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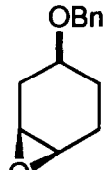
Regiochemical Control of the Ring Opening of 1,2-Epoxides by Means of Chelating Processes. 6.[1] Opening Reactions of 3,4-Epoxytetrahydropyran

Marco Chini, Paolo Crotti,* Cristina Gardelli, and Franco Macchia

Dipartimento di Chimica Bioorganica, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy

Abstract *:The regiochemical control of the ring opening of epoxides bearing polar remote functionalities, through chelation processes assisted by metal ions, was verified in the title compound (4). The use of metal assisted procedures in several ring opening reactions of 4 leads to a modification of the regiochemical outcome, and the attack of the nucleophile on the C-4 oxirane carbon is highly favored.*

The ring opening reactions of typically aliphatic or cycloaliphatic 1,2-epoxides having no particular substituents directly linked to the oxirane carbons, occur with complete or practically complete inversion of configuration. [2-4] On the other hand, the regiochemistry of the ring opening of unsymmetrical epoxides can range from a Markovnikov to a contra-Markovnikov type of cleavage.[2,5,6] In view of the anti stereoselectivity of these processes, the main aim for an effective synthetic use of these systems appears to be an adequate control of the regiochemical outcome of the ring opening. This kind of control can be nicely realized by the presence of polar remote functionalities through chelation processes assisted by metal ions, as previously observed for epoxides **1**-**3**.[1,7-9]



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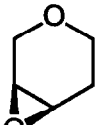

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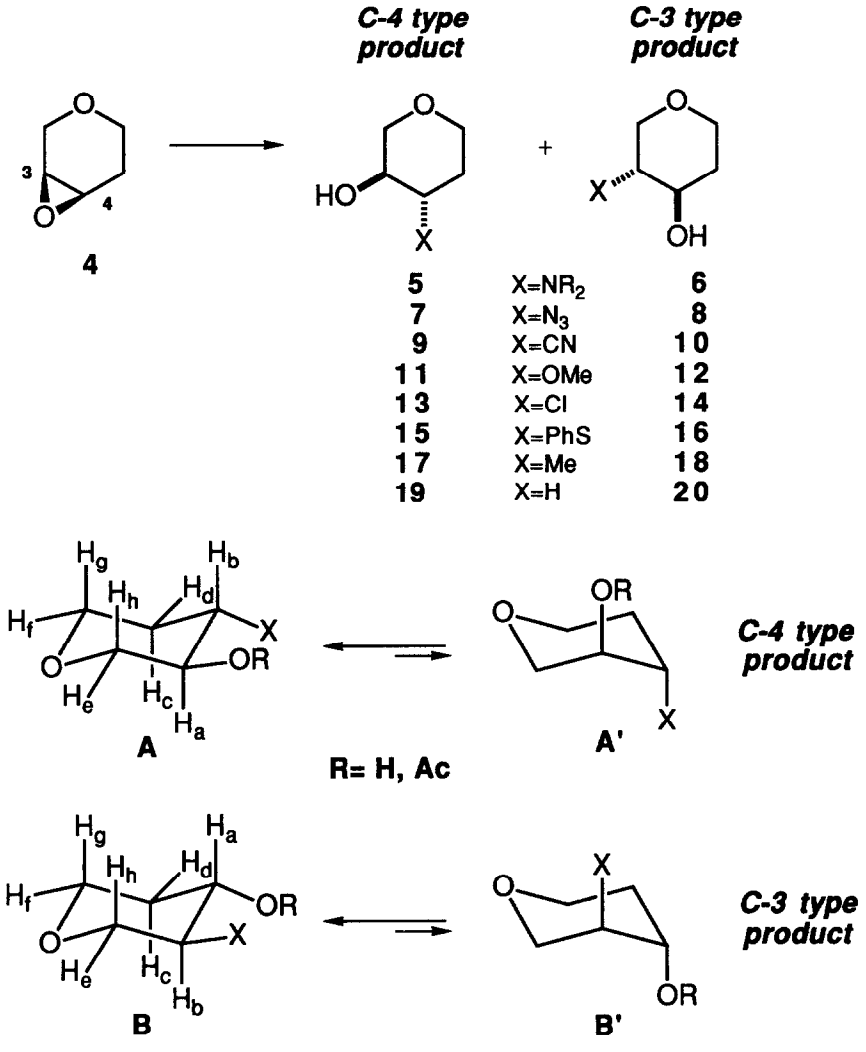
On the basis of these and other results, we desired to verify whether a remote polar group included in a cyclic system could intervene in the ring-opening processes of oxiranes by the above-mentioned mechanisms. We examined the already known 3,4-epoxytetrahydropyran (**4**)[10] which appeared to be of unquestionable synthetic interest, as it is related to pyranosidic sugar structures.

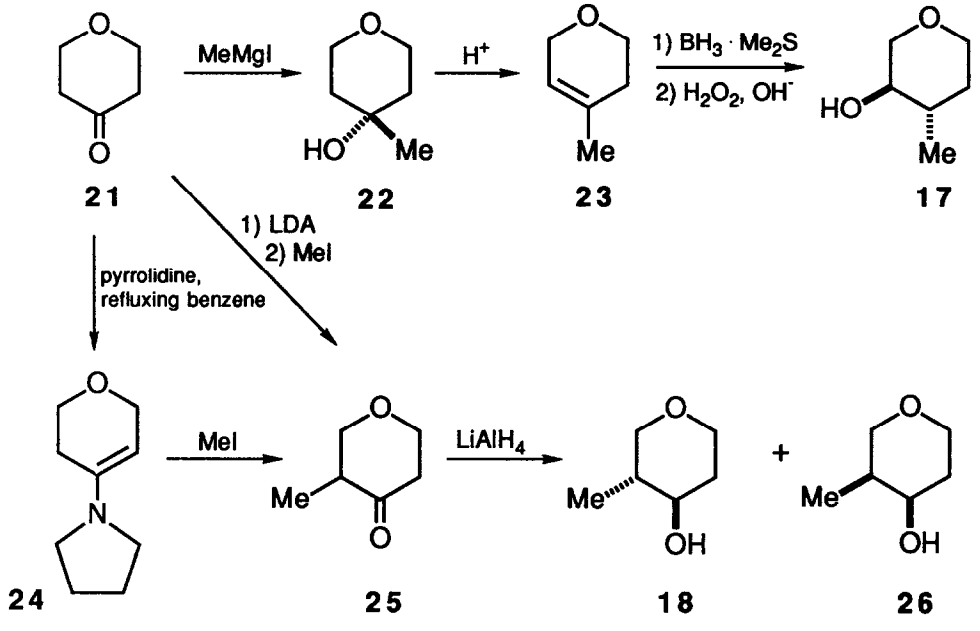
SCHEME 1



Epoxide **4** was subjected to several ring-opening reactions with different nucleophiles (NHR_2, N_3^-, Cl^-, H^-, CN^-, MeOH, PhSH, CH_3^- and H^-, Scheme 1) both under standard, non-chelating conditions (reactions carried out under classic acidic proton catalysis or without any catalysis), and under conditions which had proved to be useful in other systems in order to get evidences of the intervention of chelated species (reactions carried out in the presence of a metal salt or a metallic species).[1,7-9] The results obtained are shown in the Table.

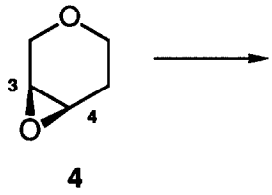
The determination of the relative amounts of the regioisomeric addition products (*C-3* and *C-4 type products*)[11] in the opening reactions of epoxide **4** was accomplished by GC analysis of the crude reaction mixture and/or by GC and ^{1}H NMR analysis of the acetylated crude reaction products. The relative structure of all the regioisomeric pairs[12] was unequivocally assigned on the basis of the ^{1}H NMR spectra of the corresponding acetylated products, by appropriate double resonance experiments on the proton H_a, α to the acetyl group, and by simple conformational consideration for these systems. The acetylation step was necessary in order both to identify unequivocally the signal of the proton H_a α to the OH group in the ^{1}H NMR spectra of the opening reaction products, and to improve, in some cases, the separation on TLC of the pairs of regioisomers (Scheme 1). The methyl alcohols **17** and **18** were also obtained by independent univocal synthetic pathways (Scheme 2). The reaction of commercially available

SCHEME 2



tetrahydropyran-4-one (**21**) with methylmagnesium iodide yielded 4-methyltetrahydropyran-4-ol (**22**) which was dehydrated to the olefin **23**. Hydroboration/oxidation of **23** afforded exclusively the *trans* methyl alcohol **17**. On the other hand, the LAH reduction of 3-methyltetrahydropyran-4-one (**25**), obtained by alkylation with methyl iodide both of the pyrrolidine enammine **24** and of the lithium enolate of ketone **21**, afforded a 77:23 mixture of the desired *trans* methyl alcohol **18** and of its *cis* isomer **26**. The two

Table. Regioselectivity of the Ring Opening Reactions of Epoxide 4 Under Non-Chelating and Chelating Conditions.



