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

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(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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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
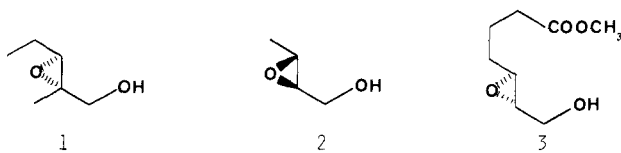
methymycin,[5] erythromycin,[6] and leukotriene C-1,[7] respectively. Epoxy alcohol 4 is a less obvious example of a potentially useful target molecule; its utility derives from its transformation into (+)-disparlure (5), the sex attractant of the gypsy moth. En-

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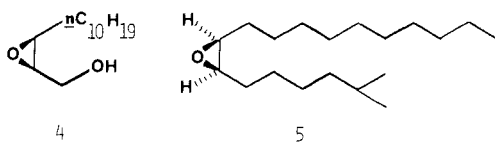
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(1) Rosowsky, A. In "The Chemistry of Heterocyclic Compounds"; Weissberger, A., Ed.; Wiley: New York, 1964; Vol. 19, Part 1, Chapter 1. Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737.

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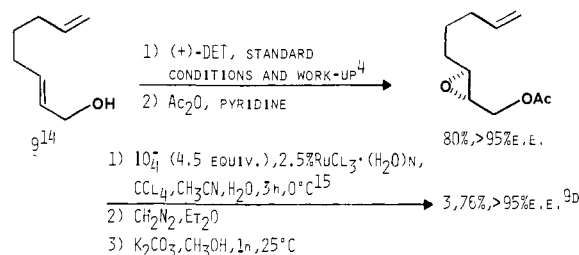
(6) Corey, E. J.; Tribulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618.

(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.
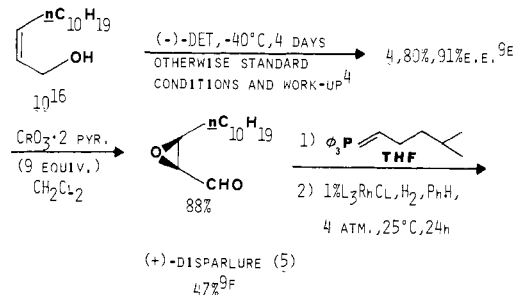

Scheme I
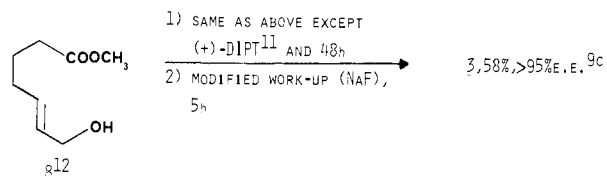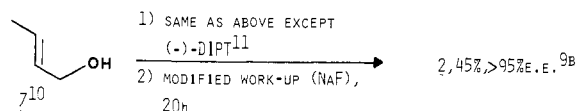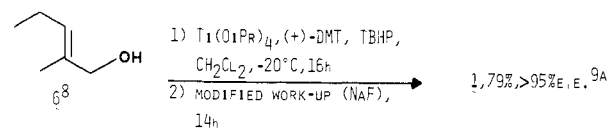
Scheme II

Scheme III

antioselective syntheses of epoxy alcohols 1 through 4 and the conversion of 4 to (+)-disparlure (5) are described here.

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

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(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) [α]^{24}$_D$ −5.8° (c 0.36, CHCl$_3$). (b) [α]^{24}$_D$ +55° (c 0.22, PhH). (c) [α]^{24}$_D$ −33.6° (c 0.36, CHCl$_3$). (d) [α]^{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, [α]^{20}$_D$ −7.8° (c 1.0, EtOH$_{abs}$). (f) [α]^{20}$_D$ +0.5° (c 10.0, CCl$_4$).

(10) Chemical Samples Co.

