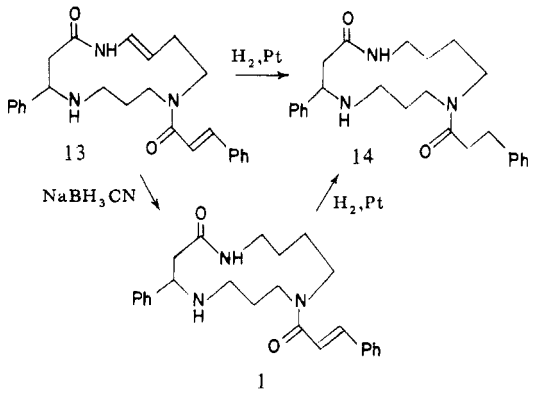
In the formation of the bicyclic 4-oxotetrahydropyrimidine derivative (**10**) from **7**, we adapted a reaction reported earlier by Bormann in which β-lactams react with cyclic imino ethers in an addition-ring expansion process.[10] Thus, heating **7** with 4-phenyl-2-azetidinone (**8**) in chlorobenzene for 21 h yielded the ring-enlarged product **10**[7] (67%, mp 195-197 °C), most probably through the intermediate **9**. The final conversion of **10** to dihydroperiphylline (**1**)[7] (most probably, through **11** and **12**) was accomplished in one step (93%) by treatment with sodium cyanoborohydride (3 equiv) in acetic acid[6,11] under conditions noted in Scheme I. This reduction sequence was mild enough to leave the double bond in the cinnamic acid residue unaffected.

The structure of **1** was established by using natural periphylline (**13**) as a reference material.[12] Hydrogenation of dihydroperiphylline (**1**)[7] with platinum oxide yielded tetrahydroperiphylline (**14**), identical (IR, NMR, TLC) with the product obtained from periphylline by the uptake of 2 mol of hydrogen. Selective reduction of periphylline (**13**)[12] by using $NaBH_3CN$ in formic acid yielded a dihydro product identical (IR, NMR, TLC) with synthetic dihydroperiphylline (**1**).



Acknowledgment. This work was supported by Grant GM-07874 from the National Institutes of Health. We thank Mr. Ralph Robinson for valuable discussions and technical assistance.

(9) L. A. Paquette, *J. Am. Chem. Soc.*, **86**, 4096 (1964); L. A. Paquette and T. Kakihana, *ibid.*, **90**, 3897 (1968).
(10) D. Bormann, *Chem. Ber.*, **103**, 1797 (1970).
(11) Reduction of quinoline to tetrahydroquinoline with $NaBH_3CN$/AcOH has been reported by G. W. Gribble and P. W. Heald, *Synthesis*, 650 (1975).
(12) We are indebted to Dr. H.-P. Husson, Institute de Chimie des Substances Naturelles, C.N.R.S., Gif-sur-Yvette, for an authentic sample of natural periphylline. A reference sample of dihydroperiphylline was not available.

Epoxy Alcohol Rearrangements: Hydroxyl-Mediated Delivery of Lewis Acid Promoters

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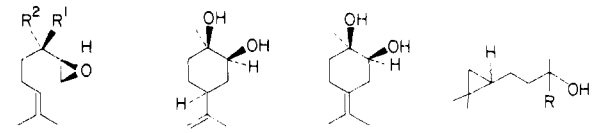
In connection with our interest in the chemistry of epoxy alcohols, we have investigated the Lewis acid mediated rearrangement of these substrates which are available stereo-[1a] and enantioselectively[1b] from allylic alcohols. Although Lewis acid promoted rearrangements of epoxides are well-known, we have observed a few novel and selective transformations which suggest that the standard behavior of epoxide substrates may be substantially altered by the presence of an α-hydroxyl substituent.

