22.3, 14.0; MS (CI, CH_4 and NH_4^+) 319 (MNH_4^+, 82), 284 (73), 192 (100), 166 (96), 136 (87); exact mass calcd for $C_{14}H_{23}NO_6H^+$ 302.1604, obsd 302.1605.

8-Cyano-5-(nitromethylene)octanenitrile (18b): IR (neat) 3098 (w), 2933 (s), 2850 (m), 1622 (m), 1508 (s) cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 1 H), 3.47 (m, 1 H), 2.21 (m, 1 H), 1.68 (m, 10 H), 1.24 (m, 10 H); ^{13}C-NMR ($CDCl_3$, 90 MHz) δ 164.4, 135.3, 40.1, 39.8, 34.2, 29.7, 26.6, 25.9, 25.8; MS (CI, CH_4, and NH_4^+) 255 (MNH_4^+, 39), 238 (100), 222 (20), 208 (20), 156 (31); exact mass calcd for $C_{14}H_{23}NO_2H^+$ 238.1807, obsd 238.1817.

2,2-Dicyclohexylnitroethylene (18c): solid (mp 44–46 °C); IR (KBr) 3099 (w), 2933, (s), 2850 (m), 1622 (m), 1508 (s) cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 1 H), 3.48 (m, 1 H), 2.21 (m, 1 H), 1.72 (m, 10 H), 1.25 (m, 10 H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 164.4, 135.3, 40.1, 39.8, 34.2, 29.7, 26.6, 25.9, 25.8; MS (EI, 70 eV) 238 (MH^+, 1), 138 (84), 67 (59), 55 (100), 41 (89); exact mass calcd for $C_{14}H_{23}NO_2H^+$ 238.1807, obsd 238.1817.

Nitromethylenecyclopentane (20): purified by vacuum distillation 45 °C (0.05 mmHg); ^1H-NMR ($CDCl_3$, 300 MHz) δ 7.09 (s, 1 H), 2.94 (t, 2 H, $J = 7.5$ Hz), 2.50 (t, 2 H, $J = 7.5$ Hz), 1.76 (m, 4 H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 163.4, 132.1, 33.9, 33.2, 25.9, 25.5. See ref 50.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the Americal Chemical Society, and the University of Michigan (Office of the Vice President for Research) for support of this work.

Supplementary Material Available: ^{13}C NMR spectra of **3e–f, 3h–l, 7d–g, 9a–d, 10c–f, 10h–i, 10k–l, 18a–c** (26 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(50) (a) Descotes, G.; Bahurel, Y.; Bourillot, M.; Pingeon, G.; Rostaing, R. *Bull. Soc. Chim. Fr.* 1970, 282. (b) Sakakibara, T.; Manandhar, M.; Ohkika, N.; Ishido, Y. *Bull. Chem. Soc. Jpn.* 1987, *60*, 3425.

Asymmetric Functionalization of Conformationally Distinctive C_s-Symmetric Cis[*n*.3.1] Bicyclic Ketones. Definition of the Absolute Course of Enantio- and Diastereodifferentiation

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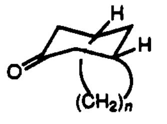
Received May 6, 1992

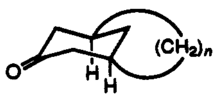
The four C_s-symmetric cis[*n*.3.1] bicyclic ketones where n = 3, 5, 7, and 9 were acetalized with (*R,R*)-2,4-pentanediol, and the resulting derivatives were cleaved with triisobutylaluminum (TRIBAL). The first three examples, all of which have their polymethylene chain rigidly fixed in a diaxial orientation, undergo ring opening with very high diastereoselectivity to give **5**. In the fourth case (n = 9), the chain is sufficiently long to be attached in a diequatorial manner. The response of **4d** to TRIBAL is to deliver a 1:1 mixture of **11** and **12**. The stereochemical course of epoxidation and cyclopropanation reactions of these enol ethers has been assessed. Where **5** and **11** are concerned, these functionalization reactions are 100% π-facially selective. Only **12** is the exception. Also examined in this study was the enantioselective deprotonation of the same ketones with the enantiomerically pure lithium amide base **27**. The resulting enolates were trapped as their silyl enol ethers and transformed directly into optically active α-hydroxy ketones and α,β-unsaturated enones by epoxidation and selenenylation–oxidative elimination, respectively. The sense of the observed enantioselectivity was the same irrespective of the diaxial or diequatorial disposition of the $(CH_2)_n$ loop. However, the asymmetry induced by this means was consistently opposite to that realized by TRIBAL-promoted acetal cleavage. When these complementary processes are compared at the α-hydroxy ketone stage, the acetal cleavage–epoxidation option was invariably 100% enantioselective; greater variability in optical purity was seen via the deprotonation–silylation–epoxidation option. The possible mechanistic basis of these observations is explored.

The conversion of cyclic, prochiral ketones into optically active enolates via their direct deprotonation with homochiral lithium amide bases has met with considerable success.[2] The regiocontrolled triisobutylaluminum (TRIBAL)-induced isomerization of chiral acetals of meso ketones to optically active enol ethers has been accorded similar interest.[3] Notwithstanding, little mechanistic insight has been gained into the factors that control these asymmetric transformations. In recent work,[4] we provided crystallographic substantiation of the conformational crossover that materializes when the polymethylene chain of cis-3,5-annulated cyclohexanones is increased from n = 3, 5, or 7 to n = 9. A loop constituted of <9 methylene groups was shown to be too short to be accommodated diequatorially as in 2. The alternative diaxial orientation depicted in 1 need therefore be adopted. To what extent might the diaxial/diequatorial dichotomy of these unique, conformationally-locked [*n*.3.1] bicyclic ketones and their corresponding chiral acetals impact on the outcome of those enantio- and diastereodifferentiating processes alluded to above? Might the topologically distinctive features of 1, 2, and their derivatives underscore the combinatorial diversity of associated asymmetric reactions and



1

(n = 3, 5, 7)



2

(n = 9)

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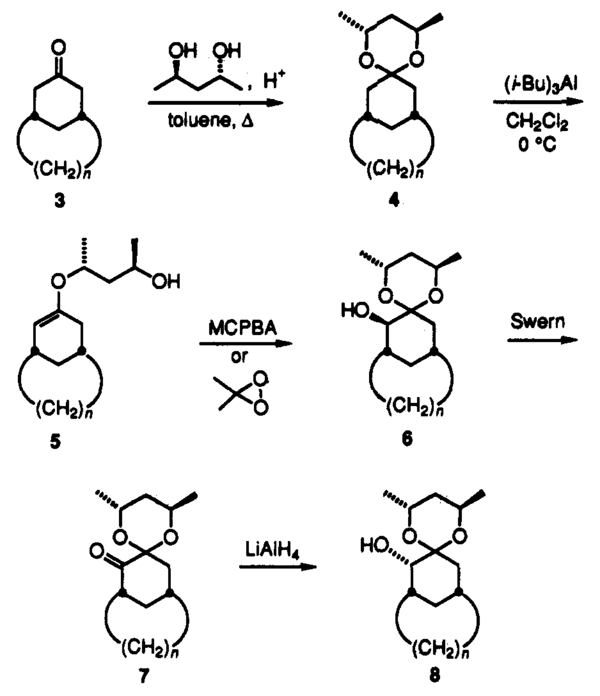
[1] National Institutes of Health Postdoctoral Fellow, 1990–1992.

[2] For a comprehensive review, consult: Cox, P. S.; Simpkins, N. S. *Tetrahedron Asymmetry* 1991, 2, 1.

[3] For a survey of this process, see: Alexakis, A.; Mangeney, P. *Tetrahedron Asymmetry* 1990, *1*, 477.

[4] Paquette, L. A.; Underiner, T. L.; Gallucci, J. C. *J. Org. Chem.* 1992, *57*, 86.

Scheme I



a, $n = 3$; **b**, $n = 5$; **c**, $n = 7$; **d**, $n = 9$

accommodate the development of useful and reliable mechanistic models?

In this paper, the following fundamental reactions have been scrutinized: (a) the diastereoselective TRIBAL-promoted isomerization of chiral acetals of general formula **4**;[5] the π-facial selectivity associated with the epoxidation[6] and cyclopropanation[5a,7] of **5**, **11**, and **12**; (c) the enantioselective enolization of ketones **3** with one of the better Koga bases;[8] and (d) the degree of stereocontrol associated with epoxidation of the resulting silyl enol ethers.[6]

Results

Diastereoselective Isomerization of Chiral Acetals. The conversion of **3** to **4** with (R,R)-2,4-pentanediol[9] was accomplished conventionally[5a] except in refluxing toluene instead of benzene in order to shorten reaction times (Scheme I). Notwithstanding these elevated temperatures, ketones **3a–c** had to be heated for at least 15 h in order to achieve reasonable levels of acetalization. In contrast, **3d** was efficiently transformed into **4d** within 2 h under these conditions (Scheme II). Evidently, the diaxial bridge arrangement present in **3a–c** retards initial hemiacetal formation and/or subsequent closure to the m-dioxane.[10]

Exposure of **4a–c** to TRIBAL in CH_2Cl_2 at 0 °C resulted in highly diastereoselective conversion to **5a–c**, respectively. Although these enol ethers are stable to chromatography on silica gel, they revert to mixtures of **3** and **4** on standing in the atmosphere. As a consequence of this lability, these intermediates were generally not isolated, but subjected directly to oxidation.

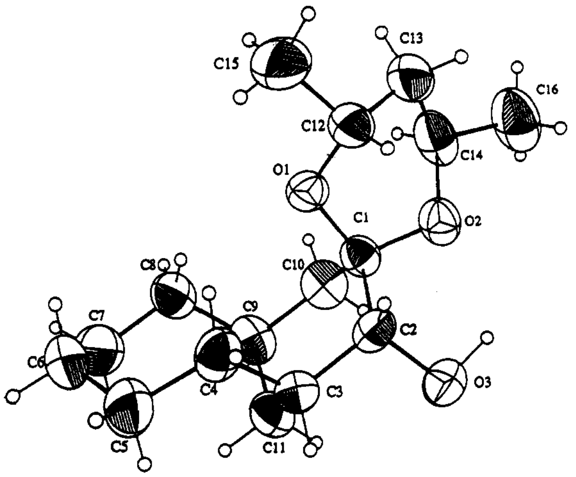
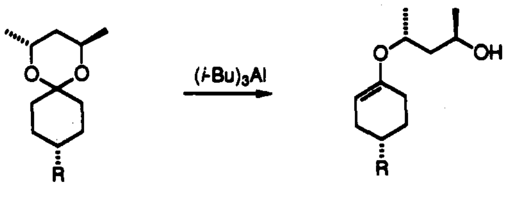


Figure 1. Computer-generated perspective drawing of the final X-ray model of **6b**.

