(C-11), 40.57 (C-3), 46.25 (C-2), 47.20 (C-4a), 53.46 (C-8a), 56.18 (OMe), 84.82 (C-8), 204.39 (C-4), 211.26 (C-1); MS, *m/e* (rel intens) 250 (M^+, 24), 96 (base), 81 (56), 67 (76), 53 (61). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.10; H, 8.90.

Tricyclic ketone 15b: mp 102–103 °C (*n*-hexane); IR 1700 (s, C=O) cm^{-1}; ^1H NMR δ 1.13 (s, 3, C-10 Hs), 1.19 (s, 3, C-12 Hs), 1.29 (s, 3, C-11 Hs), 1.34 (m, 1, H-7A), 1.38 (m, 1, H-6B), 1.40 (m, 1, H-5A), 1.68 (m, 1, H-6A), 2.00 (m, 1, H-7B), 2.10 (d, 1, $J_{2,3}$ = 6.8 Hz, H-2), 2.15 (d, 1, H-3), 2.22 (m, 1, $J_{4a,5A}$ = 4.5 Hz, $J_{4a,5B}$ = 3.4 Hz, H-4a), 2.32 (m, 1, H-5B), 3.27 (s, 3, OMe), 3.62 (dd, 1, $J_{8,7A}$ = 11.0 Hz, $J_{8,7B}$ = 4.5 Hz, H-8); ^{13}C NMR δ 13.25 (C-12), 18.30 (C-10), 20.27 (C-5), 20.57 (C-6), 24.59 (C-4a), 27.55 (C-9), 28.67 (C-11), 37.88 (C-3), 38.13 (C-2), 53.10 (C-4a), 55.52 (C-8a), 56.98 (OMe), 79.56 (C-8), 204.86 (C-4), 206.17 (C-1); MS, *m/e* (rel intens) 250 (M^+, 16), 96 (base), 8 (81), 67 (60), 55 (57). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.80; H, 8.82.

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Registry No. **1a**, 22327-33-9; (±)-**1b**, 67670-71-7; **2a**, 513-81-5; **2b**, 10034-09-0; **2c**, 78-79-5; **3**, 6617-33-0; **4**, 127279-91-8; **5**, 127279-92-9; (±)-**6a**, 127279-93-0; (±)-**6b**, 127279-94-1; (±)-**6c**, 127279-95-2; (±)-**7a**, 127279-96-3; (±)-**7b**, 127379-28-6; (±)-**8**, 127279-97-4; (±)-**9**, 127279-98-5; **12**, 127279-99-6; **13**, 127280-00-6; **14**, 127280-01-7; (±)-**15a**, 127280-02-8; (±)-**15b**, 127379-29-7.

Regiochemical Control of the Ring-Opening of 1,2-Epoxides by Means of Chelating Processes. Synthesis and Reactions of the *cis*- and *trans*-Oxides Derived from 4-(Benzyloxy)cyclohexene

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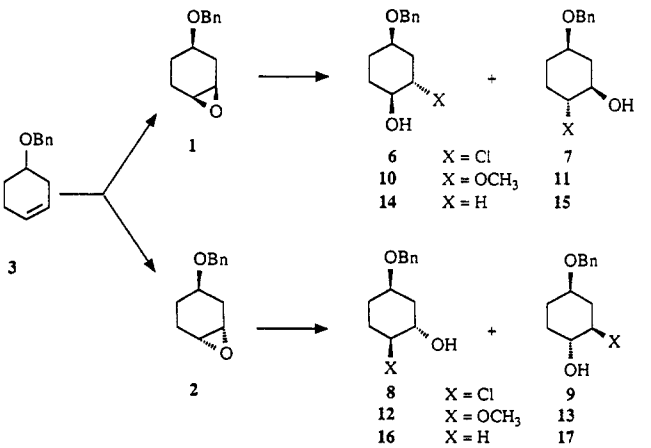
The synthesis and reactions of diastereomeric epoxides *cis*-**1** and *trans*-**2** with heteronucleophiles were carried out in order to probe the effect of remote polar functionality on the regioselectivity of nucleophilic addition to the epoxide ring. The reaction of *cis*-epoxide **1** with $TiCl_4$ in CH_2Cl_2 gave exclusively the chlorohydrin **7**, whereas the regioisomeric chlorohydrin **6** was obtained as the main product from the reaction of **1** with HCl in $CHCl_3$. The same reactions with epoxide **2** yielded chlorohydrins **8** and **9**, the main product being **8** in both cases. Chlorohydroxylation of olefin **3** via Sharpless conditions ($TiCl_4$ and TBHP) gave **7**, **8**, and **9** in a 96:6:2 ratio. The regiochemical outcome of ring-opening addition reactions with epoxide **2** is necessarily independent of any bidentate chelation effects; however, in some of the comparable nucleophilic reactions of epoxide **1**, chelation of the counterion by the oxirane oxygen and the remote benzyloxy group can substantially alter the regioselectivity of addition. Thus, the **10**:**11** regioisomeric ratio (85:15) obtained from the H^+-catalyzed methanolysis of **1** was completely inverted (2:98) when the solvolysis was carried out with concentrated methanolic $LiClO_4$. The ring-opening of **1** with $LiAlH_4$ afforded **14** and **15** in a 2:98 ratio; however, reaction of **1** with premixed $LiAlH_4$/12-crown-4 gave the opposite result, **14**:**15** = 82:18. In all of the addition reactions of **1** and **2** the ring-opened products were consistent with the well-known preference for diaxial nucleophilic ring-opening in cyclohexene oxides derivatives; our results are further interpreted as evidence for chelation control in some of the addition reactions of **1**.

Introduction

The ring-opening addition reactions of oxiranes proceed through mechanistic pathways that can range from S_N1 to S_N2 reactivity. The former is an electrophile-promoted event, followed by attack of the nucleophile, while the latter process is a nucleophilic displacement reaction that may be assisted by a proton, metal ion, or other electrophile.[3-5] The regiochemical outcome of the ring-opening process may span a range of Markovnikov to contra-Markovnikov type of cleavage, and the stereochemical course of the reaction can range from complete inversion to complete retention of configuration depending on the solvent, nucleophile, electrophilic catalyst, temperature, and the structure, configuration, and conformation of the epoxide.[3-6]

Scheme I



(1) Università di Pisa.
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(3) Buchanan, J. G.; Sable, H. I. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 1, p 1.
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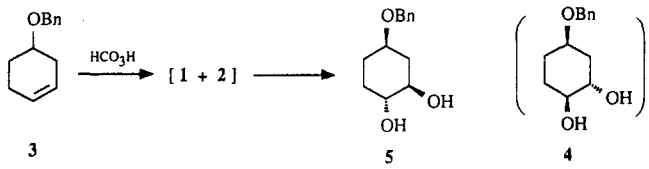
0022-3263/90/1955-4265$02.50/0

In connection with a research program aimed at developing new methods for regiocontrol of carbon–nucleophile additions to oxiranes containing remote heteroatom functionality,[7] we needed to prepare and characterize the diastereomeric (4-benzyloxy)cyclohexene oxides *cis*-1 and *trans*-2. Epoxides 1 and 2 had apparently not been prepared and isolated before; however, they were proposed as intermediates in an hydroxylation reaction of olefin 3, which afforded only one final product, initially assumed to be 4.[8,9] Diol 4 was thought to be formed by preferential



3 5 4

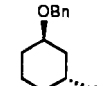
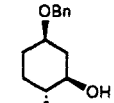
diaxial opening of both 1 and 2 in their most stable conformations, that is, with the benzyloxy group equatorial. The actual structure of the hydroxylation product was later shown to be 5;[9] this unexpected result prompted the latter investigators to conclude that the mechanism of ring-opening of epoxides 1 and 2 required further study. In this report we detail the synthesis and isolation of epoxides 1 and 2 and their ring-opening addition reactions with a variety of heteronucleophiles (Scheme I).

