Selective Generation of Free Radicals from Epoxides Using a Transition-Metal Radical. A Powerful New Tool for Organic Synthesis

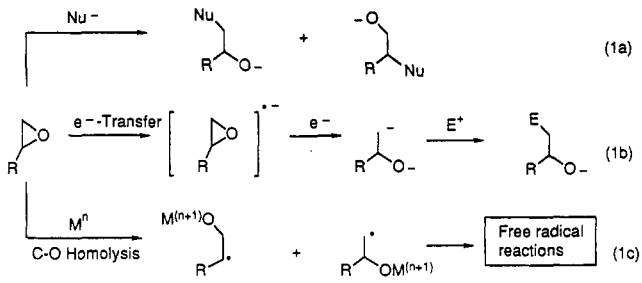
T. V. RajanBabu* and William A. Nugent*

Contribution No. 6651 from Central Research and Development, E328, The DuPont Company, Experimental Station, Wilmington, Delaware 19880-0328

*Received September 13, 1993**

Abstract: Bis(cyclopentadienyl)titanium(III) chloride reacts with epoxides by initial C–O homolysis. The regiochemistry of the opening is determined by the relative stabilities of the radicals. Depending on the reaction partners, these radicals undergo intramolecular (hex-5-enyl cyclization) or intermolecular additions to olefins. The resultant radicals are efficiently scavenged by a second equivalent of Ti(III) to afford the corresponding Ti(IV) derivative. Treatment of this intermediate with electrophiles such as H^+ or halogens provides a route to functionalized cyclopentanes and other useful products. The radical initially formed from an epoxide can also be trapped by H-atom donors such as 1,4-cyclohexadiene or *tert*-butyl thiol, resulting in an overall reduction of the epoxide. In the absence of a H-atom donor or an olefin, this radical is trapped by Ti(III), resulting in a β-oxido–Ti organometallic species which undergoes facile elimination to give an olefin. The reaction conditions are remarkably mild and are applicable to very sensitive substrates.

The considerable utility of epoxides as building blocks for organic synthesis reflects both their ready availability and their ability to undergo selective nucleophilic substitution reactions (eq 1a) with predictable stereochemistry.[1] In contrast, the two-



electron reduction of epoxides to the corresponding carbanionic species (eq 1b)[2] allows the elaboration of epoxides with electrophiles, thus providing an "umpolung" of their usual reaction mode. However, as compared to the reactions with nucleophiles, several serious limitations of this approach have been noted. These include noncompatibility of the highly reducing conditions with a number of common organic functional groups, instability of such carbanionic species toward elimination, and the narrow range of electrophiles that can be used in this sequence.

In spite of the explosive growth in free radical chemistry, the number of synthetically useful radical precursors remains limited.[3] It occurred to us that the selective one-electron reduction of an epoxide to a radical intermediate (eq 1c) would represent an invaluable synthetic tool, provided the intermediate radical could be trapped in subsequent reactions. Thus epoxides would provide an excellent source of functionalized radicals. As compared to reactions involving polar intermediates, free radical-mediated reactions are compatible with a wider array of functional groups. Furthermore, we should expect product distributions different from those of classical reactions of epoxides. The regio- and stereochemistries of the epoxide opening via C–O homolysis will be guided by the relative stability of the intermediate radicals rather than the ease of approach to the epoxide termini as is the case in nucleophilic (S_N2) openings. The stability of a carbon radical is affected by both the substitution pattern (for example, tertiary > secondary > primary) and stereoelectronic factors.[4] It seemed reasonable that reduction (eq 1c) might be accomplished with a low-valent transition-metal reagent. Precedent for this approach exists in the mechanistic proposal of Kochi, Singleton, and Andrews.[5] These researchers suggested that the deoxygenation of epoxides by chromium(II) reagents proceeds by discrete one-electron steps via the carbon-centered radical. Formation of a carbon-centered radical from a transition-metal-centered radical and its subsequent reactions are ubiquitous in living systems.[6] However, the application of this type of transformation in organic synthesis is largely limited to redox reactions[7] and has rarely been applied to carbon–carbon bond forming reactions.[8]

In this paper we report that a titanium(III) reagent, bis(cyclopentadienyl)titanium(III) chloride, promotes such a homolytic process (eq 1c) with remarkable selectivity at or below room temperature.[9] The reagent is easily generated in situ from inexpensive Cp_2TiCl_2 and is compatible with many organic functional groups. Production of free radicals in this manner allowed us to develop a variety of unique transformations of epoxides including selective reduction and deoxygenation processes and intra- and intermolecular carbon–carbon bond forming

* Abstract published in *Advance ACS Abstracts,* January 15, 1994.

(1) (a) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323. (b) Smith, J. G. *Synthesis* **1984**, 629. See also: Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221 and references cited therein.

(2) (a) Bartmann, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 653. (b) Cohen, T.; Jeong, I.-H.; Mudryk, M.; Bhupathy, M.; Awad, M. M. A. *J. Org. Chem.* **1990**, *55*, 1528.

(3) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press; New York, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417, 489.

(4) Korth, H.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1453.

(5) Kochi, J. K.; Singleton, D. M.; Andrews, L. J. *Tetrahedron* **1986**, *24*, 3503.

(6) Halliwell, B.; Gutteridge, J. M. C. *Free Radicals in Biology and Medicine*; Clarendon Press: Oxford, U.K., 1989.

(7) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press; New york, 1978.

(8) For representative examples, see footnote, **32c,d**.

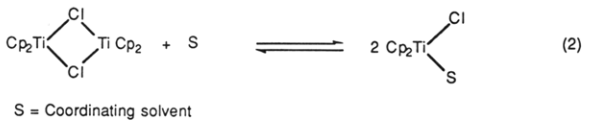
(9) For other chemistry of Ti(III) reagents, see: Lenoir, D. *Synthesis* **1989**, 883. Setlla, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337. Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717. Yanlong, Q.; Guisheng, L.; Huang, Y. *J. Organomet. Chem.* **1990**, *381*, 29. Samuel, E.; Vedel, J. *Organometallics* **1989**, *8*, 237. Citterio, A.; Cominelli, A.; Bonavoglia, F. *Synthesis*, **1986**, 308. Clerici, A.; Porta, O. *J. Org. Chem.* **1989**, *54*, 3872.

0002-7863/94/1516-0986$04.50/0

reactions.[10] The Sharpless asymmetric epoxidation provides an important source of enantiopure epoxides. The use of these substrates has allowed us to extend this chemistry in exciting and unexpected directions.

Results and Discussion

The Reagent. Bis(cyclopentadienyl)titanium(III) chloride was first reported by Green and co-workers in 1972.[11] In the solid state, the complex exists as a chloride-bridged dimer. However, in the presence of donor solvents such as THF, the dimer dissociates (eq 2)to afford the monomeric species which may be regarded



as a loosely solvated "transition-metal-centered radical". Accordingly, in our discussion of stoichiometry, the reagent will be treated as a monomeric Cp_2TiCl (**1**).

Most of the developmental work reported in this paper was performed using isolated Cp_2TiCl. The reagent was prepared by treatment of titanium(III) chloride with freshly sublimed thallium cyclopentadienide (eq 3) as described by Manzer.[12]

$$TiCl_3 + 2CpTl \rightarrow \underset{\mathbf{1}}{Cp_2TiCl} + 2TlCl \qquad (3)$$

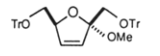
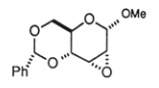
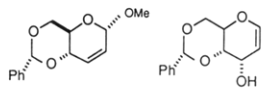
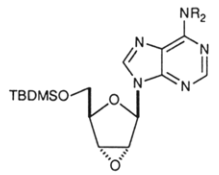
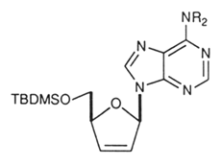
Complex **1** prepared in this manner is a greenish yellow solid which can be stored indefinitely and handled in a nitrogen-filled glovebox. However, we stress that the synthetic transformations described herein do not require the use of isolated **1**. A satisfactory reagent can be prepared by stirring a red THF solution of commercially available titanocene dichloride with powdered zinc metal (eq 4). After 15 min, the solution turns lime green; formation

$$2Cp_2TiCl_2 + Zn \rightarrow 2Cp_2TiCl + ZnCl_2 \qquad (4)$$

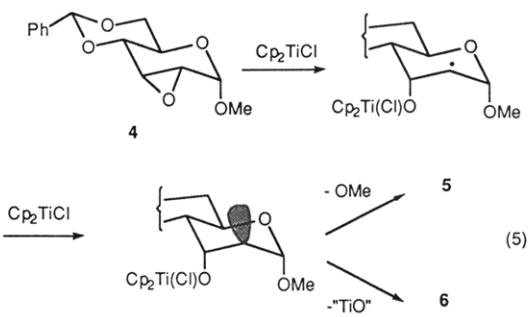
of **1** is quantitative. In principle, the Lewis acidic zinc chloride coproduced in eq 4 could alter the course of reactions conducted with the in situ reagent. However, in most cases examined to date (see below), comparable yields have been obtained for reactions using the in situ reagent versus isolated Cp_2TiCl.

Deoxygenation of Epoxides. On the basis of literature precedents, we expected that **1** would deoxygenate epoxides to the corresponding olefins. Several protocols have now been reported for the deoxygenation of simple epoxides to alkenes.[13] Nevertheless, the deoxygenation of highly functionalized epoxides still represents a synthetic challenge. During the course of our studies, we have found that **1** is an exceptionally mild and selective reagent for the deoxygenation of epoxides.[14] This is illustrated for a number of sensitive epoxide substrates, and the results are shown in Table 1. These reactions are best carried out by addition of a THF solution of the epoxide to a solution of Cp_2TiCl in THF at room temperature.

Table 1. Deoxygenation of Epoxides

entry	epoxide	product (yield)
1	 **2**	 **3** (66)
2	 **4**	 **5** (78) **6** (16)
3	 **7a** R = H **7b** R = C(O)Ph	 **8a** R = H (69) **8b** R = C(O)Ph

The deoxygenation of methyl furanoside **2** (readily made from methyl 1,6-bis-*O*-(triphenylmethyl)fructofuranoside via the Mitsunobu reaction[15]), generates the corresponding olefinic product **3** in 66% yield. The product dihydrofuran **3** is a very sensitive compound which has been the target of an extensive, yet unsuccessful, synthetic effort.[16] The mildness of this deoxygenation procedure is attested by the fact that even the acidic impurities in untreated $CDCl_3$ are sufficient to convert **3** to the corresponding fully aromatic product. As anticipated, deoxygenation of anhydrosugar **4** gives two olefins (**5** and **6** in a ratio of 5:1). This can be understood mechanistically in terms of eq 5 as competitive β-eliminations of either a titanium–oxo or a



methoxide moiety, with the former predominating.[16a] Note that the amino group of adenosine epoxide **7a**[17] is tolerated under these conditions. The resulting compounds such as **8** are potential intermediates for dideoxynucleosides, which are important in anti-AIDS chemotherapy.[18] Many 1,2-diols derived from carbohydrates and other sources are readily transformed by the Mitsunobu reaction to epoxides.[19] This reaction, in combination with our Ti(III)-mediated deoxygenation, followed by catalytic reduction of the double bond, can be considered as a facile method of dideoxygenation in carbohydrate chemistry.

(10) For preliminary accounts of this work, see: (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561–8562. (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525–4527. (c) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408–6409.

(11) Green, M. L. H.; Lucas, C. R. *J. Chem. Soc., Dalton Trans.* **1972**, 1000.

(12) Manzer, L. *Inorg. Synth.* **1982**, *21*, 84.

(13) (a) McMurry, J. E.; Silvestri, M. G.; Fleming, M. P.; Hoz, T.; Grayston, M. W. *J. Org. Chem.* **1978**, *43*, 3249. (b) van Tamelen, E. E.; Gladysz, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 5290. (c) Schobert, R. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 855. (b) Berry, M.; Davies, S. G.; Green, M. L. H. *J. Chem. Soc., Chem. Commun.* **1978**, *99*. For a review of deoxygenation of epoxides, see: Wong, H. N. C.; Fok, C. C. M.; Wong, T. *Heterocycles* **1987**, *26*, 1345.

(14) We examined several low-valent Ti, Zr, and W complexes before choosing Cp_2TiCl for further detailed studies. For a complete list, see Table 1 in the supplementary material.

(15) Mitsunobu, O. *Synthesis* **1981**, 1.

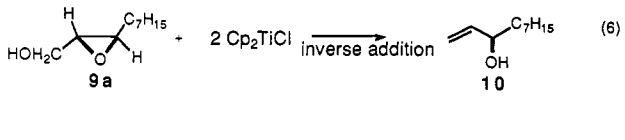
(16) Martin, O. R.; Rafka, R. J.; Szarek, W. A. *Carbohydr. Res.* **1989**, *185*, 77. (a) A small portion of **5** could also arise from epoxide opening at C_3, subsequent reduction, and elimination.

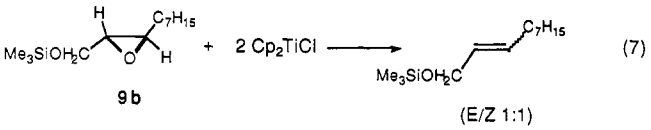
(17) For a one-step synthesis of adenosine epoxide, see: Mengel, R.; Bartke, M. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 679.

(18) (a) Manusri, M. M.; Starrett, J. E., Jr.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *J. Org. Chem.* **1989**, *54*, 4780. See also: Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. *J. Org. Chem.* **1989**, *54*, 2217 and references cited therein. (b) For a low-valent Cr-mediated synthesis of these type of compounds from halohydrins, see: Jain, T. C.; Jenkins, I. D.; Russel, A. F.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 30.

(19) For another procedure for the conversion of diols to epoxides, see; Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515–10530.

