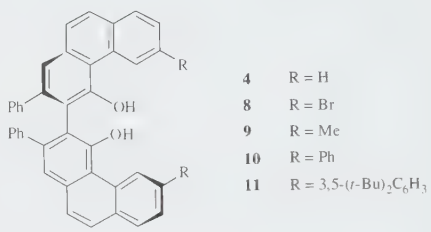
Note: All reactions use 1.0 mol/L in methacrolein.

[a]ee% was measured by conversion to chiral acetals as described in the experimental section.

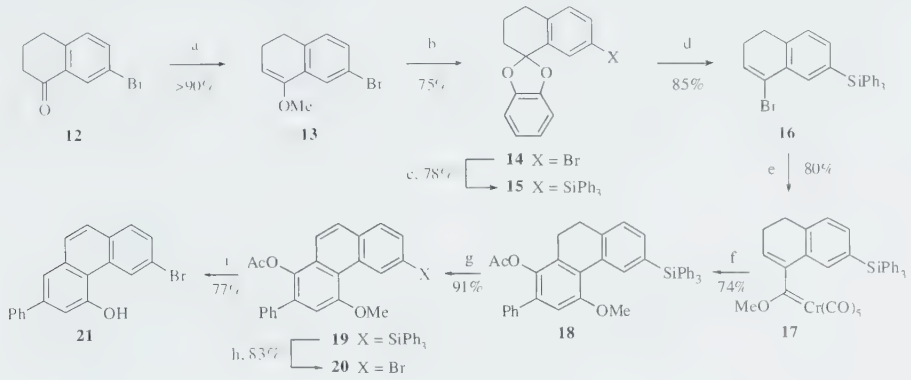
[b]ee% in parentheses was measured by GC as described in the experimental section.



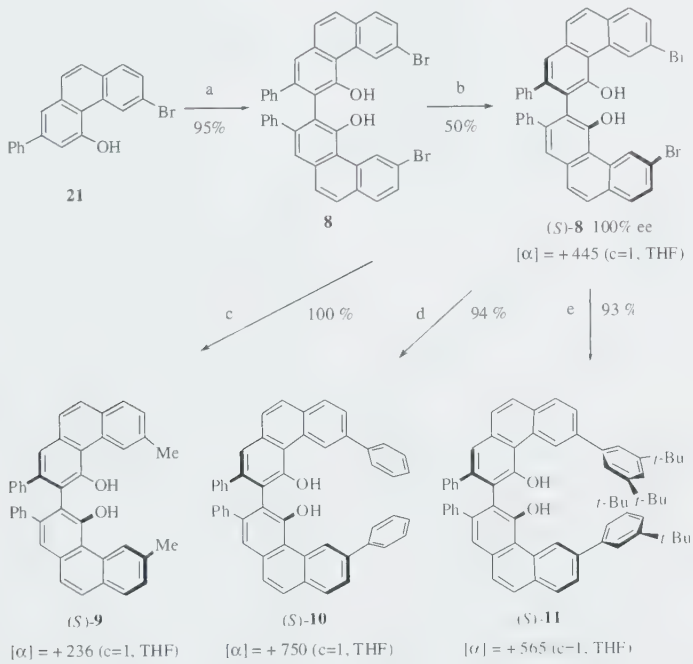
Scheme 2.



Scheme 3. (*a*) $HC(OMe)_3$, MeOH, cat CSA, benzene, reflux; (*b*) catechol, cat TsOH, benzene, reflux; (*c*) *i.* *n*-BuLi, THF, –78 °C, *ii.* Ph_3SiCl; (*d*) BBr_3, CH_2CL_2; (*e*) *i.* 2 equiv. *t*-BuLi, THF, –78 °C, *ii.* $Cr(CO)_6$, *iii.* MeOTf, CH_2CL_2; (*f*) *i.* PhC / CH, THF, 60 °C, 21 h, *ii.* Ac_2O, NEt_3, THF, 60 °C; (g) NBS, cat benzoyl peroxide, benzene, reflux; (*h*) Br_2, CH_2CL_2, reflux; (*i*) EtSH, $AlCl_3$, CH_2CL_2.



Scheme 4. (*a*) 195 °C, air; (*b*) *i.* (–)-sparteine, $CuCl_2$-$2H_2O$, MeOH–CH_2CL_2, *ii.* extract into hexane; (*c*) MeMgBr, cat Ni(II)(dpe)Cl_2, ether, reflux; (*d*) $PhB(OH)_2$, cat $Pd(PPh_3)_4$, benzene, aq. Na_2CO_3, reflux; (*e*) 3,5-(*t*-Bu)$_2C_6H_3B(OH)_2$, cat $Pd(PPh_3)_4$, benzene, aq. Na_2CO_3, reflux.



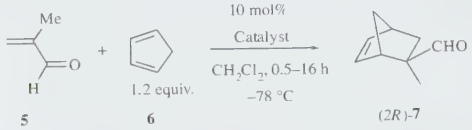
sary for the synthesis of the carbene complex **17** begins with 7-bromo-α-tetralone **12**, as indicated in Scheme 4. After evaluation of several methods for the conversion of ketones to alkenyl bromides, we found that the best procedure for the tetralone **12** was the method reported by Napolitano (9) involving the intermediacy of a catechol ketal, which was reported for α-tetralone in 40% overall yield. As reported by Napolitano for α-tetralone, we found that the direct conversion of 7-bromo-α-tetralone **12** to the catechol ketal **14** was inefficient. On a small scale, the direct reaction of **12** with catechol gave minimal yields of **14** and on a large scale this conversion failed completely. However, excellent yields of **14** could be obtained if **12** was first converted to the methyl enol ether **13**. The bromide function in the alkenyl bromide **16** is necessary for the preparation of the carbene complex **17**, but prior to the formation of the alkenyl bromide **16** by treatment of the ketal with boron tribromide the aryl bromide function in **14** was protected as its triphenylaryl silane **15**. The carbene complex **17** could then be generated by the standard Fischer procedure from **16** and chromium hexacarbonyl in 80% yield. The benzannulation of the carbene complex **17** with phenyl acetylene was carried out in two steps, (*i*) the reaction with phenylacetylene and (*ii*) the protection of the phenol function as its acetate. One attempt to carry out this transformation concurrently by the addition of acetic anhydride and triethylamine at the beginning of the reaction met with failure. Thus, this overall transformation must be carried in sequential steps. In the next step, oxida-

tion of the B ring with NBS under free-radical conditions afforded phenanthrene **19** in 91% yield. Initial attempts at this oxidation with palladium on carbon or DDQ were unsuccessful. One might wonder why we waited until after the benzannulation reaction to aromatize. We could have, for example, oxidized the compound **16** and carried the naphthyl system into the benzannulation. We chose this order because the benzannulation of alkenyl carbene complexes with alkynes is much less susceptible to side-product formation than aryl complexes (10). The triphenylsilyl group was then "deprotected" to the bromide by treatment with bromine, which after considerable optimization was found to be best achieved with two equivalents of bromine to give **20** in 83% yield. The monomer **21** was finally generated by the reaction of **20** with ethanethiol and aluminum chloride (3). It is critical to control the time of this reaction since prolonged times can lead to the reduction of the bromide in the product **21**. Since trace amounts of this reduced monomer would lead to cross-coupled products in the oxidative phenol coupling step, it was necessary to rigorously purify the monomer **21** by column chromatography.

The oxidative phenol coupling follows the procedure developed for the synthesis of VAPOL and VANOL (3). Melting **21** in the presence of air and heating at 195 °C until the monomer **21** was consumed gave racemic 6,6′-dibromo-VAPOL **8** in 95% yield. This compound was deracemized with (–)-sparteine and copper (II) according to a procedure originally reported by Kocovsky (11), which has recently been improved by our laboratory (12). This procedure gave 6,6′-dibromo-VAPOL **8** that was substantially enantioenriched (>90% ee). The optical purity could be easily improved by extracting with hexane. The racemates of VAPOL **4** and Br_2-VAPOL **8** are both substantially less soluble than the optically pure material. Thus, the pure enantiomer of **8** (>99% ee) could be easily obtained by stirring the enantioenriched **8** with enough hexane to leave only a small amount of residue undissolved. The hexane solution is decanted to leave the solid and then the hexane is removed to leave the optically pure ligand **8**. This ligand could also be crystallized from hexane and ethyl acetate to give X-ray quality crystals, which have two molecules of ethyl acetate per molecule of **8**. The conversion of the 6,6′-dibromo-VAPOL ligand **8** to the corresponding dimethyl derivative **9** was accomplished in 100% yield by the nickel-catalyzed coupling of **8** with methyl magnesium bromide (6 equiv.) (13). The two aryl-substituted VAPOL ligands **10** and **11** were prepared from the dibromide **8** by Suzuki coupling reactions in 94% and 93% yields, respectively (14).

The results from the asymmetric catalytic Diels–Alder reactions of methacrolein and cyclopentadiene with catalysts generated from VAPOL **4** and the VAPOL derivatives **8–11** are shown in Table 2. All of the VAPOL derivatives with substituents in the 6- and 6′-positions give lower asymmetric inductions than VAPOL. The best of these is the bis-(3,5-di-*t*-butylphenyl) derivative, which gives a 62% ee for the reaction. Interestingly, the diphenyl derivative **10** gives the product **7** with the opposite sense of induction to all of the other ligands. The catalyst was prepared in each case by treating the ligand with 1 equiv. of ethylaluminum dichloride at RT. The completion of catalyst formation was determined by ^{1}H NMR and it was found that for the ligands **4**, **8**, and **9** the

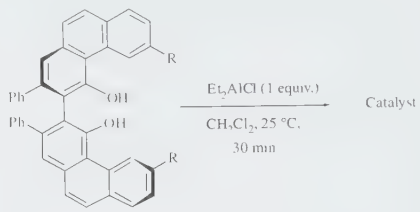
Table 2. Effect of vaulted biaryl catalysts on the reaction of **5** and **6**.



5 **6** (2*R*)-**7**

Ligand	R	Yield **7** (%)[a]	exo–endo[b]	ee% **7** (exo)[b]
(*S*)-**4**	H	>95	27	93
(*S*)-**8**	Br	>95	8.3	18
(*S*)-**9**	Me	>95	14.4	30
(*S*)-**10**	Ph[c]	76	11.7	–41
(*S*)-**11**	3,5-(*t*-Bu)$_2$C$_6$H$_3$[c]	>95	8.4	62

Note: All reactions use 0.5–1.0 mol/L in methacrolein.
[a]Determined by ^{1}H NMR with ligand as internal standard.
[b]Determined by GC of acetals prepared from (2*R*,4*R*)(–)pentanediol.
[c]Catalyst was prepared at 55 °C for 24 h.

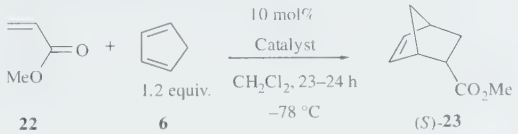


VAPOL was completely consumed within 30 min. However, for the more hindered ligands **10** and **11**, the complete consumption of the ligand required heating at 55 °C for 24 h.

