Degradation and Absolute Configurational Assignment to C_{34}-Botryococcene

James D. White,* Todd C. Somers, and G. Nagabushana Reddy

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

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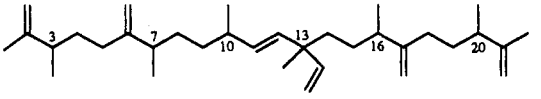
C_{34}-Botryococcene, the major hydrocarbon constituent of the B race of *Botryococcus braunii*, was degraded by ozonolysis of its dihydro derivative followed by Baeyer–Villiger oxidation to γ-valerolactone, 2,5-dimethylhexanolactone, and 2-ethyl-2,5-dimethylhexanolactone. These three lactones were correlated with enantiomerically pure, synthesized materials using a progressive induced chemical shift technique with the chiral shift reagent $Eu(hfc)_3$. The lactones were found to possess 4*S*, 2*R*,5*S*, and 2*R*,5*S* configurations respectively, thereby specifying a 3*S*,7*S*,10*R*,13*S*,16*S*,20*S* configuration for C_{34}-botryococcene. A biogenesis for botryococcene from 1*R*,2*R*,3*R* presqualene diphosphate is proposed to account for the observed 10*R*,13*S* configuration.

Botryococcus braunii (Kützing), a freshwater alga which grows under a wide variety of climatic and geographical conditions,[1] is characterized by an unusually high level of hydrocarbon production (17–90% of the dry weight).[2] This property has kindled interest in the exploitation of *B. braunii* as a renewable energy source, and despite difficulties with large-scale cultivation, the prospect of reduced harvesting costs due to the alga's bouyancy and extracellular location of hydrocarbons has provided strong economic incentive toward utilization of the organism as a source of liquid fuel.[3] Of related significance is the discovery that *B. braunii* is responsible for prolific oil-bearing sediments from the Ordovician period,[4] and as a result, chemical markers characteristic of the alga are found in commercial oils such as Sumatran crude.[5]

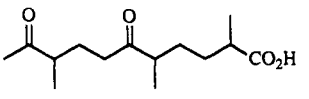
There are two races of *B. braunii*, each having similar morphology but differing in their chemical constitution. This difference is readily apparent from the dissimilar structures of the hydrocarbons present in the oil sack that surrounds the algal cell. The L-race produces a series of linear, odd-numbered C_{23}–C_{31} aliphatic dienes and trienes,[6] whereas the B-form synthesizes a novel family of highly branched C_{30}–C_{37} hydrocarbons collectively named botryococcenes.[7] The most abundant of these branched structures is C_{34}-botryococcene (1), the isolation of which was first reported by Maxwell in 1968.[8] Subsequently, a structure for 1 was reported without designation of configuration by Eglinton.[9]

The incomplete characterization of C_{34}-botryococcene presented an intriguing challenge that carries important implications for its biogenesis. In particular, the stereogenic centers of 1 contain information that pertains to the methylation of the isoprenoid chain as well as stereochemical details associated with the linkage of farnesyl moieties coupled in a nonsqualenoid ("iso") mode. We report herein a complete account of the degradation of (−)-C_{34}-botryococcene.[10] A comparison of materials obtained by degradation of 1 with substances synthesized in enantiomerically pure form afforded an unambiguous assignment of its absolute configuration.

The near-symmetrical structure of the left and right halves of 1 suggested that an appropriate degradation might yield relatively few fragments which would carry the stereochemical information of the parent molecule. In their determination of the gross structure of 1 the Bristol University group had performed an oxidative cleavage which resulted in only one product, diketo acid 2.[9] Unfortunately, the origin of 2 is ambiguous since decarboxylation of the putative malonic acid derivative 3 from the right half of 1 could have occurred in the course of the degradation. Keto acid 2 could therefore have arisen from either left- or right-hand segments of 1. Although a firm stereochemical definition of 2 was judged to be feasible by direct means, an unsatisfactory aspect of the oxidative cleavage of 1 was the erasure of stereochemistry at the quaternary center (C13) of 1.



1



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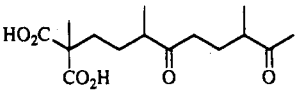

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A more informative degradation of 1 would result if the vinyl group were selectively hydrogenated so that subsequent oxidation could yield two clearly distinguishable products (Scheme I). It was hoped that these products could be separately degraded to substances whose configurations were known or could be determined by reliable methods. With this objective, 1 was reduced with diimide[11]

(1) Belcher, J. H. *Arch. Mikrobiol.* **1968**, *8*, 543.
(2) Tornabene, T. G. *Experientia* **1982**, *38*, 43.
(3) (a) Hillen, L. W.; Wake, L. V.; Warren, D. R. *Fuel* **1980**, *59*, 446. (b) Gudin, C.; Bernard, A.; Chaumont, D. *Comm. Eur. Communities (Rep). EUR. 9975* **1985**, 141. (c) Destordeur, M.; Rossi, M. E. *Comm. Eur. Communities (Rep). EUR. 9947* **1985**, 12. (d) Destordeur, M. *Ann. Mines Belg.* **1985**, *3*, 137. (e) Casadevall, E.; Dif, D.; Largeau, C.; Gudin, C.; Chaumont, D.; Desanti, O. *Biotechnol. Bioeng.* **1985**, *27*, 286. (f) Hillen, L. W.; Wake, L. V. *Proc. AIE Nat. Conf.* **1979**, New Castle, Australia, pp N18–N25. (g) Hillen, L. W.; Pollard, G.; Wake, L. V.; White, N. *Report No. MRL-R 783*; Materials Research Labs.: Melbourne, Australia, 1980.
(4) Cane, R. F. *Trans. R. Soc. S. Aust.* **1977**, *101*, 153.
(5) Moldowan, J. W.; Seifert, W. K. *J. Chem. Soc., Chem. Commun.* **1980**, 912.
(6) Wolf, F. R.; Nemethy, E. K.; Blanding, J. H.; Bassam, J. A. *Phytochemistry* **1985**, *24*, 733.
(7) Metzger, P.; Casadevall, E.; Pouet, M. J.; Pouet, Y. *Phytochemistry* **1985**, *24*, 2995.
(8) Maxwell, J. R.; Douglas, A. G.; Eglinton, G.; McCormick, A. *Phytochemistry* **1968**, *7*, 2157.
(9) Cox, R. E.; Burlingame, A. L.; Wilson, D. M.; Eglinton, G.; Maxwell, J. R. *J. Chem. Soc., Chem. Commun.* **1973**, 284.
(10) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Am. Chem. Soc.* **1986**, *108*, 5352.
(11) (a) Mori, K.; Ohki, M.; Sato, A.; Matsui, M. *Tetrahedron* **1972**, *28*, 3739. (b) Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Lett.* **1961**, 347.

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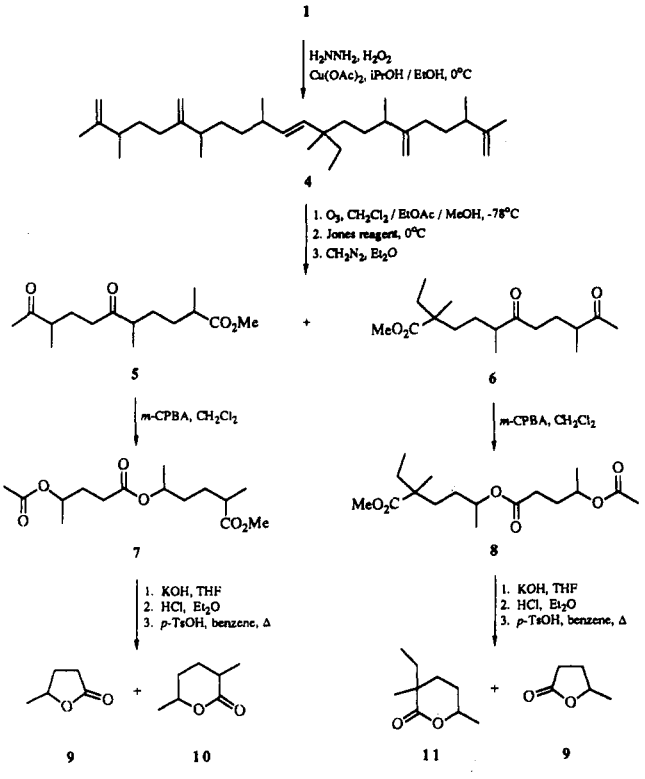
Scheme I

