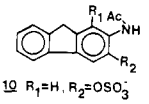
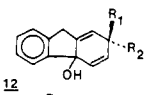
(consistent with k_5 at 5 °C of 1.2×10^{-5} s^{-1}). Intermediates similar to **2** have been detected in the solvolysis of monocyclic analogues of **1**,[3b,8] but no phosphate adduct similar to **3** has been detected in such reactions.

In basic phosphate buffers (pH > 6.8) the major hydrolysis products of **1** (with yields in 0.025 M phosphate at pH 7.8, μ = 0.5 M (KCl)) are **4** (11.1 ± 0.2%), **5**[9] (51 ± 1%), and **6**[10] (8.9 ± 0.3%).[11] Since **4** is stable to the reaction conditions, **5** is not produced by its hydrolysis. HPLC experiments confirm that **5** is formed by the decomposition of **2** at pH 7.8, while **6** is formed more rapidly from the decomposition of **1**. A minimum hydrolysis mechanism in accord with our results under these conditions is shown in Scheme I. The yields of **5** and **6** become 5.7 ± 0.2% and 65 ± 3%, respectiveiy, at pH 4.7 and 1.1 ± 0.2% and 83 ± 4%, respectively, at pH 3.6. The product yield variation with pH indicates that most of k_2^H involves acid-catalyzed reversion of **2** to the nitrenium ion **7**. Table II in the Supplementary Material provides yields for **5** and **6** under various pH conditions. Product studies indicate that **2** is converted into **5** by uncatalyzed (k_2^0) and general acid catalyzed (k_2^{ga}) paths in phosphate buffers (k_2^{ga} for $H_2PO_4^-$ is 0.22 ± 0.01 M^{-1} s^{-1}). There is precedent for the addition-elimination path involving **8** in monocyclic systems,[3b,8] but other possibilities cannot be ruled out at this time. The conversion of **3** into **4** probably occurs via an allylic rearrangement of a tight ion pair to produce **9**,[12] with subsequent elimination of H_2O. The lack of dependence of k_5 on $[phosphate]_T$ is consistent with this proposal. The minor products **10** and **11**, detected in pH invariant yields of ca. 2.0% and 1.0%, respectively,[13] are likely formed via internal return from an intimate ion pair (not shown in Scheme I).[3,4]



10 R_1=H, R_2=OSO_3^-

11 R_1=OSO_3^-, R_2=H



12 **a** R_1=AcNH, R_2=OH

b R_1=OH, R_2=AcNH

At pD 5.8 in 0.03 M KD_2PO_4/K_2DPO_4 and pD 4.8 in 0.03 M AcOD-d_4/KOAc (no KCl) at 5 °C two species, tentatively identified as the diastereomeric carbinolamides **12a** and **12b**, which decompose at rates consistent with k_3 and k_4 at 5 °C, are detected by NMR.[14] The pH dependence exhibited by k_3 is consistent with that observed for other carbinolamides.[15] Since at pH < 5.0 **6** is the predominant reaction product, it appears that k_3^H and k_4^H largely involve return to **7** via **2**. The products derived from the k_3^0 and k_3^{OH} processes have not yet been identified.

The half-life of **1** at physiological temperatures is ca. 4.0 s from extrapolation of our kinetic data. Since the sulfotransferase system which generates **1** in vivo appears to be located in the cytosol,[1] a long-lived intermediate such as **2** (half-life ca. 2.0 min at 37 °C and pH 7) may play a role in the biological effects attributed to **1**. We have demonstrated that **2** is subject to direct nucleophilic attack by H_2O and phosphate and also decomposes to **7** via k_2^H at pH > 6.0. Either of these routes may serve as a means for **2** to react with nucleophilic sites on cellular macromolecules. We are currently investigating the reactions of **2** with other nucleophilic species.

Acknowledgment. This work is supported by a grant from the American Cancer Society (BC-348). The 500 MHz NMR spectra were obtained with the assistance of Dr. C. E. Cottrell at the Ohio State University Chemical Instrument Center using Equipment funded in part by NIH Grant No. 1 S10 RR01458-01A1.

