Asymmetric Epoxidation by Chiral Ketones Derived from Carbocyclic Analogues of Fructose

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A number of carbocyclic analogues of the fructose-derived ketone **1** have been prepared and investigated for asymmetric epoxidation. The studies show that the oxygen atom of the pyranose ring of **1** has an impact on the catalyst's activity and selectivity. Conformational, electronic, and steric effects are discussed.

Chiral dioxiranes generated in situ from chiral ketones have received intensive interest in recent years.[1−4] During the course of our studies, we found that the fructose-derived ketone (**1**) displayed some highly favorable features for the asymmetric epoxidation of *trans*- and trisubstituted olefins (Scheme 1).[4] Subsequent studies with a number of carbohydrate derived ketones (**2**−**6**) showed that the catalytic properties were dependent on the precise nature of the ketone structure (Scheme 2). It was found that the rigid five-membered ring spiro ketal of **1** was superior to the six-membered cyclic ketal of **3** and the acyclic groups of **5** for both reactivity and enantioselectivity of the epoxidation.[4h] Studies with ketone **2** showed that the epoxidation was also largely affected by the size of the groups attached to the ketals (R_1, R_2, and R_3); the smaller R_1 is, the better the reactivity and selectivity. As part of our efforts to gain further understanding of the structural requirements and factors involved in asymmetric epoxidation, we have investigated some carbocyclic analogues of ketone **1** (ketones **7**−**12**, Scheme 3). Herein we wish to report the synthesis and catalytic properties of these ketones.

Ketone Design and Synthesis

Ketone **1** shows high enantioselectivity for the epoxidation of *trans*- and trisubstituted olefins. One of the compelling questions is the effect of the pyranose oxygen of **1** on the catalytic properties. For example, does this oxygen activate the ketone via the inductive effect? Also, how does this oxygen affect the Baeyer−Villiger reaction and consequently affect the catalyst's stability? Finally, does this oxygen play a role in the ketone's conformation? All these issues are important for the further understanding of the ketone catalyzed epoxidation and for the design of more efficient catalysts, which prompted us to investigate the carbocyclic analogue of **1**, ketone **7**.

Ketones **8** and **9** were designed to further probe the conformational effect on the catalysis brought by the substituents on the carbocyclic rings. The steric environment of the reacting center (carbonyl group) of the ketone is very important for the reactivity and selectivity of the

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(1) For general leading references on dioxiranes, see: (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811. (d) Clennan, E. L. *Trends Organic Chemistry*, **1995**, *5*, 231. (e) Adam, W.; Smerz, A. K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581. (f) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847.

(2) For examples of in situ generation of dioxiranes, see: (a) Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. *Photochem. Photobiol.* **1979**, *30*, 63. (b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758. (c) Gallopo, A. R.; Edwards J. O. *J. Org. Chem.* **1981**, *46*, 1684. (d) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670. (e) Corey, P. F.; Ward, F. E. *J. Org. Chem.* **1986**, *51*, 1925. (f) Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227. (g) Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett.* **1994**, *35*, 1577. (h) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391 (i) Yang, D.; Wong, M. K.; Yip, Y. C. *J. Org. Chem.* **1995**, *60*, 3887. (j) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (k) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1997**, *62*, 8964. (l) Boehlow, T. R.; Buxton, P. C.; Grocock, E. L.; Marples, B. A.; Waddington, V. L. *Tetrahedron Lett.* **1998**, *39*, 1839. (m) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1998**, *63*, 2810. (n) Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 6425. (o) Yang, D.; Yip, Y.-C.; Jiao, G.-S.; Wong, M.-K. *J. Org. Chem.* **1998**, *63*, 8952. (p) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Cheung, K.-K. *J. Org. Chem.* **1998**, *63*, 9888.

(3) For leading references on asymmetric epoxidation mediated in situ by chiral ketones, see: (a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. (b) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831. (c) Reference 2h. (d) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L *Tetrahedron* **1995**, *51*, 3587. (e) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (f) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (g) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S. G.; Jin, B. W. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2921. (h) Adam, W.; Zhao, C.-G. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3995. (i) Reference 2j. (j) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622. (k) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (l) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (m) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659. (n) Adam, W.; Saha-Moller, C. R.; Zhao, C.-G. *Tetrahedron*: *Asymmetry* **1999**, *10*, 2749. (o) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443. (p) Carnell, A. J.; Johnstone, R. A. W.; Parsy, C. C.; Sanderson, W. R. *Tetrahedron Lett.* **1999**, *40*, 8029. (q) Armstrong, A.; Hayter, B. R. *Tetrahedron* **1999**, *55*, 11119.

(4) For examples of asymmetric epoxidation mediated in situ by fructose-derived ketones, see: (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. (c) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (d) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948. (e) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099. (f) Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425. (g) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. (h) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475. (i) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646. (j) Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675. (k) Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718. (l) Shu, L.; Shi. Y. *Tetrahedron Lett.* **1999**, *40*, 8721.

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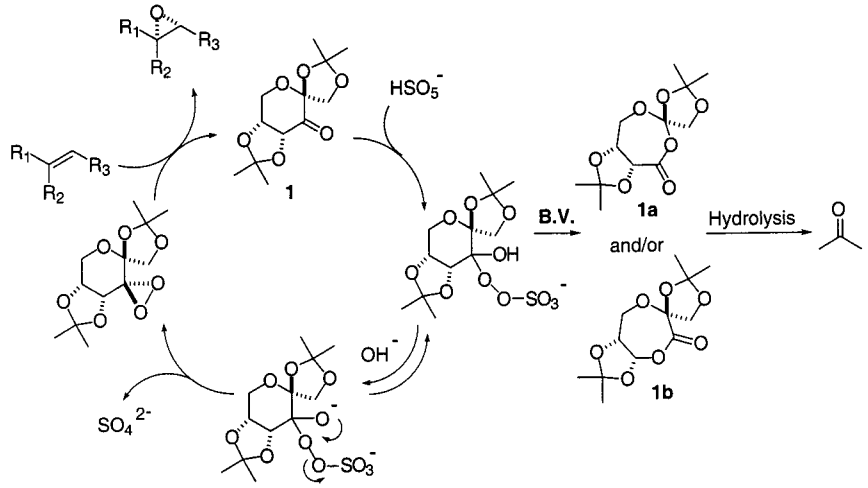
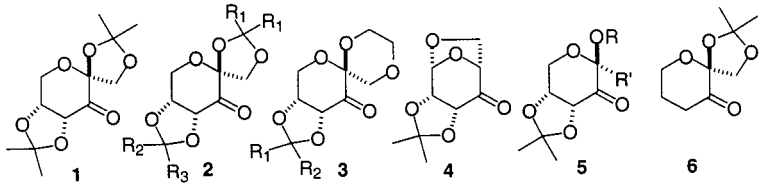
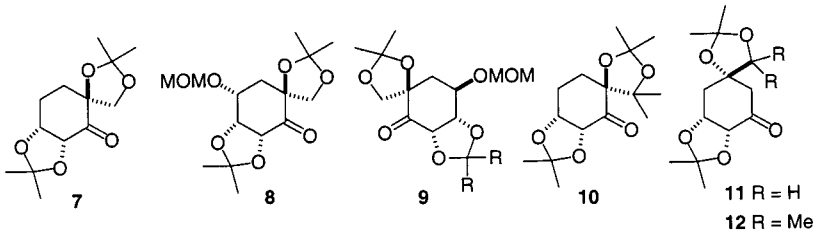
Scheme 1



Scheme 2



Scheme 3



catalyst. To further probe this aspect, ketones **10**, **11**, and **12** were investigated. In ketone **10**, two geminal methyl groups were introduced to the spiro ketal. Ketones **11** and **12** were designed to test whether the chiral element needs to be at the α position.

Ketones **7**−**12** were prepared from D-(−)-quinic acid utilizing existing methodology.[5] The synthesis of ketones **7** and **8** largely adapted the sequences utilized in the synthesis of pseudo-*β*-D-fructopyranose reported by Shing and Maryanoff (Scheme 4).[6,7] Our initial synthetic studies started with ketone **8**. Briefly, compound **13**[6,7] was protected as its MOM ether, reduced, and dihydoxylated to give triol **16b**. The acid-catalyzed ketalization of triol **16b** with 2,2-dimethoxypropane led to a mixture of **17b** and **18b**. Among various acids tested, CSA gave the best ratio (1.1:1). Separation of this mixture was difficult at this stage, however, upon oxidation, ketone **8** could be easily isolated from the mixture and obtained in 42% yield from the triol **16b**. The poor selectivity for the ketalization of triol **16b** was more or less anticipated. To avoid this problem, our earlier plan was to form the spiro ketal using diol **14e**, in which the secondary hydroxyl group was protected as a TBS ether (Scheme 5). Unfortunately, it was found that the reduction of **14d** with $LiAlH_4$ or DIBAL-H led to mostly the formation of triol **16b**, and only a small amount of the desired diol **14e** was formed.[8] Once the synthesis of ketone **8** was completed, ketone **7** was prepared in a similar way (Scheme 4).

Ketone **9** is a "pseudo" enantiomer of ketone **8**, and its synthesis is outlined in Scheme 6. The reported diol **19**[3o,6,7,9] was selectively protected as a MOM ether **20**, which was subsequently dehydrated[9e] to form enoate **21**. Upon reduction and dihydroxylation, enoate **21** was converted to triol **22**. Ketalization of **22** gave a mixture of alcohols **23** and **24** in a ratio of 3.2−3.5:1. In this case, **23** and **24** could be easily separated by flash chromatography. Ketone **9** was then obtained by the oxidation of **23**.