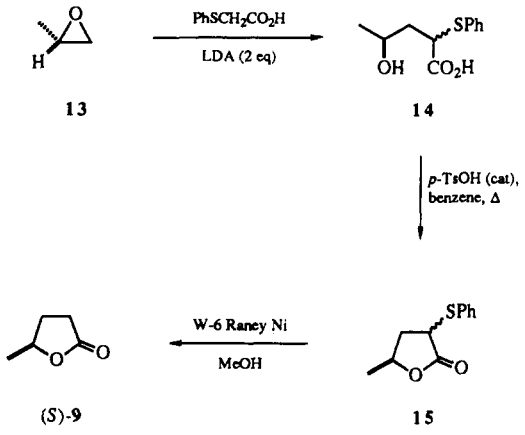


to C_{34}-dihydrobotryococcene (4) in which all of the disubstituted olefinic linkages were preserved. The latter was then subjected to exhaustive ozonolysis, with an oxidative workup using Jones' reagent.[12] The resultant mixture of carboxylic acids was treated with diazomethane to yield two diketo methyl esters, 5 and 6, which were separated by chromatography.

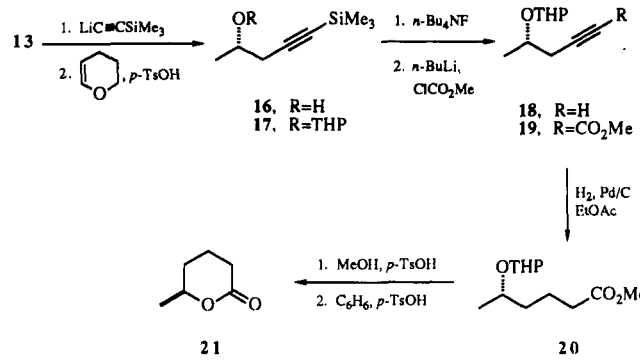
Further degradation of 5 and 6 exploited a sequence that relied on fragmentation at the keto functions of these structures in a manner that assured a predictable stereochemical outcome. The Baeyer–Villiger oxidation, which typically exhibits strong regio preference in ester formation from unsymmetrical ketones[13] and simultaneously preserves configuration at the migrating carbon,[14] was ideal for this purpose. Thus, when 5 and 6 were separately treated with *m*-chloroperbenzoic acid, they yielded the expected triesters 7 and 8, respectively. The observation of only two downfield signals at ca. δ 4.9 in the ^{1}H NMR spectra of 7 and 8, together with the absence of detectable diastereomeric impurities in their ^{13}C NMR spectra, confirmed that these substances were homogeneous. Saponification of 7, followed by acidification, afforded a pair of hydroxy acids which underwent dehydration to yield two lactones in equal amounts. The identity of these lactones as 9 and 10 was confirmed spectroscopically. Analogous saponification and acidification of triester 8 similarly furnished two hydroxy acids which underwent facile lactonization. One of these lactones was identical in all respects, including optical rotation, with γ-valerolactone (9) obtained from 7. Thus, C3 and C20 of 1 possess the same absolute configuration.

Access to further stereochemical information on these lactones was hampered by the small quantities available from degradation of natural 1, and it was therefore decided to synthesize these materials in all possible configurations for comparison with the naturally derived substances. The preparation of (*R*)- and (*S*)-9 employed a sequence adapted from that reported by Iwai[15] and began from (*R*)-(+)-[16] and (*S*)-(−)-propylene oxide[17] (12 and 13, respectively). Alkylation of the dianion of (phenylthio)acetic acid with the oxirane gave a diastereomeric mixture of 4-hydroxy-2-(phenylthio)pentanoic acids 14 which, without separation, was converted to cis and trans α-substituted γ-valerolactones 15. Reductive desulfurization with W-6 Raney nickel afforded (*R*)- and (*S*)-γ-valerolactones 9 in an overall 62% yield (Scheme II, *S* series shown).

Scheme II



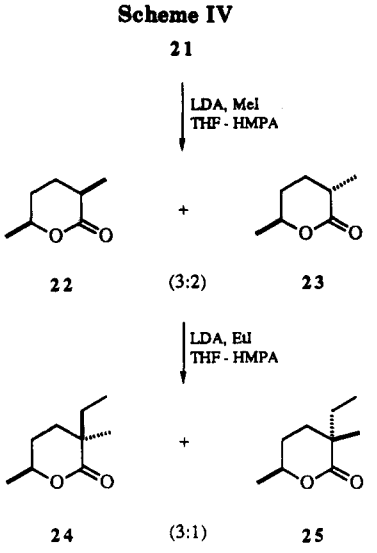
Scheme III



The availability of both antipodes of propylene oxide in optically pure form permitted extension of this preparative scheme to δ-lactones 10 and 11. For this purpose, 12 and 13 were each reacted with lithium(trimethylsilyl)acetylide. After protection of the resulting alcohol 16 as its tetrahydropyranyl ether 17, the silyl group was removed and the acetylide 18 was carboxylated with methyl chloroformate to furnish 19. Saturation of the triple bond led to 20, from which the tetrahydropyranyl ether was cleaved with acidic methanol. Lactonization of this δ-hydroxy ester gave (*R*)- and (*S*)-21 in 50% overall yield from propylene oxide (Scheme III, *S* series shown).[18] Introduction of an α-methyl substituent into 21 was accomplised via its enolate[19] and produced a 3:2 mixture of stereoisomeric lactones that were separated by gas chromatography. Comparison of the ^{1}H and ^{13}C NMR spectra

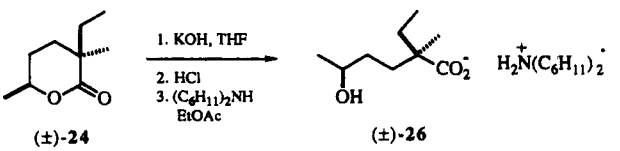
(12) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Am. Chem. Soc.* **1953**, *75*, 2548.
(13) Hassall, C. H. *Org. React.* **1957**, *9*, 73.
(14) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; Part B, p 655.
(15) Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242.
(16) Koppenhoefer, B.; Schurig, V. *Org. Synth.* **1987**, *66*, 160.
(17) Ghirardelli, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 4987.
(18) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169.
(19) Hermann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711.

Scheme IV



of these lactones with data reported by Wheeler[20] established that the predominant isomer **22** possessed the cis configuration (Scheme IV, 5*S* series shown). This substance, rather than trans isomer **23**, was found to correspond with the lactone **10** from botryococcene. A relationship is established between configurations at C7 and C10 of **1** by this chemistry that requires them to be *R,S* or *S,R*.

Synthesis of the remaining lactone **11** from degradation of **1** required introduction of an ethyl substituent into **22** and/or **23**. Since this process entailed alkylation analogous to that carried out with **21**, the mixture of cis and trans isomers, **22** and **23**, sufficed for this purpose. Ethylation of the mixture gave two trisubstituted δ-lactones **24** and **25** in the ratio 3:1 which were separated by HPLC. Again, the major isomer **24** was found to correspond with lactone **11** derived from **1**, but since this substance was previously unknown, it was not possible to ascertain its relative configuration and hence the relationship between C10 and C13 of botryococcene by direct means. This stereochemical issue was addressed by means of an X-ray crystallographic structure determination, for which racemic **24** was prepared from (±)-**21**. Saponification of (±)-**24** and conversion of the hydroxy acid to its dicyclohexylammonium salt **26** afforded a crystalline substance with excellent diffraction properties. A structure solution unambiguously defined its relative configuration as that shown.



