Braunicene. Absolute Stereochemistry of the Cyclohexane Ring

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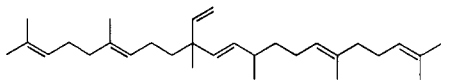
The absolute stereochemistries of the two chiral centers in the methylenecyclohexane ring of braunicene (**3**) were determined. The hydrocarbon was degraded to methyl α,2,2,3-tetramethyl-6-oxocyclohexanebutanoate (**4**) by ozonolysis and esterification. ORD and CD spectra of **4** both showed negative Cotton effects consistent with a 1*R*,3*S* configuration. Upon treatment with dry HCl in chloroform, **4** epimerized to cis keto ester **5**. Although the cis and trans isomers were not separated, the structure and preferred conformation of **5** were established from COSY, NOE, and difference decoupling studies on the equilibrium mixture. ORD and CD spectra of the equilibrium mixture had positive Cotton effects consistent with isomerization of **4** to its 1*S*,3*S* epimer. Diequatorial keto ester **5** was slightly more stable than **4**.

Botryococcus braunii is a colonial photosynthetic algae that has attracted attention because of its ability to produce and store massive quantities of hydrocarbons and the widespread distribution of these materials in geological formations.[1-4] There are two forms of *B. braunii*. Both have similar morphologies, but the hydrocarbons they produce are different. The L form synthesizes a family of linear *n*-alkadienes and trienes,[5] while the B form synthesizes a novel family of highly branched C_{30} to C_{37} isoprenoids called botryococcenes.[6,7] Pulse–chase and feeding experiments suggest that a parent C_{30} species (**1**) is the



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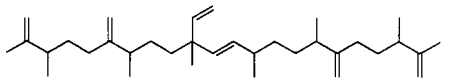

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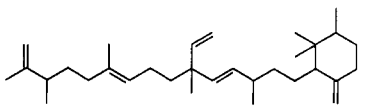

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precursor of higher members of the family, which are generated by successive methylations with *S*-adenosylmethionine.[8,9]

The center of the hydrocarbon chain in the botryococcenes contains an unusual 1′-3 isoprenoid fusion of two farnesyl residues.[10,11] There is evidence from model studies and from recent stereochemical studies of botryococcene (**2**)[12] and braunicene (**3**)[13] that the 1′-3 linkage is formed by carbocationic rearrangements related to those postulated for the conversion of presqualene diphosphate to squalene.[11,13-17] In addition, braunicene contains a trimethylmethylenecyclohexyl ring[13,18] with a substitution pattern similar to those found in isoprenoid metabolites recently isolated from the essential oil of iris rhizomes.[19-22] We now describe experiments that establish the absolute configurations of the two stereocenters in the cyclohexyl moiety of **3** obtained from the Berkeley isolate of *B. braunii*.

Results

Conversion of Braunicene (3) to Keto Esters 4 and 5. Oil obtained from cultures of the Berkeley isolate of *B. braunii* was fractionated by chromatography on silica gel and reversed-phase HPLC as previously described to give braunicene (**3**). The vinyl moiety in **3** was selectively reduced with diimide, and the resulting dihydro derivative was treated with ozone, followed by Jones oxidation and treatment with diazomethane, to yield a mixture of 3-methyl-2,6-heptadione, dimethyl (*R*)-2-ethyl-2-methylpentanedioate, and methyl α,2,2,3-tetramethyl-6-oxocyclohexanebutanoate (**4**). The keto ester was purified by normal-phase HPLC on 5-μm Hypersil by elution with 15% (v/v) *tert*-butyl methyl ether in isooctane. A ^{1}H NMR spectrum of **4** was identical with that previously reported.[13]

Upon standing in chloroform at −20 °C for several weeks, the ^{1}H NMR spectrum of **4** developed several new peaks, most notably a broad doublet at 2.10 ppm whose increase in intensity correlated with a concomitant decrease in the signal at 2.02 ppm, which we previously assigned to the equatorial proton at C1 in **4**. The isomerization was ac-