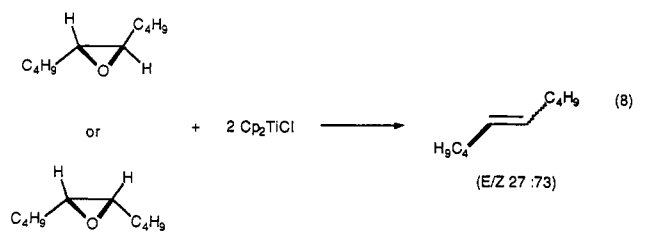
One important source of enantiomerically pure epoxides is the Sharpless asymmetric epoxidation of allylic alcohols. The course of the deoxygenation of such "Sharpless epoxyalcohols" can be altered by O-substitution at the alcohol functionality. Unprotected alcohols such as (*R*,*R*)-2,3-epoxy-1-decanol (**9a**) undergo clean deoxygenation to (*R*)-1-decen-3-ol (**10**) with no loss of stereochemistry (eq 6). The stereochemical purity (99.3%) of



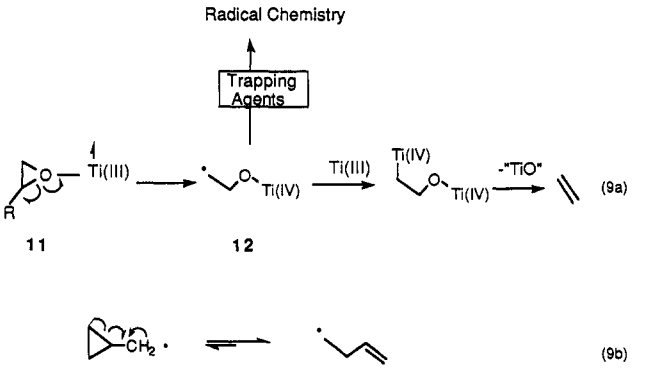


the product was ascertained by chiral GC analysis. Given the ready availability of such epoxyalcohols, this sequence provides easy access to optically active allylic alcohols. Some types of allylic alcohols, especially vinyl carbinols and sterically congested allylic alcohols, are difficult to prepare via the Sharpless kinetic resolution. However, these compounds could be readily prepared by deoxygenation of the appropriate substrates of the type **9a** which are readily available in high ee's by the Sharpless asymmetric epoxidation of disubstituted allylic alcohols.[20] It can also be noted that the yield in a kinetic resolution cannot exceed 50%; this limitation does not apply to eq 6. It is interesting to note that the hydroxy-protected derivative **9b** (eq 7) undergoes a simple deoxygenation leading to a cis/trans (1:1) mixture of primary alcohols after aqueous workup. Equation 6 has recently been applied to a series of other "Sharpless" epoxides, and the transformation appears to be general.[21] However, other factors such as benzylic stabilization of an incipient radical should also be considered in special substrates. For example, phenylglycidol yields only cinnamyl alcohol and none of the "expected" phenyl vinyl carbinol.

Validation of Eq 1c. It seemed likely that the deoxygenation reactions summarized in Table 1 were in fact proceeding by discrete one-electron steps as proposed in eq 1c. As a mechanistic probe, separate THF solutions of (*E*)- and (*Z*)-5,6-epoxydecane were added dropwise to excess **1** in THF (eq 8). Both reactions afforded identical 73:27 mixtures of (*Z*)- and (*E*)-5-decene.



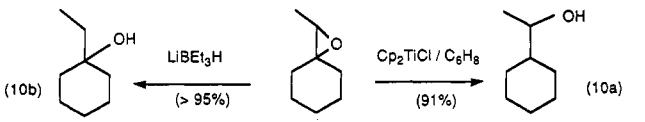
These results contrast with the retention of stereochemistry observed in the deoxygenation of epoxides by low-valent tungsten reagents[14,22,23] which can function as two-electron reductants. Reduction of epoxides with Cp_2TiCl_2/Mg ("reductive titanocene"), another two-electron reductant, proceeds with partial retention of stereochemistry.[24] The complete loss of stereochemistry in our system suggests the intervention of a long-lived intermediate. Taken together with the various stereochemical, trapping, and isotopic labeling studies delineated below, the results suggest that deoxygenation does in fact proceed in discrete one-electron steps via a radical intermediate as shown schematically in eq 9a. The intermediate σ-complex of the epoxide (**11**) with



the paramagnetic Ti(III) having a half-filled d-orbital represents an electronic analog of the cyclopropylcarbinyl moiety. Also by analogy to the extremely facile cyclopropylmethyl to homoallyl radical rearrangement (eq 9b), the release of ring strain might be expected to drive the homolytic C–O bond cleavage.

Equation 9 suggests that it might be possible to react the radical intermediate **12** with trapping agents other than Ti(III), thereby diverting the deoxygenation reaction to alternative synthetically useful pathways. A second implication is that the competing elimination process should be suppressed by keeping the concentration of the Ti(III) reagent as low as possible. This is most reasonably accomplished by slow "inverse" addition of a solution of **1** to a solution containing the epoxide and the trapping reagent.

Selective Reduction of Epoxides. One group of trapping reagents which we have examined are H-atom donors 1,4-cyclohexadiene and 2-methyl-2-propanethiol. Dropwise addition of 1.05 equiv of a THF solution of Cp_2TiCl to a mixture of 1,1′-epoxyethylcyclohexane and a 10-fold excess of cyclohexa-1,4-diene in THF at room temperature followed by acidic (1 N HCl) workup yielded 92.0% of 1-cyclohexylethanol (eq 10a). The



observed regiochemistry is opposite to what is expected for a classical S_N2-type reduction process where the course of reaction is governed by the ease of approach of the hydride reagent.[25] Indeed, when the same epoxide was treated with lithium triethylborohydride, the only product formed was 1-ethyl-1-cyclohexanol (eq 10b).

In Table 2 we report the results of this reduction procedure applied to a series of epoxides. Note that the experimental protocol for Table 2 differs not only in the presence of 1,4-cyclohexadiene but also in that "inverse addition" of the titanium reagent to the epoxide is utilized. In the case of epoxides **2**, **4**, and **7**, the regiochemistry of the major product is the same as that observed for the reduction with lithium triethylborohydride. Isomeric products **15** and **17** are not formed under borohydride reduction conditions. It should be noted that the reaction is compatible with the amino and benzamido groups as illustrated by substrates **7a**,**b**. In contrast, the super hydride reduction of the *N*-benzoyl derivative **7b** removes the benzoyl protecting group from the

(20) For a lucid account of this problem and another innovative solution using Te chemistry, see; Dittmer, D. C.; Discordia, R. P.; Zhang, Y.; Murphy, C. K.; Kumar, A.; Pepito, A. S.; Wang, Y. *J. Org. Chem.* **1993**, *58*, 718.

(21) Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1990**, 843.

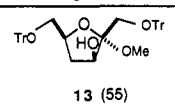
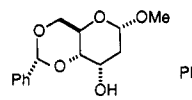
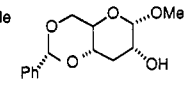
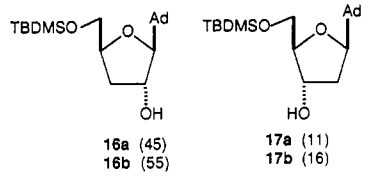
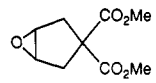
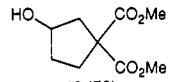
(22) Sharpless, K. B.; Umbreit, M. A.; Nieh, M. T.; Flood, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 6538.

(23) Atagi, L. M.; Over, D. E.; McAlister, D. R.; Mayer, J. M. *J. Am. Chem. Soc.* **1991**, *113*, 870.

(24) See ref 13c.

(25) The regiochemistry of the opening of Sharpless epoxides can be controlled by the appropriate choice of reagents; Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, 2719. For the use of allyltitanium triphenoxide for substitution at the more substituted carbon, see; Tanaka, T.; Inoue, T.; Kamei, K.; Murakami, K.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1990**, 906–907. For other related reactions, see also; Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

Table 2. Radical-Mediated Reduction of Epoxides

entry	epoxide	products (% yield)
1	**2**	 13 (55)
2	**4**	 14 (65)  15 (12)
3	**7a** (R = H) **7b** (R = C(O)Ph)	 16a (45) 16b (55) 17a (11) 17b (16)
4	 18	 19 (72)

amine. Even under the conditions where the concentration of the Ti(III) species is kept low by inverse addition, epoxide **7a** still gives varying amounts (up to 15%) of the deoxygenation product **8a**. Reduction of 3,3-dicarbomethoxy-6-oxa-bicyclohexane (**18**) illustrates the remarkable compatibility of the Ti reagent with ester groups. Under otherwise identical conditions, *tert*-butyl thiol, which is known to be a better H-atom donor, gave a higher yield of the product as compared to cyclohexa-1,4-diene.

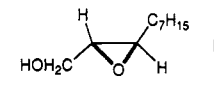
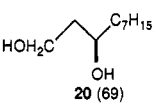
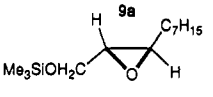
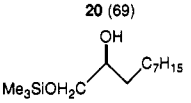
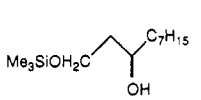
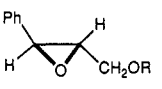
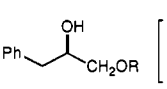
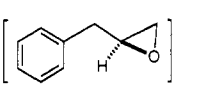
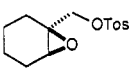
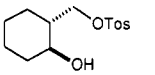
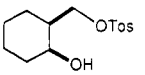
Reduction of the silylated "Sharpless epoxide" **9b** afforded, after deprotection, the enantiomerically pure 1,2- and 1,3-diols (via **21a,b**) in a 10:1 ratio. It is noteworthy that this result requires selective cleavage of the C–O bond at C(3) in contrast to epoxide **9a** where cleavage at C(2) occurred preferentially. This result is of particular interest because the asymmetric dihydroxylation of terminal aliphatic alkenes to 1,2-diols, currently the most practical route to these important intermediates, proceeds in only limited enantiomeric excess.[216] Some of these diols are naturally occurring pheromones.[27] Predominant C(2)–O homolysis may be achieved if the alcohol functionality is left unprotected. For example, in the presence of 2-methyl-2-propanethiol, epoxyalcohol **9a** gives a product **20** in 69% yield along with 4% of the corresponding 1,2-diol. Preparation of 1,2- and 1,3-diols from Sharpless epoxides have been reported in the literature by Kishi and co-workers using DIBALH and Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride), respectively.[25] The Ti(III)-mediated reactions could be an alternative where a broader functional group tolerance is needed. For example, in the reductions of **18**, **23b**, and **26**, neither the carbalkoxy nor the tosyl group is compatible with either of these aluminum hydride reagents. An overall 1,2-transposition of a "Sharpless epoxide" is illustrated by the conversion of **24b** to (2,3-epoxypropyl)benzene (**25**). Under circumstances where the incipient radical has special stabilization (benzylic in **23** and tertiary in **26**), the course of reaction will be dictated by this factor.

Competing deoxygenation is a serious problem with mono-substituted terminal epoxides like 1,2-epoxydecane, where up to 33% of 1-decene is observed even in the presence of a 10-fold excess of 1,4-cyclohexadiene. This may be due to the accessibility of the sterically unencumbered secondary/primary radicals to the Ti^{3+} species which promotes further reduction and subsequent deoxygenation in competition with bimolecular H-atom transfer.

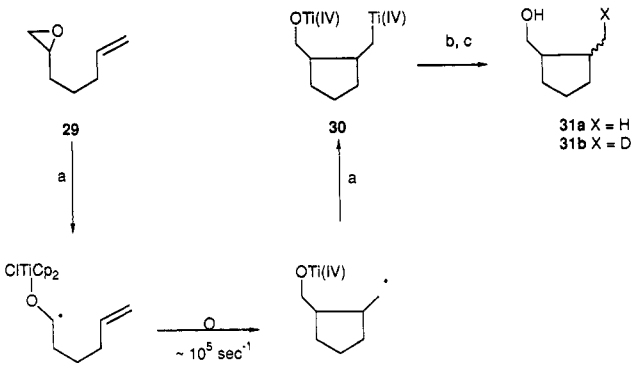
Hexenyl Radical Cyclizations. We also investigated the extension of this chemistry to the realm of carbon–carbon bond

(26) Ogino, Y.; Chen, H.; Manoury, E.; Shibata, T.; Beller, M.; Lubben, D.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 5761.
(27) Bonini, C.; Righi, G. *Tetrahedron* **1992**, *48*, 1531.

Table 3. Reduction of Sharpless Epoxides

epoxide	products
 **9a**	 **20** (69) (+ 4 % 1,2-diol)
 **9b**	 **21a** (61)  **21b** (6)
 **23a** R = H **23b** R = Tos	 **24a** R = H (62) **24b** R = Tos (->25)  **25** (41% from **23b**)
 **26**	 **27** (major)  **28** (minor)

Scheme 1. Ti(III)-Mediated Epoxyolefin Cyclization[a]

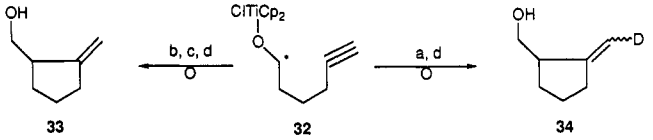


[a] (a) Cp_2TiCl/THF/rt. (b) D_3O^+. (c) Workup, H_3O^+.

forming reactions. We felt that such transformations should be available via addition of radicals, generated according to eq 1c, to olefins. Since the 5-hexenyl radical cyclization is known to be a rapid and efficient process,[28] we first considered the case of intramolecular radical additions.[29] In a preliminary experiment, we added 2 molar equiv of Cp_2TiCl in THF dropwise to a THF solution of 6,7-epoxy-1-heptene. As before, the green color of the titanium(III) species instantly discharged to red upon exposure to the epoxide. Quenching the mixture with 10% D_2SO_4 in D_2O afforded 2-methylcyclopentanemethanol which was >85% mon-odeuterated in the methyl group (~70% yield by GC). This suggests that hexenyl radical cyclization indeed takes place as proposed in Scheme 1.[30] Moreover, the resultant primary radical is efficiently scavenged by a second equivalent of titanium(III), affording the indicated alkyltitanium(IV) species **30**. The present reductive termination[31] leading to an isolable organometallic intermediate represents an attractive alternative to the tin hydride methodology, where the termination is largely limited to H-atom abstraction.[32] One significant limitation of classical hex-5-enyl radical cyclization procedures is that the transformation of a

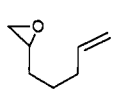
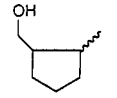
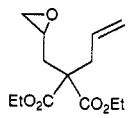
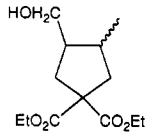
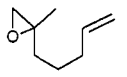
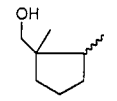
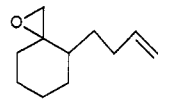
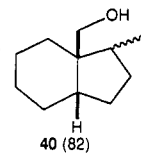
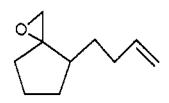
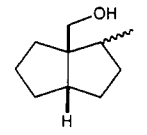
(28) For leading references, see: (a) Julia, M. *Pure Appl. Chem.* **1974**, *40*, 553. (b) Beckwith, A. L. *J. Tetrahedron* **1981**, *37*, 3073 and references cited therein. See also references cited under footnotes 3 and 34.
(29) For a complementary study of the cyclization of ω-heptenylcobalt species derived from epoxides, see: Harrowven, D. C.; Pattenden, G. *Tetrahedron Lett.* **1991**, *32*, 243.
(30) While studying the intramolecular addition–fragmentation of radicals from ω-epoxy-β-stannyl acrylate esters, Weiler found that the *exo*-6-heptenyl radical cyclization is too slow to complete with the reduction of the initially formed radical: Lowinger, T. B.; Weiler, L. *Can. J. Chem.* **1990**, *68*, 1636.
(31) For reductive terminations mediated by SmI_2 under Barbier-type conditions, see: (a) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773. (b) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439.

Scheme 2. Cyclization of 6,7-Epoxyhept-1-yne[a]



[a] (a) THF-d_8, rt. (b) THF, rt. (c) D_2O/D^+. (d) Workup (H_2O/H^+).