(±)-**24** (±)-**26**

In principle, direct comparison by optical rotation of lactones **9**, **10**, and **11** obtained from degradation of **1** with the corresponding synthetic lactones of each enantiomeric series should yield the absolute configuration of C_{34}-botryococcene. This proved impossible in practice due to the small quantities of pure, naturally derived lactones and the relatively low values of their optical rotations. Hence, a previously demonstrated NMR technique,[21] in which it was shown that correlation of the absolute configuration of synthesized materials with those obtained by degradation is possible on small, impure samples employing progressive, induced chemical shifts, was used to establish the configuration of lactones **9**, **10**, and **11**. For this purpose, the ^1H NMR spectra of racemic lactones were first mea-

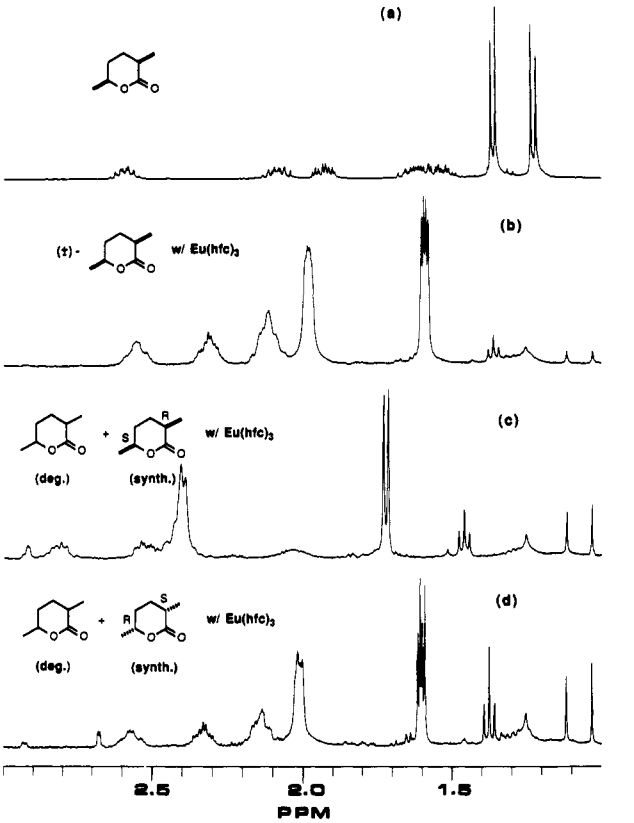


Figure 1. $Eu(hfc)_3$-induced shift comparison of **10** from degradation with synthetic **22** and its enantiomer.

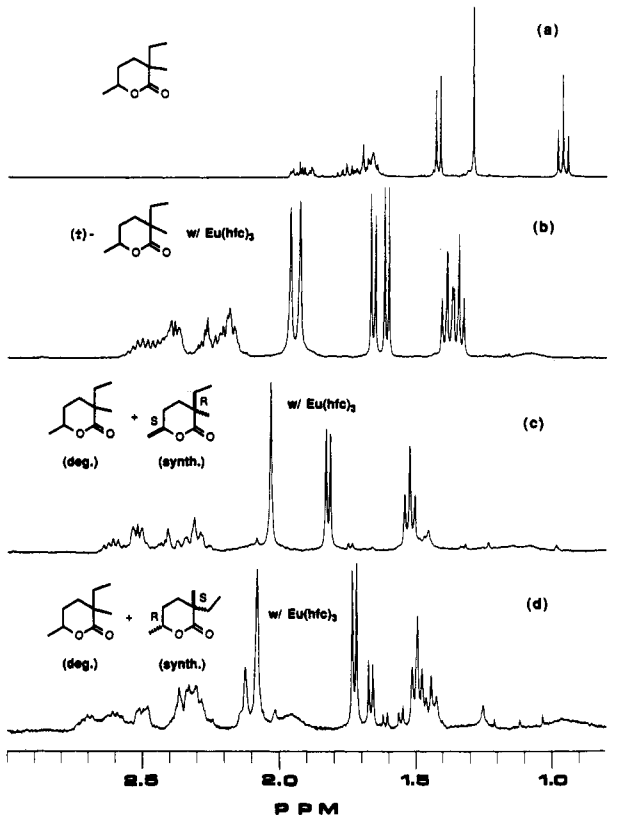


Figure 2. $Eu(hfc)_3$-induced shift comparison of **11** from degradation with synthetic **24** and its enantiomer.

(20) Wheeler, J. W.; Evans, S. L.; Velthius, H. H. V.; Blum, B. S.; de Camargo, J. M. F. *Tetrahedron Lett.* **1976**, 4029.
(21) Somers, T. C.; White, J. D.; Lee, J. J.; Keller, P. J.; Chang, C.; Floss, H. F. *J. Org. Chem.* **1986**, *51*, 464.

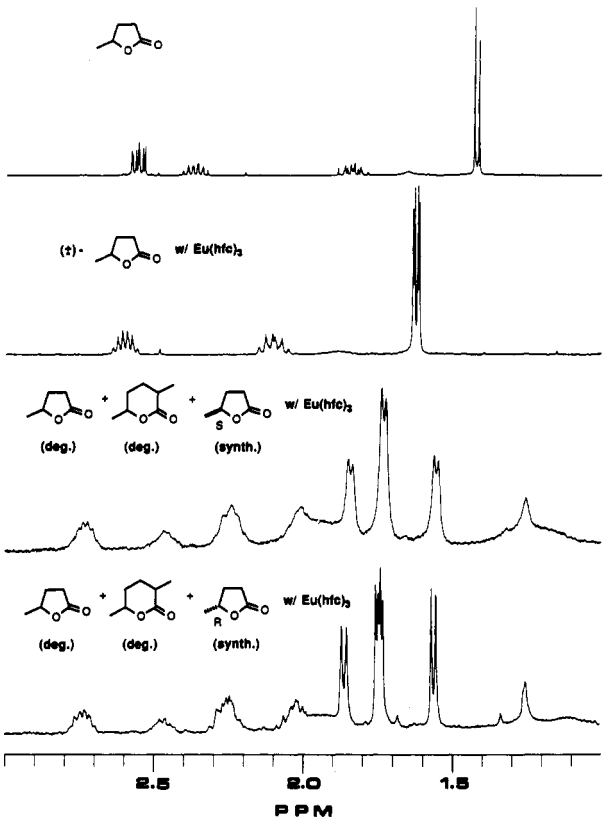
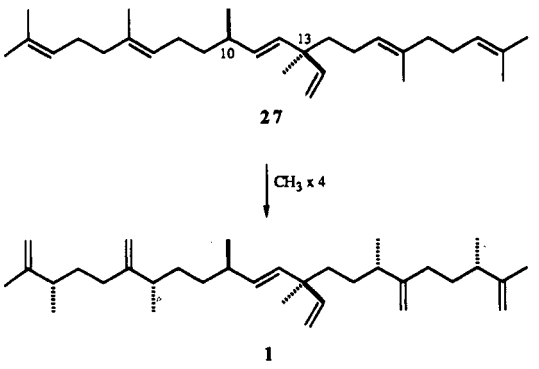


Figure 3. Eu(hfc)$_3$-induced shift comparison of **9** and **10** from degradation with synthetic enantiomers of **9**.

sured at 400 MHz in the presence of tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) [Eu(hfc)$_3$][22] in order to ascertain whether enantiomers were distinguishable in the presence of the shift reagent. As seen in Figures 1b and 2b, the diastereomeric lactone–Eu(hfc)$_3$ complexes exhibited distinctive methyl group shifts which could then be used to characterize the lactones from degradation. A 1:1 mixture of the lactones **10** and **11** with each enantiomer of the corresponding synthetic lactone was treated with successively larger quantities of Eu(hfc)$_3$ and ^{1}H NMR spectra were measured (Figures 1c,d and 2c,d). The results shown in Figures 1 and 2 confirm that unambiguous correlation exists between **10** and **11** from degradation and one of the two enantiomers (**22** and **24**) of the synthetic counterpart. These correlations prove that **10** and **11** possess 2*R*,5*S* and 2*R*,5*S* configurations, respectively. The power of this technique for the determination of absolute configuration is illustrated in Figure 3, where the ^{1}H NMR spectrum of a four-component mixture consisting of **9** and **10** from degradation, a pure enantiomer of **9**, and the shift reagent is shown. The high-field ^{1}H NMR spectrum readily permits the identification of (*S*)-**9** in this mixture.

