supported in part by Grant CA 40984 from the NIH.

Registry No. **6**, 123-32-0; **7**, 108-50-9; **8**, 120809-55-4; **9**, 108905-63-1; **10a**, 138335-69-0; **10b**, 108905-64-2; **10c**, 138335-70-3; **10d**, 138335-71-4; **11a**, 138335-72-5; **11b**, 108905-65-3; **11c**, 138335-72-5; **11d**, 138488-57-0; **12a**, 138335-74-7; **12b**, 108905-66-4; (*E*)-**12c**, 138353-27-2; (*Z*)-**12c**, 138335-75-8; (*E*)-**12d**, 138335-76-9; (*Z*)-**12d**, 138335-77-0; **13a**, 138335-78-1; **13b**, 108905-68-6; **13c**, 138353-28-3; **13d**, 138335-79-2; **14a** (isomer 1), 138335-80-5; **14a** (isomer 2), 138335-81-6; **14b** (isomer 1), 138335-82-7; **14b** (isomer 2), 138335-83-8; **14c** (isomer 1), 138335-84-9; **14c** (isomer 2), 138335-85-0; **14d** (isomer 1), 138335-86-1; **14d** (isomer 2), 138335-87-2; **15a**, 138335-88-3; (*E*)-**15b**, 138335-89-4; (*Z*)-**15b**, 138335-90-7; (*E*)-**15c**, 138335-91-8; (*Z*)-**15c**, 138335-92-9; (*E*)-**15d**, 138335-93-0; (*Z*)-**15d**, 138335-94-1; **18**, 138335-95-2; **19**, 138407-31-5; **20**, 138335-96-3; **21**, 138335-97-4; **22a**, 138335-98-5; **22b**, 108905-70-0; **22c**, 138353-29-4; **22d**, 138335-99-6; **23a**, 138336-00-2; (*E*)-**23b**, 138336-01-3; (*Z*)-**23b**, 138336-02-4; (*E*)-**23c**, 138336-03-5; (*Z*)-**23c**, 138336-04-6; (*E*)-**23d**, 138336-05-7; (*Z*)-**23d**, 138336-06-8; **24a**, 138336-07-9; **24b**, 138336-08-0; **24c**, 138336-09-1; **24d**, 138336-10-4; **25a**, 138336-11-5; **25b**, 108905-67-5; **25c**, 138336-12-6; **25d**, 138336-13-7; **26a**, 138336-14-8; **26b**, 138336-15-9; **26c**, 138432-63-0; **26d**, 138336-16-0; **27a**, 138336-17-1; **27b**, 138336-18-2; **27c**, 138336-19-3; **27d**, 138336-20-6; **28a**, 138336-21-7; **28b**, 138336-22-8; **28c**, 138336-23-9; **28d**, 138336-24-0; **28e**, 138336-25-1; **28f**, 138336-26-2; **29**, 138336-27-3; **30**, 138336-28-4; **31**, 138336-29-5; **32**, 138336-30-8; **33**, 138336-31-9; **34**, 138336-32-0; **35**, 77500-04-0; **36**, 78411-56-0; **37**, 103139-94-2; **38**, 115609-71-7; **39**, 95896-78-9; **40**, 97389-17-8; CH_3COOBu-*t*, 540-88-5; $PhCH_2NH_2$, 100-46-9.

Supplementary Material Available: Spectroscopic data and experimental procedures for the preparation of compounds **10a**, **11a**, **12a**, **13a**, **14a**, **15a**, **23c**, **25a**, **25c**, **26a**, **27c**, **29**, **31**, **32**, and **34** from their respective 2-bromo tricycles and ^1H and/or ^{13}C NMR spectra of compounds **13b**, **14d**, (*Z*)-**15d**, **22b**, (*Z*)-**23b**, **24b**, **25b**, **25c**, **28a–f**, and **29–40** (60 pages). Ordering information is given on any current masthead page.

Regiochemical Control of the Ring-Opening of 1,2-Epoxides by Means of Chelating Processes. 2.[1] Synthesis and Reactions of the *cis*- and *trans*-Oxides of 4-[(Benzyloxy)methyl]cyclohexene, 3-Cyclohexenemethanol, and Methyl 3-Cyclohexenecarboxylate

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Received March 8, 1991 (Revised Manuscript Received July 8, 1991)

The synthesis of the diastereoisomeric epoxides *cis*-**1b–d** and *trans*-**2b–d** and the products of their ring-opening by various nucleophiles are described. The results of the ring-openings of the *trans*-epoxides **2b–d** can be rationalized by combining stereoelectronic and conformational arguments. However, the regioselectivity of the ring-openings of the *cis*-epoxides **1b–d** can, in principle, be influenced by the chelation of a metal ion by the oxygen atom of the epoxy group and that of the substituent on the 4-position. The results of the reactions of the *cis*-epoxides **1b–d** indicate that, to some degree, chelation is indeed a factor. How important a factor it is is dependent both on the reaction conditions and on the concentration and nature of the metal ion. In the ring-openings of the *cis*-epoxides **1b** and **1d**, chelation seems to be a larger factor than it is in the ring-openings of *cis*-epoxide **1c**. However, in no case is chelation as large a factor as it was in the ring-openings of the *cis*-epoxide **1a**, which was studied earlier. On the other hand, the autocatalyzed methanolysis, under neutral conditions, of epoxy acid **1e**, followed by CH_2N_2 methylation of the crude product, afforded a mixture of the two regioisomeric hydroxy ethers in which the *C-2-type compound* predominates. This result suggests that intramolecular hydrogen bonding may determine the reactive conformation of **1e**.

Introduction

The ring-opening of oxiranes, when carried out under conditions of stereo- and regiochemical control, can be profitably utilized to synthesize complex molecules like organic natural products.

In an earlier study[1,2] aimed at developing methods whereby the regioselectivity of the ring-opening of epoxides by nucleophiles could be controlled by means of chelation by a metal ion, we found that *cis*-4-(benzyloxy)cyclohexene oxide (**1a**), under conditions favorable for the chelation of a metal ion by the oxygen atoms of the epoxy and benzyloxy groups, preferentially yielded *C-1-type compounds*.[3] In contrast, under conditions where such chelation was not possible, *C-2-type compounds*[3] were produced preferentially (Scheme I).[1,2] In an effort to further define the scope of this strategy for regiocontrol, we have evaluated reactions of cyclohexene oxides **1b–d** and **2b–d** with heteronucleophiles under several types of reaction conditions designed to probe for regioalternating selectivity.[1,2] Of additional interest was the possibility that epoxides **1b–d** and **2b–d** could be used in a stereoselective synthesis of the C_{23}–C_{34} cyclohexyl moiety of the potent immunosuppressive agent FK-506,[4] the subject of intense pharmaceutical interest.[5]

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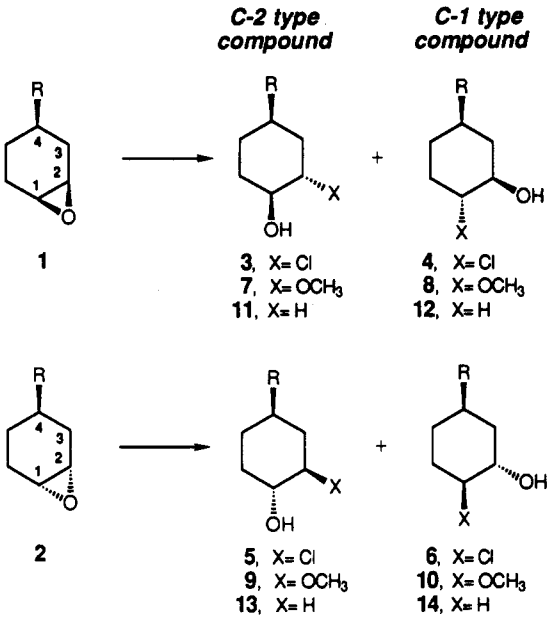
(1) For the preceding paper in this series, see: Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1990**, *55*, 4265.
(2) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *Tetrahedron Lett.* **1989**, *30*, 6563.
(3) The terms *C-1-* and *C-2-type compound* refer to the site at which the nucleophile attacks, i.e., at C-1 or C-2 of the oxirane ring of **1** and **2**. See the numbering scheme shown in Scheme I.
(4) (a) Tanaka, H.; Kuroda, A; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031 and references therein. (b) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajimina, T.; Goto, T.; Okuara, M.; Kohsaka, M.; Aoki, H.; Ochiai, T. *J. Antibiot.* **1987**, *40*, 1256.