Results and Discussion

The direct epoxidation of olefin 3[10] with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded an almost equimolar mixture of 1 and 2, which was separated by flash chromatography on silica gel. However, it seemed likely that the cis diastereomer 1 could be prepared stereoselectively through a metal-catalyzed addition reaction[11,12] of 3; in fact, Sharpless chlorohydroxylation[12] of 3 with $TiCl_4$ in the presence of *tert*-butyl hydroperoxide (TBHP) in CH_2Cl_2, followed by oxirane ring-closure of the crude chlorohydrin mixture with *t*-BuOK, gave a 92:8 mixture of 1 and 2. The Sharpless chlorohydroxylation of olefins is supposed to proceed through intermediate epoxides (1 and 2 in the present case) that are rapidly opened to chlorohydrins under the reaction conditions;[12] initial coordination of the oxidant to the benzyloxy group of 3 is presumably responsible for the observed facial selectivity of this reaction. GLC analysis of the crude mixture of chlorohydrins from the chlorohydroxylation of 3 showed the presence of 7 as the main product (92%) accompanied by two minor chlorohydrins, 8 and 9 (total 8%) in an 84:16 ratio. No chlorohydrin 6 could be detected in the mixture. Pure 7 was isolated by recrystallization of the chlorohydrin mixture and transformed to pure *cis*-1 by treatment with *t*-BuOK.

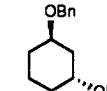
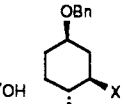
Chlorohydrin 7 was different from the main product 6 of the ring-opening of epoxide 1 with HCl in $CHCl_3$; in this case a mixture of 6 and 7 in the ratio 85:15 was obtained. The reaction of epoxide 2 with HCl in $CHCl_3$ yielded a 95:5 mixture of chlorohydrins 8 and 9 in which the predominant product was the same as in the chlorohydroxylation of 3.

Table I. Regioselectivity (%) of the Ring-Opening Reactions of *cis*-Epoxide 1

entry	reagents	reaction conditions[a]	reaction time		
1	HCl	A	1 h	85[b]	15[c]
2	TBHP–$TiCl_4$	B	40 min	0[b]	100[c]
3	MeOH–H^+	C	2 h	85[d]	15[e]
4	MeOH–H^+	D	2 h	85[d]	15[e]
5	MeOLi–MeOH	E	20 h	67[d]	33[e]
6	MeONa–MeOH	E	20 h	79[d]	21[e]
7	MeOK–MeOH	E	20 h	93[d]	7[e]
8	MeOLi–MeOH	F	48 h	71[d]	29[e]
9	MeONa–MeOH	F	48 h	85[d]	15[e]
10	MeOK–MeOH	F	48 h	92[d]	8[e]
11	MeOLi–MeOH	G	20 h	90[d]	10[e]
12	MeOLi–MeOH	H	5 days	95[d]	5[e]
13	MeONa–MeOH	H	5 days	96[d]	4[e]
14	MeOK–MeOH	H	5 days	97[d]	3[e]
15	MeOH–$LiClO_4$	I	20 h	2[d]	98[e]
16	MeOH–$LiClO_4$	J	20 h	50[d]	50[e]
17	MeOH–$NaClO_4$	J	5 days	80[d]	20[e]
18	MeOH–$LiClO_4$	K	5 days	86[d]	14[e]
19	$LiAlH_4$–Et_2O	L	2 h	2[f]	98[g]
20	$LiAlH_4$–pentane	L	2 h	2[f]	98[g]
21	$LiAlH_4$–crown-Et_2O	M	5 h	60[f]	40[g]
22	$LiAlH_4$–crown-pentane	M	5 h	82[f]	18[g]

[a] Conditions: A, 36% aqueous (or anhydrous) HCl in $CHCl_3$, room temperature; B, CH_2Cl_2 solution, −78 °C; C, 0.2 N H_2SO_4, room temperature; D, 10^{-3} M H_2SO_4 in MeOH, room temperature; E, epoxide:methoxide = 1:100, refluxing temperature; F, epoxide:methoxide = 1:100, room temperature; G, epoxide:methoxide = 1:10, refluxing temperature; H, epoxide:methoxide = 1:5, room temperature; I, ~17 M $LiClO_4$ in MeOH, refluxing temperature; J, 1.7 M $LiClO_4$ (or $NaClO_4$) in MeOH, refluxing temperature; K, 0.5 M $LiClO_4$ in MeOH, refluxing temperature; L, epoxide:$LiAlH_4$ = 1:4, room temperature; M, an equimolar amount of $LiAlH_4$ and 12-crown-4 in the solvent is stirred 24 h at room temperature and then the epoxide is added (epoxide:$LiAlH_4$ = 1:4). [b] Chlorohydrin 6, X = Cl. [c] Chlorohydrin 7, X = Cl. [d] Methoxy alcohol 10, X = OMe. [e] Methoxy alcohol 11, X = OMe. [f] Alcohol 14, X = H. [g] Alcohol 15, X = H.

Table II. Regioselectivity (%) of the Ring-Opening Reactions of *trans*-Epoxide 2

entry	reagents	reaction conditions[a]	reaction time		
1	HCl	A	2 h	95[b]	5[c]
2	TBHP–$TiCl_4$	B	40 min	84[b]	16[c]
3	MeOH–H^+	C	2 h	79[d]	21[e]
4	MeOLi–MeOH	E	20 h	95[d]	5[e]
5	MeONa–MeOH	E	20 h	97[d]	3[e]
6	MeOK–MeOH	G	6 days	98[d]	2[e]
7	MeOH–$LiClO_4$	I	20 h	54[d]	46[e]
8	MeOH–$LiClO_4$	J	5 days	71[d]	29[e]
9	MeOH–$NaClO_4$	J	5 days	74[d]	26[e]
10	MeOH–$LiClO_4$	K	5 days	71[d]	29[e]
11	$LiAlH_4$–Et_2O	L	2 h	97[f]	3[g]
12	$LiAlH_4$–pentane	L	2 h	97[f]	3[g]
13	$LiAlH_4$–crown-Et_2O	M	5 h	97[f]	3[g]
14	$LiAlH_4$–crown-pentane	M	5 h	97[f]	3[g]

[a] See footnote *a*, Table I. [b] Chlorohydrin 8, X = Cl. [c] Chlorohydrin 9, X = Cl. [d] Methoxy alcohol 12, X = OMe. [e] Methoxy alcohol 13, X = OMe. [f] Alcohol 16, X = H. [g] Alcohol 17, X = H.

When the pure diastereomeric (4-benzyloxy)cyclohexene oxides were allowed to react with $TiCl_4$ under Sharpless chlorohydroxylation conditions, epoxide 1 gave exclusively chlorohydrin 7 whereas epoxide 2 gave an 84:16 mixture

(6) Crotti, P.; Dell'Omodarme, G.; Ferretti, M.; Macchia, F. *J. Am. Chem. Soc.* **1987**, *109*, 1463.
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(12) Klunder, J. M.; Caron, M.; Uchiyama, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 912.

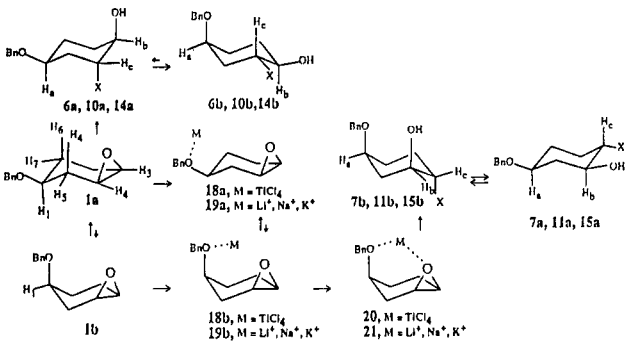
of 8 and 9 (Tables I and II). These last results lend further support to the previously mentioned hypothesis[12] that 1 and 2 are actually intermediates in the chlorohydroxylation of 3.