Catalysts prepared from VAPOL-derived ligands **8–11** were also examined with the reaction of methyl acrylate and cyclopentadiene (Table 3). These reactions were slower than those with methacrolein but all are complete in 24 h except for the catalyst generated from the VANOL ligand, which only gave a 28% yield of the product **23** after 24 h. As with the reactions with methacrolein, all of the derivatives of VAPOL gave lower asymmetric inductions than VAPOL itself. Thus, for both sets of reactions it appears that the VANOL ligand does not provide a large enough chiral pocket. Furthermore, all of the 6,6′-substituted VAPOL derivatives form aluminum catalysts where either the bound substrate does not exist in a single conformation or the substrate does not have one of its faces sufficiently differentially shielded. The VAPOL ligand seems to be optimal for this particular aluminum catalyst.

The effect of solvents on the reaction of methyl acrylate with cyclopentadiene that is catalyzed by the VAPOL-derived catalyst is shown in Table 4. There was no reaction at all in THF and in ether the reaction was very sluggish giving only a 23% yield after 24 h with 10 mol% catalyst. Clearly, the best solvent for this reaction is toluene, which gives the product in 100% yield and 97% ee, whereas methylene chloride gives 87% yield and 82% ee. It was very curious indeed to find that if the reaction in methylene chloride was stopped after 15 min, the product was isolated with 48% ee. Furthermore, if the reaction was carried out by addition of only 10% of the dienophiles at the beginning of the reaction followed by slow addition of the remaining dienophiles, the asymmetric induction for **23** was higher at the end of the

Table 3. Effect of vaulted biaryl catalysts on the reaction of **22** and **6**.



22 **6** (*S*)-**23**

Ligand	R	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
(S)-**4**	H	87	112	82
(S)-**8**	Br	>95	51	16
(S)-**9**	Me	>95	92	28
(S)-**10**	Ph[c]	>95	129	35
(S)-**11**	3,5-(t-Bu)$_2$C$_6$H$_3$[c]	>95	44	29
(S)-**3**	VANOL	28	34	21

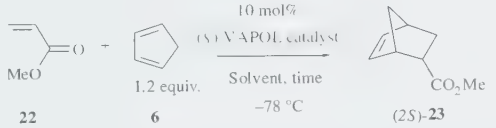
Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (J & W Cyclodex-B).

[c]Catalyst was prepared at 55 °C for 24 h.

Table 4. Solvent effect on the reaction of **22** and **6**.



22 **6** (2*S*)-**23**

Entry	Solvent	Time (h)	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
1	CH_2CL_2	24	87	112	82
2	CH_2CL_2	0.25[c]	21	—	48
3	CH_2CL_2	24[d]	80	—	89.4
4	Toluene	24	100	99	96.6
5	THF	24	0	—	—
6	Et_2O	24	23	—	—

Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (J & W Cyclodex-B).

[c]Reaction stopped at 20% conversion.

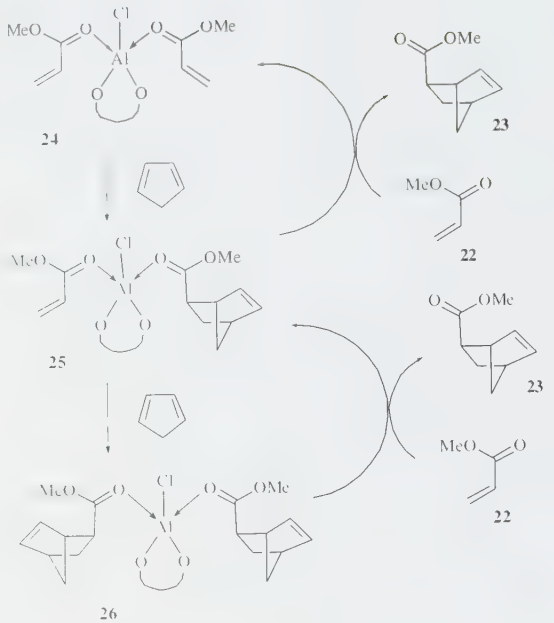
[d]10% of **22** was added at the beginning of the reaction and the rest was added slowly by syringe pump over 2.5 h.

reaction. We had observed this same type of behaviour for the reaction of methacrolein and cyclopentadiene (4*a*). We interpreted this as an asymmetric autoinduction (15) and have investigated this in some detail for the reaction of methyl acrylate and cyclopentadiene (4*c*). We chose the reaction of methyl acrylate and cyclopentadiene over that of methacrolein and cyclopentadiene since the former reacts much slower and it would be easier to follow the time course of the reaction. Also, the asymmetric induction was lower for the reaction with methyl acrylate and thus changes in induction would be more easily detected and monitored over a greater range. It is also for this reason that we chose to investigate the reaction of methyl acrylate in methylene chloride rather than in toluene.

Our explanation for the autoinductive effect observed for these reactions is illustrated in Scheme 5 for the reaction of methyl acrylate with cyclopentadiene (4*c*). It was proposed that the aluminum in the chiral catalyst could coordinate to the carbonyl group of two molecules of the starting material as in **24**, two molecules of the product as in **26**, or one molecule of each as in **25**. The fact that the particular asymmetric autoinduction we observed involves an increase in the asymmetric induction as the reaction progresses can then be accounted for if the Diels–Alder reaction of the complex **25** with one molecule of methyl acrylate and one molecule of product coordinated to the aluminum occurs with a higher selectivity than complex **24** with two molecules of starting material coordinated to the aluminum. At the beginning of the reaction there was little or no product and thus the great majority of the reaction flux will be through complex **24**. As more and more of the product is formed, more of the flux will occur through complex **25** and thus the asymmetric induction will continue to climb as the reaction progresses. In fact we have previously reported that the asymmetric induction for the reaction of methyl acrylate with cyclopentadiene is 48% ee after 20% completion and slowly rises during the course of the reaction until its culmination at 82% ee when the reaction is complete (Table 4 and ref. 4*c*).

It was reasoned that if complex **25** gives higher induction than **24** because of the greater steric size of the product com-

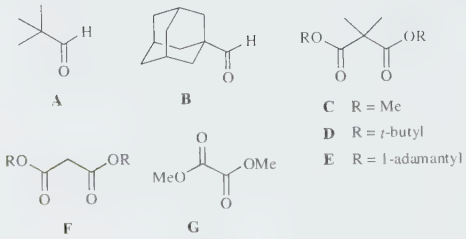
Scheme 5.



pared with that of the starting material, then one might be able to avoid the low asymmetric induction at the beginning of the reaction by the addition of a "dummy" carbonyl compound that is physically larger than methyl acrylate. This expectation was borne out in a series of experiments involving the carbonyl compounds indicated in Scheme 6. This study has been already communicated and some of this data is included in Table 5 (4*c*). As can be seen from the data in the first three entries, the addition of 0.5 equiv. of pivaldehyde at the beginning of the reaction increased the asymmetric induction at the end of the reaction from 82% to 96% ee. The larger adamantyl aldehyde B increased the induction still further to 98.5% ee. It was unexpected to find that 1,3-dicarbonyl compounds were even more effective. The di-*t*-butylmalonate D increased the induction to greater than 99% ee (Table 5, entry 5). These effects were more visible at higher temperatures. For example, the malonate E can increase the induction from 37% ee to 85% ee at 0 °C with 0.5 equiv. of E and to 92% ee with 1.0 equiv. This is quite remarkable when considering that the presence of this additive allows the temperature of the reaction to be increased by 80 °C and at the same time increases the induction from 82% ee to 92% ee. Since our initial report (4*c*) and as mentioned above, we have found that substantially increased asymmetric induction can be achieved in toluene as solvent. The asymmetric induction can be increased from 82% ee in CH_2Cl_2 to 97% ee in toluene at –78 °C (Table 5, entries 1 and 20). However, the additive effect is hardly observable in toluene. The reaction at 0 °C in toluene shows only a slight increase in induction from 46% ee to 58% ee in the presence of 0.5 equiv. of the malonate E.

The phenomenon of increased asymmetric induction with the addition of product mimics was termed "positive cooperativity" (4*c*). The strong effect that carbonyl additives had on the autoinduction for the reaction of methyl acrylate and cyclopentadiene with a catalyst generated from the VAPOL

Scheme 6.

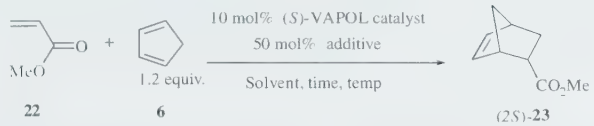


ligand prompted the study outlined in Table 6 to probe the extent to which added carbonyl compounds would exhibit positive cooperativity with the substituted VAPOL ligands **8** and **10** and with the VANOL ligand. These reactions were screened with 0.5 equiv. of the di-*t*-butyl malonate D added at the beginning of the reaction. Remarkably, the addition of malonate D had essentially no effect on the asymmetric induction with catalyst generated from 6,6′-dibromo-VAPOL **8** or from 6,6′-diphenyl-VAPOL **10**. Perhaps the major groove of these ligands (Scheme 1) is too hindered to allow for the coordination of two carbonyl groups at the same time. It was also found that the asymmetric induction from the VANOL-derived catalyst was not sensitive to the addition of the malonate D (Table 6, entries 8 and 9). In this case however, the yields were quite low with and without the additive. At this point we do not know if the structure of the active catalyst is the same from VAPOL and VANOL and, in fact, the ^{1}H NMR spectrum of the catalyst generated from Et_2AlCl and VAPOL reveals that there appears to be a mixture of several different species. In light of this fact, it is remarkable that very high asymmetric inductions can be achieved with this catalyst mixture for the reaction with methyl acrylate in toluene (Table 5, entry 20) or in CH_2Cl_2 in the presence of additives A-D (Table 5, entries 2–5).

The sluggishness of the reaction with the VANOL catalyst prompted a study of the effect of temperature on this catalyst to find conditions under which the reaction could be driven to completion and at the same time to determine the extent of any positive cooperativity with added carbonyl compounds leading to increased asymmetric induction. As the data in Table 7 shows, it was found that reasonable yields of the product could be observed in 24 h with 10 mol% catalyst if the temperature was raised to –40 °C and that at –20 °C the reaction was complete in the same time period. It is interesting to note that the VANOL and VAPOL ligands gave nearly identical results at –40 °C (Table 7, entry 7 vs. Table 5, entry 7) and at 0 °C (Table 7, entry 11 vs. Table 5, entry 13). In contrast to the VAPOL-derived ligands **8** and **10** (Table 6), the VANOL catalyst was significantly affected by the addition of additives. The degree of the effect of the malonate D was about the same as that on the VAPOL catalyst at 0 °C but the effect was less for the VANOL catalyst at –40 °C.