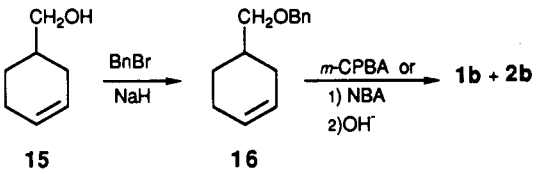
0022-3263/92/1957-1405$03.00/0

Scheme I[a]



[a] **a**, R = OBn; **b**, R = CH_2OBn; **c**, R = CH_2OH; **d**, R = $COOCH_3$; **e**, R = COOH.

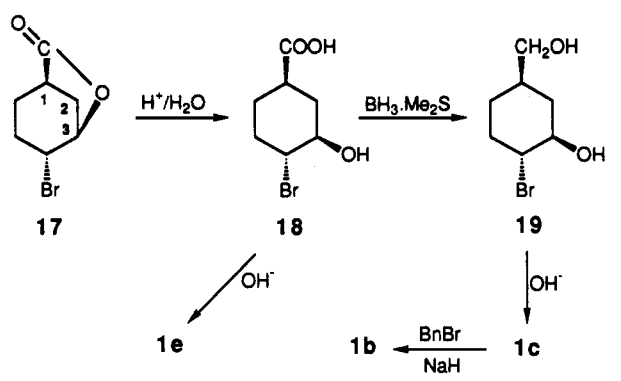
Scheme II



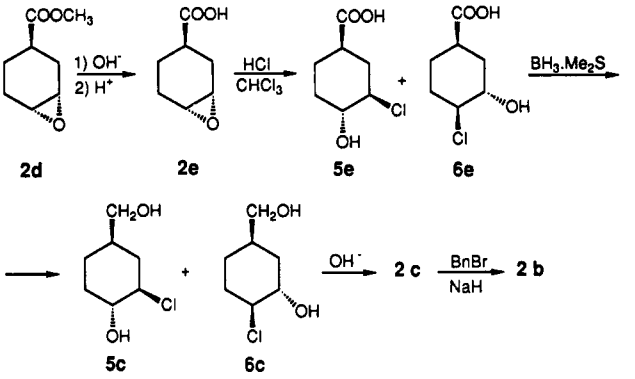
Results and Discussion

The first attempts to prepare epoxides **1b** and **2b** utilized alkene **16**. Unfortunately, both direct epoxidation of **16** by *m*-chloroperoxybenzoic acid and base-catalyzed cyclization of the bromohydrins formed by treatment of **16** with *N*-bromoacetamide (NBA) in aqueous THF gave a nearly equimolar mixture of **1b** and **2b**[6] (Scheme II). Moreover, no convenient preparative-scale method for separating the diastereoisomers could be found. An attempt to stereoselectivity synthesize at least one of the desired compounds by the $TiCl_4$-mediated chlorohydroxylation[7] of olefin **16** and ring-closure of the mixture of chlorohydrins so formed (**3b–6b**) also failed. Whereas such treatment of 4-(benzyloxy)cyclohexene gave a 92:8 mixtures of **1a** and **2a**,[1] a 57:43 mixture of **1b** and **2b** was obtained from **16**. Furthermore, it proved difficult to separate the intermediate chlorohydrins (**3b**:**4b**:**5b**:**6b** = 6:51:1:42). However, O-trimethylsilylation of the mixture of chlorohydrins and subsequent flash chromatography of the mixture of trimethylsilyl ethers so formed afforded the *O*-TMS derivatives (**4b-OTMS** and **6b-OTMS**) of the two most abundant chlorohydrins. Desilylation and ring-closure of these afforded the pure epoxides *cis*-**1b** and *trans*-**2b**, respectively. Epoxide **1b** could also be stereospecifically synthesized from the bromo lactone **17**[8] (Scheme III). Epoxide **2b** was independently synthesized from the previously described epoxide **2d**[8] (Scheme IV). Synthesis of the epoxides **1c**, **1e**, and **2c** are also shown (Schemes III and IV, respectively).

Scheme III



Scheme IV



Epoxides **1b–d** and **2b–d** were exposed to various reaction conditions which earlier had proved to be useful in providing evidence of the participation of chelated intermediates in the ring-openings of epoxides **1a** and **2a**.[1,9] Whereas epoxide **1b** reacted with anhydrous HCl to give a 91:9 mixture of chlorohydrins **3b** and **4b**, the $TiCl_4$-mediated ring-opening of **1b**, performed under the conditions of the Sharpless chlorohydroxylation of alkenes,[7] resulted in a significantly lower **3b**:**4b** ratio (compare entries 1 and 2, R = CH_2OBu, Table I). It is noteworthy that the ratio of **3b** to **4b** (64:36) in the mixture of products from the reaction of **1b** with $TiCl_4$ was also significantly different from that (6:51) observed in the mixture of products from the Sharpless chlorohydroxylation of alkene **16** (vide supra), even though **1b** is presumably an intermediate in the latter reaction. The reaction of **1b** with hydride ions, i.e., with $LiAlH_4$ in pentane, both in the presence and absence of 12-crown-4, gave a 9:1 mixture of the alcohols **11b** and **12b** (entries 15 and 16, R = CH_2OBn, Table I). The protic acid- and metal salt-catalyzed methanolysis of **1b** afforded mixtures of the regioisomeric methoxy alcohols **7b** and **8b**. Under protic acid catalysis, or at low salt concentrations in the case of metal salt catalysis, the product ratio, **7b** to **8b**, was ≥9:1 (entries 3, 4, 9–14, R = CH_2OBn, Table I). Only when a high concentration of the metal salt ($LiClO_4$) was present (entry 8, R = CH_2OBn, Table I) was a significant increase in the proportion of the methoxy alcohol

(5) See, for example: (a) Schreiber, S. L.; Smith, D. B. *J. Org. Chem.* **1989**, *54*, 9. (b) Linde, R. G., II; Egberston, M.; Coleman, R. S.; Jones, A. B.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2771. (c) Maier, M. E.; Schöffling, B. *Tetrahedron Lett.* **1990**, *31*, 3007. (d) Kocienski, P.; Stocks, M.; Donald, D.; Perry, M. *Synlett* **1990**, 38. (e) Gu, R.-L.; Sih, C. J. *Tetrahedron Lett.* **1990**, *31*, 3287.

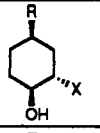
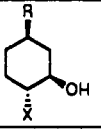
(6) The stereochemical outcome of the epoxidation of **16** by *m*-CPBA was not unexpected in light of the results of the epoxidation of an analogue of **16**, the unsaturated alcohol **15**. See: McIntosh, J. M.; Leavitt, R. K. *J. Org. Chem.* **1984**, *49*, 3407.

(7) Klunder, J. M.; Caron, M.; Uchiyama, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 912.

(8) Bellucci, G.; Marioni, F.; Marsili, A. *Tetrahedron* **1972**, *28*, 3393.

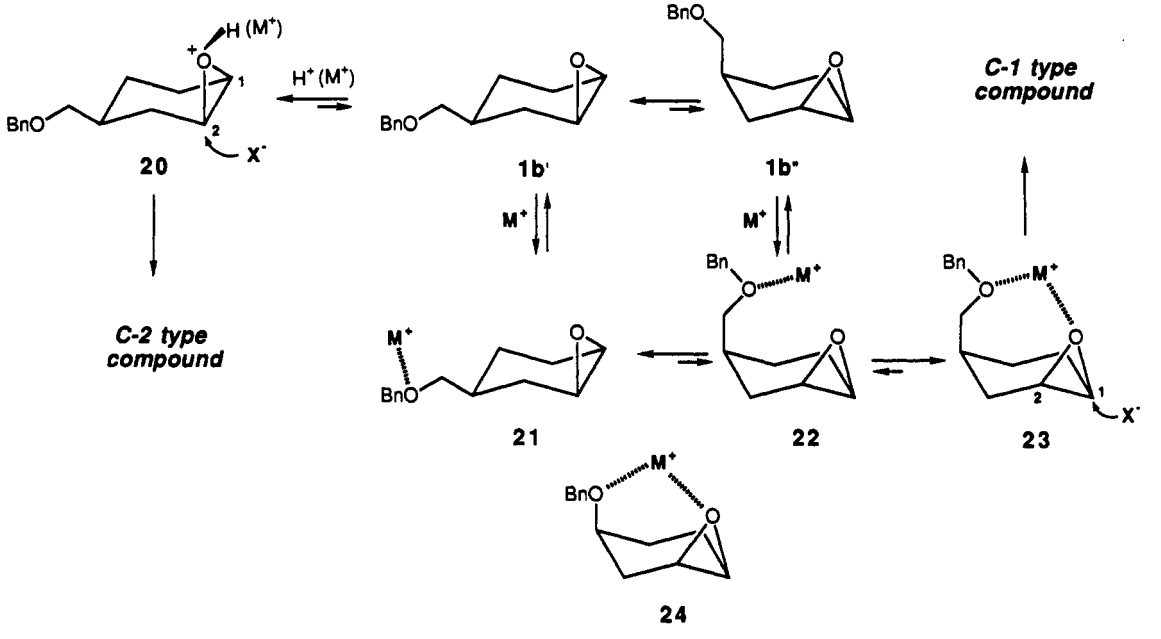
(9) Epoxide **1d**, which bears a COOMe group, appeared to be a promising candidate in view of the high syn stereoselectivity observed in the Sharpless chlorohydroxylation of the parent olefin.[7]