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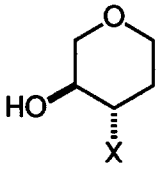
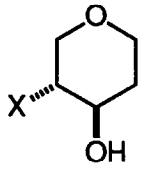


C-4 type product



C-3 type product

entry	reagents and reaction conditions	(time, °C)	%	%
1	$NHEt_2/EtOH$	(20h, 80)	15*a*	85*b*
2	$NHEt_2/H_2O$	(48h, r.t.)	30*a*	70*b*
3	$NHEt_2/CH_3CN$ 5 M $LiClO_4$	(18h, r.t.)	89*a*	11*b*
4	$NHEt_2/CH_3CN$ 10 M $LiClO_4$	(18h, r.t.)	95*a*	5*b*
5	$NHEt_2/CH_3CN$ 2.5 M $Mg(ClO_4)_2$	(18h, r.t.)	25*a*	75*b*
6	$NHEt_2/CH_3CN$ 2.5 M $Zn(O_3SCF_3)_2$	(18h, r.t.)	27*a*	73*b*
7	$NHEt_2/CH_3CN$ 2.5 M $NaClO_4$	(18h, r.t.)	89*a*	11*b*
8	$NHEt_2/CH_3CN$ 2.5 M $CaCl_2$	(18h, r.t.)	88*a*	12*b*
9	$NHEt_2/CH_3CN$ 2.5 M $KClO_4$	(18h, r.t.)	no reaction	
10	$NHMe_2/EtOH$	(60h, r.t.)	18*c,d*	82*d,e*
11	$NHMe_2/H_2O$	(40h, r.t.)	40*c,d*	60*d,e*
12	$NH(i\text{-}Pr)_2/EtOH$	(7 days, 80)	no reaction	
13	$NH(i\text{-}Pr)_2/CH_3CN$ 5M $LiClO_4$	(7 days, 80)	85*f*	15*g*
14	$NaN_3/MeOH/NH_4Cl$	(18h, 80)	83*h*	17*i*
15	$NaN_3/DMSO$	(24h, 120)	73*h*	27*i*
16	NaN_3/CH_3CN 5M $LiClO_4$	(18h, 80)	97*h*	3*i*
17	$KCN/MeOH/NH_4Cl$	(22h, 80)	85*j*	15*k*
18	KCN/CH_3CN 1.5M $LiClO_4$	(22h, 80)	98*j*	2*k*
19	$MeOH/H_2SO_4$	(1h, r.t.)	71*l*	29*m*
20	$MeOH/CH_3CN$ 5M $LiClO_4$	(18h, 80)	95*l*	5*m*
21	$MeOH/CH_3CN$ 2M $Mg(ClO_4)_2$	(18h, 80)	68*l*	32*m*
22	$HCl/CHCl_3$	(15 min, r.t.)	88*n,o*	12*o,p*
23	NH_4Cl/CH_3CN 5M $LiClO_4$	(18h, 80)	96*n*	4*p*
24	$TiCl_4/CH_2Cl_2$	(5h, 0)	86*n*	14*p*
25	$PhSH/MeOH/NEt_3$	(4h, r.t.)	87*q*	13*r*
26	$PhSH/CH_3CN$ 3M $LiClO_4$	(20h, 80)	96*q*	4*r*
27	$(CH_3)_2CuLi$	(15h, 0)	100*s*	0*t*
28	$Al(CH_3)_3$/pentane	(19h, r.t.)	100*s*	0*t*
29	$Al(CH_3)_3$/pentane/crown	(5h, r.t.)	54*s*	46*t*
30	$LiAlH_4$/pentane	(4h, r.t.)	96*u,v*	4*v,w*
31	$LiAlH_4$/pentane/crown	(5h, r.t.)	80*u*	20*w*

[a] Amino alcohol **5**, X=NEt_2. [b] Amino alcohol **6**, X=NEt_2 . [c] Amino alcohol **5**, X=NMe_2. [d] See ref. 13 and 14. [e] Amino alcohol **6**, X=NMe_2. [f] Amino alcohol **5**, X=N(*i*-Pr)$_2$. [g] Amino alcohol **6**, X=N(*i*-Pr)$_2$. [h] Azido alcohol **7** . [i] Azido alcohol **8**. [j] Hydroxy nitrile **9**. [k] Hydroxy nitrile **10**. [l] Methoxy alcohol **11**. [m] Methoxy alcohol **12**. [n] Chlorohydrin **13**. [o] Ref. 10 (dry HCl in Et_2O): **13/14** ratio=93:7. [p] Chlorohydrin **14**. [q] Thioalcohol **15** . [r] Thioalcohol **16**. [s] Methyl alcohol **17**. [t] Methyl alcohol **18**. [u] Alcohol **19**. [v] Ref. 10 (reaction in Et_2O): **19/20** ratio=93:7. [w] Alcohol **20**.

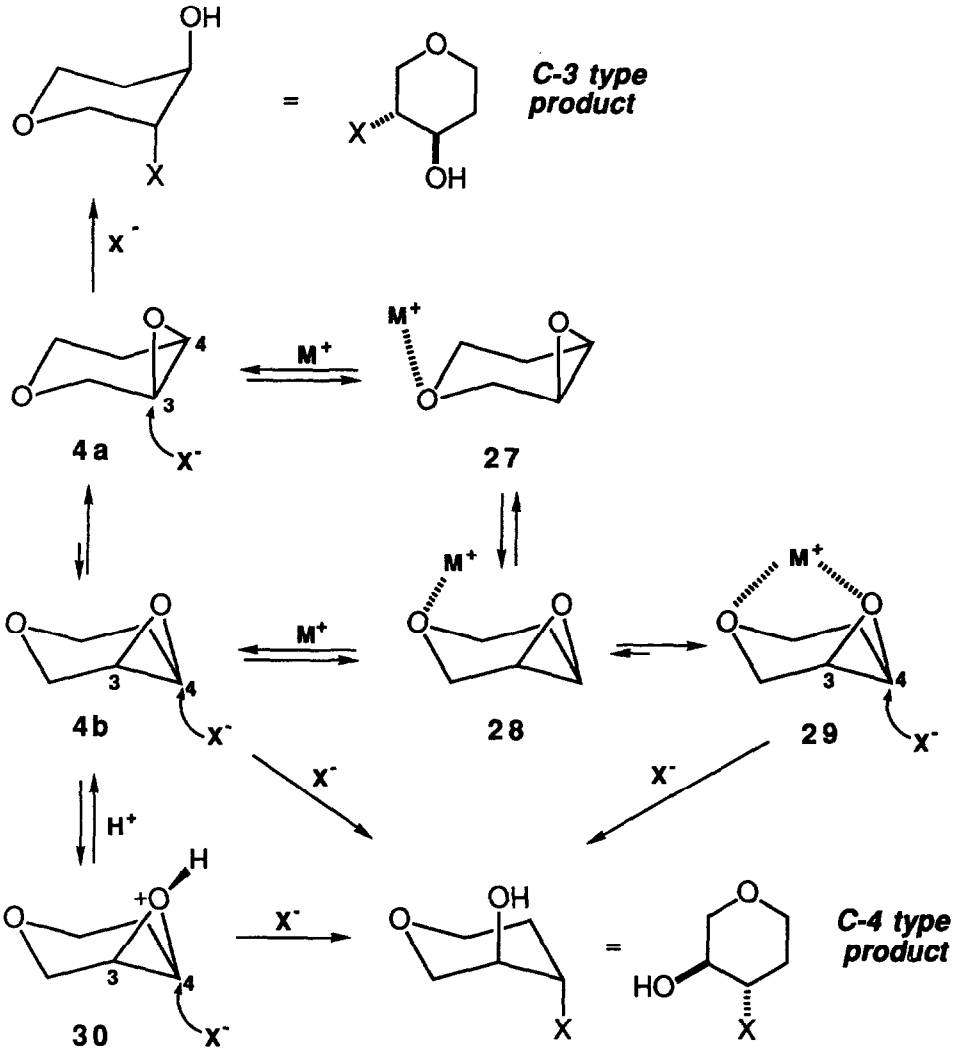
alcohols were then separated by preparative TLC and completely characterized by ^1H NMR spectroscopy. The reduction of **25** with LS-Selectride (Aldrich) was highly selective, affording almost exclusively, the *cis* isomer **26** (*cis* **26**: *trans* **18** ratio=97:3, ^1H NMR).