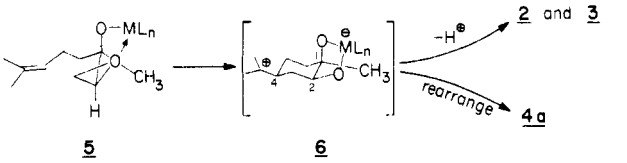
Initially, our studies were focused on 1,2-epoxylinalool, **1**.[1a]



1a R^1 = OH, R^2 = CH_3
1b R^1 = CH_3, R^2 = OH
1c R^1 = OCH_3, R^2 = CH_3

2 **3** **4a** R = CHO **4b** R = CH_2OH

This substrate (erythro-threo mixture) was transformed to *cis*-diol **2**[2,3] and up to 15% of another cyclic diol, presumably **3**, upon treatment with $OV(OEt)_3$ (CH_2Cl_2, room temperature, 10 h). We were unable to detect *trans*-diols or either starting epoxy alcohol diastereomer. Furthermore, examination[4] of the reaction mixture before disappearance of the epoxy alcohols revealed that the epoxylinalool remaining was substantially enriched in the threo isomer. We felt that the isomeric selectivity was best explained by hydroxyl-assisted delivery of the metal via a strictly defined arrangement as shown in **5**. For the erythro isomer (**1a**), cyclization involving the 6,7 double bond leads to **2** or **3** whereas the threo isomer (**1b**), which cannot cyclize, presumably decomposes. Indeed, exposure of pure **1a**[2,5] to these conditions led to cyclized products, while **1b**[2,5] slowly decomposed without formation of characterizable products. Since the total mass recovery in these experiments was quite low (<40%), we next sought a metal promoter which would exhibit the same behavior toward the erythro isomer and not decompose the threo isomer. Our first choice, $Ti(Oi\text{-}Pr)_4$, proved expeditious. Isomer **1a**[2,5] was completely consumed upon treatment with 1.4 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ at room temperature (0.2 M in substrate, CH_2Cl_2, 12 h), while **1b**[2,5] could be recovered (80%) unchanged under identical conditions. The product mixture from **1a** was more complex in this case, consisting of **2** and **3** (20-30%) and cyclopropanes **4a**[2,6] and



(1) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *Ibid.* **1974**, *96*, 5254. Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733. Sharpless, K. B.; Verhoeven, T. R. *Aldrichchim. Acta* **1979**, *12*, 63. (b) A highly efficient method for asymmetric epoxidation has recently been developed: Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. For earlier reports see: Yamada, S.; Mashiko, T.; Terashima, S. *J. Am. Chem. Soc.* **1977**, *99*, 1988. Michaelson, R. C.; Palermo, R. E.; Sharpless, K. B. *Ibid.* **1977**, *99*, 1990.
(2) Satisfactory spectral data (IR, NMR, MS) were obtained for this substance.
(3) An authentic sample of **2** (mp 70-73 °C) was prepared in optically active form from *cis*-carveol by epoxidation (*m*-chloroperbenzoic acid, CH_2Cl_2) followed by hydride reduction ($LiAlH_4$, Et_2O, room temperature).
(4) Gas chromatographic analysis of **1** is best accomplished on a 10 ft × 1/8 in. glass column packed with 10% 20 M Carbowax on Gas-Chrom Q (80/100 mesh) and programmed from 70-230 °C at 6 °C/min. Retention times: *threo*-**1b**, 20.5 min; *erythro*-**1a**, 20.9 min.
(5) The erythro isomer (**1a**) was prepared from 2,3-epoxygeraniol in 87% overall yield as follows: (a) TsCl, pyridine, -10 °C, 36 h; (b) 3:1 THF:H_2O, catalytic $HClO_4$, reflux, 1 h; (c) excess anhydrous Na_2CO_3, MeOH, room temperature, 8 h. The threo isomer was prepared in an analogous manner from 2,3-epoxy nerol.
(6) An authentic sample was prepared from 1,1-dimethyl-2-(3-oxobutyl)-cyclopropane[7] via lithio-1,3-dithiane addition followed by hydrolysis (NBS method[8]).
(7) Armand, Y.; Perraud, R.; Pierre, J. L.; Arnaud, P. *Bull. Soc. Chim. Fr.* **1965**, 1893.

†National Institutes of Health Postdoctoral Fellow, 1979-1980.
*Address correspondence to Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.

