Regiochemical Control of the Ring Opening of 1,2-Epoxides by Means of Chelating Processes. 7. Synthesis and Ring-Opening Reactions of *cis*- and *trans*-Oxides Derived from 2-(Benzyloxy)-3,6-dihydro-2*H*-pyran†,[1]

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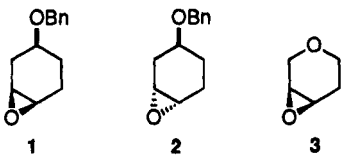
The regiochemical outcome of the ring opening of 1,2-epoxides bearing polar remote functionalities through chelation processes assisted by metal ions was verified in a conformationally semirigid cyclic oxirane system in which the polar functionality is both directly inserted into the cyclic system and present on the cyclic system itself. Diastereoisomeric cis **4** and trans epoxide **5**, derived from 2-(benzyloxy)-3,6-dihydro-2*H*-pyran, were prepared and some of their opening reactions (azidolysis, aminolysis, Cl^- addition, and $LiAlH_4$ reduction) were studied. The regioselectivity observed is largely dependent for both **4** and **5** on the opening (standard or metal-assisted) reaction conditions, and a regioalternating process is almost obtained.

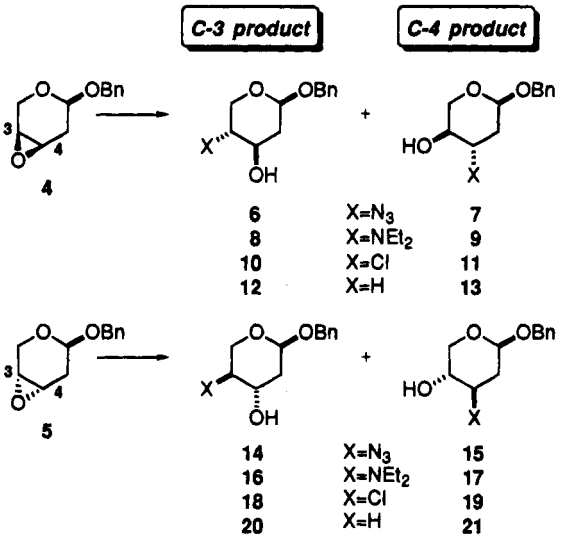
Introduction

The control of the regiochemistry of the nucleophilic addition to 1,2-epoxides is extremely useful in the synthesis of polyfunctionalized complex natural molecules. Polar remote groups have been effectively utilized to direct the regiochemistry of the nucleophilic ring opening of oxiranes through metal-assisted chelating processes.[1–5] In the case of the conformationally semirigid cycloaliphatic cis epoxide **1**, the appropriate use of chelating and nonchelating procedures makes it possible to obtain practically complete regiocontrol of the ring opening, thus making regioalternating processes possible, whereas the regiochemical outcome of trans epoxide **2** does not appear to be affected by the opening reaction conditions.[2–4] We recently found that also a polar group included in a cyclic system, as in the tetrahydropyranyl epoxide **3**,[1] can efficiently intervene in the oxirane ring-



opening process through the above-mentioned mechanism, thus leading to a marked modification of the regiochemical outcome observed under the usual nonchelating conditions. At this point, we wanted to verify the possibility of achieving regiochemical control of the ring opening in conformationally semirigid complex oxiranes, in which the heterofunctionality is both directly inserted into the cyclic system and present on the cyclic system itself, as in the diastereoisomeric epoxides cis **4** and trans **5**. Epoxides **4** and **5** were prepared from 2-(benzyloxy)-3,6-dihydro-2*H*-pyran (**25**) (Schemes 1 and 2), and some of their opening reactions were studied. These epoxides and their opening products could be of definite synthetic interest, as they are structurally closely related to pyranosidic deoxysugars.

Scheme 1



Results

Olefin **25**, the necessary precursor of epoxides **4** and **5**, was prepared as shown in Scheme 2.[6] The thermal hetero Diels–Alder condensation of the known benzyl vinyl ether (**22**)[7] with acrolein, in the presence of hydroquinone,[8] yielded 2-(benzyloxy)-3,4-dihydro-2*H*-pyran (**23**). Bromine addition at −78 °C to **23** in a nonprotic solvent (CH_2Cl_2) afforded a mixture of the corresponding

† Dedicated to Professor Giancarlo Berti on the occasion of his 70th birthday.

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(1) Preceding paper in this series: Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1994**, *50*, 1261.

(2) Chini, M.; Crotti, P.; Flippin, L. A; Macchia, F. *Tetrahedron Lett.* **1989**, *30*, 6563.

(3) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org.Chem.* **1990**, *55*, 4265.

(4) Chini, M.; Crotti, P. ; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 7043.

(5) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221.

(6) For the synthesis of **25**, we followed the procedure previously utilized for the preparation of the corresponding 2-methoxy derivative: Mash, E. A. *Synlett* **1991**, 529 and references therein.

(7) Burgstahler, A. W.; Gibbons, L. K.; Nordin, I. C. *J. Chem. Soc.* **1963**, 4986.

(8) Longley, R. I., Jr.; Emerson, W. S. *J. Am. Chem. Soc.* **1950**, *72*, 3079.

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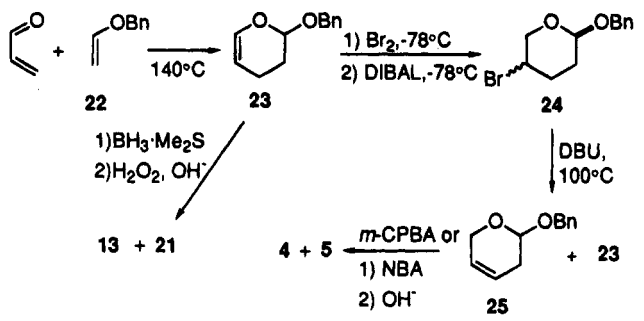
Scheme 2



dibromides, which were directly subjected to DIBAL reduction to give a reaction mixture containing the diastereoisomeric monobromides of type **24**. Treatment of this mixture with DBU at 100 °C yielded a 6:4 mixture of olefins **25** and **23**, which were separated by flash chromatography (olefin **23** can be recycled).

The direct epoxidation of **25** with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave a 28:72 mixture of epoxides **4** and **5**, which was separated by flash chromatography on silica gel. Also the base-catalyzed cyclization of the mixture of bromohydrins obtained by treatment of olefin **25** with *N*-bromoacetamide (NBA) in aqueous THF gave an almost similar mixture of epoxides **4** and **5** (**4**:**5** = 21:79).

