crystallographic solutions and refinements. G.D.M. is the recipient of a Department of Education-sponsored National Need Fellowship.

Supplementary Material Available: X-ray experimental details, tables of crystallographic data for all compounds, tables of atomic positional and thermal parameters, bond distances and angles, and torsional angles (in selected compounds), and numbering schemes for **37**, **40**, and **51A–C** (74 pages). Ordering information is given on any current masthead page.

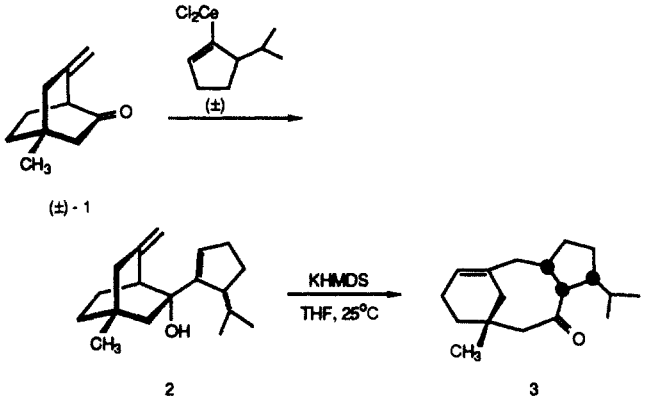
[3.3] Sigmatropy within 1-Vinyl-2-alkenyl-7,7-dimethyl-*exo*-norbornan-2-ols. The First Atropselective Oxyanionic Cope Rearrangement

Leo A. Paquette,* Neil A. Pegg, Dana Toops,[1] George D. Maynard, and Robin D. Rogers[2]

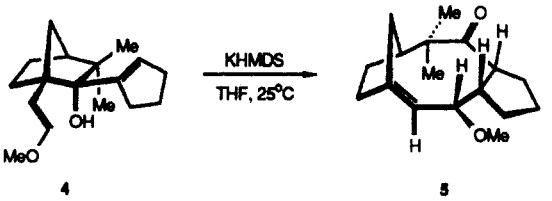
Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210, and the Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115. *Received April 12, 1989*

Abstract: The anionic oxy-Cope rearrangement of several title compounds is shown to occur rapidly at room temperature exclusively via the respective endo-chair transition states. These reactions occur with complete stereoinduction to generate stereochemically homogeneous bridgehead olefinic ketones and therefore offer especially stringent probes of transition-state topographical stereoselection. Evidence is provided to show that these conversions are remarkably atropselective as well. The illustrative example selected for study was **17**, its α-methyl group serving as a utilitarian ^{1}H NMR probe of structural homogeneity and conformation. This ketone is the product of a tandem [3.3] sigmatropic shift-methylation sequence. On being heated in tetrahydrofuran for several days, **17** is completely transformed into its more thermodynamically favored conformational isomer **18**. These results are nicely accommodated by molecular mechanics calculations. The stereochemical course of the oxy-Cope rearrangements is compared to the pathways followed by structurally related *exo*-norbornan-2-ols and allied molecules.

The anionic oxy-Cope rearrangement has emerged as an important transformation in organic synthesis.[3] When preceded by condensation of a chiral vinyl organometallic to a chiral β,γ-unsaturated ketone, the two-step conversion (e.g., **1** → **3**)[4] constitutes a carbonyl regenerative scheme that proceeds with considerable structural embellishment.[5] The emerging relationship of the carbinol center in **2** relative to those of dissymmetric elements preexisting in the pair of starting reagents falls under the category of diastereomeric differentiation.[5] While recent studies have focused on the molecular recognition aspects of the 1,2-carbonyl addition,[5,6] almost no attention has been paid to those structural features that might divert the ensuing [3.3] sigmatropic shift away from the transition-state chair topology that usually enjoys a kinetic advantage.[3,7,8]



It has been found, however, that the potassium salts of alcohols exemplified by **4** isomerize at room temperature to provide products of type **5**.[9] The stereodiagnostic centers in **5** clearly attest to exclusive adoption of an exo-boat geometry during Cope rearrangement, despite the availability of two chairlike transition-state options.



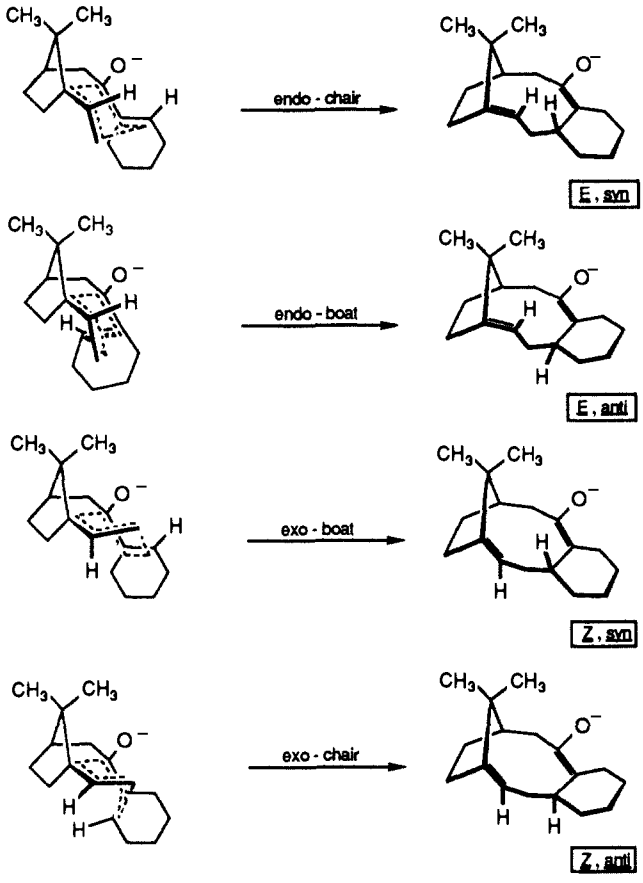
To investigate systematically the degree of control that norbornane frameworks might be capable of exerting on such sig-

* Address correspondence to this author at The Ohio State University.

(1) Undergraduate research participant, 1986–1987.
(2) Author to whom inquiries relating to the X-ray crystallographic analyses should be directed at Northern Illinois University.
(3) (a) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, 1984; Vol. 3A, p 503. (b) Hill, R. K. In *Comprehensive Organic Synthesis*; Pergamon Press; in press.
(4) Paquette, L. A.; He, W.; Rogers, R. D. *J. Org. Chem.* **1989**, *54*, in press.
(5) Paquette, L. A. In *Organic Synthesis*: Modern Trends; Chizhov, O., Ed.; Blackwell Scientific Publications: 1988; pp 1–12.
(6) (a) Paquette, L. A.; Learn, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7873. (b) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31. (c) Paquette, L. A.; Learn, K. S.; Romine, J. L. *Tetrahedron* **1987**, *43*, 4989. (d) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879. (e) Paquette, L. A.; DeRussy, D. T.; Cottrell, C. E. *Ibid.* **1988**, *110*, 890. (f) Paquette, L. A.; DeRussy, D. T.; Gallucci, J. C. *J. Org. Chem.* **1989**, *54*, in press. (g) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.
(7) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.
(8) (a) Gajewski, J. J.; Jimenez, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 468. (b) Gajewski, J. J.; Benner, C. W.; Hawkins, C. M. *J. Org. Chem.* **1987**, *52*, 5198.
(9) Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P., preceding paper in this issue.