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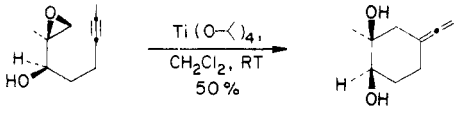
4b[2] (30–40%). These unusual products may arise by a rearrangement of complex **6**, or its C-4 epimer, by what is formally the reverse of a Prins reaction on a cyclopropane (i.e., a retrohomo Prins reaction). Diol **4b** presumably arises from Meerwein–Pondorf–Verley type reduction[9] of **4a**.

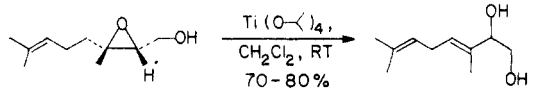
The essential involvement of the hydroxyl was revealed by the following control experiments. Methyl ether **1c**[2] (from **1a**, MeI, Ag_2O in DMF, room temperature, 50%) was subjected to the rearrangement conditions. No cyclization occurred and starting material was recovered in more than 80% yield. Simple epoxides without α-hydroxy groups were not affected by exposure to titanium(IV) alkoxides at room temperature in methylene chloride. Several other experiments relevant to the cyclization of epoxy alcohol **1a** are worth brief mention. When Al(O-*i*-Pr)$_3$ was substituted for Ti(O-*i*-Pr)$_4$ under the normal cyclization conditions, **2**, **3**, and **4** were produced in addition to several other unidentified products. Standard Lewis acid conditions (i.e., boron trifluoride etherate, 1 equiv, −78 °C, CH_2Cl_2) rapidly and *nonselectively* converted both **1a** and **1b** to complex (more than six component) mixtures.

Acetylenes can also participate in the cyclization. Allene **8**[2,10] was obtained in 50% yield from epoxy alcohol **7**[2,11] (1.4 equiv of Ti(O-*i*-Pr)$_4$, CH_2Cl_2, room temperature). This constitutes a rare case of an efficient cyclization process leading to an allene from a simple acetylene terminator.[12]

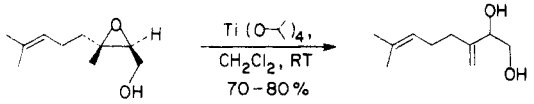


7 **8**

Reactions of 2,3-epoxynerol, **9**,[1a] and 2,3-epoxygeraniol, **10**,[1a] proved equally interesting. Exposure of these substrates to the

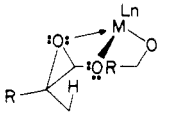


9 **11**



10 **12**

rearrangement conditions (1.2 equiv of Ti(O-*i*-Pr)$_4$, CH_2Cl_2, room temperature, 12 h) led to allylic diols **11**[13] and **12**,[13] respectively in 70–80% yield. These products were formed with high selectivity from their epoxy alcohol precursors, implying that the hydroxyl group is responsible for the observed regiocontrol. Examination of the corresponding aldehydes derived from **11** and **12** by periodate cleavage further supported the regiochemical and stereochemical assignments. Isomeric aldehydes were not detected by ^{1}H NMR. Aluminum isopropoxide also effected these rearrangements of **9** and **10**, but the products were less pure, being contaminated with up to 10% of the ethers resulting from addition of isopropyl alcohol to the epoxide moiety.[14] The methyl ether of **10**[2] (from **10**, MeI, Ag_2O, DMF, room temperature, 70%) was, as expected, recovered unchanged following exposure to Ti(O-*i*-Pr)$_4$ in CH_2Cl_2. These rearrangements proceed to afford products regiochemically complementary to those obtained by the Yamamoto[13] procedure. A rigid arrangement of the metal epoxy alcohol complex as in **13** provides an attractive rationale for these observations. After complexation, elimination with proton transfer



13

to an alkoxy ligand leads regiospecifically to the observed products. Note that strong base induced rearrangement of **9** or **10** [2.2 equiv of LiN(*i*-Pr)$_2$, from −78 to 0 °C in THF for over 20 min, then 0 °C for 4 h] leads to the same product mixture containing **12** as the major product (ca. 90% **12**, 65–70% yield).