Table I. Regioselectivity (%) of the Ring-Openings of the *cis*-Epoxides 1b–d

									
entry	reagents	reactn condtns[a]	reactn time	R = CH_2OBn[b]	R = CH_2OH[c]	R = $COOCH_3$[d]	R = CH_2OBn[b]	R = CH_2OH[c]	R = $COOCH_3$[d]
1	$HCl/CHCl_3$	A	30 min	91[e]	94[f]	83[g]	9[h]	6[i]	17[j]
2	$TiCl_4$/TBHP	B	40 min	64[e]	80[f]	19[g]	36[h]	20[i]	81[j]
3	H^+/MeOH	C	30 min	96[k]	90[l]	80[m]	4[n]	10[o]	20[p]
4	$LiClO_4$/MeOH	D	20 h	91[k]	88[l]	76[m]	9[n]	12[o]	24[p]
5		E	20 h	89[k]			11[n]		
6		F	20 h	76[k]		74[m]	24[n]		26[p]
7		G	20 h	74[k]	88[l]	72[m]	26[n]	12[o]	28[p]
8		H	20 h	73[k]	88[l]	68[m]	27[n]	12[o]	32[p]
9	$Zn(Tf)_2$[q]/MeOH	D	20 h	94[k]	90[l]	75[m]	6[n]	10[o]	25[p]
10	$Mg(ClO_4)_2$/MeOH	D	20 h	94[k]	90[l]	75[m]	6[n]	10[o]	25[p]
11		I	20 h	96[k]	90[l]	72[m]	4[n]	10[o]	28[p]
12	$NaClO_4$/MeOH	D	20 h	91[k]	90[l]	78[m]	9[n]	10[o]	22[p]
13		L	20 h	93[k]	90[l]	78[m]	7[n]	10[o]	22[p]
14	$KClO_4$/MeOH	M	20 h	96[k]	90[l]	79[m]	4[n]	10[o]	21[p]
15	$LiAlH_4$/pentane	N	3 h	90[r]	79[s]		10[t]	21[u]	
16	$LiAlH_4$/crown pentane	O	3 h	89[r]	79[s]		11[t]	21[u]	

[a] A: anhydrous HCl in $CHCl_3$; B, CH_2Cl_2 solution, −78 °C (in the case of **1d** the reaction mixture was allowed to stand for 1.5 h at −20 °C); C, 0.2 N methanolic H_2SO_4, rt; D, 1.7 M methanolic metal salt, reflux; E, 3.4 M methanolic $LiClO_4$, reflux; F, 6.8 M methanolic $LiClO_4$ reflux; G, 13.6 M methanolic $LiClO_4$, reflux; H, ~17 M methanolic $LiClO_4$, reflux; I, saturated methanolic $Mg(ClO_4)_2$ (2.3 M), reflux; L, saturated methanolic $NaClO_4$ (3 M), reflux; M, saturated methanolic $KClO_4$ (0.1 M), reflux; N, epoxide: $LiAlH_4$ = 1:4, rt; O, a 1:1 mixture of $LiAlH_4$ and 12-crown-4 in pentane was stirred for 24 h at rt and then the epoxide was added (epoxide:$LiAlH_4$ = 1:4). [b] From epoxide **1b**. [c] From epoxide **1c**. [d] From epoxide **1d**. [e] Chlorohydrin **3b**. [f] Chlorohydrin **3c**. [g] Chlorohydrin **3d**. [h] Chlorohydrin **4b**. [i] Chlorohydrin **4c**. [j] Chlorohydrin **4d**. [k] Methoxy alcohol **7b**. [l] Methoxy alcohol **7c**. [m] Methoxy alcohol **7d**. [n] Methoxy alcohol **8b**. [o] Methoxy alcohol **8c**. [p] Methoxy alcohol **8d**. [q] Tf = triflate. [r] Alcohol **11b**. [s] Diol **11c**. [t] Alcohol **12b**. [u] Diol **12c**.

Scheme V



8b observed. Similar behavior was seen in the reactions of the *cis*-epoxide **1d** with HCl and with methanol (Table I).[10] These results provided some evidence that the ring-openings of **1b** and **1d** do involve, at least to some extent, chelated intermediates. However, the degree to which chelation is a factor is much less than it was in the ring-openings of the *cis*-epoxide **1a**, studied earlier.[1] When chelation is not a factor, e.g., protic acid-catalyzed methanolysis, epoxide **1b** is believed to react almost exclusively in the form of its more stable conformer, **1b'**, in which the CH_2OBn group occupies an equatorial position. Trans-diaxial attack[11] of the nucleophile on the protonated epoxide **20**, would be expected to give a C-2-type compound,[3] which, in fact, is formed. When chelation is a factor, i.e., under metal salt catalysis, a small but significant increase in the proportion of the alternative product, the C-1-type compound,[3] is observed in some cases (entries 5–8, R = CH_2OBn, Table I). It is reasonable to assume that such a product arose by way of the sequence **1b'** → **21** → **22** →

(10) The low regioselectivity that was observed when the ring-opening of the *cis*-epoxy ester **1d** was performed under conditions where chelation was not a factor is consistent with a previous hypothesis[8] that the unfavorable inductive effect exerted by the COOMe group may partially direct the nucleophile to attack the C-1 oxirane carbon (Scheme I).

(11) (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. *Abstract of Papers*, 12th International Congress of Pure and Applied Chemistry, 1951, p 409.

Scheme VI

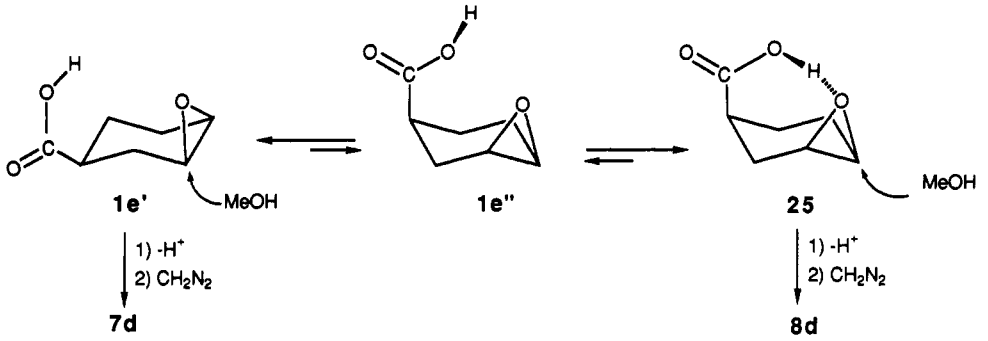


Table II. Regioselectivity (%) of the Ring-Opening of the *trans*-Epoxides 2b–d

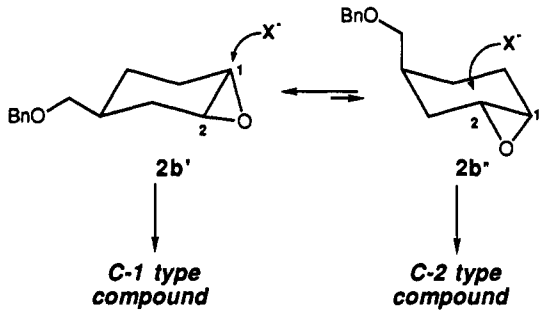
				R =	R =	R =	R =	R =	R =
entry	reagents	reactn condtns[a]	reactn time	CH_2OBn[b]	CH_2OH[c]	$COOCH_3$[d]	CH_2OBn[b]	CH_2OH[c]	$COOCH_3$[d]
1	$HCl/CHCl_3$	A	30 min	97[e]	97[f]	94[g]	3[h]	3[i]	6[j]
2	$TiCl_4$/TBHP	B	40 min	97[e]	97[f]	90[g]	3[h]	3[i]	10[j]
3	H^+/MeOH	C	30 min	98[k]	96[l]	98[m]	2[n]	4[o]	4[p]
4	$LiClO_4$/MeOH	D	20 h	94[k]	95[l]	96[m]	6[n]	5[o]	4[p]
5	$LiAlH_4$/pentane	N	3 h	85[q]			15[r]		
6	$LiAlH_4$/crown pentane	O	3 h	85[q]			15[r]		