In accordance with results previously obtained with the same epoxide,[10] the attack of the nucleophile on epoxide **4** largely occurs, under standard conditions, on the C-4 affording, mostly, *C-4 type products*. The only exceptions are the aminolysis reactions in which the regioisomeric *C-3 type products* are predominantly formed.[13] When the reactions of **4** were carried out under chelating conditions, that is in the presence of a metal ion in a non-protic solvent, a modification of the regiochemistry of the ring opening was observed and an increase of the C-4 selectivity was always obtained. However, this increase in C-4 selectivity observed was largely dependent on the type and the amount of the metal ion. In particular, an almost complete inversion of the regioselectivity was found in the aminolysis reactions. The reactions of **4** with $(CH_3)_2CuLi$ and $Al(CH_3)_3$ and $LiAlH_4$, carried out under standard conditions, were highly (in the case of the reduction reaction) or completely C-4 selective (in the case of the reactions with Me_2CuLi and $AlMe_3$), due to the presence, also in these conditions, of a metal species (lithium or aluminum) (see below).

The C-4 selectivity observed in most of the reactions of epoxide **4** under non-chelating conditions (standard conditions) can be rationalized on the basis of the unfavorable electron-withdrawing inductive effect of the pyranoid oxygen on the closest C-3 oxirane carbon, which should make the attack of the nucleophile on that oxirane carbon less favored.[10] Due to this effect, epoxide **4** is forced to react largely in its less stable conformation **4b**[15] (or in the corresponding protonated species **30**) in order to allow a diaxial opening of the oxirane ring in accordance with the Fürst-Plattner rule (Scheme 3).[16] On the other hand, the formation of the *C-3 type products*, found as the main products in the aminolysis reactions of **4**, should arise from the axial attack of the nucleophile on the C-3 carbon through the more stable conformation **4a**.[15] However, it is not easy to explain why under non-chelating conditions, the aminolysis reactions exhibit such a different regioselectivity compared with the other reactions examined.

As for the reactions carried out under chelating conditions (that is in the presence of a metal ion), the constant increase in C-4 selectivity observed in all the reactions examined can be attributed to the intervention of bidentate-chelate structures of type **29** [1,7-9] (Scheme 3). In these conditions, the initial complexation of the metal ion with the tetrahydropyranosyl oxygen of **4**, in either conformation **4a** or **4b** to give **27** or **28** , respectively, followed by an entropically favored further coordination of the metal with the oxirane oxygen, yields the chelate structure **29** in which epoxide **4** is forced to adopt the unfavored conformation **4b**. The axial attack of the nucleophile on **29**, in accordance with the Fürst-Plattner rule,[16] will take place on the oxirane C-4 carbon, leading to *C-4 type product*. The generally observed increase in

SCHEME 3



X^- = HNR_2, N_3^-, CN^-, MeOH, Cl^-, PhSH, CH_3^-, H^-

C-4 selectivity is much more marked in the aminolysis reactions, in which an almost complete inversion of regioselectivity is observed on passing from non-chelating to chelating reaction conditions. In accordance with previous results,[1,7-9,17] and as expected for chelating-assisted additions, the *C-4 /C-3 type product* regioisomeric ratio of the aminolysis of **4** is very sensitive to the amount and the type of the metal ion utilized.[9] For example, an increase in the metal ion concentration (see entries 3 and 4, Table), which should be expected to additionally favor the reaction process passing by the bidentate-chelate structure **29**, leads to an increase in the amount of the *C-4 type product.*; moreover, a different ability of the metal ion to determine the regiochemistry of the reaction (*C-4 /C-3* selectivity, entries 3-9, Table) was observed. However, the relative order of effectiveness (Na^+=Li^+=Ca^{++}>>Zn^{++}> Mg^{++}) is different from the one observed in the case of epoxide **1** in which a quite different trend was found (Li^+> Mg^{++} > Zn^{++} > Na^+).[9] Evidently, a close correlation must exist between the structure of the epoxide and, consequently, of the chelate intermediate and the effectiveness of the metal ion.[8,9] However, this type of correlation is not, at present, very clear. It may also be pointed out that the particular methodology for the aminolysis of 1,2-epoxides which makes use of metal salt catalysis, is able, in the case of epoxide **4**, to promote its reaction with the bulky NH(*i*-Pr)$_2$ in contrast to the corresponding uncatalyzed aminolysis with the same amine which completely failed (entries 12 and 13, Table).[1,9,18]

The high or complete C-4 selectivity observed with organometallic reagents like Me_2CuLi, $AlMe_3$ and $LiAlH_4$, may reasonably be attributed to the effective intervention of a chelate-bidentate structure such as **29** through the metal species present in the reaction mixture (lithium or aluminum).[7,8] However, the C-4 selectivity may be reduced, sometimes markedly, when the same reactions are carried out in the presence of a crown ether (12-Crown-4) (entries 27-31, Table). In these conditions, the reduced amount of free metal species present in the reaction medium, as a consequence of the sequestering ability of the crown ether, reduces the reaction pathway which, by means of structures like **29**, leads to *C-4 type products*, thus determining an increase in C-3 selectivity.[7]

In conclusion the insertion of a remote polar group in a cyclic system, as in **4**, may be useful to control the regiochemistry of the oxirane ring opening through chelation processes assisted by metal ions. This result appears to be of some interest in the chemistry of the naturally related compounds such as the epoxy sugars.

EXPERIMENTAL

For general experimental procedure see ref.8. Epoxide **4** was prepared as previously described.[10,15] General procedure for acetylation: the crude reaction product (0.10 g) in anhydrous pyridine (2 ml) was treated at 0°C with Ac_2O (1 ml) and then left ar r.t. for 24 h. Toluene (10 ml) is added and the reaction mixture is carefully evaporated to dryness (rotating evaporator) to give a crude reaction product containing the acetylated regioisomeric opening products.

Reaction of Epoxide 4 with $NHEt_2$. a) A solution of epoxide **4** (0.20 g, 2.0 mmol) in EtOH (3 ml) was treated with $NHEt_2$ (0.53 ml, 5.0 mmol) and the resulting mixture was stirred at 80°C for 20 h. After cooling, dilution with ether and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude liquid product (0.32 g) consisting of a 15:85 mixture of amino alcohols **5** and **6** (R=Et) (GC, Table). This crude product was acetylated to give a corresponding mixture of acetylated amino alcohols **5-Ac** and **6-Ac** (R=Et) (0.40 g) which was subjected to preparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense bands (the faster moving band contained **6-Ac**, R=Et) afforded pure **5-Ac** (0.040 g) and **6-Ac** (0.25 g) (R=Et).

trans-*3-Acetoxy-4-(N,N-diethylamino)-tetrahydropyran* (**5-Ac, R=Et**), a liquid; IR (neat) 1742 cm^{-1} (C=O); ^1H NMR δ 4.88 (ddd, 1H, $J_{a,h}=J_{a,b}=10.4$ and $J_{a,e}=5.0$ Hz, H_a), 3.85-3.96 (m, 2H, H_e and H_f), 3.27 (ddd, 1H, $J_{f,g}=J_{c,g}=11.1$ and $J_{d,g}=2.9$ Hz, H_g), 3.07 (dd, 1H, $J_{e,h}=10.9$ and $J_{a,h}=9.7$ Hz, H_h), 2.67 (ddd, 1H, $J_{a,b}=J_{b,c}=10.4$ and $J_{b,d}=4.8$ Hz, H_b), 2.28-2.62 [m, 4H, J=7.1 Hz, $N(CH_2CH_3)_2$], 1.54-1.69 (m, 2H, H_c and H_d), 1.98 (s, 3H, CH_3CO), 0.92 [t, 6H, J= 7.1 Hz, $N(CH_2CH_3)_2$]. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83; N, 6.50 . Found: C, 61.30; H, 9.64; N, 6.45.

trans-*4-Acetoxy-3-(N,N-diethylamino)-tetrahydropyran* (**6-Ac, R=Et**), a liquid; IR (neat) 1742 cm^{-1} (C=O); ^1H NMR δ 5.06 (ddd, 1H, $J_{a,b}=J_{a,c}=10.2$ and $J_{a,d}=5.0$ Hz, H_a), 3.84-3.97 (m, 2H, H_e and H_f), 3.34 (ddd, 1H, $J_{f,g}=J_{c,g}=12.0$ and $J_{d,g}=2.3$ Hz, H_g), 3.28 (dd, 1H, $J_{b,h}=10.7$ and $J_{e,h}=11.4$ Hz, H_h), 2.79 (ddd, $J_{b,h}=J_{a,b}=10.2$ and $J_{b,e}=4.6$ Hz, H_b), 2.45-2.68 [m, 4H, J=7.1 Hz, $N(CH_2CH_3)_2$], 2.06 (s, 3H, CH_3CO), 1.58-1.76 (m, 2H, H_c and H_d), 0.99 [t, 6H, J=7.1 Hz, $N(CH_2CH_3)_2$]. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83; N, 6.50. Found: C, 61.25; H, 9.95; N, 6.45.

b) A solution of epoxide **4** (0.20 g, 2.0 mmol) in H_2O (1.0 ml) containing $NHEt_2$ (1.47 ml,1.4 mmol) was stirred at r.t for 48 h. Extraction with ether and evaporation of the washed (saturated aqueous NaCl) ether extracts afforded a crude liquid reaction product (0.31 g) consisting of a 30:70 mixture of amino alcohols **5** and **6** (R=Et) (GC, Table).