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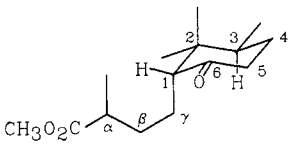
Table I. ^{1}H NMR Spectral Data[a] for 4 and 5

assignments	keto ester 4,[b] δ	keto ester 5 δ	keto ester 5 COSY cross peaks	keto ester 5 ^{1}H NOEs[c]
Cα	2.41	2.45 (1 H, dm, J = 7.2)	1.70, 1.22, 1.16	
Cβ	1.33	1.22 (1 H, m)	2.45, 1.78, 1.70, 1.26	
Cβ	1.50	1.70 (1 H, m)	2.45, 1.78, 1.26, 1.22	
Cγ	1.45	1.26 (1 H, m)	2.10, 1.78, 1.70, 1.22	
Cγ	1.65	1.78 (1 H, dm, J = 9.7)	2.10, 1.70, 1.26, 1.22	
C1[d]	2.02	2.10 (1 H, bd, J = 9.7)	2.37, 1.78, 1.26, 0.56	2.45, 2.37, 1.79, 1.26, 1.04
C5 (eq)	2.28	2.35 (1 H, m)	2.37, 1.88, 1.56	
C5 (ax)	2.38	2.37 (1 H, m)	2.35, 2.10, 1.88, 1.56	2.10, 1.88, 1.79
C4 (ax)	1.58	1.56 (1 H, m)	2.37, 2.35, 1.88, 1.79	
C4 (eq)	1.90	1.88 (1 H, m)	2.37, 2.35, 1.79, 1.56	
C3 (ax)	1.83	1.79 (1 H, dm, J = 6.7)	1.88, 1.56, 0.93	
eq methyl at C2	0.90	1.04 (3 H, s)	0.56	2.10, 1.79, 0.56
ax methyl at C2	0.84	0.56 (3 H, s)	2.10, 1.04	2.45, 1.78, 1.56, 1.04, 0.93
methyl at C3	0.98	0.93 (3 H, d, J = 6.7)	1.79	
methyl at Cα	1.14	1.16 (3 H, d, J = 7.2)	2.45	
ester methyl	3.67	3.68 (3 H, s)		

[a] Taken at 500 MHz. [b] Reference 13. [c] NOEs only listed under the protons irradiated in the experiment. [d] Equatorial in 4, axial in 5.

celerated when a chloroform solution of 4 was treated with a small quantity of dry HCl and reached equilibrium within a few hours at room temperature. Integration of the signals at 2.02 and 2.10 ppm in the equilibrium mixture at 20 °C gave a 4:5 ratio of 1:1.3. All attempts to separate keto esters 4 and 5 by HPLC and GLPC failed. The experiments described below were conducted with a mixture of the epimeric keto esters.

^{1}H NMR Studies. Although keto esters 4 and 5 were not separated, we were able to assign all of the ^{1}H resonances 5 by comparisons of NMR spectra of a nonequilibrium 1.2:1 mixture of 4 and 5 with those of 4. The numbering for the keto ester skeleton is shown below for 4, and ^{1}H NMR spectral data for 4 and 5 are presented



in Table I. Isomerization of 4 generated distinct, new resonances at 0.56, 0.93, 1.04, 1.16, and 3.68 ppm for all of the methyl groups in the molecule as well as a broad one-proton doublet at 2.10 ppm for the proton at C1. Most of the remaining signals in 4 also shifted when the keto ester isomerized to 5, but they were highly split by spin–spin coupling and were not well-resolved from the corresponding resonances in 4. We were, however, able to assign all of the protons in 5 and to establish its structure with the help of COSY, difference decoupling, and NOE difference spectra.

In a COSY spectrum of the mixture, the new broad doublet for the axial proton at C1 in 5 at 2.10 ppm was coupled to multiplets for three protons centered at 2.37, 1.78, and 1.26 ppm and to the methyl singlet at 0.56 ppm by a long-range interaction. The multiplets at 1.78 and 1.26 ppm (methylene protons at Cγ) were coupled to each other and had cross peaks to the Cβ methylene protons at 1.22 and 1.70 ppm, which in turn had cross peaks to the methine proton of Cα at 2.45 ppm. The COSY chain finally terminated with a cross peak between the methine proton of Cα and a doublet at 1.16 ppm for the methyl at Cα. Although the long-range coupling between the axial proton at C1 and the C5 protons was smaller (J < 1.0 Hz) in keto ester 5 than its epimer (J = 1.3 Hz),[13] a cross peak connected the resonance at 2.10 ppm to a signal centered at 2.37 ppm for methylene protons at C5 and, thus, also connected the C1 proton across the carbonyl moiety to the methylene protons in the ring of the new isomer. A cross peak also linked the resonance at 2.37 ppm to a signal assigned to the other C5 proton at 2.35 ppm. The remaining methylene resonances in 5 were assigned from a COSY network originating from the new doublet at 0.93 ppm for the methyl group at C3. The methyl signal had cross peaks to a multiplet centered at 1.79 ppm, which in turn was coupled to the C4 methylene protons at 1.56 and 1.88 ppm. These resonances had cross peaks to each other and to the C5 methylene resonances at 2.35 and 2.37 ppm. The cyclohexyl geminal methyls at 0.56 and 1.04 ppm were linked by strong cross peaks arising from four-bond couplings, which was verified by a decoupling experiment where irradiation at 0.56 ppm sharpened the width of the 1.04 ppm resonance from 1.24 to 0.69 Hz.