The reactions of epoxide 2 with HCl and $TiCl_4$ appear to be relatively straightforward; however, the same reactions with epoxide 1 give less obvious results. It could be envisaged that the remote benzyloxy group intervenes through a chelation process in some reactions of 1; thus, in order to verify the extent of such an effect in determining the regioselectivity of epoxide ring-opening, we examined the methanolysis under acid, base, and metal cation catalysis and the $LiAlH_4$ reductions of epoxides 1 and 2. The acid-catalyzed (H_2SO_4) methanolyses of 1 and 2 were regioselective, yielding mixtures of methoxy alcohols 10 and 11 (from 1) and 12 and 13 (from 2) in which the former products (10 and 12, respectively) predominate (see Tables I and II). The regiochemistry of adducts 10 and 12 is analogous to that of the chlorohydrins (6 and 8, respectively) found as the main products in the reaction of epoxides 1 and 2 with HCl. The base-catalyzed (alkaline methoxide) ring-openings of epoxide 2 were more regioselective than the acid-catalyzed reactions; however, compound 12 was the main product in all cases. The composition of the reaction mixtures was practically independent of the reaction conditions (type of metal counterion or amount of alkoxide; entries 4–6, Table II). On the other hand, the corresponding reactions of epoxide 1 yielded mixtures of methoxy alcohols 10 and 11 that varied markedly depending on the reaction conditions. In the reactions carried out with relatively small amounts of alkoxide (5-fold the molar amount of epoxide 1; entries 12–14, Table I), the relative proportion of methoxy alcohol 10 was ≥95%. When the concentration of alkoxide was increased to 10- and 100-fold the epoxide, the proportion of 10 decreased in favor of regioisomer 11 (entries 5–11, Table I). In addition, the ratio of 10 and 11 is also dependent on the identity of the alkoxide counterion: going through the lithium, sodium, and potassium series the proportion of product 11 decreases significantly. When the methanolysis of 1 was carried out in the presence of alkaline perchlorates, the regioselectivity also varied markedly on changing either the concentration of catalyst or the identity of the metal counterion. The reaction of 1 in 0.5 M methanolic $LiClO_4$ gave an 86:14 ratio of 10 and 11, similar to that observed in the proton-catalyzed methanolyses; however, the 10:11 ratio changed dramatically when the salt concentration was increased. For example, 10 and 11 were obtained in a 2:98 ratio with saturated methanolic $LiClO_4$ (entry 15, Table I). The 10:11 ratio changes from 50:50 in the methanolysis of 1 with 1.7 M $LiClO_4$ to 80:20 in the corresponding reaction with 1.7 M $NaClO_4$ (entries 16 and 17, Table I).

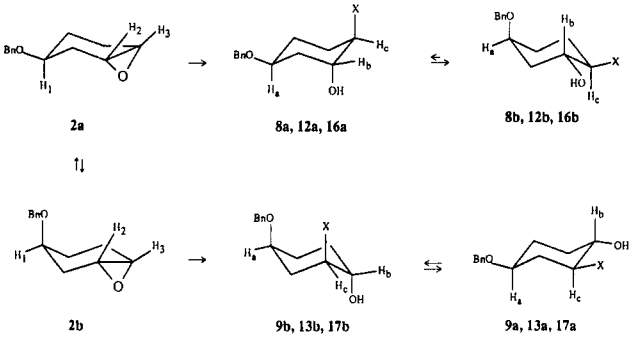
The solvolysis of epoxide 2 with 0.5 (or 1.7) M methanolic $LiClO_4$ affords a regioisomeric ratio (12:13 = 71:29) similar to that observed in the acid-catalyzed methanolysis (entries 8, 10, and 3, Table II); however, in this case the ratio of products appears to be independent of both the concentration and the type of salt. Only when the salt concentration was made extremely high was any appreciable modification of the regioselectivity observed, 12:13 = 54:46 (entry 7, Table II).

The reduction of epoxide 1 with $LiAlH_4$ in ether was highly regioselective, yielding a 2:98 mixture of alcohols 14 and 15; however, when a Li^+-specific crown ether, 12-crown-4, was premixed with the $LiAlH_4$, alcohol 14 became the main reaction product (14:15 = 60:40). When the $LiAlH_4$ reduction of 1 was carried out in pentane, the result

Scheme II



Scheme III



was identical with that obtained in ether; however, the addition of 12-crown-4 to the reducing agent had a larger effect on the regioselectivity in pentane (14:15 = 82:18). On the other hand, analogous variations in the $LiAlH_4$ reduction of epoxide 2 consistently gave a 97:3 mixture of alcohols 16 and 17.

The relatively large distance of the benzyloxy group from the two secondary oxirane carbons of 1 and 2 should serve to make the oxirane carbons electronically equivalent for practical purposes; however, in accordance with the well-known Fürst–Plattner rule,[13] the nucleophilic ring-opening of these epoxides is expected to take place exclusively in diaxial mode. Aside from possible chelation effects, the most stable conformation of epoxide 1 is probably structure 1a (Scheme II) since it has the benzyloxy substituent in an equatorial position (vide infra: conformational analysis of the ^1H NMR spectrum of epoxide 1).

The diaxial addition of HCl or $TiCl_4$ to epoxide 1 via conformation 1a would produce chlorohydrin 6. Actually 6 is the main product in the reaction of 1 with HCl, but it is completely absent in the corresponding reaction with $TiCl_4$ (in which chlorohydrin 7 is the exclusive product). The formation of 7 in the reaction of epoxide 1 with $TiCl_4$ can be guessed to arise either from complete diequatorial ring-opening of conformation 1a, in an unlikely violation of the Fürst-Plattner rule, or from diaxial ring-opening of the less stable conformer 1b. Our results suggest that conformation 1b may be stabilized by the direct assistance of Ti(IV) through a bidentate chelate structure like 20 (Scheme II). Initial complexation of $TiCl_4$ with the oxygen of the benzyloxy group of 1, in either conformation 1a or 1b (to give 18a or 18b), followed by an entropically favored coordination of the metal with the oxirane oxygen would

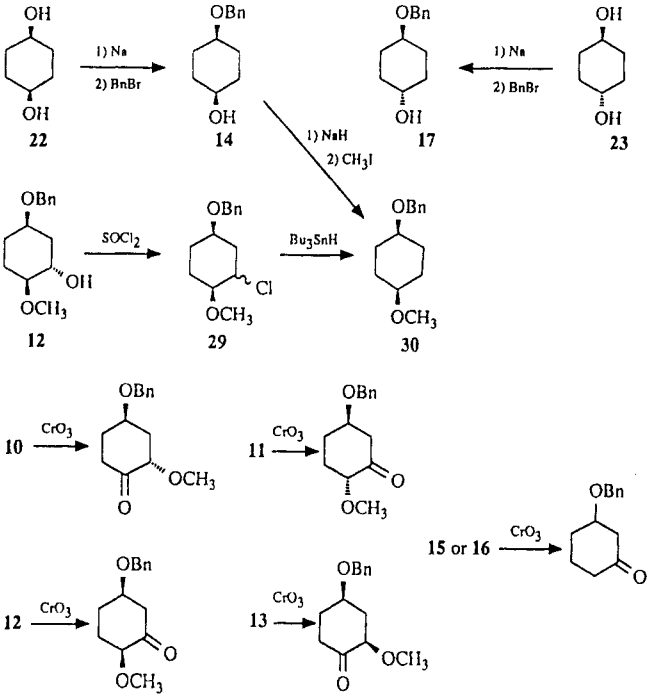
(13) (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience: New York, 1965; p 102. (b) Fürst, A.; Plattner, P. A. *Abstracts of Papers*, 12th International Congress of Pure and Applied Chemistry; 1951; p 409.

lead to the intermediate chelate structure **20**. Axial attack of the nucleophile (Cl^-) on intermediate **20** would lead to chlorohydrin **7**, as observed.[14] Apparently, a proton cannot coordinate effectively in a structure like **20**; thus, the reaction of epoxide **1** with HCl leads to a mixture of chlorohydrins **6** and **7**, in which **6** predominates. Bidentate chelation processes cannot intercede in the reactions of epoxide **2** so it is not surprising that roughly the same chlorohydrin mixture was formed in ring-openings with either $TiCl_4$ or HCl; however, it might be expected that **2** could undergo diaxial ring-opening from conformations **2a** and **2b** (Scheme III and a conformational analysis of epoxide **2**; vide infra) with similar facility, leading to formation of substantial amounts of both chlorohydrin products **8** and **9**, contrary to the results (Table II).