Reaction of Epoxide 4 with $NHEt_2$ in the presence of $LiClO_4$. A solution of epoxide **4** (0.10 g, 1.0 mmol) in anhydrous CH_3CN (2.0 ml) was treated with $NHEt_2$ (0.25 ml, 2.5 mmol) and $LiClO_4$ (2.12 g, 20.0 mmol) (10 M solution) and the resulting reaction mixture was stirred at r.t. for 18 h. Dilution with ether and evaporation of the washed (saturated aqueous NaCl) organic solvent afforded a crude reaction product (0.16 g) consisting of a 95:5 mixture of amino alcohols **5** and **6** (R=Et) (GC, Table).

The aminolysis of epoxide **4** with $NHEt_2$ in anhydrous CH_3CN was repeated in the presence of 5 M $LiClO_4$ and of different metal salts such as $Mg(ClO_4)_2$, $NaClO_4$, $Zn(OSO_2CF_3)_2$, $CaCl_2$ and $KClO_4$ (2.5 M solution) for 18 h at r.t., to give the results given in the Table (GC).

Reaction of Epoxide 4 with $NHMe_2$. a) A solution of epoxide **4** (0.20 g, 2.0 mmol) in 40% aqueous $NHMe_2$ (2.0 ml) was stirred at r.t. for 48 h. Extraction with ether and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude liquid product (0.25 g) consisting of a 40:60 mixture of amino alcohols **5** and **6** (R=Me) (GC, Table).[13,14] This crude product was acetylated to give a corresponding mixture of acetylated amino alcohols **5-Ac** and **6-Ac** (R=Me) (0.35 g) which was subjected to preparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense bands (the faster moving band contained **6-Ac**, R=Me) afforded pure **5-Ac** (0.10 g) and **6-Ac** (0.18 g) (R=Me).

trans-*3-Acetoxy-4-(N,N-dimethylamino)-tetrahydropyran* (**5-Ac, R=Me**), a liquid; IR (neat) 1740 cm^{-1} (C=O); ^1H NMR δ 4.89 (ddd, 1H, $J_{a,b}=J_{a,h}=9.2$ and $J_{a,e}=4.8$ Hz, H_a), 3.85-3.97 (m, 2H, H_e and H_f), 3.31 (ddd, 1H, $J_{f,g}=J_{c,g}=10.9$ Hz, H_g), 3.08 (dd, 1H, $J_{e,h}=11.0$ and $J_{a,h}=9.2$ Hz, H_h), 2.61 (ddd, 1H, $J_{b,c}=10.7$, $J_{a,b}=9.2$ and $J_{b,d}=4.5$ Hz, H_b), 2.25 [s, 6H, $N(CH_3)_2$] 2.01 (s,3H,CH_3CO), 1.50-1.85 (m, 2H, H_c and H_d). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H,9.15; N, 7.48. Found: C, 57.53; H, 9.27; N, 7.69.

trans-*4-Acetoxy-3-(N,N-dimethylamino)-tetrahydropyran* (**6-Ac, R=Me**), a liquid; IR (neat) 1740 cm^{-1} (C=O); ^1H NMR δ 5.00 (ddd, 1H, $J_{a,b}=J_{a,c}=9.6$ and $J_{a,d}=4.8$ Hz, H_a), 3.90 (dd, 1H, $J_{e,h}=11.6$ and $J_{e,b}=4.4$ Hz, H_e), 3.80 (ddd, 1H, $J_{f,g}=11.8$ and $J_{c,f}=J_{d,f}=3.4$ Hz, H_f), 3.33 (ddd, $J_{f,g}=J_{c,g}=11.8$ and $J_{d,g}=2.7$ Hz, H_g), 3.29 (dd, 1H, $J_{e,h}=11.6$ and $J_{b,h}=9.6$ Hz, H_h), 2.57 (ddd, 1H, $J_{a,b}=J_{b,h}=9.6$ and $J_{b,e}=4.4$ Hz, H_b), 2.31[s, 6H, $N(CH_3)_2$] , 2.02 (s, 3H, CH_3CO), 1.46-1.65 (m, 2H, H_c and H_d). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48 . Found: C, 57.88; H, 9.03; N, 7.31.

b) A solution of epoxide **4** (0.10 g, 1.0 mmol) in EtOH (1.5 ml) was treated with $NHMe_2$ (0.66 ml, 10.0 mmol) and the reaction mixture was stirred for 60 h at r.t. Extraction with ether and evaporation of

the washed (saturated aqueous NaCl) ether extracts afforded a crude liquid product (0.12 g) consisting of a 18:82 mixture of amino alcohols **5** and **6**, (R=Me).[13,14]

Reaction of Epoxide 4 with NH(*i*-Pr)$_2$. A solution of epoxide **4** (0.20 g, 2.0 mmol) in EtOH (3 ml) was treated with NH(*i*-Pr)$_2$ (0.56 ml, 4.0 mmol) and the resulting mixture was stirred at 80°C for 7 days. After cooling, usual workup afforded a crude liquid product (0.20 g) consisting of the unreacted starting epoxide.

Reaction of Epoxide 4 with NH(*i*-Pr)$_2$ in the Presence of LiClO$_4$. A solution of epoxide **4** (0.20 g, 2.0 mmol) in anhydrous CH_3CN (2.0 ml) was treated with NH(*i*-Pr)$_2$ (0.56 ml, 4.0 mmol) and $LiClO_4$ (1.06 g, 10.0 mmol) and the resulting reaction mixture was stirred for 7 days at 80°C. Usual workup afforded a crude liquid product consisting of a 85:15 mixture of amino alcohols **5** and **6** (R=*i*-Pr) (GC, Table). This crude product was acetylated to give a corresponding mixture of acetylated amino alcohols **5-Ac** and **6-Ac** (R=*i*-Pr)[12] which was subjected to semipreparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense band afforded pure trans *3-acetoxy-4-(N,N-diisopropylamino)-tetrahydropyran* (**5-Ac, R=*i*-Pr**):[12] IR (neat) 1742 cm^{-1} (C=O); ^{1}H NMR δ 4.74 (ddd, 1H, $J_{a,b}$=$J_{a,h}$=10.4 and $J_{a,e}$=5.5 Hz, H_a), 3.77-3.98 (m, 2H, H_e and H_f), 3.27 (ddd, 1H, $J_{c,g}$=$J_{f,g}$=11.7 and $J_{d,g}$=2.4 Hz, H_g), 3.05 (unresolved triplet, 1H, *J*=10.9, H_h), 3.08 [5 lines, 2H, *J*=6.9 Hz, N(CH)$_2$], 2.73 (ddd, 1H, $J_{b,c}$=$J_{a,b}$=10.4 and $J_{b,d}$=4.6 Hz, H_b), 1.94 (s, 3H, CH_3CO), 1.55-1.87 (m, 2H,H_c and H_d), 0.94 and 0.88 [2d, 6H each, *J*=6.6 Hz, 2 (*CH*$_3$)$_2$CH]. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.35; N, 5.75. Found: C, 64.29; H, 10.02; N, 5.98.