An investigation of the Diels–Alder reactions of cyclopentadiene with the *t*-butyl, *n*-propyl, and ethyl esters of acrylic acid was undertaken to compare the results with those of methyl acrylate. It was thought that if the steric bulk of the two carbonyls coordinated to the aluminum were important to the asymmetric induction of the Diels–Alder reaction (Scheme 5) then perhaps adjusting the size of the alkoxy group of the acrylate ester could have a similar ef-

Table 5. Effect of additives on the reaction of **22** and **6**.



22 **6** (2*S*)-**23**

Entry	Solvent	Additive	Temp (°C)	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
1	CH_2CL_2	None	–78	87	99	82
2	CH_2CL_2	A	–78	80	99	96
3	CH_2CL_2	B	–78	60	99	98.5
4	CH_2CL_2	C	–78	49	99	98
5	CH_2CL_2	D	–78	76	99	>99
6	CH_2CL_2	F	–78	<30	—	—
7	CH_2CL_2	None	–40	76	99	47
8	CH_2CL_2	B	–40	80	99	88
9	CH_2CL_2	C	–40	80	98	90
10	CH_2CL_2	D	–40	100	99	92
11	CH_2CL_2	E	–40	100	98	93
12	CH_2CL_2	G	–40	85	92	45
13	CH_2CL_2	None	0	84	99	37
14	CH_2CL_2	D	0	67	94	69
15	CH_2CL_2	E	0	90	95	85
16	CH_2CL_2	E[c]	0	80	99	92
17	CH_2CL_2	None	25	100	92	33
18	CH_2CL_2	D	25	80	99	56
19	CH_2CL_2	E	25	80	93	49
20	Toluene	None	–78	100	99	97
21	Toluene	E	–78	100	99	96
22	Toluene	None	0	77	99	46
23	Toluene	E	0	100	—	58

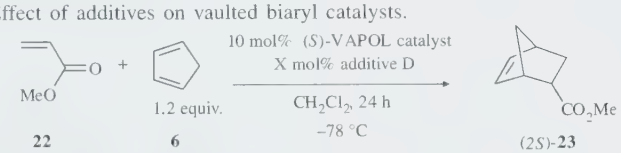
Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2. Reaction time for all reactions was 24 h except for those at 0 °C, which was 2 h and those at RT, which was 1 h.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (J & W Cyclodex-B).

[c]100 mol% additive.

Table 6. Effect of additives on vaulted biaryl catalysts.



22 **6** (2*S*)-**23**

Entry	Ligand	X	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
1	**4**(*R*)-VAPOL	0	99	>100	82[c]
2	**4**(*R*)-VAPOL	50	94	>100	98[c]
3	**4**(*S*)-VAPOL	50	86	>100	99
4	**8**(*S*)-Br_2VAPOL	0	99	65	15
5	**8**(*S*)-Br_2VAPOL	50	95	56	16
6	**10**(*S*)-Ph_2VAPOL	0	99	122	35
7	**10**(*S*)-Ph_2VAPOL	50	58	145	31
8	**3**(*S*)-VANOL	0	28	34	21
9	**3**(*S*)-VANOL	50	11	42	17

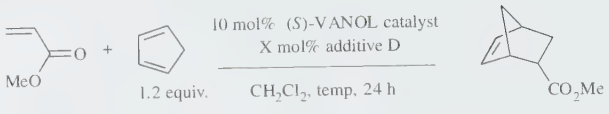
Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (J & W Cyclodex-B).

[c](2*R*)-**23** was obtained.

Table 7. Reaction of **22** and **6** with a VANOL catalyst.



22 **6** (2*S*)-**23**

Entry	X	Temp (°C)	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
1	0	–78	28	34	21
2	50	–78	11	42	17
3	0	–60	25	47	19
4	50	–60	10	50	24
5	0	–50	38	132	39
6	50	–50	41	100	57
7	0	–40	74	38	42
8	50	–40	75	74	54
9	0	–20	100	30	35
10	50	–20	100	31	57
11	0	0	97	22	29
12	50	0	95	Nd[c]	60

Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (J & W Cyclodex-B).

[c]Not determined.

fect. As expected, the asymmetric induction observed for the ethyl and *n*-propyl esters (Table 8, entries 6 and 9) were greater than that for the methyl ester (Table 5, entry 1). However, the trend does not continue to the *t*-butyl ester as the induction with this substrate falls to 9% ee (Table 8, entry 1). While the reaction of the *t*-butyl ester was unresponsive to any positive cooperativity effect with any additive (B–E), it was found that both the ethyl and *n*-propyl esters responded to carbonyl additives to a degree very similar to that of methyl acrylate (Table 8 vs. Table 5).

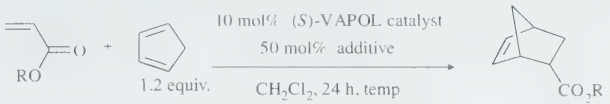
Finally, the reaction of methacrolein and cyclopentadiene was investigated in the presence of carbonyl additives to look for positive cooperativity effects. The data in Table 9 suggests that this reaction is unaffected by the presence of adamantyl aldehyde B or the di-*t*-butyl malonate D. The asymmetric induction for this reaction in CH_2Cl_2 is higher at –78 °C (93.6% ee) than it is for the same reaction with methyl acrylate (82% ee). Nonetheless, the addition of either B or D to the reaction would have been expected to produce measurable increases in induction if the positive cooperativity effect was in play here. Furthermore, no significant positive cooperativity effect was observed if the reaction temperature was raised to –40 °C or even to 0 °C where the asymmetric induction of the reaction itself was 16.9% and 5.1% ee, respectively. This lack of a positive cooperativity effect for the reaction of methacrolein and cyclopentadiene was surprising since this reaction, like the reaction of methyl acrylate, exhibits autoinduction. The degree of autoinduction for methacrolein is not as strong as that for methyl acrylate. For example, the reaction of methacrolein and cyclopentadiene has been reported to give an 81% ee after 30% conversion under conditions where an 88% ee was observed at the end of the reaction (4*a*).

The results of the present studies suggest that the VAPOL ligand appears to be optimal in forming a catalyst with diethylaluminum chloride to effect asymmetric Diels–Alder reactions with methacrolein and methyl acrylate with cyclopentadiene. Catalyst derived from the 6,6′-disubstituted VAPOL derivatives **8**, **9**, **10**, and **11** all gave reduced enantioselectivities for both of these reactions. The VANOL ligand gave lower enantioselectivities and slower rates as well. Since this is a smaller ligand, the lower rates may be due to a different catalyst structure. It was also found that carbonyl additives displayed positive cooperativity with the VAPOL catalyst on the autoinduction for the reaction with methyl acrylate but not with the substituted VAPOL catalysts derived from **8** and **10** or with the catalyst derived from the VANOL ligand. In contrast, no positive cooperativity with carbonyl additives was observed with the VAPOL catalyst on the autoinduction in the reaction of methacrolein and cyclopentadiene.

Experimental

Syntheses were performed under dry argon unless otherwise stated. THF and ether were distilled from sodium benzophenone ketyl. Methylene chloride, 1,2-dichloroethane, and acetonitrile were distilled from CaH_2. Toluene was distilled from sodium. Methacrolein was distilled from CaO. Methyl acrylate and pivaldehyde were distilled from $MgSO_4$. Cyclopentadiene was freshly cracked from dicyclopentadiene over 4 Å MS. Whatman glass-backed TLC plates (part #4861–820, 250 mm thickness, K6F Silica gel) were used for reported R_f values, except in those noted cases in which Macherey–Nagel plastic-backed TLC plates (Polygram® Sil N-HR/UV$_{254}$, 250 mm thickness) were used. IR spectra were taken on a Nicolet 20SXB FTIR spectrometer. Melting points were taken on a Hoover Unimelt apparatus and are uncorrected. Mass spectra were run on a VG Analytical 70–70EQ Double Focusing Hybrid MS (EI @ 70 eV).

Table 8. Effect of ester substituent on the reaction of **27** and **6**.



27 6 (2*S*)-**28**

Entry	R	Additive	Temp (°C)	Yield **28** (%)[a]	endo–exo[b]	ee% **28** (exo)[b]
1	*t*-butyl	None	–78	63	96	9
2		B	–78	Trace	—	—
3		C	–78	0	—	—
4		D	–78	32	96	19
5		E	–78	0	—	—
6	*n*-propyl	None	–78	33	99	92
7		B	–78	25	99	>99
8		C	–78	52	99	98
9	ethyl	None	–78	58	99	94
10		None	–40[c]	90	97	60
11		C	–40	72	98	92
12		D	–40[c]	100	Nd[d]	87
13		None	0[e]	100	93	33
14		C	0[e]	100	95	69

Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.
[b]Determined with a chiral GC column (J & W Cyclodex-B).
[c]The reaction time was 30 h.
[d]Not determined because of obscured integral.
[e]The reaction time was 2 h.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

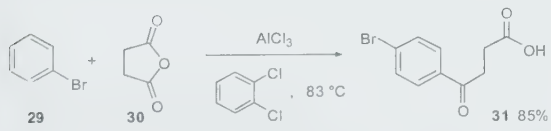
Chiral HPLC was done with a Pirkle covalent D-phenylglycine Rexchrom™ Regis column. Pump: Waters M-45 (ser. # 5615); operating pressure: 3100 psi (1 psi = 6.894 757 kPa); flow rate: 2.0 mL/min; solvent: 7:3 (*v*/*v*) hexane–isopropanol; detector (254 nm): Waters 440 Absorbance detector (ser. #07249); integrator: Spectra-Physics SP4270 (ser. #092–132).

Capillary GC was done on a Varian Star 3600 outfitted with an Alltech Econocap SE-54 column for nonchiral applications and a J & W Scientific Cyclodex-B column for chiral applications using helium carrier gas and FID detection.

Optical rotations were taken on a PerkinElmer Model 141 instrument using the sodium D line (589 nm). For ligand sample preparation, a 20 mg sample was dissolved in 2 mL THF. Concentration: 1 g/100 mL; temperature: 23 °C; path length: 1 dm; $[\alpha]_D = (100)\ a_{obs}$.

Preparation of 7-bromo-α-tetralone 12 (16)

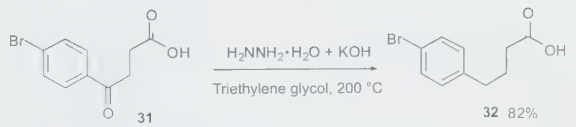
Friedel–crafts acylation of bromobenzene



29 **30** **31** 85%

A 1 L three-necked round-bottomed (RB) flask was fitted with a mechanical stirrer and was connected to an oil bubbler. It was charged with bromobenzene **29** (60.5 mL, 573 mmol), succinic anhydride **30** (37.6, 376 mmol), and *o*-dichlorobenzene (113 mL), and mechanically stirred. Aluminum trichloride (107 g, 804 mmol) was added in portions over 30 min. The solution turned rust red in colour and emitted a whitish smoke. It was warmed to 83 °C for 6 h, cooled to RT, and then poured into a mixture of HCl–ice in a 2 L Erlenmeyer flask whereupon a white curdish precipitate came out of solution. The precipitate was dissolved in ether, the entire contents were transferred in portions to a large separatory funnel, and the aqueous layer was removed. Concentration of the ether layer by distillation afforded crystals of product, which were suction filtered and then finely divided and spread out to dry in a pan in a 110 °C oven for two days. Yield: 82 g white-pinkish solid (85% yield). On a larger scale, it was not practical to dissolve the crude product in ether. In this case, crude product was allowed to oven dry directly, which took longer.