The high regioselectivity for formation of chlorohydrin **8** in the reactions of **2** with HCl or $TiCl_4$ could arise because electrostatic repulsion between the axially approaching nucleophile (Cl^-) and the axial oxygen atom of the benzyloxy group suppresses reaction via conformation **2b**, leaving **2a** as the predominant reactive conformer. The regioselectivity of methanolysis of epoxides **1** and **2** under proton catalysis can be rationalized as previously done for the reaction with HCl. Thus, in the case of **1**, axial attack of the nucleophile (MeOH) apparently occurs mostly via conformation **1a** of the protonated epoxide, and in the case of **2**, nucleophilic attack on **2a** is favored over **2b**. The reactions of epoxide **2** with MeO^-M^+ or $M^+ClO_4^-$ in methanol seem to proceed nearly exclusively through nucleophilic attack on conformation **2a** (Scheme III; Table II). The higher regioselectivity of the base-catalyzed methanolysis reactions of **2** could be due to increased electrostatic repulsion between MeO^- and the benzyloxy oxygen during axial attack on conformation **2b**;[7] however, we cannot easily rationalize the increased regioselectivity observed in reactions of epoxide **2** with methanolic M^+ClO_4.

An explanation analogous to the one given for the proton-catalyzed methanolysis of epoxide **1** is not sufficient to explain the base-catalyzed reactions of this compound. The regioselectivity of the base-catalyzed ring-opening of **1** is dependent on the methoxide concentration and on the identity of the metal counterion. A relatively low concentration of potassium methoxide led to very high regioselectivity for the formation of methoxy alcohol **10**, presumably via attack on conformation **1a**. Increasing the concentration of methoxide ion and passing through the counterions K^+, Na^+, and Li^+ significantly reduces the regioselectivity of methanolysis. The increasing proportion of methoxy alcohol **11** in these methanolysis products may reflect a chelation-assisted process (**19a** ⇌ **19b** → **21**, Scheme II), similar, albeit much less effective, to that hypothesized for the reaction of **1** with $TiCl_4$ in CH_2Cl_2. The influence of a bidentate chelation effect on the addition reactions of epoxide **1** is much more evident in metal cation assisted methanolyses with alkaline perchlorates. Under neutral conditions the absence of a strong nucleophile should relatively favor the intervention of metal cation assisted ring-opening processes, including chelation control. In these examples, as expected for chelation-assisted additions, the regioisomeric **10**:**11** ratio is very sensitive to the amount and the type of metal cation employed (Table I).

Scheme IV



The chelating ability of epoxide **1** with Li^+ is further demonstrated in its $LiAlH_4$ reduction reactions which afford very high **15**:**14** selectivity. Addition of 12-crown-4 to these reaction mixtures effectively prevents the formation of a reactive chelated intermediate of type **21** (especially in the nonpolar, noncoordinating pentane) and thus promotes reduction via conformation **1a**, leading predominantly to the formation of alcohol **14**. On the other hand, the regioselectivity of the reduction of epoxide **2** is in accordance with axial attack of the nucleophile (H^-) on conformation **2a**, giving mostly alcohol **16**, and is insensitive to the reaction conditions. In conclusion, the presence of the *cis*-benzyloxy group can lead to almost complete chelation control over the regioselectivity of several types of addition reactions of epoxide **1**.

Structures, Configurations, and Conformations

The structures of the two possible regioisomeric pairs of alcohols **14** and **15** and of **16** and **17**, obtained by $LiAlH_4$ reduction of epoxides **1** and **2**, respectively (see Tables I and II and Schemes I–III) were demonstrated by independent synthesis of one member of each pair. Thus, alcohols **14** and **17** were prepared by monobenzylation of the corresponding known[16] 1,4-diols, *cis*-**22** and *trans*-**23** (Scheme IV). Compounds **15** and **16**, which on oxidation give the same ketone, **24**, are clearly regioisomers of **14** and **17**, respectively. Bearing in mind that the configuration of the alcohols obtained in the reduction of epoxides **1** and **2** must correspond to that of the starting epoxides, the unequivocal synthesis of **14** and **17** also infers the relative configurations of **1** and **2**. The conformational equilibria of epoxides **1** and **2** (see Schemes II and III) were probed via ^1H NMR spectroscopy. The signal for the methine proton α to the benzyloxy group in **1** showed two large

(14) The regioselectivity of nucleophilic attack on the C(1) carbon of chelate intermediates **20** and **21** (Scheme II), which lead to structures **7**, **11**, and **15**, is consistent with both the stereoelectronic factors governing the Fürst–Plattner rule[13] and additional stereoelectronic factors implicated in the chelation-controlled ring-opening of 3,4-epoxy-1-alkanol derivatives.[15]

(15) Flippin, L. A.; Brown, P. A.; Jalali-Araghi, K. *J. Org. Chem.* **1989**, *54*, 3588.

(16) (a) Olberg, R. C.; Pines, H.; Ipatieff, V. N. *J. Am. Chem. Soc.* **1944**, *66*, 1096. (b) Owen, L. N.; Robins, P. A. *J. Chem. Soc.* **1949**, 320.

(17) Kuivila, H. G. *Synthesis* **1970**, 499.

Table III. Spectroscopic Data for Chlorohydrins 6–8 and Hydroxy Ethers 10–17

	^{1}H NMR:[a] δ (bandwidth,[18] Hz)			IR (CCl_4) (OH stretching), cm^{-1}			
compd	H_a	H_b	H_c	1,2 OH···O	1,3 OH···O	OH···Cl	OH_{free}
6	3.73 (22.0)	3.57 (36.6)	4.13 (39.1)[b]			3593	
7	c	c	3.94 (27.2)[b]		3510[f]	3590[g]	
8	c	c	3.94 (33.0)[b]			3596[f]	3620[h]
10	3.78 (17.0)	d	d	3596[f]			
11	e	3.09 (25.0)	e	3594[g]	3522[g]		
12	e	3.01 (32.0)	e	3597[f]			
13	e	2.96 (34.0)	e	3596[f]			
14	3.73 (29.7)	3.49 (24.2)					3630
15	3.74 (28.0)	3.56 (27.0)			3534[g]		3618[g]
16	4.08 (27.0)	3.80 (22.0)					3620
17	3.57 (32.7)	3.34 (32.7)					3630

[a] All the signals are multiplets: H_a = C*H*OBn, H_b = C*H*OH, H_c = C*H*X (see Schemes II and III). [b] X = Cl. [c] The signal of proton H_a is overlapped with the signal of proton H_b. [d] The signal of proton H_b is overlapped with the signal of proton H_c, X = OMe. [e] The signal of proton H_a is overlapped with the signal of proton H_c, X = OMe. [f] Strong band. [g] Medium band. [h] Shoulder.

vicinal coupling constants (J = 10.98 and 9.74 Hz; total bandwidth[18] 34 Hz) identifying **1a** as the predominant conformer of the *cis*-epoxide in $CDCl_3$ solution. On the other hand, the corresponding methine proton in epoxide **2** shows much smaller vicinal coupling constants, giving rise to a total bandwidth of 21 Hz. This value is intermediate between that expected for an axial and an equatorial proton;[18] thus, it suggests the existence of approximately equimolar amounts of **2a** and **2b** at conformational equilibrium.