(5) For a review of synthetic application of D-(−)-quinic acid, see: Barco, A.; Benetti, S.; Risi, C. D.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3515.

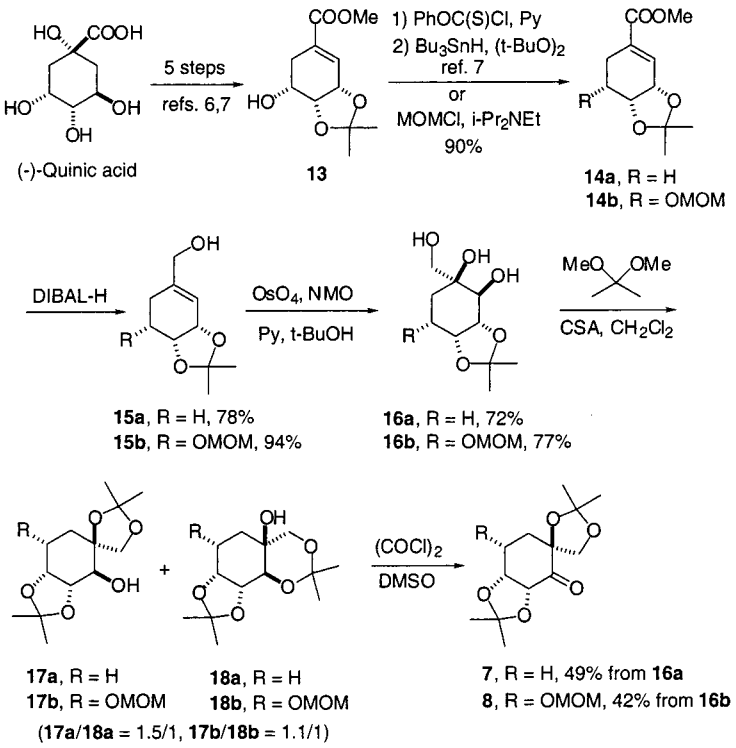
(6) (a) Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 748. (b) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1991**, *47*, 4571.

(7) McComsey, D. F.; Maryanoff, B. E. *J. Org. Chem.* **1994**, *59*, 2652.

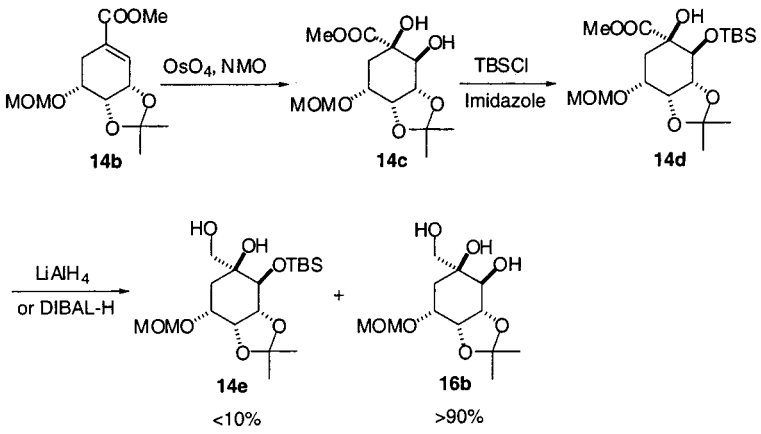
(8) This reductive cleavage of the TBS ether probably proceeded via an intramolecular hydride transfer from alkoxy aluminium hydride. For similar cleavages, see: (a) Brussee, J.; Dofferhoff, F.; Kruse, C. G.; Van der Gen, A. *Tetrahedron* **1990**, *46*, 1653. (b) De Vries, E. F. J.; Brussee, J.; Van der Gen, A. *J. Org. Chem.* **1994**, *59*, 7133. (c) Saravanan, P.; Gupta, S.; DattaGupta, A.; Gupta, S.; Singh, V. K. *Synth. Commun.* **1997**, *27*, 2695 and the references therein.

(9) (a) Lesuisse, D.; Berchtold, G. A. *J. Org. Chem.* **1985**, *50*, 888. (b) Hanessian, S.; Beaulieu, P.; Dube, D. *Tetrahderon Lett.* **1986**, *27*, 5071. (c) Falck, J. R.; Yadagiri, P. *J. Org. Chem.* **1989**, *54*, 5851. (d) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 6575. (e) Ulibarri, G.; Nadler, W.; Skrydstrup, T.; Audrain, H.; Chiaroni, A.; Riche, C.; Grierson, D. S. *J. Org. Chem.* **1995**, *60*, 2753.

Scheme 4



Scheme 5



Ketone **10** with the geminal dimethyl groups at the spiro ketal moiety was prepared from enoate **14a** (Scheme 7). Triol **25** was obtained in high yield by the addition of methylmagnesium bromide to **14a**, followed by dihydroxylation. Acetylation of triol **25** with acetic anhydride gave monoacetate **27** in 75% yield along with a small amount of diacetate **26**. Ketalization of **27** afforded acetate **28**, which was converted to ketone **10** by DIBAL-H reduction and oxidation of the resulting alcohol.

Ketone **11** was synthesized from lactone **30** by reduction, ketalization, and subsequent oxidation in 93% overall yield (Scheme 8).[3o,10] Ketone **12** was also prepared from lactone **30** (Scheme 9). Addition of methylmagnesium bromide to **30** gave triol **32**. Ketalization of **32** with 2,2-dimethoxypropane and CSA initially gave an overprotected product **32a**, which was easily converted to bisacetonide **33** by treating with MeOH and CSA. Compound **33** was then oxidized to give ketone **12**.

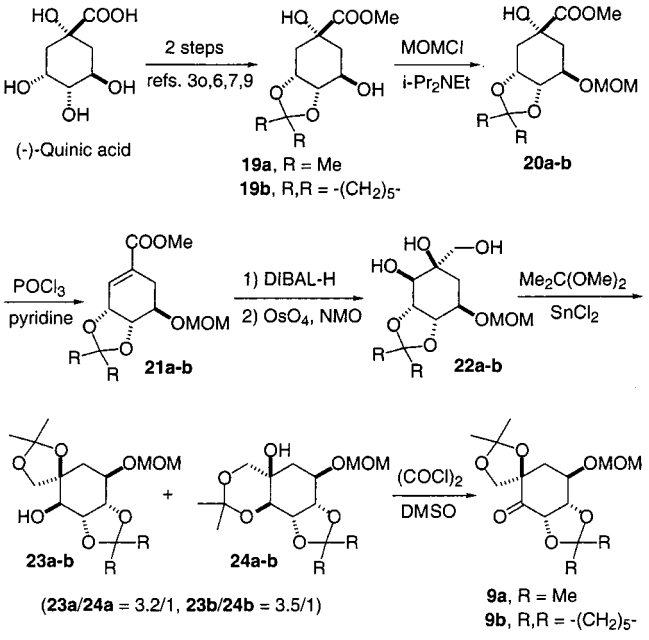
Asymmetric Epoxidation Studies

The ability of ketones **7**−**12** to asymmetrically epoxidize *trans*-β-methylstyrene, *trans*-stilbene, styrene, and 3,3-ethylenedioxycyclohexene was tested. All the epoxidations were carried out in CH_3CN−DMM (1:1 v/v) at pH 10.5−11. The results are shown in Table 1.

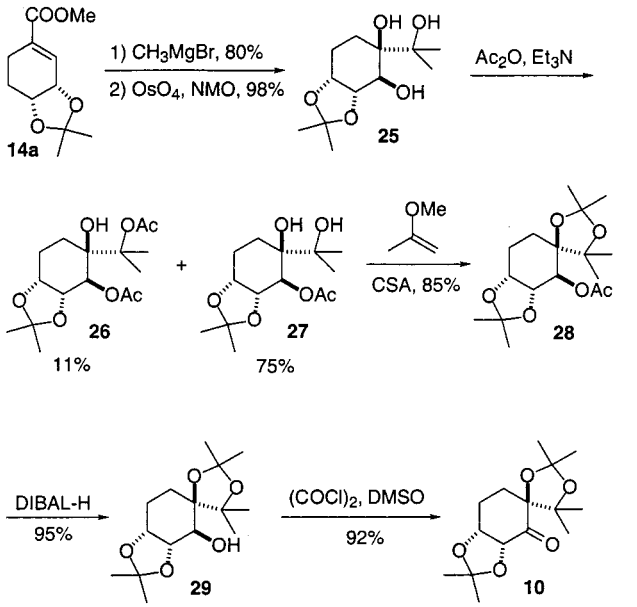
Ketones **7** and **8** are carbocyclic analogues of the fructose-derived ketone **1**. These two ketones showed very similar reactivities and enantioselectivities for all four test substrates. The most dramatic effect in replacing the pyranose oxygen with CH_2 is the decrease in reactivity. Ketone **1** gave a 75% yield of *trans*-stilbene in 1.5 h where ketones **7** and **8** gave ~10% yield in 8 h (Table 1, entries 9−11). These results indicate that the oxygen atom of the pyranose ring in ketone **1** is beneficial for the reactivity. Electronically, the oxygen atom inductively

(10) (a) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332. (b) White, J. D.; Cammack, J. H.; Sakuma, K.; Rewcastle, G. W.; Widener, R. K. *J. Org. Chem.* **1995**, *60*, 3600.