In the COSY spectrum of the mixture, the methyl at 0.93 ppm attached to C3 and the C1 proton at 2.10 ppm had cross peaks to signals at 1.79 and 1.78 ppm, respectively, that were too closely spaced to permit an umambiguious assignment. The problem was resolved by a difference decoupling experiment. Two single frequency decoupling spectra were recorded with decoupling at 2.10 and 0.93 ppm, respectively, and each was then subtracted from the fully coupled spectrum. The difference spectra shown in Figure 1a obtained with decoupling at 2.10 ppm had well-defined patterns at 2.37, 1.78, 1.26, and 0.56 ppm, while the difference spectrum presented in Figure 1b with decoupling at 0.93 ppm had a multiplet centered at 1.79 ppm with a very different pattern. Thus, the signals at 1.79 and 1.78 ppm were assigned to protons at C3 and Cγ, respectively. A large coupling constant (J = 9.7 Hz) between the C1 proton and the diastereotopic Cγ methylene proton at 1.78 ppm was detected by the collapse of the broad doublet at 2.10 ppm to a broad singlet upon irradiation at 1.78 ppm. A smaller coupling interaction was found between the C1 proton and the other Cγ methylene proton by irradiation at 1.26 ppm, which sharpened the two peaks of the C1 doublet. The large coupling constant indicates that the dihedral angle between the Cγ proton at 1.78 ppm and the C1 proton is near 180°.

Additional bond connectivities and conformational properties of 5 were established from NOE difference spectra (NOE connectivities are shown by dotted lines in Scheme I). NOEs were observed from the methyl at 0.56 ppm attached to C2 to the C4 methylene proton at 1.56 ppm, the Cγ methylene proton at 1.78 ppm, the methyl at 1.04 ppm attached to C2, the methyl at 0.93 ppm attached to C3, and the Cα methine proton at 2.45 ppm.

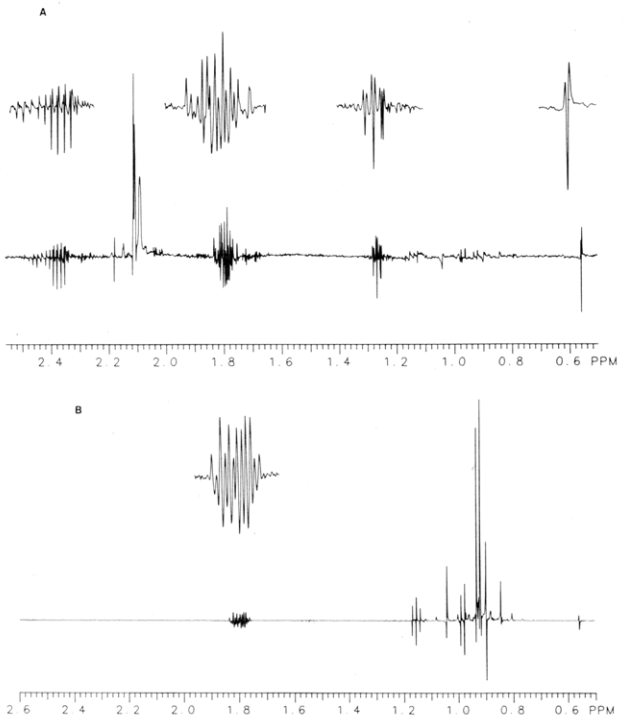
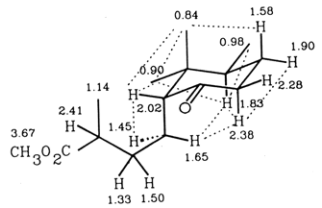


Figure 1. ^{1}H NMR (500 MHz) difference-decoupled spectra for a mixture of keto esters **4** and **5** (**4**:**5** = 1.0:1.35) at 26 °C in $CDCl_3$. A total of 128 transients (steady state = 4, block size = 8) were collected with D_1 = 4 s; 50 000 data points were collected at a 4000-Hz sweep width. Part A. On-resonance decoupling at low field peak of the C5 proton doublet centered at 2.10 ppm, off-resonance at 5.7 ppm. The insets are expansions at 0.56, 1.26, 1.78, and 2.37 ppm. Part B. On-resonance decoupling at 0.93 ppm, off-resonance at 5.7 ppm. The inset is an expansion at 1.79 ppm.