The cis **4** and the trans epoxide **5** were subjected to ring-opening reactions with different nucleophiles (N_3^-, Et_2NH, Cl^-, and H^-) both under standard conditions, which do not allow coordination (reactions carried out with protic acid catalysis or without any catalysis), and under chelating conditions (reactions carried out in the presence of a metal ion); the latter had been found to be useful in other systems in order to obtain proof of the intervention of chelated species in the opening process.[1-5] As previously pointed out,[1,3] the $LiAlH_4$ reductions carried out under classic conditions should be considered, for our purposes, as carried out under chelating conditions due to the presence of a metal species (Li^+) in the reagent.[1,3] The same reaction effected in the presence of a crown ether (12-crown-4) should instead be considered as carried out under nonchelating conditions (absence of the metal ion), due to the sequestering ability of the crown ether, specific for Li^+.[1,3] The determination of the relative amount of the regioisomeric products (*C-3* and *C-4 products*)[9] formed in the opening reactions from epoxides **4** and **5** was accomplished by GC and ^1H NMR analysis of the crude reaction product. The results obtained are summarized in Tables 1 and 2. On the basis of the results previously observed in the case of the cis **1** and trans epoxide **2**,[2-4] somewhat surprisingly we found that both the cis **4** and trans epoxide **5** exhibit a marked change in regioselectivity on passing from nonchelating to chelating conditions. In some cases, a considerable control over the regioselectivity is possible, leading to a high degree of regioalternation.[2-4]

Discussion

First of all, let us consider the reactions carried out under nonchelating conditions. In the case of the cis epoxide **4**, the attack of all the nucleophiles examined preferentially occurs on the C-4 oxirane carbon,[9] affording the corresponding *C-4 products*[9] (entries 1, 3, 5, and 9, Table 1). This result can be rationalized on the basis of a trans diaxial opening of epoxide **4** in accordance with the Fürst–Plattner rule[10] through its more stable conformation **4a** (Scheme 3) (vide infra: conformational analysis of epoxides **4** and **5** by their ^1H NMR spectra). Moreover, the unfavorable electron-withdrawing inductive effect of the pyranoid oxygen could be a further concurrent factor favoring the nucleophilic attack on the C-4 oxirane carbon,[9] as previously suggested for the opening reaction of the structurally closely related epoxide **3**.[1] Also the slightly lower C-4 regioselectivity observed, under these conditions, for the aminolysis reaction of epoxide **4** (entry 3, Table 1) is in accordance with the particular behavior already observed with this nucleophile in the corresponding reaction of **3**.[1]

Unlike findings for the cis epoxide **4**, the regioselectivity of the reactions of the trans isomer **5**, carried out under nonchelating conditions, appears to be more variable, largely depending on the type of nucleophile used. A high C-3 selectivity[9] is observed in the reactions of **5** with the azide and chloride ions (entries 1 and 5, Table 2), whereas a C-4 selectivity,[9] even if weak, is found in the aminolysis opening reaction. The $LiAlH_4$ reduction in the presence of 12-crown-4 is practically not selective (entries 3 and 9, Table 2). Evidently, in these conditions, the ring opening of epoxide **5** with N_3^- and Cl^- occurs, in spite of the unfavorable inductive effect of the pyranoid oxygen (see above),[1] largely by a diaxial opening through its conformation **5b**, to give *C-3 products*, preferentially (Scheme 4). The point in favor of the C-3 selectivity observed for **5** under these conditions, that is the preferential reactivity of **5** through its conformation **5b**, could be due to the unfavorable electrostatic interaction between the approaching negatively charged nucleophile (such as N_3^- and Cl^-) and the benzyloxy oxygen. This kind of interaction would be operating in the diaxial opening of **5** through conformation **5a**, as already suggested in order to explain some results obtained with trans epoxide **2**,[2,4] but is clearly not operating in the aminolysis reaction of **5**. By consequence, a diaxial opening through conformation **5a** is preferred and a significantly higher C-4 selectivity is accordingly observed. In the $LiAlH_4$–crown reduction reaction of **5**, the probable balance of all the above-cited effects may reasonably lead to a practically complete absence of selectivity.

For the reactions of the cis epoxide **4** carried out under chelating conditions (presence of a metal salt such as $LiClO_4$), a large increase in the C-3 selectivity was observed with all the nucleophiles used (entries 2, 4, and 6–8, Table 1). This increase may be attributed to the direct intervention of the metal species (Li^+) in the opening process by the intermediate formation of a bidentate chelate structure such as **28** (Scheme 3). This chelate species is structurally analogous to the one previously admitted for the reactions of the cis epoxide **1**, under the same opening conditions.[2-4] In accordance with the particular reactivity of epoxide **4** so far observed, the initial complexation (structures **26** and **27**) of the metal ion with the benzyloxy oxygen of **4**, in either conformation **4a** or **4b**, followed by an entropically

(9) The arbitrary *C-3* and *C-4 product* nomenclature (C-3 and C-4 regioselectivity, respectively) refers to the attacking site of the nucleophile (i.e. at the C-3 or C-4 oxirane carbon of both epoxides **4** and **5**) in accordance with the numbering scheme shown in Scheme 1.

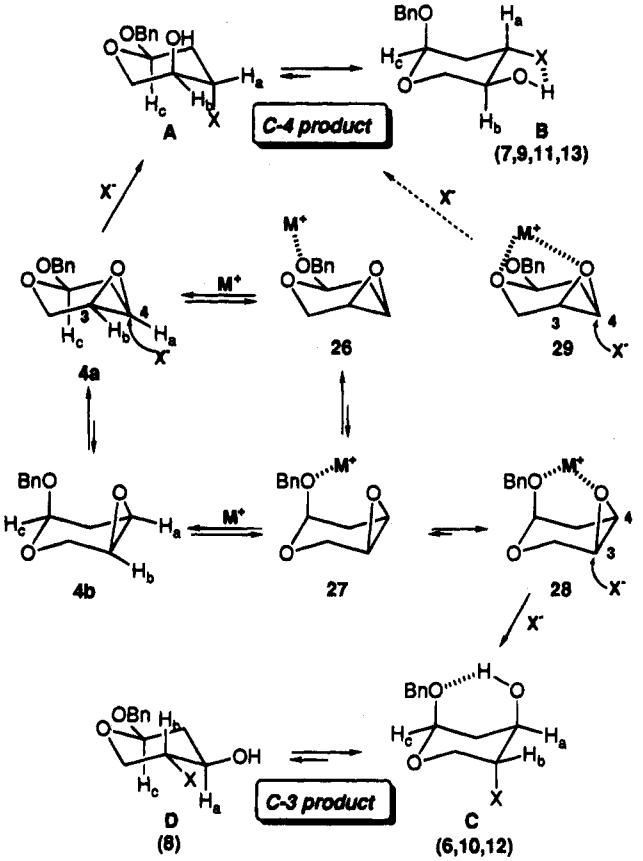
(10) (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience: New York, 1965; p 102. (b) Fürst, A.; Plattner, P. A. *Abstract of Papers*, 12th International Congress of Pure and Applied Chemistry; 1951, p 409.