Scheme 6



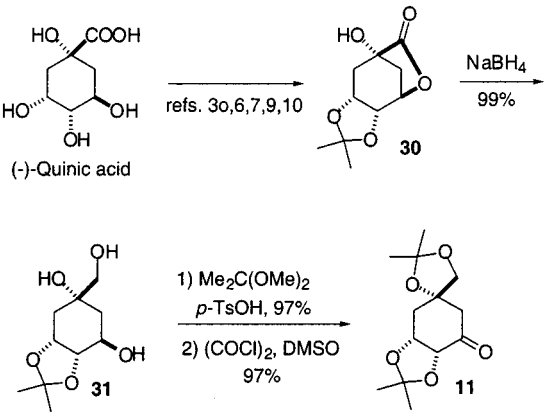
Scheme 7



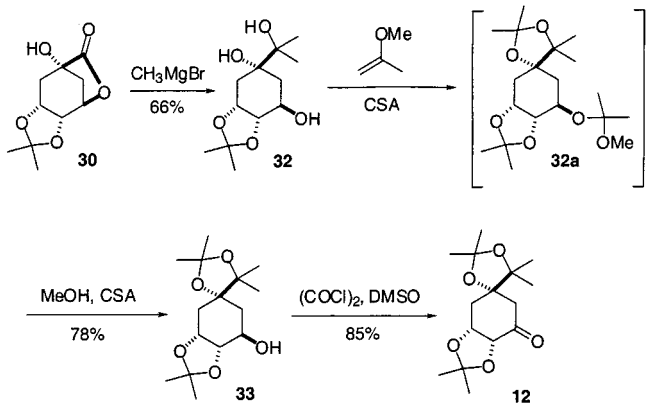
activates the carbonyl group to attack by Oxone, and its replacement with a less electronegative carbon atom reduces the catalyst activity.

Ketone **1** decomposes under the oxidative reaction conditions even at the high pH. It has been thought that the Baeyer−Villiger reaction is the major decomposition pathway, but the corresponding lactones have not been able to be isolated or detected from the reaction mixture, presumably due to the facile hydrolysis of the lactones under the aqueous reaction condition (Scheme 1). To get some ideas about this issue, the Baeyer−Villiger reaction of ketone **1** was carried out using *m*-CPBA under anhydrous conditions.[3o] Interestingly, the product was found to be lactone **1b** while lactone **1a** was barely detectable (Scheme 10). This result suggests that C_4 in ketone **1** is more prone to migrate in the Baeyer−Villiger reaction. However, when ketones **7** and **8** were subjected to the Baeyer−Villiger conditions, substantial amounts of lactones **7a** and **8a** were formed (Scheme 11), indicating that the oxygen of the pyranose ring had a significant effect on the Baeyer−Villiger reaction, thus affecting the catalyst's stability and reactivity. The replacement of the oxygen with a carbon enhanced the relative migratory aptitude of C_2, which could be a result of both electronic and conformational changes brought by the switch from the oxygen to carbon.

Scheme 8

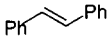
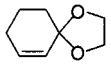


Scheme 9



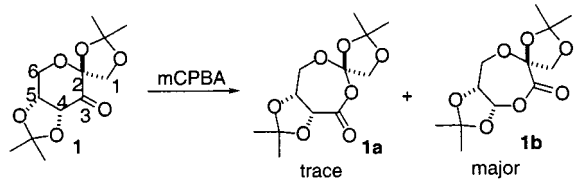
The switch from an oxygen to a carbon in the ring could also cause some conformational changes, possibly affecting catalysis. As indicated by the X-ray structures of ketones **1** and **7** (Figure 1), the spiro five-membered ring ketal moiety of **7** bends more toward C_3, consequently, the methyl group of C_8 is substantially closer to the carbonyl in **7** than in **1** (it should be pointed out that the X-ray structure may not necessarily correspond to the solution structure). There might be a number of factors causing the bending of the spiro ketal ring. The repulsive interaction between the methyl group of C_7 and the methylene group of $C_{6'}$ (i.e., interaction **a**) could be one of the contributing factors (Scheme 12). The bond length change from the C−O bond to C−C bond could be another contributing factor. As indicated previously, spiro **A** and planar **B** are likely two competing transition states for ketone **1** and spiro **A** is favored stereoelectronically (Scheme 13).[4c,h] Spiro **C** and **D** are two analogous transition states for ketone **7**. Compared to spiro **A,** spiro **C** is somewhat disfavored due to the destabilizing steric interaction between the methyl group of the spiro ketal and the olefin (interaction **b**), which provides an explanation for the observation that ketone **7** gives lower conversions and ee's than **1**. On the other hand, it is interesting to note that ketones **7** and **8** gives higher ee's for the terminal and cis-olefins than **1**, suggesting that different

Table 1. Asymmetric Epoxidation of Representative Olefins with Ketones 7−12[a]

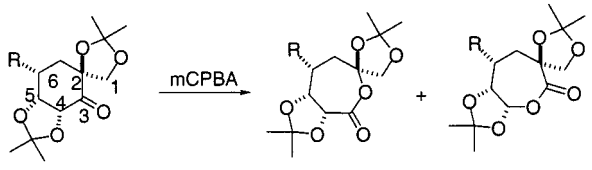
entry	substrate	ketone (equiv)	convn[b] (%)	ee (%)	config[g]
1[c]		**1** (0.3)	93	92[e]	(*R*,*R*)
2		**7** (0.3)	61	87[e]	(*R*,*R*)
3		**8** (0.3)	62	88[e]	(*R*,*R*)
4		**9a** (0.3)	67	77[e]	(*S*,*S*)
5		**9b** (0.3)	64	74[e]	(*S*,*S*)
6		**10**	NR		
7		**11** (0.5)	58	46[e]	(*R*,*R*)
8		**12** (0.5)	56	38[e]	(*R*,*R*)
9[c]		**1** (0.3)	75[d]	97[f]	(*R*,*R*)
10		**7** (0.3)	10[d]	88[f]	(*R*,*R*)
11		**8** (0.3)	11[d]	89[f]	(*R*,*R*)
12		**9b** (0.3)	15[d]	82[f]	(*S*,*S*)
13		**11** (0.5)	33[d]	66[f]	(*R*,*R*)
14		**12** (0.5)	16[d]	72[f]	(*R*,*R*)
15[c]		**1** (0.3)	100	15[e]	(*R*)
16		**7** (0.3)	88	15[e]	(*R*)
17		**8** (0.3)	73	31[e]	(*R*)
18		**9a** (0.3)	90	24[e]	(*S*)
19		**11** (0.5)	36	14[e]	(*R*)
20[c]		**1** (0.3)	53	51[e]	
21		**7** (0.3)	17	61[e]	
22		**8** (0.3)	24	65[e]	
23		**9a** (0.3)	31	29[e]	
24		**9b** (0.3)	42	35[e]	
25		**11** (0.5)	28	36[e]	
26		**12** (0.5)	16	12[e]	

[a] The reactions were carried out with substrate (1 equiv), ketone (0.3−0.5 equiv), Oxone (2.07 equiv), and K_2CO_3 (8.66 equiv) in DMM−CH_3CN (1:1, v/v) and aqueous AcOH−K_2CO_3 (prepared by mixing 100 mL of 0.1 M aqueous K_2CO_3 with 0.5 mL of AcOH) at −10 or 0 °C (−10 °C for *trans*-*β*-methylstyrene and styrene; 0 °C for *trans*-stilbene and 3,3-ethylenedioxycyclohexene). The reactions were stopped after 8 h. [b] The conversions were determined by GC (HP-17 column). [c] The results with ketone **1** were taken from refs 4c,h. [d] Isolated yields. [e] Enantioselectivity was determined by chiral GC (Chiraldex G-TA column). [f] Enantioselectivity was determined by chiral HPLC (Chiralcel OD column). [g] The absolute configurations were determined by comparing the GC and HPLC chromatograms with reported ones.

Scheme 10



Scheme 11



7 R = H **7a** (43%) **7b** (57%)
8 R = OMOM **8a** (29%) **8b** (71%)

types of olefins requires different ketone structural elements for enantioselectivity.

Both ketones **8** and **9** have a methoxy methyl ether group at C_6 but differ in their relative stereochemistry. As shown in Table 1, ketone **9** gave somewhat lower ee's for both *trans*-*β*-methylstyrene and *trans*-stilbene than **8** (Table 1, entries 4, 5, and 12), which could be due to the increased fraction of a presumably less enantioselective dioxirane conformer **9B** in which the MOM ether occupies an equatorial position rather than an axial position as in **9A** (Scheme 14). For ketone **1**, the favorable conformer **1A** is stabilized by the pyranose oxygen via anomeric effect.

Ketone **10** was initially designed to further block the approach of an olefin to the dioxirane from the bottom face by introducing two additional methyl groups to the methylene group (C_1) of the spiro ketal ring. Unfortunately, no epoxidation of *trans*-*β*-methylstyrene was observed even with 1 equiv of ketone **10** (Table 1, entry 6), and most of the ketone was recovered after the reaction. As indicated by the X-ray structure (Figure 2), one of these two methyl groups is very close to the carbonyl group. As a result, the carbonyl group is in a sterically congested environment, and the nucleophilic attack of the carbonyl by Oxone is severely retarded; consequently, Oxone will be consumed by self-decomposition.

Ketones **1** and **7**−**9** have ketals at both α positions. These ketals act as both activating groups and chiral control elements. The results obtained with ketones **11** and **12** show that moving the ketal from the α to *β* position generally lowered the enantioselectivity (Table 1, entries 7, 8, 13, and 14).[11] These results provide further support that the exact size and location of a chiral controlling element is important. It should be close and big enough to give good ee's but too close and too big will retard the reaction at the carbonyl group.

In summary, we have prepared several carbocyclic analogues of fructose-derived ketone **1**, and found that these ketones gave both lower enantioselectivity and reactivity than **1** for the asymmetric epoxidation of *trans*-olefins. The current studies further show that chiral ketone catalyzed epoxidations involve many factors and the structural requirements for the ketone catalyst are very stringent and subtle. Conformational, electronic, and steric effects are all important contributing factors. It appears that with the proper balance of conformational, electronic, and steric effects, carbocyclic ketones would give good reactivities and enantioselectivities. The discovery of effective catalysts will be facilitated by the detailed studies of the relation between ketone structure and catalytic properties.