Table 4. Cyclopentanemethanols via Epoxyolefin Cyclization

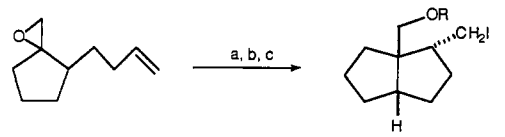
entry	epoxide	product (% yield)	isomer ratio
1	 29	 31a (70)	cis/trans 2:1
2	 35	 36 (68)	cis/trans 85:15
3	 37	 38 (94)	cis/trans 1:1
4	 39	 40 (82)	endo/exo 55:45
5	 41	 42 (88)	endo/exo 90:10

5-alkenyl radical precursor to an alkylcyclopentane necessarily entails a net loss of two functional groups.

In contrast to these results, cyclization of 6,7-epoxy-1-heptyne followed by deuteriolysis produced 2-methylenecyclopentanemethanol containing no deuterium at the methylene group. Presumably, the highly reactive vinyl radical that is formed initially abstracts a hydrogen atom from the THF solvent before it has a chance to encounter any reducting Ti species. Using THF-d_8 as the solvent for the reaction, one isolates a deuterated olefin **34** even after workup with H_2O. This further validates the free radical nature of the intermediates involved in these transformations.

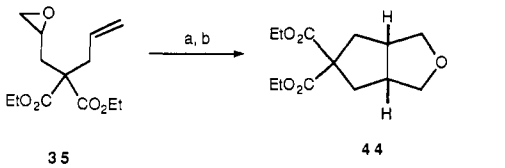
The cyclization/protonolysis was applied to a series of substituted epoxyolefins containing synthetically useful functionalities. The results are tabulated in Table 4. Several observations are noteworthy. Products **38**, **40**, and **42** indicate that this procedure is particularly suited for the introduction of quaternary centers. It should be noted that the reduction of tertiary radicals is much slower than hexenyl cyclization, and in a substrate like **37**, addition of the epoxyolefin to Cp_2TiCl is indeed the optimal way for obtaining higher yields (see the Experimental Section). Further, sensitive functional groups such as esters and acetals are tolerated. Even though nitrile or ketone functionality is tolerated (vide infra), we found that aldehydes and allylic ethers lead to reduced yields.

Treatment of the nucleophilic organotitanium derivative **30** in Scheme 1 with electrophiles other than protons should provide a route to bifunctional cyclopentane derivatives. To demonstrate this approach, we treated two of the product mixtures with iodine. The iodoalcohol **43a** was isolated in isomercially pure form as the *tert*-butyldimethylsilyl ether **43b** in 63% yield (eq 11). In contrast,



(11)

(a) Cp_2TiCl. (b) I_2. (c) Bu^tSiMe_2Cl

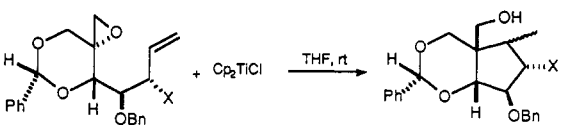


(12)

(a) Cp_2TiCl. (b) I_2.

the iodoalcohol derived from the cis organotitanium intermediate in eq 12 cyclized to tetrahydrofuran **44** in 52% isolated yield. In both cases, the isomeric products were presumably formed in low yields but were not isolated.

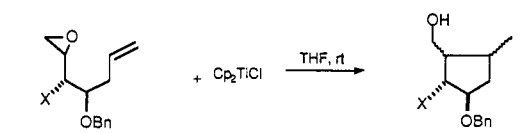
Carbohydrates are an abundant source of optically active intermediates. There is considerable interest in facile ways of converting carbohydrates to optically pure carbocyclic compounds. As illustrated in eq 13, the epoxy–olefin cyclization can be readily



45a X = H
45b X = OBn

46a X = H
46b X = OBn

(13)



47 (X = OBn)

48 (X = OBn)

(14)

applied for the synthesis of densely functionalized carbocycles from carbohydrates. A new and potentially general scheme for the synthesis of the starting epoxyolefins from pyranose sugars is given in Scheme 3.

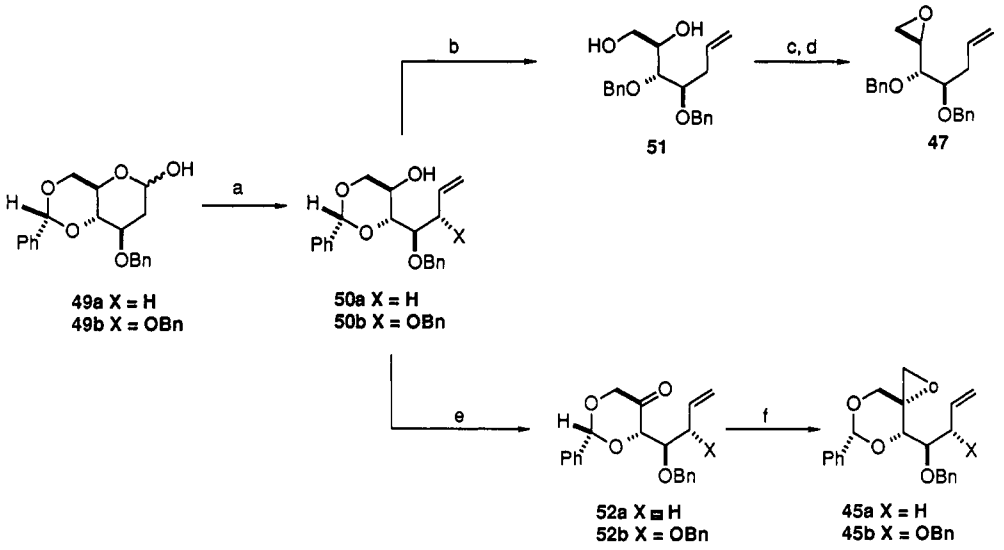
The observed stereochemistries of products **31**, **36**, **38**, **40**, **42**, and **46** are indicative of free radical processes, and these can be rationalized by invoking well-known conformational effects in the intermediates.[33,34] Of the two possible transition states leading to the isomers of **36**, the "chairlike" one (**53a**)is the more favored one over the "boat-like" one (**53b**) and this results in the

(32) For other modes of radical terminations, see via (a) fragmentation: Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133. (b) atom or group transfer: Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. Kharasch, M. S.; Skell, P. S.; Fisher, P. *J. Am. Chem. Soc.* **1948**, *70*, 1055. Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489. Barton, D. H. R.; Crich, D.; Kretzschmar, G. *Tetrahedron Lett.* **1984**, *25*, 1055. See also ref 3b. Barton, D. H. R.; Camara, J.; Cheng, X.; Gero, S. D.; Jaszberenyi, J. C.; Quiclet-Sire, B. *Tetrahedron* **1992**, *48*, 9261–9276 and references cited therein. (c) oxidative: Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 510. Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc.* **1984**, *106*, 5384. (d) β-Hydride elimination (general discussion): Scheffold, R.; Rytz, G.; Walder, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; John Wiley and Sons: New York, 1983; Vol. 2, pp 355. See also: Bhandal, H.; Pattenden, G.; Russell, J. J. *Tetrahedron Lett.* **1987**, *28*, 1317 and references cited there. Baldwin, J. E.; Li, C.-S. *J. Chem. Soc., Chem. Commun.* **1987**, 166. Branchaud, B. P.; Meier, M. S.; Choi, Y. *Tetrahedron Lett.* **1988**, *29*, 167.

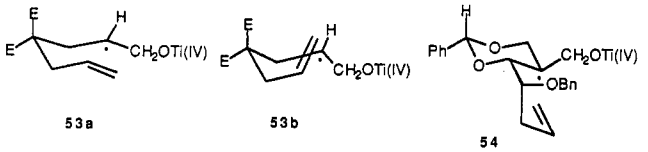
(33) Beckwith, A. L. J.; Easton, J. C.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.

(34) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.

Scheme 3. Synthesis of Epoxyolefins from Pyranosides[a]



[a] (a) See ref 35b. (b) LAH/$AlCl_3$. (c) TosCl/Py. (d) KOH/MeOH. (e) Swern Oxidation. (f) $(CH_3)_2S^+(O)CH_2^-$.

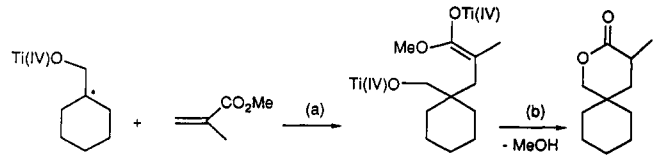


predominant cis product. The preponderance of the formation of the endo product from the highly functionalized carbohydrate substrate **45** can be explained by invoking a *cis*-decalin-like conformation **54** for the cyclization transition state.[35]

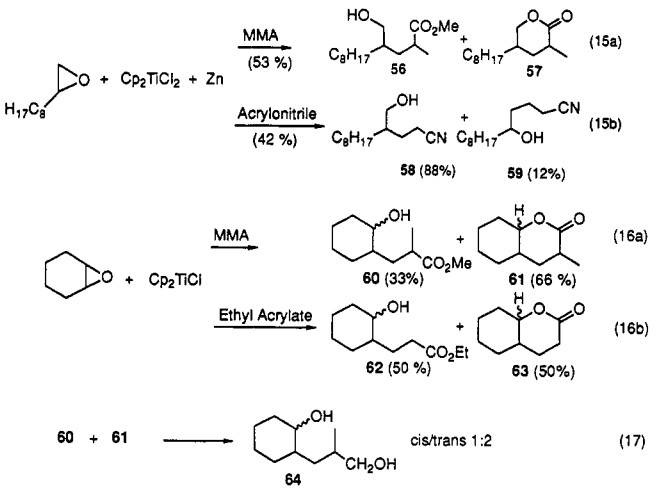
Intermolecular Additions. Radical intermediate **12** from the C–O homolysis (eq 9a) can also react with electron-deficient olefins in competition with subsequent reduction. Thus dropwise addition of the THF solution of Cp_2TiCl to a solution of 1-oxaspiro-[2.5]octane and 10 equiv of methyl methacrylate results in the formation of a spirolactone **55** in 81% yield (Scheme 4). Under these conditions, as expected, the intermediate radical from the epoxide adds to methyl methacrylate (MMA) and the resulting radical is further reduced by Ti(III). The δ-hydroxy ester formed under hydrolytic workup cyclizes to give the corresponding lactone.[36] It is surprising that under these conditions no further addition or polymerization of MMA occurred. This reaction represents an important bridge between the rich chemistries of radicals and organometallic enolates. Thus far we have made only very limited attempts to exploit the enolate chemistry of the ultimate intermediate, and these efforts have been largely unsuccessful, although some chemistry of $Cp_2Ti(Cl)$ enolates have been described in the literature.[37]

A number of other electron-deficient olefins take part in this reaction.[38] Additions of 1,2-epoxydecane and epoxycyclohexane are shown in eqs 15 and 16. Addition of MMA to epoxydecane gives a mixture of isomeric products in which the capture by the secondary radical predominates. For addition of acrylonitrile, the ratio of secondary to primary radical capture is 88 to 12. Since the hydroxyester adducts from MMA and epoxides are contaminated with the corresponding lactones, the product ratios were determined after exhaustive reduction with lithium aluminum hydride (eq 17). The diols were analyzed by NMR and GC. In additions of epoxycyclohexane, the trans product predominates (ratio of trans to cis adduct of 2:1).

Scheme 4. Intermolecular Addition of Epoxides to Olefins[a]



[a] (a) Cp_2TiCl, THF, rt. (b) H_3O^+.



The versatility of the method reflects the tolerance of a variety of functional groups. In the presence of Cp_2TiCl, the sugar-derived epoxide **4** undergoes addition to acrylonitrile, methyl vinyl ketone, and methyl methacrylate (eq 18). The stereochemistries of the products were established by measurements of coupling constants of the ring protons. These results are reported in Table 5. As pointed out earlier, the major side reactions are deoxygenation and reduction by H-atom transfer (especially in the case of methyl vinyl ketone) to give products **5**, **6**, and **14**. It should be noted that the relative amounts of axial vs equatorial bond formation in the radicals derived from **4** are the same as those reported by Giese et al.[39] in a related system. Qualitatively, it appears that the regiochemistry of the epoxide opening is affected

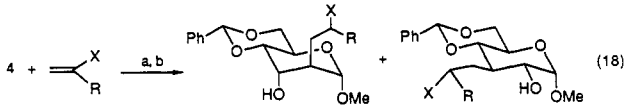
(35) For a detailed analysis, see: (a) RajanBabu, T. V.; Fukunaga, T. *J. Am. Chem. Soc.* **1989**, *111*, 296. (b) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.

(36) For a related free radical approach to δ-lactones, see: Kozikowski, A.; Nieduzak, T. R.; Scripko, J. *Organometallics* **1982**, *1*, 675.

(37) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 1664.

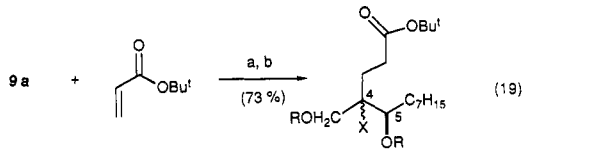
(38) For a reaction of epoxides with unsaturated chromium and tungsten carbene complexes, see: Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 9855.

(39) Giese, B.; Dupuis, J.; Groninger, K.; Hasskerl, T.; Nix, M.; Witzel, T. In *Substituent Effect in Radical Chemistry*; Viehe, H. G., Ed.; D. Reidel Publishing Co.: Dordrecht, The Netherlands, 1986; pp 283.



	R	X		
65a	H	CN	66a	67a
65b	H	C(O)Me	66b	67b
65c	Me	CO_2Me	66c	67c

(a) Ti^{3+}. (b) H_2O/H^+



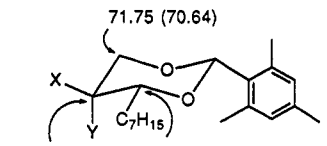
(a) Cp_2TiCl, then H_3O^+. (b) Ac_2O/Py.

R = H, OAc
68a X = β-H
68b X = α-H

by the stabilization of the incipient radical.[40] At this stage we cannot rule out reversible epoxide opening followed by addition, though from the other results cited earlier, this appears highly unlikely.

Upon treatment with Cp_2TiCl and *tert*-butyl acrylate, the epoxyalcohol **9a** undergoes C(2)–O homolysis followed by addition of the resulting radical. The two isomeric 1,3-diols were converted into the corresponding mesitylidene acetals **69a,b** by treatment with the dimethyl acetal of mesitaldehyde for tentative identification of the stereochemistry at the newly created center.