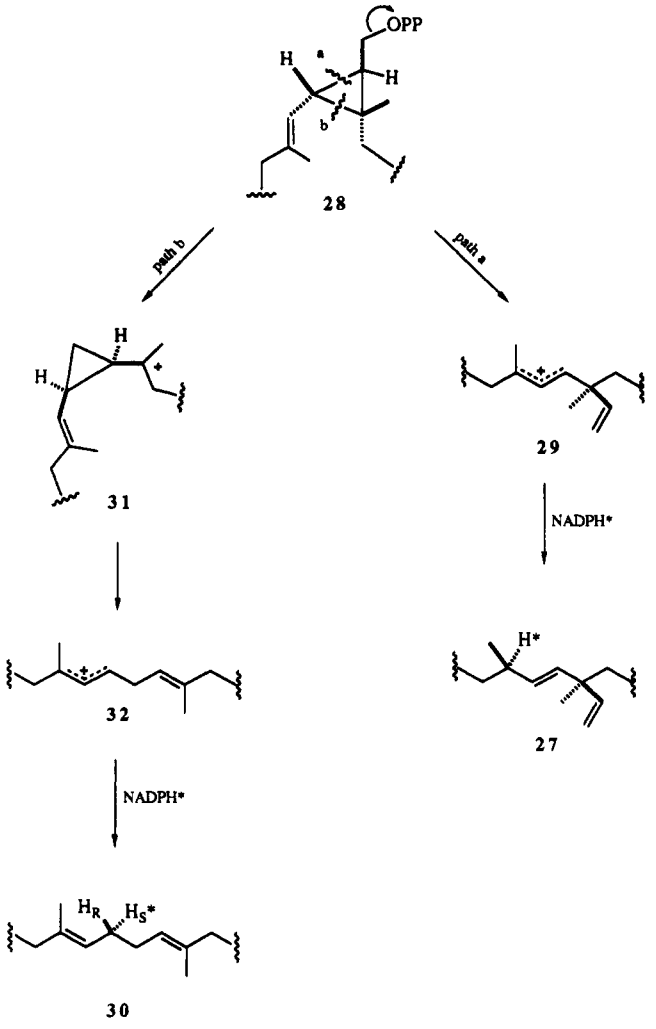
The determination of the absolute configuration of **9**, **10**, and **11** specifies the configuration of C_{34}-botryococcene (**1**) as 3*S*,7*S*,10*R*,13*S*,16*S*,20*S*. This finding carries significant biosynthetic consequences, among which is a previously unrecognized regularity in the stereochemistry of methylation of an acyclic isoprenoid. Also, details of the stereochemical pathway associated with formation of a 1′–3 ("iso") linkage between two farnesyl units are confirmed.[23] Incorporation of all four nonisoprenoid methyl substituents at C3, 7, 16, and 20 of **1** takes place from the *si* face of each trisubstituted double bond of the triterpenoid precursor **27**. Systematic stereochemistry would, of course, be anticipated if **1** were assembled from identically constituted methyl-substituted isopentenyl subunits, but it is not to be expected a priori if methyl groups are added sequentially to an intact C_{30} substrate, i.e. **27**, as biosynthetic experiments suggest.[24] The specificity observed in the methylation of **27** is logically the consequence of a binding mechanism that recognizes double bond geometry and does not permit rotation of the substrate after its attachement to the enzyme. Whether the analogous process which leads to methylated squalenes in *B. braunii*[25] exhibits similar specificity remains to be seen.



The 10*R*,13*S* configuration found for **1** brings to light stereochemical details associated with the mechanism of 1′–3 coupling of isoprenoid units which conform to a rational but hitherto unsubstantiated biogenetic hypothesis. Assuming that (1*R*,2*R*,3*R*)-presqualene diphosphate (**28**)[26] is the precursor of **27**, scission of bond a of the cyclopropane would lead to a quaternary center with the *S* configuration and an allyl cation **29**. If hydride is delivered by NADPH at the tertiary center of the allyl cation from the *si* face, the observed 10*R* configuration of **27** results. This is consistant with Poulter's proposal for the biosynthesis of irregular monoterpenes such as artemesia and yomogi alcohols.[27] However, in these monoterpenoid structures the crucial stereogenic elements are concealed. Presqualene diphosphate would represent in this view a biosynthetic junction at which pathways toward botryococcenoids and squalene (**30**) diverge (Scheme V). The mechanistically more intricate pathway to squalene, which involves cleavage of **28** at bond b and subsequent rearrangement to a second cyclopropane **31**, is also terminated by hydride delivery to an allyl cation **32** from the *si* face. In this case, however, attachment of H occurs at the less substituted terminus of the allyl unit. It is tempting to speculate that squalene biosynthesis may be the result of an evolutionary adaptation of the simpler botryococcenoid pathway, a postulate that the geochemical record tends to support.[28] The choice for scission of bond b of **28** could be a response to the need for a triterpenoid substrate

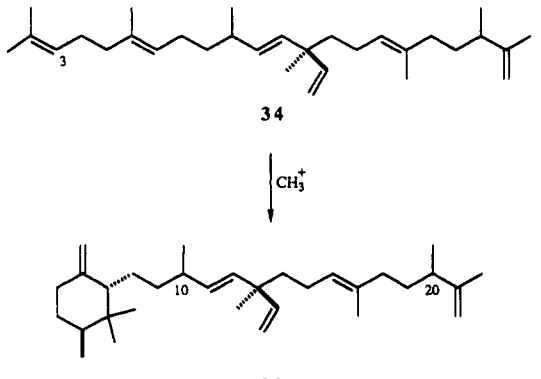
(22) Kime, K. E.; Sievers, R. E. *Aldrichchimica Acta* **1977**, *10*, 54.
(23) Poulter, C. D. *Acc. Chem. Res.* **1990**, *23*, 70.
(24) Casadevall, E.; Metzger, P.; Puech, M.-P. *Tetrahedron Lett.* **1984**, *25*, 4123.
(25) Metzger, P.; Casadevall, E. *Tetrahedron Lett.* **1983**, *24*, 4013.
(26) Poulter, C. D.; Rilling, H. C. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. C., Eds.; John Wiley: New York, 1981; Vol. I, p 413.
(27) Poulter, C. D.; Marsh, L. L.; Hughes, J. M.; Argyle, J. C.; Satterwhite, D. M.; Goodfellow, R. J.; Moesinger, S. G. *J. Am. Chem. Soc.* **1977**, *99*, 3816.
(28) (a) Eglinton, G. In *Cosmochemistry and the Origin of Life*; Ponnamperuma, C., Ed.; NATO Adv. Study Inst., Series C **1983**, *101*, 323. (b) Schopf, J. W. In *Geochemistry and the Origin of Life*; Kvenvolden, K. A., Ed.; Halsted Press: London, U.K., 1974; p 338. (c) Eglinton, G.; Murphy, M. T. J. *Organic Geochemistry: Methods and Results*; Springer Verlag: Berlin, Germany, 1969.

Scheme V



capable of undergoing enzymic cyclization to the tetracyclic nucleus of the sterols, a route foreclosed to the botryococcenoids.

Braunicene (**33**), a C_{32} congener of botryococcene, has also been shown to possess the *S* configuration at the quaternary carbon representing the linkage point of the two farnesyl subunits.[29] A subsequent cyclization, perhaps initiated by electrophilic methylation at C3 of the acyclic precursor **34**, would lead to the cyclohexyl moiety of **33**.



The two stereogenic centers of the cyclohexane of **33** have also been found to have the *S* configuration,[30] but it remains to be seen whether C10 is *R* and C20 is *S* as would be expected by analogy with **1**. The pattern in which the "iso" linkage between two farnesyl units is accompanied by monocyclization is repeated in other cyclohexane-containing botryococcenoids[31] and evidently represents a common alternative to the sequence involving proton loss that leads to **1**.