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exactly as described earlier.[4] However, the workup was quite different: At the end of the indicated time period, dimethyl sulfide (4 equiv) was added to the reaction mixture at –20 °C. After the mixture was stirred for 40 min at –20 °C (CCl₄/dry ice), the cold reaction mixture was added slowly to a vigorously stirred, saturated (∼5%) aqueous solution of sodium fluoride (the volume of this NaF solution was about twice the volume of the original reaction mixture) at room temperature. Stirring was continued for the specified time then the aqueous phase was saturated with sodium chloride. The gel-like, precipitated inorganic fluorides were removed by filtration through a pad of Celite, and the phases were separated. The aqueous phase was extracted three more times with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and concentrated to give a mixture of the desired epoxy alcohol and the recovered tartrate diester. Final purification was effected by chromatography on silica gel.[13] In the original procedure the dialkyl tartrate would be removed in a two-phase alkaline hydrolysis step, but here such a step destroys the water-soluble epoxy alcohol. Fortunately, dimethyl tartrate (DMT), diethyl tartrate (DET), and diisopropyl tartrate (DIPT) have quite different R_f values on silica gel (0.1, DMT; 0.27, DET; 0.44, DIPT; hexane:ethyl acetate, 7:3). Chromatographic separation of the epoxy alcohol from the dialkyl tartrate is easy if the appropriate tartrate ester is chosen.

Epoxy alcohol ester **3** was also prepared by an alternate sequence starting from butadiene dimer **9** (Scheme II). This is probably the best current route to this SRS precursor (**3**).

The last example is synthesis of epoxy alcohol **4** and thence (+)-disparlure (Scheme III). The crystallinity of epoxy alcohol **4** greatly simplifies its isolation (no chromatography needed). The final step involves hydrogenation of an α,β-unsaturated epoxide and gives in addition to **5** a ketonic product (ratio of **5** to byproduct is 72:28). The ketone presumably arises by rhodium(I)-catalyzed rearrangement of the unsaturated epoxide in a process similar to that reported by Noyori.[18] The ketone impurity was reduced to an alcohol (NaBH₄, EtOH, 15 min) and then easily removed by flash[19] chromatography (silica gel, 2% ether–petroleum ether) to give the pure epoxide **5** in 60% yield from the unsaturated epoxide. We have also produced pure (–)-disparlure [[α]²⁰_D –0.5° (*c* 10, CCl₄)] by this same synthetic sequence (Scheme III) with the obvious exception that (+)-DET was used in the epoxidation step. Both disparalure enantiomers gave appropriate combustion analyses and exhibited spectral and chromatographic properties

consonant with literature data.[20] Further proof of structure and absolute configuration was obtained in field tests.[21]

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(20) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1979**, *44*, 1025. Mori, K.; Takigawa, T.; Matsui, M. *Tetrahedron* **1979**, *35*, 833. Farnum, D. G.; Veysoglu, T.; Cardé, A. M.; Duhl-Emswiler, B.; Pancoast, T. A.; Reitz, T. J.; Cardé, R. T. *Tetrahedron Lett.* **1977**, 4009. Iwaki, S.; Marumo, S.; Saito, T.; Yamada, M.; Katagiri, K. *J. Am. Chem. Soc.* **1974**, *96*, 7842.

(21) Our (+)-disparlure was ∼10 times more effective than (±)-disparlure as a gypsy moth attractant. Our (–)-disparlure showed negligible activity as a moth attractant.

(22) **Note Added in Proof**: For other efficient routes to chiral, four-carbon epoxy alcohols such as **2** see: Hungerbühler, E.; Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 958. Seebach and Hungerbühler have also written a detailed and stimulating review on the usefulness of tartaric acid for "Syntheses of Enantiomerically Pure Compounds"; this review will appear in a forthcoming book entitled "Modern Synthetic Methods 1980".

Unimolecular Dissociations at Short Times. A Comparison of Angle-Resolved Mass Spectrometry and Field Ionization Kinetics

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The distribution of products arising from unimolecular dissociation of an internally excited molecule is a function of both its internal energy and the observation time.[1] Methods which allow control of these factors provide access to unimolecular rate constants[2] on one hand and give a highly resolved view of the dissociation chemistry on the other. We now show that collision-induced dissociation, done with resolution of scattering angle, gives data which are comparable to that provided by field ionization kinetics (FIK).[3] This method provides good time resolution at lifetimes approaching 10 ps and is proving an effective means of studying unimolecular chemistry;[4] the angle-resolved procedure may have comparable value since collisionally activated molecules can be selected so that they dissociate at times comparable to the fastest observed in FIK while a continuous range of longer lifetimes is also accessible.