[a] See footnote *a*, Table I. [b] From epoxide **2b**. [c] From epoxide **2c**. [d] From epoxide **2d**. [e] Chlorohydrin **6b**. [f] Chlorohydrin **6c**. [g] Chlorohydrin **6d**. [h] Chlorohydrin **5b**. [i] Chlorohydrin **5c**. [j] Chlorohydrin **5d**. [k] Methoxy alcohol **10b**. [l] Methoxy alcohol **10c**. [m] Methoxy alcohol **10d**. [n] Methoxy alcohol **9b**. [o] Methoxy alcohol **9c**. [p] Methoxy alcohol **9d**. [q] Alcohol **14b**. [r] Alcohol **13b**.

23 or the sequence **1b'** → **1b"** → **22** → **23** (Scheme V). The ring-opening of **1d** probably involves similar intermediates. However, these are not shown for the sake of simplicity. The increase in the proportion of the C-1-type compound depends on the reaction conditions and on the concentration and the nature of the metal salt.[1] In contrast, the results of the ring-opening of the epoxide **1c** provided little evidence that the reaction involved the intermediacy of chelated species (Table I). That epoxides **1b–d** showed a low tendency, compared with **1a**,[1] to react by way of chelated intermediates (**22–23**, Scheme V) may be due to one or both the following: (i) the greater bulk of the R group of **1b–d** compared with that of the R group of **1a** (Scheme I), (ii) the greater ring strain in the seven-membered cyclic bidentate structure **23** derived from **1b–d** compared with that of the more stable six-membered cyclic bidentate structure **24** derived from **1a** (Scheme V). However, it is not easy to explain why epoxides **1b–d** showed different tendencies to react by way of chelated intermediates. On the other hand, the methanolysis of **1e** under neutral conditions (neat MeOH, rt, 4 days) afforded, after methylation of the crude product with diazomethane, a 16:84 mixture of **7d** and **8d** in 90% yield. This result suggests that the most abundant reactive conformer of **1e** is stabilized by intramolecular hydrogen bonding, which makes possible the trans-axial nucleophilic attack at C-1 (Scheme VI).

The various ring-openings of the *trans*-epoxide **2b** afforded mixtures of the chlorohydrins **5b** and **6b**, the methoxy alcohols **9b** and **10b**, and the alcohols **13b** and **14b** in which the C-1-type compound predominated. The ratio of the C-1-type compound to the C-2-type compound was essentially unaffected by the reaction conditions (Table II). Because **2b** cannot assume a conformation that allows bidentate metal ion chelation, it must react by way of a simple trans-diaxial ring-opening[11] of its most stable conformer, **2b'** (Scheme VII).

Scheme VII



Structures and Configurations

The relative configurations of the diastereoisomeric epoxides **1b** and **2b** were established by stereoselectively synthesizing **1b** from the bromo lactone **17**.[8] The synthesis is stereoselective because, in the transformations **17** → **18** → **19** → **1c** → **1b** (Scheme III), the configuration of C-3 does not change. The relative configurations of the pairs of alcohols **11b** and **12b** and **13b** and **14b**, which were obtained by the $LiAlH_4$ reduction of the epoxides **1b** and **2b**, respectively, must surely correspond to those of the starting epoxides, cis in the cases of **11b** and **12b** and trans in the cases of **13b** and **14b**. The structures of alcohols **11–14b** were also unequivocally determined, as follows: hydroboration–oxidation of olefin **16** yielded a mixture of the alcohols **11–14b**, oxidation of which gave an almost equimolar mixture of the two ketones **26** and **27**. The regiochemistry of **27** was established by similarly transforming the olefin **29**,[12] an isomer of **16**, to a mixture of **27** and **28** (Scheme VIII). The $LiAlH_4$ reduction of **26** yielded a mixture of **11b** and **13b**, whereas similar reduc-

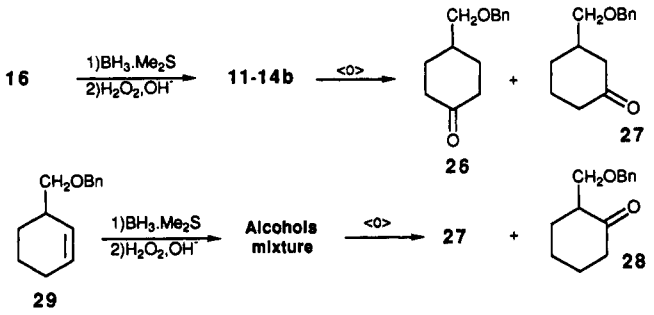
(12) Pineschi, M. Tesi di Laurea, Facoltà di Farmacia, Università di Pisa, 1990.

Table III. Spectroscopic Data for the Chlorohydrins 3,4,6b–d, the Methoxy Alcohols 7,8,10b–d, and the Alcohols 11–14b

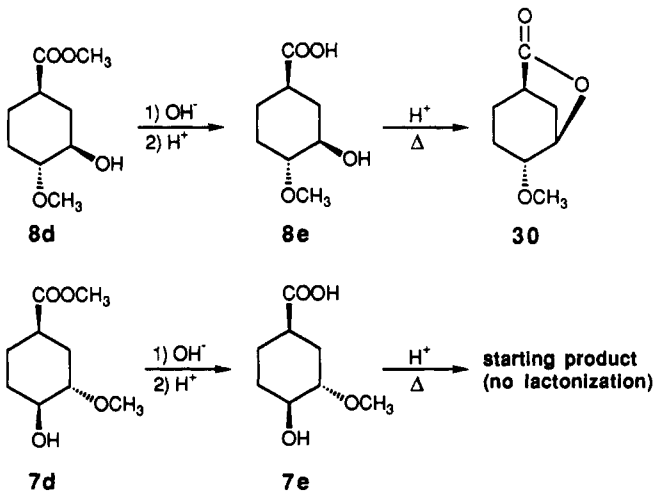
	^{1}H NMR:[a] δ ($W_{1/2}$, Hz)			IR (CCl_4) (OH stretching) cm^{-1}		
compd	H_a	H_b	H_c	OH···O	OH···Cl	OH_{free}
3b		3.73 (23.9)	3.95 (21.8)[b]		3590[e]	3625[f]
4b		3.73	c[b]		3590[f]	
6b		3.88	c[b]		3590[e]	3622[f]
3c		3.88 (16.3)	4.09 (16.8)[b]		3595[g]	3642[f]
4c		3.67	c[b]		3590	3642
6c		3.96	c[b]		3594[g]	3638[f,h]
3d	2.63 (12.0)	3.58 (22.0)	3.99 (22.5)[b]		3592[f]	3624[e]
4d	2.46 (27.0)	3.60 (29.0)	3.73 (27.0)[b]		3592	
6d	2.81 (10.5)	3.83	c[b]		3598[f]	3630[g]
7b		3.60 (20.0)	3.14 (20.0)[d]	3594		3626
8b		3.48 (29.0)	2.95 (29.0)[d]	3594		
10b		3.54 (18.7)	3.08 (17.6)[d]	3594		3620
7c		3.74 (17.3)	3.30 (17.3)[d]	3594[e]		3638[f,h]
8c		3.46 (24.2)	2.96 (24.2)[d]	3588		3640
10c		3.76 (19.8)	3.12 (19.8)[d]	3590[e]		3638[f]
7d	2.72 (12.2)	3.56 (22.0)	3.25 (22.0)[d]	3598[f]		3628[e]
8d	2.39 (27.0)	3.47 (27.0)	2.98 (27.0)[d]	3594		
10d	2.72 (11.0)	3.70 (21.0)	3.05 (21.0)[d]	3594		3620
11b		3.98 (9.6)				3626
12b		3.60 (21.6)				3622
13b		3.55 (22.0)				3622
14b		4.10 (9.0)				3626

[a] All of the spectra are of $CDCl_3$ solutions with the exception of those of the compounds of the c series (**3**, **4**, **6–8**, **10c**) which are of D_2O solutions. All the signals are multiplets: H_a = C*H*COOMe; H_b = C*H*OH; H_c = C*H*X. [b] X = Cl. [c] The signal due to H_b overlaps that due to H_c. [d] X = OCH_3. [e] Medium band. [f] Strong band. [g] Weak band. [h] Broad band.