The trans relationship between the hydroxyl group and the chlorine atom of chlorohydrins **6–9** was established by the conversion of **6–9** to starting epoxides **1** (from **6** or **7**) and **2** (from **8** or mixtures of **8** and **9**). The relative structure of the diastereomer pairs **6**, **7** and **8**, **9**, was demonstrated by reductive dehalogenation with Bu_3SnH[17] of **6** and **7** to alcohols **14** and **15**, respectively, and by the same reaction of an 85:15 mixture of **8** and **9** to an exactly corresponding mixture of **16** and **17**. The ^{1}H NMR and IR data for chlorohydrins **6–8** (see Table III) corroborate the assigned structures and configurations and make it possible to draw some additional conclusions about the conformational equilibria of these products.

The bandwidth of the ^{1}H NMR signal for H_c in chlorohydrin **7** (27.2 Hz) indicates that this compound exists in $CDCl_3$ as an equilibrium mixture of the triequatorial conformer **7a** and the triaxial conformer **7b** (Scheme II). Accordingly, the IR spectrum of a CCl_4 solution of **7** indicates the presence of both an OH···Cl interaction (3590 cm^{-1}) and a stronger 1,3 OH···O interaction (3510 cm^{-1}), which must be contributions from conformers **7a** and **7b**, respectively.[20] As for chlorohydrins **6** and **8**, the values of the ^{1}H NMR bandwidths of H_a, H_b, and H_c indicate that conformations **6b** and **8b**, each having the benzyloxy group axial, are clearly favored. The IR spectra of **6** and **8** suggest the presence of an OH···Cl interaction (3593 cm^{-1} in **6** and 3596 cm^{-1} in **8**), which is only possible in conformations **6b** and **8b**, respectively (see Table III and Schemes II and III).[18] A trans C(3)–C(4) relationship in methoxy alcohols **10–13** can be assumed on the basis of their formation under base-catalyzed methanolysis conditions since a stereospecific anti addition mechanism appears to be completely general for the ring-opening addition reactions of oxiranes with strong nucleophiles.[4,21] The cis and trans relationships between the benzyloxy and the hydroxy group in the two pairs **10**, **11** and **12**, **13** are also dictated by the anti stereospecificity of their base-catalyzed addition reactions. Within each of these pairs the regiochemical assignment was made by combined ^{1}H NMR and IR analysis and oxidative degradation. The hydroxy stretching band of **11** indicates the presence of a 1,3 OH···O interaction (3522 cm^{-1}), which is possible only in the assigned structure.[20] The presence of an IR band characteristic of a 1,2 OH···O interaction (3594 cm^{-1}) together with the above-mentioned 1,3 hydrogen bond and an intermediate bandwidth value of H_b in the ^{1}H NMR spectrum (25.0 Hz, Table III) of **11** all point to the existence of an equilibrium mixture of conformers **11a** and **11b** in the solvents employed. In the case of **10**, the low bandwidth value (17.0 Hz) of proton H_a and the presence of a vicinal OH···O hydrogen bond (3596 cm^{-1}) not only supports the assigned regiochemistry but also indicates that conformer **10b** (Scheme II) is clearly preferred under our spectroscopic conditions. The IR and ^{1}H NMR data for methoxy alcohols **12** and **13** did not provide unequivocal support for the relative structural assignments of this pair:[22] The IR spectra of both of these diastereomers show the presence of a strong vicinal OH···O interaction, and their ^{1}H NMR spectra indicate that proton H_b is axial in both. This situation is possible for **12** in conformation **12b** and for **13** in conformation **13a**, but because of overlap of proton H_a with other signals in the ^{1}H NMR spectra of **12** and **13**, it was not possible to distinguish between them. We thus determined the relative structures of this diastereomer pair by chemical correlation of one of them with the structure of benzyloxy alcohol **14**. Reaction of compound **12** with thionyl chloride in $CHCl_3$ gave compound **29**, which was converted to diether **30** by reductive dechlorination with Bu_3SnH.[23] Compound **30**

(18) Due to asymmetry in some of the methine proton ^{1}H NMR signals from our compounds, we preferred to use full bandwidth values, rather than the more commonly used half-bandwidth values,[19] for configurational and conformational analysis. We employed *cis*- and *trans*-4-*tert*-butylcyclohexanol to obtain the bandwidth values of a pure equatorial ($W_{H_{eq}}$) and pure axial ($W_{H_{ax}}$) protons, respectively: $W_{H_{eq}}$ = 15.0 Hz and $W_{H_{ax}}$ = 37.5 Hz.

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(20) (a) Tichy', M. In *Advances in Organic Chemistry, Methods and Results*; Raphael, R. A., Taylor, E. C., Wymberg, H., Eds.; Interscience: New York, 1965; Vol. 5, p 115. (b) Macchia, B.; Macchia, F.; Monti, L. *Gazz. Chim. Ital.* **1970**, *100*, 35.

(21) (a) Brewster, J. H. *J. Am. Chem. Soc.* **1956**, *78*, 4061. (b) Costantino, P.; Crotti, P.; Ferretti, M.; Macchia, F. *J. Org. Chem.* **1982**, *47*, 2917.

(22) The oxidation of methoxy alcohols **10–13** to the corresponding ketones **25–28** was carried out in order to facilitate interpretation of the ^{1}H NMR spectra of **10–13** (see Scheme IV and the Experimental Section).

(23) The reaction of **12** with thionyl chloride to give **29** may proceed with retention of configuration;[24] however, the ^{1}H NMR data do not allow us to assign the relative stereochemistry of **29** with certainty. Note that the relative configuration of C(2) in **29** is of no importance in the overall transformation **12** → **30** since that chiral center is lost in the last step.

(24) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; pp 286–287.

proved to be identical (^{1}H NMR, IR, GLC) with the diether prepared by methylation of benzyloxy alcohol **14** (Scheme IV).

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. Routine IR spectra were taken on paraffin oil mulls with a Perkin-Elmer Infracord Model 137, while spectra required for the determination of OH stretching bands were taken in dried CCl_4 with a Perkin-Elmer Model 257 double-beam grating spectrophotometer using the 3110-cm^{-1} indene band for calibration. For all solution-phase IR spectra the concentration of the solution was 5×10^{-3} M or lower to prevent intermolecular association. ^{1}H NMR spectra were determined with a Bruker AC 200 spectrometer on $CDCl_3$ solutions except in the case of epoxides **1** and **2** whose spectra were recorded in C_6D_6. GLC analyses were performed on a Perkin-Elmer 8420 apparatus (FI detector): chlorohydrins **6–9** were analyzed as trimethylsilyl ether derivatives with a 30 m × 0.53 mm (i.d.) × 1 μm (film thickness) DB-17 fused silica column, column temperature 200 °C; order of increasing retention times was **8** < **6** < **7** < **9**. Hydroxy ethers **10–13** (column 220 °C), **14–17**, and ketones **24–28** (column 200 °C) were analyzed on a 30 m × 0.25 mm (i.d.) × 0.25 μm DB-WAX fused silica capillary column; the order of increasing retention times was **10** < **11**, **12** < **13**, **15** < **14**, and **16** < **17**. In all cases, the injector and detector temperatures were 250 °C and a 2 mL/min nitrogen flow rate was employed. Preparative and semipreparative TLC were performed on a 2- and 0.5-mm Merck F_{254} silica gel plates, respectively. Petroleum ether refers to the fraction with bp 40–70 °C. Solutions were dried with $MgSO_4$ or Na_2SO_4 and filtered prior to concentration with a rotary evaporator.

Olefin **3** was prepared as previously described.[10] Pure **22** and **23** were separated from commerically available 1,4-cyclohexanediol by saponification[16b] of the corresponding diacetates.[16a]

Reaction of Olefin 3 with *m*-CPBA. A solution of olefin **3**[10] (5.0 g, 26.9 mmol) in anhydrous CH_2Cl_2 (200 mL) was treated at 0 °C with 55% *m*-CPBA (9.26 g, 29.6 mmol). The reaction mixture was stirred 2 h at 0 °C and then 15 min at room temperature. Evaporation of the washed (10% aqueous Na_2SO_3, 5% aqueous NaOH, water) organic solution afforded a liquid residue (4.8 g) consisting of a 46:54 (GLC) mixture of the diastereoisomeric epoxides **1** and **2**, which were separated in the following ways: (a) The mixture of **1** and **2** (2.0 g) was flash chromatographed through a 20 cm × 4 cm silica gel column with 65:28:7 hexane/isopropyl ether/ethyl acetate as the eluant to give 0.45 g of pure *cis*-4-(benzyloxy)-1,2-epoxycyclohexane (**1**) and 0.53 g of pure *trans*-4-(benzyloxy)-1,2-epoxycyclohexane (**2**). Epoxide **2** eluted first. (b) The mixture of **1** and **2** (0.5 g) was subjected to preparative TLC with 9:1 hexane/ether as the eluant (elution was repeated several times). Extraction of the two main bands afforded pure **1** (70 mg) and pure **2** (90 mg).