Experimental Section

Solvents were dried by distillation shortly before use from an appropriate drying agent. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was carried out on 2.5- × 7.0-cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.2 mm) manufactured by E. Merck. Flash chromatography was carried out with E. Merck silica gel 60 (230–400-mesh ASTM). High-pressure liquid chromatography (HPLC) was performed with a Waters M-45 solvent delivery system equipped with two Waters semipreparative silica columns and a refractive index detector. Gas–liquid chromatography (GC) was carried out using a Varian Aerograph 2700 with constant oven temperature and He as carrier gas.

Melting points were measured on a Büchi melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on either a Perkin-Elmer 727B or a Nicolet 5DXB FT-IR spectrometer. Optical rotations were measured in 1-dm cells (1-mL capacity) on a Perkin-Elmer Model 243 polarimeter at ambient temperature. Nuclear magnetic resonance spectra (NMR) were recorded on either an IBM NR-80F or a Bruker AM-400 spectrometer. Carbon NMR spectra were measured on a Bruker AM-400 spectrometer. Chemical shifts are reported downfield from internal Me_4Si on the δ scale. *J* values are given in hertz. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were determined on a Kratos MS-50. Elemental analyses were performed by Desert Analytics (formerly MicAnal), Tucson, AZ.

28,29-Dihydrobotryococcene (4). Botryococcene (**1**) (332 mg, 0.712 mmol) was dissolved in 25 mL of *i*-PrOH, 75 mL of EtOH, and 0.5 mL of a 1.0×10^{-3} M aqueous $Cu(OAc)_2$ solution. The mixture was cooled in an ice bath and flushed with N_2. A 3-mL aliquot of a solution of 9.16 mL of 30% H_2O_2 (89.7 mmol total) in 21 mL of EtOH was added, followed by 200 μL (42.7 mmol total) of 85% $H_2NNH_2 \cdot H_2O$. Addition was repeated every 10 min until the total H_2O_2 solution had been transferred. After 20 min the mixture was concentrated in vacuo, and water and pentane were added. The organic phase was separated, and the aqueous layer was washed twice with pentane. The combined organics were washed with brine and dried ($MgSO_4$). Concentration afforded 354 mg of a light yellow oil that was chromatographed on 35 g of silica gel 60 (230–400 mesh) containing 17% by weight of $AgNO_3$. Pure **4** (136 mg, 41%) was eluted with EtOAc–hexane (1:3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (1 H, d, J = 15.8), 5.03 (1 H, dd, J = 15.8, 7.7), 4.69 (8 H, bs), 2.2–1.8 (9 H, m), 1.66 (6 H, s), 1.6–1.1 (14 H, m), 1.02 (6 H, d, J = 6.8), 0.98 (6 H, d, J = 6.8), 0.94 (3 H, d, J = 6.7), 0.86 (3 H, s), 0.74 (3 H, t, J = 7.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (×2), 150.0 (×2), 137.1, 133.4, 109.5 (×2), 107.1 (×2), 41.0 (×2), 40.7, 40.1, 38.7, 38.3, 37.5, 35.2, 33.6, 33.5, 33.4, 33.3, 31.6 (×2), 29.9, 22.7, 21.5, 20.5, 20.3, 19.8 (×2), 18.9 (×2), 8.5. Anal. Calcd for $C_{14}H_{60}$: C, 87.10; H, 12.90. Found: C, 86.88; H, 12.74.

Methyl (2*R*,5*S*,9*S*)-2,5,9-Trimethyl-6,10-dioxoundecanoate (5) and Methyl (2*R*,5*S*,9*S*)-2-Ethyl-2,5,9-trimethyl-6,10-dioxoundecanoate (6). Dihydrobotryococcene (**4**) (136 mg, 0.290 mmol) was dissolved in 10 mL of CH_2Cl_2, 2 mL of MeOH, and 2 mL of EtOAc, and the solution was cooled to −78 °C. O_3 was passed through the solution for 15 min and an additional 3 mL of MeOH was added. The O_3 flow was interrupted, and the blue solution was stirred for 30 min and then flushed with N_2 and warmed to room temperature. The solvent was removed in vacuo, and the resultant colorless oil was dissolved in Me_2CO and treated with an excess of Jones reagent at 0 °C. After 30 min, *i*-PrOH

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(31) Huang, Z.; Poulter, C. D. *J. Org. Chem.* **1988**, *53*, 5390.

was added, and the mixture was filtered through a pad of Celite. Concentration of the solution gave a light yellow oil that was redissolved in Et_2O and treated with excess CH_2N_2 at room temperature. Evaporation of the solvent and chromatography (25 g of silica gel 60, EtOAc–hexane, 1:3) afforded 30.6 mg (35%) of **6** and 48.5 mg of slightly impure **5**. The sample of **5** was subjected to preparative HPLC (μPorisil, EtOAc–hexane, 1:4) giving 27.5 mg (35%) of pure **5**: $[\alpha]^{25}_D = -1.09°$ (c = 1.37, $CHCl_3$); IR (neat 1735, 1715, 1710, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (3 H, s), 2.35–2.60 (5 H, m), 2.16 (3 H, s), 1.92 (1 H, m), 1.65 (2 H, m), 1.30 (2 H, m), 1.15 (3 H, d, J = 7.0), 1.11 (3 H, d, J = 7.2), 1.06 (3 H, d, J = 7.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 212.1, 176.9, 51.6, 46.2 (×2), 39.5, 38.3, 31.3, 30.5, 28.0, 26.2, 17.2, 16.4, 16.3; MS m/z 270 (M^+). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.82; H, 9.55.

6: $[\alpha]^{25}_D = +10.6°$ (c = 0.38, $CHCl_3$); IR (neat) 2975, 1735, 1720, 1715, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (3 H, s), 2.38–2.60 (4 H, m), 2.15 (3 H, s), 1.92 (1 H, m), 1.70–1.22 (7 H, m), 1.11 (3 H, d, J = 7.2), 1.10 (3 H, s), 1.05 (3 H, d, J = 7.1), 0.80 (3 H, t, J = 7.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8, 212.2, 177.6, 51.6, 46.6, 46.2 (×2), 38.3, 36.2, 32.0, 28.0, 27.8, 26.2, 20.6, 16.6, 16.4, 8.9; MS m/z 298 (M^+). Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.66; H, 9.98.

Methyl [2*R*,5*S*(*S*)]-5-[(4-Acetoxy-1-oxopentyl)oxy]-2-methylhexanoate (7). To a suspension of 82.0 mg (0.380 mmol, 80–85%) of *m*-chloroperbenzoic acid and 53.6 mg (0.638 mmol) of $NaHCO_3$ in 3 mL of dry CH_2Cl_2 was added 27.9 mg (0.103 mmol) of **5**. The mixture was stirred at room temperature for 5 days and then warmed at 40 °C for 3 days. The mixture was diluted with CH_2Cl_2 and washed with 10% aqueous Na_2SO_3, water, and brine. Concentration gave a colorless oil that was chromatographed (3 g of silica gel 60, EtOAc–hexane, 1:5), affording 20.1 mg (64%) of **7**: $[\alpha^{25}_D = -4.30°$ (c = 0.54, $CHCl_3$); IR (neat) 1730 (broad), 1375, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (2 H, m), 3.68 (3 H, s), 2.20–2.40 (3 H, m), 2.03 (3 H, s), 1.93–1.44 (6 H, m), 1.24 (3 H, d, J = 6.1), 1.21 (3 H, d, J = 6.4), 1.16 (3 H, d, J = 7.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 172.6, 170.6, 70.9, 70.0, 51.6, 39.3, 33.5, 30.9, 30.7, 30.6, 29.5, 21.3, 19.9, 17.1; MS (CI, CH_4) 303 (M + 1), 243, 227, 195, 161, 143, 129, 117, 101. Anal. Calcd for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67. Found: C, 59.80; H, 8.71.