0002-7863/90/1512-277$02.50/0

Scheme I



matropic processes, we undertook study of an epimeric group of molecules, the 1-vinyl-2-cycloalkenyl-7,7-dimethyl-*exo*-norbornan-2-ols. In each of these reactants, the spatial orientation of the 1-vinyl group in the activated complex is to be revealed by the configuration about the medium-ring double bond in the product (Scheme I). The stereochemistry adopted by the double bond of the allylic alcohol moiety would perforce be transferred to the homoallylic ring juncture site. The test was expected to make known in strikingly stereospecific fashion the consequences of projecting the allylic double bond endo on overall stereocontrol of the oxyanionic Cope process. This report concerns these reactions and their possible relevance to the rapid construction of functionalized tricyclic bridgehead olefinic ketones.

Results

Dissection of the Stereochemical Composite. Synthesis and Rearrangement of the 1,2-Divinyl Example. At the outset, it was considered advisable to rid the reacting substrate of all extraneous steric biases. The most compelling of such experiments involves alcohol **7**. Although the intermediacy of four transition-state geometries are likewise possible in this example, the two olefinic protons at the terminal carbon of the 2-vinyl substituent become nondistinguishable. Consequently, the double bond stereochemistry in the oxy-Cope product becomes the sole focus of attention.

Direct condensation of the readily available,[10] optically pure bicyclic ketone **6** with vinylmagnesium bromide simply induced deprotonation. While the addition of anhydrous cerium trichloride[4,6,9,11] did improve matters, yields in the 70% range were realized only when several cerate addition-quench cycles[12] were carefully implemented (see Experimental Section). Later, it was noted that dichlorocerates derived from vinyllithium reagents added efficiently in only one pass.

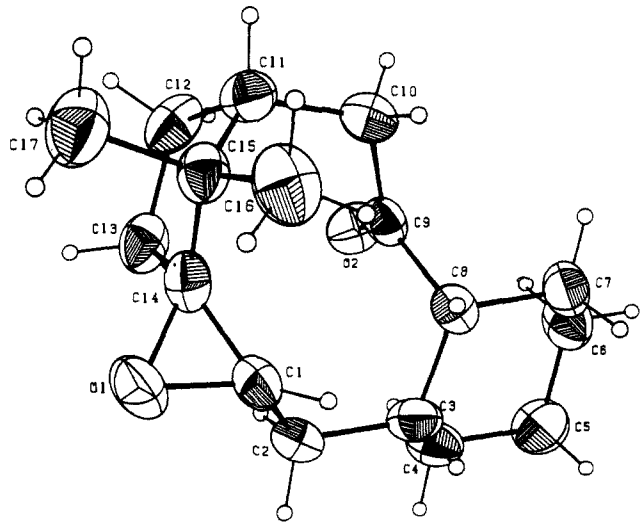
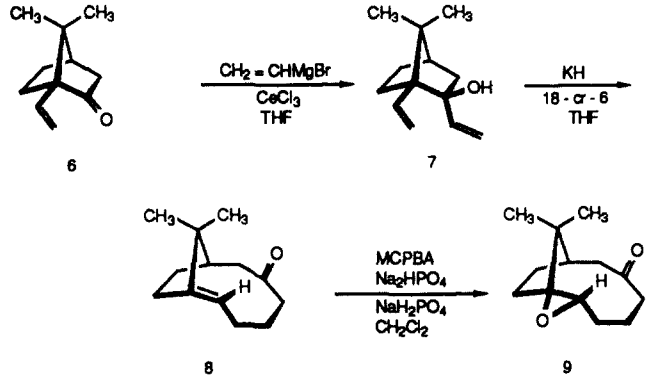


Figure 1. Computer-generated perspective drawing of **12** as determined by X-ray analysis. The atom numbering is arbitrary.

Following the admixture of **7** with iodine-pretreated potassium hydride[13] and 18-crown-6 in tetrahydrofuran, isomerization to **8**



was complete within 15 min at room temperature. The ring-expanded ketone that formed exclusively was shown to possess an *E* double bond on the basis of nuclear Overhauser effect studies. Specifically, the vinyl proton and syn-methyl group in **8** were determined to be in close spatial proximity on the strength of a 12% NOE enhancement.

This olefin geometry defines for **8** a relatively rigid conformation. Molecular models indicate the derived epoxide **9** to be somewhat less constrained. Nonetheless, the extensive backside steric screening of its oxirane substructure totally inhibits ring opening by such reagents as sodium azide,[14] triflic acid in dimethyl sulfoxide,[15] or boron trifluoride etherate[16] under standard conditions.

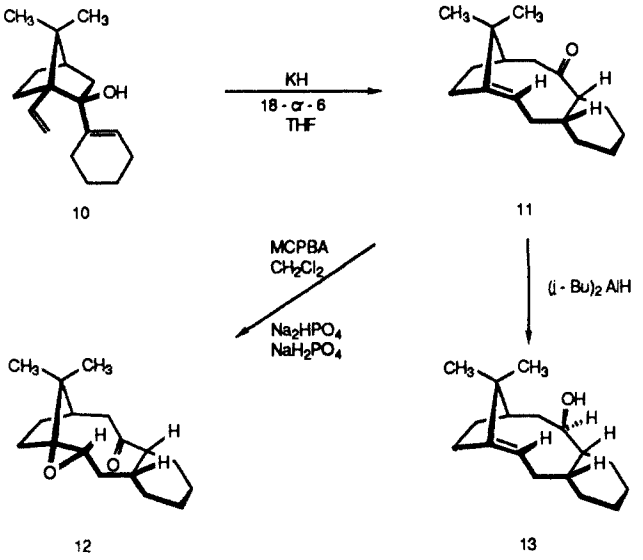
These secondary consequences of the oxyanionic Cope rearrangement aside, the structural features inherent to **8** require that the potassium alkoxide of **7** isomerize via one of two pathways where its 1-vinyl substituent is projected endo (Scheme I).