Scheme I. Chemical Shift Assignments and NOE Connectivities (Dotted Lines) for Trans Keto Ester 4 and Cis Keto Ester 5



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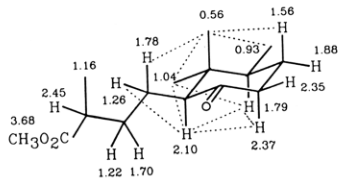

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When the resonance at 1.04 ppm was irradiated, NOEs were observed to signals at 0.56 ppm (methyl at C2), 2.10 ppm (C1 proton), and 1.79 ppm (C3 proton). Irradiation of the C1 resonance gave NOEs to 1.04 ppm (methyl at C2), 1.79 ppm (C3 proton), 2.37 ppm (C5 proton), and 2.45 ppm (Cα proton). Irradiation of the C5 methylene region generated NOEs to the doublet at 2.10 ppm but not to the resonance for the C1 equatorial proton at 2.02 ppm in axial isomer **4**. This experiment established the axial locations of the protons at 1.79, 2.10, and 2.37 ppm. The axial position for the 2.37 ppm C5 proton is also predicted by the COSY cross peaks to the C1 proton. The results of the NOE experiments were sufficient to complete chemical shift assignments and to establish the relative stereochemistry and preferred conformation of the methylenecyclohexyl moiety in **5**.

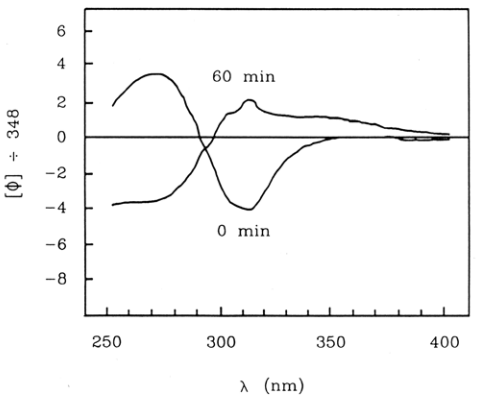


Figure 2. ORD spectra of keto ester **4** and the mixture (**4**:**5** = 1.0:1.3, 60 min after introduction of HCl) at 20 °C in $CDCl_3$ and a concentration of 5.75 mM.

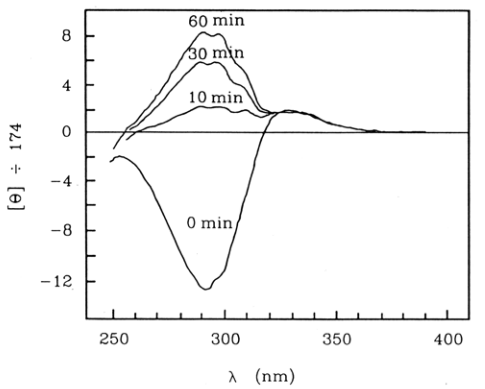


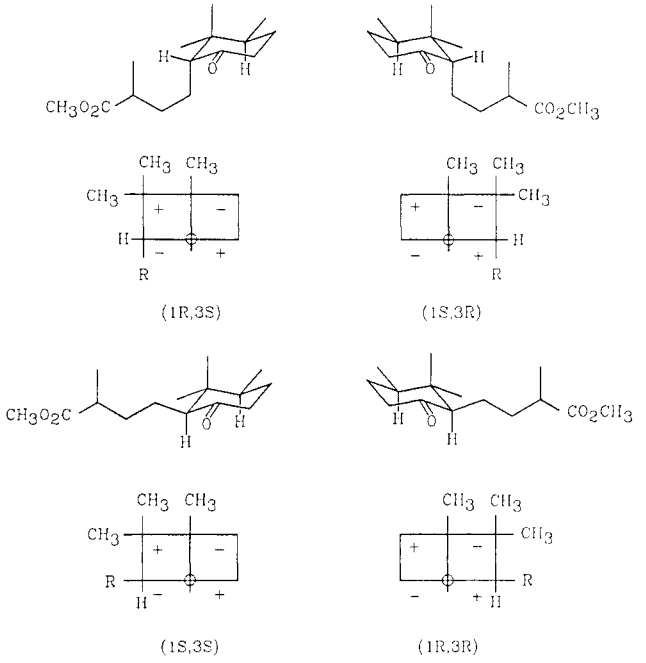
Figure 3. CD curves of keto ester **4**, 5.75 mM, and mixtures of **4** and **5** at 10, 30, and 60 min after the introduction of HCl at 20 °C in $CDCl_3$.

