The Journal of
Organic
Chemistry

VOLUME 58, NUMBER 25 DECEMBER 3, 1993

Communications

Regio- and Enantioselective Catalytic Epoxidation of Conjugated Polyenes. Formal Synthesis of LTA_4 Methyl Ester

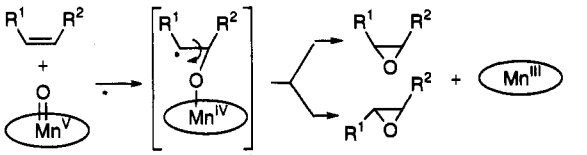
Sukbok Chang,[1] Nam Ho Lee,[2] and Eric N. Jacobsen*,[1]

Department of Chemistry, University of Illinois, Urbana, Illinois 61801, and Department of Chemistry, Harvard University, Cambridge, Massachusetts 02139

Received October 5, 1993•

Summary: The (salen)Mn(III)-catalyzed asymmetric epoxidation reaction exhibits regioselectivity for attack at cis double bonds of conjugated dienes to afford enantiomerically enriched *trans*-vinyl epoxides as the major products.

The (salen)Mn-catalyzed asymmetric epoxidation of olefins lacking polar directing groups has been developed into an effective method for the preparation of a variety of optically active compounds.[3,4] One important characteristic of this process is the lack of stereospecificity in the oxidation of acyclic conjugated cis alkenes. The generation of mixtures of cis and trans isomers as primary products is ascribable to a stepwise oxygen atom transfer mechanism involving a radical intermediate that can partition to either epoxide (eq 1).[5,6] As expected, the extent of trans epoxide



(1)

formation depends on the identity of the double bond substituents R^1 and R^2. For example, cis-β-substituted styrene derivatives afford cis epoxides as major products,[3b] but enynes and dienes undergo oxidation to form the trans epoxides preferentially.[3f] This latter feature, taken together with the general observation that cis olefins are more reactive than their trans counterparts in epoxidation reactions catalyzed by heme proteins and their models,[7] suggests a strategy for the regio- and enantioselective synthesis of trans,trans-diene monoepoxides by epoxidation of cis,trans-conjugated dienes (eq 2).[8,9] We report

• Abstract published in *Advance ACS Abstracts*, November 15, 1993.

(1) Harvard University.

(2) University of Illinois. Current address: Cheil Foods and Chemicals, Kyonggi-Do, Korea.

(3) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296. (c) Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703. (d) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (e) Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055. (f) Lee, N. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533. (g) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320. (h) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.2.

(4) For related studies of epoxidation with chiral (salen)Mn complexes, see: (a) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Asymmetry* **1991**, *2*, 481. (b) O'Connor, K. J.; Wey, S. J.; Burrows, C. J. *Tetrahedron Lett.* **1992**, *33*, 1001. (c) Reddy, D. R.; Thornton, E. R. *J. Chem. Soc., Chem. Commun.* **1992**, 172. (d) Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. *Chem. Lett.* **1992**, 2231.

(5) For detailed mechanistic studies of epoxidation catalyzed by achiral salen complexes, see: (a) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309. (b) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606.

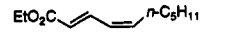
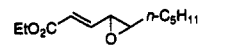
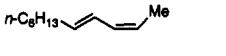
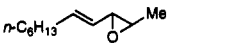
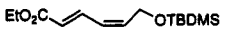
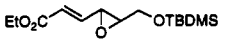
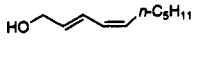
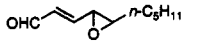
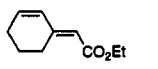
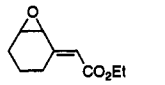
(6) Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6497.

(7) (a) Allain, E. J.; Hager, L. P.; Deng, L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 4415. (b) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5791. (c) Ostovic, D.; Bruice, T. C. *J. Am. Chem. Soc.* **1988**, *110*, 6907.

(8) Regioselective epoxidation of 1,3-dienes catalyzed by achiral (salen)-Mn complexes has been noted recently: Thomsen, D. S.; Schiøtt, B.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1992**, 1072. In these reactions, selectivity was examined as a function of olefin substitution, rather than geometry. For related porphyrin-catalyzed reactions of dienes, see: Suslick, K. S.; Cook, B. R. *J. Chem. Soc., Chem. Commun.* **1987**, 200.