Stereochemical Course of the 2-(1-Cyclohexenyl) Series. The dichlorocerate reagent derived from 1-lithiocyclohexene adds to **6** from its endo surface to give **10** in 76% yield. Since the KH-promoted isomerization of this alcohol likewise resulted in efficient formation of a single product of [3.3] sigmatropy, it was imme-

(10) Fischer, N.; Opitz, G. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. V, p 877.
(11) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *285*, C21. (c) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.
(12) Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1835.
(13) Macdonald, T. L.; Natalie, K. J., Jr.; Prasad, G.; Sawyer, J. S. *J. Org. Chem.* **1986**, *51*, 1124.
(14) (a) VanderWerf, C. A.; Heisler, R. Y.; McEwen, W. E. *J. Am. Chem. Soc.* **1954**, *76*, 1231. (b) Vince, R.; Deluge, S. *J. Med. Chem.* **1974**, *17*, 578.
(15) Trost, B.; Fray, M. J. *Tetrahedron Lett.* **1988**, *29*, 2163.
(16) Naqvi, S. M.; Horwitz, J. P.; Filler, R. *J. Am. Chem. Soc.* **1957**, *79*, 6283.

diately made clear that the added stereochemical marker was not causing competitive operation of more than one oxy-Cope rearrangement pathway. Stereochemical definition of the double bond geometry in **11** was again arrived at by direct NOE measurements. In this instance, the 13% integral enhancement observed for the vinylic proton upon double irradiation of the proximate bridgehead methyl singlet provided direct evidence for the *E* arrangement. However, definition of the ring fusion stereochemistry could not be arrived at reliably in this manner. The ^{1}H NMR spectrum of epoxide **12** offered no advantages in this regard, although a lack of chemical reactivity similar to that earlier described for **9** was again encountered.

Consequently, **12** was subjected to three-dimensional X-ray crystallographic analysis (Table I, Supplementary Material). The ORTEP diagram (Figure 1) reveals several important structural features. The most significant of these is the cis,syn orientation of the two stereogenic cyclohexyl protons relative to the *gem*-dimethyl substituted bridge. This observation requires that **10**



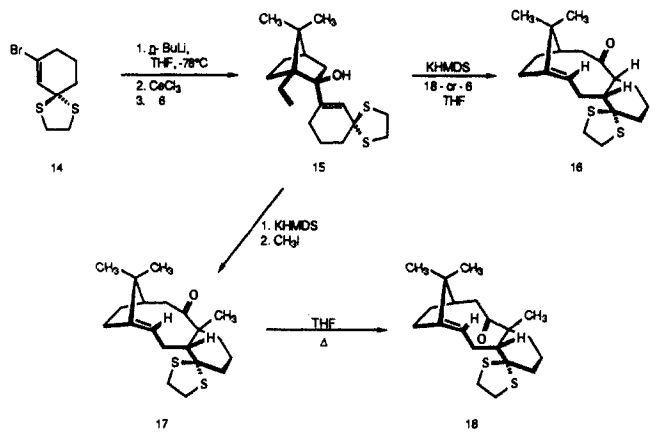
10 **11** **12** **13**

undergo isomerization specifically by way of the endo-chair arrangement (Scheme I). The uniquely stereodefined enolate anion that is initially produced therefore experiences protonation from that molecular surface which is less sterically congested. It is unlikely that the cis ring fusion present in **11** and **12** is thermodynamically advantaged, although this issue has not been investigated per se.

A direct consequence of adoption by **10** of the endo-chair transition state is initial projection of the newly developed carbonyl group in an upward direction such that the oxygen is oriented proximal to the apical syn-methyl substituent. This conformation does not persist in epoxide **12** whose carbonyl group is seen to be "tucked" under (Figure 1). Are both conformations indeed available to **11** or is atropisomerism operative such that a reasonable energy barrier inhibits those σ bond rotations that would allow the carbonyl group to be endo-oriented? If so, the release of medium-ring strain accompanying oxirane formation might well be accompanied by conformational flexing along the carbonyl sector. These intriguing questions are dealt with in the sequel.

Suffice it to emphasize at this point that the conformations unique to **11** and **12** should allow stereocontrolled attack at their respective carbonyl groups by various nucleophiles. A case in point is the reduction of **11** by Dibal-H. This reaction leads cleanly to alcohol **13**. The configuration of the new chiral center has been assigned on the basis of steric approach control to the thermodynamically less favored atropisomer (see below).

[3.3] Sigmatropy in a Sterically More Congested Example. Our interest in examining a more heavily substituted example was spurred on by knowledge that vinyl bromide **14** can be produced readily.[17] Conversion of **14** to its dichlorocerate appeared to be



14 **15** **16** **17** **18**

modulated somewhat by the presence of the sulfur atoms since a 6.5-h reaction time was now required to form the organometallic efficiently. Subsequent condensation with **6** afforded the *exo*-norbornanol **15** in 77% yield. Treatment of **17** with 18-crown-6 and potassium hydride (or more conveniently with potassium hexamethyldisilazide) in tetrahydrofuran, followed by quenching with aqueous ammonium chloride solution, resulted in conversion to **16** with 100% stereoselectivity.[6g]

The formation of this bridgehead olefinic ketone correlates with adoption of an endo-chair alignment (Scheme I) such that an *E*,syn enolate anion is generated regiospecifically. In an attempt to link the oxy-Cope isomerization to a second utilitarian reaction, the initially formed intermediate was treated directly with 10 equiv of methyl iodide. This tandem process gave rise principally to **17** (55%). A byproduct lacking the dithiolane moiety was also produced in lesser amounts. Although diminution in the relative quantity of methyl iodide did noticeably curtail formation of this uncharacterized substance, the level of **17** was also adversely affected. Consequently, the original protocol is currently viewed as being close to optimal.

Turning to the structure of **17**, we immediately observed the anticipated intense (17%) NOE effect operating between the vinyl proton and proximate bridgehead methyl group. Strikingly, however, no significant NOE interaction was noted to the third, newly introduced methyl substitutent. Consequently, these data require that **17** exist in a conformation that effectively directs these alkyl groups away from each other.

Earlier, we pointed out that adoption by *exo*-norbornanols such as **15** of the endo-chair arrangement for [3.3] sigmatropy has the initial effect of orientating the carbonyl oxygen in an upward direction. Adoption of this conformation by **17** is sufficient to lock the methyl groups in question into nonsterically interfering regions of the molecule (Figure 2). Since the oxyanionic Cope process proceeds at room temperature, an opportunity is thereby available for conformational control to be exercised in a manner that would permit the existence of discrete atropisomers.[18] This is indeed the case. When refluxed in tetrahydrofuran for several days, **17** is completely transformed into its conformational isomer **18**. The several σ bond rotations that must operate during this process are impeded from taking place readily because of the structural features present in **17**. Once the carbonyl oxygen becomes "tucked under" as in **18**, a lower energy conformation is attained. This arrangement does, however, require that the methyl substituent α to the carbonyl be brought into closer proximity to the syn-oriented bridgehead methyl (Figure 3). Indeed an 8% NOE effect involving these two groups is clearly evident in the ^{1}H NMR spectrum of **18**.