***cis*-4-(Benzyloxy)-1,2-epoxycyclohexane (1):** ^{1}H NMR δ 7.30–7.06 (m, 5 H), 4.26 (s, 2 H), 2.92 (m, $J_{1,4}$ = 9.7 Hz, $J_{1,5}$ = 4.1 Hz, $J_{1,6}$ = 11.0 Hz, $J_{1,7}$ = 6.9 Hz, 1 H), 2.66 (m, 1 H), 2.65 (m, 1 H).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.30; H, 7.95.

***trans*-4-(Benzyloxy)-1,2-epoxycyclohexane (2):** ^{1}H NMR δ 7.28–7.09 (m, 5 H), 4.20 (d, *J* = 12.1 Hz, 1 H), 4.14 (d, *J* = 12.1 Hz, 1 H), 3.26 (m, bandwidth 21.0 Hz, 1 H), 2.84 (m, 2 H).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.25; H, 7.60.

Chlorohydroxylation of Olefin 3. Following the Sharpless procedure,[12] olefin **3** (8.4 g, 45.0 mmol) in anhydrous CH_2Cl_2 (660 mL) was allowed to react at −78 °C with 18 mL of a 3 M solution of TBHP in toluene and 5.9 mL (54.0 mmol) of $TiCl_4$. After 40 min the usual workup[12] afforded 13.8 g of a crude solid product consisting of chlorohydrins **7** (92%), **8** (6%), and **9** (2%). Recrystallization from petroleum ether afforded 8.2 g of pure **7**.

***c*-5-(Benzyloxy)-*t*-2-chloro-*r*-1-cyclohexanol (7):** mp 69–70 °C; IR, see Table III; ^{1}H NMR δ 7.34–7.25 (m, 5 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 4.52 (d, *J* = 11.8 Hz, 1 H), 3.94 (m, bandwidth 27.2 Hz, 1 H), 3.73–3.64 (m, 2 H).

Anal. Calcd for $C_{13}H_{17}ClO_2$: C, 64.86; H, 7.11. Found: C, 64.60; H, 7.31.

Base-Catalyzed Cyclization of 7. A stirred solution of chlorohydrin **7** (6.2 g, 25.8 mmol) in 250 mL of anhydrous benzene was treated with *t*-BuOK (2.88 g, 25.8 mmol) at room temperature for 1 h. A second 2.88-g portion of *t*-BuOK was added, and after 1 h, the reaction mixture was filtered and concentrated with a rotary evaporator to give 4.8 g of pure (GLC) epoxide **1**.

Chlorohydroxylation Reaction of Epoxide 1. Following the Sharpless procedure,[12] epoxide **1** (0.102 g, 0.5 mmol) in 11 mL of anhydrous CH_2Cl_2 was allowed to react at −78 °C with 0.2 mL of a 3 M solution of TBHP in toluene and 66 μL (0.6 mmol) of $TiCl_4$. Workup afforded a crude solid residue consisting exclusively of chlorohydrin **7** (GLC and ^{1}H NMR).

Reaction of Epoxide 1 with HCl. Method a. A solution of **1** (0.204 g, 1 mmol) in $CHCl_3$ (20 mL) was treated with 10 mL of 36% aqueous HCl, and the two-phase reaction mixture was vigorously stirred at room temperature for 1 h. The organic layer was separated, washed (water, saturated aqueous $NaHCO_3$, water), dried, filtered, and concentrated with a rotary evaporator to give 0.22 g of an oily residue consisting of an 85:15 mixture of chlorohydrins **6** and **7** (GLC), which was separated by semipreparative TLC using 7:3 hexane/ethyl acetate as the eluant. Extraction of the two main bands afforded 20 mg of **7** and 130 mg of *c*-4-(benzyloxy)-*t*-2-chloro-*r*-1-cyclohexanol (**6**).

Method b. A solution of **1** (0.102 g, 0.5 mmol) in 10 mL of anhydrous benzene was treated with anhydrous gaseous HCl for 1 h at room temperature. Evaporation of the washed (water, saturated aqueous $NaHCO_3$, water) organic solution afforded an oily product consisting of an 85:15 mixture of **6** and **7** (GLC).

***c*-4-(Benzyloxy)-*t*-2-chloro-*r*-1-cyclohexanol (6):** IR, see Table III; ^{1}H NMR δ 7.34–7.24 (m, 5 H), 4.51 (d, *J* = 11.9 Hz, 1 H), 4.46 (d, *J* = 11.9 Hz, 1 H), 4.13 (m, bandwidth 39.1 Hz, 1 H), 3.73 (m, bandwidth 22 Hz, 1 H), 3.57 (m, bandwidth 36.6 Hz, 1 H).

Anal. Calcd for $C_{13}H_{17}ClO_2$: C, 64.86; H, 7.11. Found: C, 64.55; H, 6.90.

Base-Catalyzed Cyclization of 6. Proceeding as described for the analogous reaction of chlorohydrin **7**, treatment of 100 mg of chlorohydrin **6** with *t*-BuOK afforded 80 mg of pure (GLC, ^{1}H NMR) epoxide **1**.

Reaction of Epoxide 2 with HCl. Method a. Following the procedure described above for the analogous reaction of epoxide **1**, treatment of 0.30 g of **2** in 100 mL of $CHCl_3$ with 10 mL of 36% aqueous HCl afforded a crude product consisting of a 95:5 mixture of chlorohydrins **8** and **9**. Preparative TLC with 7:3 hexane/ethyl acetate as the eluant and extraction of the most intense band afforded 0.21 g of pure **8**.

Method b. The reaction of a benzene solution of epoxide **2** with anhydrous HCl afforded a 95:5 mixture of **8** and **9** (GLC, see Table II).

***t*-5-(Benzyloxy)-*t*-2-chloro-*r*-1-cyclohexanol (8):** IR, see Table III; ^{1}H NMR δ 7.33–7.25 (m, 5 H), 4.50 (s, 2 H), 3.94 (m, bandwidth 33.0 Hz, 1 H), 3.82–3.70 (m, 2 H).

Anal. Calcd for $C_{13}H_{17}ClO_2$: C, 64.86; H, 7.11. Found: C, 64.60; H, 7.16.

Chlorohydroxylation Reaction of Epoxide 2. Proceeding as described for the corresponding reaction of epoxide **1**, treatment of 51 mg (0.25 mmol) of **2** in 6 mL of anhydrous CH_2Cl_2 with 0.10 mL of a 3 M solution of TBHP in toluene and 33 μL (0.3 mmol) of $TiCl_4$ at −78 °C, afforded a crude product that consisted of an 84:16 mixture of **8** and **9** (GLC, see Table II).

Base-Catalyzed Cyclization of 8 and an 8/9 Mixture. Proceeding as described above for the corresponding reaction of epoxide **7**, treatment of pure **8** or a 95:5 mixture of **8** and **9** with *t*-BuOK afforded epoxide **2** (GLC and ^{1}H NMR).

Reaction of Epoxide 1 with MeOK in Anhydrous MeOH. Epoxide **1** (0.102 g, 0.50 mmol) was added to 20 mL of a freshly prepared 2.5 M solution of MeOK in anhydrous MeOH, and the reaction mixture was allowed to reflux for 20 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with water. Evaporation of the dried ether extracts afforded 0.11 g of an oily residue consisting of a 93:7 mixture of hydroxy ethers **10** and **11**, which was separated by semipreparative TLC using 2:3 hexane/ethyl acetate as the eluant. Extraction of the most intense band afforded 70 mg of pure **10**.