Methyl [2*R*,5*S*(*S*)]-5-[(4-Acetoxy-1-oxopentyl)oxy]-2-ethyl-2-methylhexanoate (8). To a suspension of *m*-chloroperbenzoic acid (60.0 mg, 0.279 mmol, 80–85%) and $NaHCO_3$ (40.0 mg, 0.477 mmol) in 3 mL of dry CH_2Cl_2 was added 23.7 mg (79.5 μmol) of **6**. This mixture was stirred at room temperature for 5 days, heated at reflux for 24 h, diluted with CH_2Cl_2, and washed sucessively with 10% aqueous Na_2SO_3, water, and brine. The solution was dried ($MgSO_4$), concentrated, and chromatographed (6 g of silica gel 60, EtOAc–hexane, 1:5) to afford 21.9 mg (83%) of **8**: $[\alpha]^{25}_D = +5.4°$ (c = 1.08, $CHCl_3$); IR (neat) 1730 (broad), 1460, 1370, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (1 H, m), 4.84 (1 H, m), 3.66 (3 H, s), 2.32 (2 H, m), 2.03 (3 H, s), 1.90–1.25 (8 H, m), 1.24 (3 H, d, J = 6.2), 1.20 (3 H, d, J = 6.3), 1.11 (3 H, s), 0.81 (3 H, t, J = 7.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 172.6, 170.6, 71.3, 70.1, 51.6, 46.0, 34.3, 32.0, 31.0 (×2), 30.7, 21.3, 20.7, 19.9 (×2), 8.9. Anal. Calcd for $C_{17}H_{30}O_6$: C, 61.80; H, 9.15. Found: C, 62.01; H, 9.26.

(4*S*)-4-Methyl-γ-butyrolactone (9) and (2*R*,5*S*)-Dimethyl-δ-valerolactone (10) from 7. A solution of 11.0 mg of **7** (36.4 μmol), 1 mL of THF, and 1 mL of 2.5 N KOH was heated at 70 °C for 18 h and acidified with 1 M HCl. Solid NaCl was added, and the solution was continuously extracted with Et_2O for 24 h, dried ($MgSO_4$), and concentrated. Dry C_6H_6 was added, and the flask was fitted with a reflux condenser and dropping funnel containing 4-Å molecular sieves. The mixture was heated at reflux for 4 h and was concentrated to afford 8.8 mg of a 1:1 mixture of **9** and **10**. Chromatography (3 g of silica gel 60, Et_2O–pentane, 1:1) afforded **9** and **10**, identical with materials synthesized independently (vide infra).

2-Ethyl-2,5-dimethyl-δ-valerolactone (11) and 4-Methyl-γ-butyrolactone (9) from 8. A solution of **8** (8.3 mg, 25.1 μmol) in 1 mL of THF and 1 mL of 2.5 N KOH was heated at 70 °C for 12 h and acidified with 3.0 M HCl. Solid NaCl was added, and the solution was continuously extracted with Et_2O for 20 h, dried ($MgSO_4$), and concentrated. Dry benzene (20 mL) was added, and the flask was fitted with a reflux condenser and a dropping funnel containing 4-Å molecular sieves. The apparatus was purged with argon and heated at reflux for 2.5 h. Concentration afforded 5.5 mg (86%) of a 1:1 mixture of **9** and **11**. These lactones were separated as described for **9** and **10** and were shown to be identical with materials synthesized independently (vide infra).

(4*S*)-4-Methyl-2-(phenylthio)-γ-butyrolactone (15). To a solution of 7.2 mL (0.050 mol) of *i*-Pr_2NH in 100 mL of THF at −78 °C was added 36.8 mL (0.056 mol) of a 1.5 M solution of *n*-BuLi in hexane. After stirring this solution at −78 °C for 15 min, 4.40 g (0.028 mol) of (phenylthio)acetic acid in 20 mL of THF was added, and the mixture was allowed to stir for 15 min. To the resulting solution was added 2.0 mL (0.028 mol) of **13** in one portion. The mixture was allowed to warm to room temperature over a period of 3 h and was stirred for 16 h. The mixture was quenched with 50 mL of 2 N NaOH and was extracted with Et_2O. The organic phase was discarded, and the aqueous phase was acidified and extracted with Et_2O. The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave a clear oil which was redissolved in dry C_6H_6 containing a catalytic amount of *p*-toluenesulfonic acid. The solution was allowed to stand overnight, the solvent was evaporated, and the crude product was chromatographed (silica, CH_2Cl_2) to afford 4.87 g (82%) of **15** as a 1:1 mixture of stereoisomers: IR (neat) 3050, 3000, 2950, 1780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (2 H, m), 7.34–7.25 (3 H, m), 4.55–4.45 (1 H, m), 4.03–3.90 (1 H, m), 2.74–1.74 (2 H, m), 1.33–1.28 (3 H, dd, J = 6.4, 6.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 174.5, 133.0, 132.7, 132.4, 132.0, 129.2, 129.1, 128.4, 128.1, 75.5, 74.9, 46.3, 45.2, 37.3, 37.2, 20.9, 20.7. Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.45; H, 5.81. Found: C, 63.69; H, 5.76.

(4*S*)-4-Methyl-γ-butyrolactone (9). A solution of **15** (4.20 g, 0.20 mol) in 30 mL of MeOH was added to a suspension of 20 g of freshly prepared Raney nickel (W6) in 150 mL of MeOH, and the mixture was refluxed for 6 h. The nickel was filtered off, the filtrate was evaporated, and the crude product was chromatographed (silica, Et_2O/CH_2Cl_2, 1:4) to give 3.10 g (78%) of **9**: $[\alpha]^{23}_D = -29.0°$ (c = 2.25, $CHCl_3$) [lit.[15] $[\alpha]^{23}_D = -29.6°$ (c = 1.29, CH_2Cl_2)]; IR (neat) 2950, 1780, 1180, 1040, 940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68–4.63 (1 H, m), 2.58–2.54 (2 H, m), 2.42–2.34 (1 H, m), 1.89–1.80 (1 H, m), 1.42 (3 H, d, J = 6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 77.3, 29.7, 29.1, 21.1.

(*S*)-5-(Trimethylsilyl)-4-pentyn-2-ol (16). To a solution of 4.17 g (43.0 mmol) of (trimethylsilyl)acetylene in 50 mL of THF at −78 °C was added dropwise 29.0 mL (44.0 mmol) of a 1.5 M solution of *n*-BuLi in hexane. After 5 min, 4 mL of freshly distilled HMPA was added followed by 3.2 mL (46.0 mmol) of (*S*)-propylene oxide (**13**). The mixture was allowed to warm to 0 °C over 6 h and stirred at ambient temperature for 10 h. After addition of 10 mL of H_2O, the product was extracted with Et_2O and dried ($MgSO_4$). Concentration of the solution and chromatography (EtOAc–hexane, 1:3) gave 5.52 g (83%) of **16** as a colorless oil: $[\alpha]^{23}_D = +13.5°$ (c = 3.0, $CHCl_3$); IR (neat) 3400, 2950, 3170, 1250, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (1 H, m), 2.65 (1 H, m), 2.65 (1 H, bs), 2.39 (2 H, d, J = 6.6), 1.25 (3 H, d, J = 6.0), 0.16 (9 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.4, 87.2, 66.2, 30.4, 22.2, 0.1. Anal. Calcd for $C_8H_{16}OSi$: C, 61.48; H, 10.32. Found: C, 61.21; H, 10.41.

(*S*)-5-(Trimethylsilyl)-2-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-pentyne (17). To a solution of 2.99 g (19.1 mmol) of **16** in 50 mL of CH_2Cl_2 was added 4.0 mL (3.70 g, 44.0 mmol) of dihydropyran and 73 mg (2 mol %) of *p*-toluenesulfonic acid. The mixture was stirred at room temperature for 3 h, transferred to a separatory funnel, diluted with Et_2O, washed with saturated $NaHCO_3$, H_2O, and brine, and dried (Na_2SO_4). Concentration of the solution gave 4.70 g of a pale yellow oil which, after chromatography (75 g of silica gel 60, EtOAc–hexane, 1:7), afforded 4.12 g (90%) of **17** as a 1:1 mixture of diastereomers: IR (neat) 2950, 2175, 1250, 1025, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (2 H, m), 3.93 (4 H, m), 3.49 (2 h, m), 2.66–2.25 (4 H, m), 1.93–1.45 (12 H, m), 1.30 (3 H, d, J = 6.2), 1.22 (3 H, d, J = 6.2), 0.14 (18 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.3, 104.0, 98.0, 95.9, 85.8, 85.7, 71.4, 70.3, 62.5, 61.8, 30.8, 30.7, 28.4, 27.4, 25.4, 25.3, 21.2, 19.6, 19.1, 18.8, −0.1 (×2); HRMS calcd for $C_{13}H_{24}O_2Si$ 240.1546, found 240.1557.