It is of interest that the presence of the bridgehead double bond is critical for maintaining a barrier to interconversion that is not surpassed readily at room temperature. Studies to be reported elsewhere have demonstrated that addition across this π linkage with accompanying $sp^2 \rightarrow sp^3$ change at both carbon centers leads

(17) Shih, C.; Swenton, J. S. *J. Org. Chem.* **1982**, *47*, 2825.

(18) (a) Ōki, M. *Top. Stereochem.* **1983**, *14*, 1. (b) Ōki, M. *Acc. Chem. Res.* **1984**, *17*, 154.

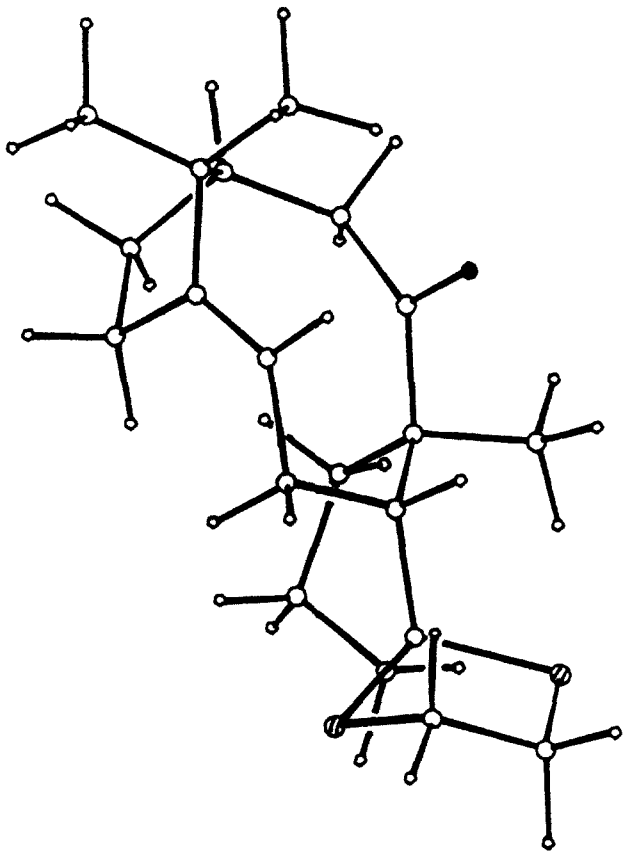


Figure 2. Energy-minimized conformation of atropisomer **17**.

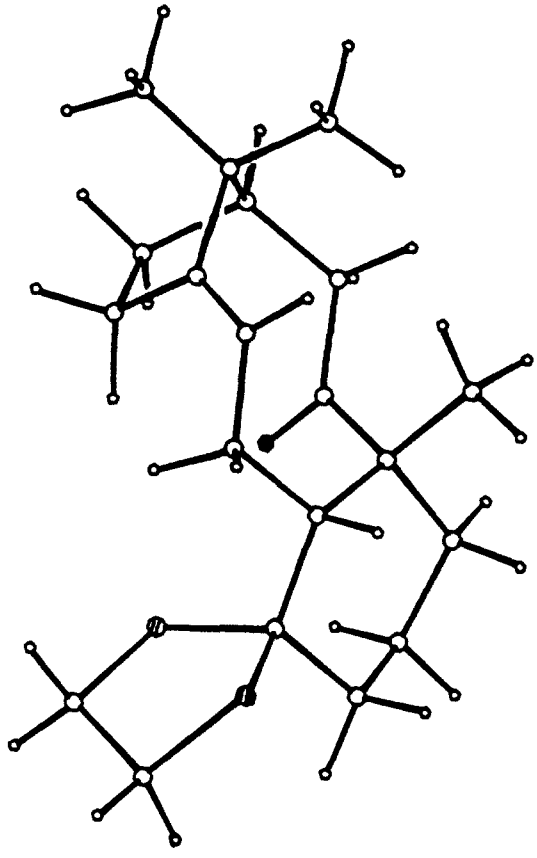


Figure 3. Energy-minimized conformation of atropisomer **18**. The greater proximity of the non-geminal methyl groups relative to **17** is to be especially noted.

to considerably more facile conformational isomerization.[19]

These observations are in line with recent findings by Shea and his co-workers[20] who have established that suitable derivations of the related tricyclo[9.3.1.$0^{3,8}$]pentadecene ring system are likewise prone to exist as discrete, independently characterizable conformers.

The conversion of ***15*** (and presumably **10** and related alcohols as well) *to a single atropisomer therefore constitutes an exceedingly rare example of an atropselective reaction.*

Because we had not anticipated that **18** would be so greatly preferred relative to **17** when their interconnective energy barrier was exceeded, the global energy minima of these structures were calculated with the aid of MODEL (KS 2.93)[21] in combination with its companion program BAKMDL.[22] The heats of formation and strain energies of the final structural candidates were then determined by MMX methods. Strikingly, the three-dimensional

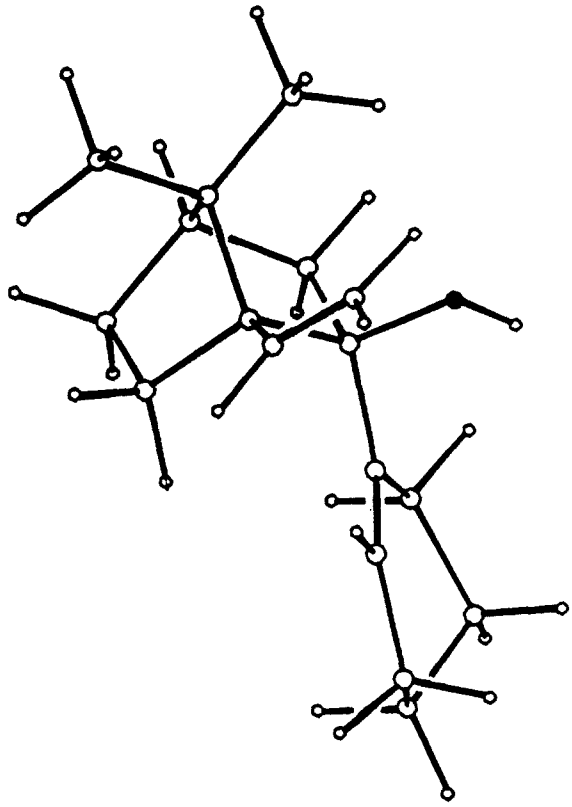
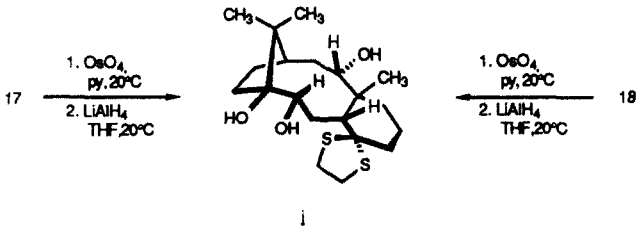


Figure 4. Minimized exo-chair arrangement within **10**. See Table I.

arrangement calculated for **18** (Figure 3, E_s = 65.7 kcal/mol) has the effect of lowering nonbonded steric interactions and other contributory factors to a value that is 4.3 kcal/mol less than that present in **17** (Figure 2, E_s = 70.0 kcal/mol). Efforts to take

(19) For example, sequential osmylation–$LiAlH_4$ reduction of both **17** and **18** affords **i** exclusively, as confirmed by X-ray crystallographic analysis (Rogers, R. D., private communication). Note also the conversion of **11** → **12**.



i

(20) (a) Shea, K. J.; Gilman, J. W. *Tetrahedron Lett.* **1983**, 657. (b) Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953.