Table 1. Regioselectivity (%) of the Ring-Opening Reactions of the Cis Epoxide 4

entry	reagents	solvent	reaction conds (°C)[a]	reaction time	*C-3 product*[b]	*C-4 product*[b]	yield, %
1	NaN_3/NH_4Cl	MeOH:H_2O 8:1	A (80)	18 h	6[c]	94[d]	92
2	$NaN_3/LiClO_4$	CH_3CN	B (80)	18 h	86[c]	14[d]	93
3	Et_2NH	EtOH	C (80)	18 h	24[e]	76[f]	50[k]
4	$Et_2NH/LiClO_4$	CH_3CN	D (rt)	18 h	82[e]	18[f]	95
5	HCl	$CHCl_3$	E (rt)	30 min	5[g]	95[h]	94
6	$NH_4Cl/LiClO_4$	CH_3CN	F (65)	18 h	56[g]	44[h]	94
7	$LiAlH_4$	Et_2O	G (rt)	2 h	43[i]	57[j]	97
8	$LiAlH_4$	pentane	G (rt)	2 h	42[i]	58[j]	98
9	$LiAlH_4$/crown	pentane	H (rt)	5 h	9[i]	91[j]	96

[a] Conditions: A, epoxide:NaN_3:NH_4Cl = 1:5:2.2, ref 16; B, 2.5 M $LiClO_4$, epoxide:NaN_3:$LiClO_4$ = 1:1.4:5; C, epoxide:Et_2NH = 1:5; D, 3.0 M $LiClO_4$, epoxide:Et_2NH:$LiClO_4$ = 1:5:12; E, 36% aqueous HCl; F, 2.0 M $LiClO_4$, epoxide:NH_4Cl:$LiClO_4$ = 1:1.5:4, ref 17; G, epoxide:$LiAlH_4$ = 1:4; H, $LiAlH_4$ (2.0 mmol) and 12-crown-4 (2.2 mmol) in the solvent are stirred for 15 h at rt and then the epoxide (1.0 mmol) is added, see ref 3. [b] See ref 9. [c] Azido alcohol **6**, X = N_3. [d] Azido alcohol **7**, X = N_3. [e] Amino alcohol **8**, X = NEt_2. [f] Amino alcohol, **9**, X = NEt_2. [g] Chlorohydrin **10**, X = Cl. [h] Chlorhydrin **11**, X = Cl. [i] Alcohol **12**, X = H. [j] Alcohol **13**, X = H. [k] 50% unreacted epoxide was still present.

Scheme 3



favored coordination with the oxirane oxygen, would lead to the bidentate chelate structure **28**, in which epoxide **4** is forced to adopt the less stable conformation **4b**. The axial attack of the nucleophile on intermediate **28** would lead to the formation of *C-3 products*, as experimentally observed (entries 2, 4, and 6–8, Table 1). These results indicate that the alternative and competitive incursion of a bidentate chelate structure of type **29** (Scheme 3), in which the pyranosidic oxygen is involved in the metal-chelation with the oxirane oxygen, although highly probable, is not operating in the case of epoxide **4**. If the ring opening of **4** proceeded through the intermediate chelate structure **29**, in which epoxide **4** is forced to react in its more stable conformation **4a**, as under standard conditions, an increase in the C-4 selectivity would have to be observed, contrary to experimental observations (Table 1). On the other hand, intermediate structures closely related to **29** have previously been largely suggested in order to rationalize the results obtained under chelating conditions with epoxide **3**.[1]

The increase in C-4 selectivity observed in the case of the trans epoxide **5** on passing from nonchelating to chelating conditions should be attributed to the intervention of a bidentate chelate structure such as **32**. Structure **32** is the only one possible in the trans isomer **5**, the coordination between the benzyloxy and the oxirane oxygen being prevented for structural reasons (Scheme 4). The chelate structure **32** should reasonably arise from an initial complexation (structures **30** and **31**) of the metal species with the pyranosidic oxygen of **5** either in conformation **5a** or **5b**, followed by a further entropically favored coordination of the metal with the oxirane oxygen. The axial attack of the nucleophile on **32**, in which epoxide **5** is forced to react in conformation **5a**, would lead to *C-4 products*, as experimentally found (entries 2, 4, and 6–8, Table 2).

In conclusion, the alternate use of chelating and nonchelating procedures makes it possible to obtain a fair control of the regioselectivity for both the cis **4** and trans epoxide **5**. This result could be of considerable interest in the related synthetic chemistry of pyranosidic deoxysugars.

Structures, Configurations, and Conformations

The relative configuration of the cis **4** and trans epoxide **5** was unequivocally inferred in the following way. $LiAlH_4$ reduction of the cis epoxide **4** yields a mixture of the regioisomeric cis alcohols **12** (*C-3 product*) and **13** (*C-4 product*) (Scheme 1 and Table 1). The cis alcohol **13** was also obtained, as the minor product, together with its trans diastereoisomer **21** [**21/13** = 60/40] in the hydroboration–oxidation reaction of olefin **23** (Scheme 2).[11] On the other hand, the IR spectrum of a dilute CCl_4 solution of alcohol **12** exhibits a characteristic OH···O interaction (3548 cm^{-1}, Table 3)[3,4,12] which is possible only when a 1,3-cis relationship is present between the intereacting groups, such as the hydroxyl and benzyloxy groups in **12** (see Scheme 3). Bearing in mind that the configuration of the alcohols obtained in the reduction of an epoxide must correspond to that of

(11) (a) Srivastava, R. M.; Brown, R. K. *Can. J. Chem.* **1970**, *48*, 2334. (b) Anselmi, C.; Catelani, G.; Monti, L. *Gazz. Chim. Ital.* **1983**, *113*, 167.

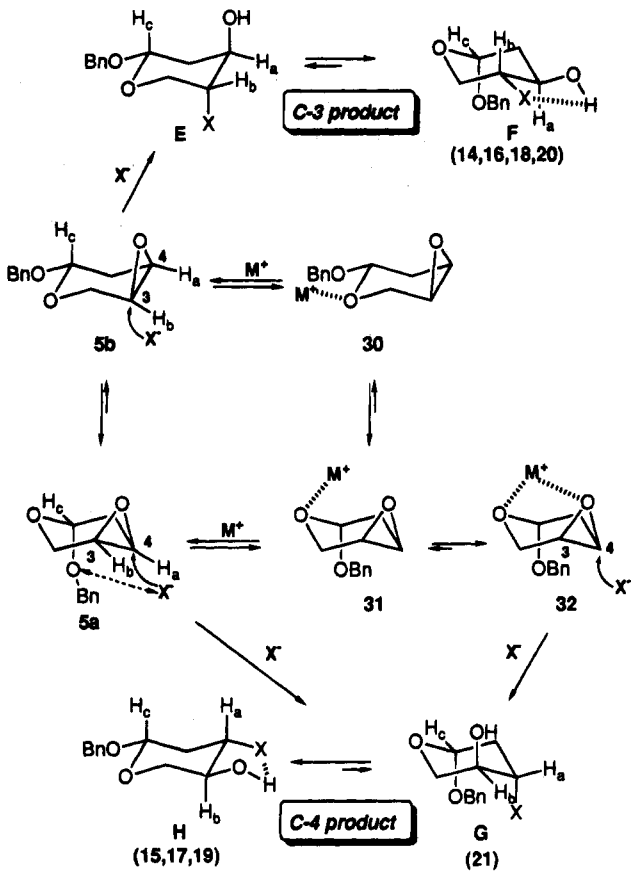
(12) (a) Tichy', M. In *Advances in Organic Chemistry, Methods and Results*; Raphael, R. A., Taylor, E. C., Winberg, H., Eds.; Interscience: New York, 1965; Vol. 5, p 115. (b) Macchia, B.; Macchia, F.; Monti, L. *Gazz. Chim. Ital.* **1970**, *100*, 35.