Experimental Section

General Methods. THF and diethyl ether were distilled from sodium-benzophenone ketyl. Dichloromethane was distilled from calcium hydride. (−)-Quinic acid and Oxone were purchased from Aldrich and used without further purification (it has been found that the oxidation activity of the purchased Oxone occasionally varies with different batches). All glassware used for the epoxidation was carefully washed to be free of any trace metals which may catalyze the decomposition of Oxone. Melting points were obtained using chromatographically purified material unless otherwise stated, and are uncorrected. The 300 MHz ^1H NMR and 75.5 MHz ^{13}C NMR spectra were measured on a Bruker ACE−300 spectrometer in $CDCl_3$. Proton chemical shifts (*δ*) are given relative to internal TMS (0.00 ppm), and carbon chemical shifts are given relative to $CDCl_3$ (77.23 ppm). Elemental analyses were performed by M−H−W Laboratories (Phoenix, AZ). X-ray

(11) A related epoxidation study on ketone **11** has recently been reported see: ref 3n.

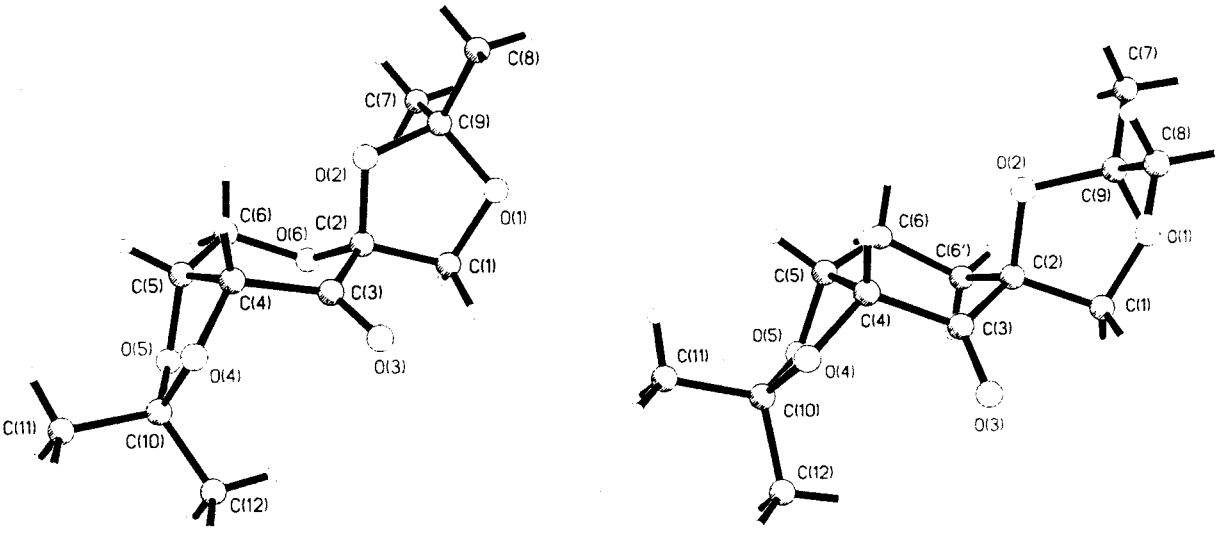
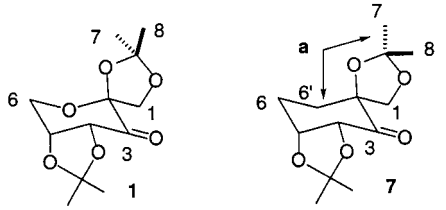
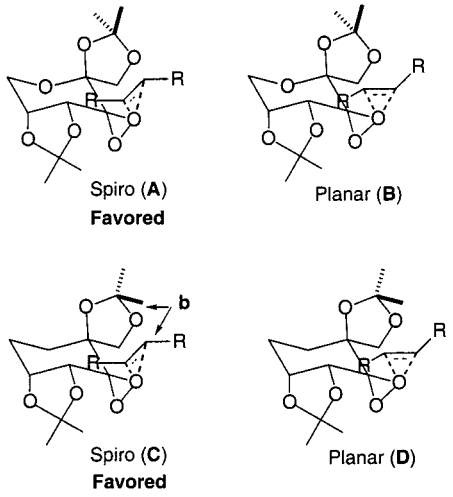


Figure 1. X-ray structure of ketones **1** (left) and **7** (right) (ORTEP view).

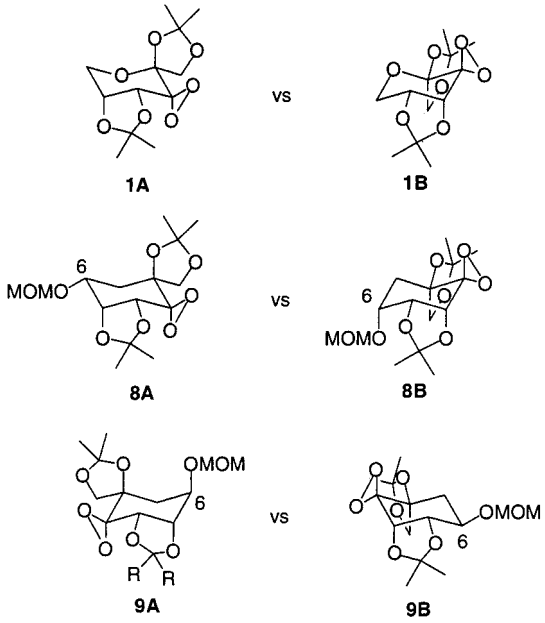
Scheme 12



Scheme 13



Scheme 14



crystallographic analyses of ketones **1**, **7**, and **10** were performed at the X-ray Crystallographic Laboratory of Colorado State University. Silica gel 60 (230−400 mesh) from E. Merck Co. was employed for all flash chromatography.

Preparation of Ketone 7. To a solution of ester **14a**[7] (1.91 g, 9.0 mmol) in THF (10 mL) was added dropwise DIBAL-H (1.0 M in hexane, 18.0 mL, 18.0 mmol) at −20 °C over 15 min. Upon stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), filtered, and washed with ether. The filtrate was concentrated and purified by flash chromatography (hexanes−ethyl acetate, 2:1 v/v) to give **15a** as a colorless syrup (1.3 g, 78.5%).

To a solution of **15a** (1.1 g, 6.0 mmol), *N*-methylmorpholine oxide (NMO) (1.17 g, 10.0 mmol), pyridine (3 mL, 38 mmol), and water (0.54 mL, 30 mmol) in *t*-BuOH (12 mL) was added OsO_4 (0.015 g) under N_2 with stirring. Upon refluxing for 3 h, the reaction mixture was cooled, quenched with saturated aqueous $Na_2S_2O_3$ (5 mL), and concentrated. The resulting residue was filtered through a short silica gel plug and washed with EtOAc and EtOAc−MeOH (5:1). The filtrate was concentrated, and the resulting residue was purified by flash chromatography (EtOAc to EtOAc−MeOH 10:1 v/v) to give triol **16a** as a light yellow oil (0.93 g, 72%): $[\alpha]^{25}_D = -95.0$ (*c* 1.55, $CHCl_3$); IR (NaCl) 3405 cm^{-1}; ^1H NMR δ 4.32 (ddd, J = 5.2, 4.2, 2.4 Hz, 1H), 4.05 (dd, J = 7.5, 5.2 Hz, 1H), 3.73 (d, J = 11.4 Hz, 1H), 3.69 (m, 1H, OH), 3.68 (d, J = 7.5 Hz, 1H), 3.49 (d, J = 11.4 Hz, 1H), 3.30 (br s, 2H, OH), 2.14 (dddd, J = 15.0, 12.0, 6.3, 4.2 Hz, 1H), 1.96 (dm, J = 15.0 Hz, 1H), 1.62 (dd, J = 14.1, 4.5 Hz, 1H), 1.52 (m, 1H), 1.51 (s, 3H), 1.38 (s, 3H); ^{13}C NMR δ 108.9, 80.0, 77.1, 74.0, 72.9, 70.2, 28.6, 27.0, 26.5, 21.5.

To a solution of **16a** (0.72 g, 3.3 mmol), 2,2-dimethoxypropane (0.52 mL, 5.0 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added CSA (5 mg). Upon stirring at 0 °C for 5 h, the reaction mixture was quenched with triethylamine (0.1 mL) and washed with water. The aqueous layers were extracted with CH_2Cl_2 (3 × 15 mL), and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified via flash chromatography (hexanes−ethyl acetate, 3:1 v/v) to

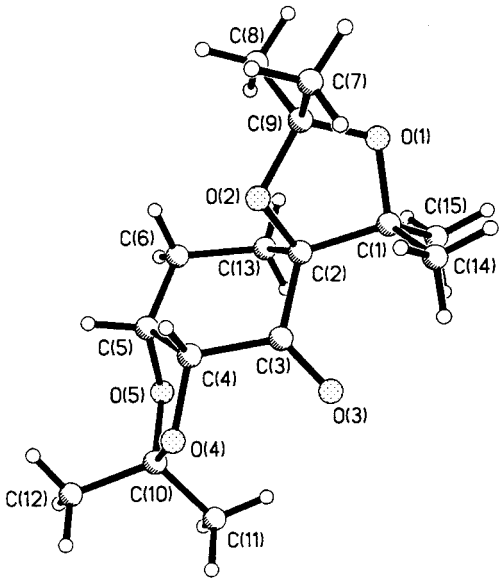


Figure 2. X-ray structure of ketone **10** (ORTEP view).

give a white solid (0.83 g, 97%) (a mixture of **17a** and **18a** in a ratio of 1.5:1 as shown by ^{1}H NMR).