Reaction of Epoxide 4 with NaN_3 in DMSO. A solution of epoxide **4** (0.20 g, 2.0 mmol) in DMSO (20 ml) was treated with NaN_3 (0.65 g, 10.0 mmol) and the reaction mixture was stirred at 120°C for 24 h. After cooling, dilution with water, extraction with ether and evaporation of the washed (saturated aqueous NaCl) ether extracts afforded a crude liquid product (0.25 g) consisting of a 73:27 mixture of azido alcohols **7** and **8** (GC, Table). This crude product was acetylated to give a corresponding mixture (0.35 g) of acetylated azido alcohols **7-Ac** and **8-Ac** which was subjected to preparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense bands (the faster moving band contained **8-Ac**) afforded pure **7-Ac** (0.20 g) and **8-Ac** (0.060 g).

trans-*4-Azido-3-acetoxytetrahydropyran* (**7-Ac**), a liquid; IR (neat) 2110 (N_3) and 1747 cm^{-1} (C=O); ^{1}H NMR δ 4.69 (ddd, 1H, $J_{a,b}$=$J_{a,h}$=8.5 and $J_{a,e}$=4.5 Hz, H_a), 3.94 (dd, 1H, $J_{e,h}$= 11.2 and $J_{a,e}$=4.5 Hz, H_e), 3.85 (ddd, 1H, $J_{f,g}$=12.0 and $J_{c,f}$=$J_{d,f}$=4.0 Hz, H_f), 3.54 (ddd, 1H, $J_{b,c}$=10.1, $J_{a,b}$=8.5 and $J_{b,d}$=4.7 Hz, H_b), 3.38 (ddd, 1H, $J_{f,g}$=12.0, $J_{c,g}$=10.3 and $J_{d,g}$=2.8 Hz, H_g), 3.18 (dd, 1H, $J_{e,h}$=11.2 and $J_{a,h}$=8.5 Hz, H_h), 1.92-2.13 (m, 1H, H_d), 2.03 (s, 3H, CH_3CO), 1.53-1.73 (m, 1H, H_c). Anal. Calcd for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.98; N, 22.69. Found: C, 45.61; H, 5.74; N, 22.59.

trans-*3-Azido-4-acetoxytetrahydropyran* (**8-Ac**), a liquid; IR (neat) 2110 (N_3) and 1747 cm^{-1} (C=O); ^{1}H NMR δ 4.78 (ddd, 1H, $J_{a,b}$=10.1, $J_{a,c}$=8.9 and $J_{a,d}$=4.8 Hz, H_a), 3.89 (m,2H, H_e and H_f), 3.50 (m,1H, H_g), 3.39 (ddd, 1H, $J_{b,h}$=$J_{a,b}$=10.1 and $J_{b,e}$=2.6 Hz, H_b), 3.14 (dd, 1H, $J_{e,h}$=11.6 and $J_{b,h}$=10.1 Hz, H_h), 2.05 (s,3H, CH_3CO), 1.79-1.95 (m, 1H, H_d), 1.51-1.72 (m, 1H, H_c). Anal. Calcd for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.98; N, 22.69. Found: C, 45.37; H, 5.80; N, 22.52.

Reaction of Epoxide 4 with NaN_3-NH_4Cl. A solution of epoxide **4** (0.10 g, 1.0 mmol) in a 8:1 MeOH/H_2O mixture (5.0 ml) was treated with NaN_3 (0.33 g, 5.0 mmol) and NH_4Cl (0.118 g, 2.2 mmol) and the reaction mixture was stirred at 80°C for 18 h. Dilution with water, extraction with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and NaCl) ether extracts afforded a crude liquid product (0.13 g) consisting of a 83:17 mixture of azido alcohols **7** and **8** (GC, Table).

Reaction of Epoxide 4 with NaN_3-$LiClO_4$ in CH_3CN. A solution of epoxide **4** (0.10 g, 1.0 mmol) in anhydrous CH_3CN (2.0 ml) was treated with NaN_3 (0.087 g, 1.34 mmol) and $LiClO_4$ (1.06 g, 10.0 mmol) and the reaction mixture was stirred at 80°C for 18 h. Usual workup afforded a crude liquid product (0.14 g) consisting of a 97:3 mixture of azido alcohols **7** and **8** (GC, Table).

Reaction of Epoxide 4 with KCN-NH_4Cl. A solution of epoxide **4** (0.20 g, 2.0 mmol) in a 8:1 MeOH/H_2O mixture (10 ml) was treated with KCN (0.65 g, 10.0 mmol) and NH_4Cl (0.23 g, 4.3 mmol) and the reaction mixture was stirred at 80°C for 22 h. Dilution with water, extraction with ether and

evaporation of the washed (saturated aqueous $NaHCO_3$ and NaCl) ether extracts afforded a crude liquid product (0.24 g) consisting of a 85:15 mixture of hydroxy nitriles **9** and **10** (GC, Table). This crude product was acetylated to give a corresponding mixture (0.31 g) of acetylated nitriles **9-Ac** and **10-Ac** which was subjected to preparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense bands (the faster moving band contained **10-Ac**) afforded pure **9-Ac** (0.18 g) and **10-Ac** (0.020 g).

trans-*3-Acetoxytetrahydropyran-4-carbonitrile* (**9-Ac**), a liquid; IR (neat) 2247 (CN) and 1743 cm^{-1} (C=O); ^1H NMR δ 4.93 (ddd, 1H, $J_{a,b}=J_{a,h}=7.0$ and $J_{a,e}=3.5$ Hz, H_a), 4.02 (dd, 1H, $J_{e,h}=12.0$ and $J_{a,e}=3.5$ Hz, H_e), 3.89 (ddd, $J_{f,g}=11.3$, $J_{c,f}=6.1$ and $J_{d,f}=3.7$ Hz, H_f), 3.57 (ddd, 1H, $J_{f,g}=11.3$, $J_{c,g}=7.9$ and $J_{d,g}=3.2$ Hz, H_g), 3.42 (dd, $J_{e,h}=12.0$ and $J_{a,h}=7.0$ Hz, H_h), 2.94 (ddd, $J_{a,b}=J_{b,c}=7.0$ and $J_{b,d}=4.5$ Hz, H_b), 2.11-2.26 (m, 1H, H_d), 2.13 (s, 3H, CH_3CO), 1.84-2.01 (m, 1H, H_c). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.27. Found: C, 56.54; H, 6.27; N, 8.01.

trans-*4-Acetoxytetrahydropyran-4-carbonitrile* (**10-Ac**), a liquid; IR (neat) 2247 (CN) and1743 cm^{-1} (C=O); ^1H NMR δ 5.06 (ddd, 1H, $J_{a,b}=J_{a,c}=9.0$ and $J_{a,d}=4.4$ Hz, H_a), 4.14 (dd, 1H, $J_{e,h}=11.8$ and $J_{b,e}=4.1$ Hz, H_e), 3.98 (ddd, 1H, $J_{f,g}=12.2$ and $J_{c,f}=J_{d,f}=4.0$ Hz, H_f), 3.63 (dd, $J_{e,h}=11.8$ and $J_{b,h}=9.0$ Hz, H_h), 3.56 (m,1H, H_g), 2.85 (ddd, 1H, $J_{a,b}=J_{b,h}=9.0$ and $J_{b,e}=4.1$ Hz, H_b), 2.11-2.24 (m, 1H, H_d), 2.13 (s, 3H, CH_3CO), 1.53-1.72 (m, 1H, H_c). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.27. Found: C, 56.43; H, 6.35; N, 8.42.

Reaction of Epoxide 4 with KCN-$LiClO_4$ in CH_3CN. A solution of epoxide **4** (0.10 g, 1.0 mmol) in anhydrous CH_3CN (1.0 ml) was treated with KCN (0.097 g, 1.5 mmol) and $LiClO_4$ (0.16 g, 1.5 mmol) and the reaction mixture was stirred at 80°C for 22 h. Usual workup gave a crude liquid product (0.12 g) consisting of a 98:2 mixture of hydroxy nitriles **9** and **10** (GC, Table).

Reaction of Epoxide 4 with 0.2 N H_2SO_4 in Anhydrous MeOH. A solution of epoxide **4** (0.10 g, 1.0 mmol) in a 0.2 N H_2SO_4 in anhydrous MeOH (10 ml) was stirred at r.t. for 1 h. Dilution with water, extraction with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and NaCl) ether extracts afforded a crude liquid product (0.12 g) consisting of a 71:29 mixture of methoxy alcohols **11** and **12** (GC and ^1H NMR, Table).[12] This crude product was acetylated to give a corresponding mixture (0.16 g) of acetylated methoxy alcohols **11-Ac** and **12-Ac** which was subjected to preparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense band afforded pure trans-*3-acetoxy-4-methoxytetrahydropyran* (**11-Ac**)[12] (0.090 g), a liquid; IR (neat) 1739 cm^{-1} (C=O); ^1H NMR δ 4.70 (ddd, 1H, $J_{a,b}=J_{a,h}=6.0$ and $J_{a,e}=3.4$, H_a), 3.86 (dd, 1H, $J_{e,h}=11.9$ and $J_{a,e}=3.4$ Hz, H_e), 3.76 (ddd, 1H, $J_{f,g}=11.6$ and $J_{c,f}=J_{d,f}=4.0$ Hz, H_f), 3.29-3.52 (m, 3H, H_b, H_g and H_h), 3.34 (s, 3H, OCH_3), 1.93-2.03 (m, 1H, H_d), 2.03 (s,3H,CH_3CO), 1.50-1.70 (m, 1H, H_c). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found; C, 55.32; H, 8.26.