(21) We thank Professor W. C. Still (Columbia University) for making his program available for use.

(22) Professor K. Steliou (University of Montreal) is thanked for providing us with updates of this software package.

Table II. Calculated Strain Energies and Heats of Formation for Alcohol **10** and Its Four Possible Product Enolates

alcohol ground-state geometry	strain energy, kcal/mol	ΔH_f, kcal/mol	product enolate	strain energy, kcal/mol	ΔH_f, kcal/mol
endo-chair	37.2	−37.4	*E*, syn	56.7	−19.9
endo-boat	36.8	−37.9	*E*, anti	65.4	−11.3
exo-chair[a]	37.6	−37.1	*Z*, syn	55.6	−20.7
exo-boat[a]	37.6	−37.1	*Z*, anti	55.5	−21.0

[a] The minimum energy conformation that most closely corresponds to entry into the exo-chair and exo-boat manifolds is the identical bisected structure. No other minima were seen within 3 kcal/mol of the representation shown in Figure 5.

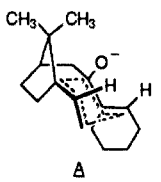
possible advantage of this distinctive product energy difference are currently underway.

Discussion

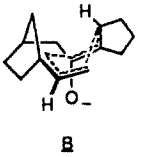
In all three examples studied herein, the product structure constitutes a "snap-shot" of the conformational bias for the respective oxy-Cope transition state. A strong preference for the endo-chair assembly is seen, without any evidence for involvement of the other three mechanistic options (Scheme I). To gain a more quantitative appreciation of the reasons underlying this particular stereochemical selection, minimum energy ground-state conformations were determined as described above for the starting *exo*-2-norbornanol **10** and its product enolates because of our inability to calculate internally consistent transition-state geometries. In line with expectation, several energetically similar conformations of **10** were uncovered. Close scrutiny of these conformers, which were selected to be within 3 kcal/mol of the global minimum, allowed selection of three that could most easily engage in proper orbital alignment for the impending anionic oxy-Cope isomerization (Table II and Figures 4 and 5). The energies of the product enolates are also compiled in Table II.

With the exception of the endo-boat product enolate, which is disfavored by 8.7 kcal/mol relative to endo-chair product, the global minimum energies of the enolates were virtually indistinguishable. For this reason, examination of the calculated starting material geometries proved to be much more informative, despite the fact that transition states are what truly matters (Curtin–Hammett principle). Thus, it became immediately apparent that the olefinic termini were too distant for reaction to materialize when the norbornanol was aligned in endo-boat fashion (4.62 Å). Furthermore, no particularly favorable exo-boat or exo-chair geometries were discovered. The best "best" exo orientation (Figure 4) places the cyclohexyl π-cloud *perpendicular* to that present in the ethylenic substituent. We believe that the combination of such unfavorable geometry and relatively large internuclear π–π distance (3.96 Å) precludes ready entry into the exo-chair or exo-boat manifolds. In contrast, the norbornanol conformer necessary for operation of the endo-chair pathway (Figure 5) allows for excellent orbital alignment at a significantly reduced distance between the double bond termini (3.45 Å).

It is informative to compare the strong endo-chair preference exhibited by these *exo*-norbornanols (A) with the exo-boat ar-

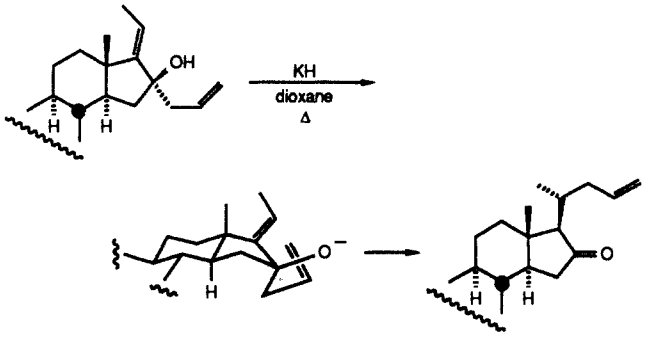


A

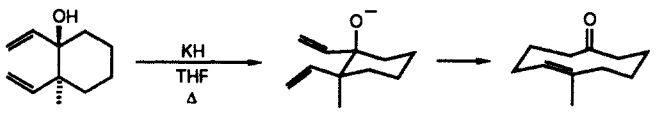


B

rangement most often adopted by structurally related *endo*-norbornanols (B).[9] With but one exception,[9] sigmatropic ring expansion occurs rapidly in both systems. The overall kinetic acceleration has been linked to the general adoption of early transition states. The predisposition for an exo and endo pathway simply underscores the inability on the part of those transition states having nonproximal π-termini to compete effectively. Beyond that, we see that A and B share in common an axial oxyanionic bond. Several examples are known whose oxy-Cope rearrangement proceeds via chair transition states having this stereochemical feature. Alkoxides **19** and **20** are cases in point.[23,24]

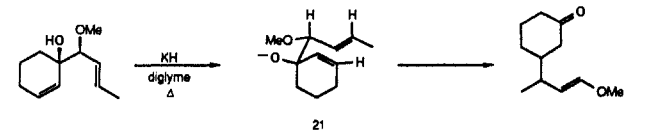


19

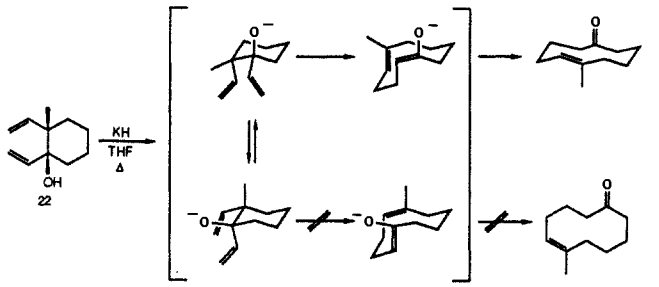


20

On the other hand, chairlike transition states having an equatorial oxyanionic bond, e.g., **21**,[25] are also known. In a conformationally dynamic situation such as that found in **22**, there appears in fact to be a preference for adoption of this geometry,[24] although the generality of the phenomenon remains to be tested. One has to be cognizant of the steric demands stemming from solvation of the ion pair that would drive matters in the same direction. Relative product stabilities probably should also not be overlooked, at least in certain examples.