To a solution of DMSO (0.624 g, 8.0 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise oxalyl chloride (0.36 mL, 4.0 mmol) at −78 °C. The solution was stirred at −78 °C for 10 min, then removed from the cold bath for 3 min, and recooled to −78 °C. A solution of the above mixture (**17a** and **18a**) (0.83 g, 1.9 mmol for **17a**) in dry CH_2Cl_2 (5 mL) was added. After the solution was stirred at −78 °C for 1 h, triethylamine (1.55 mL, 11.2 mmol) was added dropwise, and the resulting mixture was stirred at −78 °C for 10 min and then warmed to room temperature. Upon addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with ether, washed with water and brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes−ether, 10:1 to 2:1) and subsequent recrystallization from hexane to give ketone **7** as a white solid (0.41 g, 49% from **16a**): mp 62.0−63.5 °C; $[\alpha]^{25}_D$ = −119.7 (*c* 1.22, $CHCl_3$); IR (NaCl) 1730 cm^{-1}; ^{1}H NMR δ 4.83 (d, *J* = 5.1 Hz, 1H), 4.67 (d, *J* = 8.7 Hz, 1H), 4.60 (ddd, *J* = 5.1, 3.6, 2.1 Hz, 1H), 3.57 (d, *J* = 8.7 Hz, 1H), 2.39 (dddd, *J* = 15.0, 9.9, 8.4, 3.6 Hz, 1H), 2.09 (dddd, *J* = 15.0, 2.4, 2.1, 2.1 Hz, 1H), 2.00−1.93 (m, 2H), 1.45 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 1.27 (s, 3H); ^{13}C NMR δ 205.8, 110.8, 109.9, 85.1, 79.3, 78.0, 68.2, 32.1, 27.3, 27.2, 26.3, 26.2, 22.0. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.80; H, 7.94. Alcohol **18a**: IR (NaCl) 3488 cm^{-1}; ^{1}H NMR δ 4.36 (ddd, *J* = 5.1, 4.2, 2.4 Hz, 1H), 4.03 (dd, *J* = 7.5, 5.1 Hz, 1H), 3.77 (d, *J* = 7.5 Hz, 1H), 3.76 (d, *J* = 12.0 Hz, 1H), 3.46 (d, *J* = 12.0 Hz, 1H), 3.01 (br s, 1H, OH), 2.20 (dddd, *J* = 15.0, 10.2, 7.8, 4.2 Hz, 1H), 1.99 (dddd, *J* = 15.0, 5.1, 2.7, 2.4 Hz, 1H), 1.51 (s, 3H), 1.50−1.45 (m, 2H), 1.49 (s, 6H), 1.36 (s, 3H); ^{13}C NMR δ 108.5, 100.1, 76.5, 75.6, 74.2, 69.6, 67.0, 29.9, 28.7, 26.4, 25.2, 21.7, 18.3.

Preparation of Ketone 8. To a solution of alcohol **13**[6,7] (10.3 g, 45.2 mmol) in dry CH_2Cl_2 (55 mL) were added diisopropylethylamine (12 mL, 70.0 mmol), chloromethyl methyl ether (5.6 mL, 70.0 mmol), and a catalytic amount of DMAP at 0 °C. Upon stirring at room-temperature overnight, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes−ethyl acetate, 4:1 v/v) to give MOM ether **14b** as a colorless syrup (10.4 g, 90%): $[\alpha]^{25}_D$ = −52.0 (*c* 0.99, $CHCl_3$); IR (NaCl) 1718, 1648 cm^{-1}; ^{1}H NMR δ 6.72 (t, *J* = 3.3 Hz, 1H), 4.80 (d, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.74 (m, 1H), 4.49 (m, 1H), 3.89 (ddd, *J* = 10.5, 5.5, 2.4 Hz, 1H), 3.78 (s, 3H), 3.42 (s, 3H), 2.76 (dd, *J* = 16.8, 5.5 Hz, 1H), 2.48 (ddt, *J* = 16.8, 10.5, 2.7 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 166.8, 135.3, 129.1, 110.5, 95.3, 74.6, 73.7, 72.2, 55.7, 52.2, 27.8, 26.6, 24.9.

To a solution of **14b** (8.8 g, 34.0 mmol) in dry THF (10 mL) was added dropwise a solution of diisobutylaluminum hydride (DIBAL-H) (1.0 M in hexane, 70.0 mL, 70.0 mmol) over 20 min at −15 °C. Upon stirring at 0 °C for 1 h, the reaction mixture was quenched with the saturated aqueous NH_4Cl, filtered, washed with ether, and concentrated to give alcohol **15b** as a colorless syrup (7.9 g, 94%), which was used directly for the next step: ^{1}H NMR δ 5.57 (m, 1H), 4.74 (d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.63 (m, 1H), 4.43 (dd, *J* = 5.4, 2.4 Hz, 1H), 3.99 (br s, 2H), 3.83 (ddd, *J* = 10.2, 5.4, 2.4 Hz, 1H), 3.37 (s, 3H), 2.34 (ddm, *J* = 15.6, 10.2 Hz, 1H), 2.23 (br s, 1H, OH), 2.19 (dd, *J* = 15.6, 5.4 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 138.0, 120.3, 109.8, 95.4, 74.9, 74.1, 72.9, 65.7, 55.6, 27.8, 26.7, 26.5.

To a solution of **15b** (7.8 g, 32.0 mmol), *N*-methylmorpholine oxide (NMO) (6.0 g, 51.0 mmol), pyridine (15 mL, 192 mmol), and water (3 mL, 160 mmol) in *t*-BuOH (60 mL) was added OsO_4 (0.06 g) under N_2 with stirring. Upon refluxing for 5 h, the reaction mixture was cooled, quenched with saturated aqueous $Na_2S_2O_3$ (20 mL), and concentrated. The resulting residue was filtered through a short silica gel plug and washed with ethyl acetate and CH_2Cl_2-EtOH (2:1). The filtrate was concentrated, and the resulting residue was recrystallized from hexane-CH_2Cl_2 to give triol **16b** as white crystals (6.8 g, 77%): mp 95.0−97.0 °C; $[\alpha]^{25}_D$ = −31.1 (*c* 0.35, $CHCl_3$); IR (NaCl) 3421 cm^{-1}; ^{1}H NMR δ 4.75 (d, *J* = 6.9 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.42 (t, *J* = 4.5 Hz, 1H), 4.25 (dt, *J* = 11.1, 4.5 Hz, 1H), 4.10 (dd, *J* = 7.2, 4.5 Hz, 1H), 3.70 (d, *J* = 7.2 Hz, 1H), 3.66 (d, *J* = 11.1 Hz, 1H), 3.49 (d, *J* = 11.1 Hz, 1H), 3.39 (s, 3H), 1.89 (dd, *J* = 13.5, 4.5 Hz, 1H), 1.75 (dd, *J* = 13.5, 11.1 Hz, 1H), 1.53 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 110.0, 96.1, 80.3, 77.7, 75.6, 73.4, 70.5, 69.4, 55.7, 32.7, 28.4, 26.3. Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97. Found: C, 51.88; H, 7.89.

To a suspension of **16b** (1.38 g, 5.0 mmol) in 2,2-dimethoxypropane (20 mL) was added catalytic amount of CSA at 0 °C with stirring. After being stirred at 0 °C for 2 h, the reaction mixture was slowly warmed to room temperature and stirred at this temperature for additional 2 h. The reaction was then quenched with triethylamine (0.2 mL) and diluted with water and ether. The aqueous solution was extracted with ether. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes−ethyl acetate, 5:1 to 1:1 v/v) to afford a colorless syrup (a mixture of **17b** and **18b** in a ratio of 1.1:1 as shown by ^{1}H NMR).

To a solution of DMSO (0.69 g, 8.9 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise oxalyl chloride (0.43 mL, 4.45 mmol) at −78 °C. The solution was stirred at −78 °C for 10 min, then removed from the cold bath for 3 min, and recooled to −78 °C. A solution of the above mixture (**17b** and **18b**) in dry CH_2Cl_2 (5 mL) was added. After the solution was stirred at −78 °C for 1 h, triethylamine (1.86 mL, 13.5 mmol) was added dropwise, and the resulting mixture was stirred at −78 °C for 10 min, then warmed to room temperature. Upon addition of saturated aqueous NH_4Cl (20 mL), the reaction mixture was extracted with ether, washed with water and brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes−ethyl acetate, 5:1 to 2:1) to give ketone **8** as a light yellow syrup, which was further recrystallized from hexane to give white crystals (0.66 g, 42% from **16b**): mp 53.0−54.0 °C; $[\alpha]^{25}_D$ = −41.7 (*c* 0.64, CH_2Cl_2); IR (NaCl) 1743 cm^{-1}; ^{1}H NMR δ 4.82 (d, *J* = 5.1 Hz, 1H), 4.80 (d, *J* = 6.9 Hz, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 4.70 (ddd, *J* = 5.1, 3.3, 1.2 Hz, 1H), 4.67 (d, *J* = 8.8 Hz, 1H), 4.50 (ddd, *J* = 11.1, 5.4, 3.3 Hz, 1H), 3.61 (d, *J* = 8.8 Hz, 1H), 3.43 (s, 3H), 2.25 (ddd, *J* = 13.5, 5.4, 1.2 Hz, 1H), 2.17 (dd, *J* = 13.5, 11.1 Hz, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.26 (s, 3H); ^{13}C NMR δ 204.1, 111.4, 111.1, 96.5, 83.2, 78.6, 77.9, 70.0, 68.4, 55.9, 36.7, 27.2, 27.1, 26.2 (2C). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 57.14; H, 7.69.