Reaction of Epoxide 4 with MeOH-$LiClO_4$ in CH_3CN. A solution of epoxide **4** (0.10 g, 1.0 mmol) in CH_3CN (1.0 ml) containing MeOH (0.4 ml, 10.0 mmol) and $LiClO_4$ (0.53 g, 5.0 mmol) was stirred at 80°C for 18 h. Dilution with ether and evaporation of the washed (saturated aqueous NaCl) ether extracts afforded a crude liquid residue consisting of a 95:5 mixture of hydroxyethers **11** and **12** (GC, Table). The same reaction was repeated using $Mg(ClO_4)_2$ as the metal salt (2M solution) to give the result shown in the Table.

Reaction of Epoxide 4 with HCl-$CHCl_3$. A solution of epoxide **4** (0.10 g, 1.0 mmol) in anhydrous $CHCl_3$ (10 ml) was treated with 36% aqueous HCl (10 ml) and the reaction mixture was stirred at r.t. for 15 min. Evaporation of the washed (saturated aqueous $NaHCO_3$ and NaCl) organic solvent afforded a crude liquid reaction product (0.13 g) consisting of a 88:12 mixture of chlorohydrins **13** and **14** (GC and ^1H NMR, Table)[10,12] which was subjected to semipreparative TLC. Extraction of the most intense band afforded pure trans-*4-chlorotetrahydropyran-3-ol* (**13**)[10,12] (0.070 g), a liquid; IR (CCl_4) 3601 cm^{-1} (OH); ^1H NMR δ 4.04 (dd, 1H, $J_{e,h}=11.5$ and $J_{a,e}=4.4$ Hz, H_e), 3.85-3.95 (m, 1H, H_f), 3.83 (dd, 1H, $J_{a,b}=J_{a,h}=8.0$ and $J_{a,e}=4.4$ Hz, H_a), 3.60 (ddd, 1H, $J_{b,c}=J_{a,b}=8.0$ and $J_{b,d}=3.7$ Hz, H_b), 3.31-3.45 (8 lines, 1H, $J_{f,g}=12.5$, $J_{c,g}=9.8$ and $J_{d,g}=2.9$ Hz, H_g), 3.20 (dd, 1H, $J_{e,h}=11.5$ and $J_{a,h}=8.0$ Hz, H_h), 2.12-2.25 (m, 1H, H_d), 1.77-1.96 (m, 1H, H_c). Anal. Calcd for $C_5H_9ClO_2$: C, 43.97; H, 6.64. Found: C, 43.69; H, 6.74. **13-Ac**, a liquid; IR (neat) 1747 cm^{-1} (C=O); ^1H NMR δ 4.78 (ddd, 1H, $J_{a,b}=J_{a,h}=7.0$ and $J_{a,e}=3.8$ Hz, H_a), 3.94-4.04 (m, 2H, H_b and H_e), 3.80-3.91 (8 lines, 1H, $J_{f,g}=11.8$, $J_{c,f}=6.1$ and $J_{d,f}=3.9$ Hz, H_f), 3.39-

3.52 (8 lines, 1H, $J_{f,g}$= 11.8, $J_{c,g}$=8.0 and $J_{d,g}$=3.2 Hz, H_g), 3.31 (dd, 1H, $J_{e,h}$=12.0 and $J_{a,h}$=7.0 Hz, H_h), 2.09-2.32 (m, 1H, H_d), 2.04 (s, 3H, CH_3CO), 1.78-1.97 (m, 1H, H_c). Anal. Calcd for $C_7H_{11}ClO_3$: C, 47.07; H, 6.20. Found: C, 47.25; H, 6.54.

Reaction of Epoxide 4 with NH_4Cl-$LiClO_4$ in CH_3CN. A solution of epoxide **4** (0.10 g, 1.0 mmol) in anhydrous CH_3CN (1.0 ml) was treated with NH_4Cl (0.106 g, 2.0 mmol) and $LiClO_4$ (1.064 g, 10.0 mmol) and the reaction mixture was stirred at 80°C for 18 h. Dilution with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and NaCl) ether solution afforded a crude liquid reaction product (0.13 g) consisting of a 96:4 mixture of chlorohydrins **13** and **14** (GC and ^1H NMR, Table).

Reaction of Epoxide 4 with $TiCl_4$. A solution of epoxide **4** (0.050 g, 0.5 mmol) in anhydrous CH_2Cl_2 (10 ml) was treated at 0°C with $TiCl_4$ (0.16 ml, 1.5 mmol) and the reaction mixture was stirred for 5 h at the same temperature, then diluted with CH_2Cl_2 (20 ml). Saturated aqueous Na_2SO_4 (10 ml) was added and stirring prolonged for 30 min. Evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude liquid reaction product (0.060 g) consisting of a 86:14 mixture of chlorohydrins **13** and **14** (GC and ^1H NMR, Table).

Reaction of Epoxide 4 with PhSH-NEt_3. A solution of epoxide **4** (0.10 g, 1.0 mmol) in MeOH (1.0 ml) was treated with PhSH (0.3 ml, 3.0 mmol) and Et_3N (0.41 ml, 3.0 mmol) and the reaction mixture was stirred 4 h at r.t. Dilution with water, extraction with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and NaCl) ether extracts afforded a crude liquid product (0.20 g) consisting of a 87:13 mixture of thioalcohols **15** and **16** (GC and ^1H NMR, Table)[12] which was subjected to preparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense band afforded pure *trans-4-phenylthiotetrahydropyran-3-ol* **(15)**[12] (0.14 g), a liquid; IR (CCl_4) 3645 (free OH) and 3585 cm^{-1} (1,2 OH···O); ^1H NMR δ 7.44-7.51 (m, 2H), 7.26-7.35 (m, 3H), 4.10 (dd, 1H, $J_{e,h}$=11.1 and $J_{a,e}$=4.4 Hz, H_e), 3.87 (ddd, 1H, $J_{f,g}$=11.6, $J_{c,f}$=$J_{d,f}$=4.1 Hz, H_f), 3.34-3.56 (m, 2H, H_b and H_g), 3.23 (dd, 1H, $J_{c,h}$=11.1 and $J_{a,h}$=9.8 Hz, H_h), 2.99 (ddd, 1H, $J_{a,h}$=9.8, $J_{a,b}$=8.9 and $J_{a,e}$=4.4 Hz, H_a), 2.05 (8 lines, 1H, $J_{c,d}$=10.1 and $J_{d,g}$=$J_{d,f}$=$J_{d,b}$=4.1 Hz, H_d), 1.71 (m,1H, H_c). Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.82; H, 6.71. Found; C, 62.93; H, 6.70. **15-Ac**, a liquid; IR (neat) 1747 cm^{-1} (C=O); ^1H NMR δ 7.42-7.55 (m, 2H), 7.15-7.38 (m, 3H), 4.82 (ddd, 1H, $J_{a,b}$=$J_{a,h}$=7.4 and $J_{a,e}$=3.8 Hz, H_a), 4.05 (dd, 1H, $J_{e,h}$=11.7 and $J_{a,e}$=3.8 Hz, H_e), 3.90 (8 lines, 1H, $J_{f,g}$=11.6 Hz, $J_{d,f}$=4.6 and $J_{c,f}$=3.2 Hz, H_f), 3.53 (7 lines, 1H, $J_{f,g}$=11.6, $J_{c,g}$=8.6 and $J_{d,g}$=3.2 Hz, H_g), 3.36 (dd, 1H, $J_{e,h}$=11.7 and $J_{a,h}$=7.4 Hz, H_h), 3.32 (ddd, 1H, $J_{b,c}$=11.7 and $J_{a,b}$=$J_{a,c}$=7.4 Hz, H_b), 2.09 (s, 3H, CH_3CO), 1.62-1.79 (m, 2H, H_c and H_d). Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39. Found: C, 61.96; H, 6.31.