Scheme VIII



Scheme IX



tion of **27** gave a mixture of **12b** and **14b**. As for the chlorohydrins **3b**, **4b**, and **6b**,[13] that the hydroxyl group and the chlorine atom were, as expected, trans to each other was confirmed by cyclizing the chlorohydrins, under basic catalysis, to the epoxides **1b** (from **3b** and **4b**) and **2b** (from **6b**). The relative structures of the pairs of chlorohydrins **3b** and **4b** and **5b**[13] and **6b** were established by reductively dechlorinating **3b** and **6b** by treatment with Bu_3SnH to the alcohols **11b** and **14b**, respectively (Scheme I). The structures of the chlorohydrins **3c**, **4c**, and **6c** were established by comparing their properties with those of the products of the catalytic debenzylation of the corresponding O-benzylated chlorohydrins **3b**, **4b**, and **6b**, respectively. At the same time, that the chlorohydrins **3c**, **4c**, and **6c** were formed by the BH_3·Me_2S reduction of the chlorohydrins **3d**, **4d**, and **6d**, respectively, established the structures of the latter (Scheme I).

That the methoxy and hydroxy groups of the hydroxy ethers **7b–d**, **8b–d**, **9b–d**,[13] and **10b–d** are trans to each other was deduced from the general rule[14] that the acid-catalyzed ring-opening of simple cycloaliphatic epoxides usually yields products of overall anti addition.[14] This is consistent with the stereoselectivity shown in the reactions of the parent epoxides **1,2a–d** with HCl. The relative regiochemistry of the members of the pairs **7b**, **8b–7d**, **8d** and **9b,10b–9d,10d** were established from the results of the reactions shown in Scheme IX. As for the pair **9d**[13] and **10d**, their relative structures were inferred from the results of the following reactions. Thus, the $LiAlH_4$ reduction of the mixture of **9d** and **10d** (in which **10d** is the major component) from the methanolysis of the epoxide **2d** (entry 3, R = $COOCH_3$, Table II) yielded a mixture of the corresponding alcohols **9c** and **10c** (Scheme I) in which the ratio of **9c** to **10c** was almost identical to that of **9d** to **10d** in the mixture of parent esters. GC analysis of the mixture showed that the minor component was identical with authentic **9c**,[5] which was prepared by an alternative route.[12] That the $LiAlH_4$ reduction of pure **7d**, **8d**, and **10d** gave **7c**, **8c**, and **10c**, respectively, established the structures of the latter compounds, whereas the catalytic O-debenzylation of **7b**, **8b**, and **10b** gave **7c**, **8c**, and **10c**, respectively, made it possible to infer the structures of the former (Scheme I). The ^{1}H NMR spectra and the IR spectra of

(13) The chlorohydrins **5b–d** and methoxy alcohols **9b** and **9d** were not isolated in pure form because only very small amounts were present in the reaction mixtures from the ring-openings of the corresponding epoxides **2** (Table II). However, their presence was confirmed by GC and ^{1}H NMR analysis of the crude reaction mixtures.

(14) (a) Buchanan, J. G.; Sable, H. Z. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley Interscience: New York, 1972; Vol 1, p 1. (b) Barili, P. L.; Bellucci, G.; Macchia, B.; Macchia, F.; Parmigiani, G. *Gazz. Chim. Ital.* **1971**, *101*, 300.

dilute CCl_4 solutions[1] of all the compounds isolated were entirely consistent with the assigned structures and configurations (Table III).

Experimental Section

For general information, see ref 1. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions (unless otherwise indicated) were recorded at 200 and 50 MHz, respectively. The crude products from the ring-openings of the epoxy acids **1e** and **2e** were analyzed only after they were treated with excess CH_2N_2/Et_2O. In the case of the epoxides **1c** and **2c**, the reaction mixtures were diluted or washed or both diluted and washed with saturated aqueous NaCl. Epoxides **1d** and **2d** were prepared as previously described.[8]

4-[(Benzyloxy)methyl]cyclohexene (16). Commercially available 3-cyclohexene-1-methanol (4.72 g, 42.1 mmol) in anhydrous THF (30 mL) was O-alkylated by treatment with BnBr (0.88 g, 5.19 mmol) in the presence of NaH (3.79 g of an 80% suspension in mineral oil, 0.12 mol).[15] Distillation of the crude liquid product (9.97 g) afforded pure **16**: liquid; bp 90–92 °C (0.3 Torr); ^1H NMR δ 7.46 (m, 5 H), 5.80 (s, 2 H), 4.58 (s, 2 H), 3.50–3.30 (m, 2 H); ^{13}C NMR δ 139.3, 128.9, 128.1, 128.0, 127.6, 126.6, 75.9, 73.6, 34.5, 29.2, 26.3, 25.2. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.96. Found: C, 83.20; H, 9.10.

Chlorohydroxylation of Olefin 16. The method of Sharpless[7] was applied. Thus, a solution of olefin **16** (6.0 g, 29.7 mmol) in anhydrous CH_2Cl_2 (600 mL) was allowed to react at −78 °C with *tert*-butyl hydroperoxide (11.8 mL of a 3 M solution in toluene) and a solution of $TiCl_4$ (3.9 mL, 35.5 mmol) in anhydrous CH_2Cl_2 (10 mL). After 45 min, the usual workup[7] afforded a liquid residue (6.5 g) which by GC analysis contained chlorohydrins **3b** (6%), **4b** (51%), **5b**[13] (1%), and **6b** (42%). A solution of the mixture of chlorohydrins **3–6b** (5.5 g) in anhydrous pyridine (28 mL) was treated at 0 °C with Me_3SiCl (39 mL). The mixture was warmed to rt and was kept there for 12 h. The mixture was then diluted with petroleum ether and was washed (water, cold 10% aqueous HCl, saturated aqueous $NaHCO_3$, water). Concentration afforded a liquid residue (7.0 g) which contained the *O*-TMS derivatives (**3–6b-OTMS**) of the chlorohydrins **3–6b**. Flash chromatography of 2.5-g portions of the residue on silica gel (4 × 20 cm column; hexane/AcOEt, 95:5) gave pure **4b-OTMS** (0.95 g) and pure **6b-OTMS** (0.65 g). A solution of **4b-OTMS** (0.95 g) in 8:2 EtOH/H_2O (10 mL) was treated with 10% aqueous HCl (0.3 mL). After 30 min, the solution was diluted with water and was extracted with Et_2O. Concentration of the extracts afforded crude ***c*-5-[(benzyloxy)methyl]-*t*-2-chloro-*r*-1-cyclohexanol (4b)** (0.70 g): a liquid; IR, see Table III; ^1H NMR δ 7.36–7.26 (m, 5 H), 4.49 (s, 2 H), 3.31 (d, 2 H, J = 6.0 Hz) and the data in Table III; ^{13}C NMR δ 129.1, 128.3, 128.2, 75.5, 75.2, 73.8, 68.1, 37.2, 37.1, 34.9, 30.4, 29.8. Anal. Calcd for $C_{14}H_{19}ClO_2$: C, 66.00; H, 7.52. Found: C, 66.15; H, 7.69.

Similar treatment of **6b-OTMS** (0.65 g) afforded pure ***t*-5-[(benzyloxy)methyl]-*c*-2-chloro-*r*-1-cyclohexanol (6b)** (0.43 g): a liquid; IR, see Table III; ^1H NMR δ 7.37–7.26 (m, 5 H), 4.51 (s, 2 H), 3.38 (d, 2 H, J = 6.6 Hz); ^{13}C NMR δ 139.1, 129.1, 128.2, 73.7, 71.5, 64.4, 33.1, 33.0, 29.8, 25.5. Anal. Calcd for $C_{14}H_{19}O_2Cl$: C, 66.00; H, 7.52. Found: $C_{14}H_{19}ClO_2$: 66.10; H, 7.47.

