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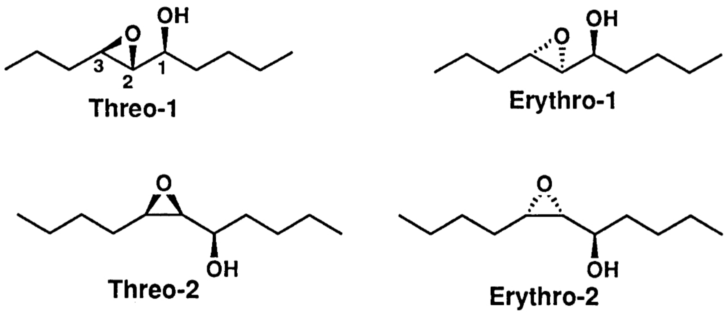
Regioselective Nucleophilic Opening of *erythro*- and *threo*-2,3-Epoxy Alcohols[#]

Kenneth S. KIRSHENBAUM[+] and K. Barry SHARPLESS[*]
Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, MA, U.S.A. 02139
[+]DuPont Chemical Company, Boston, MA, U.S.A. 02118

The epoxide opening reactions of *erythro* and *threo* epoxy alcohols with a variety of nucleophiles, both in the presence and absence of $Ti(O\underline{i}Pr)_4$, were examined. In general, opening of *threo* epoxy alcohols proceeded faster and with higher selectivity than the same reaction with the corresponding *erythro* isomers.

In recent years there has been much interest in developing both new methods of formation and new reactions involving epoxy alcohols.[1)] Reported here are the results of a study involving the regioselective nucleophilic opening of a 2,3-epoxy-1-ol moiety in racemic substrates where neither the epoxide, nor the hydroxyl, occupy a terminal position. The four main substrates used are shown in Fig. 1. In all cases, reaction procedure and isolation and analysis of products were similar to those previously reported.[2)]



Threo-1

Erythro-1

Threo-2

Erythro-2

Fig. 1.

Excluding hydride, all four of the above substrates open under the reaction conditions with a wide range of nucleophiles (PhSH, PhSNa, $HNEt_2$,[3)] Cl^-, N_3^-, PhCOOH), both in the presence, as well as absence of $Ti(O\underline{i}Pr)_4$ to

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[#] Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

give only the C-3 opened products.[4)] This striking regioselectivity is in contrast to the previously reported results obtained when opening trans-2,3-epoxy-1-hexanol.[2a)]

Table 1. Reactions Involving Substrate threo-1

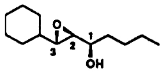
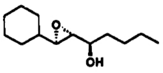
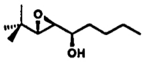
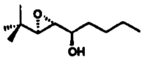
Entry	Nucleophile	$Ti(OiPr)_4$ (equiv.)	Regioselectivity C-3/C-2$^{a)}$	Yield %	Time h
1	PhSH	0	-	0	$24^{b)}$
2	PhSH	1.1	100:1	57	$24^{c)}$
3	PhSNa	0	100:1	<20	$24^{c)}$
4	PhSNa	1.1	100:1	67	$<3^{c)}$

a) 100:1 means that none of the C-2 opened product was observed. b) Refluxed in benzene. c) Room temperature in benzene.

As exemplified in Table 1, reactions run in the presence of the metal isopropoxide are much faster and usually require less severe reaction conditions than in the control reactions when the metal is absent. In some cases no reaction was observed, in the absence of the metal, even under forcing conditions.

In general, the threo isomers (threo-1, threo-2) gave better yields and reacted faster than the corresponding erythro isomers (erythro-1, erythro-2). In addition, epoxides derived from trans allylic alcohols (1) reacted faster than their cis counterparts (2).

Table 2. Reaction of $ClTi(OiPr)_3$ with C-4 Substituted Epoxy Alcohols$^{a)}$

Entry	Substrate	Erythro (E) or Threo (T)	Regioselectivity C-3:C-2	Yield$^{b)}$ %
1		T	>100:1	86.4
2		E	5.8:1	68.2
3		T	>100:1	76.4
4		E	no reaction	0

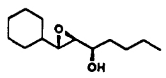
a) Room temperature in benzene. b) Isolated as the chlorodiol.

Differences in the regioselectivity of opening *erythro* vs. *threo* epoxy alcohols become apparent as the alkyl substitution at C-4 increases. Table 2 shows that with disubstitution at C-4 (entry 2), the regioselectivity of opening the *erythro* epoxy alcohol falls off sharply and with trisubstitution at C-4 (entry 4), the *erythro* epoxy alcohol fails to react. The corresponding *threo* isomers, on the other hand, open in good yield, exclusively at C-3 (entries 1,3).