^{13}C-Chemical shifts (δ) for **69a** and **69b** (in brackets)



69a X = $CH_2CH_2CO_2Bu^t$; Y = H
69b X = H; Y = $CH_2CH_2CO_2Bu^t$

The major acetal has peaks at δ 37.95 (*C*H), 71.75 (*C*H_2O), and 82.16 (*C*HO) for three carbons of the 1,3-dioxin ring. The corresponding peaks in the minor isomer appear at δ 36.79, 70.64, and 81.51. Since chemical shifts of the corresponding carbons for *trans*-1,2-dialkylcycloalkanes in general appear at lower fields, it is reasonable to assume that the mesitylidene acetal has an all equatorial configuration in the major product. Thus this structure, **69a**, would correspond to a 4*S*,5*R* structure **68a** for the major dihydroxy ester adduct.

Conclusions

Epoxides are among the most versatile synthons in organic chemistry. They are readily accessible, often in enantiomerically pure form, from olefins, diols, and carbonyl compounds. The chemistry described in this paper expands the synthetic utility of epoxides to include free radical mediated reactions. Applications in all major classes of free radical reactions, viz. inter- and intramolecular addition to olefins, H-atom abstraction reaction, and electron-transfer reduction, are represented. The use of a transition-metal-centered radical for the generation of an organic radical is another salient feature of this work. As illustrated with Ti(III), a judicious choice of ligands around the metal to control its redox properties is key to successful application of this concept. Ligands could also control the regio- and stereochemical course of the subsequent reactions of the incipient radical, even though this report only deals with substrate control.

The exceptionally mild reaction conditions under which epoxides react with Cp_2TiCl should make this an attractive method for the generation of highly functionalized radicals.

Experimental Section

General Procedure. Infrared spectra were determined on a Nicolet Model 7199 FT spectrometer. ^{1}H NMR spectra were measured at 300 and 360 MHz on GE QE300 and Nicolet 360WB spectrometers, respectively, and the chemical shifts are reported in δ units relative to the tetramethylsilane (TMS) signal at 0.00 ppm. The coupling constants (*J*) are reported in Hz. ^{13}C NMR spectra were measured at 75 MHz on a GE QE300 spectrometer and were calibrated against the δ = 0.00 line of TMS. The assignments of proton and carbon signals were made by double irradiation and/or carbon–proton correlation experiments. Unless otherwise indicated, all spectra were recorded in $CDCl_3$. High-resolution mass spectra were measured on a VG Analytical ZAB-SE mass spectrometer. Optical measurements were done on a Perkin-Elmer 241 polarimeter. Gas chromatography was performed on a Varian 5890 Gas Chromatograph using an HP methyl silicone capillary column (25 m × 0.2 mm, 0.33-μm film) run with temperature programming. A chiral column Chiraldex GTA was purchased from Advanced Separation Technologies Inc. (Whippany, NJ). Satisfactory combustion analysis data (±0.4%) are reported as Anal. C, H, halogen, etc.

All anhydrous reactions were carried out in oven-dried or flame-dried glassware under dry nitrogen or in a Vacuum Atmospherics drybox. All solvents for reactions were purified before use. HPLC grade solvents were used for column chromatography which was performed according to the method described by Still.[41] Analytical and preparative thin-layer chromatography was done on E. Merck plates coated with 0.25- and 1.00-mm thicknesses of silica gel containing a fluorescent indicator coated on glass. Melting points are uncorrected. Yields reported are for chromatographically pure isolated products unless mentioned otherwise. In general the yields are not optimized.

Bis(cyclopentadienyl)titanium(IV) dichloride was purchased from Aldrich and was used without purification. Cyclopentadienylthalium was sublimed before use. Unless otherwise mentioned, the reactions described here were carried out with isolated $(Cp_2TiCl)_2$, prepared according to the procedure of Manzer.[12] Our experience suggests that all the reactions reported in this paper can be carried out with the reagent generated in situ[11] from commercially available Cp_2TiCl_2 (Aldrich) and granulated zinc.[42] Examples for each class of reaction are included in this experimental section.

In Situ Preparation of Cp_2TiCl from Cp_2TiCl_2 and Zn. To 499 mg (2 mmol) of titanocene dichloride dissolved in 4 mL of anhydrous THF was added 392 mg (6 equiv) of activated zinc, and the mixture was vigorously stirred for 60 min under nitrogen with *rigorous* exclusion of oxygen in a drybox. Unreacted zinc was filtered off using a small disposable pipette with a cotton plug at the bottom. The solid collected was washed with an additional 1 mL of THF. This green filtrate was used for subsequent reactions.

Deoxygenation of Methyl 2,3-Anhydro-1,6-bis-*O*-(triphenylmethyl)-α-D-*lyxo*-hexulofuranoside (2): Preparation of Methyl 1,6-Bis-*O*-(triphenylmethyl)-2,3-dideoxy-2,3-didehydro-α-D-fructofuranoside (3). In an oven-dried flask, 5.09 g (7.50 mmol) of methyl 1,6-bis-*O*-(triphenylmethyl)-α-D-fructofuranoside was dissolved in 70 mL of anhydrous THF. With good stirring, 3.94 g (15.00 mmol) of triphenylphosphine and 2.50 mL (15.75 mmol) of diethyl azodicarboxylate were added. The flask was connected to a condenser, and the mixture was heated for 45 min at 80 °C under nitrogen. To the reaction were added 300 mL of CH_2Cl_2 and 150 mL of water. The organic layer was separated, and the aqueous layer was extracted with more CH_2Cl_2 (200 mL × 2). The combined organic layers were washed with NaCl and dried. Column chromatography on silica gel using 10% ethyl acetate/hexanes yielded 4.43 g (89%) of **2**: mp 87–89 °C; ^{1}H NMR 3.05 (s, 3 H), 3.05–3.22 (m, 4 H), 3.90 (d, *J* = 3, 1 H), 3.97 (d, *J* = 3, 1 H), 4.18 (t, *J* = 6, 1 H), 7.08–7.55 (m, aromatic). Anal. ($C_{45}H_{40}O_5$) C, H.

A solution of 0.320 g (0.48 mmol) of **2** in 5 mL of THF was added to a solution of 0.230 g (1.07 mmol) of Cp_2TiCl under nitrogen. After 20 min the reaction was brought outside the box and was quenched with 10 mL of saturated NaH_2PO_4. After 4 min, 15 mL of water was added.

(40) Barton, D. H. R.; Hartwig, W.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1982**, 447.

(41) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(42) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1967; Vol. I.

The product was extracted into ether (40 mL × 3), and the ether extract was dried and concentrated. Column chromatography on silica gel using 10% ether/hexanes yielded 0.207 g (66%) of the desired olefin **3** as a white amorphous solid. This olefin is very sensitive to acidic impurities. For example, commercial $CDCl_3$, not treated with a 4-Å molecular sieve, readily converts **3** into fully aromatic 2,4-bis(trityloxymethyl)furan in quantitative yield. **3**: mp (recrystallized from hexane) 77–80 °C; $[\alpha]^{25}_D$ −27.5 ± 0.8°; IR 3080, 3060, 2930, 2870, 2830, 1595, 1490, 1100, 1075, 745, 705 cm^{-1}; ^1H NMR 3.10 (s, 3 H), 3.29 (ABq, ν_A = 3.29, ν_B = 3.36, J_{AB} = 12, 2H), 3.34 (ABX, ν_A = 3.26, ν_B = 3.42, J_{AB} = 8.0, 2 H), 5.10 (m, 1 H), 5.78 (dd, J = 6, 3, 1 H), 6.30 (dd, J = 6, 1, 1 H), 7.00–7.70 (m, aromatic); ^{13}C NMR (C_6D_6) 49.05 (OCH_3), 67.82, 68.57 (C_1 and C_6, assignment not determined), 86.26 (C_5), 87.17, 87.27 (quarternary carbons CPh_3), 114.79 (C_2), 133.37 (C_4), 144.64 (C_3); FAB MS 667.33 (M + Na; calcd for mass $C_{45}H_{40}NaO_4$, 667.28). Anal. ($C_{45}H_{40}O_4$) C, H, O.

Deoxygenation of Methyl 2,3-Anhydro-4,6-*O*-benzylideneallopyranoside (4). Deoxygenation of **4**[43] gave, after chromatography, the olefins **5** and **6** in 78 and 16% yields, respectively. Compounds **5**[44] and **6**[44] have been described in the literature.

9-(2,3-Anhydro-5-*O*-(*tert*-butyldimethylsilyl)ribofuranosyl)-9*H*-purine-6-amine (Adenosine-α-epoxide, 7a) and the Corresponding *N*-Benzoyl Derivative (7b). The epoxide **7a** was prepared according to the procedure described in the literature.[45] The bis benzoyl derivative **7b** was prepared in 75% yield by benzoylation of **7a** using benzoyl chloride in pyridine under catalysis of 4-(dimethylamino)pyridine. **7b**: ^1H NMR 0.01 (2 s, 6 H, $SiMe_2$), 0.82 (s, 9 H, Bu^{t}Si), 3.75 (d, J = 6, 2 H, $H_{5'}$), 4.10 (d, J = 2, 1 H, $H_{3'}$), 4.39 (t, J = 6, 1H, $H_{4'}$), 4.41 (d, J = 2, 1 H, $H_{2'}$), 6.26 (s, 1 H, $H_{1'}$), 7.38 (t), 7.50 (t), 7.85 (d), 8.30 (s), 8.68 (s).

Deoxygenation of 7a. To a solution of 0.094 g (0.44 mmol) of Cp_2TiCl in 2 mL of THF was added 0.073 g (0.20 mmol) of **7a** in 3 mL of THF over 5 min. After 30 min at room temperature, 5 mL of NaH_2PO_4 was added. The reaction was stirred for 5 min, and excess methylene chloride was added. The organic layer was separated, and it was further washed with saturated NaCl. The dried organic layer was concentrated, and the product, **8a**[46] (0.050 g, 69%), was purified by preparative thin-layer chromatography using 75% ethyl acetate in hexane as the eluant.

Deoxygenation of 7b. Under conditions described above, **8b** was produced. **8b**: ^1H NMR 0.01 (s, 1 H, $SiMe_2$), 0.90 (s, 9 H, Bu^{t}Si), 3.81 (ABX, J_{AB} = 10, J_{AX} = J_{BX} = 5, 2 H, $H_{5'}$), 5.01 (m, 1 H, $H_{4'}$), 6.08 (dt, J = 6, 2, 1 H, $H_{3'}$), 6.45 (dt, J = 6, 2, 1 H, $H_{2'}$), 7.18 (m, 1 H, $H_{1'}$), 7.38 (t, J = 6, 4 H), 7.50 (t, m, J = 6, 2 H), 7.92 (d, J = 6, 4 H), 8.30 (s, 1H), 8.64 (s, 1 H); FAB MS 556.41 (M + H; calcd for $C_{30}H_{34}N_5O_4Si$ 556.23). Anal. ($C_{30}H_{33}N_5O_4Si$) H, N, Si. C: calcd 64.84, found 63.90.

Deoxygenation of (2*R*,3*R*)-2,3-Epoxy-1-decanol (9a). A solution of the epoxyalcohol (0.35 g, 2.0 mmol) in THF (10 mL) was added dropwise to a solution of Cp_2TiCl (1.28 g, 6.0 mmol) in THF (10 mL). The reaction was quenched with 10% sulfuric acid (25 mL) and was extracted into ether (3 × 50 mL). The combined ether extracts were washed with saturated sodium hydrogen carbonate and water (25 mL), and the solvent was removed at reduced pressure. The product was purified by flash chromatography with 7:1 hexane/ethyl acetate. Removal of solvent from cuts 16–24 afforded the product (*R*)-1-decen-3-ol (**10**) as a colorless liquid (0.25 g, 79% yield): ^1H NMR 0.88 (t, br, J = 7, 3H), 1.30 (m, 10H), 1.54 (m, 2H), 1.64 (s, 1H), 4.10 (q, J = 7, 1H), 5.00–5.30 (m, 2H), 5.80–5.95 (m, 1 H); ^{13}C NMR 14.24, 22.87, 25.58, 29.48, 29.79, 32.06, 37.42, 73.47, 114.54, 141.68. A portion of the product was converted to the allylic acetate by treatment with 1:1 (volume) acetic anhydride/pyridine. The acetate was analyzed by chiral capillary column gas chromatography (cyclodex B, 130 °C) under conditions where the racemic allylic acetate gave baseline resolved peaks with retention times of 7.6 and 7.8 min and was found to have an enantiomeric excess of 99.3%.

The corresponding trimethyl silyl ether (**9b**) gave a 1:1 mixture of (*Z*)- and (*E*)-1-(trimethylsiloxy)-2-decene.

Deoxygenation of (*Z*)- and (*E*)-5,6-Epoxydecane. Solutions containing either (*Z*)- or (*E*)-5,6-epoxydecane (0.16 g, 1 mmol) and *tert*-butylbenzene (internal standard, 0.16 g) in THF (10 mL) were added dropwise to a solution of Cp_2TiCl (0.43 g, 2.0 mmol) in THF (15 mL). After the mixture was quenched with 10% sulfuric acid and extracted into hexane, the isomeric ratio of *cis*- to *trans*-5-decenes was determined by gas chromatography. A normalized *Z*:*E* ratio of 73 to 27 was observed independent of epoxide stereochemistry. The only other observed product was a small amount (3%) of 5-decanol.

Reduction of 2-Methyl-1-oxaspiro[2.5]octane (Eqs 10a,b). In an inert atmosphere box, 0.175 g (1.39 mmol) of the epoxide and 1.31 mL (13.86 mmol) of cyclohexa-1,4-diene were dissolved in 3 mL of anhydrous THF and to this solution was added with constant stirring 0.311 g (1.45 mmol) of Cp_2TiCl in 5 mL of THF over 15 min. After 40 min, the reaction was quenched with 5 mL of ice-cold 1 N HCl. The product was extracted into ether, and the combined ether extract was washed with $NaHCO_3$ and brine. The crude product (GC yield 91%) was filtered through a short column of silica gel (20% ether/hexane as the solvent) to get two fractions which were analyzed by gas chromatography. The first of these (retention time 11.16 min; 0.002 g, 0.9%) was identified as 1-(1-chlorocyclohexyl)ethanol from the following data: ^1H NMR inter alia 1.26 (d, J = 6, CH_3), 3.71 (m, 1 H) (HRMS, from GCMS, 219.1005 (M^+ for the trimethylsilylated derivative; calcd 219.0972). The second fraction (0.113 g; 64%) was identified as 1-cyclohexylethanol (retention time on a HP Methyl Silicone column 60 °C/5 min, programmed to increase at 20 °C/min to 250 °C, 9.56 min; 98.0%) contaminated with 1.5% of 1-ethyl-1-cyclohexanol (identified by comparison with an authentic sample prepared by $LiEtBH_4$ reduction of the epoxides, retention time 8.90 min). The yield loss in isolation is presumably due to the volatility of the components. 1-Cyclohexylethanol: ^1H NMR 0.83–1.40 (m, superimposed on a doublet at 1.18 (J = 6, CH_3), total 9 H), 1.60–2.00 (m, 6 H), 3.56 (dq, J = 6, 6, 1 H, CHOH); ^{13}C NMR 20.43, 26.21, 26.30, 26.60, 28.41, 28.82, 45.27, 72.22; HRMS 113.0983 ($M^+ - CH_3$; calcd for M = $C_8H_{16}O$ 113.0966); 185.1373 ($M^+ - CH_3$; calcd for M = $C_{11}H_{24}OSi$ (trimethylsilylated alcohol) 185.1362).