Table 2. Regioselectivity (%) of the Ring-Opening Reactions of the Trans Epoxide 5

entry	reagents	solvent	reaction conds (°C)[a]	reaction time	*C-3 product*[b]	*C-4 product*[b]	yield, %
1	NaN_3/NH_4Cl	MeOH:H_2O 8:1	A (80)	18 h	80[c]	20[d]	92
2	$NaN_3/LiClO_4$	CH_3CN	B (80)	18 h	17[c]	83[d]	92
3	Et_2NH	EtOH	C (80)	18 h	37[e]	63[f]	97
4	$Et_2NH/LiClO_4$	CH_3CN	D (rt)	18 h	11[e]	89[f]	96
5	HCl	$CHCl_3$	E (rt)	30 min	97[g]	3[h]	93
6	$NH_4Cl/LiClO_4$	CH_3CN	F (65)	18 h	28[g]	72[h]	96
7	$LiAlH_4$	Et_2O	G (rt)	2 h	30[i]	70[j]	99
8	$LiAlH_4$	pentane	G (rt)	2 h	18[i]	82[j]	98
9	$LiAlH_4$/crown	pentane	H (rt)	5 h	52[i]	48[j]	94

[a,b] See corresponding footnotes in Table 1. [c] Azido alcohol **14**, X = N_3. [d] Azido alcohol **15**, X = N_3. [e] Amino alcohol **16**, X = NEt_2. [f] Amino alcohol **17**, X = NEt_2. [g] Chlorohydrin **18**, X = Cl. [h] Chlorohydrin **19**, X = Cl. [i] Alcohol **20**, X = H. [j] Alcohol **21**, X = H.

Scheme 4



the starting compound, this result makes it possible to assign the cis and trans configuration unequivocally to diastereoisomeric epoxides **4** and **5**, respectively. As for the conformations of the two epoxides **4** and **5**, they were ascertained by a ^1H NMR conformational study in C_6D_6 on the basis of the signal of the proton α to the benzyloxy group (H_c proton, Schemes 3 and 4). For that proton the cis epoxide **4** shows a signal with a large (J = 7.7 Hz) and a small (J = 4.0 Hz) coupling constant (Table 3), suggesting for this compound a preference for conformation **4a** in which the benzyloxy group is equatorial (H_c axial, Scheme 3). In consideration of the definite preference found in the case of epoxide **3** for that conformation, corresponding to **4b**, in which the pyranoid and the oxirane oxygen are as far away as possible,[13] the presently found preference of epoxide **4** for conformation **4a** could be due to the absence, in this conformer, of the additional interaction (dipole–dipole and steric interaction) between the oxirane oxygen and the benzyloxy group, which is unfavorably present in the alternative conformation **4b**. In the case of the trans epoxide **5**, the ^1H NMR spectrum exhibits for proton H_c (Table 3) a signal showing intermediate values of the coupling constants (J = 4.6 and 3.0 Hz). These data appear to indicate for **5** a situation of conformational equilibrium between **5a** and **5b** (Scheme 4) in which both conformers are consistently present, with a reasonable preference for conformer **5a** in which the benzyloxy group is axial (H_c equatorial), as a consequence of the well-known anomeric effect.[14]

The structure and configurations of the opening products obtained as regioisomeric pairs (*C-3* and *C-4 products*) in the above-mentioned opening reaction of both the cis **4** and trans epoxide **5** (Schemes 1, 3, and 4 and Tables 1 and 2) was unequivocally determined by simple considerations based on the configuration of the starting epoxide, the anti stereoselectivity commonly observed in the opening reactions of typically aliphatic and cycloaliphatic epoxides under the conditions used,[1-5] an examination of their ^1H NMR spectra [coupling constants and/or half-bandwidth ($W_{1/2}$)[15] of the signal of the protons α to OH, X, and OBn groups (protons H_a, H_b, and H_c, Schemes 3 and 4, and Table 3)], and finally by the use of appropriate double resonance experiments. In the case of *C-3 products* from cis epoxide **4** [azido alcohol **6**, chlorohydrin **10**, and alcohol **12** (see above), with the exception of the amino alcohol **8**], the structures assigned were confirmed by the presence of a 1,3 OH···O interaction in the IR spectra of these compounds in dilute CCl_4 solution (Table 3).[3,4,12] As a consequence, the conformational equilibrium for these compounds (**6**, **10**, and **12**) appears to be considerably shifted toward conformer **C** in order to allow the 1,3 OH···O hydrogen bond (Scheme 3). In the case of all the other compounds, the conformations having more substituents in the equatorial position, and allowing the presence of a 1,2 hydrogen bond between the OH and the X group (X = N_3, NEt_2, or Cl), appear to be highly favored [conformer **B**, for *C-4 products*, and conformer **D**, for amino alcohol **8** (*C-3 product*), from cis epoxide **4** (Scheme 3); conformer **F**, for *C-3 products*, and **H**, for *C-4 products*, from trans epoxide **5** (Scheme 4)]. The only exception is given by alcohol **21** in which the diaxial conformer **G** appears to be favored in order to allow the 1,2 OH···O hydrogen bond between the OH group and the oxygen of the pyranoid ring (Table 3 and Scheme 4).[1]

(13) Catelani, G.; Monti, L.; Tognetti, P. *Carbohydr. Res.* **1981**, *97*, 189.

(14) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019.

(15) Jackman, L. M.; Sternhell S. *Application of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry*, 2nd ed.; Pergamon Press: London, 1969; p 286.