The cis stereochemistry for **5** was also supported by a big upfield shift in the resonance for the axial methyl at C2, which moved from 0.84 ppm in **4** to 0.56 ppm in **5**. The source of the upfield shift may be a diamagnetic contribution from the equatorial carbon–carbon bond at C5 in **5**, which is absent in the trans isomer. The upfield shift appears to be a general phenomenon for compounds containing methylenecyclohexyl rings with the substitution pattern seen in braunicene (**3**). For example, **3** had a *trans*-methylenecyclohexyl moiety, while γ-irigermanal, a triterpene whose structure was recently reported by Marner and co-workers,[19] contains a cis-substituted methylenecyclohexyl unit. In **3** the axial and equatorial geminal methyls are at 0.75 and 0.87 ppm, respectively. The geminal methyls in γ-irigermanal resonate at 0.57 and 0.91 ppm. Although stereochemical assignments were not made in this case, our data with **3**, **4**, and **5** suggest that the signal at 0.57 ppm is the axial methyl resonance. These high-field signals may be diagnastic for the relative stereochemistries of substituted methylenecyclohexyl units in isoprenoids.

ORD and CD Studies. As shown in Figure 2, the ORD spectrum of a chloroform solution of keto ester **4** immediately after ozonolysis of braunicene (**3**) had a negative Cotton effect and a cross-over point (λ_0) at 292 nm typical of a saturated ketone.[23] As expected, the CD spectrum

(23) Crabbé, P. *Optical Rotory Dispersion and Circular Dichroism in Organic Chemistry*; Holden-Day, Inc.: San Francisco, 1965; pp 72–85.

Scheme II. Octant Projections of the Diastereomeric Keto Esters



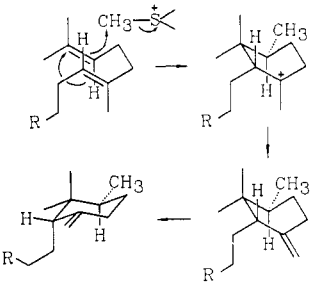
of **4** (see Figure 3) also had a negative Cotton effect with a minimal value for the molar ellipicity (θ) at 292 nm. Treatment of the solution with dry HCl produced dramatic changes in both spectra. After 1 h when a 1:1.3 equilibrium mixture of **4** and **5** had been established, the ORD and CD spectra of the solution had positive Cotton effects. However, θ_{max} remained at 292 nm, and λ_0 shifted only slightly to 298 nm.

There are two chromophores in keto esters **4** and **5**, a cyclohexyl ketone and a side-chain methyl ester. Both are adjacent to chiral centers and, since **3** is not racemic, should be active in ORD and CD spectra. Because the ester is separated from the cyclohexane ring by two methylenes, it is reasonable to assume that its contribution will be similar to that of an acyclic α-methyl methyl ester, a system that typically has a very weak Cotton effect near 240 nm and a stronger Cotton effect near 210 nm.[24,25] However, the contribution of the cyclohexyl ketone should be considerably more substantial, with a Cotton effect near 290 nm.[23] The spectra presented in Figures 2 and 3 indicate that isomerization of **4** to **5** occurred at C1. We have no evidence by optical measurements for an additional isomerization of the chiral center at Cα; however, the very slow development of additional NOEs from the Cα methine signal to the axial methyl at C2 and the axial proton at C1 upon prolonged treatment with acid may result from isomerization at that center.

In a previous study we showed that **4** contained a trans-substituted methylenecyclohexyl moiety[13] and, thus, was either the 1*R*,3*S* or the 1*S*,3*R* stereoisomer. Furthermore, in its preferred conformation the side chain at C1 of **4** was axial. Both stereoisomers are shown in Scheme II with accompanying octant projections. Upon application of the octant rules to **4**, the side chain (R) adjacent to the carbonyl moiety is located in a negative quadrant, the more remote methyls at C2 are in a positive quadrant, and the methyl at C3 across from the carbonyl is at a node in the 1*R*,3*S* isomer. Upon isomerization to the 1*S*,3*S* isomer,

(24) Listowsky, I.; Arigad, G.; England, S. *J. Org. Chem.* **1970**, *35*, 1080–1085.
(25) Korver, O.; Gorkom, M. V. *Tetrahedron* **1974**, *30*, 4041–4048.