Preparation of Ketone 9a. To a solution of **19a**[3o] (6.3 g, 25.0 mmol), diisopropylethylamine (6.3 mL, 35.0 mmol) and DMAP (catalytic) in CH_2Cl_2 (50 mL) at 0 °C was added dropwise chloromethyl methyl ether (2.81 g, 35.0 mmol). After

being stirred at 0 °C for 15 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), and concentrated to give **20a** as a yellow syrup which was used for the next step without further purification.

To a solution of the above crude **20a** in pyridine (50 mL) at 0 °C was added $POCl_3$ (2.5 mL). After being stirred at room temperature for 3 h, the reaction mixture was diluted with ether and quenched with saturated aqueous NH_4Cl at 0 °C. The aqueous layers were extracted with ether (4 × 30 mL), washed with water (3 × 50 mL), dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes−ether, 2:1) to give **21a** as a colorless syrup (3.7 g, 54% from **19a**): $[\alpha]^{25}_D = -34.4$ (*c* 0.57, $CHCl_3$); IR (NaCl) 1719 cm^{-1}; ^1H NMR δ 6.89 (dt, J = 3.6, 1.5 Hz, 1H), 4.73 (s, 2H), 4.73 (m, 1H), 4.20 (dd, J = 6.9, 6.0 Hz, 1H), 3.94 (td, J = 6.9, 4.2 Hz, 1H), 3.76 (s, 3H), 3.38 (s, 3H), 2.73 (dm, J = 17.1 Hz, 1H), 2.35 (ddt, J = 17.1, 6.9, 1.5 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 166.9, 134.6, 130.0, 109.8, 95.8, 75.9, 73.2, 72.4, 55.7, 52.3, 28.1, 27.1, 26.1

To a solution of **21a** (2.3 g, 8.5 mmol) in dry THF (10 mL) was added dropwise a solution of DIBAL-H (1.0 M in hexane, 18.0 mL, 18.0 mmol) over 20 min at −15 °C. Upon stirring at 0 °C for 1 h, the reaction mixture was quenched with the saturated aqueous NH_4Cl, filtered, and washed with ether. The filtrate was concentrated to give the allylic alcohol as a colorless syrup (2.2 g, 100%) which was used directly for the next step.

To a solution of the above allylic alcohol (2.2 g, 8.5 mmol), NMO (1.76 g, 15.0 mmol), pyridine (4.2 mL, 27.0 mmol), water (0.85 mL, 24.0 mmol) in t-BuOH (16 mL) was added OsO_4 (0.015 g) under N_2 with stirring. Upon refluxing for 6 h, the reaction mixture was cooled, quenched with saturated aqueous $Na_2S_2O_3$ (5 mL), and concentrated. The resulting residue was filtered through a short silica gel plug, and washed with ethyl acetate and CH_2Cl_2-EtOH (2:1). The filtrate was concentrated, and the residue was purified by flash chromatography (ethyl acetate−hexane, 2:1 to 1:0 v/v) to give triol **22a** as a light yellow syrup (1.4 g, 77%): $[\alpha]^{25}_D = +25.7$ (*c* 0.35, $CHCl_3$); IR (NaCl) 3439 cm^{-1}; ^1H NMR δ 4.74 (d, J = 6.7 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H), 4.32−4.23 (m, 2H), 3.94 (dt, J = 7.5, 4.8 Hz, 1H), 3.77 (m, 2H), 3.68 (dd, J = 6.3, 5.4 Hz, 1H), 3.61 (dd, J = 11.2, 4.2 Hz, 1H), 3.55 (dd, J = 11.2, 6.0 Hz, 1H), 3.38 (s, 3H), 1.98 (dd, J = 14.7, 4.8 Hz, 1H), 1.80 (dd, J = 14.7, 7.5 Hz, 1H), 1.49 (s, 3H), 1.36 (s, 3H); ^{13}C NMR δ 109.6, 95.8, 78.2, 77.5, 73.6, 73.3, 73.1, 67.9, 55.8, 34.0, 27.9, 25.6.

To a solution of triol **22a** (0.42 g, 1.5 mmol) in 2,2-dimethoxypropane (5 mL) was added a solution of catalytic amount of $SnCl_2$ in 1,2-dimethoxyethane (0.2 mL) at −10 °C with stirring. After stirring at −10 °C for 12 h, the reaction mixture was slowly warmed to 0 °C and stirred at this temperature for another 2 h. The reaction mixture was then quenched with triethylamine (0.2 mL) and diluted with water and ether. The aqueous solution was extracted with ether. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated to give a yellow syrup (a mixture of **23a** and **24a** in a ratio of 3.2:1 as judged by ^1H NMR). The mixture was separated by flash chromatography (hexanes−ethyl acetate, 5:1 to 1:1 v/v) to afford **23a** as a colorless oil (0.29 g, 62%) and **24a** as a colorless oil (0.09 g, 19%). **23a**: $[\alpha]^{25}_D = -51.1$ (*c* 0.19, $CHCl_3$); IR (NaCl) 3485 cm^{-1}; ^1H NMR δ 4.77 (d, J = 6.6 Hz, 1H), 4.70 (dd, J = 6.6, 0.6 Hz, 1H), 4.33 (dd, J = 6.0, 3.1 Hz, 1H), 4.22 (d, J = 9.0 Hz, 1H), 4.11 (dd, J = 7.8, 6.0 Hz, 1H), 3.88 (dd, J = 3.1, 2.4 Hz, 1H), 3.84 (d, J = 9.0 Hz, 1H), 3.57 (ddd, J = 12.3, 7.8, 4.5 Hz, 1H), 3.39 (s, 3H), 2.62 (d, J = 2.4 Hz, 1H, OH), 2.06 (dd, J = 12.9, 12.3 Hz, 1H), 1.82 (ddd, J = 12.9, 4.5, 0.6 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 109.5, 109.2, 95.3, 81.9, 78.0, 77.5, 74.2, 71.5, 70.6, 55.6, 34.5, 28.1, 27.7, 26.6, 25.9. Anal. Calcd for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23. Found: C, 56.50; H,7.99. **24a**: ^1H NMR δ 4.78 (d, J = 6.9 Hz, 1H), 4.69 (d, J = 6.9 Hz, 1H), 4.41−4.32 (m, 2H), 3.85 (d, J = 6.6 Hz, 1H), 3.80 (m, 1H), 3.78 (d, J = 12.0 Hz, 1H), 3.57 (d, J = 12.0 Hz, 1H), 3.40 (s, 3H), 3.21 (br s, 1H, OH), 1.86 (ddd, J = 14.8, 7.5, 0.9 Hz, 1H), 1.70 (dd, J = 14.8, 8.8 Hz, 1H), 1.51 (s, 3H), 1.50 (s, 6H), 1.36 (s, 3H).

Ketone **9a** was prepared in a way similar to that of ketone **8**, using DMSO (0.117 g, 1.5 mmol), oxalyl chloride (0.072 mL, 0.75 mmol), **23a** (0.16 g, 0.5 mmol), triethylamine (0.34 mL, 2.45 mmol), and CH_2Cl_2 (total 2.0 mL). Ketone **9a** was obtained as a colorless syrup (0.15 g, 98%) after flash chromatography (hexanes−ethyl acetate, 5:1 to 2:1): $[\alpha]^{25}_D = -42.9$ (*c* 0.49, CH_2Cl_2); IR (NaCl) 1741 cm^{-1}; ^1H NMR δ 4.73 (d, J = 6.9 Hz, 1H), 4.64 (d, J = 7.3 Hz, 1H), 4.62 (d, J = 6.9 Hz, 1H), 4.57 (ddd, J = 7.3, 4.2, 1.2 Hz, 1H), 4.34 (d, J = 9.0 Hz, 1H), 3.80 (ddd, J = 6.0, 4.2, 3.3 Hz, 1H), 3.78 (d, J = 9.0 Hz, 1H), 3.34 (s, 3H), 2.44 (dd, J = 15.2, 3.3 Hz, 1H), 2.29 (ddd, J = 15.2, 6.0, 1.2 Hz, 1H), 1.50 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 203.7, 111.6, 111.4, 95.0, 82.2, 79.9, 77.5, 72.3, 70.8, 55.8, 37.3, 26.7, 26.5, 26.1, 24.7. Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.74; H, 7.49.

Preparation of Ketone 9b. Enoate **21b** was prepared from **19b**[9d] in a way similar to that of **21a**: colorless syrup (57% yield); $[\alpha]^{25}_D = -47.8$ (*c* 0.41, $CHCl_3$); IR (NaCl) 1722, 1654 cm^{-1}; ^1H NMR δ 6.91 (ddd, J = 3.3, 1.8, 1.2 Hz, 1H), 4.74 (s, 2H), 4.73 (m, 1H), 4.20 (dd, J = 6.6, 6.0 Hz, 1H), 3.97 (td, J = 6.6, 4.5 Hz, 1H), 3.77 (s, 3H), 3.39 (s, 3H), 2.73 (ddt, J = 17.7, 4.5, 1.2 Hz, 1H), 2.35 (ddt, J = 17.7, 6.6, 1.8 Hz, 1H), 1.70−1.50 (m, 8H), 1.40 (m, 2H); ^{13}C NMR δ 166.9, 134.9, 129.9, 110.4, 95.8, 75.5, 73.2, 72.0, 55.7, 52.3, 38.0, 35.6, 27.2, 25.2, 24.2, 23.9.