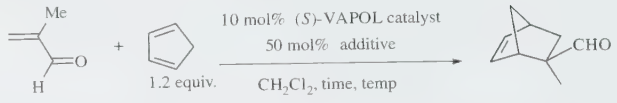
Wolff–Kischner reduction of 31



31 **32** 82%

A 1 L three-necked flask was equipped with a thermometer and a condenser–receiving flask. KOH (45 g, 804 mmol) and triethylene glycol (350 mL) were added and mechanically stirred. The mixture was warmed to 100 °C with a heating mantle to dissolve the KOH. It was then cooled to

Table 9. Effect of additives on the reaction of **5** and **6**.



5 6 (2*R*)-7

Entry	Additive	Time	Temp (°C)	Yield **7** (%)[a]	exo–endo[b]	ee% **7** (exo)[b]
1	None	0.5 h	–78	51	93	93.6
2	B	0.5 h	–78	65	94	94.6
3	D	0.5 h	–78	53	92	93.7
4	None	1 h	–40	73	80	16.9
5	D	1 h	–40	80	81	17.3
6	None	15 min	0	84	71	5.1
7	D	15 min	0	80	77	10.8

Note: All reactions use 0.5–1.0 mol/L in **5**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (Astec B-MB column) after reduction to the alcohol with $NaBH_4$.

80 °C, whereupon 68 g (265 mmol) of the keto acid **31** from the previous step and 34 mL of hydrazine monohydrate (702 mmol) were added. After stirring at 90–100 °C for 1 h, the mixture was warmed by a heating mantle to 200 °C and stirred at that temperature for 1 h. Liquid was distilled off into the receiving flask. The solution was cooled to near RT and poured into 400 mL of H_2O. Aq HCl (6 N, 220 mL) was added, which precipitated out a white suspension, and an oil settled on the bottom. On sitting overnight the oil solidified. The solid was filtered, then dissolved in ether (it was exceedingly soluble in ether), dried over $MgSO_4$, filtered, and left to crystallize in a crystallizing dish on air evaporation of ether to afford 52.98 g of **32** as a light tan solid (82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.96 (quintet, 2H), 2.38 (t, 2H, J = 7.4 Hz), 2.64 (t, 2H), 7.04 (d, 2H, J = 8.2 Hz), 7.38 (d, 2H, J = 8.2 Hz), acid proton not reported.

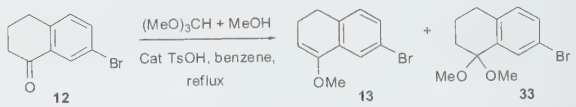
Cyclization of carboxylic acid (32)

32 **12** 75%

This reaction was run in open air. Polyphosphoric acid (PPA, 250 g) was warmed in a 1 L Erlenmeyer flask to 70 °C. The bromoaryl carboxylic acid **32** (52.98 g, 218 mmol) was melted at 50 °C and then added to the PPA and the mixture was swirled with a glass rod for a few minutes while keeping the temp between 70 and 90 °C. Additional PPA (200 g) was added and the mixture was kept at 80 °C for 1 h and swirled occasionally and it became a dark orange color. Heat was removed and ice was added, which turned the mixture yellowish. The mixture was extracted three times with ether (1 × 200 mL, 2 × 100 mL). The combined ether layers were washed sequentially with 200 mL H_2O, 100 mL 5% aq KOH, 100 mL H_2O, 100 mL 3% aq HOAc, 100 mL 5% aq $NaHCO_3$, and 100 mL H_2O, then dried over $MgSO_4$ and filtered into a crystallizing dish. Air evaporation of ether afforded 36.8 g of clear blocky crystals covered with an orange thin film (75% yield). The product could be crystallized from MeOH to yield colourless crystals: mp 75 to 76 °C (lit. value (16) mp 71–73 °C). R_f = 0.23 (hexane–EtOAc, 9:1). IR (neat film, NaCl, cm^{-1}): 2946 (w), 1676 (s), 1585 (m), 1221 (m), 1190 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.10 (quintet, 2H, J = 6.3 Hz), 2.62 (t, 2H, J = 6.5 Hz), 2.88 (t, 2H, J = 6.0 Hz), 7.12 (d, 1H, J = 8.13 Hz), 7.53 (dd, 1H, J = 8.2, 1.9 Hz), 8.11 (d, 1H, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.9, 29.0, 38.6, 120.5, 129.8, 130.5, 133.9, 135.9, 143.0, 196.8.

Preparation of the catechol ketal 14 from 7-bromo-α-tetralone (12)

Preparation of methyl vinyl ether (13)

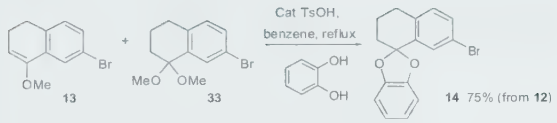


12 13 33

A 250 mL three-necked RB flask equipped with a side arm adapter, to which was connected a condenser and receiving flask, was charged with 7-bromotetralone **12** (20 g, 88.8 mmol), trimethyl orthoformate (25 mL, 228.5 mmol), *p*-toluenesulfonic acid monohydrate (980 mg, 5.15 mmol), methanol (23 mL), and benzene (60 mL). The magnetically stirred solution was warmed under N_2 to gentle reflux for 40 h so that solvent distilled very slowly over into the receiving flask. After cooling to RT, it was partitioned between 500 mL ether and 250 mL satd. aq $NaHCO_3$. The organic layer was removed by separatory funnel and washed with 1 × 150 mL satd. aq $NaHCO_3$ and 1 × 150 mL brine, then dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to afford 22 g of an orange oil, which was used in the next step without purification.

Conversion of 13 to ketal 14

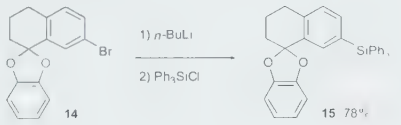
A 250 mL three-necked RB flask equipped as described in the last step was charged with 22 g of the crude starting material **13**, catechol (11.75 g, 106.7 mmol), *p*-toluenesulfonic acid monohydrate (150 mg, 0.79 mmol), and benzene (150 mL) and was brought to reflux under N_2 for 4 h so that



13 33 14 75% (from 12)

solvent distilled slowly into the receiving flask. After cooling to RT, 1.5 mL triethylamine was added. The mixture was partitioned between 200 mL ether and 100 mL water. The organic layer was removed by separatory funnel, washed with 1 × 100 mL H_2O, 2 × 75 mL 10% aq NaOH, 1 × 100 mL brine, then dried over $MgSO_4$, and filtered. The solvent was removed in vacuo to afford 27 g of a light tan crude product. The product was purified in portions by SiO_2 chromatography (hexane eluent) to yield 21 g of the white crystalline product **14** (75% yield): mp 101–104 °C. R_f = 0.45 (hexane–EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.03–2.10 (m, 2H), 2.22–2.26 (m, 2H), 2.82 (t, 2H, J = 6.3 Hz), 6.81–6.88 (m, 4H), 7.04 (d, 1H, J = 8.3 Hz), 7.41 (dd, 1H, J = 8.3, 2.1 Hz), 7.68 (d, 1H, J = 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.8, 28.4, 34.0, 108.6, 114.4, 120.0, 121.5, 129.3, 130.4, 132.7, 136.4, 137.1, 147.0. EI-MS *m/z* (%): 318 [M^+] (69, ^{81}Br), 316 [M^+] (69, ^{79}Br), 301 (16), 299 (17), 290 (16), 288 (17), 209 (22), 207 (22), 128 (100), 107 (36). Anal. calcd. for $C_{16}H_{13}O_2Br$: C 60.59, H 4.10; found: C 60.24, H 4.13.

Synthesis of the catechol ketal of 7-triphenylsilyl-α-tetralone (15)



14 15 78%

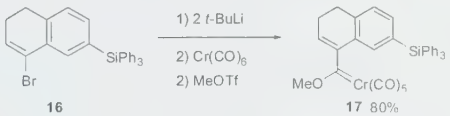
A 250 mL RB flask was charged with aryl bromide **14** (2.04 g, 6.4 mmol) and covered with Ar. It was dissolved in 50 mL THF and then cooled to –78 °C. *t*-BuLi in pentane (7.8 mL, 1.7 mol/L, 13.2 mmol) was added over 10 min whereupon the solution turned brown. After stirring at –78 °C for 40 min, a solution of triphenylsilylchloride (2.08 g, 7.1 mmol) in 20 mL THF was added dropwise over 5 min. After stirring an additional 1.25 h, the cold bath was removed. Over the next few hours the colour evolved from a dark blue, to a greenish olive, to a light brown, and finally to a clear light orange. The solution was stirred for 20 h at RT. Satd. aq $NaHCO_3$ (3 mL) was added and the THF was removed by rotory evaporator to leave a gummy residue. The residue was partitioned between 100 mL ether and 100 mL satd. aq $NaHCO_3$. The organic layer was washed with brine and then dried over $MgSO_4$. Purification by SiO_2 chromatography (hexanes–EtOAc, 9:1) afforded 2.5 g of a clear, colourless waxy oil, which foamed up under high vacuum (78% yield). On runs of larger scale, a white solid crystallized out on removal of solvent: mp 125.8–128 °C. R_f = 0.375 (hexane–EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.05–2.09 (m, 2H), 2.25–2.29 (m, 2H), 2.87 (t, 2H, J = 6.2 Hz), 6.64–6.75 (m, 4H, catechol protons), 7.16 (d 1H, J = 7.6 Hz), 7.75 (s, 1H), 7.24–7.63 (m, 16 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.1, 28.8, 34.6, 108.1, 115.0, 121.1, 127.8, 128.2, 129.5, 133.8, 134.1, 136.2, 136.36, 136.44, 137.2, 139.2, 147.2, (one sp^2 C not located). EI-MS *m/z* (%): 497 [M^++1] (43), 496 [M^+] (100), 416 (27), 339 (22), 259 (38), 181 (17).