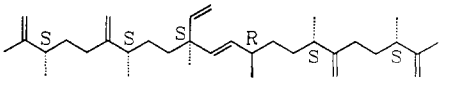
Scheme III. Cyclization Initiated by Electrophilic Methylation



the side chain moves near the nodal plane, leaving the geminal methyls in a positive quadrant. Thus, one would predict that epimerization at C1 in (1*R*,3*S*)-**4** would generate a negative to positive change in the Cotton effects of its ORD and CD spectra. A similar analysis for (1*S*,3*R*)-**4** predicts the opposite trend. We conclude that keto esters **4** and **5** are the 1*R*,3*S* and 1*S*,3*S* diastereomers, respectively. Thus, braunicene has the 16*S*,20*S* configuration for the two chiral centers in the methylenecyclohexane ring (note that group priorities at C16 change upon oxidation of the exocyclic methylene).

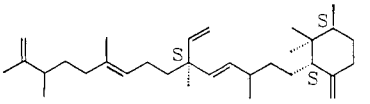
Discussion

Several lines of evidence, including product, pulse–chase, and feeding experiments, indicate that the C_{31}–C_{37} botryococcenes are formed by successive methylations of the parent triterpene **1** by *S*-adenosylmethionine.[6-9] This scheme predicts that the two chiral centers at C10 and C13 common to all botryococcenes should have the same absolute stereochemistry as the 10*S*,13*R* configuration found by White and co-workers in **2**.[12] The absolute configuration of C10 in **3** was recently shown to be *S*.[13]



(3S,7S,10S,13R,16S,20S)

2



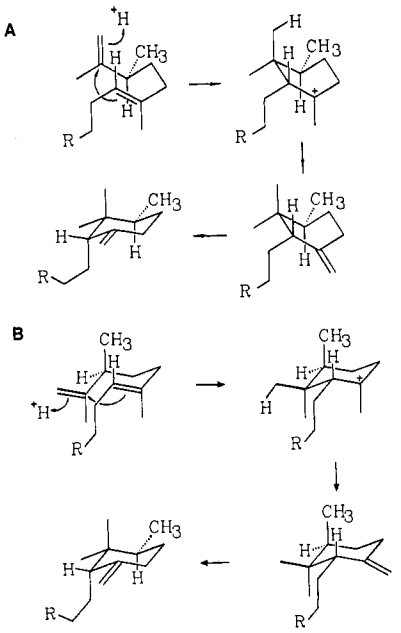
(10S,16S,20S)

3

The methylenecyclohexane ring in braunicene has a 16*S*,20*S* configuration. Two mechanisms that account for the observed stereochemistry are shown in Schemes III and IV. The first is an electrophilic methylation at the *si* face of the terminal double bond with the hydrocarbon chain folded into a boat conformation as depicted in Scheme III. Cyclization and elimination gives the boat conformer of **3**, which can relax to the preferred 16*S*,20*S* chair conformation. This mechanism is similar to those proposed by Krick and co-workers[20,21] for monocyclic methylated triterpenes in iris and by Metzger et al.[7] for a C_{34} monocyclic hypermethylated botryococcene.

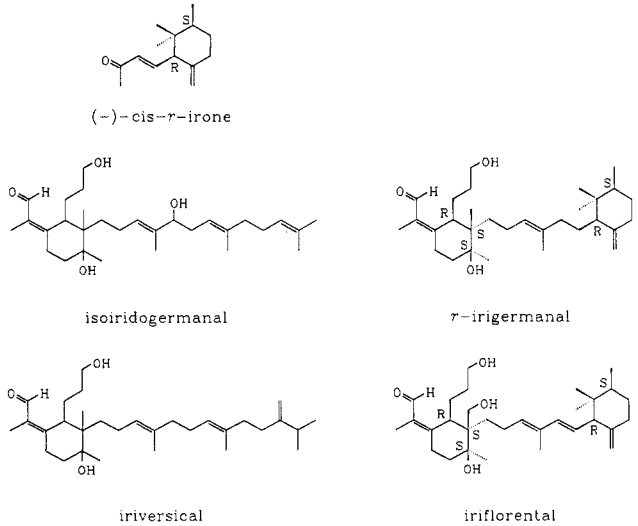
The recent stereochemical studies of White and co-workers[12] suggest another possibility. The *S*-adenosylmethionine mediated methylations that convert **1** to **2** generate *S* stereocenters in the isoprenoid chain. If **2** is indeed produced by four successive methylations of **1**, one