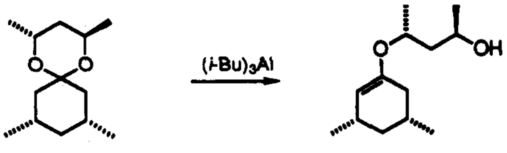
Treatment of **5a–c** either with buffered ($NaHCO_3$) m-chloroperbenzoic acid[6a] or with dimethyldioxirane[6c] led to rapid reaction at 0 °C. The epoxides could not be isolated due to rapid intramolecular cyclization involving the neighboring hydroxyl. In line with the S_N2 nature of the oxirane ring opening, reconstitution of the acetal functionality is necessarily stereospecific. Consequently, the β configuration of the hydroxyl group in **6** defines the course of epoxidation. The structural features of both **5** and **6**, which are founded on an X-ray crystallographic study of **6b** (Figure 1), reflect the excellent control of asymmetry that operates during acetal cleavage in **4** and electrophilic attack on **5**.

Swern oxidation of **6a–c** has afforded the α-keto acetals **7**, which when reduced with lithium aluminum hydride gave **8a–c** exclusively. As a consequence, hydride delivery occurs in an axial fashion trans to the pentamethylene bridge.[4] As observed in related systems,[4,11] these equatorial alcohols are more polar than their axial epimers **6**. No spectroscopic or chromatographic evidence was obtained that would indicate that **8** had been produced during the epoxidation of **5**.

The preceding experiments reveal that enol ether formation from **4a–c** occurs in the same absolute sense as that reported for the ring openings of **9** and **10** with TRIBAL.[5c]



9



10

However, the intrinsically different response of **4d** became fully apparent when a 1:1 mixture of **11** and **12** (^1H NMR

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(5) (a) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955. (b) Gassman, P. G.; Burns, S. J. *J. Org. Chem.* **1988**, *53*, 5574. (c) Naruse, Y.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 6021. (d) Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 1363.

(6) (a) Rubottom, G. M.; Vasquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (b) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *43*, 5703. (c) Adam, W.; Prechtl, F. *Chem. Ber.* **1991**, *124*, 2369.

(7) Sugimura, T.; Futagawa, T.; Tai, A. *Chem. Lett.* **1990**, 2291.

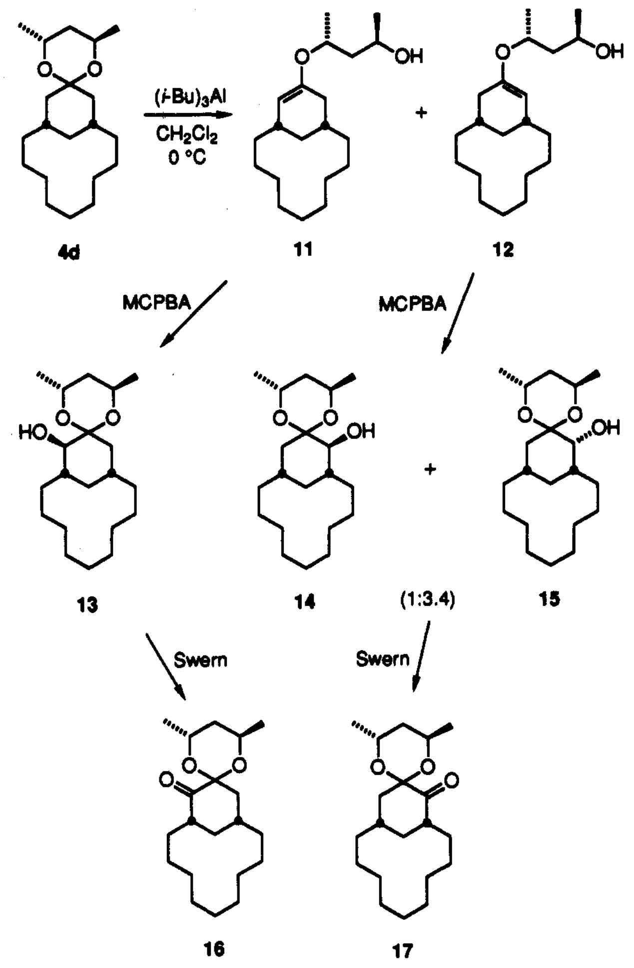
(8) (a) Kim, H.; Kawasaki, H.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 6537. (b) Izawa, H.; Shirai, R.; Kawasaki, H.; Kim, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7221. (c) Kim, H.; Shirai, R.; Kawasaki, H.; Nakajima, M.; Koga, K. *Heterocycles* **1990**, *30*, 307. (d) Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657. (e) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Chem. Soc.* **1992**, *114*, 761.

(9) Ho, K.; Harada, T.; Tai, A.; Izumi, Y. *Chem. Lett.* **1979**, 1049.

(10) Reddy, C. P.; Rao, R. B. *Tetrahedron* **1982**, *38*, 1825.

(11) (a) Rubottom, G. M.; Gruber, J. M.; Juve, H. D., Jr.; Charleson, D. A. *Org. Synth.* **1986**, *64*, 118. (b) Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 59.

Scheme II



analysis) was produced under entirely comparable conditions. Direct oxidation of these enol ethers with *m*-CPBA gave rise to the three hydroxy acetals **13–15**. The nonpolar axial alcohol **15** was readily separated from the polar equatorial stereoisomers **13** and **14**. The overall $\alpha:\beta$ ratio was determined to be 1:1.7. The distribution of the inseparable β alcohols **13** and **14** was 5.0:1.

Characterization of the individual constituents of this mixture was achieved as follows. Swern oxidation of **15** gave **17** whose absolute stereochemistry was made known by X-ray diffraction methods (Figure 2). Comparable oxidation of the **13**/**14** mixture produced two ketones (ratio 5.0:1) that proved separable by column chromatography. Since the minor component proved identical to **17**, the major is required to be **16**.

Thus, we see that the epoxidation of **11** occurs with high π-facial selectivity to afford solely **13**. In contrast, **12** experiences only 3-fold faster electrophilic attack on its α-face relative to the β option. This departure from the superb control exhibited by **5** and **11** has its origin in the differing stereochemical relationship between the enol ether double bond in **12** and the pendant hydroxyl-terminated ether chain. Exclusive β-face attack returned when dimethyldioxirane was used as the oxidant for **11** and **12**. Under these conditions, however, partial hydrolysis of the acetal occurs and the resulting α-hydroxy ketone proved difficult to remove chromatographically.

The reactivity profiles just discussed would be clarified to a greater extent if **11** and **12** were available in isomerically pure condition. Since their sensitivity precluded chromatographic separation, the more robust acetates **18** and **19** were prepared and easily fractionated (Scheme III).

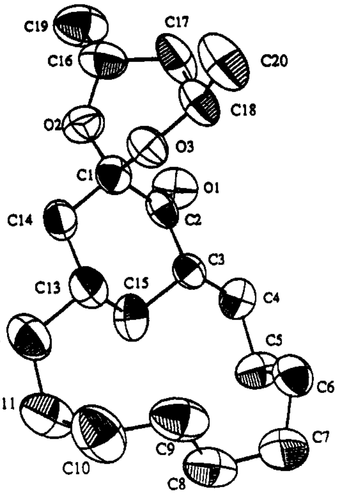


Figure 2. Computer-generated perspective drawing of the final X-ray model of **17**.

Scheme III

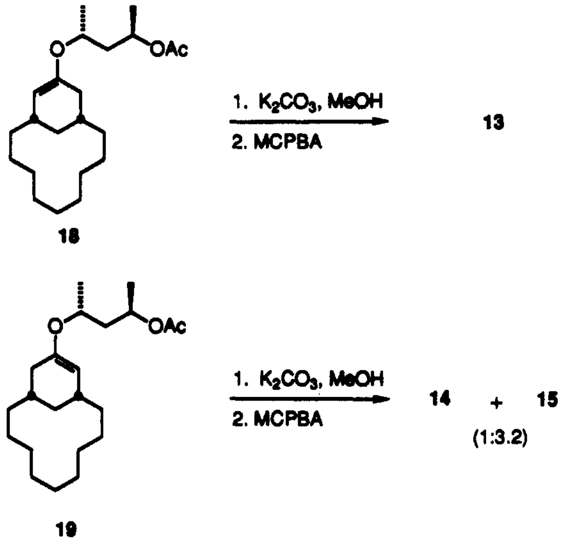
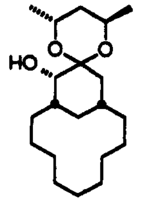


Table I. Product Distributions from Hydride Reductions of Ketones 16 and 17

ketone	hydride reducing agent	alcohol ratios
16	LiAlH$_4$	77% of **20**, 23% of **13**
16	L-Selectride	>90% of **20**, <10% of **13**
17	LiAlH$_4$	23% of **15**, 77% of **14**
17	L-Selectride	33% of **15**, 67% of **14**