Table 3. Spectroscopic Data for Compounds 4–21

	^{1}H NMR δ			IR (CCl_4) (OH stretching), cm^{-1}			
compd	H_a ($W_{1/2}$, Hz)[a,b]	H_b ($W_{1/2}$, Hz)[a,b]	H_c (J, Hz)[c]	1,2 OH–X	1,2 OH–O	1,3 OH–O	free OH
4	2.60[a,d]	2.35[a,e]	4.02 (7.7 and 4.0)[d]				
5	2.83[a,f]	2.58[a,g]	4.51 (4.6 and 3.0)[d]				
6	3.74 (9.5)[a,g]	3.42 (9.2)[b,g]	4.83 (3.1)[f]			3533[j]	
7	*h*	*h*	4.87 (3.5 and 1.7)[d]	3605[j]			3626[j]
8	3.57 (21.0)[a,i]	*h*	4.45 (8.0 and 2.2)[d]	3475[j]			
9	3.00 (24.0)[b,i]	*h*	4.92 (3.6 and 1.2)[d]	3483[j]			
10	*h*	*h*	4.84 (3.4)[f]	3595[k]		3529[j]	
11	4.16 (25.0)[b,i]	*h*	4.83 (3.4 and 1.8)[d]	3601[j]			
12	3.95 (9.9)[a,g]		4.84 (2.9)[f]			3548[j]	
13		3.65 (18.0)[a,g]	4.64 (2.9)[f]		3607[l]		3624[j]
14	3.91 (24.0)[a,i]	3.33 (20.0)[b,i]	4.90 (3.6 and 1.5)[d]	3605[j]			
15	3.41 (18.0)[b,i]	3.53 (18.0)[a,i]	4.55 (7.6 and 2.6)[d]	3605[j]			
16	3.93 (24.0)[a,i]	*h*	4.88 (1.8)[f]	3487[j]			
17	*h*	3.44 (25.0)[a,i]	4.44 (9.2 and 2.2)[d]	3493[j]			
18	4.00 (22.0)[a,g]	*h*	4.95 (3.6 and 1.4)[d]	3601[j]			
19	3.77 (22.0)[b,i]	3.65 (22.0)[a,i]	4.48 (8.6 and 2.3)[d]	3601[j]			
20	4.11 (21.9)[a,g]		4.94 (2.9)[f]				3618[j]
21		3.73 (10.2)[a,g]	4.74 (2.9)[f]		3603[j]		3624[l]

[a] *CH*OH (oxirane *CH*O in the case of **4** and **5**). [b] *CH*X. [c] *CH*OBn (see Schemes 1, 3, and 4). [d] Doublet of doublets. [e] Doublet. [f] Unresolved triplet. [g] Multiplet. [h] The signal overlaps with other signals. [i] Doublet of doublets of doublets. [j] Strong band. [k] Weak band. [l] Shoulder.

Experimental Section

For general experimental information, see ref 3. Benzyl vinyl ether (**22**) was prepared as previously described.[7]

2-(Benzyloxy)-3,4-dihydro-2*H*-pyran (23). A mixture of acrolein (1.85 g, 33.0 mmol) and benzyl vinyl ether (**22**) (6.0 g, 44.0 mmol) was heated at 140 °C for 18 h, under stirring, in a stainless steel sealed vessel, in the presence of hydroquinone (0.018 g). After cooling, dilution with ether and evaporation of the washed (water) organic solution afforded a crude liquid product (7.0 g) which was subjected to flash chromatography with 98:2 hexane/AcOEt as the eluant to give pure **23** (4.90 g, 78% yield), as a liquid: ^{1}H NMR ($CDCl_3$) δ 7.18–7.29 (m, 5H), 6.16–6.21 (m, 1H), 5.00 (t, 1H, J = 3.4 Hz), 4.78 and 4.53 (AB dd, 2H, J = 12.1 Hz), 4.69–4.76 (m, 1H), 2.04–2.18 (m, 2H), 1.74–1.91 (m, 1H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.81;H, 7.45.

2-(Benzyloxy)-3,6-dihydro-2*H*-pyran (25). A solution of olefin **23** (6.28 g, 33.0 mmol) in anhydrous CH_2Cl_2 (17 mL) was treated dropwise at −78 °C with Br_2 (1.71 mL, 33.0 mmol): immediate decolorization was observed. After 15 min, a 1 M DIBAL solution in cyclohexane (36.3 mL) was added at the same temperature and the resulting reaction mixture was further stirred for 15 min. A solution of KF (13.6 g) in water (2.0 mL) was carefully added under vigorous stirring, and the reaction temperature was slowly warmed to rt. Filtration on Celite, and evaporation of the organic solution, afforded an oily product (8.9 g) which was filtered on a silica gel column with 1:1 petroleum ether/CH_2Cl_2 as the eluant to give a reaction mixture containing the diastereoisomeric monobromides of type **24** (4.91 g, 55% yield), which were not separated but directly used in the next step.

A solution of the above-purified mixture of monobromides **24** (4.91 g, 18.2 mmol) in DMF (10 mL) was treated with DBU (2.85 mL, 19.1 mmol) and the reaction mixture was heated under stirring at 100 °C for 2 h. After cooling, dilution with ether and evaporation of the washed (water) ether solution afforded a crude reaction product (3.40 g, 98% yield) consisting of a 6:4 mixture of olefins **25** and **23** (^{1}H NMR and GC) which was subjected to flash chromatography with 95:5 hexane/AcOEt as the eluant to yield **23** (1.10 g) and pure **25** (1.85 g), as a liquid: ^{1}H NMR ($CDCl_3$) δ 7.19–7.34 (m, 5H), 5.67 (s, 2H), 4.86 (t, 1H, J = 3.7 Hz), 4.78 and 4.52 (AB dd, 2H, J = 12.0 Hz), 3.92–4.25 (m, 2H), 2.02–2.39 (m, 2H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.64; H, 7.39.

Epoxidation Reactions of Olefin 25. (a) A solution of olefin **25** (1.65 g, 8.7 mmol) in CH_2Cl_2 (90 mL) was treated at 0 °C with 51% *m*-CPBA (3.23 g, 9.6 mmol), and the reaction mixture was stirred at the same temperature for 24 h. The organic solution was washed (5% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, 5% aqueous NaOH, and water) and evaporated to give an oily residue (1.46 g, 81% yield) consisting of a 28:72 mixture of the cis **4** and trans epoxide **5** (^{1}H NMR and GC), which was subjected to preparative TLC with 85:15 petroleum ether/AcOEt as the eluant. Extraction of the two most intense bands (the faster moving band contained **5**) afforded pure cis **4** (0.38 g) and trans epoxide **5** (0.92 g).

***cis*-2-(Benzyloxy)-4,5-epoxytetrahydropyran (4)**, a liquid: ^{1}H NMR (C_6D_6) δ 7.07–7.29 (m, 5H), 4.75 and 4.35 (AB dd, 2H, J = 12.2 Hz), 3.93 (d, 1H, J = 13.3 Hz), 3.22 (dd, 1H, J = 13.3 and 1.5 Hz), 2.60 (dd, 1H, J = 4.8 and 4.0 Hz), 2.35 (d, 1H, J = 4.0 Hz), 2.06 (dd, 1H, J = 15.1 and 7.7 Hz), 1.53 (ddd, 1H, J = 15.1, 4.8, and 4.0 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.63; H, 6.71.

***trans*-2-(Benzyloxy)-4,5-epoxytetrahydropyran (5)**, a solid: mp 33–34 °C; ^{1}H NMR (C_6D_6) δ 7.04–7.26 (m, 5H), 4.57 and 4.21 (AB dd, 2H, J = 12.0 Hz), 3.70 (three lines, 2H), 2.83 (unresolved triplet, 1H, J = 4.5 Hz), 2.58 (m, 1H), 1.95 (dd, 1H, J = 15.3 and 4.6 Hz), 1.64 (ddd, 1H, J = 15.3, 4.5, and 3.0 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.72; H, 6.95.