Ti(III)-Mediated Reduction of 2 in the Presence of 1,4-Cyclohexadiene. The standard procedure described for the reduction of **7b** (vide infra) yielded the 4-deoxy derivative **13** as the exclusive product. An authentic sample of this compound was prepared by super hydride reduction of **2**. **13**: mp 87–89 °C; IR (KBr) 3550, 3450 cm^{-1}; ^1H NMR 1.60 (dd, J = 12, 3, 1 H), 2.50 (ddd, 12, 8, 3, 1 H), 3.04 (s, 3 H), 3.22 (ABX, ν_A = 3.08, ν_B = 3.36; J_{AB} = 12, J_{AX} = J_{BX} = 3, 2 H), 3.43 (ABq, ν_A = 3.42, ν_B = 3.44, J_{AB} = 9, 2 H), 3.30 (d, J = 8, OH, 1 H), 4.18 (m, 1 H), 4.30 (dd, J = 7, 3, 1 H), 7.18–7.62 (m, aromatic). Anal. ($C_{45}H_{42}O_5$) C, H.

Preparation of Authentic 13. In a dry flask under nitrogen, 0.661 g (1 mmol) of **2** was dissolved in 5 mL of THF and to this solution was added 1.1 mL of a 1 M solution of $LiEt_3BH$ in THF. After 3 days it was quenched by adding 10 mL of saturated NH_4Cl. The product (80% yield) was extracted into ether and purified by chromatography.

Reduction of 4. The reduction of **4** using the standard protocol gave a mixture of two alcohols **14** and **15** in a ratio of 5:1 as judged by ^1H NMR and capillary gas chromatography. On the basis of recovered starting material (ca. 14%), the yield of the reduction was 77%. The deoxygenation to give **5** and **6** is the major side reaction under these conditions. The structures were confirmed by comparison of physical properties with those of authentic samples. Compounds **5**[47], **6**[47], **14**,[48] and **15**[48] have been described in the literature. **14**: ^1H NMR 1.94 (ddd, J = 14.5, 4, 4, 1 H, H_{2ax}), 2.16 (dd, J = 14.5, 3, 1 H, H_{2eq}), 3.06 (d, J = 6.5, exch D_2O, 1 H, OH), 3.38 (s, 3 H, CH_3O), 3.57 (dd, J = 10, 3 1 H, H_4), 3.75 (dd, J = 10, 10, 1 H, H_{6ax}), 4.18 (m, br, 1 H, H_3), 4.19–4.35 (m, 2 H, H_5 and H_{6eq}), 4.76 (d, J = 4, 1 H, H_1), 5.60 (s, 1H, benzylidene CH), 7.26–7.60 (m, aromatic); ^{13}C NMR 35.13 (C_2), 55.02 (OCH_3), 57.81 (C_5), 64.60 (C_3), 68.96 (C_6), 79.31 (C_4), 98.21 (C_1), 101.67 (benzylidene CH); HRMS 266.1147 (M^+; calcd for $C_{14}H_{18}O_5$ 266.1154).

Reduction of 7a,b. The adenosine derivative **7b** (0.066 g, 0.12 mmol) and 0.20 mL (2.10 mmol) of cyclohexa-1,4-diene were dissolved in 1 mL of anhydrous THF, and from a dropping funnel was added 0.027 g (0.12 mmol) of titanocene monochloride dissolved in 2 mL of THF. The dropping funnel was rinsed down with more THF (1 mL), and the reaction mixture was stirred for 15 min. The reaction was quenched by adding 10 mL of saturated KH_2PO_4, and the product was extracted into ether. The major products **16b** and **17b** were isolated by preparative thin-layer chromatography on silica plates using 50% ethyl acetate/hexanes as the eluant. The compound of higher R_f was identified as 3′-deoxy derivative **16b** (36.3 mg, 55.0%), and the slow-moving component was identified as the 2′-deoxy derivative **17b** (10.3 mg, 16.0%). In addition ca. 15% of the deoxygenated product **8b** was also present in the reaction mixture as judged by ^1H NMR of the crude product and comparison of TLC with

(43) Richtmyer, N. K. β-D-Altrose. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic; New York, 1962; pp 107–113.

(44) Inch, T. D.; Lewis, G. J. *Carbohydr. Res.* **1970**, *15*, 1.

(45) Robbins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. *Tetrahedron Lett.* **1984**, *25*, 367.

(46) Jain, T. C.; Jenkins, I. D.; Russel, A. F.; Verheyden, J. P. H.; Hoffatt, J. G. *J. Org. Chem.* **1974**, *39*, 30.

(47) Lemieux, R. U.; Fraga, E.; Watanabe, K. A. *Can. J. Chem.* **1968**, *46*, 61.

(48) Inch, T. D.; Lewis, G. J. *Carbohydr. Res.* **1970**, *15*, 1.

that of an authentic sample prepared by the deoxygenation reaction described earlier.

16b: IR 3420, 3060, 3030, 2950, 2920, 2850, 1700, 1595, 1570, 1490, 1250, 1130, 1070, 830 cm^{-1}; ^1H NMR 0.10 (2s, 6 H, $SiMe_2$), 0.85 (s, 9 H, Bu^{t}Si), 2.10 (m, 1 H, $H_{3'}$), 2.30 (m, 1 H, $H_{3'}$), 3.90 (d, ABq, 4, 12 (J_{AB}), 2 H, $H_{5'}$), 4.60 (m, 2 H, $H_{2'}$, $H_{4'}$), 4.72 (m, br, 1 H, OH), 6.00 (d, J = 3, 1 H, $H_{1'}$), 7.35 (t, J = 7, 4 H), 7.45 (t, J = 7, 2H), 7.85 (d, J = 7, 4 H), 8.46 (s, 1 H), 8.62 (s, 1 H); FAB MS 574.34 (M + H; calcd for $C_{30}H_{36}N_5O_5Si$ 574.25).

17b: ^1H NMR 0.06 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, Bu^{t}Si), 2.55 (m, 1 H, $H_{2'}$), 2.75 (m, 1 H, $H_{2'}$), 3.85 (d, br, J = 5, 3 H O*H*, $H_{5'}$), 4.10 (dd, J = 6, 3 Hz, 1 H, $H_{3'}$), 4.70 (m, 1 H, $H_{4'}$), 6.52 (t, J = 6, 1 H, $H_{1'}$), 7.35 (t, J = 6, 4 H), 7.50 (t, J = 6, 2 H), 7.85 (d, J = 6, 4 H), 8.32 (s, 1 H), 8.62 (s, 1H); FABMS 574.34 (M + H; calcd for $C_{30}N_5O_5Si$ 574.25).

The reduction carried out on the unprotected derivative **7a** yielded **16a**[49] (45%) and **17a**[50] (11%) in addition to the deoxygenated product **8a**[46] (15%). Preparation of these compounds and their spectra have been described in the literature.

Reduction of Compound 18. A solution of Cp_2TiCl (0.36 g, 1.7 mmol) in THF (25 mL) was added dropwise to a solution of **18** (200 mg, 1.0 mmol) and 1,4-cyclohexadiene (0.80 g, 10 mol) in THF (5 mL). The reaction was quenched with 10% aqueous acetic acid (50 mL), extracted into ether (2 × 50 mL), and washed with saturated $NaHCO_3$ (10 mL). After removal of the solvent, the residue was subjected to flash chromatography (1:1 hexane/ethyl acetate). Cuts 20–30 contained the product 1,1-dicarbomethoxycyclopentan-3-ol (**19**, 105 mg, 52%): ^1H NMR 1.77 (m, 1 H), 1.85–2.0 (m, 1 H), 2.10–2.35 (m, 2 H), 3.72 (s, 3 H), 3.75 (s, 3 H), 4.39 (m, 1 H); ^{13}C NMR 32.15, 35.10, 43.48, 52.66, 52.80, 59.16, 73.12, 172.60, 173.41; HRMS 203.0974 (M + H; calcd for $C_9H_{15}O_5$ 203.0914). The principal side product was the product of deoxygenation, 1,1-dicarbomethoxycyclopent-3-ene, which eluted in cuts 7–10.

Reduction of 18 Using 2-Methyl-2-propanethiol as the H-Atom Source (Use of In Situ Generated Cp_2TiCl). A solution of Cp_2TiCl in anhydrous THF was prepared from 249 mg (1.0 mmol) of Cp_2TiCl_2 and excess zinc. This solution was added to a solution of the epoxide (68 mg, 0.50 mmol) and 450 mg of 2-methyl-2-propanethiol and 2 mL of THF. After 10 min the reaction was quenched with 1 mL of 1 N HCl in ether. After 5 min the precipitated Cp_2TiCl_2 was filtered off. Excess water was added, and the product was extracted into ether. Chromatography on silica gel (50% ethyl acetate/hexane) gave **47** mg (72%) of the desired product identified by its spectral properties.

Reduction of (2*R*,3*R*)-2,3-Epoxy-1-decanol (9a). A solution of Cp_2TiCl (0.43 g, 2 mmol) in THF (30 mL) was added dropwise over the course of 40 min to a solution of **9a** (172 mg, 1 mmol), and 2-methyl-2-propanethiol (0.90 g, 10 mmol) in THF (10 mL). Thereupon 10% sulfuric acid (25 mL) was added, and the mixture was stirred for 15 min. The product was extracted into ether (3 × 25 mL), and the combined ether extracts were washed with saturated $NaHCO_3$ (5 mL). After removal of the solvent, the product was purified by flash chromatography (ethyl acetate, then 95:5 ethyl acetate/methanol) to afford the product (120 mg, 69%) as a colorless oil. A portion of the product was converted to the bis(trifluoroacetate) ester with trifluoroacetic anhydride, was analyzed by capillary gas chromatography (Chiraldex G-TA column, 100 °C), and was shown to contain 94% (*R*)-1,3-decanediol (**20**) and 6% (*S*)-1,2-decanediol: $[\alpha]^{25}D$ −5.8 (*c* 0.52, methanol); ^1H NMR 0.89 (dist t, J = 7, 3 H), 1.20–1.38 (br m, 10 H), 1.38–1.56 (m, 2 H), 1.56–1.78 (m, 2 H), 3.46 (br s, 1 H, exchanges with D_2O), 3.65 (br s, 1 H, exchanges with D_2O), 1.70–1.90 (m, 3 H); ^{13}C NMR 13.94 , 22.52, 25.51, 29.19, 29.54, 31.73, 37.60, 38.23, 60.87, 71.29. Anal. ($C_{10}H_{22}O_2$) C, H.

Reduction of (2*R*,3*R*)-2–,3-Epoxy-1-decanol Trimethylsilyl Ether (9b). The epoxide **9a** (172 mg, 1 mmol) was first silylated overnight with excess (trimethylsilyl)dimethylamine (1 g) in THF (5 mL). Removal of the solvent left **9b**, which was used without purification. Reduction followed a procedure identical to that for **9a** except that hydrofluoric acid (1 mL) was additionally added during the quench. The chromatographed product (116 mg, 67%) was a white solid which gas chromatographic analysis showed to consist of 91% (S)-1,2-decanediol (99.1% ee) and 9% (*R*)-1,3-decanediol. Recrystallization from hexane (−25 °C) afforded the substantially pure 1,2-diol: $[\alpha]^{25}D$ −12.5 (*c*, 1, EtOH); ^1H NMR 0.88 (br t, J = 7, 3 H), 1.28 (m, 12 H), 1.43 (m, 2 H), 2.75 (br s, 2 H), 3.43 (dd, J = 8, 12, 1 H), 3.65 (dd, J = 4, 12, 1 H), 3.7 (m, 1 H); ^{13}C NMR 14.11, 22.68, 25.63, 29.30, 29.55, 29.71, 31.89, 33.12, 66.80, 72.40. Anal. ($C_{10}H_{22}O_2$) C, H.

Reduction of (2*S*,3*S*)-(−)-Phenylglycidol (23a). Phenylglycidol (150 mg, 1 mmol) was dissolved in 4 mL of THF, and 90 mg of 2-methyl-2-propanethiol was added. To this solution was added, with excellent stirring, the Cp_2TiCl solution (prepared from 2 mmol of Cp_2TiCl_2 and Zn in 5 mL of THF) slowly over 15 min. The reaction mixture was stirred for 30 min and then quenched with 2 mL of 1 N HCl in ether (Aldrich). After 4 min, precipitated titanium residues were filtered with the aid of Celite and the solid residue was washed with excess ether. Excess saturated sodium dihydrogen phosphate (10 mL) and ether (10 mL) were added, and the mixture was stirred for 10 min. The organic layer was separated, and the aqueous layer was repeatedly extracted with ether. The combined ether layer was dried and concentrated. Chromatography yielded 93 mg (62%) of the diol (**24a**) and 24 mg (18%) of cinnamyl alcohol, each identified by comparison with authentic samples.

An authentic sample of **24a** was prepared by treating (2,3-epoxy-1-propyl)benzene in CH_2Cl_2 with water in the presence of nafion-H.[51] The corresponding bis(trifluoroacetate) was prepared by treating the alcohol with a 25% solution of trifluoroacetic anhydride in CH_2Cl_2. The racemic trifluoroacetate gave baseline separation on a Chiraldex-GTA column (20 m) at 100 °C (retention times: 2*S*, 9.14; 2*R*, 9.62 min). The enantiomeric purity of the diol derived from the Ti-mediated reduction was ascertained as at least 99% ee.

A similar reaction done with cyclohexadiene in the place of 2-methyl-2-propanethiol gave mostly (88%) cinnamyl alcohol.

Transposition of a Sharpless Epoxide. Phenylglycidol was converted into the corresponding tosylate **23b** by the procedure described by Dittmer et al.[52]

To 290 mg of the tosylate dissolved in 5 mL of anhydrous THF was added 900 mg of 2-methyl-2-propanethiol. To this mixture was added 2 mmol of Cp_2TiCl prepared from titanocene dichloride and zinc as described earlier. The addition was carried out over 10 min with excellent stirring at ~0 °C. The reaction mixture was stirred for 10 min, during which time it was allowed to warm to room temperature. The reaction was subsequently quenched with 2 mL of 1 N HCl in ether. It was further stirred for 5 min and 10 mL of ether was added. The precipitated titanium residues were filtered off with the aid of celite in a pressure funnel, and the residue was thoroughly washed with ether. The combined ether layer was treated with 5 mL of saturated NaH_2PO_4 for 10 min. The organic layer was separated. The aqueous layer was extracted with ether (10 mL × 5), and the combined organic layer was washed with brine (10 mL × 2). It was dried and concentrated. The product alcohol tosylate **24b** may be isolated by column chromatography: ^1H NMR 2.25 (s, 3 H, CH_3), 2.78 (m, 2 H), 3.82 (m, 1 H), 4.10 (m, 2 H), 7.10–7.40 (aromatic), 7.80 (d, J = 8, 2 H). However, for the preparation of the transposed epoxide, the crude product was directly taken to the next step.