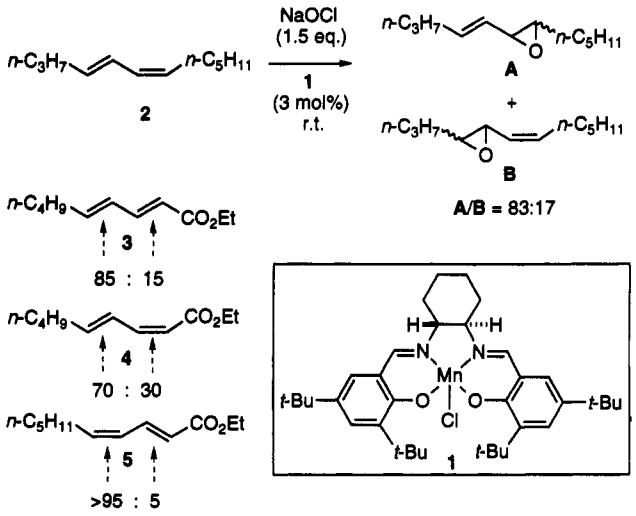
0022-3263/93/1958-6939$04.00/0

Table I. Enantioselective Epoxidation of Conjugated Dienes Catalyzed by 1[a]

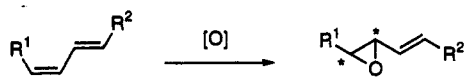
substrate	major product	isolated yield[b] (%)	ee (%) of major product[c]	trans/cis epoxide (t/c)
		81	87	9.0
		50	92	1.1
		58	83[d]	7.3
		16[e]	83	2.3
		58	77	

[a] Reaction conditions as reported previously:[3f] 0 °C, NaOCl (Clorox); pH 11.3, 1.5 equiv; 4-phenylpyridine *N*-oxide; 0.2 equiv, **1**; 3 mol %, substrate; 1 M in CH_2Cl_2. [b] Yield of regioisomerically pure epoxide isolated as a mixture of cis and trans isomers. [c] Ee's were determined by GC (Cyclodex B 30 m capillary column, J&W Scientific) unless otherwise noted. [d] Ee determined by ^1H NMR using Eu(hfc)$_3$ as chiral shift reagent. [e] Oxidation of the allylic alcohol to the aldehyde was competitive with epoxidation. Generation of water-soluble byproducts via this pathway is responsible for low yield of epoxy aldehyde.

Scheme I. Regioselectivity in Epoxidation of Cis,Trans Dienes Catalyzed by 1



herein the successful application of this strategy to the synthesis of a variety of optically active vinyl epoxides, including a key intermediate in the synthesis of LTA_4.

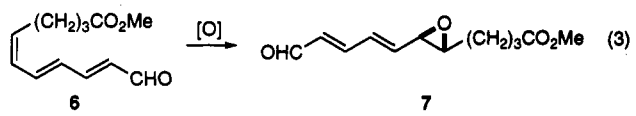


(2)

Reaction of diene **2** with NaOCl catalyzed by salen complex **1** exhibited significant (83:17) selectivity for oxidation of the cis double bond (Scheme I). Regioselectivity in epoxidation of conjugated dienyl esters such as **3**–**5** was evidently dictated by a steric bias for attack at the cis double bond balanced against an electronic preference for oxidation of the double bond distal to the ester group. For dienes such as **5**, in which both steric and electronic factors favor oxidation at the same double bond, regioselectivity was essentially absolute.

A series of conjugated cis,trans dienes was subjected to epoxidation with NaOCl catalyzed by **1**, and results are summarized in Table I. In all cases, epoxidation at the cis double bond constituted the dominant pathway, with formation of the corresponding trans epoxide as the major product with moderate-to-good enantioselectivity. Product isolation by flash chromatography resulted in only modest recovery (16–81% yield), largely as a result of the sensitivity of the epoxides. However, the reactions were generally clean, with negligible levels (<5%) of bis-epoxide generated, even upon extended exposure of the reaction mixture to excess NaOCl.

On the basis of this demonstrated selectivity in the monooxygenation of model dienes, (salen)Mn-catalyzed oxidation of triene **6** was studied as a possible synthetically viable route to **7** (eq 3). Epoxy aldehyde **7** has been



(3)

employed as the penultimate intermediate in the synthesis of the key arachidonic acid metabolite LTA_4,[10] and substantial interest still exists in viable routes to this important compound and its derivatives.[11] Synthesis of the requisite aldehyde **6** was accomplished from triene **8a** (Scheme II)[12] by a desilylation (Bu_4NF)/Swern oxidation sequence. Unfortunately, epoxidation of **6** to **7** occurred with only 65% enantioselectivity. Cis–trans isomerization of the Lewis acid sensitive triene was found to take place under the conditions of epoxidation, and the resulting all-trans triene underwent a slower but less enantioselective epoxidation to the same product **7**. This problem was circumvented by carrying out the epoxidation on protected alcohol derivatives **8a–f**, which were configurationally stable in the presence of the mildly Lewis acidic (salen)-Mn complexes. Of the derivatives screened in the epoxidation reaction, phenoxyacetate **8d** exhibited highest enantioselectivity.