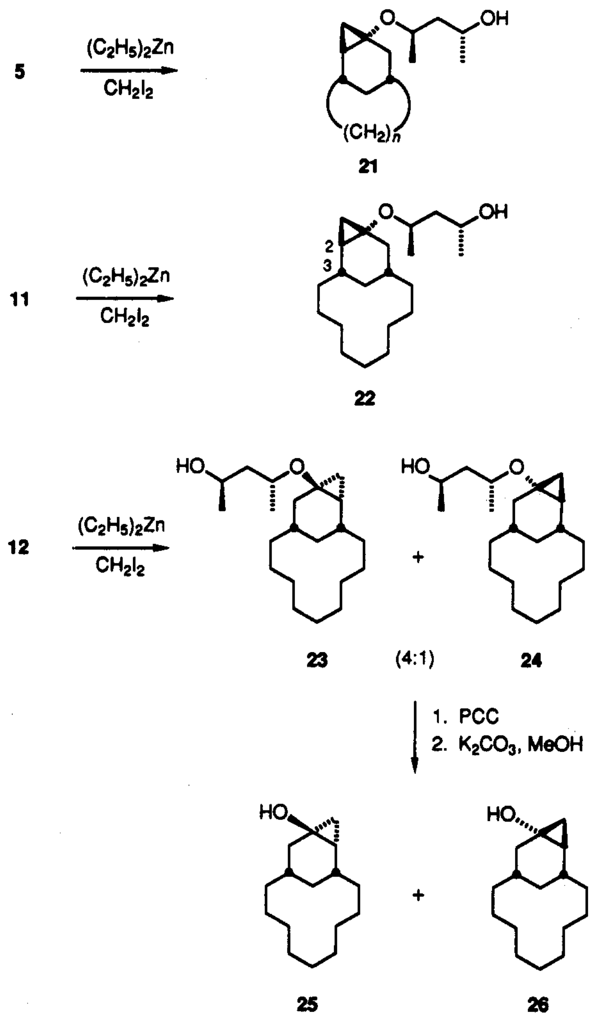
These stereoisomers were individually saponified and epoxidized. Since the more polar acetate was transformed exclusively into **13**, it need be derived from **11**. Under similar conditions, the less polar acetate (necessarily **19**) afforded **14** and **15** in a 1:3.2 ratio.

Independent hydride reduction of **16** and **17** made it possible to access all four hydroxy acetals. A compilation of the results is provided in Table I. While isomer **16** gave rise to a preponderance of α-alcohol **20** as a consequence



20

Scheme IV

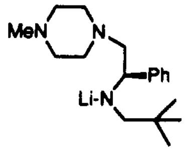


of kinetically preferred equatorial attack, 17 afforded predominantly the β-alcohol resulting from axial hydride delivery. This changeover is believed to be conformationally driven (see Discussion).

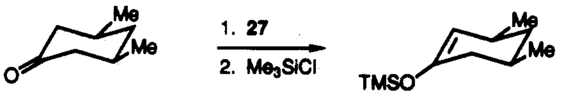
Cyclopropanation of the enol ethers with $(C_2H_5)_2Zn$ and CH_2I_2[5a] was also investigated. In the axially bridged systems **5a–c**, methylene insertion occurred with high π-facial selectivity to deliver uniquely the diastereomerically pure products **21a–c** in good yield (Scheme IV). It has been tacitly assumed that cyclopropanation proceeds stereoselectively in the same sense as epoxidation, i.e., from that direction anti to the polymethylene chain.

Comparable treatment of **11** led as well to a single cyclopropanated ether, viz. **22**, while **12** was converted into an inseparable mixture of diastereomers **23** and **24** (ratio 4:1). The product ratio was determined by oxidation of the mixture with pyridinium chlorochromate followed by β-elimination of the cyclopropanols with K_2CO_3 in methanol.[5a] The cyclopropyl protons in **25** and **26** are very well resolved and easily integrated. In addition, the quaternary carbinol carbon resident in each isomer is distinctively shifted in the ^{13}C NMR spectrum and is likewise amenable to quantification. The β stereochemistry of the cyclopropyl ring in **22** is based on the large axial–axial coupling between C_2–H and C_3–H (13.1 Hz). The assignments to **23** and **24** follow from the ensuing series of experiments. Simmons–Smith cyclopropanation of a 1:1 mixture of **11** and **12** with subsequent PCC oxidation and β-elimination afforded **25** and **26** in a 1:1.5 ratio. Since **25** and **26** are "π-facial isomers" and **11** is necessarily transformed into a cyclopropanol enantiomeric with **26**, it follows that the major diastereomer produced from **12** must be a precursor to **25**, namely **23**. Consequently, the cyclopropanation stereoselectivity being followed by **12** compares closely in direction and magnitude to that operative during epoxidation.

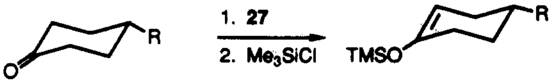
Enantioselective Enolization of the Ketones. Earlier work in the Koga laboratory has shown that cis-3,5-disubstituted (**28**) and 4-substituted cyclohexanones (**29**) are asymmetrically deprotonated by the chiral lithium amide base **27** with very respectable levels of kinetic resolution.[8,12] Of significance to the present study is the finding that the sense of asymmetric induction is the same in the two systems. Further, the efficiency of the enantioselective deprotonation declines as the 4-substituent in **29** is made smaller and the ring simultaneously becomes more conformationally flexible.



27



28 (90% ee)



29

R = *t*-Bu (84% ee)
= *i*-Pr (66% ee)
= Me (58% ee)

Ketones **3a–d** were transformed into their trimethylsilyl enol ethers by exposure to **27** according to a modification of Koga's original procedure.[8] The differences surface only at that stage where the silyl enol ethers are processed. If the O-silylated product was to be oxidized with dimethyldioxirane, no aqueous workup was mandated.[11] On the other hand, if *m*-CPCA was to serve as oxidant, washing of the reaction mixture with a buffered aqueous solution was highly desirable and even necessary. In this way, one or more substances present in the initial step that otherwise interfere with peracid oxidation (but not with the action of the dioxirane) are effectively removed. In either case, the silyl enol ethers were not characterized, but directly oxidized to α-hydroxy ketones **30** and **31** (Scheme V). To facilitate characterization, all four homologues of **31** were independently prepared by acid-catalyzed hydrolysis of the enantiopure hydroxy acetals **6** and **13** obtained in the manner detailed earlier. Once the rotations of the authentic samples were available, both the absolute sense of deprotonation and level of kinetic resolution were made clearly apparent (Table II).

*In every instance, the asymmetry induced by **27** was opposite that realized by TRIBAL-promoted acetal cleavage.* Excellent enatioselectivity is demonstrated by ketones **3b** and **3c**. The greater enolizability of **3a**[4] relative to **3b–d** may underlie the loss of selectivity in this case. The stereochemical response of **3d**, although modest, is

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(12) (a) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543. (b) Koga, K. In *Organic Synthesis: Modern Trends*: Chizhov, O., Ed.; Blackwell Scientific: Boston, 1987; pp 285–291.

Scheme V

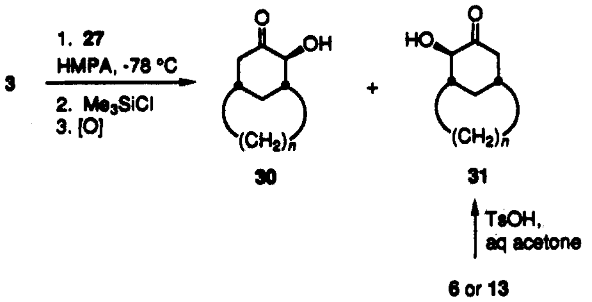
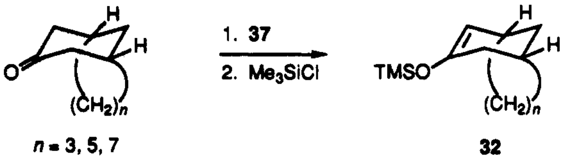


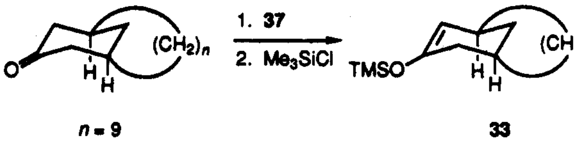
Table II. Results of the Enantioselective Hydroxylation of Ketones 3a–d

ketone	method^a	major product, $[\alpha]_D$ 30	31	% ee^b
3a	A		+5.5°	100
	B	−2.0°		36
3b	A		−32.4°	100
	B	+33.3°		100
3c	A		−27.3°	100
	B	+26.0°		95
3d	A	−43.1°		100
	B		+20.1°	47

^{a}Method A: conversion to acetal 4, TRIBAL-promoted ring cleavage, oxidation with *m*-CPBA, and aqueous acid hydrolysis. Method B: deprotonation with 37, O-trimethylsilylation, and oxidation with *m*-CPBA or dimethyldioxirane. ^{b}Error limits ±5%.

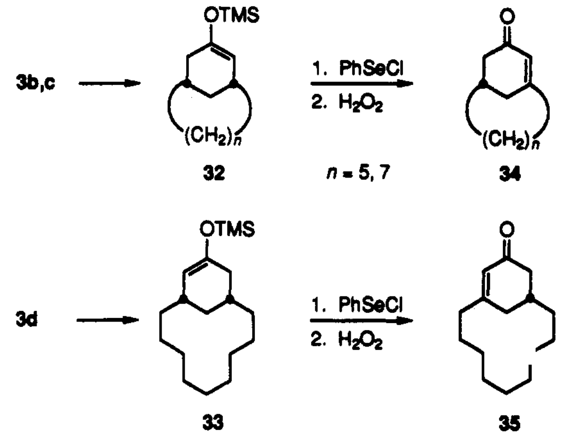
nonetheless greater than that realized by the chiral acetal method. It is instructive to recognize that the kinetic preference exhibited by 3a–d for conversion to 32 and 33 parallels exactly that observed for 28 and 29.





The versatility of these O-silylated enolates for providing desymmetrized, optically active derivatives of 3 is illustrated by their conversion to α,β-unsaturated ketones 34[13] (Scheme VI).[14] Thus, treatment of the unpurified samples of 32 and 33 produced as before with 2,6-di-*tert*-butylpyridine followed by PhSeCl afforded the 2-phenylseleno derivatives.[15] Direct oxidation with hydrogen peroxide furnished 34 and 35. Since asymmetry is induced upon enolate formation, these enones are presumably produced with the same levels of enantiomeric excess as the corresponding α-hydroxy ketones.