The crude tosylate was dissolved in 2 mL of methanol, and 2 mL of 1 N sodium hydroxide was added to the solution at 0 °C. The mixture was stirred while the reaction was followed by TLC (silica gel, 50% ether/hexanes). When all the tosylate was consumed (~30 min), 15 mL of ether was added and the product was isolated by the usual workup. Pure epoxide (56 mg, 41% yield from the starting epoxy tosylate) was isolated by column chromatography on silica gel using 20% ether/hexane. It was identified as (2,3-epoxypropyl)benzene by comparison of the GC retention times and ^1H NMR spectrum with those of an authentic sample.

The sample was subjected to chiral GC analysis on a Chiraldex-GTA column (20 m) at 90 °C to ascertain the optical purity. It was determined as >99% of the 2*R* isomer. For comparison, under these conditions, the corresponding racemate gave baseline separation of the two enantiomers (*S*/*R* of 11.03 and 11.68 min, respectively).

Reactions of (1*S*)-(−)-1-((Tosyloxy)methyl)-7-Oxabicyclo[4.1.0]-heptane (26). The title compound was prepared according to the procedure described in the literature,[52] and it was subjected to the reduction conditions reported in the previous experiment.

The tosylate (140 mg, 0.37 mmol) was dissolved in 3 mL of anhydrous THF and 700 mg of 2-methyl-2-propanethiol. In the meantime, a solution of Cp_2TiCl in THF (from 194 mg of Cp_2TiCl_2 and excess Zn) was prepared as described above. The solution was added dropwise to the solution of the epoxide at 0 °C. The reaction was quenched after 10 min by adding 0.9 mL of 1 N HCl in ether. After 10 min, the precipitated Cp_2TiCl_2 was filtered off and the solution was concentrated. The major products (70 mg, 67%) were isolated by column chromatography on silica gel and identified as a mixture of two tosylates, the trans (**27**) and the cis (**28**) isomers in a ratio of 2:1.

27: ^1H NMR 1.05–2.05 (m), 2.45 (s, 3 H), 3.40 (m, br, 1 H), 4.06, 4.24 (ABX qd, J_{AB} = 10 J_{AX} = 5, J_{BX} = 4), 7.35 (d, J = 8, 2 H), 7.80

(49) Norbeck, D. w.; Kramer, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 7217.
(50) Ogilvie, K. *Can. J. Chem.* **1973**, *51*, 3799.
(51) Olah, G. *Synthesis* **1981**, 280.
(52) See reference under footnote 20.

(d, J = 8, 2 H); ^{13}C NMR 21.82, 24.89, 25.30, 27.98, 35.72, 46.31, 70.66 (CHO), 72.35 (CH_2O), 128.10, 130.01, 133.45, 144.86; FAB MS 285.12 (M + H; calcd for $C_{14}H_{21}O_4S$ 285.12).

28: ^{1}H NMR 1.10–1.90 (m, 10 H), 2.45 (s, 3 H), 4.02 (m, br, 1 H), 3.84, 4.09 (ABX aq, J_{AB} = 12, J_{AX} = 6, J_{BX} = 8, 2 H), 7.35 (d, J = 8, 2 H), 7.80 (d, J = 8, 2 H); ^{13}C NMR 20.14, 21.83, 22.89, 25.02, 32.98, 41.34, 66.83 (CHO), 72.21 (CH_2O), 128.10, 130.03, 133.50, 144.87; FAB MS 285.11 (M + H; calcd for $C_{14}H_{21}O_4S$ 285.12). The structures of the major and minor isomers were established by the relative chemical shifts of CH_2O and CHOH in the ^{13}C NMR spectrum. In the more congested cis isomer, these carbons come at a higher field.[35b] A fast minor component (11 mg) has been tentatively identified as one resulting from chlorine trapping. ^{1}H NMR 1.30–2.40 (m), 2.10–2.30 (1 H), 2.35 (s, 1 H), 2.45 (s, 3 H), 4.02, 4.02, 4.18 (AB q, J_{AB} = 10, 2 H), 4.05 (m, 1 H), 7.36 (d, J = 8, 2 H), 7.82 (d, J = 8, 2 H); ^{13}C NMR 20.54, 20.87, 21.87, 29.45, 30.44, 61.24, 72.81, 74.29; FAB MS 319.09 (M + H; calcd for $C_{14}H_{20}ClSO_4$ 319.08).

General Procedure for Reductive Cyclization Reactions. A solution of Cp_2TiCl (0.43 g, 2 mmol) in THF (25 mL) was added dropwise to a solution of the epoxide (1.0 mmol) in THF (25 mL). An excess (50 mL) of 10% sulfuric acid was added, and the mixture was extracted into ether (3 × 50 mL) and washed with saturated sodium hydrogen carbonate and water (50 mL each). After removal of the solvent, the crude product was purified by flash chromatography.

Cyclization of 6,7-Epoxyhept-1-ene (29). The crude product obtained following the general procedure was analyzed by gas chromatography versus *tert*-butylbenzene as an internal standard. GC analysis indicated a 2:1 mixture of *cis*- and *trans*-2-methylcyclopentane-1-carbinol (**31a**) in a combined 70% yield. Consistent with this, the area of the methyl doublet at δ 0.96 in the ^{1}H NMR was two times that of the doublet at δ 0.82. Likewise in the ^{13}C NMR the upfield methyl group at δ 15.03 was larger than that of δ 20.26, and the same pattern was observed in the hydroxymethyl group resonances at δ 63.64 and 66.06.

^{2}H Labeling Studies (Scheme 1). Cyclization of 6,7-epoxyhept-1-ene was carried out as in the previous example except that the reaction was quenched with 10% D_2SO_4 (10 mL) and the reaction mixture was silylated with (dimethylamino)trimethylsilane. Chemical ionization GC MS analysis was carried out. For one isomer the molecular ion was observed at m/e = 187 while the other gave a M–CH_3 peak at m/e = 172. ^{13}C NMR also indicated that the methyl group was ca. 85% substituted with a single deuterium. In a separate experiment the reaction was run on one-half the usual scale in solvent THF-d_8. After protonolysis, GC MS analysis indicated no observable incorporation of deuterium into either of the product alcohols.

Cyclization of 6,7-Epoxyhept-1-yne (Scheme 2). The product obtained following the general procedure was isolated by flash chromatography (60:40 hexane/ether). Most of the solvent from cuts 10-15 was removed by distillation under nitrogen; the last traces were removed at reduced pressure on a rotary evaporator. The product, **33** (42 mg, 37%), was a single material by GC. NMR was consistent with formulation of 2-methylenecyclopentane-1-carbinol: ^{13}C NMR 25.45, 29.58, 33.55, 46.23, 65.10, 106.08, 153.43; ^{1}H NMR 1.50–2.00 (m, 5 H), 2.33 (m, 2 H), 2.61 (m, 1 H), 3.58 (d, J = 6, 2 H), 4.90 (m, 1 H), 5.00 (m, 1 H). An identical reaction mixture was quenched with 10% D_2SO_4 in D_2O (10 mL); the ^{13}C NMR spectrum of the isolated product indicated no incorporation of deuterium. In a separate experiment, both the epoxide and Cp_2TiCl were dissolved in THF-d_8 (5 and 10 mL, respectively) and the reaction was carried out as above. Under these circumstances the singlet at δ 106.08 ppm was reduced in intensity and was replaced by a 1:1:1 triplet (δ 105.79, J = 23.8); total integration of the triplet was ca. 70% that of the singlet.

Reductive Cyclization of 4,4-Dicarbethoxy-6,7-epoxyhept-1-ene (35). Compound **36** was isolated as a colorless liquid by flash chromatography in hexanes/ethyl acetate (1:1). The stereochemistry was assigned to be 85% cis on the basis of the relative integration of doublets in the ^{1}H NMR at δ 0.95 (major) and 1.04 (minor). **36**; ^{13}C NMR (major isomer) 13.97, 14.63, 35.24, 36.14, 41.60, 44.51, 59.00, 61.37, 61.44, 62.69, 172.74; HRMS 211.0979 (calcd for $C_{11}H_{15}O_4$ ($M^+ - H_2O - C_2H_5$) 211.0971). Anal. ($C_{13}H_{22}O_5$) C, H.

Cyclization of 6,7-Epoxy-6-methylhept-1-ene (37). Compound **38** was isolated as a colorless liquid by flash chromatography in hexanes/ethyl acetate (60/40). ^{1}H NMR showed doublets of roughly equal intensity at δ 0.86 and 0.90. **38**: ^{13}C NMR (mixture of isomers) 14.36, 14.81, 17.74, 21.70, 21.72, 23.47, 33.19, 33.43, 35.44, 36.30, 38.90, 43.44, 45.23, 45.29, 67.23, 70.81; HRMS 110.1097 (calcd for C_8H_{14} ($M^+ - H_2O$) 110.1095). Anal. ($C_8H_{16}O$) C, H.

Cyclization of 4-(But-3-enyl)-1-oxaspiro[2.5]octane (39). Compound **40** was isolated as a viscous oil by flash chromatography in hexane/ethyl acetate (75:25). The stereochemistry was assigned to be 55% endo on the basis of the relative integration of doublets in the ^{1}H NMR at δ 0.94 (major) and 0.96 (minor). **40**: ^{13}C NMR (mixture of isomers) 13.48, 14.71, 20.29, 21.33, 21.63, 23.11, 23.70, 24.60, 25.25, 27.03, 27.82, 28.22, 29.72, 30.10, 36.56, 38.56, 39.06, 39.97, 44.87, 46.71, 64.79, 65.07; HRMS 150.1408 (calcd for $C_{11}H_{18}$ ($M^+ - H_2O$) 150.1409). Anal. ($C_{11}H_{20}O$) C, H.

Cyclization of 4-(But-3-enyl)-1-oxaspiro[2.4]heptane (41). Compound **42** was isolated as a low-melting solid by flash chromatography in hexane/ethyl acetate (75:25). The stereochemistry was assigned to be 90% endo on the basis of the relative integration of doublets in the ^{1}H NMR at δ 0.93 (major) and 1.01 (minor). **42**; ^{13}C NMR (major isomer, $CDCl_3$) 14.49, 26.47, 30.45, 31.65, 33.39, 35.20, 39.46, 46.09, 57.14, 69.21; HRMS 136.1254 (calcd for $C_{10}H_{16}$ ($M^+ - H_2O$) 136.1252). Anal. ($C_{10}H_{18}O$) C, H.

Preparation of Iodoalcohol 43a. For this experiment the usual order of addition for the reductive cyclizations was reversed to optimize the efficiency of scavenging the primary alkyl radicals after cyclization. A solution of epoxide **35** (0.30 g, 2.0 mmol) in THF (50 mL) was added dropwise to a solution of Cp_2TiCl (0.86 g, 4.0 mmol) in THF (50 mL). After 10 min, iodine (0.50 g, 2.0 mmol) was added and the reaction was stirred for 1 h. The reaction was quenched with 10% sulfuric acid, extracted with ether, and dried ($MgSO_4$). After removal of the solvent, the azeotropically dried crude **43a** was treated with *tert*-butyldimethylsilyl chloride (0.36 g, 2.4 mmol), triethylamine (0.51 g, 5 mmol), and 4-(dimethylamino)pyridine (0.02 g, 0.2 mmol) in dichloromethane (25 mL). After removal of the solvent, the resultant silyl ether was purified by flash chromatography in hexane. The product **43b** was obtained from cuts 9–13 as a colorless liquid (0.50 g, 63% yield): ^{1}H NMR 0.00 (s, 6 H), 0.89 (s, 9 H), 0.98–1.65 (overlapping m, 8 H), 1.80–2.24 (overlapping m, 4 H), 3.01 (dd, J = 8, 9, 1 H), 3.26 (d, J = 9, 1 H), 3.43 (d, J = 9, 1 H), 3.48 (dd, J = 3, 8, 1 H); ^{13}C NMR –5.59, –5.46, 9.24, 18.18, 25.90, 26.24, 29.66, 30.22, 32.71, 34.83, 47.94, 50.41, 57.77, 69.66; HRMS 337.0536 (calcd for $C_{12}H_{22}OSiI$ ($M^+ - C_4H_9$) 337.0487).

Preparation of Bicyclic Tetrahydrofuran 44. A solution of Cp_2TiCl (0.43 g, 2.0 mmol) in THF (25 mL) was added dropwise to a solution of epoxide **35** (0.25 g, 1.0 mmol) in THF (25 mL). After 10 min, iodine (0.25 g, 1.0 mmol) was added and the reaction was stirred for 1 h. Saturated aqueous ammonium chloride (50 mL) was added, and the mixture was extracted with ether (3 × 50 mL). The combined ether extracts were extracted with 5% sodium hydrogen sulfite and water (50 mL each), and the solvent was distilled off at reduced pressure. The residue was applied to a flash chromatography column with a few milliliters of dichloromethane and eluted with 60:40 hexane/ethyl acetate. Removal of solvent from cuts 12–15 afforded **44** (0.13 g, 52%) as a colorless liquid: ^{1}H NMR 1.05 (t, J = 7, 3 H), 1.07 (t, J = 7, 3 H), 1.92 (dd, J = 7, 12, 2 H), 2.56 (dd, J = 7, 12, 2 H), 2.79 (m, 2 H), 3.53 (dd, J = 7, 9, 2 H), 3.68 (d, J = 9, 2 H), 4.17 (q, J = 7, 2 H), 4.20 (q, J = 7, 2 H); ^{13}C NMR 13.87, 40.06, 43.50, 61.14, 61.21, 62.87, 73.86, 170.74, 171.62; HRMS 211.0979 (calcd for $C_{11}H_{15}O_4$ ($M^+ - OC_2H_5$) 211.0971).

Synthesis of Epoxyolefins 45a,b (Scheme 3). These epoxyolefins were prepared from 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose[35b] and the corresponding 2-deoxy derivative[35b] by the following sequence: (1) Ph_3P^+–CH_2^-; (2) trifluoroacetic anhydride/DMSO; $EtN(i\text{-}Pr)_2$ (3) $Me_2S^+(O)CH_2^-$ (see the supplementary material for details).