21



22

Whatever the actual situation, the norbornanols presently examined rearrange via an axial oxyanionic mode and do so rapidly. The release of strain imbedded in bicyclo[2.2.1]heptane frameworks is considered to be contributory to this acceleration.

The stereoinduction as relfected in **8**, **11**, **16**, and **17** is seen to be extremely efficient. Since the high optical activity of **6** is never in risk of destruction, the derived products necessarily possess the same level of enantiomeric purity. Additionally, the absolute configurational assignments depicted above can be made with confidence.

Finally, we again call attention to the striking observation that the rapidity of these reactions (complete within 10–15 min at room temperature) allows for operation of atropselectivity at a very high level of efficiency. The barrier to conformational isomerization between molecules such as **17** and **18** is sufficiently high that samples of each pure diastereomer can be prepared with ease. Ōki has stressed the point that reactions of conformational isomers often differ in rate, sometimes with kinetic inequalities as large

(23) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172.
(24) Clive, D. L. J.; Russell, G. C.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632.
(25) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.

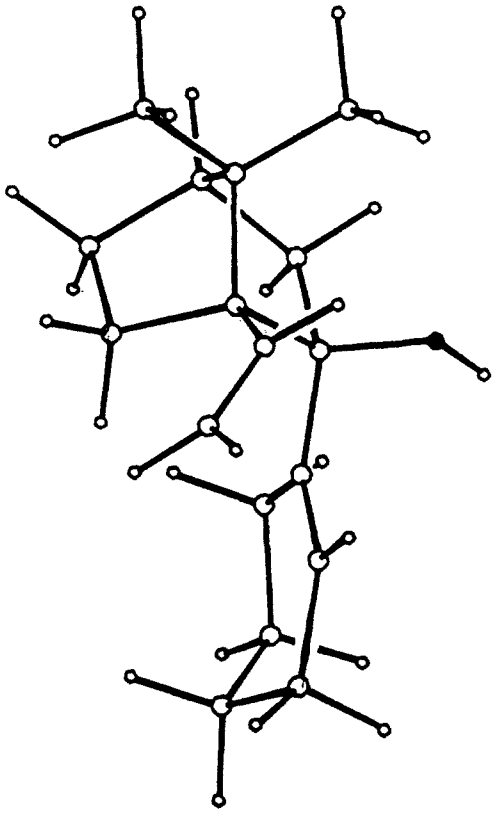


Figure 5. Minimized endo-chair arrangement within **10**.

as 10000-fold.[18] Nonetheless, conformational effects on reactivity are virtually unstudied in ring sizes larger than cyclohexyl.[20,27] Accordingly, oxy-Cope rearrangements such as those described herein may prove to be generally serviceable in gaining access to medium-ring compounds having intrinsic atropisomeric properties.

Experimental Section

(−)-(1*S*)-1,2-Divinyl-7,7-dimethyl-*exo*-norbornan-2-ol (7). A 6.81-g (19 mmol) sample of cerium trichloride heptahydrate was dried by heating at 140 °C and 0.1 Torr for 2 h. The cooled dry solid was covered with 5 mL of dry tetrahydrofuran, and the mixture was stirred at room temperature for several hours to form a fine slurry. A solution of vinylmagnesium bromide in tetrahydrofuran (17.6 mL of 1.08 M, 19 mmol) was added over 15 min to the cold (−78 °C) slurry and stirred at this temperature for 30 min before a solution of **6** (2.0 g, 12.2 mmol) in the same solvent (5 mL) was introduced during 1.5 h. The mixture was stirred at −78 °C for 2 h, at which time 767 μL (19 mmol) of dry methanol was added, and stirring was continued 10 min longer. A second 17.6-mL aliquot of 1.08 M vinylmagnesium bromide was added over 30 min, and the mixture was again stirred at −78 °C for 2 h. The process was repeated an additional time before the reaction mixture was quenched with saturated ammonium chloride solution and poured into ether (100 mL). The separated organic phase was washed with brine (3 × 50 mL), dried, and concentrated. The residual yellow oil was purified by MPLC (silica gel, elution with 3% ethyl acetate in petroleum ether) to give 1.65 g (70%) of **7** and 350 mg (18%) of recovered **6**.

For **7**: colorless oil; IR (neat, cm^{-1}) 3470, 3070, 2945, 2930, 2870, 1650, 1475, 1450, 1410, 1385, 1365; ^1H NMR (300 MHz, C_6D_6) δ 6.12 (dd, J = 17.7, 11.0 Hz, 1 H), 5.81 (dd, J = 17.3, 10.7 Hz, 1 H), 5.22 (dd, J = 11.0, 2.2 Hz, 1 H), 5.01 (d of t, J = 17.7, 2.2 Hz, 2 H), 4.88 (dd, J = 10.7, 1.2 Hz, 1 H), 2.05–2.00 (m, 1 H), 1.71–1.55 (m, 4 H), 1.37 (s, 3 H), 1.36–1.17 (m, 2 H), 0.95–0.89 (m, 1 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 143.64, 136.26, 117.16, 112.17, 82.39, 59.16, 50.44, 46.56, 44.31, 27.00, 26.66, 21.95, 21.28; MS m/z (M^+) calcd 192.1514, obsd 192.1573; $[\alpha]^{25}_D$ −93.4° (c 1.0, CH_3OH). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.35; H, 10.69.

Oxyanionic Rearrangement of 7. Potassium hydride (25% mineral oil suspension, 14.8 mmol) was washed with petroleum ether (3 × 2 mL) and suspended in dry tetrahydrofuran (5 mL). The magnetically stirred suspension was treated with a 10 mol % solution of iodine in tetrahydrofuran until the brown-orange color persisted for 5 min. Next, 3.92 g (14.8 mmol) of 18-crown-6 was added followed by 567 mg (2.97 mmol) of **7** dissolved in 2 mL of the same solvent. This mixture was stirred at room temperature for 15 min, cooled to −78 °C, and quenched with absolute ethanol (1 mL) and saturated ammonium chloride solution (15 mL). The product was extracted into ether (2 × 15 mL), and the combined organic layers were washed with brine, dried, and concentrated. Purification of the residue by MPLC on silica gel (elution with 5% ethyl acetate in petroleum ether) gave 490 mg (86%) of **8** as a clear, colorless oil: IR (neat, cm^{-1}) 3030, 3020, 2940, 2820, 1680, 1470, 1435, 1420, 1385; ^1H NMR (300 MHz, $CDCl_3$) δ 4.91–4.87 (m, 1 H), 2.62–2.54 (m, 2 H), 2.35–1.93 (series of m, 8 H), 1.89–1.74 (m, 2 H), 1.69–1.60 (m, 1 H), 1.11 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.72, 146.77, 122.45, 51.73, 47.74, 45.47, 38.48, 27.49, 27.16, 26.37, 25.61, 24.01, 19.88; MS m/z (M^+) calcd 192.1514, obsd 192.1507. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: c, 81.17; H, 10.51.