***c*-4-(Benzyloxy)-*t*-2-methoxy-*r*-1-cyclohexanol (10):** IR, see Table III; ^{1}H NMR δ 7.36–7.26 (m, 5 H), 4.54 (d, *J* = 12.0 Hz,

1 H), 4.46 (d, J = 12 Hz, 1 H), 3.78 (m, bandwidth 17.0 Hz, 1 H), 3.55–3.31 (m, 2 H), 3.37 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.35; H, 8.49.

Oxidation of Compound 10. Hydroxy ether **10** (0.040 g, 0.17 mmol) in 5 mL of purified acetone was treated with 50 μL of an 8 M aqueous solution of CrO_3. After 2 min the reaction mixture was diluted with water and extracted with ether. The organic layer was washed (water, saturated aqueous $NaHCO_3$, water), dried, filtered, and concentrated with a rotary evaporator to give 35 mg of crude ketone **25**. The crude material was purified by semipreparative TLC with 4:1 hexane/ether as the eluant to give 20 mg of pure **25**.

***trans*-4-(Benzyloxy)-2-methoxycyclohexanone (25)**: IR 5.81 μm; ^{1}H NMR δ 7.39–7.26 (m, 5 H), 4.63 (d, J = 18.5 Hz, 1 H), 4.60 (d, J = 18.5 Hz, 1 H), 4.10 (m, 1 H), 3.97 (m, 1 H), 3.43 (s, 3 H).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.54; H, 7.98.

Methanolysis of Epoxide 1 in the Presence of $LiClO_4$. Epoxide **1** (0.204 g, 1.0 mmol) was added to 5 mL of saturated methanolic $LiClO_4$ (~17 M), and the mixture was allowed to reflux for 20 h. The reaction mixture was cooled, diluted with water, and extracted with ether, and the dried ether extracts were concentrated with a rotary evaporator to afford 0.21 g of a semisolid residue consisting of a 98:2 mixture of **11** and **10**. The crude product was separated by semipreparative TLC with 2:3 hexane/ethyl acetate as the eluant. Extraction of the most intense band gave 0.13 g of pure **11**.

***c*-5-(Benzyloxy)-*t*-2-methoxy-*r*-1-cyclohexanol (11)**: mp 65–66 °C (recrystallized from hexane); IR, see Table III; ^{1}H NMR δ 7.35–7.26 (m, 5 H), 4.55 (s, 2 H), 3.52 (m, 2 H), 3.40 (s, 3 H), 3.09 (m, bandwidth 25.0 Hz, 1 H).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.39; H, 8.30.

Oxidation of Compound 11. Proceeding as described above for the oxidation of hydroxy ether **10**, treatment of 40 mg of **11** with CrO_3 gave ketone **26**.

***trans*-5-(Benzyloxy)-2-methoxycyclohexanone (26)**: IR 5.73 μm; ^{1}H NMR δ 7.37–7.27 (m, 5 H), 4.54 (d, J = 10.9 Hz, 1 H), 4.51 (d, J = 10.9 Hz, 1 H), 3.81–3.67 (m, 2 H), 3.41 (s, 3 H).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.48; H, 8.05.

Methanolysis of Epoxide 2 in the Presence of $LiClO_4$. Epoxide **2** (0.204 g, 1.0 mmol) was added to 10 mL of a saturated methanolic solution of $LiClO_4$, and the reaction mixture was allowed to reflux for 20 h. Routine workup of the reaction mixture afforded 0.21 g of a crude product consisting of a 54:46 mixture of **12** and **13**. Semipreparative TLC with 2:2:1 hexane/isopropyl ether/ethyl acetate as the eluant afforded 70 mg of pure **12** and 60 mg of pure **13**.

***t*-5-(Benzyloxy)-*t*-2-methoxy-*r*-1-cyclohexanol (12)**: IR, see Table III; ^{1}H NMR δ 7.31–7.25 (m, 5 H), 4.49 (s, 2 H), 3.92–3.76 (m, 2 H), 3.40 (s, 3 H), 3.01 (m, bandwidth 32.0 Hz, 1 H).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.05; H, 8.69.

***t*-4-(Benzyloxy)-*t*-2-methoxy-*r*-1-cyclohexanol (13)**: IR, see Table III; ^{1}H NMR δ 7.36–7.32 (m, 5 H), 4.58 (d, J = 11.9 Hz, 1 H), 4.54 (d, J = 11.9 Hz, 1 H), 3.51–3.32 (m, 2 H), 3.40 (s, 3 H), 2.96 (m, bandwidth 34.0 Hz, 1 H).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.27; H, 8.88.

Oxidation of Compound 12. Oxidation of hydroxy ether **12** with CrO_3 in acetone afforded ketone **27**.

***cis*-5-(Benzyloxy)-2-methoxycyclohexanone (27)**: IR 5.84 μm; ^{1}H NMR δ 7.40–7.25 (m, 5 H), 4.54 (d, J = 11.9 Hz, 1 H), 4.46 (d, J = 11.9 Hz, 1 H), 3.94 (m, bandwidth 19.0 Hz, 1 H), 3.73 (m, bandwidth 15.2 Hz, 1 H), 3.44 (s, 3 H).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.55; 7.61.

Oxidation of Compound 13. Oxidation of hydroxy ether **13** with CrO_3 in acetone afforded ketone **28**.

***cis*-4-(Benzyloxy)-2-methoxycyclohexanone (28)**: IR 5.81 μm; ^{1}H NMR δ 7.44–7.14 (m, 5 H), 4.56 (d, J = 12.1 Hz, 1 H), 4.48 (d, J = 12.1 Hz, 1 H), 3.95 (m, bandwidth 22.7 Hz, 1 H), 3.73 (m, bandwidth 17.6 Hz, 1 H).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.98; H, 7.41.

***cis*-4-(Benzyloxy)-1-cyclohexanol (14).** Compound **22**[16] (2.9 g, 25.0 mmol) in 20 mL of anhydrous dioxane was treated with 0.57 g of sodium and 2.97 mL (25.0 mmol) of benzyl bromide.[10] The crude product (4.8 g) was distilled to give 3.1 g of pure **14**: bp 115–120 °C (0.15 Torr); IR, see Table III; ^{1}H NMR δ 7.35–7.25 (m, 5 H), 4.52 (s, 2 H), 3.73 (m, bandwidth 29.7 Hz, 1 H), 3.49 (m, bandwidth 24.2 Hz, 1 H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.54; H, 8.61.

***trans*-4-(Benzyloxy)-1-cyclohexanol (17).** Proceeding as described above for the preparation of compound **14**, diol **23**[16] (2.9 g, 25.0 mmol) was treated sodium and benzyl bromide in anhydrous dioxane to afford, after distillation, 2.9 g of **17**: bp 126–128 °C (0.1 Torr); IR, see Table III; ^{1}H NMR δ 7.35–7.24 (m, 5 H), 4.51 (s, 2 H), 3.57 (m, bandwidth 32.7 Hz, 1 H), 3.34 (m, bandwidth 32.7 Hz, 1 H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.79; H, 8.57.

Dehalogenation of Chlorohydrin 6. Chlorohydrin **6** (0.25 g, 1.1 mmol) in 5 mL of anhydrous benzene was treated at room temperature with 0.66 mL (2.64 mmol) of Bu_3SnH for 20 h. The reaction mixture was diluted with water and extracted with ether. Concentration of the dried ether extracts afforded a crude product that was purified by semipreparative TLC with 2:3 hexane/ethyl acetate as the eluant to give 0.15 g of pure **14** (GLC and ^{1}H NMR).

Dehalogenation of Chlorohydrin 7. Proceeding as described above, dehalogenation of chlorohydrin **7** afforded crude **15**. Semipreparative TLC afforded pure material.