Cyclization of the Sugar Epoxide 45a. Compound **46a**: ^{1}H NMR (for the endo isomer) 1.21 (d, J = 8, 3 H, CH_3), 1.92 (ddd, J = 12, 8, 6, 1 H, H_{6a}), 2.18 (dd, J = 12, 6, 1 H, H_{6b}), 2.30 (qm, J = 8, 1 H, H_5), 2.75 (s, br, 1 H, OH), 3.45, 3.51 (ABq, J_{AB} = 10, 2 H, CH_2OH), 3.85, 4.09 (ABq, J_{AB} = 10, 2 H, H_4's), 4.00 (d, J = 6, 1 H, H_7), 4.26 (s, 1 H, H_{7a}), 4.55 (s, 2 H, CH_2Ph), 5.47 (s, 1 H, PhC*H*), 7.20–7.53 (m, aromatic); NOE $CH_3 \rightarrow H_{6a}$, H_5, H_{4eq}; $H_7 \rightarrow H_{6a}$, CH_3; $H_{7a} \rightarrow H_2$, CH_2OH (the methyl resonance of the exo isomer is at δ 1.04); ^{13}C NMR (endo isomer) 17.82 (CH_3), 35.84 (C_5), 39.82 (C_6), 46.24 (C_{4a}), 66.92 (two carbons, C_4, CH_2OH), 71.30 (CH_2Ph), 83.84 (C_7), 85.09 (C_{7a}), 99.26 (C_2); ^{13}C NMR (exo isomer) 12.70 (CH_3), 33.51 (C_5), 39.20 (C_6), 45.50, 62.68, 71.67, 83.58, 86.01, 99.97 (assignments were confirmed by chemical shift correlation mapping and attached proton test (APT) experiments); FAB MS 262.85 ((M – benzyl alcohol) + H; calcd for $C_{15}H_{19}O_4$ 263.13). Anal. ($C_{22}H_{26}O_4$) C, H.

Cyclization of **45b** yielded essentially a single cyclic product (>95% of the methyl-bearing compound), albeit in only 20% yield. This cyclic product **46b** was assigned the exo-methyl structure on the basis of the ^{1}H (δ 1.06) and ^{13}C chemical shifts as compared to model compound **46a** and others reported in the literature.[35b] **46b**: ^{1}H NMR 1.06 (d, J = 7, 3 H), 2.65 (m, br, 1 H), 2.86 (dq, J = 7, 6, 1 H), 3.42 (s, br, 2 H), 3.76,

3.85 (ABq, J_{AB} = 12, 2 H), 3.85–3.97 (m, 2 H), 4.26 (s, br, 1 H), 4.47–4.67 (a set of ABq, 4 H), 5.40 (s, 1 H), 7.25–7.25–7.55 (m, aromatic).

Synthesis of 47. The starting material **47** (X = OBn) was prepared from the Wittig product **50** (Scheme 3) by the following sequence: (1) TFA/CH_2Cl_2/H_2O; (2) TosCl/pyridine; (3) KOH/MeOH; (4) acetic anhydride/pyridine. The starting material for **47** (X = OAc) was prepared from **50** via (1) LAH/$AlCl_3$, (2) TosCl/pyridine, and (3) KOH/MeOH.

Cyclization of 47 (X = OBn). Compound **48** (1,2-trans, 1,5-cis, 45%): ^{1}H NMR δ 1.01 (d, J = 7, 1 H), 1.45 (dt, J = 13, 6, 1 H), 2.00 (m, br, 1 H), 2.12 (m, 1 H), 2.20–2.35 (m, 2 H), 3.75 (m, 2 H), 3.90–4.05 (m, 2 H), 4.40–4.70 (2 ABq, 4 H), 7.25–7.40 (m, aromatic); ^{13}C NMR 16.26, 31.71, 37.92, 48.38, 62.69, 71.43, 71.73, 84.82, 88.22. **48** (1,2-trans, 1,5-*trans*, 30%): ^{1}H NMR 1.04 (d, J = 7, 3 H), 1.60 (m, 2 H), 1.97 (m, 2 H), 2.55 (s, br, 1 H), 3.61 (dd, J = 11, 7, 1 H), 3.75 (m, 1 H), 3.84 (dd, J = 7, 3, 1 H), 3.95 (m, 1 H), 4.40–4.70 (2 ABq, 4 H), 7.25–7.40 (m, aromatic); ^{13}C NMR 19.56, 31.79, 38.04, 53.74, 64.04, 70.94, 71.78, 83.11, 88.14. **48** (1,2-cis, 1,5-cis, 15%): ^{1}H NMR δ 0.98 (d, J = 6, 3 H), 1.74 (m, 1 H), 1.85 (m, 1 H), 2.30 (m, 2 H), 2.60 (s, br, 1 H), 3.79 (qm, J = 11, 2 H), 4.12 (m, 2 H), 4.40–4.65 (2 ABq, 4 H), 7.25–7.40 (m, aromatic; ^{13}C NMR 16.36, 32.05, 37.72, 46.16, 60.44, 71.30, 72.24, 83.80, 88.14. **48** (1,2-cis, 1,5-trans, 10%): ^{1}H NMR 1.04 (d, J = 6, 3 H), 1.26 (m, 1 H), 1.80 (m, 1 H), 2.12 (m, 1 H), 2.34 (dt, J = 12, 6, 1 H), 2.61 (s, br, 1 H), 3.70 (m, 1 H), 3.84 (dm, J = 10, 1 H), 3.95 (ddd, J = 6, 6, 3, 1 H), 4.10 (dd, J = 8, 3, 1 H), 4.45–4.72 (2 ABq, 4 H), 7.25–7.40 (m, aromatic); ^{13}C NMR 19.23; 31.10, 38.63, 50.27, 61.02, 71.24, 71.64, 83.97, 87.00; FAB MS 327.20 (M + H; calcd for $C_{21}H_{26}O_2$ 326.19). The preparation of authentic samples of the 1,2-cis compounds has been described in the literature.[35b] This paper also describes in detail methods for assigning stereochemistry in highly functionalized cyclopentanes.

Intermolecular Addition of Methyl Methacrylate to 1-Oxaspiro[2.5]octane: A [3 + 3] Lactone Annulation (Scheme 4). A solution of bis(cyclopentadienyl)titanium(III) chloride (0.43 g, 2.0 mmol) in THF (20 mL) was added dropwise to a stirred solution of the epoxide (112 mg, 1.00 mmol) and methyl methacrylate (1.00 g, 10 mmol) in THF (20 mL). After 10 min, the reaction was rapidly quenched by addition of 10% sulfuric acid (40 mL) and the product was extracted with ether (3 × 40 mL). The combined organic phase was washed with saturated sodium bicarbonate then with water and was dried ($MgSO_4$). After distillation of the solvent, flash chromatography (hexane/ethyl acetate 60:40) afforded **55** (148 mg, 81%) as a white solid: mp 58–59 °C; ^{1}H NMR 1.23 (d, J = 7, 3 H), 1.25–1.60 (m, 11 H), 1.96 (dd, J = 7, 11, 1 H), 2.59 (m, 1 H), 3.99 (s, 2 H); ^{13}C NMR 16.20, 21.26, 21.65, 25.76, 31.94, 33.55, 36.15, 38.85, 76.24, 176.19. Anal. ($C_{11}H_{18}O_2$) C, H.

Intermolecular Additions of Epoxydecane (Eqs 15a,b). (a) Addition to Methyl Methacrylate. By following the procedure reported above, the adducts were prepared in the yields shown. The products were separated by flash chromatography on silica gel using 20–30% ethyl acetate in hexane as the solvent. δ-Hydroxy esters **56**, (53%): IR (neat) 3450, 1738 cm^{-1}; ^{1}H NMR 0.87 (t, J = 7, 3 H), 1.15 (d, J = 6), 1.16 (d, J = 7) together 3 H, 1.20–1.37 (m, 14 H), 1.40–1.50 (m, 2 H), 1.60–1.85 (two sets of m together 1 H), 2.40–2.65 (two sets of m, 1 H), 2.91 (s, br, 1 H), 3.42–3.57 (2 AB m, 2 H), 3.66 (two s, separated by 1 Hz, 3 H). The ratios of the sets of peaks are correlated to the GC separation of the C(2) (methyl) isomers of the lactones. By careful separation, the slower moving hydroxy ester can be isolated and characterized: ^{13}C NMR 14.01 (CH_3), 18.02 (CH_3), 22.63, 26.86, 29.28, 29.55, 29.97, 31.44, 31.88, 35.68, 37.70 (CH), 38.99 (CH), 51.53 (OCH_3), 65.25, 157.67 (CO); CI MS 259.3 (M + H); calcd for $C_{15}H_{31}O_3$ 259.2), 241.2 (M – OH; calcd 241.2), 227.2 (M – OCH_3); calcd 227.2). Minor amounts of adducts from the capture of the primary radical can be seen in the proton–carbon correlated spectrum, the diastereotopic CHO appearing at 71.35 and 72.20 ppm. The proton signals are buried under those of the major components. *Diastereomeric lactones* **57**: IR (neat) 1737 cm^{-1}; ^{1}H NMR 0.85–0.93 (t, br, 3 H), 1.20–1.60 (m, 20 H), 1.90–2.18 (two sets of m), 2.40–2.70 (two sets of m) (these two signals integrate to 1 H (α-H of the lactones)), 3.94 (dd, J = 10, 10, 1 H, H_{6ax}), 3.96 (dd, J = 10, 8, 1 H, H_{6ax}) together 1 H, 4.25 (dd, J = 10, 5, 1 H, H_{6eq}), 4.34 (ddd, J = 10, 4, 2, 1 H, H_{6eq}) together 1 H; CI MS 227.2 (M + H; calcd for $C_{14}H_{26}O_2$ 226.2).

(b) Reaction of 1,2-Epoxydecane with Acrylonitrile in the Presence of Titanocene Monochloride. A mixture of 2.98 g (12 mmol) of titanocene dichlorde and 0.98 g (15 mmol) of activated zinc in 15 mL of freshly distilled THF was stirred for 2 h under nitrogen. In a separate flask, a mixture of 0.93 mL (5 mmol) of 1,2-epoxydecane and 6.60 mL (100 mmol) of acrylonitrile were dissolved in 50 mL of THF. The green Ti(3+) solution was slowly added via a cannula to the epoxide solution, and the mixture was stirred for 10 min. Ice-cold, 5% sulfuric acid (30 mL) was added, and stirring was continued for 1 min more. The product was extracted into ether (100 mL × 3), each time collecting the ether layer in a flask containing 90 mL of saturated sodium bicarbonate solution. The bicarbonate layer was drained off, and the ether layer was washed with 90 mL of water. The ether layer was dried with anhydrous magnesium sulfate and was concentrated. The products **58** and **59** were isolated as a mixture (438 mg, 42% yield) by column chromatography on silica gel using 20% ethyl acetate/hexanes as the solvent system. The ratio of the major to the minor product was determind by GC as 88:12. In addition, two chlorohydrins (19% total yield, 1-chloro vs 2-chloro 1:2) were also isolated, **58** and **59**: IR (neat) 3350, 2250 cm^{-1}; ^{1}H NMR 0.87 (t, J = 7, 3 H), 1.30 (s, br, 14 H), 1.60–1.85 (m, 3 H), 2.12 (m, 1 H, br, OH), 2.44 (AB m, J = 6, 2 H), 3.48, 3.63 (ABX, br, J_{AB} = 11, J_{AX} = 4, J_{BX} = 6, 2 H); ^{13}C NMR 13.97 (CH_3), 14.91, 22.52, 26.69, 27.13, 29.15, 29.40, 29.76, 30.46, 31.73, 39.32 (CH), 64.34 (CH_2O), 120.02 (CN) (the peak corresponding to the CHOH of the minor product comes at δ 70.83 ppm); CI MS 212.2 (M + H; calcd for $C_{13}H_{26}NO$ 212.2), 194.2 (M – OH; calcd 194.2).

LAH-Reduction Products of the MMA Adducts 56 and 57: ^{1}H NMR 0.75–1.00 (m, 3 H), 1.05–1.80 (m), 3.20–3.65 (m, 4 H); ^{13}C NMR 13.53 (CH_3), 16.74 (CH_3), 22.16, 26.44, 28.82, 29.11, 29.63, 30.79, 31.40, 32.38 (CH), 34.91, 37.29 (CH), 65.52 (CH_2O), 67.78 (CH_2O) (the diastereomer has the following characteristic peaks: 14.03 (CH_3), 17.32 (CH_3), 22.63, 27.03, 29.30, 29.59, 30.00, 31.88, 32.35, 33.46 (CH), 35.10, 38.01 (CH), 65.13 (CH_2O), 68.00 (CH_2O)); HRMS (bis(trimethylsilyl) derivative) 359.2817 (M$^+$ – CH_3; calcd for $C_{19}H_{43}O_2Si_2$ 359.2802).

Additions to Epoxycyclohexane (Eq 16a,b). (a) Addition of MMA. A 50-mL round-bottomed flask fitted with a dropping funnel was flame dried and taken inside the glovebox. The flask was charged with 0.101 mL of distilled epoxycyclohexane and 1.00 mL of MMA (passed over basic alumina under nitrogen) in 10 mL of THF. The dropping funnel was charged with 0.450 g (2.10 mmol) of Cp_2TiCl in 5 mL of THF. The Ti(3+) solution was slowly added to the flask with good stirring, and the mixture was stirred for 10 min. The reaction was quenched with 10 mL of 10% H_2SO_4, and the product was extracted into ether. The ether extract was washed with sodium bicarbonate and dried. The products (79–88%) were separated by column chromatography using 30% ether in hexane as the solvent. Hydroxy esters **60**: IR (Neat) 3510, 1740 cm^{-1}; ^{1}H NMR 1.18 (d, J = 6), 1.00–1.90 (m), 1.80 (m, br, exchange with D_2O), 2.55 (m), 3.65 (s, 3 H), 3.75 (m, br, 1 H) (from the position of the C*H*O proton, this compound has been tentatively identified as one of the diastereomers of the cis hydroxy ester); ^{13}C NMR 18.18 (CH_3), 20.49 (CH_2), 25.19 (CH_2), 26.91 (CH_2), 32.97 (CH_2), 36.11 (CH_2), 37.35 (CH), 39.89, (CH), 51.53 (CH_3), 68.72 (CHO); HRMS (silylated derivative) 257.1530 (M$^+$ – CH_3; calcd for $C_{13}H_{25}O_3Si$ 257.1573). A broad multiplet at δ 3.18 may be assigned as the C*H*O of the trans isomer (5–8% in the crude reaction mixture).[53,54] Cis and trans δ-lactones **61**: IR (neat) 1780 cm^{-1}; ^{1}H NMR 1.32 (d, J = 8), 1.15 (d, J = 7), together 3 H, 0.95–2.20 (m), 2.50–2.80 (two sets of m, 1 H), 3.88 (ddd, J = 11, 11, 4), 3.95 (ddd, 10, 10, 4), C*H*O from the two diastereomers of the trans lactones, 4.51 (m) from the cis lactone, together the above signals account for 1 H; FAB MS 169.31 (M + H; calcd for $C_{10}H_{17}O_2$ 169.12); ^{13}C NMR (the major, i.e. trans, isomer) 17.58, 24.08, 25.04, 30.64, 32.31, 36.27, 36.67, 39.81, 84.43.

From the NMR spectrum of the crude products, the overall ratio of the trans to cis adducts may be calculated to be 2:1, the same as the numbers arrived at by examination of the spectrum of the LAH-reduction products (see the following experiment).