Supplementary Material Available: Table I containing buffer independent pseudo-first-order rate constants for the hydrolysis of **1** at 20 °C, and Table II containing buffer independent yields of **5** and **6** produced during the hydrolysis of **1** (3 pages). Ordering information is given on any current masthead page.

Intermolecular Addition of Epoxides to Activated Olefins: A New Reaction

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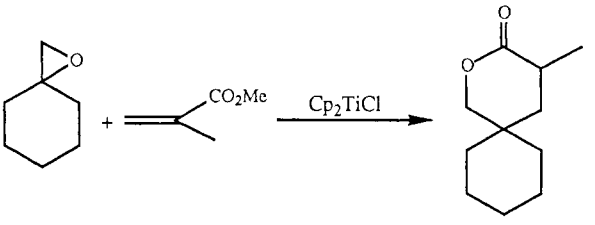
Epoxides play an increasingly pivotal role in organic synthesis. This reflects both their ready availability and their ability to undergo selective substitution reactions with nucleophiles. It occurred to us that the utility of epoxides as synthetic intermediates would be further enhanced by the availability of methods for their selective elaboration by electrophiles. We now report such a reaction, the addition of epoxides to activated olefins.

Our strategy utilizes a transition-metal-centered radical to effect the homolysis of an epoxide C-O bond.[1] Thus dropwise addition of a green THF solution (2 equiv) of Cp_2TiCl[2] to a solution of the epoxide of methylenecyclohexane (1 equiv) and excess methyl methacrylate (10 equiv) in THF results in the formation of the spirolactone **1** in 81% yield (eq 1). The carbon-centered radical



(1)

1

formed by the homolysis of the C-O bond (presumably via the cyclopropylcarbinyl-like intermediate **2**[1b]) adds to methyl methacrylate (MMA), and the resulting radical **3** is efficiently scavenged by a second equivalent of Ti(III) rather than undergo further additions (Scheme I). Under these conditions, no ole-

(7) ^1H NMR for **4**: (500 MHz, D_2O) δ 2.19 (3 H, s), 3.96 (2 H, s), 7.28-7.61 (5 H, m), 8.29 (1 H, s); ^{31}P NMR (121.5 MHz, D_2O) δ -3.2 (relative to trimethyl phosphate). Treatment of **4** with *E. coli* alkaline phosphatase yields **5** (ref 10).

(8) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 2448-2449.

(9) Pan, H.-L.; Fletcher, T. L. *J. Org. Chem.* **1960**, *25*, 1106-1109.

(10) Bell, F.; Gibson, J. A. *J. Chem. Soc.* **1955**, 3560-3562.

(11) See Supplementary Material for determination of product yields.

(12) Goering, H. L.; Greiner, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 3464-3466. Goering, H. L.; Pombo, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2515-2521. Goering, H. L.; Koermer, G. S.; Linsay, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 1230-1234.

(13) Smith, B. A.; Springfield, J. R.; Gutmann, H. R. *Molec. Pharmacol.* **1987**, *31*, 438-445.

(14) Spectral data for **12a** and **12b** will be published at a later date.

(15) Novak, M.; Bonham, G. A.; Mulero, J. J.; Pelecanou, M.; Zemis, J. N.; Buccigross, J. M.; Wilson, T. C. *J. Am. Chem. Soc.*, in press. Sayer, J. M.; Conlon, P. *J. Am. Chem. Soc.* **1980**, *102*, 3592-3600.

(1) (a) Kochi, J. K.; Singleton, D. M.; Andrews, L. J. *Tetrahedron* **1968**, *24*, 3505. (b) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561.

(2) Most of these studies were carried out with isolated $[Cp_2TiCl]_2$ prepared according to the procedure of Manzer.[2a] In a typical reaction, Cp_2TiCl (430 mg, 2 mmol) dissolved in 10 mL of THF was added to a mixture of the epoxide and 10 equiv of the olefin in 10 mL of THF over 5 min, and the mixture was stirred for 10 min. The reaction was quenched with cold 10% H_2SO_4 and extracted into ether. The ether extract was dried after being washed with $NaHCO_3$, and the products were isolated by chromatography. The reaction can also be done with in situ generated reagent prepared by reduction of the commercially available Cp_2TiCl_2 with activated zinc[2b] (and containing an equivalent of $ZnCl_2$) giving somewhat lower yields. In the in situ preparation, excess zinc was removed by cannula transfer of the supernatant liquid into a mixture of the epoxide and the acceptor. (a) Manzer, L. E. *Inorg. Synth.* **1982**, *21*, 84. (b) Green, M. L. H.; Lucas, C. R. *J. Chem. Soc., Dalton Trans.* **1972**, 1000.