Alternatively, the mixture of the two epoxides **4** and **5** could be separated by flash chromatography with 95:5 hexane/AcOEt as the eluant.

(b) A solution of olefin **25** (0.19 g, 1.0 mmol) in a 3:1 THF/H_2O mixture (12 mL) was treated at rt with *N*-bromoacetamide (NBA) (0.15 g, 1.1 mmol) and the resulting reaction mixture was left 3 h in the dark, at the same temperature. Dilution with ice–water, extraction with ether, and evaporation of the washed (water) ether extracts afforded a crude oily reaction product (0.27 g) [IR_{neat} 3421 cm^{-1} (OH)] which was dissolved in anhydrous benzene (10 mL) and treated with *t*-BuOK (0.11 g, 1.0 mmol). The reaction mixture was stirred 1 h at rt; then a new portion of *t*-BuOK (0.11 g) was added and stirring was prolonged for an additional hour. Evaporation of the washed (water) organic solution afforded a crude liquid product (0.18 g, 87% yield) consisting of a 21:79 mixture of cis **4** and trans epoxide **5** (^{1}H NMR and GC).

Azidolysis of Epoxides 4 and 5 with NaN_3–NH_4Cl. The following procedure is typical.[16] A solution of the cis epoxide **4** (0.103 g, 0.50 mmol) in an 8:1 MeOH/H_2O (2.5 mL) mixture was treated with NaN_3 (0.16 g, 2.5 mmol) and NH_4Cl (0.059 g, 1.1 mmol) and the resulting reaction mixture was stirred at 80 °C for 18 h. Dilution with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and water) ether extracts afforded a crude liquid product (0.115 g, 92% yield) consisting of a 6:94 mixture of azido alcohols **6** and **7** (^{1}H NMR and GC, Table 1) which was subjected to semipreparative TLC with

(16) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the most intense band afforded pure ***t*-4-azido-*c*-2-(benzyloxy)tetrahydropyran-*r*-5-ol (7)** (0.080 g), as a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.20–7.31 (m, 5H), 4.63 and 4.37 (AB dd, 2H, J = 12.7 Hz), 3.50–3.79 (m, 4H), 2.11 (ddd, 1H, J = 13.2, 4.7, and 1.7 Hz), 1.61 (ddd, 1H, J = 13.2, 11.6, and 3.5 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.06; N, 16.84. Found: C, 57.96; H, 6.19; N, 16.70.

The crude reaction product (0.115 g, 92% yield) from the trans epoxide **5**, consisting of an 8:2 mixture of azido alcohols **14** and **15** (^{1}H NMR and GC, Table 2), was subjected to semipreparative TLC with 5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the two most intense bands (the faster moving band contained **14**) afforded pure azido alcohols **14** (0.070 g) and **15** (0.015 g).

***t*-5-Azido-*t*-2-(benzyloxy)tetrahydropyran-*r*-4-ol (14)**, a solid: mp 40–41 °C; IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.21–7.32 (m, 5H), 4.60 and 4.35 (AB dd, 2H, J = 11.9 Hz), 3.91 (ddd, 1H, J = 11.4, 9.1, and 4.8 Hz), 3.70 (dd, 1H, J = 10.9 and 5.1 Hz), 3.49 (unresolved triplet, 1H, J = 10.9 Hz), 3.33 (ddd, J = 10.9, 8.8, and 5.1 Hz), 2.10 (ddd, 1H, J = 13.1, 4.8, and 1.5 Hz), 1.62 (ddd, J = 13.1, 11.4, and 3.6 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.06; N, 16.84. Found: C, 57.58; H, 6.23; N, 16.63.

***t*-4-Azido-*t*-2-(benzyloxy)tetrahydropyran-*r*-5-ol (15)**, a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.21–7.31 (m, 5H), 4.49–4.79 (AB dd, 2H, J = 12.0 Hz), 4.02 (dd, 1H, J = 11.7 and 4.1 Hz), 3.53 (ddd, 1H, J = 12.2, 8.2, and 4.1 Hz), 3.41 (ddd, 1H, J = 12.2, 10.0, and 4.7 Hz), 3.21 (dd, 1H, J = 11.7 and 8.2 Hz), 2.17 (ddd, 1H, J = 13.5, 4.7, and 2.6 Hz), 1.67 (ddd, 1H, J = 13.5, 10.0, and 7.6 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.06; N, 16.84. Found: C, 58.05; H, 6.18; N, 16.59.

Azidolysis of Epoxides 4 and 5 with NaN_3–$LiClO_4$. The following procedure is typical. A solution of the cis epoxide **4** (0.103 g, 0.50 mmol) in anhydrous CH_3CN (1.0 mL) was treated with NaN_3 (0.044 g, 0.68 mmol) and anhydrous $LiClO_4$ (0.26 g, 2.5 mmol), and the reaction mixture was stirred at 80 °C for 18 h. After cooling, dilution with ether and evaporation of the washed (water) organic solution afforded a crude liquid product (0.116 g, 93% yield) consisting of an 86:14 mixture of azido alcohols **6** and **7** (^{1}H NMR and GC, Table 1) which was subjected to semipreparative TLC with 5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the two most intense bands (the faster moving band contained **6**) afforded azido alcohol **7** (0.010 g) and pure ***t*-5-azido-*c*-2-(benzyloxy)-tetrahydropyran-*r*-4-ol (6)** (0.065 g), as a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.23–7.30 (m, 5H), 4.70 and 4.45 (AB dd, 2H, J = 11.8 Hz), 4.15 (dd, 1H, J = 12.7 and 2.5 Hz), 3.53 (dd, 1H, J = 12.7 and 3.4 Hz), 2.12 (dt, 1H, J = 14.4 and 3.1 Hz), 1.78 (dt, 1H, J = 14.4 and 3.5 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.06; N, 16.84. Found: C, 57.78; H, 6.25; N, 16.97.

The same reaction carried out on the trans epoxide **5** (0.114 g, 92% yield) gave a crude reaction product consisting of a 17:83 mixture of azido alcohols **14** and **15** (^{1}H NMR and GC, Table 2).

Amminolysis of Epoxides 4 and 5 with $NHEt_2$ in EtOH. The following procedure is typical. A solution of the cis epoxide **4** (0.206 g, 1.0 mmol) in anhydrous EtOH (3.0 mL) was treated with $NHEt_2$ (1.02 mL, 5.0 mmol) and the reaction mixture was stirred at 80 °C for 18 h. After cooling, dilution with ether and evaporation of the washed (water) ether solution afforded a crude product (0.24 g) consisting of a 12:38:50 mixture of amino alcohols **8** and **9** (50% yield) and the unreacted starting epoxide **4** (^{1}H NMR and GC, Table 1), which was subjected to semipreparative TLC with 5:4:1:0.1 $CHCl_3$/petroleum ether/AcOEt/NEt_3 as the eluant. Extraction of the two most intense slower moving bands (the one with the higher R_f contained **8**) afforded pure amino alcohols **8** (0.020 g) and **9** (0.080 g).