The regioselectivity of the hydride reduction of epoxy alcohols **1** and **2** was also examined. Sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), diisobutylaluminum hydride (DIBAL) and lithium aluminum hydride (LAH) were used as sources of hydride.[6b)]

As can be seen in Table 3, in contrast to opening **1** and **2** with other nucleophiles, the *erythro* isomers are reduced more selectively than their *threo* counterparts (entries 2 vs. 6, 11 vs. 12). At low temperatures, reduction of *erythro*-**1** (entry 5) and *erythro*-**2** (entry 12) with Red-Al occurs at C-2, providing essentially pure 1,3-diols. Reduction of the *threo* substrate shown in entry 13 demonstrates that the poor regioselectivities observed when reducing *threo* epoxides **1** and **2** can be changed dramatically by increasing steric bulk at the C-4 position.

Table 3 Regioselectivity of Hydride Reduction[a)]

Entry	Substrate	Reducing Agent	Temp/°C (Time/d)	C-2/C-3[b)] (1,3/1,2-diol)	Yield/%
1	*Threo*-**1**	Red-Al	-20 (3)	4.8/1	76
2	*Threo*-**1**	Red-Al	0 (1)	1.4/1	80
3	*Threo*-**1**	LAH	0 (1)	1/1.4	88
4	*Threo*-**1**	DIBAL	0 (2)	only C-3	c)
5	*Erythro*-**1**	Red-Al	-20 (5)	64/1	78
6	*Erythro*-**1**	Red-Al	0 (3)	9.8/1	81
7	*Erythro*-**1**	LAH	0 (1)	1/2.0	81
8	*Erythro*-**1**	Red-Al	rt (0.5)	9/1	92
9	*Erythro*-**1**	DIBAL	rt (2)	only C-3	c)
10	*Threo*-**2**	Red-Al	0 (3)	-	No Reaction
11	*Threo*-**2**	Red-Al	rt (3)	1/3.5	71
12	*Erythro*-**2**	Red-Al	0 (1.5)	only C-2	69
13		Red-Al	rt (1)	only C-2	91

a) See ref. 6b. b) Regioselectivities were measured by ^{1}H NMR. c) The DIBAL reductions were never clean and yields were poor.

It should be noted that LAH, and especially DIBAL, open the epoxides predominately, if not exclusively, at C-3 (entries 3,4,7,9). The observation that reduction with DIBAL occurs exclusively at C-3 is in keeping with the idea that DIBAL delivers its hydride intermolecularly, and this case should thus be classified along with the other nucleophiles presented here (i.e., intermolecular attack). The differences in the regioselectivities of reduction observed between DIBAL and Red-Al suggest that Red-Al reduction occurs _intra_molecularly with the epoxy alcohol coordinated to the aluminum as has been previously suggested.6)

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References

1) C. H. Behrens and K. B. Sharpless, Aldrichimica Acta, 16, 67 (1983); B. E. Rossiter, "Asymmetric Synthesis," ed by J. D. Morrison Academic Press, New York (1985), Vol. 5, Chap. 7; A. Pfenninger, Synthesis, 1986, 89.
2) a) M. Caron and K. B. Sharpless, J.Org.Chem., 50, 1557 (1985); b) C. H. Behrens, S. Y. Ko, K. B. Sharpless, and F. J. Walker, ibid., 50, 5687 (1985); c) C. H. Behrens and K. B. Sharpless, ibid. 50, 5696 (1985); d) K. S. Kirshenbaum, (1985). Ph.D. Dissertation, Massachusetts Institute of Technology, Cambridge, Massachusetts. This thesis contains full details on the processes reported here and also describes related opening studies with epoxides derived from homoallylic alcohols.
3) Reaction with this nucleophile was extremely slow.
4) No C-2 opened product was ever detected with these four substrates (1-2).
5) _Threo_ yields ranged from 57-90% and _erythro_ yields ranged from 23-83%.
6) a) J. M. Finan, Y. Kishi, Tetrahedron Lett., 23, 2719 (1982); b) S. M. Viti, Tetrahedron Lett., 23, 4541 (1982). Reactions were performed using either 5 equiv. Red-Al in THF, 3-4 equiv. LAH in THF, or 2 equiv. DIBAL in a THF/CH_2Cl_2 mixture.

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