In angle-resolved mass spectrometry[5] the collisionally induced dissociation of an ion, m_1^+, to give a product, m_2^+, is monitored as a fuction of the laboratory scattering angle, θ. Large (approximately 10 eV) energy depositions are accessible at scattering angles of ca. 1° for kilovolt energy ions. The methodology has previously been shown to allow selection of the internal energy deposited in an ion [6,7] and thus to serve as a means of obtaining

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(11) Both (–)- and (+)-diisopropyl tartrate (DIPT) were prepared in about 50–60% distilled yield by the method of Austin (Austin, P. C. *J. Chem. Soc.* **1928**, 1831). When the epoxidation of **7** was performed by using (+)-DIPT, the enantiomer of **2** [i.e., 2(*S*),3(*S*)-epoxybutan-1-ol, [α]²⁴_D –54.5° (*c* 0.24, PhH)] was produced in 40% yield.

(12) We are indebted to Dr. Y. Arai of Ono Pharmaceutical Co. for a generous sample of this allylic alcohol. He prepared it in several steps from propargyl alcohol. When allylic alcohol **8** was subjected to the standard epoxidation conditions and workup,[4] epoxidation occurred but further reaction (apparently involving cyclization to a diol lactone) also took place. For examples of highly selective cyclizations and other rearrangements of epoxy alcohols mediated by titanium(IV) alkoxides, see: Morgans, D. J.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.*, preceding paper in this issue.

(13) On larger scales, and depending on the exact case, vacuum distillation has proven to be an alternative to chromatography for this separation.

(14) Takahashi, S.; Shibano, T.; Hagihara, N. *Tetrahedron Lett.* **1967**, 2451. Walker, W. E.; Manyik, R. M.; Atkins, K. E.; Farmer, M. L. *Ibid.* **1970**, 3817. Smutny, E. J. *Ann. N.Y. Acad. Sci.* **1973**, *214*, 125–142. Tsuji, J. *Ibid.* **1980**, *333*, 250–263.

(15) The use of acetonitrile in addition to carbon tetrachloride and water is an important factor in making this modification (Carlsen, P. H. J.; Katsuki, T.; Sharpless, K. B., unpublished results) of the well-known RuO₄-catalyzed olefin cleavage procedure better than those already in the literature. For a 1-mmol scale reaction, we have found that the optimum solvent ratio is 2 mL of CCl₄, 2 mL of CH₃CN, and 3 mL of H₂O.

(16) When the procedure of Ames et al.[17] was performed using 1-bromodecane and the dianion of propargyl alcohol, 2-tridecyn-1-ol was obtained in 90% distilled yield (bp 97–100 °C (0.3 torr)). Partial hydrogenation over 5% Pd-BaSo₄, in the presence of synthetic quinoline, in ethanol gave the (*Z*)-allylic alcohol **10** in 96% distilled yield ((bp 85–89 °C (0.1 torr)).

(17) Ames, D. E.; Covell, A. N.; Goodburn, T. G. *J. Chem. Soc.* **1963**, 5889.

(18) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623.

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

(1) Beckey, H. D.; Hey, H.; Levsen, K.; Tenschert, G. *Int. J. Mass Spectrom. Ion Phys.* **1969**, *2*, 101. Robertson, A. J. B.; Viney, B. W. *J. Chem. Soc. A* **1966**, 1843.

(2) Andlauer, B.; Ottinger, C. *J. Chem. Phys.* **1971**, *55*, 1471. Hertel, I.; Ottinger, C. *Z. Naturforsch. A* **1967**, *22A*, 20. Baer, T. *Gas Phase Ion Chem.* **1979**, *1*, Chapter 5.

(3) Derrick, P. J. *Int. Rev. Sci. Phys. Chem. Ser. Two* **1975**, *5*, 1. Nibbering, N. M. M. *Philos. Trans. R. Soc. London, Ser. A* **1979**, *No. 293*, 103.

(4) Brown, P.; Pettit, G. R. *Org. Mass Spectrom.* **1970**, *3*, 67. Brown, P. *Ibid.* **1970**, *3*, 1175.

(5) Laramee, J. A.; Carmody, J. J.; Cooks, R. G. *Int. J. Mass Spectrom. Ion Phys.* **1979**, *31*, 333. Hubik, A. R.; Hemberger, P. H.; Laramee, J. A.; Cooks, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 3997.

(6) Hemberger, P. H.; Laramee, J. A.; Hubik, A. R.; Cooks, R. G., submitted for publication.