The preparation of vinyl bromide 16 (9)

15 16 85%

A 500 mL RB flask was charged with starting material **15** (5.0 g, 10.08 mmol) and was covered with Ar. Methylene chloride (200 mL) was added to dissolve the solid and the solution was cooled to between –30 and –35 °C. A 1 mol/L solution of BBr_3 (10.25 mL, 10.15 mmol) in CH_2Cl_2 was added over 5 min. The reaction was slowly warmed to –15 °C over 3 h and then to 0 °C over 2 h, after which time it was stored overnight at –15 °C. Satd. aq $NaHCO_3$ (10 mL) was added and the mixture was concentrated until ~50 mL CH_2Cl_2 remained. Hexane (300 mL) was added and the solution was washed sequentially with 1 × 150 mL H_2O, 1 × 100 mL 10% aq NaOH, 1 × 150 mL 5% aq KOH, 1 × 150 mL H_2O, then dried over $MgSO_4$, and filtered. The crude product was purified by SiO_2 chromatography (hexane–EtOAc, 9:1) to give 4.0 g of **16** as a white crystalline solid (85% yield): mp 146–148 °C. R_f = 0.38 (hexane–EtOAc, 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (dt, 2H, J = 4.8, 8.0 Hz), 2.84 (t, 2H, J = 8.0 Hz), 6.38 (t, 1H, J = 4.8 Hz), 7.05 (d, 1H, J = 7.3 Hz), 7.33 (t, 6H, J = 7.1 Hz), 7.38 (t, 3H, J = 7.0 Hz), 7.50 (d, 1H, J = 7.3 Hz), 7.53 (d, 6H, J = 7.1 Hz), 7.74 (s, 1H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 25.3, 27.6, 121.6, 126.9, 127.9, 129.6, 130.7, 132.38, 132.45, 134.2, 136.3, 136.5, 137.9. EI-MS *m/z* (%): 469 [M^++1] (33, ^{81}Br), 468 [M^+] (97, ^{81}Br), 467 [M^++1] (36, ^{79}Br), 466 [M^+] (100, ^{79}Br), 391 (83), 389 (86), 312 (30), 259 (55), 181 (40), 105 (30). Anal. calcd. for $C_{28}H_{23}SiBr$: C 71.97, H 4.92; found: C 71.81, H 5.09.

Synthesis of chromium carbene complex (17)

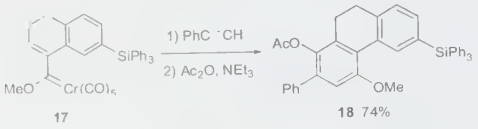


16 17 80%

A 100 mL RB flask with a stir bar was charged with vinyl bromide **16** (3.0 g, 6.42 mmol) and then covered with Ar. THF was added (32 mL) and after the solid dissolved the solution was cooled to –78 °C. A 1.7 mol/L solution of *t*-BuLi in pentane (12.84 mmol, 7.6 mL) was added over 5–10 min. The solution was stirred at –78 °C for 15 min, was warmed to 0 °C for 10 min, and was then transferred by cannula into a separate flask containing a stirred slurry of $Cr(CO)_6$ (1.41 g, 6.42 mmol) in 39 mL of THF under Ar. After stirring at RT for 1.7 h the solvent was removed by rotary evaporator and then high vacuum (19 h) to afford a light brown foam. The foam was dissolved in 45 mL argon-sparged (AS) CH_2Cl_2 under Ar and then cooled to 0 °C. Methyl triflate (1.09 mL, 9.63 mmol) was added over 5 min. The mixture was warmed to RT and stirred for 55 min. The deep red so-

lution was then concentrated down to a few mL of volume by rotary evaporator, applied to the top of a SiO_2 column, and eluted with hexane–EtOAc (9:1), which after removal of solvent afforded 3.2 g of carbene complex **17** as a red solid (80% yield). R_f = 0.275 (hexane–EtOAc, 9:1). IR (neat film, NaCl, cm^{-1}): 2062 (m), 1988 (w), 1940 (s). ^1H NMR (300 MHz, CD_2Cl_2) δ: 2.47 (m, 2H), 2.86 (m, 2H), 4.14 (br s, 3H, methoxy), 5.76 (t, 1H, J = 4.5 Hz), 7.38 (t, 6H, J = 7.0 Hz), 6.78 (s, 1H), 7.52 (d, 6H, J = 7.6 Hz), 7.24–7.57 (m, 5H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 22.7, 27.8, 66.1, 123.4, 128.3, 128.6, 129.7, 130.0, 130.1, 132.2, 134.3, 135.9, 136.4, 136.6, 137.8, 216.5 (CO), 225.1 (CO), 358.6 (carbene C). MS (FAB, nitrobenzyl alcohol) *m/z* (%): 622 [M^+] (3), 594 [M^+ – CO] (5), 483 (44), 482 (87), 467 (37), 452 (18), 259 (100).

The benzannulation reaction of complex 17 with phenylacetylene (3)



17 **18** 74%

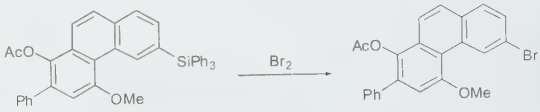
Carbene complex **17** (3.2 g, 5.15 mmol) was dissolved in 150 mL of THF in a 250 mL single-necked RB flask, which had the joint replaced with a threaded high-vacuum Teflon stopcock. Phenylacetylene (0.85 mL, 7.72 mmol) was added and the solution was deoxygenated by the freeze-pump-thaw method (3 cycles, –196 °C and 20 °C). The flask was charged with Ar at RT and then sealed and warmed at 60 °C for 21 h. After cooling to RT, triethylamine (1.79 mL, 12.87 mmol) and 1.19 mL acetic anhydride (12.6 mmol) were added. The flask was resealed and warmed to 60 °C for 8 h and then stirred at RT overnight. The crude mixture was concentrated down to a few mL of volume by rotorary evaporator, applied to the top of a SiO_2 column, and eluted with hexane–EtOAc 9:1). The product fraction was collected (R_f = 0.22, hexane–EtOAc (9:1)) as well as a more polar yellow band, which was the arene chromium tricarbonyl complex of the product. This yellow compound was dissolved in $CHCl_3$ and stirred overnight in open air to remove the chromium. This was then passed through a short SiO_2 pad to filter off the green flocculent chromium byproduct. The resulting product was combined with the earlier collected product to afford 2.3 g of a white crystalline solid (74% yield); mp 228–229.5 °C. IR (neat film, NaCl, cm^{-1}): 3067 (w), 3048 (w), 2933 (w), 1761 (ms), 1460 (m), 1428 (m), 1367 (m), 1211 (s), 1186 (s), 1108 (ms), 1059 (m), 701 (vs). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.07 (s, 3H), 2.78 (t, 2H, J = 6.4 Hz), 2.50–2.85 (m, 2H), 3.56 (s, 3H), 6.76 (s, 1H), 7.21–7.29 (m, 2H), 7.31–7.39 (m, 14H), 7.58 (d, 6H, J = 7.0 Hz), 8.51 (s, 1H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 20.5, 23.1, 28.9, 55.4, 111.6, 123.8, 127.0, 127.5, 127.8, 128.8, 129.4, 131.1, 131.5, 133.1, 134.1, 134.6, 135.1, 136.5, 136.9, 138.0, 138.5, 139.6, 154.7, 169.4. EI-MS *m/z* (%): 604 [M^+ + 2] (10), 603 [M^+ + 1] (27), 602 [M^+] (51), 562 (15), 561 (48), 560 [M^+ – ketene] (100), 483 (14), 259 Ph_3Si^+ (73), 230 (19), 181 (14). Anal. calcd. for $C_{41}H_{34}O_3Si$: C 81.70, H 5.64; found: C 81.53, H 5.62.

Aromatization of the B-ring of intermediate (18)

18 **19** 91%

A 500 mL RB flask was charged with starting material **18** (2.17g, 3.6 mmol), N-bromosuccinimide (673 mg, 3.78 mmol), benzoyl peroxide (89 mg, 0.36 mmol), and benzene (200 mL). The magnetically stirred solution was refluxed for 9 h. Upon cooling, the solution was filtered through a short plug of Al_2O_3 and then purified by SiO_2 chromatography (hexane–EtOAc, 5:1) to afford 1.97 g of **19** as a white crystalline solid (91% yield); mp 237 to 238 °C. R_f = 0.31 (hexane–EtOAc, 4:1). IR (neat film, NaCl, cm^{-1}): 3066 (w), 3048 (w), 2922 (w), 1763 (m), 1428 (m), 1197 (s), 1108 (ms), 1049 (mw). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 3.61 (s, 3H), 6.98 (s, 1H), 7.28–7.39 (m, 11H), 7.47 (d, 2H, J = 7.3 Hz), 7.63 (d, 6H, J = 7.2 Hz), 7.73 (m, 4H), 7.83 (d, 1H, J = 7.8 Hz), 9.89 (s, 1H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 20.7, 55.4, 109.6, 120.5, 120.8, 127.6, 127.9, 128.4, 128.8, 129.1, 129.5, 132.0, 132.8, 132.9, 133.0, 133.2, 134.6, 136.6, 136.9, 137.3, 137.8, 138.0, 156.6, 169.7, (1C not located). EI-MS *m/z* (%): 602 [M^+ + 2] (8), 601 [M^+ + 1] (15), 600 [M^+] (30), 560 (21), 559 (45), 558 [M^+ – ketene] (100), 481 (8), 465 (10), 387 (10), 260 (17), 259 Ph_3Si^+ (66,), 230 (19), 181 (14), 220 (15), 181 (8).

Bromo-desilylation of phenanthrene (19)

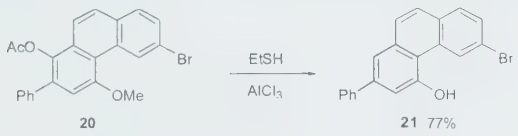


19 **20** 83%

A 100 mL RB flask with a stir bar was charged with phenanthrene **19** (342 mg, 0.57 mmol), CH_2Cl_2 (20 mL), and 5.1 mL of a 0.3 mol/L solution of Br_2 in CH_2Cl_2 (1.54 mmol). The mixture was brought to reflux for 3.5 h and then stirred at RT for 20 h. A small amount of SiO_2 was poured into the reaction mixture. Solvent was removed in vacuo to adsorb the crude reaction material on the silica. This SiO_2 adsorbate was applied to the top of a silica gel column and eluted with hexane–EtOAc (4:1) to afford 199 mg of **20** as a white solid (83% yield). The desired product elutes from the column after an orange impurity elutes. On scaling up the reaction, it was more efficacious to use slightly less Br_2 (~2 equiv.) to avoid this separation. Melting point 203.5–205 °C. R_f = 0.36 (hexane–EtOAc, 4:1). IR (neat film, NaCl, cm^{-1}): 2922 (w), 1761 (ms), 1589 (mw), 1440 (m), 1368 (m), 1212 (m), 1196 (vs), 1048 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.17 (s, 3H), 4.11 (s, 3H), 7.13 (s, 1H), 7.32–7.44 (m, 4 H), 7.56 (d, 1H, J = 7.9 Hz), 7.61 (dd, 1H, J = 7.6, 1.4 Hz), 7.64–7.68 (m, 1H), 7.70 (d, 2H, J = 9.5 Hz), 9.84 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7, 55.9, 109.6, 120.5, 121.1, 127.7, 127.8, 127.9, 128.4, 128.6, 129.0, 129.4, 129.6, 130.0, 131.1, 132.7, 134.9, 136.5, 137.7, 156.4, 169.6. EI-MS *m/z* (%): 423 [M^+ + 1] (5,

^{81}Br), 422 [M$^+$] (18, ^{81}Br), 421 [M$^+$ + 1] (5, ^{79}Br), 420 [M$^+$] (19, ^{79}Br), 381 (23), 380 (99), 379 (25), 378 (100), 365 (14), 363 (14), 300 (19), 298 (14), 284 (32).