***t*-4-Bromo-3-hydroxy-*r*-1-cyclohexanecarboxylic Acid (18).** A solution of the bromo lactone **17**[8] (14.9 g, 70.7 mmol) in 9:1 THF/H_2O (150 mL) was treated with 36% aqueous HCl (0.5 mL). The mixture was refluxed for 1 h. Evaporation of the solvent afforded a solid residue (14.4 g) which consisted of nearly pure **18**: mp 162–163 °C (benzene); IR 1715 cm^{-1}; ^1H NMR (CD_3OD) δ 3.80 (m, 1 H, $W_{1/2}$ = 25.7 Hz), 3.60 (m, 1 H, $W_{1/2}$ = 25.7 Hz); ^{13}C NMR (CD_3OD) δ 177.6, 75.1, 58.9, 49.0, 42.5, 36.6, 30.4. Anal. Calcd for $C_7H_{11}BrO_3$: C, 37.69; H, 4.97. Found: C, 37.50; H, 5.01.

***t*-4-Bromo-*c*-3-hydroxy-*r*-1-cyclohexanemethanol (19).** A solution of the acid **18** (7.70 g, 36.3 mmol) in anhydrous THF (350 mL) was slowly treated with a solution of BH_3·Me_2S complex (30 mL of a 10 M solution in Me_2S) in anhydrous THF (60 mL). The mixture was stirred for 48 h at rt. Evaporation of the solvent yielded a solid residue which consisted of nearly pure **19** (7.4 g): mp 114–116 °C (benzene); IR 3367 cm^{-1}; ^1H NMR (D_2O) δ 4.15 (ddd, 1 H, J = 4.4, 10.2, and 11.9 Hz), 3.93 (ddd, 1 H, J = 4.5, 10.0, and 10.7 Hz), 3.66 (d, 2 H, J = 6.0 Hz); ^{13}C NMR δ 71.6, 66.2, 61.3, 35.0, 33.2, 27.6, 23.7. Anal. Calcd for $C_7H_{13}BrO_2$: C, 40.21; H, 6.26. Found: C, 40.35; H, 6.37.

***c*-3,4-Epoxy-*r*-1-cyclohexanemethanol (1c).** Bromo diol **19** (2 g, 9.6 mmol) in *i*-PrOH (30 mL) was treated with 1 N aqueous NaOH (9.6 mL) at rt. The mixture was then diluted with Et_2O, washed with saturated aqueous NaCl, and concentrated to afford pure **1c** (1.0 g):[6] a liquid; IR 3378 cm^{-1}; ^1H NMR δ 3.36 (m, 2 H), 3.18 (d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 68.3, 53.4, 52.1, 35.7, 27.7, 25.2, 21.6. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.73; H, 9.54.

***c*-4-[(Benzyloxy)methyl]-*r*-1,2-epoxycyclohexane (1b).** (a) A literature procedure[15] was followed. Thus, treating a solution of the epoxy alcohol **1c** (5.2 g, 40.6 mmol) in anhydrous THF (55 mL) with BnBr (7.16 g, 41.9 mmol) in the presence of NaH (2.26 g of an 80% dispersion in mineral oil, 85.3 mmol) gave crude **1b** (8.05 g). Fast filtration through a silica gel column (petroleum ether/Et_2O 9:1) afforded pure **1b**: a liquid; ^1H NMR (C_6D_6) δ 7.29–7.09 (m, 5 H), 4.25 (s, 2 H), 2.97 (d, 2 H, J = 5.5 Hz), 2.80 (m, 2 H); ^{13}C NMR δ 139.0, 128.8, 128.0, 75.7, 73.5, 53.1, 51.9, 33.7, 28.1, 25.2, 21.9. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.15; H, 8.45.

(b) A literature procedure[1] was followed. Thus, treating a solution of chlorohydrin **4b** (1.04 g, 4.1 mmol) in anhydrous benzene (60 mL) with *t*-BuOK in two portions (0.23 g, 2.63 mmol, each) gave pure epoxide **1b** (0.80 g).

***t*-3,4-Epoxy-*r*-1-cyclohexanecarboxylic Acid (2e).** *trans*-Epoxide **2d**[8] (0.88 g, 5.64 mmol) in THF (65 mL) was treated with 1 M ethanolic KOH (20 mL). The mixture was allowed to stand for 12 h at rt. Titration to a phenolphthalein end point with 1 N aqueous H_2SO_4, extraction with $CHCl_3$, and concentration of the washed (saturated NaCl) extract afforded pure **2e** (0.75 g): a liquid; IR, 1706 cm^{-1}; ^1H NMR δ 3.26 (m, 2 H); ^{13}C NMR δ 180.1, 53.0, 52.2, 39.0, 31.6, 27.4, 23.1. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.39; H, 7.25.

***t*-3,4-Epoxy-*r*-1-cyclohexanemethanol (2c).** Gaseous HCl was gently bubbled through a solution of **2e** (0.73 g, 5.28 mmol) in $CHCl_3$ (50 mL) for 30 min at rt. Evaporation of the solvent yielded a solid residue (0.90 g) which consisted of a 90:10 mixture of the chlorohydrins **6e** and **5e**. The residue was dissolved in anhydrous THF (50 mL) and the solution was treated at 0 °C with BH_3·Me_2S complex (5 mL of a 10 M solution in Me_2S). After the mixture had stood for 12 h at rt, MeOH (10 mL) was slowly added. Evaporation of the solvent afforded a liquid residue (0.81 g), a mixture of chlorohydrins **5c** and **6c**. The residue was dissolved in *i*-PrOH (25 mL). The solution was titrated to a phenolphthalein end point with 1 N aqueous NaOH. Dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) organic extract afforded epoxide **2c** (0.51 g): a liquid; IR 3378 cm^{-1}; ^1H NMR δ 3.45 (m, 2 H), 3.18 (m, 2 H). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.90; H, 9.67.

***t*-4-[(Benzyloxy)methyl]-*r*-1,2-epoxycyclohexane (2b).** (a) In the manner previously described for **1c**, treating a solution of **2c** (0.50 g, 3.90 mmol) in anhydrous THF (10 mL) with NaH (0.23 g of an 80% dispersion in mineral oil, 7.8 mmol) and BnBr (0.73 g, 4.29 mmol) afforded pure **2b**: a liquid; ^1H NMR δ 7.29–7.13 (m, 5 H), 4.26 (s, 2 H), 3.00 and 3.01 (2 d, 1 H each, J = 6.0 Hz), 2.88–2.72 (m, 2 H); ^{13}C NMR δ 139.2, 128.9, 128.1, 75.4, 73.5, 53.4, 52.5, 30.7, 26.9, 24.6, 23.7. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.19; H, 8.45.

(b) In the manner previously described for **4b**, treating a solution of chlorohydrin **6b** (0.52 g, 2.05 mmol) in anhydrous benzene (30 mL) with *t*-BuOK (0.29 g × 2, 2.63 mmol × 2) afforded pure epoxide **2b** (0.40 g).

Reaction of Olefin 16 with *m*-CPBA. A literature procedure[1] was followed. A solution of **16** (0.20 g, 1.0 mmol) in anhydrous CH_2Cl_2 (8 mL) was treated at 0 °C with 55% *m*-CPBA (0.312 g, 1.0 mmol) to give a liquid residue, a 55:45 mixture of **1b** and **2b** (by ^1H NMR analysis).[6]

Reaction of Olefin 16 with NBA. A literature procedure[16] was followed. A solution of **16** (1.0 g, 4.95 mmol) in 3:1 THF/H_2O (60 mL) was treated with a solution of NBA (0.76 g, 5.5 mmol) in THF (10 mL). The usual workup[16] afforded a liquid residue (1.47 g), a mixture of bromohydrins (IR 2.97 μm). The residue was dissolved in anhydrous benzene (30 mL). The solution was

(15) Balsamo, A.; Crotti, P.; Macchia, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 3065.

treated with *t*-BuOK.[1] Evaporation of the washed (water) benzene solution afforded a liquid residue (0.85 g), a 56:44 mixture of **1b** and **2b**.

***c*-3,4-Epoxy-*r*-1-cyclohexanecarboxylic Acid (1e).** A solution of the bromo acid **18** (0.55 g, 2.5 mmol) in *i*-PrOH (10 mL) was titrated to a phenolphthalein end point over 3.5 h with 0.965 M aqueous NaOH (5.2 mL). Aqueous 1 N H_2SO_4 (2.5 mL) was then added. The solution was saturated with solid NaCl and was extracted with Et_2O. Evaporation of the solvent afforded pure **1e**: a liquid; IR 1706 cm^{-1}; ^1H NMR δ 3.27 (m, 2 H); ^{13}C NMR δ 180.8, 52.5, 51.4, 38.0, 26.4, 24.2, 21.3. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.35; H, 7.31.