The enantioselective synthesis of aldehyde **7** was thus completed by deprotection of **9d** and in situ oxidation (Scheme II). The enantiomeric composition of **9d** (80–83% ee) was retained in the final product **7**.

This study demonstrates both a viable new enantioselective route to vinyl epoxides and the application of the

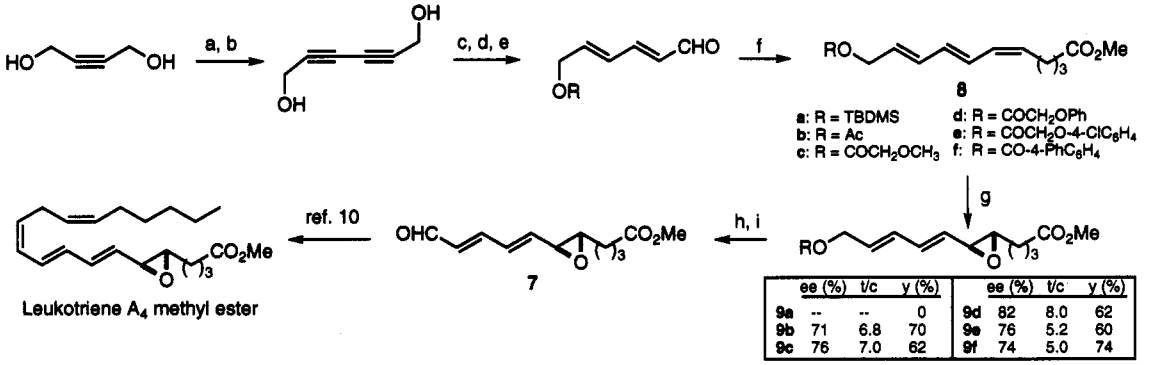
(9) For highly enantioselective dihydroxylation of trans,trans-dienes, see: Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570

(10) Corey, E. J.; Arai, Y.; Mioskowski, C. *J. Am. Chem. Soc.* **1979**, *101*, 6748.

(11) (a) Franck-Neumann, M.; Colson, P. J. *Synlett* **1991**, 891 and references cited therein. (b) Green, R. H.; Lambeth, P. F. *Tetrahedron* **1983**, *39*, 1687. (c) Nicolaou, K. C.; Ramphal, J. Y.; Petasis, N. A.; Serhan, C. N. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1100.

(12) Complete experimental details are provided as supplementary material.

Scheme II. Formal Synthesis of LTA_4[a]



	ee (%)	t/c	y (%)		ee (%)	t/c	y (%)
9a	--	--	0	9d	82	8.0	62
9b	71	6.8	70	9e	76	5.2	60
9c	76	7.0	62	9f	74	5.0	74

[a]Reagents and Conditions: (a) $SOCl_2$, pyridine, 84%; (b) $NaNH_2$, $(H_2CO)_n$, 70%; (c) $LiAlH_4$, THF, 39%; (d) **8a**: TBDMSCl, imidazole, CH_2Cl_2; **8b–8f**: P–Cl, NEt_3, DMF; (e) DMSO, $(COCl)_2$; (f) $[Ph_3P(CH_2)_4CO_2Me]^+I^-$, KHMDS, THF; (g) NaOCl, pH 11.3, 1.2 equiv, 4-phenylpyridine *N*-oxide (20 mol %), 1 (4 mol%); (h) NH_3, CH_3OH, rt; (i) MnO_2 (act.).

(salen)Mn-catalyzed epoxidation reaction to a complex, highly functionalized class of substrates. Current efforts are directed toward elucidation of the factors controlling cis–trans selectivity in epoxide formation and further refinement in the enantioselectivity attainable in epoxidation of such conjugated polyenes.

Acknowledgment. We thank Prof. Douglas Taber for helpful discussions. This work was supported by the National Institutes of Health (GM-43214). E.N.J. gratefully acknowledges awards from the National Science Foundation (PYI program), the David and Lucille Packard Foundation, the Sloan Foundation, the Camille and Henry Dreyfus Teacher Scholar Program, the Lilly Grantee Program, American Cyanamid, Merck, and Pfizer.

Supplementary Material Available: Experimental procedures and characterization details for all reactions in Scheme II (7 pages). This material is contained in 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.