Reduction of 20 to the phenanthrol 21 (3)

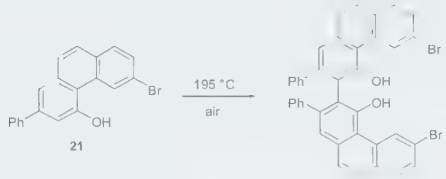


20 **21** 77%

A 200 mL RB flask with stir bar was charged with freshly sublimed $AlCl_3$ (405 mg, 3.03 mmol), CH_2Cl_2 (100 mL), and ethanethiol (0.475 mL, 6.4 mmol). Caution: flask needs to be openly vented to allow gases to escape on addition of ethanethiol. A gentle stream of N_2 was directed down into the open neck of the flask. After stirring for 5 min at RT, starting material (421 mg, 1.0 mmol) was added, which turned the mixture orange. The flask was then sealed with a septum and punctured with a needle connected to an N_2 bubbler. The mixture was stirred 9 h. The solution turned murky within 2 to 3 h after the addition of the starting material. The solution was carefully quenched with satd. aq $NaHCO_3$ (caution: vent flask to open air) and then partitioned between 50 mL H_2O and 100 mL ether. The aqueous layer was removed by separatory funnel and re-extracted with 50 mL ether. The combined organic layers were washed with 50 mL brine, dried over $MgSO_4$, filtered, and then stripped of volatiles. Trituration from CH_2Cl_2–hexane afforded a white powder that was contaminated with a small amount (ca. 5%) of a compound that resulted from reduction of the bromide in **21**. Repeated trial runs of this reaction indicated that the amount of this impurity increased with reaction times greater than 8 to 9 h. Reaction glassware was deodorized from the stench of EtSH by immersion in dilute aqueous bleach solution. Pure product was isolated by SiO_2 chromatography (hexane–EtOAc, 5:1). It elutes just before the bromine-reduced impurity. Yield: 270 mg (77%) of light peach-coloured powder, which could be crystallized to colourless needles by slow evaporation from ether; mp 178 to 179 °C (ether). R_f = 0.29 (hexane–EtOAc, 4:1). Note: the phenananthrol monomer **21** as well as the phenanthrol dimers described below are prone to decomposition as evidenced by their turning yellow and orange on handling. Chromatography should be done expeditiously. They should not be stored as solutions (especially CH_2Cl_2) open to air. They are more stable as solids. A useful method for crashing out solid is to dissolve the compound in CH_2Cl_2, add hexane, and then slowly remove solvent on a rotory evaporator. IR (neat film, NaCl, cm^{-1}): 3335 (br), 3052 (w), 2921 (w), 1587 (w), 1393 (w). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.76–6.10 (variable) (s, 1H, O**H**), 7.20 (d, 2H, *J* = 5.9 Hz), 7.35 (t, 1H, *J* = 7.2 Hz), 7.44 (t, 2H, *J* = 7.5 Hz), 7.61–7.69 (m, 6H), 9.77 (s, 1H). ^{13}C NMR (75MHz, CD_2Cl_2) δ: 112.6, 117.8, 119.7, 121.0, 127.5, 127.9, 128.17, 128.23, 129.3, 129.9, 131.3, 131.5, 131.9, 135.7, 140.2, 155.5 (2C not located). EI-MS *m/z* (%): 351 [M$^+$ + 1] (24, ^{81}Br), 350 [M$^+$] (99, ^{81}Br), 349 [M$^+$ + 1] (24, ^{79}Br), 348 [M$^+$] (100, ^{79}Br), 270 (32), 269 (54), 268 (26), 241 (47), 239 (46), 120 (26).

Synthesis of (*S*)-6,6′-dibromo-2,2′-diphenyl-3,3′-bis(phenanthren-4-ol) 8 (3)

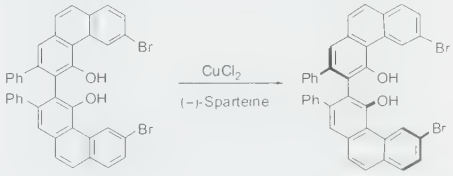
Oxidative coupling of 21



21 **8** 95%

Phenanthrene **21** (310.8 mg, 0.89 mmol) was added to a 25 × 150 mm test tube containing a micro stir bar. It was heated for a total of 14 h at 195 °C during which time it solidified to a dark brown cake. Heating was interrupted briefly after ca. 6 h to wash down sublimed starting material from the sides of the test tube with a small amount of EtOAc. (Care should be exercised in evaporating of the last of this EtOAc as it tends to spray the reaction mixture along the sides of the test tube.) The crude brown product was obtained (303 mg, 97% crude yield), which NMR indicated was the dimerized product **8** contaminated with ~5%–10% unreacted starting material. This material was used in the next step without purification. HPLC retention times for the two enantiomers: 11.33 and 17.45 min.

Deracemization of 8

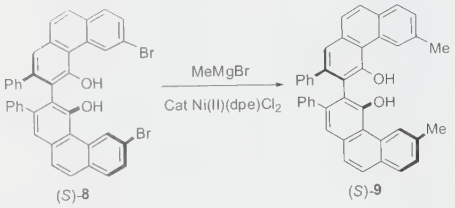


8 (*S*)-**8**

A sample of $CuCl_2 \cdot 2H_2O$ (73 mg, 0.428 mmol) was dissolved under Ar in 6.7 mL AS MeOH in a 100 RB flask. A solution of 200 mg (–)-sparteine (0.853 mmol) in 13 mL AS MeOH was added by cannula, which turned the solution a murky lime green. The solution was stirred for 0.5 h at RT. In a separate flask, 213 mg of the crude biphenanthrol **8** (~0.31 mmol) was partially dissolved in 10 mL AS CH_2Cl_2. This solution was transferred by cannula into the reaction mixture with concurrent addition of 10 mL AS MeOH. The remaining undissolved starting material was dissolved in 6.5 mL AS CH_2Cl_2 and transferred into the reaction flask with concurrent addition of 6.5 mL AS MeOH. The mixture turned black. It was stirred for 24 h, quenched with 1 mL concd HCl, and then partitioned between 50 mL H_2O and 50 mL CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, then adsorbed onto a small amount of SiO_2 and chromatographed (hexane–EtOAc, 5:1) to afford 108 mg of (*S*)-**8** as a white or pale yellow solid (50% yield). R_f = 0.38 (hexane–EtOAc, 4:1). The optical purity of **8** was determined to be >98% ee by chiral HPLC analysis on Pirkle D-phenyl glycine column with 70:30 mixture of hexane–*i*PrOH at 2 mL/min. The chiral HPLC retention time of (*S*)-**8** was 16.9 min. X-ray quality crystals were grown by dissolving a

sample in a minimum amount of hot EtOAc, allowing this to cool to RT, and then layering with hexane, which produced clear faintly pale green crystals. Crystallography as well as ^{1}H NMR indicated the crystal contained two equiv. of EtOAc. Absolute configuration is assigned to the (*S*)-isomer by analogy with the parent molecule VAPOL, which upon deracemization with (–)-sparteine–$CuCl_2$ affords (*S*)-(+)-VAPOL (12). On scaling up the reaction, the material obtained from the chromatography column was not always enantiopure. In this case the enantiopurity was upgraded by stirring the scalemic powder for 1 h in enough hexane to allow a small amount to remain undissolved. The decanted hexane was found to contain enantiopure material. $[\alpha]_D$ + 445° (*c* 1.0, THF). IR (neat film, NaCl, cm^{-1}): 3482 (s), 3139 (w), 3052 (w), 3027 (w). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.60 (s, 2H), 6.64 (d, 4H, *J* = 7.5 Hz), 6.94 (t, 4H, *J* = 7.6 Hz), 7.05 (t, 2H, *J* = 7.3 Hz), 7.40 (s, 2H), 7.65 (d, 2H, *J* = 8.7 Hz), 7.69 (d, 2H, *J* = 8.3 Hz), 7.75 (t, 4H, *J* = 9.5 Hz), 9.91 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 116.0, 117.1, 121.3, 123.2, 126.9, 127.4, 127.6, 128.6, 128.8, 129.4, 129.6, 131.27, 131.35, 131.42, 135.3, 139.5, 142.2, 153.3. EI-MS *m/z* (%): 699 [M^+ + 1] (23, ^{81}Br), 698 [M^+] (65, ^{81}Br), 697 [M^+ + 1] (48, ^{81}Br^{79}Br), 696 [M^+] (100, ^{81}Br^{79}Br), 695 [M^+ + 1] (26, ^{79}Br, ^{79}Br), 694 [M^+] (41, ^{79}Br, ^{79}Br), 618 (22), 616 (18), 536 (5), 268 (72), 239 (27), 149 (42). Anal. calcd. for $C_{40}H_{24}O_2Br_2 \cdot 2(C_4H_8O_2)$: C 6.07, H 4.62; found: C 66.16, H 4.57.

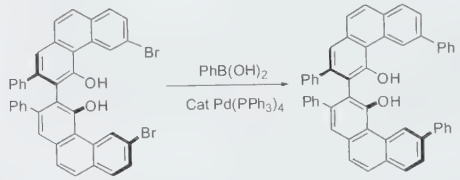
Coupling of (S)-8 with methyl Grignard reagent — Synthesis of (S)-9 (13)



(*S*)-**8** (*S*)-**9**

The optically pure dibromide (*S*)-**8** (10 mg, 14.4 µmol) and Ni(II)dpeCl_2 (1 mg,1.9 µmol) were added to a 5 mL RB flask and then covered with Ar. Ether (3 mL) was added via syringe and the solution was cooled to 0 °C. A 3 mol/L solution (29 µL) of CH_3MgBr in ether (86.4 µmol) was added dropwise. The solution was stirred for 0.5 h and was then warmed to reflux for 20.5 h. Additional ether (3 mL) was added during the reflux period to replace evaporated solvent. On cooling to RT, 3 mL of 10% aq HCl was added and the reaction mixture was partitioned between 20 mL ether and 5 mL H_2O. The organic layer was washed with brine and then dried over $MgSO_4$. Solvent was removed in vacuo to afford 7.6 mg (93% yield) of (*S*)-**9** as a pale tan solid that was pure by proton NMR. Chiral HPLC retention time: 23.3 min. $[\alpha]_D$ + 236° (*c* 1.0, THF). R_f = 0.34 (hexane–EtOAc, 9:1, plastic plate). IR (neat film, NaCl, cm^{-1}): 3480 (s), 3054 (w), 2922 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.60 (s, 6H), 6.60 (s, 2H), 6.64 (d, 4H, *J* = 7.8 Hz), 6.92 (t, 4H, *J* = 7.5 Hz), 7.03 (t, 2H, *J* = 7.5 Hz), 7.38 (s, 2H), 7.74 (d, 2H, *J* = 8.2 Hz), 7.80 (d, 2H, *J* = 7.9 Hz), 9.54 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.5, 115.6, 117.9, 123.2, 126.1, 126.7, 127.5, 127.9, 128.3, 128.6, 128.8, 129.1, 130.4, 130.7, 135.5, 136.8, 139.8, 141.4, 153.5. EI-MS *m/z* (%): 568 [M^+ + 2] (10), 567 [M^+ + 1] (44), 566 [M^+] (100), 552 (7), 475 (7), 383 (11), 283 (30), 255 (8).