Reaction of Epoxides 1b–e with HCl in $CHCl_3$. The following procedure is typical. The epoxide (0.30 g) was added to gaseous HCl-saturated $CHCl_3$ (20 mL). After 30 min at rt, the mixture was washed with saturated aqueous NaCl and was concentrated. GC analysis of the residue gave the results shown in Table I.

The crude product from the reaction of **1b** (0.32 g) was transformed by standard procedures into a mixture of the corresponding trimethylsilyl ethers **3b-OTMS** and **4b-OTMS** (0.35 g). Preparative TLC (petroleum ether/AcOEt 95:5) of the mixture gave pure **3b-OTMS** (0.21 g). This was deprotected, as described above for **4b-OTMS**, to yield pure ***t*-2-chloro-*c*-4-[(benzyloxy)methyl]-*r*-1-cyclohexanol (3b)**: a liquid; IR, see Table III; ^1H NMR δ 7.37–7.26 (m, 5 H), 4.51 (s, 2 H), 3.38 (d, 2 H, J = 6.6 Hz), and the data in Table III; ^{13}C NMR δ 139.1, 129.1, 128.3, 128.2, 73.8, 73.2, 63.1, 34.8, 33.8, 28.4, 24.8. Anal. Calcd for $C_{14}H_{19}ClO_2$: C, 66.00; H, 7.52. Found: C, 66.15; H, 7.63.

The crude solid product (0.35 g) from the reaction of **1c** was recrystallized (benzene) to give pure ***t*-2-chloro-*c*-4-(hydroxymethyl)-*r*-1-cyclohexanol (3c)**: a solid, mp 108–109 °C; IR, see Table III; ^1H NMR (D_2O) δ 3.51 (d, 2 H, J = 6.5 Hz), and the data in Table III; ^{13}C NMR δ 71.7, 66.5, 61.4, 35.3, 33.4, 27.8, 23.9. Anal. Calcd for $C_7H_{13}ClO_2$: C, 51.07; H, 7.96. Found: C, 51.24; H, 8.15.

Preparative TLC (Et_2O/petroleum ether 3:2) of the crude liquid product (0.31 g) from the reaction of **1d** gave pure **methyl *t*-3-chloro-*c*-4-hydroxy-*r*-1-cyclohexanecarboxylate (3d)**: a liquid; IR, see Table III; ^1H NMR δ 3.64 (s, 3 H), and the data in Table III; ^{13}C NMR δ 175.7, 74.1, 63.4, 52.6, 39.8, 34.8, 29.5, 25.3. Anal. Calcd for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80. Found: C, 50.05; H, 9.00.

Chlorohydroxylation Reaction of Epoxides 1b–d. General Procedure. The method of Sharpless[7] was applied. A solution of the epoxide (1 mmol) in anhydrous CH_2Cl_2 (22 mL) was treated, successively, at −78 °C with TBHP (0.4 mL of a 3 M solution in toluene) and $TiCl_4$ (0.13 mL, 1.2 mmol). After 40 min, the usual workup[7] afforded a crude product, which was analyzed by GC. The results are shown in Table I. In the case of **1d** the reaction mixture was allowed to stand for 1.5 h at −20 °C before workup.

The solid residue (0.19 g) from the reaction of **1d**[7] was recrystallized (hexane) to give pure **methyl *t*-4-chloro-*c*-3-hydroxy-*r*-1-cyclohexanecarboxylate (4d)**: a solid, mp 98–99 °C; IR, see Table III; ^1H NMR δ 3.69 (s, 3 H), and the data in Table III. Anal. Calcd for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80. Found: C, 49.65; H, 6.71.

Reaction of Epoxides 2b–d with HCl in $CHCl_3$. Epoxides **2b–d** (0.10 g) were treated with gaseous HCl-saturated $CHCl_3$ (10 mL) in the manner described above for epoxides **1b–d**. GC analysis of the crude products gave the results shown in Table II.

Semipreparative TLC (petroleum ether/Et_2O 3:2) of the crude product (0.12 g) from the reaction of **2d** gave pure **methyl *c*-4-chloro-*t*-3-hydroxy-*r*-1-cyclohexanecarboxylate (6d)**: a solid, mp 64–65 °C; IR, see Table III; ^1H NMR δ 3.71 (s, 3 H), and the data in Table III; ^{13}C NMR δ 175.6, 71.9, 64.7, 52.6, 36.8, 33.1, 31.0, 26.0 Anal. Calcd for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80. Found: C, 50.05; H, 6.95.

Chlorohydroxylation Reaction of Epoxides 2b–d. Treatment of epoxides **2b–d** (1 mmol) in the manner described above afforded mixtures of corresponding crude chlorohydrins. GC analysis gave the results shown in Table II.

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H^+-Catalyzed Methanolysis of Epoxides 1b–e. General Procedure. A solution of the epoxide (0.30 g) in 0.2 N methanolic solution H_2SO_4 (30 mL) was stirred at rt for 1 h. Dilution with water, extraction with Et_2O, and evaporation of the washed (saturated $NaHCO_3$, water) and dried extracts gave a crude product. GC analysis gave the results shown in Table I. (In the case of **1c**, the extract was washed only with saturated aqueous NaCl.)

Preparative TLC (petroleum ether/*i*-Pr_2O/AcOEt 2:2:1) of the crude product (0.30 g) from the reaction of **1b** gave pure ***c*-4-[(benzyloxy)methyl]-*t*-2-methoxy-*r*-1-cyclohexanol (7b)**: a liquid; IR, see Table III; ^1H NMR δ 7.36–7.26 (m, 5 H), 4.52 (d, 2 H, J = 1.3 Hz), 3.36 (s, 3 H), and the data in Table III; ^{13}C NMR δ 139.1, 128.9, 128.1, 80.7, 73.7, 73.5, 71.5, 57.0, 33.2, 29.1, 28.2, 24.6. Anal. Calcd for $C_{15}H_{22}O_3$: C, 72.16; H, 8.86. Found: C, 72.44; H, 8.75.

Preparative TLC (petroleum ether/Et_2O 1:1) of the crude product (0.28 g) from the reaction of **1d** gave pure **methyl *c*-4-hydroxy-*t*-3-methoxy-*r*-1-cyclohexanecarboxylate (7d)**: a liquid; IR, see Table III; ^1H NMR δ 3.70 (s, 3 H), 3.41 (s, 3 H), and the data in Table III; ^{13}C NMR δ 175.8, 81.0, 71.3, 57.1, 52.3, 38.8, 28.8, 24.7. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.56. Found: C, 57.61; H, 8.35.

Methanolysis of Epoxides 1b–d in the Presence of $LiClO_4$. General Procedure. The epoxide (0.30 g) was added to saturated methanolic $LiClO_4$ (4 mL of a ~17 M solution). The mixture was refluxed for 20 h. The usual workup[1] afforded the crude product. GC analysis gave the results shown in Table I.

Preparative TLC (petroleum ether/*i*-Pr_2O/AcOEt 5:3:2) of the crude product (0.28 g) from the reaction of **1b** (Table I) gave pure **7b** (0.11 g) and ***c*-5-[(benzyloxy)methyl]-*t*-2-methoxy-*r*-1-cyclohexanol (8b)** (0.035 g). **8b**: a liquid; IR, see Table III; ^1H NMR δ 7.39–7.26 (m, 5 H), 4.45 (s, 2 H), 3.40 (s, 3 H), 3.31 (d, 2 H, J = 6.2 Hz); ^{13}C NMR δ 130.2, 129.0, 128.2, 127.6, 85.7, 75.6, 73.9, 57.2, 37.0, 36.0, 28.3, 28.0. Anal. Calcd for $C_{15}H_{22}O_3$: C, 72.16; H, 8.86. Found: C, 72.31; H, 8.94.

Preparative TLC (petroleum ether/Et_2O 1:1) of the crude product (0.29 g) from the reaction of **1d** gave pure **7d** (0.12 g) and **methyl *c*-3-hydroxy-*t*-4-methoxy-*r*-1-cyclohexanecarboxylate (8d)**. **8d**: a liquid; IR, see Table III; ^1H NMR δ 3.68 (s, 3 H), 3.41 (s, 3 H) and the data in Table III; ^{13}C NMR δ 175.7, 84.7, 73.3, 66.5, 57.2, 52.5, 34.8, 27.7, 27.4. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.56. Found: C, 57.23; H, 8.45.

Similarly, the methanolysis of epoxides **1b–d** in the presence of varying amounts of $LiClO_4$ and also of other metal salts gave the results shown in Table I (entries 4–14 and footnote *a*).