For preparative purposes the following workup is prescribed. After TLC indicates complete consumption of starting material, the CH_2Cl_2 is removed in vacuo to yield a faintly yellow residue. This material is dissolved in anhydrous Et_2O (usually 10–15 times the total volume of solvent used for the reaction). Ice-cold 5% H_2SO_4 is added (in equal volume to the organic phase) and the two-phase mixture is shaken or stirred vigorously for 10–15 min. The initial white heavy precipitate will gradually dissolve, leaving two clear layers. This treatment is necessary to completely hydrolyze the Ti(IV) diol complexes. Subsequent standard workup yields the desired product.

These examples are among the first recognized cases of hydroxyl-directed Lewis acid mediated epoxide rearrangements.[15] These early transition metal alkoxides [Ti(OR)$_4$, VO(OR)$_3$] are, to be sure, very weak Lewis acids; that fact is revealed by their lack of reactivity toward simple epoxides. However, the presence of an adjacent hydroxyl moiety renders (via rapid metal alkoxide/epoxy alcohol exchange) the Lewis acid/Lewis base interaction intramolecular and thereby greatly increases the rates[16] of processes dependent on this interaction.

The selectivity of the epoxy alcohol rearrangements described here suggests that they may be useful in complex molecule synthesis. The related metal alkoxide catalyzed epoxidations of olefinic alcohols[1] have shown how valuable hydroxyl-directed processes can be in complicated situations. We feel that these metal alkoxide promoted rearrangements of epoxy alcohols may be the harbingers of a new class of reactions in which a mild Lewis acid catalyst is delivered intramolecularly. These reactions would entail a metal alkoxide exchange with a hydroxyl group which resides in the molecule near the Lewis base center which is then activated by coordination, through enforced propinquity, to the weakly Lewis acidic metal center. Thus an appropriately situated hydroxyl may permit selective reaction for a number of Lewis acid induced transformations and allow greater control over the stereo-,

(8) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(9) Ti(Oi-Pr)$_4$ is known to be less effective for such reductions than Al(O-*i*-Pr)$_3$; cf. Haslam, J. H. U.S. Patent 2 719 863, 1957; *Chem. Abstr.* **1957**, *50*, 4217. Coordination of the α-hydroxyl may enhance the rate of reduction in the present case. However, the appropriate control experiments have not been run.

(10) The homogeneity of this substance was further supported by its 25-MHz ^{13}C NMR spectrum which in $CDCl_3$ showed only nine resonances at 204.9, 96.98, 73.98, 73.49, 72.23, 41.33, 30.51, 26.99, and 25.24 parts per million from Me_4Si.

(11) Available from epoxidation[1a] of 2-methyloct-1-en-6-yn-3-ol. We are grateful to Professor W. S. Johnson and Dr. Bruno Frei for a generous sample of the allylic alcohol.

(12) The propargylsilane terminator has recently been shown to be effective for allene formation in cyclization processes. See: Peterson, P. E.; Despo, A. D.; Chiu, S. K.; Hood, T. "Abstracts of Papers", 179th National Meeting of the American Chemical Society, Organic Division, 1980; Despo, A. D.; Chiu, S. K.; Flood, T.; Peterson, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 5120. Peterson, P. E.; Despo, A. D. *Ibid.*, in press. Schmid, R.; Huesmann, P. L.; Johnson, W. S. *Ibid.* **1980**, *102*, 5122.

(13) Tanaka, S.; Yasuda, A.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1975**, *97*, 3252.

(14) Other transition-metal alkoxides [OV(OR)$_3$, Zr(OR)$_4$·ROH, Nb(OR)$_5$, and Ta(OR)$_5$] were also tried for rearrangement of **9** and **10**. The zirconium, niobium, and tantalum alkoxides exhibited the same behavior as Ti(OR)$_4$ (i.e., **9** → **11** and **10** → **12**). However, OV(OR)$_3$ gave complex, uncharacterized mixtures in which **11** or **12** were only minor components.