Scheme IV. Cyclization Initiated by Protonation



predicts that the C_{32} botryococcene also has an *S* stereocenter at C20. This is the same absolute stereochemistry found at C20 in **3**. Thus, one can envision proton-initiated cyclizations as illustrated in Scheme IV. With the hydrocarbon chain folded into a boat conformer similar to that proposed for the methylation mechanism (part A) or in a chair conformer (part B), a proton-initiated cyclization from the *si* face of the disubstituted double bond will also generate a (16*S*,20*S*)-methylenecyclohexane ring.[26]

The trans-substituted methylenecyclohexyl moiety in braunicene is an unusual isoprenoid structure that thus far has only been reported in *trans*-γ-irone. The only other member of the botryococcene hydrocarbons known to contain a cyclohexyl substituent is a C_{34} derivative of unknown stereochemistry with a hypermethylated six-membered ring. Methylenecyclohexyl units also occurred in γ-irigermanal and iriflorental, triterpenes isolated from the essential oil of iris rhizomes. The two aldehydes, together with a linear isomer iriversical, are C_{31} isomers apparently



formed by methylation of the terminal double bond in the isoprene side chain. Iriversical contains an isopropyl-substituted double bond typical of structures produced during side-chain methylation of sterols, while γ-irigermanal and iriflorental have methylenecyclohexyl moieties. However, the methylenecyclohexane rings in the C_{31} aldehydes are cis-substituted. The essential oil also contains *cis*-γ-irone, a fragrant violet-scented C_{14} ketone formed by oxidative degradation of iriflorental.[19-22] Although small quantities of *trans*-γ-irone have also been isolated from the essential oil,[27] it is unclear if the trans isomer is a primary metabolite or results from isomerization of the cis compound.

γ-Irigermanal and iriflorental have the same absolute stereochemistry at C3 in the methylenecyclohexyl moiety that we found for **3** but the opposite stereochemistry at C1. These results are compatible with either the methylation or the protonation mechanism. *cis*-γ-Irone isolated from iris rhizomes along with the methylated triterpenes also has the 1*R*,3*S* stereochemistry;[22] however, (1*S*,3*R*)-γ-irone was reported in the essential oil of iris from a different locale.[27,28] Thus, one anticipates that the enantiomeric precursor triterpenes are also naturally occurring species. Thus far, all of the botryococcenes have the same absolute stereochemistries.

Experimental Section

Spectra. CD and ORD spectra were recorded on a Jasco J-20 spectropolarimeter in a 1-cm quartz cell. ^1H NMR spectra were recorded on Varian XL-300, XL-400, or VXR-500 spectrometers in deuteriochloroform at 26 °C and referenced to internal tetramethylsilane. COSY spectra were obtained according to the protocol of Bax and co-workers[29] with a delay, D3, of 0.05 s between the second pulse and acquisition period to enhance long-range interactions.

Methyl (1*R*,3*S*)-α,2,2,3-Tetramethyl-6-oxocyclohexanebutanoate ((1*R*,3*S*)-4). Cultures of *B. braunii* (Berkeley isolate) were grown as previously reported,[13] and **3** was purified by chromatography. The vinyl moiety in **3** was selectively reduced with diimide. The dihydro derivative was treated with ozone at −78 °C, and the resulting ozonides were oxidized with Jones reagent. The residue was treated with diazomethane at room temperature, and the resulting mixture was purified by normal-phase HPLC (5-μm Hypersil, 30 cm × 3.9 mm) upon elution with 15% (v/v) *tert*-butyl methyl ether and isooctane to give a colorless oil whose ^1H NMR spectrum was identical with that previously reported for **4**:[13] ORD ($CDCl_3$, 5.7 mM, 20 °C) $[\phi]_{271}$ +1253 (pk), $[\phi]_{292}$ 0, $[\phi]_{312}$ −1392 (tr); CD ($CDCl_3$, 5.7 mM, 20 °C) $[\theta]_{292}$ −2192 (max), $[\theta]_{318}$ 0, $[\theta]_{328}$ +331 (max).

Epimerization of (1*R*,3*S*)-4. A 2-mg sample of (1*R*,3*S*)-**4** in 0.7 mL of deuteriochloroform was sealed under nitrogen in an NMR tube. The ^1H NMR spectrum of the sample was recorded periodically over a period of 3 months at room temperature. At the end of this time, normal ^1H, COSY, NOE difference, and single frequency difference decoupling spectra were recorded.

In a separate experiment, a 2-mg sample of (1*R*,3*S*)-**4** was dissolved in 0.6 mL of deuteriochloroform. The solution was cooled to −78 °C, and hydrogen chloride gas was bubbled through the sample for 5 s. ^1H NMR spectra were recorded at 20 °C over a 450-min period, during which the sample isomerized to a mixture that gave a spectrum identical with the one obtained above.