LAH-Reduction Products of the Crude Adducts 60 and 61 (Eq 17): ^{1}H NMR 0.70–1.92 (m, 15 H), 2.70–2.90 (s, br, 1 H, exchange with D_2O), 3.00–3.20 (s, br, exchange with D_2O), 3.18 (t, d, J = 10, 4, and axial C*H*O from the trans hydroxy compound), 3.25–3.70 (m, 2 H, CH_2O), 3.80 (m, part of equatorial C*H*O), 3.89 (m, rest of equatorial C*H*O), peaks at 3.18, 3.80, and 3.89 account for 1 H. (The ratio of cis to trans adducts calculated from these intensities is 1:2. These assignments are also corroborated by the carbon–proton correlation and attached proton test experiments). ^{13}C NMR ($CDCl_3$/CD_3SOCD_3/D_2O) inter alia 67.21, 68.24, 68.36, 68.85 (all OCH_2 from the four possible diastereomers, two cis and two trans), 67.99, 69.88 (O*C*H from the minor, i.e., cis, adducts), 74.76, 75.12 (O*C*H from the major, i.e. trans, adducts); HRMS (bis-TMS derivatives) 316.2306 (M$^+$; calcd for $C_{16}H_{36}O_2Si_2$ 316.2254).

(b) Addition of Ethyl Acrylate. The standard reaction conditions described above gave a mixture of the trans lactone (40%), trans-hydroxy

(53) House, H. O.; Babad, H.; Toothill, R. B.; Noltes, A. W. *J. Org. Chem.* **1962**, *27*, 4141.

(54) House, H. O.; Schellenbaum, M. *J. Org. Chem.* **1963**, *28*, 34.

Table 5. NMR Data for 66a,b and 67a,b

	H_1	H_2	H_3	H_4	H_5	H_{6ax}	H_{6eq}	OC*H*O	O*H*	CH_3
66a	4.60 (s)	2.26 (ddd) (5,5,2)	4.00 (m)	3.65 (dd) (10,3)	4.20–4.30 (m)	3.79 (dd) (10,10)	4.34 (dd) (10,6)	5.63 (s)	3.17 (d) (1)	3.44 (s)
66b	4.56 (s)	2.03–2.13 (m)	3.97 (s br)	3.73 (dd) (10,3)	4.20 (ddd) (10,10,5)	3.79 (dd) (10,10)	4.32 (dd) (10,5)	5.61 (s)	3.21 (s)	3.40 (s)
67a	4.69 (d) (4)	3.45 (m)	1.90–2.20 (m)	3.31 (dd) (10,9)	3.79 (ddd) (10,10,4)	3.69 (dd) (10,10)	4.27 (dd) (10,4)	5.50 (s)	1.90–2.20 (br)	3.48 (s)
67b	4.70 (d) (4)	3.38–3.60	1.75–2.10	3.30 (dd) (9,9)	3.70 (m)	3.62 (dd) (10,10)	4.26 (dd) (10,4)	5.47 (s)	2.32 (br)	3.42 (s)

ester (10%), and cis-hydroxy ester (30%) and a trace of the cis lactone, all identified by comparison of physical properties with those of authentic samples.

Intermolecular Addition of Acrylonitrile to Methyl 2,3-Anhydro-4,6-*O*-Benzylidene-α-D-allopyanoside (4). Addition of 2 equiv of Cp_2TiCl in 15 mL of THF to a mixture of the sugar epoxide **4** and acrylonitrile (5 equiv) in 10 mL of THF yielded a mixture of adducts of which the major product (32%) was identified as **66a**: IR (neat) 3500, 2240 cm^{-1}; ^1H NMR 1.78–2.00 (m, 2 H, CH_2CH_2CN), 2.26 (ddd, J = 5, 5, 2, 1 H, H_2), 2.48 (t, J = 7.5, 2 H, CH_2CN), 3.17 (d, J = 7, 1 H, O*H*), 3.44 (s, 3 H, OCH_3), 3.65 (dd, J = 10 ($J_{4,5}$), 3 ($J_{3,4}$), 1 H, H_4), 3.79 (dd, J = 10 ($J_{5,6a}$), 10, ($J_{6a,6e}$), 1 H, H_{6a}), 4.00 (m, br, 1 H, H_3), 4.20–4.30 (m, 1 H, H_5), 4.34 (dd, J = 10, 6 ($J_{5,6e}$), 1 H, H_{6e}), 4.60 (s, 1 H, H_1), 5.63 (s, 1 H, PhC*H*), 7.34–7.54 (m, aromatic H); NOE H_1 → H_2, CH_2CN, CH_2CH_2CN, OCH_3; H_2 → CH_2CH_2CN, H_1, H_3; H_3 → H_2, H_4; H_4 → benzylidene H, H_3; benzylidene H → H_4, H_{6ax} (these assignments and the structure were confirmed by the detailed analysis of the COSY and NOESY spectra); ^{13}C NMR 16.04 (CH_2CN), 25.83 (CH_2CH_2CN), 44.71 (C_2), 55.68 (OCH_3), 58.50 (C_5), 68.56 (C_3), 69.23 (C_6), 76.71 (C_4), 101.16 (C_1), 102.36 (benzylidene C), 118.45 (CN), 126.23, 128.23, 129.14, 137.12 (aromatic carbons) (assignments were also confirmed by the Attached Proton Test); CI MS 320.2 (M^+ + H; calcd for $C_{17}H_{22}NO_5$ 320.1426); 288.1 (M – OCH_3; calcd 288.1). Three other minor isomers (total yield ca. 5%) are also formed in this reaction in a ratio 5:3:1 as judged by the integration of the anomeric proton intensity (at δ 4.69, 4.66, and 4.80, respectively). The larger of these isomers is characterized as **67a** by the following spectral data: IR (KBr) 3380, 2240 cm^{-1}; ^1H NMR 1.90–2.20 (m, 4 H, $CHCH_2CH_2CN$, O*H*), 2.61 (dt, J = 1, 8, 2 H, CH_2CN), 3.31 (dd, J = 9, 10, 1 H, H_4), 3.45 (m, simplifies upon addition of D_2O, 1 H, H_2), 3.48 (s, 3 H, OCH_3), 3.69 (dd, J = 10, H_{6ax}), 3.79 (ddd, J = 10, 10, 5, 1 H, H_5), 4.27 (dd, J = 10, 5, 1 H, H_{6eq}) 4.69 (d, J = 4, 1 H, H_1), 5.50 (s, 1 H, benzylidene H), 7.20–7.60 (m, aromatic); NOE H_1 → OCH_3, H_2; H_4 → benzylidene H, H_{6a}.

Addition of Methyl Vinyl Ketone to 4. To a solution of 0.265 g (1.0 mmol) of the sugar epoxide **4** and 0.85 mL (10.0 mmol) of methyl vinyl ketone in 25 mL of distilled THF was added 0.440 g (2.0 mmol) of Cp_2TiCl in 10 mL of THF. The mixture was stirred for 10 min, and the reaction was worked up. The mixture was added to 10% H_2SO_4 and 40 mL of ether. The ether layer was separated and was added to 50 mL of saturated sodium bicarbonate. The aqueous layer was further extracted with ether, each time adding the ether extract into the bicarbonate solution. The ether layer was separated, dried, and concentrated. Column chromatography on silica gel using 50% ethyl acetate in hexane gave the following products in addition to the reduction product **14** (7%). **66b**; (45%) ^1H NMR 1.65–1.85 (m, 2 H, CH_2), 2.03–2.13 (m, 1 H, H_2), 2.18 (s, 3 H, CH_3CO), 2.56 (t, J = 8, 2 H, CH_2CO), 3.21 (s, br, 1 H, OH), 3.40 (s, 3 H, CH_3), 3.73 (dd, J = 10, 3, 1 H, H_4), 3.79 (dd, J = 10, 1 H, H_{6ax}), 3.97 (s, br, 1 H, H_3), 4.20 (ddd, J = 10, 10, 5, 1 H, H_5), 4.32 (dd, J = 10, 5, 1 H, H_{6eq}), 4.56 (s, 1 H, H_1), 5.61 (s, 1 H, benzylidene H), 7.30–7.55 (m, aromatic); ^{13}C NMR 23.48 (CH_2), 29.84 (CH_3), 41.73 (CH_2CO), 45.10 (C_2), 55.39 (OCH_3), 58.50 (C_5), 68.76 (C_3), 69.27 (C_6), 76.73 (C_4), 102.00 (C_1), 102.22 (benzylidene CH). **67b** (9% of a mixture of two adducts from which the major isomer (70%) has been identified as **67b** by comparison of the NMR spectrum with that of the minor adduct from the acrylonitrile reaction (see the table of NMR data)): ^1H NMR inter alia 1.75–2.10 (m, 3 H, CH_2, H_3), 2.00 (s, 3 H, CH_3), 2.32 (d, br), 2.65 (ddd, J = 5, 5, 5, 2 H, CH_2CO), 3.30 (dd, J = 9, 9, 1 H, H_4), 3.42 (s, 3 H, OCH_2), 3.62 (dd, J = 10, 10, 1 H, H_{6ax}), 3.70 (m, 1 H, H_5), 4.26 (dd, J = 10, 4, 1 H, H_{6eq}), 4.70 (d, J = 4, 1 H, H_1), 5.47 (s, 1 H, benzylidene *H*), 7.25–7.70 (m, aromatic).

Addition of Methyl Methacrylate to 4. For this reaction, isolated Cp_2TiCl and 10 equiv of methyl methacrylate were used. The following products were isolated and characterized: **66c** (73% yield): IR (neat) 3520, 1730 cm^{-1}; ^1H NMR 1.22 (d, J = 7, CH_3), 1.24 (d, J = 7, CH_3) together 3 H, 1.43–1.54 (m), 1.75–1.85 (m) together 2 H CH_2C_2 of one of the diastereomers, 1.52–1.63 (m), 1.85–1.95 (m) CH_2C_2 of the other isomer, together 2 H, 2.10–2.20 (m, 1 H, H_2 of both isomers, 2.54 (m, 1 H, α-H of both isomers), 3.19, 3.22 (d, J = 6, exchange with D_2O, 1 H, O*H*), 3.39, 3.41 (2 s, OCH_3), 3.68 (dd, J = 10, 5, 1, H, H_4), 3.79 (dd, J = 10, 1 H, H_{6a}), 3.78, 3.79 (2 s, together 3 H, CO_2CH_3), 3.91–4.01 (m, 1 H, H_3), 4.20 (ddd, J = 10, 10, 5, H_5), 4.32 (dd, J = 10, 5, 1 H, H_{6e}), 4.53, 4.47 (2 s, br, together 1 H, H_1), 5.61 (s, 1 H, benzylidene *H*), 7.30–7.55 (m, aromatic); NOE H_1 → $CH_2CHCO_2CH_3$, $CHCO_2CH_3$, H_2, OCH_3; H_2 → CO_2CH_3, $CH_2CHCO_2CH_3$, H_3, H_1; H_3 → $CH_2CHCO_2CH_3$, $CHCO_2CH_3$, H_2, O*H*; $CHCO_2CH_3$ → CO_2CH_3, $CH_2CHCO_2CH_3$, H_3, H_1; ^{13}C NMR 17.37 (CH_3), 33.71 (CH_2CH), 37.80 (CH), 43.65 (C_2), 51.77 (C_4), 58.44 (C_5), 55.51 (OCH_3), 69.03 (C_3), 69.31 (C_6), 76.84 (CO_2CH_3), 102.23 (two carbons, C_1 and benzylidene C). The other major diastereomer (isomeric at the α-carbon) has an almost identical spectrum with very minor shifts in the carbon positions. From the positions of H_1 (4.66, d, J = 4), H_{6e} (4.24, dd, J = 9, 4), and H_4 (3.23, dd, J = 10, 9) as compared to those in **66a,b**, the other major regioisomer (8%) was identified as **66c** (see the table of NMR data).) CI MS 367.2 (M + H; calcd for $C_{19}H_{27}O_7$ 367.2), 335.1 (M – OCH_3; calcd for M = $C_{18}H_{23}O_6$ 335.18), 317.1 (M – (OCH_3 + H_2O); calcd 317.1).

Yet another isomer (3%) with H_1 at δ = 4.79 appears structurally similar to a compound formed in the acrylonitrile reaction. In both systems these isomers have not been fully characterized.

Addition of (2*R*,3*R*)-2,3-Epoxy-1-decanol to *tert*-Butyl Acrylate. A solution of Cp_2TiCl (0.43 g, 2 mmol) in THF (20 mL) was added dropwise over the course of 40 min to a solution of **9a** (172 mg, 1 mmol) and *tert*-butyl acrylate (1.28 g, 10 mmol) in THF (5 mmol). The reaction was quenched with 10% acetic acid (50 mL). The product was extracted into ether (2 × 50 mL) and washed with saturated sodium bicarbonate and water (25 mL each). After removal of the solvent, the residue was purified by flash chromatography (15 cuts 88:10:2 CH_2Cl_2/EtOAc/MeOH then 15 cuts 95:5 EtOAc/MeOH) to afford the product (222 mg, 73%) as a mixture of isomers **68** (**R** = **H**): ^{13}C NMR 13.95, 19.96, 22.54, 23.72, 25.92, 26.20, 28.01, 29.08, 29.20, 29.55, 31.75, 33.19, 33.44, 33.80, 35.43, 43.74, 62.67, 64.19, 74.60, 74.93, 80.39, 173.45. GC analysis (SP2100, 200 °C) was best accomplished by first diacetylating the diol functionality (1:1 Ac_2O/pyridine). The chromatogram of **68** (**R** = **Ac**) revealed, in addition to a trace of 1,2-adduct, that the two diastereomers of the 1,3-adduct were present in a 70:30 ratio with the major isomer at a shorter retention time. Assignments were confirmed by GC-MS (HRMS 313.2503; M^+ – C_4H_9O calcd 313.2015) and analysis of the isolated compound: $C_{27}H_{44}O_4$ calcd C 65.25, H 9.91; found C 64.95, H 10.15; FAB MS M + H 387.33 (calcd for $C_{21}H_{38}O_6$ 387.27); M – C_4H_7 331.23 (calcd 331.21).

The two isomeric 1,3-diols were converted into the corresponding mesitylidene acetals **69a,b** by treatment with the dimethyl acetal of mesitaldehyde for tentative identification of stereochemistry at the newly created center. The major acetal has peaks at δ 37.95 (CH), 71.75 (CH_2O), 82.16 (CHO), for three carbons of the 1,3-dioxin ring. The corresponding peaks in the minor isomer appear at δ 36.79, 70.64, and 81.51. Since chemical shifts of the corresponding carbons for *trans*-1,2-dialkyl cycloalkanes in general appear at lower field, it is reasonable to assume that the mesitylidene acetal has an all equatorial configuration in the major product. Thus this structure, **69a**, would correspond to a 4*S*,5*R* structure **68a** (**R** = **H**) for the major dihydroxy ester adduct.

Acknowledgment. The authors would like to acknowledge the invaluable technical assistance of M. S. Beattie and D. M. Lattomus for much of the experimental work described here.

Supplementary Material Available: Text describing the preparation and characterization of epoxides 6,7-epoxyhept-1-yne, 2-methyl-1-oxaspiro[2.5]octane, **18**, **29**, **35**, **37**, **39**, **41**, **45a,b**, and **47** and mesitylidene acetals **69a,b** and a table listing low-valent Ti, Zr, and W complexes (8 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.