0002-7863/89/1511-4525$01.50/0

Scheme I

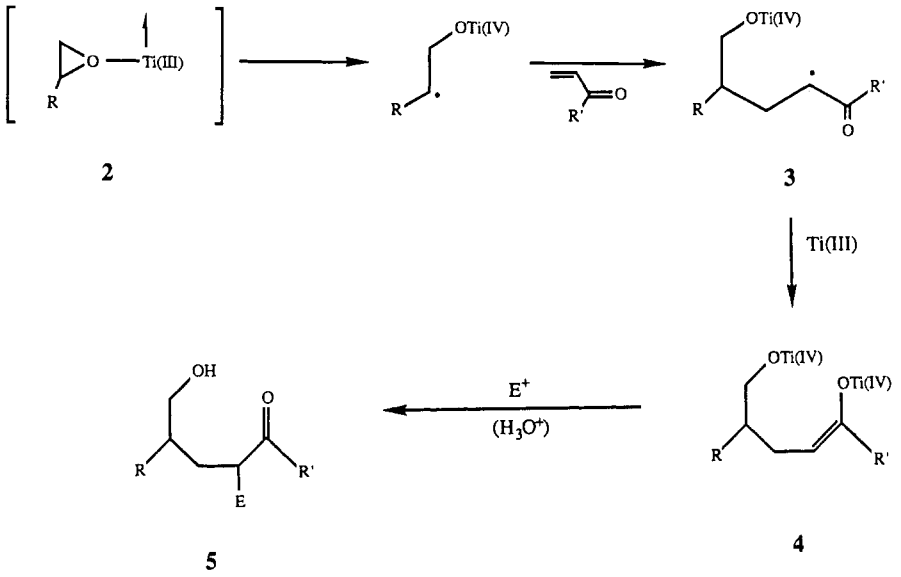
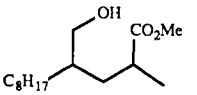
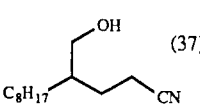
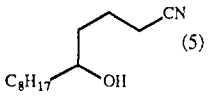
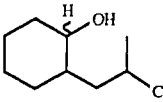
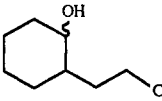


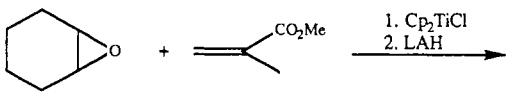
Table I. Addition of Epoxides to Activated Olefins

entry	epoxide	method[a]	olefin	adduct (% yield)
1	1,2-epoxydecane	B	MMA	 (79)[b]
2	1,2-epoxydecane	B	acrylonitrile	 (37)  (5)
3	**6**	A	MMA	 (82)[b]; cis/trans 1:2
4	**6**	A	ethyl acrylate	 (70)[b]; cis/trans 3:5
5	**8**	A	acrylonitrile	**9a** (32), **10a** (3)[c]
6	**8**	A	methyl vinyl ketone	**9b** (45), **10b** (7)[c]
7	**8**	A	MMA	**9c** (73)[d]

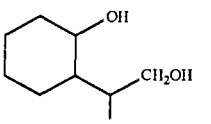
[a] Method A: using isolated Cp_2TiCl; method B: in situ preparation. [b] Isolated as mixture of lactones and hydroxy esters. [c] Mixture of other diastereomers (3%) is also formed. [d] A mixture of diastereomers (11%) including **10c** is also formed.

fin-derived oligomers are formed. This novel reductive radical termination leading to an enolate also represents an attractive alternative to the tin hydride methodology[3] where the termination is largely limited to hydrogen abstraction.[4]