Epoxidation of 8. To a cold (0 °C), magnetically stirred solution of **8** (220 mg, 1.1 mmol) in dichloromethane (10 mL) containing Na_2HPO_4 (243 mg, 1.6 equiv) and NaH_2PO_4 (243 mg, 1.6 equiv) was added *m*-chloroperbenzoic acid (217 mg, 1.1 equiv) in portions during 10 min. The reaction mixture was stirred at room temperature for 2 h, and the organic layer was washed in turn with saturated sodium thiosulfate (25 mL), saturated sodium bicarbonate (25 mL), and saturated sodium chloride solutions (15 mL) before drying and solvent evaporation. Chromatographic purification of the residue on silica gel (elution with 20% ethyl acetate in petroleum ether) furnished pure **9** (230 mg, 97%) as colorless needles: mp 69–70 °C; IR (KBr, cm^{-1}) 3000–2830, 1695, 1485, 1365, 1235, 1040, 895, 845; ^1H NMR (300 MHz, $CDCl_3$) δ 2.75–1.75 (series of m, 11 H), 1.30–1.10 (m, 3 H), 1.08 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.86, 70.39, 60.54, 51.01, 45.35, 41.82, 38.65, 26.31, 25.43, 24.85, 23.79, 20.98, 17.19; MS m/z (M^+) calcd 208.1463, obsd 208.1493; $[\alpha]^{20}_D$ −57° (c 0.1, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.68. Found: C, 75.54; H, 10.26.

(−)-(1*S*)-1-Vinyl-2-(1-cyclohexenyl)-7,7-dimethyl-*exo*-norbornan-2-ol (10). A solution of *n*-butyllithium in hexanes (250 mL of 1.6 M, 400 mmol) was cooled to −78 °C, diluted with dry *N,N,N′,N′*-tetramethylethylenediamine (200 mL), stirred for 5 min, and treated with cyclohexanone tosylhydrazone (26.72 g, 100 mmol) in one portion. The red-orange solution was stirred at −78 °C for 2 h and at room temperature for 3 h, at which time nitrogen evolution had ceased, and the reaction mixture had taken on a brown-black hue. The solution was returned to −78 °C and 1,2-dibromotetrafluoroethane (104 g, 400 mmol) was added dropwise during 10 min. The mixture was stirred at −78 °C for 1 h, warmed to −20 °C, and treated with 100 mL of saturated ammonium chloride solution. The separated aqueous phase was extracted with petroleum ether (3 × 100 mL), and the combined organic layers were washed with 1 M hydrochloric acid (10 × 200 mL) and brine (2 × 200 mL) prior to drying and solvent evaporation. The residue was subjected to chromatography on basic alumina (elution with petroleum ether) to give 1-bromocyclohexene as a colorless oil (8.2 g, 51%): ^1H NMR (80 MHz, C_6D_6) δ 6.08–5.98 (m, 1 H), 2.43–2.29 (m, 2 H), 2.19–2.03 (m, 1 H), 1.87–1.63 (m, 3 H), 1.49–1.25 (m, 1 H), 0.88–0.82 (m, 1 H).

Cerium trichloride heptahydrate (7.82 g, 21 mmol) was dried by heating the solid at 140 °C and 0.3 Torr for 3 h. The evacuated flask was filled with argon, and 30 mL of dry tetrahydrofuran was added to form a slurry. In a separate flask, a cold (−78 °C) solution of 1-bromocyclohexene (3.22 g, 20 mmol) in dry tetrahydrofuran was treated with *tert*-butyllithium (25 mL of 1.6 M in hexanes, 40 mmol) and transferred via cannula to the cold (−78 °C) cerium trichloride slurry. Following two 15-min stirring periods at −78 °C and −30 °C, **6** (1.50 g, 9.15 mmol) was added, and the reaction was allowed to proceed for 12 h (no **6** remained at this point). Saturated ammonium chloride solution (30 mL) was introduced, and the usual workup followed. MPLC purification (silica gel, elution with 2% ethyl acetate in petroleum ether) gave **10** as a white solid, mp 36–37 °C (1.72 g, 76%): IR (neat, cm^{-1}) 3460, 3065, 3040, 2920, 2830, 1625, 1470, 1450, 1435, 1415; ^1H NMR (300 MHz, C_6D_6) δ 6.44 (dd, J = 17.8, 11.1 Hz, 1 H), 5.68–5.65 (m, 1 H), 5.18 (dd, J = 11.2, 2.2 Hz, 1 H), 5.02 (dd, J = 17.8, 2.2 Hz, 1 H), 2.13–2.01 (m, 4 H), 1.96–1.86 (m, 2 H), 1.78–1.69 (m, 1 H), 1.66–1.49 (m, 3 H), 1.42–1.39 (m, 2 H), 1.38 (s, 3 H), 1.35–1.16 (m, 2 H),

(26) Shirahama, H.; Hayano, K.; Kanemoto, Y.; Misumi, S.; Ohtsuka, T.; Hashiba, N.; Furusaki, N.; Murata, S.; Noyori, R.; Matsumoto, T. *Tetrahedron Lett.* **1980**, *21*, 4835.

(27) Sheldrick, G. M. SHELX76, a system of computer programs for X-ray structure determination as locally modified, University of Cambridge, England, 1976.

(28) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 72, 99, 149. (Present distributor: D. Reidel, Dordrect.)

(29) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. M. MULTAN 80, A system of computer programs for the automatic solution of crystal structures from X-ray diffraction data, Universities of York, England, and Louvain, Belguim.

0.99–0.88 (m, 2 H), 0.82 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 141.64, 137.62, 120.53, 113.44, 84.12, 57.90, 50.53, 45.27, 41.97, 25.67, 24.80, 24.74, 22.59, 21.61, 21.17, 20.41 (1C not observed); MS m/z (M^+) calcd 246.1983, obsd 246.1990; $[\alpha]^{25}_D$ −46.6° (c 1.0, CH_3OH). Anal. Calcd for $C_{17}H_{26}O$: C, 82.86; H, 10.64. Found: C, 82.92; H, 10.40.