(15) Sheves and Mazur [Sheves, M.; Mazur, Y. *Tetrahedron Lett.* **1976**, 2987] report a pertinent example, but the precise role of the hydroxyl in their case has not been established.

(16) It has been shown that there is a favorable change in $T\Delta S^{\ddagger}$ of ca. 5 kcal/mol for every step converted from an intermolecular to an intramolecular step (Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 1). This change corresponds to an increase in rate of about 10^3 at 25 °C.

regio-, and chemoselective aspects of these processes.[9,17]

Acknowledgment. We are grateful to Professors William S. Johnson and Samuel Danishefsky for helpful discussions and the National Science Foundation (Grant CHE 77-14628) for financial support.

(17) See ref 1b, note 6, for an example of a $Ti(OR)_4$-catalyzed transesterification which is facilitated through coordination of a proximate hydroxyl group.

Asymmetric Epoxidation Provides Shortest Routes to Four Chiral Epoxy Alcohols Which Are Key Intermediates in Syntheses of Methymycin, Erythromycin, Leukotriene C-1, and Disparlure

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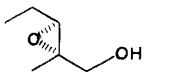
Received August 13, 1980

The epoxide functional group is one of the most useful intermediates in organic synthesis.[1] The paramount reason for the synthetic importance of the epoxide moiety is the existence of regio- and stereoselective methods both for constructing it and for controlling its subsequent reactions.[2] However, in the realm of stereoselectivity, one great challenge which had not been met was the formation of enantiomerically pure epoxides from achiral olefins.[3] Having recently discovered a highly enantioselective method for epoxidizing olefinic alcohols,[4] we wished to demonstrate its synthetic utility. Three attractive initial targets were epoxy alcohols **1**,[5] **2**,[6] **3**;[7] these are key intermediates in syntheses of



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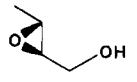

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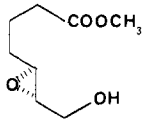

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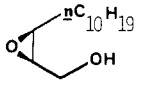
methymycin,[5] erythromycin,[6] and leukotriene C-1,[7] respectively. Epoxy alcohol **4** is a less obvious example of a potentially useful target molecule; its utility derives from its transformation into (+)-disparlure (**5**), the sex attractant of the gypsy moth. Enantioselective syntheses of epoxy alcohols **1** through **4** and the conversion of **4** to (+)-disparlure (**5**) are described here.



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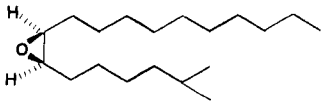

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*Address correspondence to the Chemistry Department, Massachusetts Institute of Technology, Cambridge, MA 02139.

(1) Rosowsky, A. In "The Chemistry of Heterocyclic Compounds"; Weissberger, A., Ed.; Wiley: New York, 1964; Vol. 19, Part 1, Chapter 1. Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737.

(2) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63. Berti, G. *Top. Stereochem.* **1973**, *7*, 93. Buchanan, J. G.; Sable, H. Z. In "Selective Organic Transformations"; Thyagarajan, B. S., Ed.; Wiley: New York, 1972; Vol. 2, p 1. Swern, D. *Org. Peroxides* **1971**, *2*, 355.

(3) For earlier examples of partially successful asymmetric epoxidations of allylic alcohols, see: Yamada, S.; Mashiko, T.; Terashima, S. *J. Am. Chem. Soc.* **1977**, *99*, 1988. Michaelson, R. C.; Palermo, R. E.; and Sharpless, K. B. *Ibid.* **1977**, *99*, 1990.