Triol **22b** was prepared from **21b** in a way similar to that of triol **22a**: white crystals (71% yield); mp 104.0−105.5 °C (recrystallized from hexanes−ether); $[\alpha]^{25}_D = +25.3$ (*c* 0.28, $CHCl_3$); IR (NaCl) 3420 cm^{-1}; ^1H NMR δ 4.76 (d, J = 6.6 Hz, 1H), 4.72 (d, J = 6.6 Hz, 1H), 4.29 (dd, J = 4.8, 1.8 Hz, 1H), 4.26 (d, J = 4.8 Hz, 1H), 4.04 (td, J = 6.3, 4.8 Hz, 1H), 3.71−3.64 (m, 1H), 3.67 (d, J = 11.1 Hz, 1H), 3.54 (d, J = 11.1 Hz, 1H), 3.41 (s, 3H), 1.95 (dd, J = 14.8, 4.8 Hz, 1H), 1.89 (dd, J = 14.8, 6.3 Hz, 1H), 1.75−1.50 (m, 8 H), 1.45−1.30 (m, 2H); ^{13}C NMR δ 110.4, 95.8, 77.9, 73.7, 73.6, 73.2, 69.3, 68.2, 56.0, 37.9, 35.1, 33.4, 25.2, 24.2, 23.8. Anal. Calcd for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23. Found: C, 56.61; H, 8.03.

Ketalization of **22b** (1.2 g, 3.77 mmol) in a way similar to that of **22a** led to the formation of a mixture of **23b** and **24b** in a ratio of 3.5:1. The mixture was separated by flash chromatography (hexanes−ethyl acetate, 5:1 to 1:1 v/v) to give **23b** as a white crystal (1.05 g, 77%) and **24b** as a colorless syrup (0.25 g, 19%). **23b**: mp 106−108 °C; $[\alpha]^{25}_D = -38.8$ (*c* 0.41, $CHCl_3$); IR (NaCl) 3484 cm^{-1}; ^1H NMR δ 4.78 (d, J = 6.9 Hz, 1H), 4.71 (d, J = 6.9 Hz, 1H), 4.32 (dd, J = 5.7, 3.0 Hz, 1H), 4.26 (d, J = 8.9 Hz, 1H), 4.09 (dd, J = 7.8, 5.7 Hz, 1H), 3.92 (br d, J = 3.0 Hz, 1H), 3.83 (d, J = 8.9 Hz, 1H), 3.55 (ddd, J = 12.6, 7.8, 4.5 Hz, 1H), 3.40 (s, 3H), 2.61 (br s, 1H, OH), 2.07 (t, J = 12.6 Hz, 1H), 1.78 (ddd, J = 12.6, 4.5, 0.9 Hz, 1H), 1.70−1.30 (m, 10 H), 1.46 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 109.8, 109.4, 95.2, 81.9, 77.6, 77.1, 74.5, 71.5, 70.5, 55.6, 38.3, 35.2, 34.2, 27.8, 26.5, 25.2, 24.2, 23.9. Anal. Calcd for $C_{18}H_{30}O_7$: C, 60.32; H, 8.44. Found: C, 60.65; H, 8.32. **24b**: IR (NaCl) 3486 cm^{-1}; ^1H NMR δ 4.81 (d, J = 6.9 Hz, 1H), 4.71 (d, J = 6.9 Hz, 1H), 4.40−4.30 (m, 2H), 3.90−3.80 (m, 2H), 3.77 (d, J = 11.7 Hz, 1H), 3.57 (d, J = 11.7 Hz, 1H), 3.40 (s, 3H), 3.22 (br s, 1H, OH), 1.84 (ddd, J = 14.7, 7.2, 1.8 Hz, 1H), 1.75−1.25 (m, 11H), 1.50 (s, 6H).

Alcohol **23b** (1.10 g, 3.08 mmol) was oxidized in a way similar to that of **23a** to afford ketone **9b** as a colorless syrup (1.05 g, 97%): $[\alpha]^{25}_D = -38.8$ (*c* 0.76, CH_2Cl_2); IR (NaCl) 1742 cm^{-1}; ^1H NMR δ 4.77 (d, J = 6.9 Hz, 1H), 4.66 (d, J = 6.9 Hz, 1H), 4.63 (d, J = 7.2 Hz, 1H), 4.59 (ddd, J = 7.2, 3.9, 1.5 Hz, 1H), 4.38 (d, J = 9.0 Hz, 1H), 3.86 (ddd, J = 6.0, 3.9, 3.0 Hz, 1H), 3.83 (d, J = 9.0 Hz, 1H), 3.37 (s, 3H), 2.49 (dd, J = 15.0, 3.0 Hz, 1H), 2.32 (ddd, J = 15.0, 6.0, 1.5 Hz, 1H), 1.80−1.20 (m, 10H), 1.47 (s, 3H), 1.43 (s, 3H); ^{13}C NMR δ 204.0, 112.3, 111.6, 94.9, 82.2, 79.6, 77.2, 72.7, 70.8, 55.8, 37.3, 36.4, 34.1, 26.7, 26.1, 25.2, 24.1, 23.6. Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.39; H, 7.76.

Preparation of Ketone 10. To a solution of enoate **14a** (0.954 g, 4.5 mmol) in dry THF (10 mL) was added dropwise methylmagnesium bromide (3 M in ether, 4.5 mL, 13.5 mmol)

at 0 °C under N_2. Upon stirring at 0 °C for 1 h and at room temperature for additional 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (3 × 20 mL), washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes−ethyl acetate, 3:1 to 2:1 v/v) to give the allylic alcohol as a colorless oil (0.76 g, 80%).

To a solution of the above allylic alcohol (0.7 g, 3.3 mmol), NMO (0.71 g, 6.0 mmol), pyridine (1.67 mL, 20 mmol), and water (0.3 mL, 16 mmol) in *t*-BuOH (7 mL) was added OsO_4 (0.01 g) under N_2. Upon refluxing under N_2 for 4 h, the reaction mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ (3 mL) (stirred for 15 min), concentrated, and purified by flash chromatography (hexanes−ethyl acetate, 2:1 to 1:2 v/v) to give triol **25** as a white solid (0.8 g, 98%). mp 111.0−112.0 °C; $[\alpha]^{23}_D = -91.9$ (*c* 0.42, $CHCl_3$); IR (NaCl) 3384 cm^{-1}; ^1H NMR δ 4.32 (ddd, J = 5.1, 4.5, 2.4 Hz, 1H), 4.12 (dd, J = 7.5, 5.1 Hz, 1H), 3.88 (d, J = 7.5 Hz, 1H), 3.90 (br s, 1H, OH), 3.35 (br s, 1H, OH), 2.10 (dddd, J = 15.0, 11.1, 7.8, 4.5 Hz, 1H), 1.94 (dddd, J = 15.0, 3.9, 2.4, 2.4 Hz, 1H), 1.60−1.50 (m, 2H), 1.50 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.16 (s, 3H); ^{13}C NMR δ 108.8, 80.8, 76.8, 76.1, 75.7, 74.2, 28.8, 26.5, 26.3, 25.7, 23.9, 22.2. Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.53; H, 9.09.

To a solution of **25** (0.68 g, 2.76 mmol), triethylamine (0.6 mL, 4.3 mmol), DMAP (catalytic) in dry CH_2Cl_2 (10 mL) was added acetic anhydride (0.32 g, 3.2 mmol) at 0 °C with stirring. Upon stirring at 0 °C for 15 h, then room temperature for 5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (3 × 20 mL), washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes−ether 5:1 to 1:1) gave monoacetate **27** as a colorless syrup (0.6 g, 75%) and bisacetate **26** (0.10 g, 11%). **27**: $[\alpha]^{25}_D = -105.3$ (*c* 0.74, $CHCl_3$); IR (NaCl) 3468, 1742, 1718 cm^{-1}; ^1H NMR δ 5.22 (d, J = 7.8 Hz, 1H), 4.33 (ddd, J = 5.1, 4.2, 2.1 Hz, 1H), 4.20 (dd, J = 7.8, 5.1 Hz, 1H), 2.93 (s, 1H, OH), 2.12 (s, 3H), 2.12 (m, 1H), 1.99 (m, 1H), 1.94 (s, 1H, OH), 1.73−1.65 (m, 2H), 1.55 (s, 3H), 1.36 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H); ^{13}C NMR δ 170.2, 109.1, 79.1, 77.2, 76.3, 76.1, 74.1, 27.9, 26.7, 26.5, 25.5, 25.3, 21.92, 21.86. Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.39; H, 8.49.

A solution of diol **27** (0.52 g, 1.8 mmol) and CSA (catalytic amount) in 2-methoxypropene (5 mL) was stirred at 0 °C for 4 h. The reaction mixture was then quenched by adding several drops of triethylamine, concentrated, and purified by flash chromatography (hexanes−ether, 10:1 to 2:1 v/v) to give **28** as a white crystal (0.5 g, 85%): mp 118.0−120.0 °C; $[\alpha]^{25}_D = -109.9$ (*c* 0.74, $CHCl_3$); IR (NaCl) 1740 cm^{-1}; ^1H NMR δ 5.04 (d, J = 7.8 Hz, 1H), 4.31 (m, 1H), 4.15 (dd, J = 7.8, 5.1 Hz, 1H), 2.15−2.00 (m, 2H), 2.11 (s, 3H), 1.83 (ddd, J = 14.1, 4.2, 3.3 Hz, 1H), 1.63 (m, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR: δ 170.5, 109.1, 107.5, 85.4, 82.9, 79.7, 73.9, 73.2, 30.1, 29.2, 27.9, 27.2, 26.8, 25.9, 25.3, 22.3, 22.0. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 61.97; H, 8.58.