(*S*)-2-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-4-pentyne (18). Tetra-*n*-butylammonium fluoride (25.0 mL of a 1.0 M solution

in THF, 25.0 mmol) was added via syringe to a solution of 17 (4.01 g, 16.7 mmol) in 30 mL of THF. After 1 h at ambient temperature, 100 mL of H_2O was added followed by 200 mL of Et_2O. The organic phase was separated and washed with 100 mL of H_2O and 100 mL of brine. The aqueous phase was extracted with Et_2O, and the organic solution was dried ($MgSO_4$). Concentration of the solution and chromatography (75 g of silica gel 60, EtOAc–hexane, 1:7) afforded 2.20 g (78%) of 18: IR (neat) 2942, 2121, 1201, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (2 H, m), 3.94 (4 H, m), 3.50 (2 h, m), 2.61–2.28 (4 H, m), 2.00 (2 H, m), 1.90–1.47 (12 H, m), 1.33 (3 H, d, J = 6.2), 1.25 (3 H, d, J = 6.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.8, 96.8, 81.5, 81.2, 71.0, 70.6, 69.8 (×2), 62.7, 62.4, 31.0, 30.9, 27.2, 25.8, 25.5 (×2), 21.1, 19.8, 19.6, 18.9; MS m/z 168 (M^+), 101, 97, 85 (100), 83, 71, 67, 57, 55.

Methyl (*S*)-5-[(Tetrahydro-2*H*-pyran-2-yl)oxy]hexynoate (19). To a flame-dried three-neck flask fitted with an argon inlet and thermometer were added 2.17 g (12.9 mmol) of 18 and 20 mL of THF. The stirred solution was cooled to −78 °C, and 10.1 mL (1.6 M in hexane, 16.1 mmol) of *n*-BuLi was added dropwise while the temperature was maintained below −60 °C. After 10 min, 6.0 mL of freshly distilled methyl chloroformate (7.31 g, 77.4 mmol) was added rapidly (the temperature initially rose to −20 °C and then fell to −70 °C). The solution was stirred for 1 h at −70 °C, allowed to warm slowly to room temperature over 2 h, and stirred for an additional 1.5 h. H_2O (50 mL) was added, and the mixture was transferred to a separatory funnel and diluted with 100 mL of Et_2O. The organic phase was separated and washed successively with H_2O and brine and dried ($MgSO_4$). Concentration of the solution and chromatography (70 g of silica gel 60, EtOAc–hexane, 1:6) afforded 2.70 g (92%) of 19 as a light yellow oil: IR (neat) 2950, 2230, 1715, 1430, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (2 H, m), 4.03–3.84 (4 H, m), 3.76 (6 H, s), 2.77–2.42 (4 H, m), 1.91–1.45 (12 H, m), 1.34 (3 H, d, J = 6.2), 1.26 (3 H, d, J = 6.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (×2), 98.1, 96.9, 86.8, 86.5, 74.2 (×2), 70.5, 70.0, 62.7, 62.4, 52.6 (×2), 31.0, 30.9, 27.5, 26.2, 25.5 (×2), 21.4, 19.7, 19.4, 19.3; MS m/z 227 (M + 1), 194, 167, 156, 151, 141, 129, 125, 101, 93, 85 (100). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.74; H, 7.88.

Methyl (*S*)-5-[(Tetrahydro-2*H*-pyran-2-yl)oxy]hexanoate (20). To a solution of 2.63 g (11.6 mmol) of 19 in 100 mL of EtOAc was added 260 mg of 10% Pd/C, and the flask was attached to a hydrogenation apparatus. After 3 h under 1 atm of hydrogen uptake had ceased, and the solution was filtered through a pad of Celite. Concentration of the filtrate afforded 2.59 g (97%) of 20: IR (neat) 2950, 1740, 1440, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (1 H, m), 4.63 (1 H, m), 3.97–3.68 (4 H, m), 3.67 (6 H, s), 3.48 (2 H, m), 2.32 (4 H, m), 1.93–1.40 (20 H, m), 1.23 (3 H, d, J = 6.2), 1.12 (3 H, d, J = 6.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 174.0, 98.9, 95.7, 73.7, 70.6, 62.8, 62.5, 51.5, 51.4, 36.8, 35.9, 34.1, 34.0, 31.2 (×2), 25.6, 25.5, 21.6, 21.3, 20.9, 20.1, 19.8, 19.1; MS m/z 231 (M + 1), 186, 168, 157, 154, 147, 145, 130, 101, 85. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.70; H, 9.56.

(*S*)-5-Methyl-δ-valerolactone (21). *p*-Toluenesulfonic acid (87 mg, 0.458 mmol) was added to a solution of 530 mg (2.29 mmol) of 20 in 40 mL of MeOH in a flame-dried flask under argon and stirred at 40 °C for 1.5 h. Anhydrous K_2CO_3 (95 mg, 0.687 mmol) was added followed, after 10 min, by C_6H_6. The MeOH was removed azeotropically by repeated addition of C_6H_6 and concentration of the solution in vacuo. The solution was concentrated to 15 mL, and the flask was fitted with a dropping funnel containing 4-Å molecular sieves and a reflux condenser. The apparatus was flushed with argon, and 45 mL of C_6H_6 was added followed by 131 mg (0.687 mmol) of *p*-toluenesulfonic acid. The mixture was heated at reflux for 2 h, cooled to room temperature, and diluted with 40 mL of H_2O and 40 mL of Et_2O. The organic layer was separated, and the aqueous phase was washed with two 20-mL portions of Et_2O. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give a pale yellow oil. Chromatography of this oil (20 g of silica gel 60, EtOAc–hexane, 1:1) afforded 203 mg (78%) of 21: $[\alpha]^{22}_D$ = −35.5° (*c* = 1.5, EtOH) [lit.[32] $[\alpha]^{20}_D$ = −34.30° (*c* = 2.1, EtOH)]; IR (neat) 2950, 1730, 1240, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (1 H, m), 2.62–2.40 (2 H, m), 1.97–1.80 (3 H, m), 1.53 (1 H, m), 1.38 (3 H, d, J = 6.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 76.9, 29.6, 29.2, 21.7, 18.5.

(2*R*,5*S*)-2,5-Dimethyl-δ-valerolactone (22) and (2*S*,5*S*)-2,5-Dimethyl-δ-valerolactone (23). To a flame-dried flask equipped with an argon inlet and thermometer was added 9 mL of THF and 685 μL (495 mg, 4.89 mmol) of freshly distilled $(i\text{-Pr})_2NH$. The solution was cooled to 0 °C, and 3.05 mL (1.6 M in hexane, 4.89 mmol) of *n*-BuLi was added dropwise via a syringe. After 1 h the solution was cooled to −78 °C, 21 (507 mg, 4.44 mmol) in 2 mL of THF was added dropwise, and the mixture was stirred at −78 °C for 30 min. HMPA (928 μL, 956 mg, 5.33 mmol) was added followed by 304 μL (694 mg, 4.89 mmol) of MeI in 2 mL of THF. The reaction mixture was maintained at −40 °C for 3 h and then allowed to warm to room temperature overnight. Saturated aqueous NH_4Cl was added dropwise until the mixture was neutral to litmus, Et_2O was added, and the organic phase was separated. The aqueous layer was saturated with NaCl and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated, and the resultant dark oil was chromatographed (60 g of silica gel 60, Et_2O–pentane, 1:1) to afford 424 mg (74%) of lactones 22 and 23 as a 3:2 mixture. Preparative gas–liquid chromatography ($^3/_8$-in. × 16-ft Carbowax 20M on Chromosorb P, 155 °C, 50-mg injections) was used to separate the lactones.