Reaction of Epoxide 4 with PhSH-$LiClO_4$ in CH_3CN. A solution of epoxide **4** (0.10 g, 1.0 mmol) in anhydrous CH_3CN (1.0 ml) was treated with PhSH (0.31 ml, 3.0 mmol) and $LiClO_4$ (0.32 g, 3.0 mmol) and the reaction mixture was stirred at 80°C for 20 h. Usual workup afforded a crude liquid reaction product (0.20 g) consisting of a 96:4 mixture of thioalcohols **15** and **16** (GC and ^1H NMR, Table).

4-Methyltetrahydropyran-4-ol (22). A solution of tetrahydropyran-4-one (**21**) (1.5 g, 15.0 mmol) in anhydrous ether (10 ml) was dropwise added to an excess of CH_3MgI [prepared from 1.6 g (66.0 g-atoms) of Mg and 8.5 g (60.0 mmol) of CH_3I] in anhydrous ether (30 ml), then the reaction mixture was gently refluxed for 2 h. Usual workup afforded a crude liquid product (0.58 g) consisting of alcohol **22** practically pure, which was directly used in the next step. An analytical sample of crude **22** was purified by semipreparative TLC (a 8:2 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense band afforded pure **22**, as a liquid; IR (neat) 3200 cm^{-1} (OH); ^1H NMR δ 3.49-3.72 (m, 2H), 1.35-1.61 (m, 2H), 1.14 (s, 3H). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.49. Found: C, 62.10; H, 10.37.

4-Methyl-5,6-dihydro(2*H*)-pyran (23). A solution of alcohol **22** (0.58 g) in anhydrous benzene (20 ml) was refluxed for 3 h in a Dean-Stark apparatus in the presence of *p*-toluenesulfonic acid (0.060 g). Evaporation of the washed (saturated aqueous $NaHCO_3$) organic solution afforded a crude liquid reaction product (0.51 g) mostly consisting of olefin **23** (GC and ^1H NMR) which was purified by filtration on a short silica gel column. Elution with hexane afforded pure olefin **23** (0.45 g) as a liquid; ^1H NMR δ 5.38 (m,1H), 4.07 (m, 2H), 3.76 (t, *J*= 5.6 Hz, 2H), 2.00 (m,2H), 1.69 (s, 3H). Anal.Calcd for $C_6H_{10}O$: C, 73.42; H, 10.26. Found: C, 73.54; H, 10.48.

Hydroboration-Oxidation of Olefin 23. A solution of olefin **23** (0.198 g, 2.0 mmol) in anhydrous THF (15 ml) was treated under stirring at 0 °C with 10 M BH_3·Me_2S (2.0 ml), then the reaction mixture was stirred at r.t. for 12 h. Water was carefully added in order to destroy the excess of borane and the resulting reaction mixture was treated at 40°C with 2.5 N aqueous NaOH (0.2 ml) and 36% H_2O_2 (0.14 ml). After 1 h stirring at r.t., dilution with water, extraction with ether and evaporation of the washed (water) ether extracts afforded a crude liquid product (0.14 g) mostly consisting of methyl alcohol **17** which was purified by preparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense band afforded pure trans-*4-methyltetrahydropyran-3-ol* (**17**) (0.11 g), as a liquid; IR (CCl_4) 3624 (free OH) and 3601 cm^{-1} (1,2 OH··O); ^1H NMR δ 3.86 (dd, 1H, $J_{e,h}$=10.7 and $J_{a,e}$=5.3 Hz, H_e), 3.78 (ddd, 1H, $J_{f,g}$=10.6, $J_{c,f}$=5.0 and $J_{d,f}$=3.8 Hz, H_f), 3.29 (ddd, 1H, $J_{f,g}$=$J_{c,g}$=116 and $J_{d,g}$=2.7 Hz, H_g), 3.19 (ddd, 1H, $J_{a,b}$=$J_{a,h}$=9.2 and $J_{a,e}$=5.3 Hz, H_a), 2. 99 (dd, 1H, $J_{e,h}$= 10.7 and $J_{a,h}$=9.2 Hz, H_h), 1.56-1.67 (m, 1H, H_d), 1.18-1.51 (m, 2H, H_b and H_c), 1.00 (dd, 3H, *J*=6.2 Hz, CH_3). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.49. Found: C, 62.25; H, 10.21. **17-Ac**, a liquid; IR (neat) 1740 cm^{-1} (C=O); ^1H NMR δ 4.45 (ddd, 1H, $J_{a,b}$=$J_{a,h}$=9.2 and $J_{a,e}$=4.6 Hz, H_a), 3.89 (dd, 1H, $J_{e,h}$= 10.8 and $J_{a,e}$=4.6 Hz, H_e), 3.80 (ddd, 1H, $J_{f,g}$= 11.4, $J_{c,f}$=6.8 and $J_{d,f}$= 4.2 Hz, H_f), 3.30 (ddd, 1H, $J_{f,g}$=$J_{c,g}$=11.4 and $J_{d,g}$=2.4 Hz, H_g), 3.04 (dd, 1H, $J_{e,h}$= 10.8 and $J_{a,h}$=9.2 Hz, H_h), 1.99 (s, 3H, CH_3CO), 1.30-1.75 (m, 3H, H_b, H_c and H_d), 0.92 (d, 3H, J=6.4 Hz, CH_3). Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.91. Found: C, 60.91; H, 8.74.

3-Methyltetrahydropyran-4-one (25). a) A solution of 4-pyranone (**21**) (1.0 g, 10.0 mmol) in anhydrous benzene (10 ml) and pyrrolidine (1.40 g, 20.0 mmol) was refluxed for 24 h in a Dean-Stark apparatus. Benzene and excess of amine were removed under vacuum (rotating evaporator) and the crude oily enamine **24** [IR (neat) 1647 cm^{-1} (C=C)] was taken up in anhydrous benzene (10 ml) then treated with excess of CH_3I. The resulting reaction mixture was gently refluxed for 24 h: water was added and refluxing prolonged for 30 min. Evaporation of the organic solution afforded an oily product (0.70 g) mostly consisting of methyl ketone **25** (^1H NMR) which was purified by preparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense band afforded pure **25** (0.32 g), as a liquid; IR (neat) 1714 cm^{-1} (C=O); ^1H NMR δ 4.12-4.30 (m,2H, H_e and H_f), 3.72 (ddd, 1H, $J_{f,g}$=$J_{c,g}$=11.5 and $J_{d,g}$=3.1 Hz, H_g), 3.32 (unresolved triplet, 1H, $J_{e,h}$=$J_{b,h}$=10.7 Hz, H_h), 2.50-2.77 (m, 2H, H_b and H_c), 2.40 (ddd, 1H, $J_{c,d}$=13.9 and $J_{d,g}$=$J_{d,f}$=3.1 Hz, H_d), 0.99 (d, 3H, *J*=6.8 Hz, CH_3). Anal.Calcd for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.15; H, 8.64.

b) A solution of diisopropylamine (1.54 ml, 11.0 mmol) in anhydrous THF (6.0 ml) was treated under stirring at 0°C with 1.6 M BuLi in hexane (6.8 ml). After 10 min a solution of ketone **21** (1.0 g, 10.0 mmol) in anhydrous THF (2 ml) was added and the reaction mixture was maintained at 0°C with stirring for 20 min. MeI (0.68 ml, 11.0 mmol) was added at 0°C, then the reaction mixture was allowed to warm to r.t., then left at this temperature for 20 h. Dilution with Et_2O and saturated aqueous NH_4Cl, and evaporation of the washed (water) organic solution afforded a crude liquid product (0.68 g) which was subjected to preparative TLC (a 8:2 mixture of hexane and AcOEt was used as the eluant). Extraction of the fastest moving band afforded pure ketone **25** (0.20 g).