Coupling of (*S*)-8 with phenyl boronic acid — Synthesis of (*S*)-10 (14)

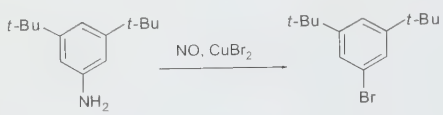


(*S*)-**8** (*S*)-**10**

Ethanol, aq Na_2CO_3 (2 mol/L), and benzene were sparged (>10 min) with inert gas (Ar or N_2) prior to use. A 25 mL RB flask was charged with $Pd(PPh_3)_4$ (2.3 mg, 2.2 µmol) and optically pure (*S*)-**8** (25 mg, 35.9 µmol). The flask was filled with Ar and 1.5 mL benzene and aq Na_2CO_3 (0.75 mL, 2 mol/L) was added by syringe. A solution of phenyl boronic acid (10.9 mg, 89.7 µmol) in 0.5 mL EtOH was added. The mixture was refluxed for 7 h and then stirred overnight at RT. The reaction mixture was diluted with 30 mL ether and washed with 25 mL brine containing a pipette tipful of HCl. The organic layer was dried over $MgSO_4$, filtered, adsorbed onto a small amount of SiO_2, and chromatographed (hexane–EtOAc, 9:1) to afford 23.4 mg of (*S*)-**10** as a white solid film (94% yield). $[\alpha]_D$ 749.5° (*c* 1.0, THF). R_f = 0.25 (hexane–EtOAc, 9:1, plastic plate). Chiral HPLC retention time: 22.4 min. IR (neat film, NaCl, cm^{-1}): 3481 (s), 3058 (w), 2923 (m), 2852 (w). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.66 (d, 6H), 6.94 (t, 4H, *J* = 7.6 Hz), 7.04 (t, 2H, *J* = 7.1 Hz), 7.27, (t, 2H, *J* = 7.1 Hz), 7.39 (t, 6H), 7.64 (d, 2H, *J* = 8.7 Hz), 7.76 (d, 4H, *J* = 7.4 Hz), 7.81 (d, 2H, *J* = 8.5 Hz), 7.87 (d, 2H, *J* = 7.5 Hz), 7.96 (d, 2H, *J* = 8.3 Hz), 10.04 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 115.9, 118.2, 123.3, 125.5, 126.8, 127.1, 127.2, 127.5, 128.8, 130.6, 132.0, 135.6, 139.6, 139.7, 141.7, 153.5, (6 C not located). EI-MS *m/z* (%): 692 [M^+ + 2] (17), 691 [M^+ + 1] (57), 690 [M^+] (100), 672 (8), 614 (20), 615 (11), 446 (13), 346 (15), 345 (25).

Coupling of (*S*)-8 with 3,5-di-*t*-butylphenyl Grignard reagent — Synthesis of (*S*)-11

Synthesis of 3,5-di-t-butylbromobenzene (17).

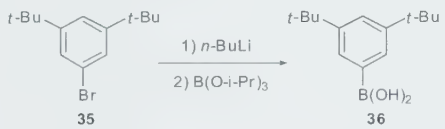


34 **35** 54%

A 25 mL RB flask with stir bar was charged with pulverized $CuBr_2$ (544 mg, 2.43 mmol) and 5 mL freshly distilled CH_3CN. NO gas was bubbled through the mixture for 10 min. The reaction mixture was then cooled to –30 °C, while maintaining NO gas bubbling. A solution of 500 mg of the *tert*-butylated aniline **34** (2.43 mmol) in 1.5 mL CH_3CN was added over 5 min. After stirring 5 additional minutes, the cold bath was removed, NO gas flow was

reduced to a trickle, and the solution stirred at RT for 1 h 10 min. The reaction was partitioned between 50 mL H_2O and 100 mL ether. The murky green organic layer was then washed with brine, dried over $MgSO_4$, filtered, and adsorbed onto a small amount of SiO_2. Purification by SiO_2 chromatography (hexane) afforded 355 mg of a clear, colourless oil, which crystallized on sitting at RT (54% yield). R_f = 0.40 (hexane). ^{1}H NMR (500 MHz, CD_3CN) δ: 1.09 (s, 18H), 7.13 (s, 2H), 7.19 (s, 1H). The aryl protons showed the same chemical shift in $CDCl_3$. EI-MS *m/z* (%): 271 (3), 270 [M^+] (24, ^{81}Br), 269 (3), 268 [M^+] (24, ^{79}Br), 256 (15), 255 (99), 254 (10), 253 (100).

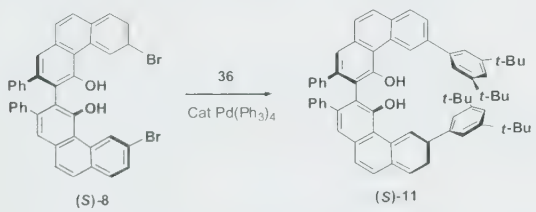
Synthesis of boronic acid 36 (18)



35 **36**

A 25 mL RB flask with stir bar was charged with 320 mg of aryl bromide **35** (1.19 mmol) and then covered with Ar. THF (5 mL) was added and after dissolution the flask was cooled to –78 °C, whereupon 0.48 mL of a 2.5 mol/L solution of *n*-BuLi in hexanes (1.2 mmol) was added dropwise. After stirring at –78 °C for 1 h, a solution of 0.68 mL triisopropyl borate in THF (1 mL, 2.9 mmol) was added all at once by syringe to give a clear solution. The cold bath was removed and while warming to RT the solution became cloudy. After stirring 1 h the mixture was poured into a vigorously stirred mixture of 10% aq HCl (30 mL) and ether (40 mL) and stirred a few minutes. Both the aqueous and organic layers were clear and colourless. The organic layer was removed, washed with 30 mL H_2O, dried over $MgSO_4$, and filtered. Rotary evaporation of the solvent yielded **36** as a white solid, which was used in the next step without purification. ^{1}H NMR analysis (500 MHz, $CDCl_3$) of the aryl region suggested a mixture of two compounds; major: δ 7.52 (s, 2H), 8.06 (s, 1H); minor: δ 7.63 (s, 2H), 7.94 (s, 1H). In addition there was a pronounced singlet at δ 4.54, which is attributed to the BOH of the desired product.

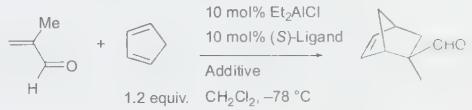
Suzuki coupling of (S)-8 with 36 — Synthesis of (S)-11 (14)



(S)-8 **(S)-11**

Ethanol, aq Na_2CO_3 (2 mol/L), and benzene were sparged (>10 min) with inert gas (Ar or N_2) prior to use. Optically pure (*S*)-**8** (66 mg, 75.9 μmol, based on MW 872.6, containing two equiv. of EtOAc) was dissolved in a minimum of CH_2Cl_2 in a 25 mL RB flask, the solvent was removed by rotory evaporator, and then the ethyl acetate was removed on high vacuum. To the flask was added $Pd(PPh_3)_4$ (6 mg, 5.2 μmol) and the solids were covered with Ar. Benzene (4 mL) and aq Na_2CO_3 (2 mL 2 mol/L) was added. To the vigorously stirred mixture was added a solution of crude boronic acid **36** (89 mg, ~304 μmol, based on 80% purity) in EtOH (2 mL). The mixture was refluxed for 14 h and then stirred at RT for 11 h. The reaction mixture was partitioned between 50 mL ether and 25 mL brine containing a pipette tip of HCl. The organic layer was dried over $MgSO_4$, filtered, and adsorbed onto a small amount of SiO_2. Purification by chromatography on silica gel (hexane–EtOAc, 9:1) afforded 70.0 mg of (*S*)-**11** as a clear, colourless solid film (100% yield). $[\alpha]_D$ 565° (*c* 1.0, THF). R_f = 0.42 (hexane–EtOAc, 9:1). Chiral HPLC retention time: 5.7 min. IR (neat film, NaCl, cm^{-1}): 3486 (m, sharp), 2962 (s, sharp), 2863 (w), 1594 (m, sharp). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (s, 36H), 6.55 (s, 2H), 6.69 (d, 4H, *J* = 7.2 Hz), 6.94 (t, 4H, *J* = 7. 5 Hz), 7.04 (t, 2H, *J* = 6.6 Hz), 7.37 (s, 2H), 7.56 (s, 4 H), 7.43 (s, 2H), 7.64 (d, 2H, *J* = 8.7 Hz), 7.81 (d, 2H, *J* = 8.8 Hz), 7.85 (d, 2H, *J* = 7.7 Hz), 7.96 (d, 2H, *J* = 8.1 Hz), 9.95 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.6, 115.8, 118.4, 121.4, 122.3, 123.4, 126.2, 126.9, 127.6, 127.7, 128.8, 128.9, 129.1, 130.6, 131.8, 135.6, 139.8, 141.2, 141.3, 141.8, 151.2, 153.7 (2 C not located). EI-MS *m/z* (%): 916 [M^+ + 1] (30), 915 [M^+] (42), 710 (69), 709 (87), 576 (63), 575 (82), 574 (86), 481 (26), 259 (50), 183 (33), 57 (100).