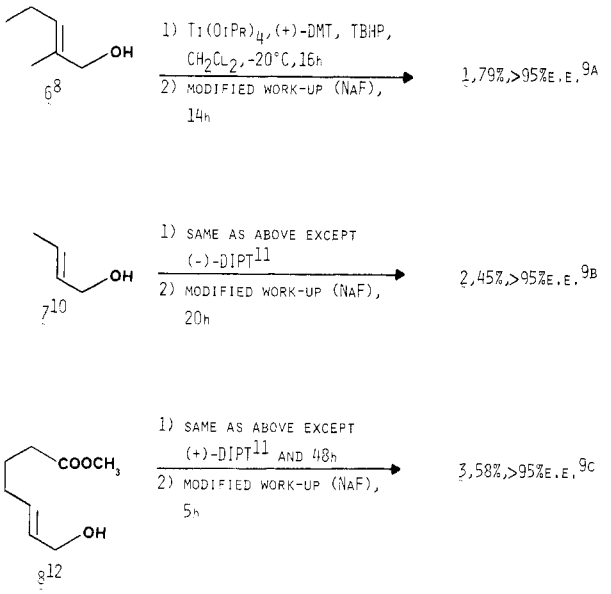
(4) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(5) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. Oxidation of levorotatory epoxy alcohol **1** with Collins reagent gave in 70% yield the dextrorotatory aldehyde prepared by Masamune's group.

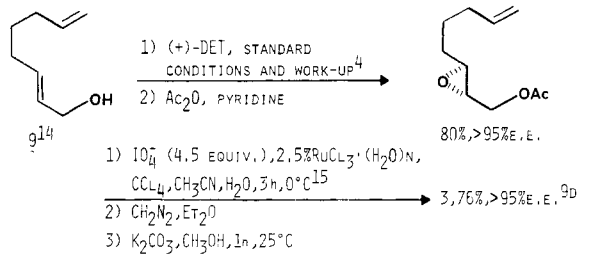
(6) Corey, E. J.; Tribulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618.

(7) (a) Corey, E. J.; Clark, D. A.; Goto, G.; Marfot, A.; Mioskowski, C.; Sammuelson, B.; Hammarstrom, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436. (b) Cohen, N.; Banner, B. L.; Lopresti, R. J. *Tetrahedron Lett.* **1980**, 4163.

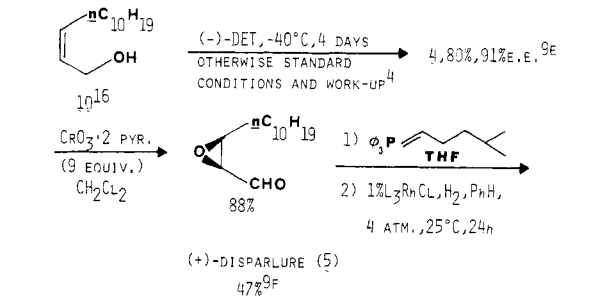
Scheme I



Scheme II



Scheme III



In the first report[4] on the asymmetric epoxidation procedure, it was emphasized that a limitation existed for cases where the epoxy alcohol produced is fairly water soluble. For this reason it was not surprising that the original procedure[4] gave poor results when applied to allylic alcohols **6**, **7**, and **8**. Fortunately, a modified workup has been found which allows isolation of epoxy alcohols such as **1**, **2**, and **3** in fair (45%) to good (79%) yields. This modified workup is far from a perfect solution to the problem, and other approaches are under study. In the meantime it is now possible to produce usable amounts of some chiral, water-soluble epoxy alcohols. The general epoxidation conditions are shown in Scheme I; the first stage of these epoxidations was executed

(8) Prepared by $LiAlH_4$ reduction of the corresponding aldehyde. The aldehyde was obtained by aldol condensation of propionaldehyde according to: Doebner, Von O.; Weissenborn, A. *Chem. Ber.* **1902**, *35*, 1143.

(9) (a) $[\alpha]^{24}_D$ −5.8° (*c* 0.36, $CHCl_3$). (b) $[\alpha]^{24}_D$ +55° (*c* 0.22, PhH). (c) $[\alpha]^{24}_D$ −33.6° (*c* 0.36, $CHCl_3$). (d) $[\alpha]^{24}_D$ −33.3° (*c* 0.24, $CHCl_3$). (e) 66% yield after recrystallization from pentane, >95% e.e., mp 62.5–63.0 °C, $[\alpha]^{20}_D$ −7.8° (*c* 1.0, $EtOH_{abs}$). (f) $[\alpha]^{20}_D$ +0.5° (*c* 10.0, CCl_4).

(10) Chemical Samples Co.

0002-7863/81/1503-464$01.00/0