Scheme VI



Discussion

The hydride reduction experiments summarized in Table I are considered first. The finding that 16 is transformed predominantly to α-alcohol 20 while 17 reacts to produce mainly β-alcohol 14 reveals to some extent the conformational features adopted by these ketones during reaction. Thus, the observed crossover in stereochemical preference implies that the carbonyl π-faces within the diastereomers are sterically encumbered in opposite directions. Both keto ketals were examined computationally by means of the MODEL KS 2.96 program.[16] Following preliminary energy minimization analysis,[17] the resulting structures were subjected to a multiconformer run that encompassed all three rings. In each case, over 500 conformers were generated and minimized to ensure proper identification of the global energy minimum. Final optimization was accomplished in MMX. For 16, the chair (A) and boat (B) conformers were found to differ energetically by less than 0.6 kcal/mol (Figure 3). In contrast, the boat form of 17 (see C) enjoys an energy advantage over its chair counterpart well in excess of 3 kcal/mol.

Our experimental results conform to a mechanistic model in which the dioxolane ring in both ketones is boat-shaped, presumably because this particular geometry projects both methyl groups is a pseudoequatorial orien-

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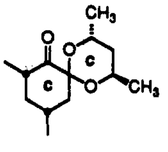
[13] Since racemic enone 34a is recognized to be an unstable compound (House, H. D.; Kleschick, W. A.; Zaiko, E. J. *J. Org. Chem.* **1978**, *43*, 3653), no attempt was made to prepare this substance in optically active condition.

[14] The racemic forms of 34a–d are already known: (a) ref 13. (b) Gioia, B.; Ballabio, M.; Beccalli, E. M.; Cecchi, R.; Marchesini, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 560. (c) Marchesini, A.; Pagnoni, U. M.; Pinetta, A. *Tetrahedron Lett.* **1973**, 4299. (d) Hirano, S.; Hiyama, T.; Fujita, S.; Kawaguti, T.; Hayashi, Y.; Nozaki, H. *Tetrahedron* **1974**, *30*, 2633.

[15] (a) House, H. O.; Sieloff, R. F.; Lee, T. V.; DeTar, M. B. *J. Org. Chem.* **1980**, *45*, 1800. (b) For a more recent asymmetric variant, see: Hiroi, K.; Sato, S. *Synthesis* **1985**, 635.

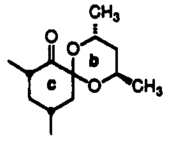
[16] We thank Prof. W. C. Still (Columbia) for making his program available for use and Prof. K. Steliou (Montreal) for providing us with updates of his software package.

[17] In order to ensure that the flexible large rings in these systems are not contributory to inadvertent arrival at false minima, the corresponding structurally simpler non-bridged dimethyl derivatives shown below were also examined to a comparable level of detail. The extent to which the energy trends are parallel in the two series is exceptionally good (b = boat, c = chair).



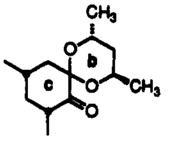
A'

E_S = 1.8 kcal/mol
E_T = 23.1 kcal/mol



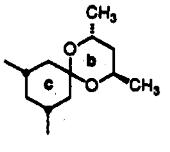
B'

E_S = 3.1 kcal/mol
E_T = 24.5 kcal/mol



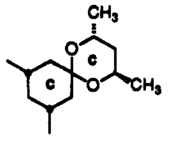
C'

E_S = 3.2 kcal/mol
E_T = 24.5 kcal/mol



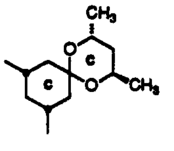
D'

E_S = 5.4 kcal/mol
E_T = 27.3 kcal/mol



E'

E_S = 6.8 kcal/mol
E_T = 28.7 kcal/mol



F'

E_S = 6.8 kcal/mol
E_T = 28.7 kcal/mol

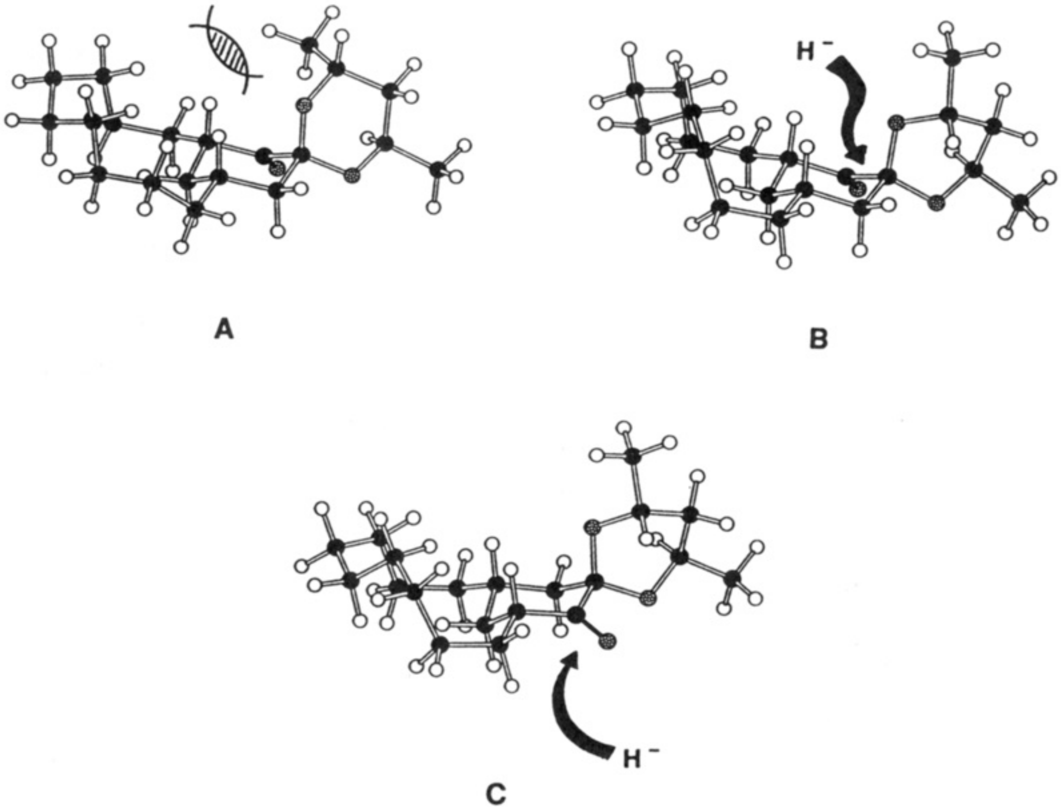


Figure 3. Global minimum energy transformations of c,c-**16**, c,b-**16**, and c,b-**17** on which is superimposed the trajectory of hydride attack (c = chair, b = boat; Chem 3-D output). For **A**: E_S = 17.4 kcal/mol, E_T = 43.7 kcal/mol. For **B**: E_S = 18.0 kcal/mol, E_T = 44.3 kcal/mol. For **C**: E_S = 17.9 kcal/mol, E_T = 44.2 kcal/mol.

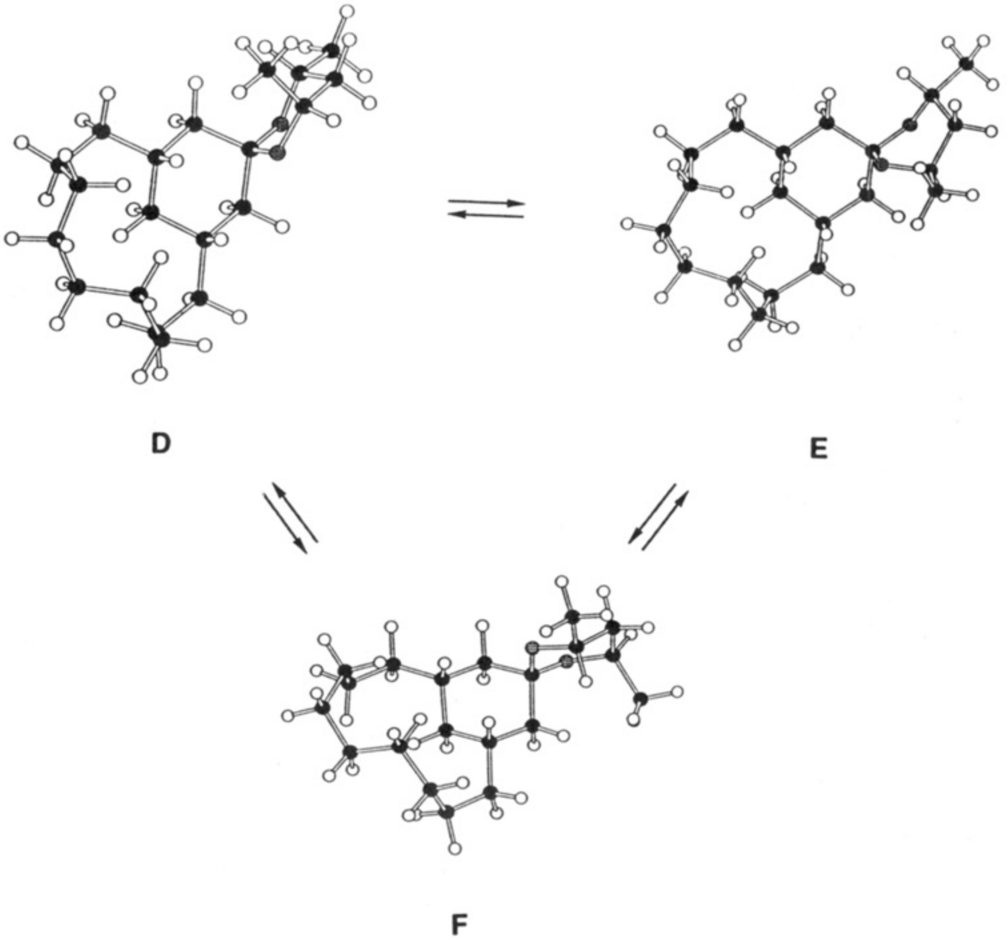
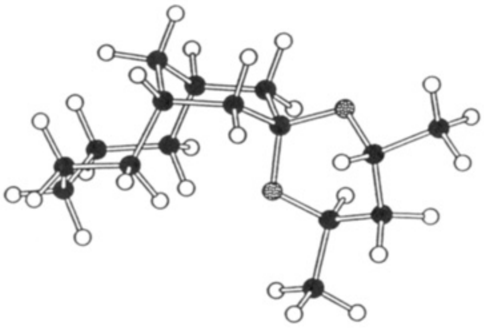


Figure 4. Global minimum energy conformations of c,c-**4d**, c,b-**4d**, and the alternative c,c-**4d** (Chem 3-D output). For **D**: E_S = 21.7 kcal/mol, E_T = 48.5 kcal/mol. For **E**: E_S = 20.3 kcal/mol, E_T = 47.1 kcal/mol. For **F**, E_S = 21.7 kcal/mol, E_T = 48.6 kcal/mol.