ORD and CD Studies. A sample of (1*R*,3*S*)-**4** (3.5 mg, 14 μmol) was dissolved in 2.40 mL of deuteriochloroform (0.58 mmol/dL). CD and ORD spectra were recorded at 20 °C. Gaseous hydrogen chloride was bubbled through the sample at 20 °C for 5 s, and CD spectra were recorded after 10, 30, 45, 60, and 150 min. An ORD spectrum was also recorded at 60 min.

(26) A similar mechanism for formation of the methylenecyclohexane ring in **3** was recently proposed by Murakami and co-workers,[18] although stereochemical aspects were not addressed.

(27) Rautenstrauch, V.; Willhalm, B.; Thommen, W.; Ohloff, G. *Helv. Chim. Acta* **1984**, *67*, 325-331.
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A 0.40-mL portion of the solution was removed after 60 min and analyzed by NMR. The ratio of trans to cis isomers was approximately 1:1.3 as judged from the intensities of the resonances at 2.02 and 2.10 ppm and the ester methyls at 3.67 and 3.68 ppm. CD and ORD spectra of (1*R*,3*S*)-**4** and the mixture of (1*R*,3*S*)-**4** and (1*S*,3*S*)-**5** between 250 and 450 nm in isooctane were virtually identical with those obtained in deuteriochloroform.

Acknowledgment. This work was supported by Grant GM 21328 from the National Institutes of Health. We thank Dr. Fred Wolf of Amoco Corporation for helpful discussions.

Stereoselective Reactions. 14.[1] Efficient Enantioselective Construction of Quaternary Carbon Centers by the Sequential Dialkylation of (*S*)-γ-[(Trityloxy)methyl]-γ-butyrolactone. Synthesis of Optically Active β,β-Disubstituted γ-Butyrolactones

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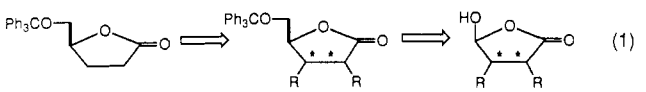
Sequential dialkylation of the lithium enolate, generated from (*S*)-γ-[(trityloxy)methyl]-γ-butyrolactone (**1**), with two different alkyl halides created chiral quaternary carbon centers with extremely high diastereoface selection. A unique conformation of **1**, shown by NMR analysis and MM2 force field calculations, is proposed to be the controlling factor of the stereoselectivity.

Molecules with an appropriate carbon arrangement and asymmetric carbon centers have been developed as a chiral pool in modern synthetic chemistry.[3] Asymmetric carbon centers of these molecules are directly incorporated into the chiral centers of the target molecules. Although this type of methodology assures the integrity of the absolute configuration and optical purity, this approach lacks flexibility and efficiency. Based on these considerations, we designed a new type of chiral synthon (**1**).[4]

A basic scheme for the use of **1** as a chiral synthon is represented in eq 1. The first step of the transformation to **2** is the creation of new asymmetric carbon centers on the ring carbons under the influence of the resident asymmetric center of **1**. The second step to **3** is removal



(1)

1 **2** **3**

of the resident asymmetric center which has played its role in the asymmetric induction, via oxidative cleavage of the glycol part of **2**. The product (**3**) contains a four-carbon unit with two asymmetric carbon centers and two differentiated carbonyl functionalities.

Successful syntheses of a variety of optically active compounds by this approach have been published from our laboratories and others.[4-6] However, factors which control the diastereoface differentiation in the creation of new asymmetric centers, the most important step, remain to be elucidated. In the present article we describe the details of an efficient construction of quaternary carbon centers[7] and the determination of the conformation of **1** which is probably responsible for the high diastereoface differentiation.[8] Furthermore, molecular mechanics calculations performed on **1** appear to be generally consistent with the experimental results.

Results and Discussion

Sequential Dialkylation of 1. The chiral synthon **1** was prepared from L-glutamic acid as described before.[4a] Methylation of **1** (lithium diisopropylamide (LDA)–THF, then MeI (R^1X)) afforded a crystalline product **4** in 73% yield.[4a] Alkylation of **4** (LDA/hexamethyl phosphoric triamide (HMPA)–THF, then R^2X) gave, after detritylation, **5a** (R^1 = Me) with nearly complete stereoselectivity (Table I, runs 1–4).

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(2) Visiting Professor from Seoul National University, Korea.
(3) Reviews: Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Otto Salle Verlag: Munich, 1980; Vol. 2, p 91. Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon: Oxford, 1983. Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic: New York, 1984; Vol. 4, Chapter 1.
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