***cis*-3-(Benzyloxy)-1-cyclohexanol (15)**: IR, see Table III; ^{1}H NMR δ 7.36–7.26 (m, 5 H), 4.58 (d, J = 11.8 Hz, 1 H), 4.50 (m, d, J = 11.8 Hz, 1 H), 3.74 (m, bandwidth 28.0 Hz, 1 H), 3.56 (m, bandwidth 22.0 Hz, 1 H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.37; H, 8.72.

Dehalogenation of a Mixture of Chlorohydrins 8 and 9. An 84:16 mixture of chlorohydrins **8** and **9** (50 mg) in 5 mL of anhydrous benzene was allowed to reflux with 0.20 mL of Bu_3SnH for 20 h. Standard workup of the reaction mixture afforded an oily residue consisting of an 85:15 mixture of **16** and **17**.

LAH Reduction of Epoxide 1. Epoxide **1** (0.102 g, 0.50 mmol) was added to a stirred suspension of 100 mg of $LiAlH_4$ in 10 mL of anhydrous ether (or pentane) at room temperature. After 2 h the excess hydride was destroyed by addition of water and 10% aqueous NaOH. Concentration of the dried ether solution with a rotary evaporator gave 100 mg of an oily residue consisting of an 98:2 mixture of **15** and **14** (GLC), which was separated by semipreparative TLC with 2:3 hexane/ethyl acetate as the eluant to afford pure **15** (GLC and ^{1}H NMR).

LAH Reduction of Epoxide 1 in the Presence of 12-Crown-4. A suspension of $LiAlH_4$ (78 mg, 2.0 mmol) in 5 mL of anhydrous ether (or pentane) was treated with 0.36 mL (2.2 mmol) of 12-crown-4, and the mixture was allowed to react for 20 h at room temperature. Epoxide **1** (0.102 g, 1.0 mmol) was added, and the reaction mixture was stirred for 5 h at room temperature. Routine workup of the reaction mixtures afforded a crude oily product consisting of **14** and **15** (Table I, entries 21 and 22).

LAH Reduction of Epoxide 2. The reaction of epoxide **2** (0.102 g, 0.50 mmol) with 100 mg of $LiAlH_4$ in 10 mL of anhydrous ether (or pentane) afforded 0.10 g of a crude product consisting of a 97:3 mixture of **16** and **17**. Semipreparative TLC with 2:3 hexane/ethyl acetate as the eluant afforded 60 mg of pure **16**.

***trans*-3-(Benzyloxy)-1-cyclohexanol (16)**: IR, see Table III; ^{1}H NMR δ 7.35–7.24 (m, 5 H), 4.54 (d, J = 12.0 Hz, 1 H), 4.49 (d, J = 12.0 Hz, 1 H), 4.08 (m, bandwidth 27.0 Hz, 1 H), 3.80 (m, bandwidth 32.7 Hz, 1 H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.74; H, 8.57.

When epoxide **2** was allowed to react with $LiAlH_4$/12-crown-4 in ether (or pentane), a 97:3 mixture of **16** and **17** was obtained.

Oxidation of Compounds 15 and 16. Oxidation of 60 mg of hydroxy ether **16** with CrO_3 in acetone afforded 55 mg of crude **24**. Semipreparative TLC of the crude material with 4:1 hexane/ether as the eluant gave 20 mg of pure ketone **24**. Oxidation

of **15** afforded the same ketone, **24** (GLC and ^1H NMR).

3-(Benzyloxy)cyclohexanone (24): IR 5.81 μm; ^1H NMR δ 7.60–7.43 (m, 5 H), 4.63 (s, 2 H), 3.95 (m, 1 H).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.16; H, 7.64.

***cis*-1-(Benzyloxy)-4-methoxycyclohexane (30).** To a suspension of 90 mg (3.0 mmol) of NaH (80 wt % in mineral oil) in 6 mL of anhydrous THF at 50–55 °C was added 0.17 g (0.9 mmol) of hydroxy ether **14**. Methyl iodide (0.26 mL, 4.1 mmol) was then added, and the reaction mixture was allowed to stir for 12 h at 60 °C. After cooling, ether and water were added to the reaction mixture and the organic layer was separated and washed with additional portions of water. Evaporation of the dried ether solution afforded 0.18 g of a crude product. Semipreparative TLC of the crude material with 7:2:1 hexane/isopropyl ether/ethyl acetate afforded 0.14 g of pure **30**: ^1H NMR δ 7.34–7.24 (m, 5 H), 4.52 (s, 2 H), 3.50–3.39 (m, 1 H), 3.31–3.24 (m, 1 H), 3.32 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.14. Found: C, 76.63; H, 9.40.

Conversion of Compound 12 to Compound 30. A solution of hydroxy ether **12** (0.39 g, 1.65 mmol) in 35 mL of anhydrous $CHCl_3$ was treated at 0 °C with $SOCl_2$ (0.36 mL, 4.4 mmol). After 30 min at 0 °C the reaction mixture was refluxed for 5 h and then cooled to room temperature. Evaporation of the washed (water, saturated aqueous $NaHCO_3$, water), dried, and filtered organic solution gave 0.36 g of an oily residue consisting of a 1:1 mixture of **12** and chloride **29**. The mixture was separated by preparative TLC with 5:3:2 hexane/isopropyl ether/ethyl acetate as the eluant. Extraction of the fastest moving band afforded 0.12 g of chloride **29**:[23] ^1H NMR δ 7.34–7.25 (m, 5 H), 4.50 (s, 2 H), 4.25–4.14 (m, bandwidth 20.9 Hz, 1 H), 3.74–3.64 (m, bandwidth 19.2 Hz, 1 H), 3.27–3.17 (m, bandwidth 19.3 Hz, 1 H).

Anal. Calcd for $C_{14}H_{19}ClO_2$: C, 66.00; H, 7.51. Found: C, 66.25; H, 7.30.

A solution of 100 mg of **29** in 4 mL of anhydrous benzene was treated with 0.50 g of Bu_3SnH at 60 °C for 24 h. Evaporation of the washed (water) organic solution afforded a crude product consisting mostly of diether **30**. Semipreparative TLC of the crude material using 7:2:1 hexane/isopropyl ether/ethyl acetate as the eluant and extraction of the slowest moving band afforded a pure diether that was fully consistent (IR, ^1H NMR, GLC) with compound **30**.

H^+-Catalyzed Methanolysis of Epoxides 1 and 2. General Procedure. A solution of the epoxide (0.051 g, 0.25 mmol) in 5 mL of a 0.2 N (or 10^{-3} N) solution of H_2SO_4 in anhydrous MeOH was stirred at room temperature for 2 h. Dilution of the reaction mixture with water, extraction with ether, and evaporation of the washed (water, saturated aqueous $NaHCO_3$, water) and dried ether extracts gave a crude product that was analyzed by GLC (see Tables I and II). The solvolysis products were shown to be completely stable under the reaction conditions employed.

Li^+-Catalyzed Methanolysis of Epoxides 1 and 2. General Procedure. The epoxide (0.051 g, 0.25 mmol) was added to 5 mL of a solution of $LiClO_4$ in anhydrous MeOH (see Tables I and II). After the indicated reaction time at reflux temperature, dilution of the reaction mixture with water, extraction with ether, and evaporation of the dried ether layer gave a crude product that was analyzed by GLC (see Tables I and II).

The ring-opening reactions of **1** and **2** in a 1.7 M solution of methanolic $NaClO_4$ were performed under the same experimental conditions as described above for the Li^+-catalyzed solvolysis.

Base-Catalyzed Methanolysis of Epoxides 1 and 2. General Procedure. The epoxide (0.051 g, 0.25 mmol) in 2 mL of anhydrous MeOH was added to a stirred methanolic solution of freshly prepared MeOLi, MeONa, or MeOK (see Tables I and II). The reaction mixture was allowed to reflux (or in some cases to stand at room temperature) for the indicated reaction time. Dilution of the reaction mixture with water, extraction with ether, and evaporation of the dried ether extracts gave a crude product that was analyzed by GLC (see Tables I and II).

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