Diels–Alder reaction of methacrolein and cyclopentadiene

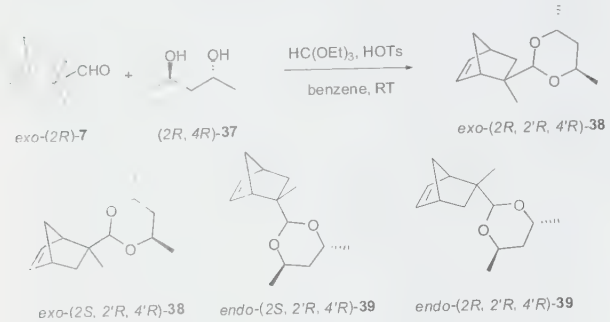


5 1.2 equiv. **6** (2*R*)-**7**

A sample of the desired ligand (45–75 mg) was added to a 5 mL RB flask containing a stirbar and the flask was flushed with Argon. Methylene chloride (1 to 2 mL) was added by syringe followed by 1 equiv. Et_2AlCl (1 mol/L solution in hexane), which turned the solution a deep blood-red color. After stirring at RT for 0.5 h the flask was cooled to –78 °C. Methacrolein (10 equiv. relative to ligand) was then added by syringe. After stirring at –78 °C for 0.5–0.75 h, 12–14 equiv. of cyclopentadiene was added. If an additive was used, it was added 15 min before the cyclopentadiene was added. After 0.5 h at –78 °C, the reaction was quenched by the addition of 1 mL brine. The mixture was then partitioned between 20 mL CH_2Cl_2 and 10 mL H_2O and stirred vigorously. The organic layer was dried over $MgSO_4$, filtered, and then taken to near dryness on the rotory evaporator. The yield of the exo product **7** was determined on this concd CH_2Cl_2 solution by ^{1}H NMR using the ligand as an internal standard. The product was separated from the ligand by bulb-to-bulb distillation under high vacuum into a –78 °C trap prior to the measurement of the exo–endo ratio and the ee%, which were each determined by one of the two methods indicated below. Catalyst formation for ligands **10** and **11** were much slower as indicated by ^{1}H NMR. For these ligands, catalyst formation required heating at 55 °C for 24 h. ^{1}H NMR for *exo*–**7** (500 MHz, $CDCl_3$) δ: 0.76 (d 1H, *J* = 11.9 Hz), 1.00 (s, 3H), 1.38 (s, 2H), 2.23 (dd, 1H, J = 11.9, 3.5 Hz), 2.80 (s, 1H), 2.87 (s, 1H), 6.06 (dd, 1H, J = 5.2, 2.9 Hz), 6.25 (dd, 1H, J = 5.1 Hz, 2.9 Hz), 9.62 (s, 1H).

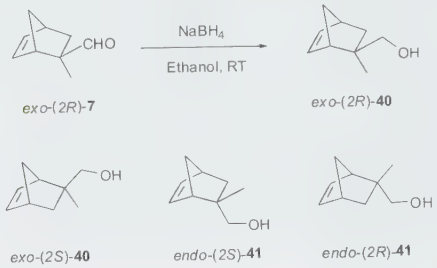
This data matches that previously reported for this compound (19).

Analysis of exo-adduct 7 by conversion to chiral acetals



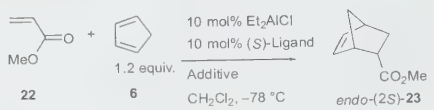
This method was originally developed by Yamamoto (20). A pipette tip of product **7** (~20 mg) was mixed with 25–30 mg (2*R*,4*R*)-(–)-pentanediol, 40 mL triethyl orthoformate, a small crystal of $TsOH{\cdot}H_2O$, and 1 to 2 mL benzene and stirred overnight. The de% of the exo product (and hence ee% of the exo product) and the exo–endo ratio were determined by GC on an Alltech Econocap capillary column (cat. #19646, ser. # 2475–9): 0.32 mm i.d., 0.25 mm film thickness, and 30 m in length. Column temperature was 50 °C for 2 min and then ramped up at 4 °C per min. Under these conditions, the following retention times were observed: (2*R*,2′*R*,4′*R*)-**38** (23.15 min); (2*S*,2′*R*,4′*R*)-**38** (23.25 min), **39** (21.98 and 22.93 min, not assigned). It was previously established that (*S*)-VAPOL is selective for (2*R*,2′*R*,4′*R*)-**38** (4*a*). Spectral data for (2*R*,2′*R*,4′*R*)-**38**: IR (neat, cm^{-1}): 3139 (w), 3059 (m), 2979 (s), 2932 (s), 2878 (s), 2700 (w), 1572 (w), 1451 (s), 1398 (m), 1376 (s), 1333 (s), 1289 (m), 1241 (s), 1181 (m), 1158 (s), 1135 (s), 1093 (m), 1081 (m), 1007 (s), 972 (m), 906 (m), 839 (m), 721 (s). ^{1}HNMR ($CDCl_3$) δ: 0.76 (d, 1H, J = 12.0 Hz), 0.86 (s, 3H), 1.19 (d, 3H, J = 6.2 Hz), 1.29–1.31 (m, 2H), 1.34 (d, 3H, J = 7.1 Hz), 1.60 (d, 1H, J = 8.4 Hz), 1.74–1.82 (m, 2H), 2.66 (s, 1H), 3.90–3.94 (m, 1H), 4.27–4.66 (m, 1H), 4.66 (s, 1H), 6.01–6.11 (m, 2H). ^{13}C NMR (CDC_3) δ: 17.25, 18.77, 21.96, 36.87, 37.10, 43.07, 45.45, 47.15, 48.06, 67.68, 67.74, 99.48, 135.54, 137.15. MS *m*/*z* (%): 222 [M^+] (4), 157 (22), 115 (78), 69 (100). HRMS *m*/*z*: calcd. for $C_{14}H_{22}O_2$: 222.1620; found: 222.1662. Anal. calcd. for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.88, H 10.26. Spectral data for (2*S*,2′*R*,4′*R*)-**38** (prepared from (*R*)-VAPOL): ^{1}H NMR ($CDCl_3$) δ: 0.74 (dd, 1H, J = 2.7, 12.0 Hz), 0.86 (s, 3H), 1.20 (d, 3H, J = 6.2 Hz), 1.28–1.33 (m, 2H), 1.36 (d, 3H, J = 7.0 Hz), 1.58–1.85 (m, 3H), 2.75 (bs, 2H), 3.89–3.96 (m, 1H), 4.30–4.35 (m, 1H), 4.70 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 17.26, 18.57, 21.93, 36.83, 37.35, 43.25, 45.48, 47.41, 47.94, 67.43, 67.98, 99.43, 135.74, 137.10. IR (neat, cm^{-1}): 3060 (w), 2972 (s), 2941 (s), 2877 (m), 1449 (m), 1398 (w), 1375 (m), 1333 (m), 1288 (w), 1241 (w), 1217 (w), 1158 (s), 1135 (s), 1102 (w), 1081 (w), 1059 (s), 1024 (m), 1003 (s), 982 (w), 722 (s). MS *m*/*z* (%): 222 [M^+] (18), 157 (70), 115 (100), 69 (13). HRMS calcd. for $C_{14}H_{22}O_2$ *m*/*z*: 222.1620; found: 222.1617. Anal calcd. for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.85, H 10.12.

Analysis of exo-adduct 7 by reduction to alcohol 40



The aldehyde **7** (71.7 mg) distilled from the reaction described above was dissolved in 1.2 mL of ethanol and treated with $NaBH_4$ (24 mg). After 1 h the reaction was quenched by the slow addition of water. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of ethanol. The aqueous phase was extracted with ether (2 × 5 mL) and the combined organic layer was washed with 15 mL of brine and dried over $MgSO_4$. Removal of solvent left 77 mg of crude product, which was purified by chromatography on silica gel with a 5:1 mixture of hexanes – ethyl acetate to give 61 mg of **40** as a white solid. The de% of the exo product (and hence ee% of the exo product) and the exo–endo ratio were determined by GC on an Astec B-MB capillary column (Beta-cyclodextrin Dimethyl, *t*-Butyl, ser. # 9606–29) of 0.25 mm i.d. and 30 m in length. Column temperature was isothermal at 140 °C. Under these conditions, the following retention times were observed: (2*R*)-**40** (6.12 min); (2*S*)-**40** (6.01 min); **41** (5.67 and 5.41 min, not assigned).

Diels–Alder reaction of methacrolein and cyclopentadiene



A sample of the desired ligand (45 mg) was added to a 5 mL RB flask containing a stir bar and the flask was then flushed with argon. Methylene chloride (1 to 2 mL) was added by syringe followed by 1 equiv. Et_2AlCl (1 mol/L solution in hexane), which turned the solution a deep blood-red color. After stirring at RT for 0.5 h, the flask was cooled to –78 °C. Methyl acrylate (10 equiv. relative to ligand) was then added by syringe. After stirring 0.5–0.75 h at –78 °C, 12–14 equiv. of cyclopentadiene was added. If an addtive was used it was added 15 min before methyl acrylate. After 24 h at –78 °C the reaction was quenched by the addition of 1 mL brine. The mixture was then partitioned between 20 mL of CH_2Cl_2 and 10 mL of H_2O and stirred vigorously. The organic layer was dried over $MgSO_4$, filtered, and then taken to near dryness on a rotatory evaporator. The yield of *endo*-**23** was determined on this concentrated CH_2Cl_2 solution by ^{1}H NMR using the ligand as an internal standard. The product was separated from the ligand by bulb-to-bulb distillation under high vacuum into a –78 °C trap prior to the measurement of the exo–endo ratio and the ee%, which were

both determined by the method indicated below. Catalyst formation for ligands **10** and **11** were much slower as indicated by ^{1}H NMR. For these ligands, catalyst formation required heating at 55 °C for 24. Spectral data for *endo*-**23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (d, 1H), 1.40–1.45 (m, 2H), 1.88–1.96 (m, 1H), 2.92–2.99 (m, 2H), 3.21 (s, 1H), 3.63 (s, 3H), 5.94 (dd, 1H, J = 5.6, 2.8 Hz), 6.20 (dd, 1H, J = 5.6, 3.0 Hz).

Analysis of endo-adduct 23 by GC

endo-(2*S*)-**23** *endo*-(2*R*)-**23** *exo*-(2*R*)-**42** *exo*-(2*S*)-**42**

The methyl ester **23** distilled from the reaction described above was directly assayed for endo–exo selectivity and for enantioselectivity by chiral GC on a J & W Cyclodex-B capillary column (part #1122532, ser. #5094942) of 0.25 mm i.d., 0.25 mm film thickness, and 30 m in length, and with column temperature 90 °C (isothermal). The oven was baked at 200 °C a few minutes before each run, which improved GC peak resolution. Under these conditions, the following retention times were observed: (2*S*)-**23** (16.43 min), (2*R*)-**23** (15.90 min), **42** (12.79 and 12.98 min, not assigned). It was previously shown that (*S*)-VAPOL gives selectively the *endo*-(2*S*) isomer of **23** (4).

Acknowledgment

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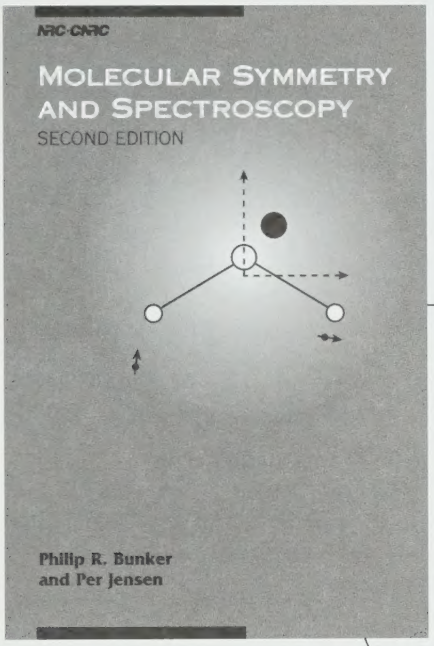

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