Oxy-Cope Rearrangement of 10. Potassium hydride in oil (0.9 mmol) was washed with petroleum ether, suspended in tetrahydrofuran, and titrated with iodine as described above. Subsequently, 18-crown-6 (242 mg, 0.91 mmol) and alcohol **10** (150 mg, 0.61 mmol) were introduced, and stirring was continued at room temperature until no **10** remained (~10 min). The usual workup and MPLC purification provided **11** as a clear, colorless oil (118 mg, 79%); IR (neat, cm^{-1}) 2975, 2960–2880, 2840, 1685, 1460, 1445, 1385; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17–5.12 (m, 1 H), 2.93–2.89 (m, 1 H), 2.58 (dd, J = 11.7, 1.0 Hz, 1 H), 2.24–2.12 (m, 2 H), 2.04–1.85 (m, 6 H), 1.81–1.51 (m, 6 H), 1.45–1.29 (m, 3 H), 1.26 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.35, 146.34, 122.20, 51.89, 49.49, 45.38, 43.29, 41.88, 32.19, 30.95, 27.40, 26.47, 25.16, 24.25, 22.42, 22.18, 20.90; MS m/z (M^+) calcd 246.1984, obsd 246.1980; $[\alpha]^{25}_D$ −58.3° (c 0.19, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O$: C, 82.26; H, 10.64. Found: C, 82.53; H, 10.60.

Epoxidation of 11. Exposure of **11** (150 mg, 0.60 mmol) to m-chloroperbenzoic acid (1.1 equiv) at 0 °C in dichloromethane and phosphate buffer as for **8** followed by chromatographic purification gave **12** in 90% yield as white needles, mp 75–77 °C: IR (KBr, cm^{-1}) 3020–2800, 1695, 1450, 1095; ^{1}H NMR (300 MHz, C_6D_6) δ 2.80–2.70 (m, 2 H), 2.33 (d, J = 11.2 Hz, 1 H), 2.23 (t, J = 9.7 Hz, 1 H), 2.15–2.00 (m, 1 H), 1.90–0.95 (series of m, 15 H), 1.02 (s, 3 H), 0.71 (s, 3 H); ^{13}C NMR (5 MHz, C_6D_6) ppm 212.15, 71.10, 60.20, 49.56, 47.73, 43.23, 41.27, 38.01, 30.16, 30.00, 27.47, 26.50, 25.25, 24.18, 22.63, 20.69, 20.13; MS m/z (M^+) calcd 262.1933, obsd 262.1948; $[\alpha]^{23}_d$ +102° (c 0.23, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.64; H, 10.00.

Reduction of 11. Diisobutylaluminum hydride (2.8 mL of 1.0 M in hexanes, 2.3 equiv) was added to a solution of **11** (300 mg, 1.2 mmol) in dry tetrahydrofuran (10 mL) under argon. After overnight stirring at room temperature, the reaction mixture was quenched with methanol, acidified with 2 N hydrochloric acid, and extracted with ether (3 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried, and evaporated. The residue was purified by column chromatography to give 275 mg (91%) of **13** as a white solid, mp 154–155 °C: IR ($CHCl_3$, cm^{-1}) 3610, 3640–3050, 3050–2800, 1450, 1025; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (dd, J = 12.5, 2.4 Hz, 1 H), 3.38 (d, J = 7.5 Hz, 1 H), 2.55–2.45 (m, 1 H), 2.25–1.10 (series of m, 19 H), 1.10 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.29, 119.16, 67.91, 48.24, 46.06, 45.48, 41.73, 40.48, 32.16, 30.56, 27.21, 25.99 (2C), 25.82, 23.92, 23.53, 21.58; MS m/z (M^+) calcd 248.2140, obsd 248.2125; $[\alpha]^{23}_D$ −192° (c 0.36, $CHCl_3$). Anal. Calcd for $C_{17}H_{28}O$: C, 82.19; H, 11.37. Found: C, 82.10; H, 11.24.

Tandem Anionic Rearrangement–Methylation of 15. The preparation of **15** and **16** has been described elsewhere.[6g] A solution of **15** (5.0 g, 14.9 mmol) in dry tetrahydrofuran (50 mL) was added to potassium hexamethyldisilazide (150 mL of 0.5 M in toluene, 5 equiv) diluted with tetrahydrofuran (100 mL) at room temperature under argon. After 15 min, freshly distilled methyl iodide (10 mL, 10 equiv) was introduced, and stirring was continued for 1 h before quenching was accomplished with saturated ammonium chloride solution (100 mL). After the usual workup, the crude product was purified by column chromatography. Following elution of a byproduct (0.9 g), there was obtained 2.9 g (55%) of **17** as a white solid, mp 47–48.5 °C: IR ($CHCl_3$, cm^{-1}) 3100–2800, 1655, 1470, 1445, 1395, 1160, 1060, 1035; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (dd, J = 7.2, 4.7 Hz, 1 H), 3.40–3.10 (m, 4 H), 2.99 (dd, J = 6.8, 5.2 Hz, 1 H), 2.80–1.35 (series of m, 14 H), 1.38 (s, 3 H), 1.25 (s, 3 H), 1.10 (s, 3 H), 1.00–0.80 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 218.79, 144.63, 125.33, 72.88, 56.19, 52.52, 48.50, 46.80, 45.76, 39.80, 38.81, 35.85, 32.66, 28.79, 28.29, 26.88, 25.66, 23.86, 20.96, 18.71; MS m/z (M^+) calcd 350.1738, obsd 350.1787; $[\alpha]^{23}_D$ −146° (c 0.46, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}OS_2$: C, 68.54; H, 8.63. Found: C, 68.75; H, 8.84.

Conformational Isomerization of 17. A solution of **17** (100 mg, 0.29 mmol) in dry tetrahydrofuran (15 mL) was refluxed under an argon atmosphere for 5 days. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography to give **18** (52 mg, 52%) as a white powder, mp 145.5–146.5 °C: IR ($CHCl_3$, cm^{-1}) 3070–2800, 1675, 1470, 1390, 1345, 1275, 1260–1200, 1170, 1050; ^{1}H NMR (300 MHz, C_6D_6) δ 5.21 (m, 1 H), 3.00–2.70 (m, 6 H), 2.70–2.35 (m, 4 H), 2.20–1.70 (m, 6 H), 1.58 (t, J = 5.4 Hz, 1 H), 1.50–1.20 (m, 3 H), 1.10 (s, 3 H), 1.07 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.49, 148.72, 120.90, 74.61, 60.53, 51.30, 50.94, 45.53, 43.28, 40.82, 38.73, 36.78, 35.47, 30.84, 30.00, 25.56, 25.35, 22.21, 21.39, 19.83; MS m/z (M^+) calcd 350.1738, obsd 350.1736, $[\alpha]^{23}_D$ −87° (c 0.2, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}OS_2$: C, 68.54; H, 8.63. Found: C, 68.42; H, 8.67.

Acknowledgment. We thank the National Institutes of Health for financial support (Grant CA-12115). G.D.M. is the recipient of a Department of Education-sponsored National Need Fellowship.

Supplementary Material Available: X-ray experimental data and tables of crystal data, bond distances and angles, final fractional coordinates, thermal parameters, and least-squares planes for **12** (9 pages); table of observed and calculated structure factors for **12** (2 pages). Ordering information is given on any current masthead page.