***c*-2-(Benzyloxy)-*t*-5-(*N*,*N*-diethylamino)tetrahydropyran-*r*-4-ol (8)**, a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.21–7.29 (m, 5H), 4.80 and 4.50 (AB dd, 2H, J = 11.9 Hz), 3.98 (dd, 1H, J = 11.5 and 4.3 Hz), 3.57 (ddd, 1H, J = 10.3 and 4.8 Hz), 3.30 (unresolved triplet, 1H, J = 11.5 Hz), 2.39–2.70 (m, 5H), 2.30 (ddd, 1H, J = 12.4, 4.8, and 2.2 Hz), 1.58 (m, 1H), 0.99 (t, 6H, J = 7.0 Hz), and see Table 3. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.01; N, 5.01. Found: C, 68.71; H, 9.19; N, 5.27.

***c*-2-(Benzyloxy)-*t*-4-(*N*,*N*-diethylamino)tetrahydropyran-*r*-5-ol (9)**, a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.21–7.30 (m, 5H), 4.65 and 4.37 (AB dd, 2H, J = 12.1 Hz), 3.77 (5 lines, 1H), 3.48–3.61 (m, 2H), 3.00 (ddd, 1H, J = 12.5, 10.0, and 4.0 Hz), 2.56 and 2.31 (2m, 2H each), 1.79 (ddd, 1H, J = 12.5, 4.0, and 1.2 Hz), 1.55 (ddd, 1H, J = 12.5 and 3.6 Hz), 1.00 (t, 6H, J = 7.0 Hz), and see Table 3. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.01; N, 5.01. Found: C, 68.59; H, 9.25; N, 5.21.

The crude reaction product (0.135 g, 97% yield) from the trans epoxide **5** (0.50 mmol), consisting of a 37:63 mixture of amino alcohols **16** and **17** (^{1}H NMR and GC, Table 2), was subjected to semipreparative TLC with 7:3:0.1 petroleum ether/AcOEt/NEt_3 as the eluant. Extraction of the two most intense bands (the faster moving band contained **16**) afforded pure amino alcohols **16** (0.035 g) and **17** (0.085 g).

***t*-2-(Benzyloxy)-*t*-5-(*N*,*N*-diethylamino)tetrahydropyran-*r*-4-ol (16)**, a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.23–7.31 (m, 5H), 4.37 and 4.62 (AB dd, 2H, J = 12.1 Hz), 3.93 (ddd, 1H, J = 11.0 and 5.3 Hz), 3.63–3.68 (m, 2H), 2.39–2.74 (m, 5H) 2.25 (ddd, 1H, J = 12.8, 5.3, and 1.6 Hz), 1.49 (ddd, J = 12.8, 11.0, and 2.0 Hz), 1.00 (t, 6H, J = 7.0 Hz), and see Table 3. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.01; N, 5.01. Found: C, 68.49; H, 9.09; N, 5.14.

***t*-2-(Benzyloxy)-*t*-4-(*N*,*N*-diethylamino)tetrahydropyran-*r*-5-ol (17)**, a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.24–7.39 (m, 5H), 4.82 and 4.50 (AB dd, 2H, J = 11.7 Hz), 4.14 (dd, 1H, J = 10.9 and 4.9 Hz), 3.44 (ddd, 1H, J = 9.8 and 4.9 Hz), 3.13 (dd, 1H, J = 10.9 and 9.8 Hz), 2.20–2.62 (m, 5H), 1.92 (ddd, 1H, J = 12.6, 2.2, and 2.0 Hz), 1.49 (ddd, 1H, J = 12.6 and 9.2 Hz), 0.98 (t, 6H, J = 7.0 Hz), and see Table 3. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.01; N, 5.01. Found: C, 68.55; H, 9.30; N, 4.87.

Aminolysis of Epoxides 4 and 5 with Et_2NH–$LiClO_4$. The following procedure is typical. A solution of the cis epoxide **4** (0.103 g, 0.50 mmol) in anhydrous CH_3CN (2.0 mL) was treated with $NHEt_2$ (0.25 mL, 2.5 mmol) and $LiClO_4$ (0.63 g, 6.0 mmol) and the reaction mixture was stirred at rt for 18 h. Dilution with ether and evaporation of the washed (water) ether solution afforded a crude reaction product (0.133 g, 95% yield) consisting of an 82:18 mixture of amino alcohols **8** and **9** (^{1}H NMR and GC, Table 1).

The same reaction carried out on the trans epoxide **5** afforded a crude reaction product (0.134 g, 96% yield) consisting of a 11:89 mixture of amino alcohols **16** and **17** (^{1}H NMR and GC, Table 2).

Reaction of Epoxides 4 and 5 with HCl–$CHCl_3$. The following procedure is typical. A solution of cis epoxide **4** (0.103 g, 0.50 mmol) in $CHCl_3$ (12 mL) was treated with 36% aqueous HCl (4 mL) and the resulting reaction mixture was vigorously stirred at rt for 30 min. Evaporation of the washed (saturated aqueous $NaHCO_3$, and water) organic solution afforded a crude liquid product (0.114 g, 94% yield) consisting of a 5:95 mixture of chlorohydrins **10** and **11** (^{1}H NMR and GC, Table 1) which was subjected to semipreparative TLC with 5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the most intense band afforded pure ***c*-2-(benzyloxy)-*t*-4-chlorotetrahydropyran-*r*-5-ol (11)** (0.095 g), as a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.22–7.33 (m, 5H), 4.63 and 4.37 (AB dd, 2H, J = 11.8 Hz), 4.16 (ddd, 1H, J = 11.7, 8.8, and 4.8 Hz), 3.51–3.82 (m, 3H), 2.31 (ddd, 1H, J = 13.4, 4.8, and 1.8 Hz), 1.94 (ddd, 1H, J = 13.4, 11.7, and 3.4 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{15}ClO_3$: C, 59.38; H, 6.22. Found: C, 59.09; H, 6.34.

The crude reaction product (0.112 g, 93% yield) from the trans epoxide **5** consisting of a 97:3 mixture of chlorohydrins **18** and **19** was subjected to semipreparative TLC with 5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the most intense band afforded pure ***t*-2-(benzyloxy)-*t*-5-chlorotetrahydropyran-*r*-4-ol (18)** (0.085 g), as a solid: mp 98–99 °C; IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.23–7.30 (m, 5H), 4.63 and 4.38 (AB dd, 2H, J = 11.9 Hz), 3.70–3.79 (m,

3H), 2.20 (dd, 1H, J = 13.3, 5.1, and 1.4 Hz), 1.67 (dd, 1H, J = 13.3, 11.3, and 3.6 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{15}ClO_3$: C, 59.38; H, 6.22. Found: C, 59.25; H, 6.49.