Related additions of 1,2-epoxydecane and epoxycyclohexane to various activated olefins are shown in Table I. For example, addition of MMA to epoxydecane gives a mixture of regioisomeric adducts in which the secondary radical capture predominates. Since the hydroxy ester adducts from MMA and epoxydecane as well as epoxycyclohexane are invariably contaminated with varying amounts of lactones, the isomer ratios were determined by exhaustive reduction with LAH (eq 2) and analysis by NMR



6



7 (2)

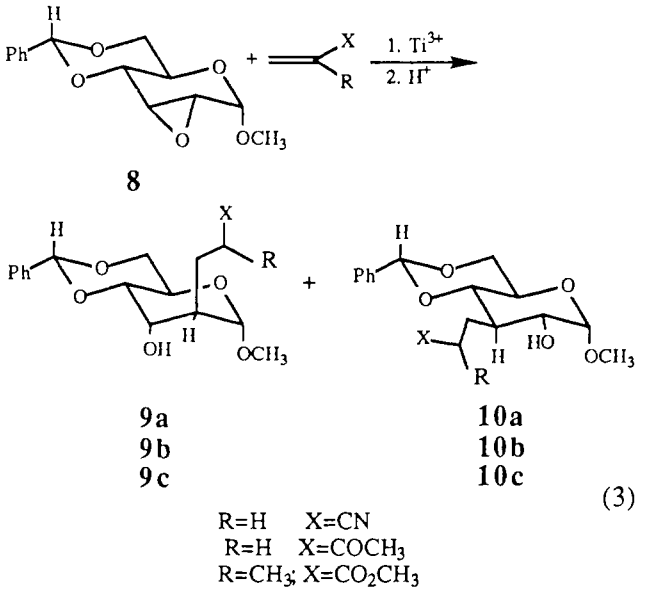
of the respective diols. The ratio of the primary versus secondary radical-derived products from epoxydecane and acrylonitrile is 88:12, and the ratio of cis versus trans adducts from epoxycyclohexane and MMA is ca. 1:2 (Table I). Since the acrylate adducts can be readily converted into δ-valerolactones, this overall

(3) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. (b) Curran, D. P. *Synthesis* **1988**, 417, 489.

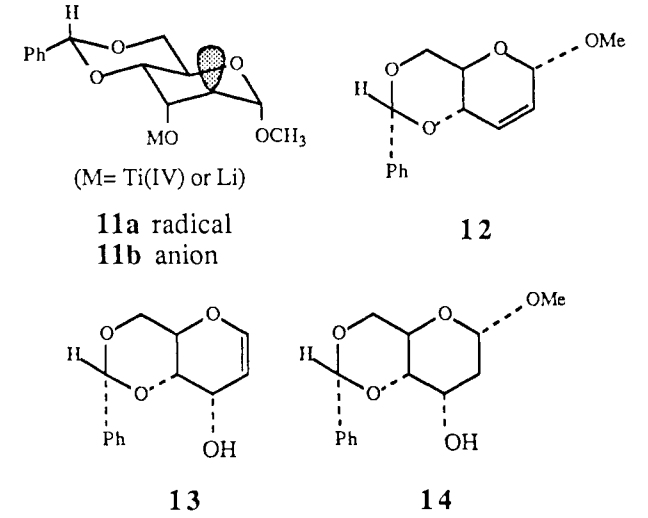
(4) For other modes of radical terminations, see: (a) Via fragmentation: Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133. (b) Atom or group transfer: Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **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. (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: For a general discussion, see: Scheffold, R.; Rytz, G.; Walder, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; John Wiley and Sons: New York, 1983; Vol. 2, p 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.

scheme represents a novel [3 + 3] annulation to prepare such lactones[5] from epoxides. The major lactone from epoxydecane and MMA can be prepared in overall 60% yield.

The functional group compatibility and some stereochemical questions are probed in the addition of acrylonitrile, MMA, and methyl vinyl ketone to the carbohydrate epoxide[6] shown in eq 3.