To a solution of acetate **28** (0.47 g, 1.43 mmol) in dry THF (2 mL) was added dropwise DIBAL-H (1 M in hexane, 3.0 mL, 3.0 mmol) at −20 °C over 15 min. Upon stirring at 0 °C for additional 0.5 h, the reaction mixture was then quenched with saturated aqueous NH_4Cl (1 mL), filtered, and washed with ether. The filtrate was concentrated and purified by flash chromatography (hexanes−ether, 2:1, v/v) to give **29** as a colorless syrup (0.39 g, 95%): $[\alpha]^{25}_D = -46.1$ (*c* 0.93, $CHCl_3$); IR (NaCl) 3485 cm^{-1}; ^1H NMR δ 4.33 (ddd, J = 5.7, 4.2, 2.7 Hz, 1H), 4.13 (dd, J = 6.6, 5.7 Hz, 1H), 3.67 (d, J = 6.6 Hz, 1H), 2.48 (br s, 1H, OH), 2.03 (dddd, J = 15.0, 11.5, 5.1, 4.2 Hz, 1H), 1.87 (dtd, J = 15.0, 4.2, 3.0 Hz, 1H), 1.70−1.60 (m, 2H), 1.52 (s, 3H), 1.50 (s, 3H), 1.45 (s, 6H), 1.37 (s, 3H), 1.29 (s, 3H); ^{13}C NMR δ 108.7, 107.6, 85.2, 83.8, 80.5, 73.4, 72.1, 30.1, 29.4, 28.2, 26.30, 26.25, 26.0, 25.4, 23.1. Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.16; H, 8.93.

Ketone **10** was prepared in a way similar to that of ketone **8**, using DMSO (0.302 g, 3.87 mmol), oxalyl chloride (0.175 mL, 1.94 mmol), **29** (0.37 g, 1.29 mmol), triethylamine (0.75 mL), and CH_2Cl_2 (total 3 mL). Ketone **10** was obtained as a white crystal (0.34 g, 92%) after flash chromatography (hexanes−ether 10:1) and subsequent recrystallization from hexane. mp 89.0−90.5 °C; $[\alpha]^{25}_D = -119.6$ (*c* 1.14, $CHCl_3$); IR (NaCl) 1738 cm^{-1}; ^1H NMR δ 4.85 (d, J = 6.0 Hz, 1H), 4.65 (m, 1H), 2.31 (dddd, J = 15.0, 13.5, 4.8, 4.2 Hz, 1H), 2.17 (dddd, J = 14.4, 4.8, 1.8, 1.5 Hz, 1H), 2.06 (dm, J = 15.0 Hz, 1H), 1.85 (ddd, J = 14.4, 13.5, 4.5 Hz, 1H), 1.52 (s, 3H), 1.47 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR δ 205.1, 109.8, 108.1, 90.0, 82.1, 80.9, 79.1, 31.0, 30.2, 29.3, 27.3, 26.4 (2C), 23.7, 22.0. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.59; H, 8.51.

Preparation of Ketone 11. To a suspension of triol **31**[30] (0.438 g, 2.0 mmol), 2,2-dimethoxypropane (0.44 mL, 3.0 mmol) in dry CH_2Cl_2 (4 mL) was added a catalytic amount of *p*-TsOH. Upon stirring at room temperature for 2 h, the reaction mixture was quenched with several drops of triethylamine, concentrated, and purified by flash chromatography (hexanes−ethyl acetate, 2:1 to 1:1 v/v) to give the alcohol as a colorless oil (0.5 g, 97%): IR (NaCl) 3456 cm^{-1}; ^1H NMR δ 4.30 (ddd, J = 5.7, 5.4, 5.1 Hz, 1H), 4.11 (ddd, J = 9.4, 6.0, 3.8 Hz, 1H), 3.87 (dd, J = 6.0, 5.7 Hz, 1H), 3.80 (d, J = 8.4 Hz, 1H), 3.74 (d, J = 8.4 Hz, 1H), 2.20 (br s, 1H, OH), 2.10−2.00 (m, 2H), 1.93 (dd, J = 14.7, 5.4 Hz, 1H), 1.55 (dd, J = 13.8, 9.4 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 6H), 1.35 (s, 3H); ^{13}C NMR δ 109.6, 109.1, 79.7, 79.3, 74.5, 73.3, 68.8, 39.2, 36.6, 28.3, 27.5, 27.3, 25.9.

Ketone **11** was prepared in a way similar to **8** utilizing the Swern oxidation. Ketone **11** was obtained as a white solid (0.44 g, 97%) from the above alcohol (0.452 g, 1.75 mmol) after the purification by flash chromatography (hexanes−ether, 10:1 to 5:1 v/v): mp 109.0−110.5 °C; $[\alpha]^{25}_D = -59.0$ (*c* 1.15, $CHCl_3$); IR (NaCl) 1719 cm^{-1}; ^1H NMR δ 4.60 (ddd, J = 6.3, 4.9, 3.0 Hz, 1H), 4.30 (d, J = 6.3 Hz, 1H), 3.81 (d, J = 8.5 Hz, 1H), 3.77 (d, J = 8.5 Hz, 1H), 2.67 (dd, J = 14.0, 2.4 Hz, 1H), 2.54 (dd, J = 14.0, 0.6 Hz, 1H), 2.33 (ddd, J = 15.3, 3.0, 2.4 Hz, 1H), 2.15 (dd, J = 15.3, 4.9 Hz, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR δ 204.6, 111.0, 110.6, 81.8, 78.8, 75.4, 74.0, 49.1, 36.2, 27.5, 27.3, 26.9, 26.0. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.82; H, 7.85.

Preparation of Ketone 12. To a solution of lactone **30** (1.06 g, 5.0 mmol) in dry THF (10 mL) was added dropwise methylmagnesium bromide (3 M in ether, 7.0 mL, 21.0 mmol) at 0 °C under N_2. Upon stirring at room temperature over 5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes−ethyl acetate, 1:1 v/v) to give triol **32** as a colorless syrup (0.8 g, 66%).

A solution of **32** (0.42 g, 1.7 mmol) and CSA (catalytic) in 2-methoxypropene (5 mL) was stirred at 0 °C for 1 h. At this point, the reaction mixture turned into a clear solution, and no starting material was left as shown by TLC. Upon addition of MeOH (5 mL), the reaction mixture was stirred at 0 °C for another 10 min, then quenched with several drops of triethylamine, concentrated, and purified by flash chromatography (hexanes−ethyl acetate, 2:1 to 1:1 v/v) to give alcohol **33** as a light yellow syrup (0.39 g, 78%): $[\alpha]^{25}_D = -47.8$ (*c* 1.37, $CHCl_3$); IR (NaCl) 3459 cm^{-1}; ^1H NMR δ 4.35 (m, 1H), 4.13 (m, 1H), 3.85 (dd, J = 7.8, 5.7 Hz, 1H), 2.20−2.05 (m, 2H), 1.72 (dd, J = 15.6, 5.7 Hz, 1H), 1.54 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.27 (m, 1H), 1.25 (s, 3H), 1.21 (s, 3H); ^{13}C NMR δ 109.2, 107.4, 83.6, 83.0, 81.9, 73.9, 69.6, 36.8, 33.7, 30.0, 29.8, 28.6, 26.1, 24.5, 23.8.

Ketone **12** was prepared in a way similar to **8** utilizing the Swern oxidation. Ketone **12** was obtained as white needles (0.32 g, 85%) from alcohol **33** (0.38 g, 1.33 mmol) after recrystallization from hexane. mp 145.0−146.0 °C; $[\alpha]^{25}_D = -46.4$ (*c* 0.86, $CHCl_3$); IR (NaCl) 1722 cm^{-1}; ^1H NMR δ 4.72 (m, 1H), 4.37 (d, J = 6.0 Hz, 1H), 2.83 (dd, J = 12.9, 3.0 Hz, 1H), 2.47 (dm, J = 15.6 Hz, 1H), 2.43 (d, J = 12.9 Hz, 1H), 1.97 (dd, J = 15.6, 4.8 Hz, 1H), 1.47 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H); ^{13}C NMR δ 205.5, 110.6, 108.4, 86.7, 83.1, 79.1, 76.0, 46.3, 33.2, 29.9, 29.8, 27.4, 26.3, 24.9, 23.9. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.70; H, 8.69.

General Procedure for Asymmetric Epoxidation. To a stirred solution of *trans*-β-methylstyrene (0.024 g, 0.20 mmol), ketone **7** (0.0154 g, 0.06 mmol), and Bu_4NHSO_4 (5 mg, 0.016 mmol) in DMM−CH_3CN (1:1 v/v) (3 mL) was added 2 mL of aqueous buffer (prepared by mixing 100 mL 0.1 M aqueous K_2CO_3 with 0.5 mL acetic acid, pH 9.3). The mixture was cooled to −10 °C via a NaCl−ice bath. A solution of Oxone (0.255 g, 0.42 mmol) in aqueous Na_2EDTA (4×10^{-4} M, 1.2 mL) and a solution of K_2CO_3 (0.24 g, 1.73 mmol) in water (1.2 mL) were added dropwise simultaneously through two separate syringes via syringe pump over a period of 8 h. Upon quenching with pentane and water, the reaction mixture was extracted with pentane (3×10 mL), washed with brine, and dried (Na_2SO_4). The crude reaction mixture was analyzed by GC (61% conversion; 87% ee by chiral GC analysis with G-TA column).

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Supporting Information Available: X-ray structural data of ketones **1**, **7**, and **10** containing atomic coordinates and bond lengths and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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