G

Figure 5. Global minimum energy conformation of **4b** ($E_S = 23.6$ kcal/mol, $E_T = 47.8$ kcal/mol.

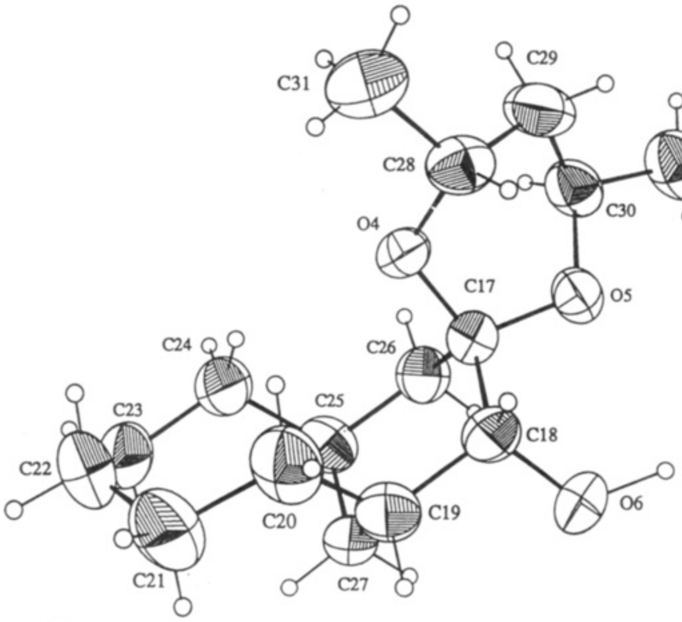


Figure 6.

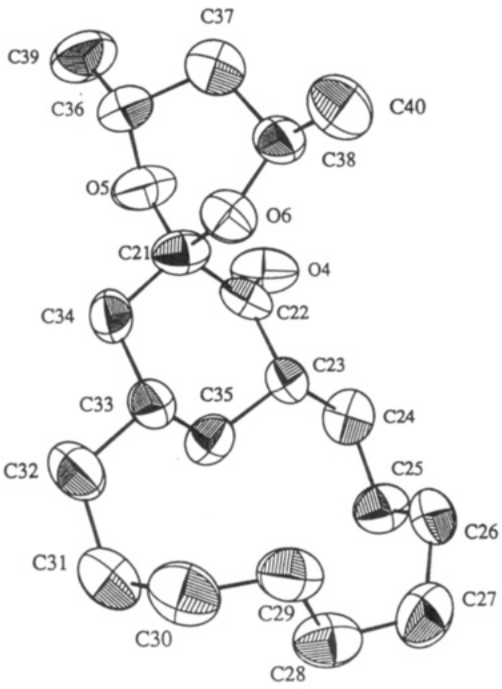


Figure 7.

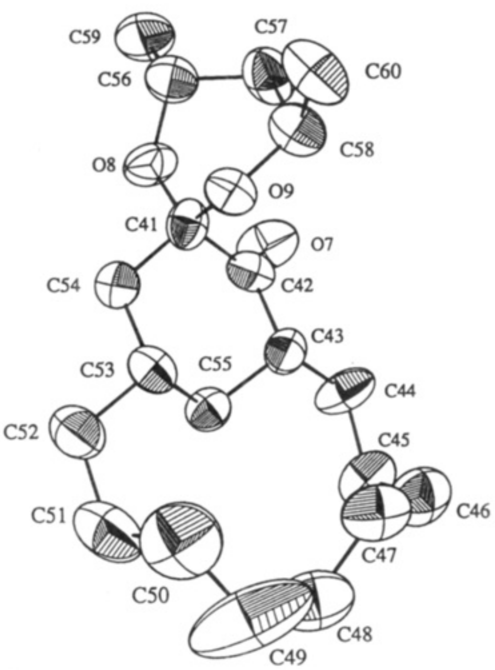


Figure 8.

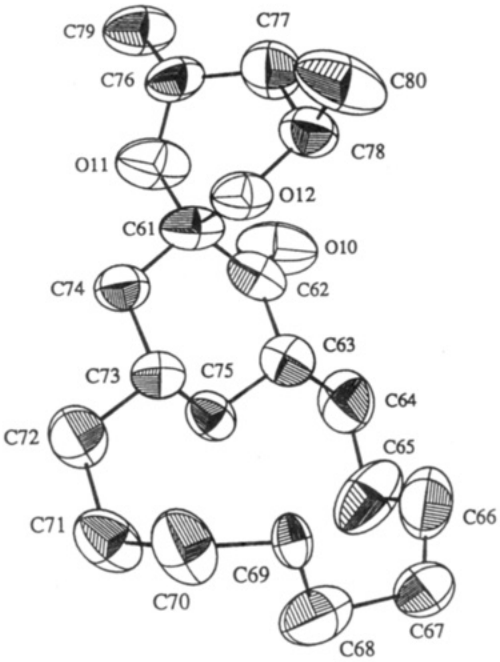
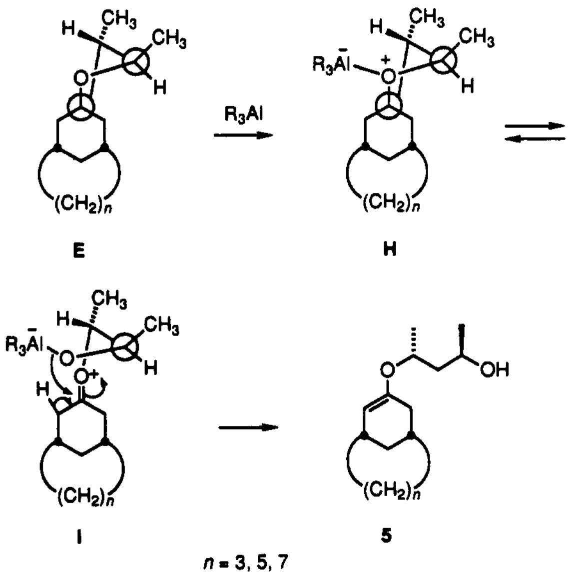


Figure 9.

tation and skirts all possible 1,3-diaxial C–C interactions. The major consequence of the conformational features common to **B** and **C** is more ready hydride attack on the *re* and *si* faces of their carbonyl groups, respectively, as indicated by the arrows (Figure 3). In chair form **a**, an axial methyl substituent from the dioxolane ring is positioned almost directly above the ketone functionality and can be expected to inhibit entry of the nucleophile from the *re* face. Although hydride attack from the α direction might well be expected with conformation **A**, this trajectory is evidently less kinetically favorable than that operating on **B**.

In considering those factors responsible for the diastereoselectivity observed in the TRIBAL-catalyzed cleavages of acetals **4a–d**,[3] the conformations defined as **D**, **E**, and **F** warrant consideration (Figure 4). The rigid chair conformation of the dioxolane ring in **D** and **F** generates the 1,3-diaxial CH_3/H and CH_3/CH_2 interactions that result in overall structural destabilization. Furthermore, when the polymethylene chain is diaxially bridged as in

4a–c, additional nonbonded steric compression develops between the axial oxygen and several proximate CH_2 units from the loop (see **G** in Figure 5). Since comparable untoward interactions are not present in **E**, this boat option is once again the most likely ground-state possibility. In this likelihood, complexation of the Lewis acid to the β-oxygen (the α-oxygen in **G** is heavily shielded, see Figure 5) would lead via **E** (redrawn below in a Newman projection) through **H** to **I**.[3] Since intramolecular abstraction of the indicated α-proton in **I** introduces none of the serious steric interactions associated with the α′ alternative, **5a–c** are produced exclusively.



When the bridge is linked diequatorially as in **4d**, the distinctions between **D**, **E**, and **F** become much less pronounced and all three conformers could well be involved in the cleavage process. The absence of an observable diastereoselectivity preference in the ring opening of **4d** (1:1 distribution of **11** and **12**) is noteworthy. It would be of interest to compare this response with those of acetals that do not have the capability of adopting a strongly biased dioxolane conformation.

The same complications do not plague the enantioselective deprotonation of ketones **4**. The sense of enantioselectivity, which is the same whether the polymethylene chain is positioned diaxially or diequatorially, parallels that noted earlier in structurally simpler cyclohexanones such as **28** and **29**. It remains unclear, however, why the stereochemical course that is universally adopted across these systems is followed so strictly. Mechanistic studies presently under investigation in the Koga laboratories[8] will hopefully shed light on this important question.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^1H NMR spectra were recorded at 300 MHz and ^{13}C spectra at 75 MHz on a Bruker AC-300 instrument. Mass spectra were recorded on a Kratos MS-30 spectrometer at The Ohio State University Chemical Instrument Center. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. All separations were carried out under flash chromatography conditions on Fluka silica gel H. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried prior to use.