Depending on the reactivity of the acceptor, the initially formed radical (**11a**) participates in the addition reaction or is further reduced by Ti(3+) to the carbanion (**11b**). Elimination of the β-groups to give **12** and **13** or hydrogen atom transfer from some



substrates (methyl vinyl ketone for example) to give a reduction product **14** are the major side reactions in these cases. It should be noted that the relative amounts of axial versus equatorial bond formation in the radical **11a** are the same as those observed by Giese et al. in a related system.[7] Qualitatively, it appears that the regioselectivity of the ring opening is affected by the stereoelectronic stabilization of the incipient radical.[8] However, we cannot rule out the possibility of a reversible ring opening followed by slow addition to the olefin.

The use of transition-metal-centered radicals for the generation of useful organic radicals may be broadly applicable in synthesis. Moreover, the reductive termination strategy for the reactions of these radicals illustrated here is only one of the possibilities. Reactions of the titanium enolate **4** with electrophiles may conceivably be used for its subsequent elaboration.[9] The compatibility of Cp_2TiCl with a variety of common functional groups and the ease with which epoxides[10] can be generated should make this an attractive method for the synthesis of polyfunctional molecules.

Supplementary Material Available: Details of isolation and characterization (IR, ^1H NMR, ^{13}C NMR, HRMS, elemental analysis) of products **1**, **7**, **9a**, **9b**, **9c**, **10a**, **10b**, **14** and those described in Table I (8 pages). Ordering information is given on any current masthead page.

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

(6) Sugar epoxide **8** is very sensitive toward both nucleophiles and electrophiles. See, for example: Tsuda, N.; Yokota, S.; Kudo, T.; Mitsunobu, O. *Chem. Lett.* **1983**, 289.

(7) Giese, B.; Dupuis, J.; Groninger, K.; Hasskerl, T.; Nix, M.; Witzel, T. In *Substituent Effects in Radical Chemistry*; Viehe, H. G., Ed.; D. Reidel Publishing Co., Dordrecht, 1986, p 283.

(8) Barton, D. H. R.; Hartwig, W.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1982**, 447. See, also: Korth, H.-G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. II* **1986**, 1453.

(9) Reaction of an in situ generated Cp_2TiCl-enolate: Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 1664.

(10) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323.

Carcerand Interiors Provide a New Phase of Matter[1]

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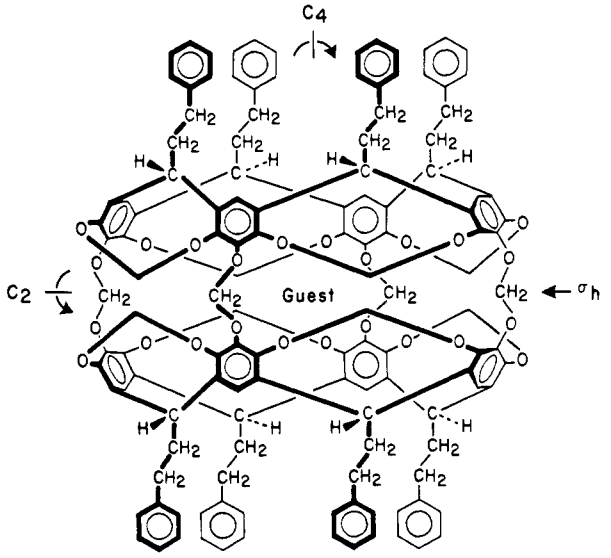
Earlier papers reported the synthesis and properties of a noncollapsible molecular cell (a carcerand) whose interior was occupied by various components of the medium to give a mixture of carceplexes whose separation and study were inhibited by their insolubility.[2,3] Here we report three new soluble carceplexes (**1**·G) which differ only in their imprisoned guests.



1·G

The syntheses involved **2** (prepared from resorcinol and dihydrocinnamaldehyde, 69%),[4] bromination (NBS) of which gave

(1) We warmly thank the National Science Foundation for Grant CHE 84-19994 for support of this work.

(2) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 2575–2576.

(3) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Marti, K.; Sampson, R. M.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1988**, *110*, 2554–2560.

(4) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305–1312.

0002-7863/89/1511-4527$01.50/0