Reduction of Ketone 25. a) A solution of ketone **25** (0.12 g, 1.05 mmol) in pentane (5 ml) was treated with $LiAlH_4$ (0.10 g) and the reaction mixture was stirred at r.t. for 8 h. Usual workup afforded a crude oily product (0.11 g) consisting of a 77:23 mixture of diastereoisomeric methyl alcohols *trans* **18** and *cis* **26** (GC and ^1H NMR) which was subjected to preparative TLC (a 8:2:0.1 mixture of hexane:AcOEt:MeOH was used as the eluant). Extraction of the most intense bands (the faster moving band contained **26**) afforded pure methyl alcohols **18** and **26**.

trans-*3-methyltetrahydropyran-4-ol* (**18**), a liquid; IR (CCl_4) 3622 cm^{-1} (free OH); ^1H NMR δ 3.89 (m, 1H, H_f), 3.76 (dd, 1H, $J_{e,h}$=11.7 and $J_{e,b}$=5.3 Hz, H_e), 3.21-3.47 (m, 2H, H_a and H_g), 2.92 (unresolved triplet, 1H, $J_{e,h}$=$J_{b,h}$=11.7 Hz, H_h), 1.73-1.88 (m, 1H, H_d), 1.41-1.65 (m, 2H, H_b and H_c), 0.86 (d, 3H, *J*=6.6 Hz, CH_3). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.49. Found: C, 62.14; H, 10.56. **18-Ac**, a liquid; IR (neat) 1740 cm^{-1} (C=O); ^1H NMR δ 4.59 (ddd, 1H, $J_{a,c}$=$J_{a,b}$=9.9 and $J_{a,d}$=4.6 Hz, H_a), 3.92-4.05 (m, 1H, H_f), 3.87 (dd, 1H, $J_{e,h}$=12.5 and $J_{b,e}$=5.6 Hz, H_e), 3.40-3.53 (m, 1H, H_g), 3.10 (unresolved triplet, 1H, *J*=11.0 Hz, H_h), 2.07 (s, 3H, CH_3CO), 1.92-2.11 (m, 1H, H_b), 1.51-1.90 (m, 2H, H_c and H_d), 0.85 (d, 3H, *J*=6.7 Hz, CH_3). Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.91. Found: C, 61.04; H, 8.69.

cis-3-methyltetrahydropyran-4-ol (**28**), a liquid; IR (CCl_4) 3626 cm^{-1} (free OH); ^1H NMR δ 3.86 (dd, 1H, $J_{a,h}$=6.2 and $J_{a,b}$=$J_{a,c}$=3.3 Hz, H_a), 3.74 (ddd, 1H, $J_{f,g}$=11.5, $J_{c,g}$=9.0 and $J_{d,g}$=3.5 Hz, H_g), 3.55 (ddd, 1H, $J_{f,g}$=11.5 and $J_{c,f}$=$J_{d,f}$=4.0 Hz, H_f), 3.46 (d, 2H, J=6.4 Hz, H_e and H_h), 1.57-1.97 (m, 3H, H_b, H_c and H_d), 0.85 (d, 3H, J=7.2 Hz, CH_3). Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.91. Found: C, 60.94; H, 8.95. **28-Ac**, a liquid; IR (neat) 1737 cm^{-1} (C=O); ^1H NMR δ 5.01 (q, 1H, $J_{a,b}$=$J_{a,c}$=$J_{a,d}$=4.0 Hz, H_a), 3.41-3.70 (m, 4H, H_e, H_f, H_g, and H_h), 1.90-2.14 (m, 1H, H_b), 2.06 (s, 3H, CH_3CO), 1.74-1.82 (m, 2H, H_c and H_d), 0.84 (d, 3H, J=7.0 Hz, CH_3). Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.91. Found: C, 60.59; H, 8.78.

b) A solution of ketone **25** (0.20 g, 1.75 mmol) in anhydrous THF (2.5 ml) was added to a 1M LS-Selectride (Aldrich) solution in THF (2.1 ml) at 0°C. The resulting mixture was stirred for 2 h at 0°C, then 2 h at r.t. Water (1 ml) and EtOH (1.5 ml) were added and the organoborane was oxidized with 6N NaOH (0.9 ml) and 36% H_2O_2 (1.2 ml). After 30 min stirring at r.t., the reaction mixture was saturated with anhydrous K_2CO_3, the organic phase separated, and the aqueous phase extracted with ether. Evaporation of the combined organic solutions afforded a crude reaction product (0.19 g) consisting of a 97:3 mixture of alcohols **26** and **18** (^1H NMR) which was subjected to semipreparative TLC (a 8:2:0.1 mixture of hexane, AcOEt and MeOH was used as the eluant). Extraction of the most intense band afforded pure *cis* alcohol **26**.

Reaction of Epoxide 4 with Me_2CuLi. 1.6 M MeLi in ether (3.75 ml) was added at -15°C to a suspension of CuI (0.57 g, 3.0 mmol) in anhydrous ether (5 ml). After 15 min at the same temperature, the epoxide **4** (0.10 g, 1.0 mmol) was added and the reaction mixture was slowly (4 h) warmed to 0°C, then kept under stirring at this temperature for 18 h. Usual workup afforded a crude reaction product (0.11 g) consisting of methyl alcohol **17** practically pure (GC and ^1H NMR, Table).

Reaction of Epoxide 4 with $AlMe_3$. A solution of epoxide **4** (0.10 g, 1.0 mmol) in pentane (5 ml) was treated under nitrogen, at -50°C with 2M $AlMe_3$ in hexane (1.5 ml). The reaction mixture was slowly warmed to 0°C, stirred 3 h at this temperature, then 19 h at r.t. Dilution with ether (30 ml), followed by carefull addition of water and 5% aqueous HCl, and evaporation of the washed (saturated aqueous $NaHCO_3$ and water) ether solution afforded a crude liquid product (0.085 g) consisting of methyl alcohol **17** practically pure (GC and ^1H NMR, Table).

Reaction of Epoxide 4 with $AlMe_3$ in the Presence of 12-Crown-4. A solution of $AlMe_3$ (3.0 mmol) in pentane (5 ml) was treated at 0°C, under nitrogen, with 12-Crown-4 (0.5 ml, 3.1 mmol) and the resulting suspension was stirred at r.t. for 15 h. Epoxide **4** (0.10 g, 1.0 mmol) in pentane (2 ml) was added and the reaction mixture was stirred for 5 h at r.t. Usual workup afforded a crude liquid product consisting of a 54:46 mixture of the two methyl alcohols **17** and **18** (GC and ^1H NMR, Table).

Reduction of Epoxide 4 with $LiAlH_4$. A solution of epoxide **4** (0.10 g, 1.0 mmol) in pentane (5 ml) was treated with $LiAlH_4$ (0.10 g) and the resulting suspension was stirred 4 h at r.t. Usual workup afforded a crude liquid product (0.10 g) consisting of a 96:4 mixture of alcohols **19** and **20** (GC and ^1H NMR, Table),[10] which was subjected to semipreparative TLC (a 8:2 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense bans afforded pure *tetrahydropyran-3-ol* (**19**) as an oil: IR (CCl_4) 3614 (free OH) and 3595 cm^{-1} (1,2 OH···O); ^1H NMR δ 3.50-3.83 (m, 4H), 3.34-3.48 (m, 1H), 1.73-2.00 (m, 2H), 1.45-1.50 (m, 2H). Anal. Calcd for $C_5H_{10}O_2$: C, 58.80; H, 9.86. Found: C, 58.76; H, 9.74.

A sample of pure *tetrahydropyran-4-ol* (**20**) was obtained by $LiAlH_4$ reduction of ketone **21**: IR (CCl_4) 3622 cm^{-1} (free OH). **20** is a commercially available product, too.

Reaction of Epoxide 4 with $LiAlH_4$ in the Presence of 12-Crown-4. A suspension of $LiAlH_4$ (0.078 g, 2.0 mmol) in pentane (5 ml) was treated with 12-Crown-4 (0.36 ml, 2.2 mmol) and the mixture was stirred at r.t. for 15 h. Epoxide **4** (0.10 g, 1.0 mmol) in pentane (2 ml) was then added and stirring of the reaction mixture was prolonged for 5 h at r.t. Usual workup afforded a crude reaction product consisting of a 80:20 mixture of alcohols **19** and **20** (GC and ^1H NMR, Table).

References and Notes

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11. The *C-3* and *C-4 type product* nomenclature refers to the attacking site of the nucleophile (i.e. at the C-3 or C-4 oxirane carbon of **4**, respectively) in accordance with the numbering scheme shown for **4** in Scheme 1 and in the Table.
12. The amino alcohol **6** (R=*i*-Pr), the methoxy alcohol **12**, the chlorohydrin **14** and the thioalcohol **16** (or their acetates) were not obtained in the pure state because they did not separate on preparative TLC from the corresponding regioisomer. However their presence was confirmed by GC and ^{1}H NMR analysis of the crude reaction mixtures.
13. A practically reverse regiochemical result was previously reported[14] for the reaction of **4** with dimethylamine: **5**:**6** (R=Me) ratio= 33:67. The regiochemical assignement of **5** and **6** (R=Me) was made by the Russian authors by the mass spectra of these compounds.[14b] However, as a consequence of the univocal assignement of the exact structure of compounds **5** and **6** (R=Me) made in this paper by ^{1}H NMR spectroscopy, the attribution proposed by the Russian authors must be reversed. A paper concerning the complete re-examination of the mass spectra of compounds **5** and **6** (R=Me) and of their acetates is in preparation and will appear in the next future.
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