22: mp (hexane) 51.0–51.5 °C; $[\alpha]^{25}_D$ = −95.2° (*c* = 1.5, $CHCl_3$), IR (KBr) 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (1 H, m), 2.60 (1 H, m), 2.08 (1 H, m), 1.94 (1 H, m), 1.68–1.47 (2 H, m), 1.36 (3 H, d, J = 6.0), 1.22 (3 H, d, J = 6.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 74.4, 33.0, 28.4, 25.6, 21.1, 16.2. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.26; H, 9.47.

23: mp (hexane) 75.0–75.5 °C; $[\alpha]^{28}_D$ = −13.2° (*c* = 1.2, $CHCl_3$); IR (KBr) 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (1 H, m), 2.43 (1 H, m), 2.07–1.92 (2 H, m), 1.59 (2 H, m), 1.37 (3 H, d, J = 6.1), 1.31 (3 H, d, J = 6.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 78.2, 35.8, 31.0, 28.6, 22.2, 17.4. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.77; H, 9.23.

(2*R*,5*S*)-2-Ethyl-2,5-dimethyl-δ-valerolactone (24) and (2*S*,5*S*)-2-Ethyl-2,5-dimethyl-δ-valerolactone (25). Lithium diisopropylamide in THF was prepared by addition of 1.25 mL (1.94 mmol, 1.44 M in hexane) of *n*-BuLi to a solution of 0.272 mL (196 mg, 1.94 mmol) of freshly distilled $(i\text{-Pr})_2NH$ in 1.5 mL of THF at 0 °C. The solution was cooled to −78 °C, and 207 mg (1.62 mmol) of a mixture of 22 and 23 in 1.5 mL of THF was added dropwise. After 30 min a solution of 0.168 mL (328 mg, 2.10 mmol) of EtI and 0.394 mL (405 mg, 2.26 mmol) of HMPA in 1 mL of THF was added. The reaction was warmed to −40 °C for 3 h and then kept at room temperature overnight. The mixture was neutralized with saturated NH_4Cl and diluted with Et_2O. The organic phase was separated, and the aqueous layer was extracted with three portions of EtOAc. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (10 g of silica gel 60, EtOAc–hexane, 1:5) to afford 139 mg (54%) of 24 and 25 as a 3:1 mixture which was separated by HPLC (μPorisil, EtOAc–hexane, 1:5).

24: $[\alpha]^{25}_D$ = −30.7° (*c* = 1.7, $CHCl_3$); IR (neat) 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (1 H, m), 1.92–1.55 (6 H, m), 1.37 (3 H, d, J = 6.5), 1.24 (3 H, s), 0.91 (3 H, t, J = 7.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 77.5, 41.3, 32.4, 30.9, 27.8, 25.4, 22.0, 8.4. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.37; H, 10.56.

25: $[\alpha]^{25}_D$ = +9.1° (*c* = 0.73, $CHCl_3$); IR (neat) 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (1 H, m), 1.93–1.44 (6 H, m), 1.37 (3 H, d, J = 6.1), 1.26 (3 H, s), 0.90 (3 H, t, J = 7.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 77.7, 42.0, 33.2, 30.8, 28.0, 26.6, 22.1, 8.7. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.36; H, 10.50.

Dicyclohexylammonium (2*RS*,2*SR*)-2-Ethyl-5-hydroxy-2-methylhexanoate (26). A solution of 8.6 mg (55.0 μmol) of (±)-24 in 1 mL of THF and 2 mL of 2.5 M KOH was stirred at room temperature overnight and acidified with 3.0 M HCl. The mixture was extracted with three portions of a mixture of Et_2O–EtOAc (1:1), and the combined organic extract was washed with brine and dried ($MgSO_4$). Concentration of the solution gave a colorless oil that was taken up in EtOAc and treated with 16 μL (15 mg, 82.5 μmol) of dicyclohexylamine. The solution was allowed to stand at room temperature with slow evaporation of the solvent.

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Colorless prisms were deposited and were washed with Et_2O and dried in vacuo: mp (hexane–CH_2Cl_2) 108–109 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (1 H, m), 2.97 (2 H, m), 2.07–1.15 (26 H, m), 1.15 (3 H, d, J = 6.1), 1.08 (3 H, s), 0.86 (3 H, t, J = 7.4). Anal. Calcd for $C_{21}H_{41}NO_3$: C, 70.94; H, 11.62; N, 3.94. Found: C, 71.12; H, 11.55; N, 4.03.

Compound **26** crystallized in space group $P1$ with a = 9.698 (2) Å, b = 11.001 (2) Å, c = 11.074 (4) Å, α = 71.61 (2) °, β = 104.21 (2)°, γ = 95.43 (2)°, V = 1086 Å^3, Z = 2, d_{calc} = 1.09 g/cm^3, and d_{obsd} = 1.08 g/cm^3. All nonequivalent reflections in the range 3° < 2θ < 42° were measured by the 0–2θ technique on a Syntex P1 diffractometer with graphite-monochromated Mo Kα radiation. A total of 1680 independent reflections having $F^2 > 3\sigma(F^2)$ afforded R = 10.2% and R_w = 12.8%.

Determination of the Configuration of Lactones 9, 10, and 11. Comparison of the lactones from degradation with synthetic lactones **9**, **20**, and **22** was carried out as follows. A solution of the pair of naturally derived and synthetic lactones (1–2 mg) in 0.5 mL of $CDCl_3$ was treated with successive quantities of Eu(hfc)$_3$, and the 400-MHz ^1H NMR spectra were recorded. This procedure was then repeated using the enantiomerically pure synthetic lactone. Increasing induced shifts of the methyl signals were observed for stereochemically unmatched lactones in each case. The configuration of **9** was thus determined as *S*. Lactones **10** and **11** were likewise shown to be homochiral with (2*R*,5*S*)-**22** and (2*R*,5*S*)-**24**, respectively.

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Synthesis and Complexation Properties of Suitcase-Shaped Macrotricyclic and Butterfly-Shaped Macrobicyclic Polyether Ligands

Haoyun An, Jerald S. Bradshaw,* Krzysztof E. Krakowiak, Chengyue Zhu, N. Kent Dalley, and Reed M. Izatt

Center for Advanced Separations, Department of Chemistry, Brigham Young University, Provo, Utah 84602

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Ten suitcase-shaped macrotricyclic polyethers (**1–10**) containing nitrogen and carbon bridgehead atoms have been synthesized. These new cage compounds were prepared by connecting together two hydroxymethyl-substituted or two secondary amine-containing butterfly-shaped macrobicyclic polyethers by means of linear bifunctional connecting groups. Intermediate bis(hydroxymethyl)-substituted butterfly-shaped macrobicyclic polyether **14** was prepared by treating *N*,*N*′-bis(2-hydroxyethyl)ethylenediamine with 5-methylene-3,7-dioxanonane-1,9-diyl ditosylate to give bislariat 1,4-diaza-13-crown-4 (**11**) which was cyclized with 3-chloro-2-(chloromethyl)-1-propene followed by hydroboration. Intermediate bissecondary amine-containing butterfly-shaped macrobicyclic polyethers **18** and **19** were prepared by treating *N*,*N*′-bis(2-hydroxyethyl)ethylenediamine with 6-tosyl-3,9-dioxa-6-aza-1,11-undecanediyl ditosylate (**33**) to give *N*-tosyl-*N*′,*N*″-bis(2-hydroxyethyl)triaza-15-crown-5 (**12**). Lariat crown ether **12** was cyclized with **33** followed by reduction with $LiAlH_4$ to give **18**, or with 4-tosyl-4-aza-1,7-heptanediyl ditosylate (**36**) to give **19**. Some of the suitcase-shaped macrotricycles interacted with various cations. One was selective for Pb^{2+} ions and another interacted strongly with Hg^{2+}. A crystal structure for the **13**–$NaClO_4$ complex also is reported.

Introduction

The successful design, synthesis, and use of macropolycyclic compounds capable of the selective recognition of metal cations and other species are of great interest to workers in catalysis, separations, extraction, enzyme functions, and other areas of chemistry. A variety of macrocyclic,[1] macrobicyclic,[2–4] macrotricyclic,[5–13] macrotetracyclic,[13,14] and macropentacyclic[15,16] polyethers have been synthesized in a search for preorganized synthetic host molecules. Basket-shaped macrotricyclic host mole-

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