Reaction of Epoxides 4 and 5 with NH_4Cl–$LiClO_4$. The following procedure is typical.[17] A solution of the cis epoxide **4** (0.103 g, 0.50 mmol) in anhydrous CH_3CN (1.0 mL) was treated with NH_4Cl (0.040 g, 0.75 mmol) and $LiClO_4$ (0.212 g, 2.0 mmol) and the reaction mixture was stirred at 65 °C for 18 h. Dilution with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and water) ether extracts afforded a crude reaction product (0.114 g, 94% yield) consisting of a 56:44 mixture of chlorohydrins **10** and **11** which was subjected to semipreparative TLC with 5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the two most intense bands (the faster moving band contained **10**) afforded **11** (0.035 g) and pure ***c*-2-(benzyloxy)-*t*-5-chlorotetrahydropyran-*r*-4-ol (10)** (0.042 g), as a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.23–7.31 (m, 5H), 4.72 and 4.47 (AB dd, 2H, J = 11.8 Hz), 4.28 (dd, J = 12.8 and 2.0 Hz), 3.83 (m, 2H), 3.55 (dd, 1H, J = 12.8 and 4.8 Hz), 2.34 (ddd, 1H, J = 14.3 and 3.3 Hz), 1.76 (ddd, 1H, J = 14.3, 6.0, and 3.6 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{15}ClO_3$: C, 59.38; H, 6.22. Found: C, 59.61; H, 6.28.

The crude reaction product (0.116 g, 96% yield) from the trans epoxide **5** consisting of a 28:72 mixture of chlorohydrins **18** and **19** (^{1}H NMR and GC) was subjected to semipreparative TLC with 5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the two most intense bands afforded pure chlorohydrins **18** (0.018 g) and ***t*-2-(benzyloxy)-*t*-4-chlorotetrahydropyran-*r*-5-ol (19)** (0.065 g), as a solid: mp 106–107 °C; IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.22–7.31 (m, 5H), 4.80 and 4.50 (AB dd, 2H, J = 11.9 Hz), 4.11 (dd, 1H, J = 11.9 and 4.7 Hz), 3.77 (ddd, 1H, J = 11.0, 8.8, and 4.7 Hz), 3.65 (ddd, 1H, J = 8.8 and 4.7 Hz), 3.19 (dd, 1H, J = 11.9 and 8.8 Hz), 2.35 (ddd, 1H, J = 13.2, 4.7, and 2.3 Hz), 1.93 (ddd, 1H, J = 13.2, 11.0, and 8.6 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{15}ClO_3$: C, 59.38; H, 6.22. Found: C, 59.26; H, 6.43.

Hydroboration–Oxidation of Olefin 23. A solution of olefin **23** (0.386 g, 2.0 mmol) in anhydrous THF (4.0 mL) was treated dropwise at 0 °C with a solution of 10 M BH_3·MeS_2 (0.27 mL) in anhydrous THF (2.0 mL) and the reaction mixture was stirred at the same temperature for 1 h and then 4 h at rt. Aqueous 3 N NaOH (0.85 mL) was carefully added, then the reaction mixture was cooled at 0 °C and treated with 36% H_2O_2 (0.85 mL). After 1 h of refluxing under stirring, dilution with water, extraction with ether, and evaporation of the washed (water) ether extracts afforded a crude liquid product (0.374 g, 90% yield) consisting of a 60:40 mixture of alcohols **21** and **13** (^{1}H NMR and GC) which was subjected to preparative TLC with 5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the two most intense bands (the faster moving band contained **13**) afforded pure alcohols **13** (0.124 g) and **21** (0.186 g).

***cis*-2-(Benzyloxy)tetrahydropyran-5-ol (13)**, a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.21–7.30 (m, 5H), 4.71 and 4.43 (AB dd, 2H, J = 11.9 Hz), 3.56–3.61 (m, 2H, H_d), 1.63–1.83 (m, 4H), and see Table 3. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.29; H, 7.84.

***trans*-2-(Benzyloxy)tetrahydropyran-5-ol (21)**, a liquid: IR; see Table 3; ^{1}H NMR δ 7.19–7.30 (m, 5H), 4.73 and 4.56 (AB dd, 2H, J = 12.0 Hz), 3.93 (dd, 1H, J = 11.8 and 2.1 Hz), 3.42 (ddd, 1H, J = 11.8 and 4.4 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.34; H, 7.41.

$LiAlH_4$ Reduction of Epoxides 4 and 5. The following procedure is typical. A solution of the cis epoxide **4** (0.103 g, 0.50 mmol) in anhydrous ether (10 mL) was treated with $LiAlH_4$ (0.060 g, 2.0 mmol) and the reaction mixture was stirred 2 h at rt. The usual workup afforded a crude product (0.101 g, 97% yield) consisting of a 43:57 mixture of alcohols **12** and **13** (^{1}H NMR and GC, Table 1) which was subjected to semipreparative TLC with 5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the two most intense bands (the faster moving band contained **12**) afforded pure alcohols **13** (0.055 g) and ***cis*-2-(benzyloxy)tetrahydropyran-4-ol (12)** (0.030 g), as a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.22–7.29 (m, 5H), 4.73 and 4.43 (AB dd, 2H, J = 11.9 Hz), 4.07 (ddd, 1H, J = 11.4 and 3.0 Hz), 3.52 (ddd, 1H, J = 11.4, 5.0, and 3.2 Hz), and see Table 3. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.43; H, 7.52.

The same reaction was carried out using pentane as the solvent to give the results shown in Table 1.

The crude reaction product (0.103 g, 99% yield) from the trans epoxide **5**, consisting of a 30:70 mixture of alcohols **20** and **21** (^{1}H NMR and GC, Table 2) was subjected to semipreparative TLC with 5:5:0.1 petroleum ether/benzene/MeOH as the eluant. Extraction of the two most intense bands (the faster moving band contained **20**) afforded pure alcohols **21** (0.058 g) and ***trans*-2-(benzyloxy)tetrahydropyran-4-ol (20)** (0.018 g), as a liquid: IR, see Table 3; ^{1}H NMR ($CDCl_3$) δ 7.19–7.29 (m, 5H), 4.64 and 4.38 (AB dd, 2H, J = 11.9 Hz), 3.65–3.86 (m, 2H), and see Table 3. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.48; H, 7.50.

The same reaction carried out using pentane as the solvent gave the results shown in Table 2.

$LiAlH_4$ Reduction of Epoxides 4 and 5 in the Presence of 12-Crown-4. Following a previously described procedure,[3] treatment of the cis epoxide **4** (0.103 g, 0.50 mmol) in pentane (5.0 mL) with a suspension of $LiAlH_4$ (0.039 g, 1.0 mmol) previously left in contact with 12-crown-4 (0.18 mL, 1.1 mmol) for 15 h at rt, afforded, after 5 h at rt, a crude oily product (0.100 g, 96% yield) consisting of a 9:91 mixture of alcohols **12** and **13** (^{1}H NMR and GC, Table 1).

The same reaction carried out on the trans epoxide **5** afforded a crude reaction product (0.098 g, 94% yield) consisting of a 52:48 mixture of alcohols **20** and **21** (^{1}H NMR and GC, Table 2).

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