Ketalization with (*R*,*R*)-2,4-Pentanediol. A mixture of **4d** (1.50 g, 6.75 mmol), (*R*,*R*)-2,4-pentanediol (880 mg, 8.45 mmol), and collidinium tosylate (20 mg) in toluene (40 mL) was heated to reflux under a Dean-Stark apparatus. After 2 h (15 h in the other three examples), the reaction mixture was cooled, poured into saturated $NaHCO_3$ solution, and extracted with ether (2 × 50 mL). The combined organic layers were washed with brine, dried, and evaporated. Column chromatography of the residue on silica gel (elution with 2% ethyl acetate in petroleum ether) gave **4d** (2.00 g, 95%) as a colorless solid, mp 43–45 °C (from hexane): ^1H NMR (300 MHz, C_6D_6) δ 4.02 (m, 1 H), 3.91 (m, 1 H), 2.21 (dd, J = 12.1, 2.8 Hz, 1 H), 2.13 (dd, J = 13.4, 2.8 Hz, 1 H), 1.94 (dt, J = 12.8, 2.3 Hz, 1 H), 1.89–1.74 (m, 2 H), 1.40–1.20 (series of m, 22 H), 1.13 (d, J = 6.3 Hz, 3 H), 1.09 (d, J = 6.3 Hz, 3 H), 0.12 (dt, J = 11.8, 11.5 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 101.5, 62.5, 62.4, 44.2, 42.1, 41.9, 35.0, 34.9, 34.6, 33.6, 33.4, 26.4, 26.3, 25.1, 25.0, 24.2, 22.8, 22.7, 22.2 (2 C); MS *m/z* (M^+) calcd 308.2715, obsd 308.2723; $[\alpha]^{22}_D$ −39.7° (c 1.57, benzene).

Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76. Found: C, 78.04; H, 11.77.

For **4a**: 26% yield with 57% recovered ketone; colorless oil; ^1H NMR (300 MHz, C_6D_6) δ 3.93 (m, 2 H), 2.40–2.15 (m, 3 H), 2.10–1.90 (m, 3 H), 1.85 (br t, J = 12.0 Hz, 2 H), 1.65–1.45 (m, 4 H), 1.40–1.25 (m, 4 H), 1.09 (d, J = 6.3 Hz, 3 H), 1.08 (d, J = 8.0 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 100.5, 62.4, 62.0, 42.0, 39.2, 39.1, 32.7 (2 C), 31.4, 27.7, 27.5, 22.2, 21.9, 17.3; MS *m/z* (M^+) calcd 224.1776, obsd 224.1742; $[\alpha]^{20}_D$ −44.6° (c 1.00, benzene).

4b: 81% yield with 14% recovered ketone; colorless solid; mp 49–50 °C (from hexane); ^1H NMR (300 MHz, C_6D_6) δ 4.05–3.83 (m, 2 H), 2.25–2.00 (m, 5 H), 1.85–1.60 (m, 9 H), 1.40–1.22 (m, 6 H), 1.09 (d, J = 6.3 Hz, 3 H), 1.08 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 100.8, 62.2, 61.9, 42.1, 41.3, 37.0, 33.1, 32.9, 32.8, 31.4, 30.9, 28.0, 25.9, 25.8, 22.0, 21.8; MS *m/z* (M^+) calcd 252.2089, obsd 252.2093; $[\alpha]^{20}_D$ −62.9° (c 0.84, benzene).

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.31; H, 11.22.

For **4c**: 78% yield with 15% recovered ketone; colorless solid; mp 83–84 °C (from hexane); ^1H NMR (C_6D_6) δ 4.05–3.85 (m, 2 H), 2.55–2.40 (m, 2 H), 2.25–2.05 (m, 3 H), 1.95–1.65 (m, 6 H), 1.60–1.40 (m, 8 H), 1.35–1.25 (m, 4 H), 1.20–1.05 (m, 1 H), 1.11 (d, J = 4.7 Hz, 3 H), 1.09 (d, J = 4.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 100.8, 62.2, 62.0, 42.6, 42.1, 38.6, 34.4, 34.3, 28.8, 28.1, 27.5, 26.9, 26.8, 24.6, 24.5, 22.0, 21.8, 20.2; MS *m/z* (M^+) calcd 280.2402, obsd 280.2399; $[\alpha]^{20}_D$ −55.1° (c 0.64, benzene).

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 76.95; H, 11.57.

General Procedure for Acetal Ring Opening and Oxidation. To a cold (0 °C) solution of **4b** (251 mg, 0.99 mmol) in CH_2Cl_2 (10 mL) was added TRIBAL (5 mL of 1.0 M in toluene). The reaction mixture was stirred at 0 °C for 2–4 h, poured into cold 1 N NaOH (16 mL), and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried and concentrated to leave a residue that was taken up in CH_2Cl_2 (3 mL), cooled to 0 °C, and treated with dimethoxydioxirane (12 mL of 0.1 N in acetone). After 15 min of stirring, the solvent was evaporated and the residue was taken up in ether and dried. Alternatively, the enol ether was oxidized in CH_2Cl_2 (buffered with 200 mg of $NaHCO_3$) with *m*-chloroperbenzoic acid (261 mg, 1.25 mmol). The reaction mixture was stirred at 0 °C for 30 min, quenched with saturated Na_2SO_3 solution, and extracted with ether. The combined ethereal phases were washed with 1 N NaOH (2 × 10 mL) and brine prior to drying and solvent evaporation. Purification of the residue by chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether) gave 226 mg (84%) of **6b**, colorless solid, mp 87–89 °C (from 2% ethyl acetate in hexane): ^1H NMR (300 MHz, C_6D_6) δ 3.90–3.78 (m, 2 H), 3.70 (s, 1 H), 2.08 (s, 1 H), 2.21–2.11 (m, 1 H), 2.09–2.00 (m, 3 H), 1.96–1.65 (m, 9 H), 1.39–1.29 (m, 3 H), 1.23–1.17 (m, 2 H), 0.98 (d, J = 6.3 Hz, 3 H), 0.96 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 100.6, 71.2, 63.0, 62.6, 40.8, 39.2, 36.8, 33.0, 32.6, 31.4, 29.2, 25.7, 25.3, 21.8 (2 C), 21.6; MS *m/z* (M^+) calcd 268.2038; obsd 268.2019; $[\alpha]^{21}_D$ −72.8° (c 1.09, benzene).

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.54; H, 10.49.

For **6a**: colorless oil (27% with *m*-CPBA); ^1H NMR (300 MHz, C_6D_6) δ 4.06 (m, 1 H), 3.84 (m, 1 H), 3.76 (br s, 1 H), 3.08 (d, J = 4.1 Hz, 1 H), 2.28–2.15 (series of m, 3 H), 2.10 (dd, J = 14.4, 7.7 Hz, 1 H), 1.91 (br s, 1 H), 1.75 (d, J = 14.4 Hz, 1 H), 1.71–1.17 (series of m, 4 H), 1.01 (d, J = 6.3 Hz, 3 H), 0.95 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 99.5, 75.4, 63.6, 62.5, 40.8, 37.9, 37.0, 31.7, 29.5, 27.8, 27.7, 21.8 (2 C), 17.8; MS *m/z* (M^+)

calcd 240.1725, obsd 240.1756; $[\alpha]^{21}{}_D$ −38.1° (*c* 1.54, benzene).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.30; H, 10.23.

For **6c**: colorless solid; mp 97–98 °C (from 2% ethyl acetate in hexane) (88% with *m*-CPBA, 48% with dimethyldioxirane); ^1H NMR (300 MHz, C_6D_6) δ 3.93–3.77 (m, 2 H), 3.76 (s, 1 H), 2.56 (s, 1 H), 2.44–1.95 (series of m, 6 H), 1.89–1.78 (m, 3 H), 1.70–1.42 (m, 9 H), 1.34–1.19 (m, 4 H), 0.99 (d, *J* = 5.8 Hz, 3 H), 0.98 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 100.8, 72.9, 63.0, 62.7, 40.9, 40.4, 37.5, 34.0, 28.9, 26.9, 26.7, 26.2, 24.5, 24.0, 21.9, 21.7, 21.6, 20.2; MS *m/z* (M^+) calcd 296.2351, obsd 296.2351; $[\alpha]^{21}{}_D$ −66.4° (*c* 0.36, benzene).

Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.89; H, 10.89.

General Procedure for Oxidation of α-Hydroxy Acetals. To a cold (−78 °C) solution of oxalyl chloride (78.3 mg, 0.62 mmol) in CH_2Cl_2 (3 mL) was added 0.1 mL of DMSO. After 2 min of stirring, a solution of **6b** (127.6 mg, 0.48 mmol) in CH_2Cl_2 (2 mL) was introduced, followed 15 min later with triethylamine (0.25 mL). After 30 min at 0 °C, the reaction mixture was diluted with ether, washed with water, dilute HCl, and brine, dried, and evaporated. The product was isolated by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether) to give 124 mg (98%) of **7b**: colorless oil; IR (neat, cm^{-1}) 1730; ^1H NMR (300 MHz, C_6D_6) δ 4.27 (m, 1 H), 3.93 (m, 1 H), 2.76 (dd, *J* = 15.0, 7.0 Hz, 1 H), 2.32–2.17 (m, 3 H), 1.85–1.74 (m, 3 H), 1.70–1.57 (m, 2 H), 1.50–1.25 (series of m, 8 H), 1.21–1.15 (m, 1 H), 1.12 (d, *J* = 6.3 Hz, 3 H), 1.06 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 208.7, 99.3, 64.8, 64.2, 44.6, 44.2, 39.7, 31.8, 31.6, 29.7, 28.9, 28.1, 24.9, 22.7, 21.9, 21.2; MS *m/z* (M^+) calcd 266.1882, obsd 266.1918; $[\alpha]^{20}{}_D$ +62.7° (*c* 0.93, benzene).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.19; H, 9.87.

For **16**: colorless solid, mp 75–76 °C (from hexane); 98% yield; IR (KBr, cm^{-1}) 1730; ^1H NMR (300 MHz, C_6D_6) δ 4.68–4.57 (m, 1 H), 4.04–3.94 (m, 1 H), 3.10–2.99 (m, 1 H), 2.30–2.12 (m, 2 H), 2.05–1.95 (m, 1 H), 1.74–1.64 (m, 2 H), 1.50–1.10 (series of m, 18 H), 1.19 (d, *J* = 6.2 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 0.95–0.80 (m, 1 H), 0.35 (dt, *J* = 13.2, 13.1 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 209.2, 99.6, 66.0, 63.8, 47.0, 46.2, 39.3, 35.3, 33.4, 32.4, 26.3, 26.1, 26.0, 24.9, 24.8, 24.2, 22.5, 22.0, 21.9, 20.5; MS *m/z* (M^+) calcd 322.2508, obsd 322.2515; $[\alpha]^{21}{}_D$ +89.3° (*c* 0.91, benzene).

Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.47; H, 10.66.

For **17**: colorless solid; mp 56–59 °C (from hexane); 98% yield; IR (KBr, cm^{-1}) 1730; ^1H NMR (300 MHz, C_6D_6) δ 4.05–3.92 (m, 1 H), 3.75–3.65 (m, 1 H), 2.91–2.80 (m, 1 H), 2.29 (dt, *J* = 13.1, 3.6 Hz, 1 H), 2.25–2.10 (m, 1 H), 2.05–1.93 (m, 1 H), 1.90–1.78 (m, 1 H), 1.75–1.55 (m, 2 H), 1.50–1.10 (series of m, 17 H), 1.23 (d, *J* = 6.3 Hz, 3 H), 0.99 (d, *J* = 6.3 Hz, 3 H), 0.95–0.80 (m, 1 H), 0.39 (dt, *J* = 13.3, 13.2 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.7, 100.2, 65.1, 63.9, 47.5, 46.1, 39.3, 34.4, 33.6, 32.5, 26.6, 26.2, 26.1, 24.9, 24.8, 24.1, 22.4, 22.2, 22.0, 21.8; MS *m/z* (M^+) calcd 322.2508, obsd 322.2540; $[\alpha]^{21}{}_D$ −56.8° (*c* 0.66, benzene).

General Procedure for Hydride Reduction of α-Keto Acetals. A solution of **7b** (55.6 mg, 0.21 mmol) in absolute ethanol (4 mL) was cooled to 0 °C and treated with lithium aluminum hydride (25 mg, 0.64 mmol). After 15 min of stirring, the reaction mixture was quenched in the standard way and product was isolated by chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether) to give **8b** (53.6 mg, 96%) as a colorless crystalline solid, mp 79–80 °C (from hexane): ^1H NMR (300 MHz, C_6D_6) δ 4.49 (m, 1 H), 3.91 (m, 1 H), 3.82 (br s, 1 H), 2.40 (s, 1 H), 2.21–2.10 (m, 4 H), 2.10–1.98 (m, 2 H), 1.85–1.58 (m, 5 H), 1.51 (dd, *J* = 13.1, 5.5 Hz, 1 H), 1.35–1.15 (m, 6 H), 1.08 (d, *J* = 5.6 Hz, 3 H), 1.06 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 101.4, 78.7, 65.7, 62.0, 40.3, 40.1, 38.8, 32.9, 32.8, 31.1, 27.7, 25.8, 25.1, 24.6, 22.4, 22.3; MS *m/z* (M^+) calcd 268.2038, obsd 268.2043; $[\alpha]^{21}{}_D$ −6.1° (*c* 0.84, benzene).

The reductions of **16** and **17** were carried out in similar fashion with 1.5 equiv of L-Selectride (Aldrich) in THF. Oxidative workup (NaOH, H_2O_2) followed by column chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) gave the hydroxy acetals in comparable yield.

For **13**: colorless oil; ^1H NMR (300 MHz, C_6D_6) δ 4.57–4.46 (m, 1 H), 3.90–3.87 (m, 1 H), 3.33 (t, *J* = 10.2 Hz, 1 H), 2.23–2.06 (series of m, 2 H), 1.99 (d, *J* = 10.0 Hz, 1 H), 1.80 (dd, *J* = 13.3, 2.8 Hz, 1 H), 1.75–1.00 (series of m, 22 H), 1.12 (d, *J* = 6.2 Hz, 3 H), 1.00 (d, *J* = 6.2 Hz, 3 H), 0.12 (dt, *J* = 13.3, 13.1 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 100.8, 82.2, 65.1, 62.4, 42.1 41.2, 40.4, 34.2, 33.0, 32.3, 30.6, 26.3, 26.1, 25.3, 24.9, 24.1, 22.8, 22.7, 22.5, 22.2; MS *m/z* (M^+) calcd 324.2664, obsd 324.2643; $[\alpha]^{21}{}_D$ −1.7° (*c* 1.75, benzene).

For **14**: colorless oil; ^1H NMR (300 MHz, C_6D_6) δ 4.37–4.28 (m, 1 H), 3.98–3.89 (m, 1 H), 3.32 (d, *J* = 9.8 Hz, 1 H), 2.25–1.70 (series of m, 7 H), 1.65–1.05 (series of m, 19 H), 1.07 (d, *J* = 5.6 Hz, 3 H), 1.05 (d, *J* = 3.9 Hz, 3 H), 0.30 (dt, *J* = 11.3, 11.2 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 100.8, 81.1, 65.4, 62.3, 42.2, 40.1, 38.5, 34.4, 32.8, 32.3, 30.5, 26.1, 26.0, 25.3, 25.1, 23.9, 22.8, 22.6, 22.4, 22.2; MS *m/z* (M^+) calcd 324.2664, obsd 324.2700; $[\alpha]^{21}{}_D$ −24.2° (*c* 1.95, benzene).

For **15**: colorless solid; mp 85–87 °C (from hexane); ^1H NMR (300 MHz, C_6D_6) δ 3.95–3.79 (m, 2 H), 3.76 (s, 1 H), 2.29 (s, 1 H), 2.10–1.85 (series of m, 4 H), 1.75–1.10 (series of m, 22 H), 1.01 (d, *J* = 6.3 Hz, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 101.4, 73.4, 63.7, 62.8, 40.8, 39.5, 37.8, 35.1, 33.1, 30.3, 26.5 (2 C), 26.4, 25.3, 24.4, 24.3, 22.8, 22.6, 22.2, 22.0; MS *m/z* (M^+) calcd 324.2664, obsd 324.2685; $[\alpha]^{21}{}_D$ −35.6° (*c* 1.35, benzene).

Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.03; H, 11.18. Found: C, 74.14; H, 11.25.

For **20**: colorless oil; ^1H NMR (300 MHz, C_6D_6) δ 3.91–3.79 (m, 2 H), 3.78 (s, 1 H), 2.19 (s, 1 H), 2.06–1.97 (m, 2 H), 1.89 (d, *J* = 13.0 Hz, 1 H), 1.77 (br d, *J* = 11.9 Hz, 1 H), 1.70–1.06 (series of m, 22 H), 1.02 (d, *J* = 6.3 Hz, 3 H), 0.96 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 102.3, 72.5, 62.7, 62.3, 41.6, 37.5, 37.2, 34.9, 33.4, 30.5, 26.5, 26.4, 26.3, 25.2, 24.5, 24.3, 22.8, 22.6, 22.0, 21.8; MS *m/z* (M^+) calcd 324.2664, obsd 324.2598; $[\alpha]^{21}{}_D$ −38.1° (*c* 1.18, benzene).

TRIBAL-Induced Isomerization and Acetylation of 4d. The TRIBAL-induced isomerization of **4d** (251 mg, mmol) was performed in the predescribed manner. The unpurified residue was dissolved in CH_2Cl_2 (5 mL), cooled to 0 °C, and treated with triethylamine (0.2 mL) and acetyl chloride (0.1 mL). After 10 min, a catalytic amount of 4-(dimethylamino)pyridine was introduced and the mixture was stirred for 15 min before being quenched with ice-cold water. The mixture was taken up in ether and the organic layer was washed rapidly with cold water, 1 N HCl, saturated $NaHCO_3$ solution, and brine prior to drying. After solvent evaporation, the residual oil was purified by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether) to give 110 mg of nonpolar acetate, 60 mg of a mixed fraction, and 60 mg of polar acetate.

Each acetate (56 mg) was dissolved in methanol (2 mL) containing K_2CO_3 (13 mg), and the mixture was stirred at room temperature for 20 h, taken up in ether, washed with brine, and dried. Solvent removal gave the alcohol (28 mg, 90%).

General Procedure for Cyclopropanation of the Chiral Enol Ethers. A solution of **4b** (128.6 mg, 0.46 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and treated with TRIBAL (2.5 mL of 1.0 M in toluene). The reaction mixture was stirred for 4 h, poured into NaOH solution (20 mL), and processed as before to give enol ether **5b**. This unpurified material was taken up in dry THF (10 mL), cooled to 0 °C, treated sequentially with diethylzinc (2.4 mL of 1.1 M in toluene) and diiodomethane (0.44 mL), and stirred at room temperature for 20 h. Aqueous NH_4Cl solution was introduced, and the product was extracted into ether (2 × 50 mL). The combined organic extracts were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in petroleum ether) gave 120 mg (88%) of **21b** as a colorless solid, mp 68–69 °C: ^1H NMR (300 MHz, C_6D_6) δ 4.15–4.02 (m, 1 H), 3.98 (tq, *J* = 6.3, 3.9 Hz, 1 H), 2.51 (s, 1 H), 1.99 (d, *J* = 4.1 Hz, 2 H), 1.98–1.90 (m, 1 H), 1.85–1.78 (m, 1 H), 1.75–1.60 (m, 6 H), 1.60–1.30 (m, 7 H), 1.20 (dd, *J* = 10.8, 6.7 Hz, 1 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 1.10 (d, *J* = 6.2 Hz, 3 H), 0.96 (dd, *J* = 10.8, 5.0 Hz, 1 H), 0.81 (ddd, *J* = 15.0, 5.7, 4.3 Hz, 1 H), 0.19 (dd, *J* = 6.7, 5.1 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 70.3, 63.8, 57.9, 45.9, 36.1, 35.9, 32.8, 31.7, 30.5, 29.9, 26.0, 25.2, 24.0, 23.9, 21.6, 21.1, 18.7; MS *m/z* (M^+) calcd 266.2246, obsd 266.2223; $[\alpha]^{20}{}_D$ −12.8° (*c* 0.65, benzene).

For **21a**: colorless oil (56% yield); ^1H NMR (300 MHz, C_6D_6) δ 4.15–4.00 (m, 2 H), 2.67 (s, 1 H), 2.16–1.97 (m, 3 H), 1.88 (br s, 1 H), 1.64–1.54 (m, 2 H), 1.52–1.30 (m, 6 H), 1.12 (d, *J* = 6.2

Hz, 3 H), 1.08 (d, J = 6.3 Hz, 3 H), 1.12–0.97 (m, 3 H), 0.84 (dd, J = 10.4, 5.2 Hz, 1 H), 0.20 (dd, J = 6.3, 5.3 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 69.5, 64.4, 57.0, 46.3, 35.7, 35.1, 33.6, 27.6, 27.3, 25.7, 25.5, 24.2, 21.1, 18.3, 17.3; MS *m/z* ($M^+ - H_2O$) calcd 220.1825, obsd 220.1829; $[\alpha]^{21}_D$ −27.6° (*c* 1.74, benzene).