H^+-Catalyzed Methanolysis of Epoxides 2b–d. The same general procedure as that used for **1b–d** was followed.

Preparative TLC (petroleum ether/*i*-Pr_2O/AcOEt 5:3:2) of the crude product (0.29 g) from the reaction of **2b** gave pure ***t*-5-[(benzyloxy)methyl]-*t*-2-methoxy-*r*-1-cyclohexanol (10b)**: a liquid; IR, see Table III; ^1H NMR δ 7.35–7.26 (m, 5 H), 4.50 (s, 2 H), 3.37 (s, 3 H), and the data in Table III. Anal. Calcd for $C_{15}H_{22}O_3$: C, 76.16; H, 8.86. Found: C, 76.31; H, 8.62.

Preparative TLC (petroleum ether/Et_2O 1:1) of the crude product (0.28 g) from the reaction of **2d** gave pure **methyl *t*-3-hydroxy-*c*-4-methoxy-*r*-1-cyclohexanecarboxylate (10d)**: a liquid; IR, see Table III; ^1H NMR δ 3.68 (s, 3 H), 3.38 (s, 3 H) and the data in Table III; ^{13}C NMR δ 175.8, 82.9, 70.0, 66.5, 57.0, 52.4, 36.8, 29.0, 25.2. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.56. Found: C, 57.64; H, 8.44.

Methanolysis of Epoxides 2b–d in the Presence of $LiClO_4$. The same general procedure as that used for **1b–d** was followed. The results are shown in Table II.

Methanolysis of Epoxy Acid 1e. A solution of epoxy acid **1e** (0.30 g) in anhydrous MeOH (20 mL) was allowed to stand for 4 days at rt. Evaporation of the solvent afforded a liquid residue (0.36 g) which, after dissolution in Et_2O, was methylated by treatment with excess of CH_2N_2. Evaporation of the solvent afforded a residue (0.38 g, 90% yield) which consisted of an 84:16 mixture of **8d** and **7d** (by GC analysis).

$LiAlH_4$ Reduction of Epoxides 1b–c. The following procedure is typical. The epoxide (1.5 mmol) was added to a stirred suspension of $LiAlH_4$ (0.22 g, 6.0 mmol) in pentane (30 mL) at rt. After 2 h, the usual workup yielded a crude product, which was analyzed by GC (Table I).

Preparative TLC (petroleum ether/Et_2O 3:2) of the crude product (0.27 g) from the reaction of **1b** gave pure ***cis*-4-[(benzyloxy)methyl]-1-cyclohexanol (11b)**: a liquid; IR, see Table III; ^1H NMR δ 7.36–7.26 (m, 5 H), 4.51 (s, 2 H), 3.32 (d, 2 H, J = 6.5 Hz), and the data in Table III; ^{13}C NMR δ 139.0, 129.0, 128.2, 128.1, 75.7, 73.7, 67.7, 37.4, 32.6, 24.6. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.51; H, 9.24.

$LiAlH_4$ Reduction of Epoxides 2b,c. The reduction of epoxides **2b,c** in the manner described above afforded crude products, which were analyzed by GC (Table II).

Preparative TLC (petroleum ether/Et_2O 3:2) of the crude product (0.29 g) from the reaction of **2b** gave pure ***trans*-3-[(benzyloxy)methyl]-1-cyclohexanol (14b)**: a liquid; IR, see Table III; ^1H NMR δ 7.36–7.26 (m, 5 H), 4.50 (s, 2 H), 3.30 (d, 2 H, J = 6.3 Hz). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.54; H, 8.97.

$LiAlH_4$ Reduction of Epoxides 1b,c and 2b,c in the Presence of 12-Crown-4. The reduction of epoxides **1b,c** and **2b,c** in the manner described previously[1] afforded crude products, which were analyzed by GC. The results are shown in Tables I and II, respectively.

Acknowledgment. We gratefully acknowledge partial financial support of this work by the Consiglio Nazionale delle Ricerche, the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Roma, Italy), NATO Collaborative Science Grant RG 86/0147, and NSF Grant INT-8816449.

Registry No. **1b**, 137946-34-0; **1c**, 91108-45-1; **1d**, 1630-02-0; **1e**, 76704-24-0; **2b**, 138124-71-7; **2c**, 91108-46-2; **2d**, 1630-01-9; **2e**, 76704-23-9; **3b**, 137946-36-2; **3b**-OTMS, 137946-45-3; **3c**, 137946-38-4; **3d**, 94904-76-4; **4b**, 137946-37-3; **4b**-OTMS, 137946-44-2; **4c**, 137946-39-5; **4d**, 94904-78-6; **5c**, 138008-20-5; **5e**, 138008-19-2; **6b**, 138258-88-5; **6b**-OTMS, 138008-16-9; **6c**, 138008-10-3; **6d**, 94904-77-5; **6e**, 76644-34-3; **7b**, 138124-72-8; **7c**, 138230-39-4; **7d**, 138124-73-9; **7e**, 138008-22-7; **8b**, 138008-11-4; **8c**, 138008-13-6; **8d**, 138008-14-7; **8e**, 138008-21-6; **10b**, 138008-12-5; **10c**, 138124-74-0; **10d**, 138008-15-8; **11b**, 137946-40-8; **12b**, 137946-41-9; **13b**, 137946-42-0; **14b**, 137946-43-1; **15**, 1679-51-2; **16**, 137946-35-1; **17**, 19914-91-1; **18**, 138008-17-0; **19**, 138008-18-1; **26**, 132452-43-8; **27**, 108743-93-7; **28**, 76886-31-2; **29**, 137946-46-4; **30**, 137946-47-5.

Supplementary Material Available: Synthesis of and spectroscopic and analytical data for compounds **4c**, **6–8c**, **10c**, **7e**, **8e**, **12b**, **13b**, **26–28**, and **30** (6 pages). Ordering information is given on any current masthead page.

Stereoselective Acetalization of 1,3-Alkanediols by *l*-Menthone: Application to the Resolution of Racemic 1,3-Alkanediols and to the Determination of the Absolute Configuration of Enantiomeric 1,3-Alkanediols

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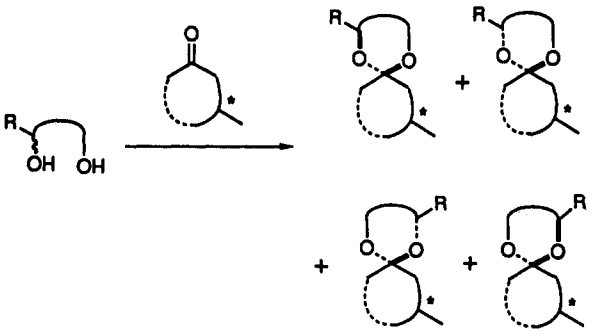
Received May 16, 1991

A general and reliable method for the resolution of racemic 1,3-alkanediols, which involves their conversion into diastereomeric spiroacetals derived from *l*-menthone, is described. Thus, the reaction of the *bis*-*O*-trimethylsilyl derivatives of racemic 1,3-alkanediols with *l*-menthone in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate affords the diastereomeric spiroacetals **3** and **4**. The two can be readily separated by silica gel column chromatography. Hydrolysis of each diastereomer under acidic conditions liberates the corresponding enantiomerically pure diol. An empirically derived correlation of configuration and ^1H NMR chemical shifts for spiroacetals **3** and **4** has been developed which is rationalized based on long-range effects due to the magnetic anisotropy inherent to the menthane ring in a rigid spiroacetal conformation. The method described here should be widely applicable to the determination of the absolute configuration of various 1,3-alkanediols.

Introduction

Enantiomerically pure 1,2- and 1,3-alkanediols and derivatives thereof are useful chiral building blocks.[1] Because many 1,2- and 1,3-diols are readily available only as racemic mixtures, a reliable general method for the resolution of such mixtures would be extremely valuable. One of the most promising approaches to the resolution of racemic 1,2- and 1,3-alkanediols involves their conversion into diastereomeric acetals by reaction with a chiral ketone.[2] As Scheme I shows, such acetalization generates a new asymmetric center from what was the carbonyl carbon atom of the ketone and thus produces four diastereomeric spiroacetals. Therefore, in this approach, it is indispensable to use a proper ketone which undergoes a stereoselective acetalization at the dioxy carbon to afford a pair of diastereomeric acetals.[3]

Scheme I



We found that the acetalization of racemic 1,3-alkanediols (*rac*-**1**) by *l*-menthone proceeds with high stereoselectivity to afford, of four possible diastereomers, only the

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