For **21c**: colorless oil (40% yield); ^{1}H NMR (300 MHz, C_6D_6) δ 4.10–3.94 (m, 2 H), 2.56 (br s, 1 H), 2.15–2.02 (m, 2 H), 1.94–1.64 (m, 5 H), 1.58–1.32 (m, 14 H), 1.20 (dd, J = 10.9, 6.8 Hz, 1 H), 1.14 (d, J = 6.3 Hz, 3 H), 1.10 (d, J = 6.2, Hz, 3 H), 0.99 (dd, J = 10.9, 5.0 Hz, 1 H), 0.77 (dt, J = 15.4, 4.6 Hz, 1 H), 0.22 (dd, J = 6.7, 5.1 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 70.9, 64.3, 58.3, 46.2, 37.7, 32.7, 31.8, 31.5, 30.9, 27.5, 27.2, 26.8, 24.8, 24.3, 23.0, 21.6, 21.3, 20.8, 19.4; MS *m/z* (M^+) calcd 294.2559, obsd 294.2577; $[\alpha]^{21}_D$ −18.7° (*c* 2.87, benzene).

For **22**: colorless oil (62% yield); ^{1}H NMR (300 MHz, C_6D_6) δ 4.13–4.01 (m, 1 H), 4.00–3.93 (m, 1 H), 2.69 (br s, 1 H), 2.16 (dd, J = 12.6, 4.6 Hz, 1 H), 1.69 (ddd, J = 11.6, 10.5, 0.9 Hz, 1 H), 1.60–1.20 (m, 19 H), 1.15–0.95 (series of m, 6 H), 1.12 (d, J = 6.2 Hz, 3 H), 1.11 (d, J = 6.3 Hz, 3 H), 0.46 (dt, J = 13.0, 9.5 Hz, 1 H), 0.23 (t, J = 5.0 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 70.8, 64.3, 61.2, 46.2, 38.5, 37.0, 36.2, 34.5, 32.5, 30.6, 26.2 (2 C), 25.6, 25.4, 24.7, 24.2, 23.6, 22.9, 22.5, 21.4, 20.4; MS *m/z* ($M^+ - CH_3$) calcd 307.2659, obsd 307.2648; $[\alpha]^{20}_D$ +8.7° (*c* 2.07, benzene).

For **23**/**24**: colorless oil (60% yield); ^{13}C NMR for major isomer **23** (75 MHz, C_6D_6) ppm 70.9, 64.3, 59.8, 46.0, 39.6, 34.4, 34.3, 33.8, 33.6, 26.5, 26.4, 26.2, 26.1, 25.9, 24.2, 24.0, 23.6, 22.8, 21.8, 21.2, 16.6. Apparent peaks for minor constituent **24** include 64.2, 46.5, 38.7, 36.2, 32.5, 27.3, 25.5, 24.3, 23.5, 22.5, 22.2, 19.0.

Enantioselective Oxidation of 3 to α-Hydroxy Ketones 30 and/or 31. A solution of the parent amine of **27** (86.5 mg, 0.30 mmol) in dry THF (5 mL) was cooled to −78 °C, treated with *n*-butyllithium (0.21 mL of 1.3 M in hexane), stirred for 30 min, and treated with HMPA (0.05 mL). The reaction mixture was allowed to warm to room temperature for 5 min and recooled to −78 °C, at which point trimethylchlorosilane (0.13 mL) was introduced. A solution of **3b** (41.3 mg, 0.25 mmol) in THF (3 mL) was added, and stirring was maintained for 20 min prior to warming to rt (15 min). Following solvent evaporation, the residue was washed with hexane and filtered. The filtrate was concentrated and the unpurified enol silane was taken up in CH_2Cl_2 (3 mL), cooled to 0 °C, and treated with dimethyldioxirane (DMDO) in acetone (12 mL of 0.01 N). After 30 min, the reaction mixture was warmed to rt, stirring for 10 min, quenched with saturated Na_2SO_3 solution, and extracted with ether. The combined organic phases were washed with 1 N HCl (3 × 5 mL) and brine prior to drying and solvent evaporation. The residue was purified by silica gel chromatography (elution with 25% ethyl acetate in petroleum ether) to return 15.1 mg of unreacted **3b** and give 23.0 mg of product.

Alternatively, the silylation reaction mixture was quenched at −78 °C with saturated $NaHCO_3$ solution, warmed to room temperature, and freed of solvent. The residue was extracted into petroleum ether and washed with saturated NH_4Cl solution and brine prior to drying and concentration. The remaining oil was dissolved in CH_2Cl_2, buffered with $NaHCO_3$, and oxidized in the usual fashion with *m*-CPBA (150 mg) or DMDO. The overall results were as follows: **3a** (55%, *m*-CPBA); **3b** (51% DMDO); **3c** (10%, *m*-CPBA), **3d** (50%, DMDO).

For **31a**: colorless solid; mp 175–179 °C; IR (KBr, cm^{-1}) 3500–3000, 1730; ^{1}H NMR (300 MHz, C_6D36) δ 3.76 (s, 1 H), 3.50 (br s, 1 H), 2.67 (dd, J = 16.4, 6.7 Hz, 1 H), 2.07 (br s, 3 H), 1.85 (br s, 1 H), 1.50–1.00 (series of m, 7 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 197.9, 77.8, 43.1, 37.7, 31.8, 30.9, 29.2, 27.8, 18.8; MS *m/z* (M^+) calcd 154.0994, obsd 154.0999; $[\alpha]^{21}_D$ +5.5° (*c* 2.14, benzene).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.92; H, 9.15.

For **31b**: colorless oil; IR (neat, cm^{-1}) 3500–3000, 1725; ^{1}H NMR (300 MHz, C_6D_6) δ 3.68 (s, 1 H), 3.08 (s, 1 H), 3.02 (dd, J = 13.5, 6.7 Hz, 1 H), 2.05–1.80 (series of m, 4 H), 1.60–1.40 (series of m, 6 H), 1.20–0.95 (m, 5 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.3, 79.1, 43.9, 43.2, 36.1, 32.4, 30.9, 29.4, 24.9, 24.0, 22.4; MS *m/z* (M^+) calcd 182.1307, obsd 182.1320; $[\alpha]^{22}_D$ −32.4° (*c* 1.42, benzene).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.19; H, 9.97.

For **31c**: colorless solid; mp 97–98 °C; IR (KBr, cm^{-1}) 3700–3000, 1715; ^{1}H NMR (300 MHz, C_6D_6) δ 3.60 (br s, 1 H), 3.13 (dd, J = 13.0, 7.2 Hz, 1 H), 2.28 (br s, 1 H), 2.00–1.78 (m, 4 H), 1.73 (d, J = 13.8 Hz, 1 H), 1.52–1.00 (series of m, 12 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.6, 80.9, 44.8, 44.6, 37.6, 29.8, 26.9, 26.7, 26.3, 23.7, 23.2, 21.4, 20.0; MS *m/z* (M^+) calcd 210.1620, obsd 210.1605; $[\alpha]^{21}_D$ −27.3° (*c* 1.45, benzene).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.98; H, 10.66.

For **30d**: colorless solid; mp 108–109 °C; IR (KBr, cm^{-1}) 3750–3000, 1720; ^{1}H NMR (300 MHz, C_6D_6) δ 3.87 (d, J = 3.5 Hz, 1 H), 3.41 (ddd, J = 11.1, 3.4, 1.2 Hz, 1 H), 2.25 (dt, J = 13.3, 3.3 Hz, 1 H), 2.21–2.11 (m, 1 H), 1.74 (br d, J = 13.8 Hz, 1 H), 1.54 (td, J = 13.2, 1.3 Hz, 1 H), 1.45–1.00 (series of m, 18 H), 0.86–0.75 (m, 1 H), 0.18 (dt, J = 13.7, 11.8 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 209.9, 80.4, 47.0, 45.1, 37.1, 34.3, 31.2, 30.9, 26.2, 26.1, 24.5, 24.4, 24.0, 22.2, 22.1; MS *m/z* (M^+) calcd 238.1933, obsd 238.1932; $[\alpha]^{20}_D$ −43.1° (*c* 1.45, benzene).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.59; H, 10.99.

General Procedure for Oxidation to Enones 34 and 35. The silyl enol ethers were prepared as described above (nonaqueous workup). This unpurified intermediate (from 80.3 mg of **3b**) was dissolved in CH_2Cl_2 (3 mL), cooled to 0 °C, and treated sequentially with 2,6-*tert*-butylpyridine (0.22 mL) and phenylselenenyl chloride (195.6 mg). The reaction mixture was warmed to rt and quenched with 1 N HCl (3 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were cooled to 0 °C, treated with 30% hydrogen peroxide (1 mL), and stirred for 15 min. Following aqueous workup, the enone was purified by silica gel chromatography (elution with 20% ethyl acetate in petroleum ether) to return 20.8 mg (26%) of unreacted **3b** and give 16.8 mg (21%) of **34b**: $[\alpha]^{21}_D$ +123.9° (*c* 1.48, benzene).

For **34c**: (43% yield); $[\alpha]^{21}_D$ +58.8° (*c* 3.79, benzene).

For **35**: (49% yield); $[\alpha]^{21}_D$ +20.1° (*c* 3.89, benzene).

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Supplementary Material Available: 300-MHz ^{1}H NMR spectra of **4a**, **8b**, **13**, **14**, **17**, **20**, **21a–c**, **22**, **30d**, and **31a–c** together with crystallographic details, crystallographic experimental procedures, tables of bond distances and angles, final fractional coordinates, and thermal parameters for **6b** and **17** as well as final computed atomic coordinates for **A**–**G** and their simpler dimethyl analogues **A′**–**G′** (34 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.