Different Pathways in the Base-Promoted Isomerization of Benzyl Oxiranyl Ethers

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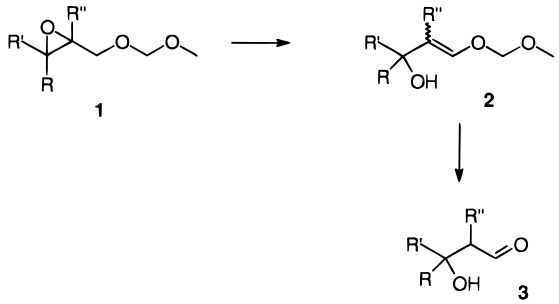
The base-promoted isomerization of benzyl oxiranyl ethers was investigated. In particular it was shown that the reaction may proceed toward two main regioisomeric products: a benzyl vinyl ether or a 2-aryl-3-(hydroxyalkyl)oxetane, depending on subtle variations in the substitution on the phenyl ring. Disubstituted oxetanes were obtained in a stereoselective manner, thus providing a good entry to this class of synthetically useful compounds.

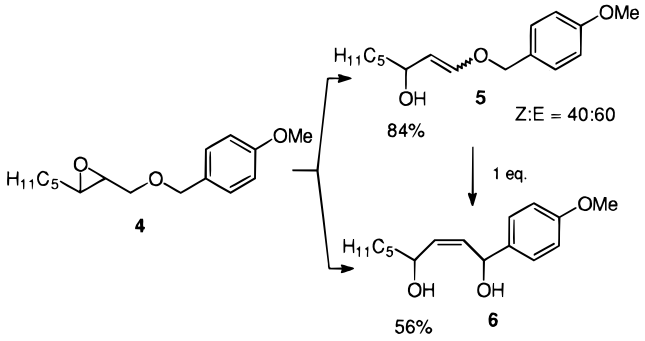
We have recently reported[1,2] that oxiranyl ethers **1** can be isomerized to hydroxy enethers **2** with good regio- and stereocontrol, the latter being mainly due to steric interactions in the transition state for a *syn*-periplanar β-elimination[3] pathway (Scheme 1).

Scheme 1



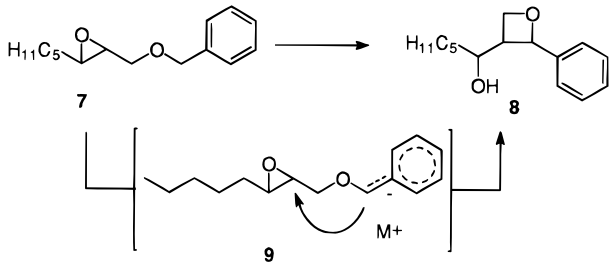
Due to the possibility of preparing **1** following the Sharpless epoxidation protocol,[4] enethers **2** may be considered masked enantiopure 3-hydroxy aldehydes **3** if the carbon−oxygen bond of the methoxymethyl group could be easily cleaved to afford the free carbonyl group. Some problems related to the latter process [2] (formation of variable amounts of α,β-unsaturated aldehydes) prompted us to extend our base-promoted methodology to differently protected oxiranyl alcohols in order to avoid acidic cleavage conditions. At first we chose 1-[(4-methoxybenzyl)oxy]-2,3-epoxyoctane (**4**), easily prepared from 1-hydroxy-2,3-epoxyoctane with sodium hydride and 4-methoxybenzyl bromide. When **4** was treated with 1 equiv of the equimolar mixture lithium diisopropylamide and potassium *tert*-butoxide (LIDAKOR)[5] in tetrahydrofuran, the expected enether **5** was obtained as a *Z*:*E* mixture in a 40:60 ratio (Scheme 2). The use of two equiv of base led to a mixture of **5** and the unsaturated diol **6**, the former in a 23:77 *Z*:*E* isomeric composition and the latter, which was then purified by chromatography and fully characterized, as pure *Z* isomer.

Scheme 2



Treatment of **5** with 1 equiv of base gave **6** as well. We can assume that **6** is formed by initial deprotonation of the benzylic position of **5** followed by a 1,2-Wittig rearrangement[6] with migration of the vinylic moiety.[7] This unexpected pathway induced us to submit other benzyloxy oxiranes to treatment with mixed metal bases. The unsubstituted 1-(benzyloxy)-2,3-epoxyoctane (**7**), after reaction with both 1 and 2 equiv of lithium diisopropylamide/potassium *tert*-butoxide, gave 2-phenyl-3-(1-hydroxyhexyl)oxetane (**8**) as the only product (Scheme 3).

Scheme 3



Oxetane **8** is certainly formed by attack of the initially formed benzylic carbanion **9** on the oxirane ring via a 4-*exo* ring closure.[8]

The reaction is stereospecific, only one diasteroisomer being formed in the ring closure. This is probably due

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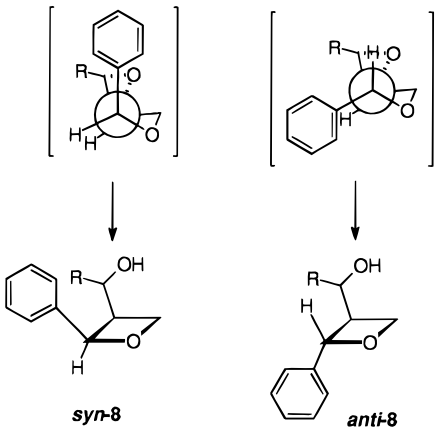
to steric interactions between the phenyl ring and the alkyl chain in the transition state for a *syn*-selective closure which is completely absent in the transition state for the *anti* one (Scheme 4).

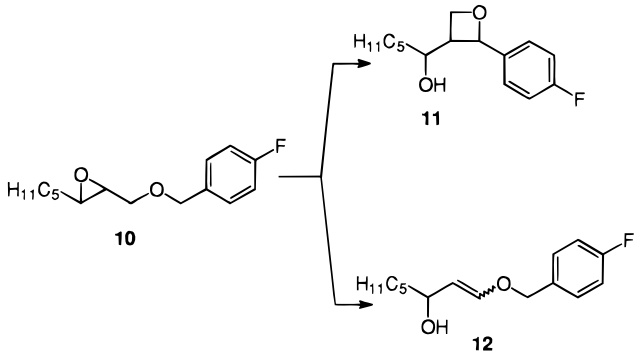
Scheme 4



The *anti* relationship in compound **8** has been verified by NOE experiments. Irradiation of the hydrogen atom at carbon 2 of the ring caused a nuclear Overhauser effect on the methine bonded to the hydroxyl group while irradiation on hydrogen at carbon 3 caused an effect on the phenyl hydrogen atoms in the *ortho* position.

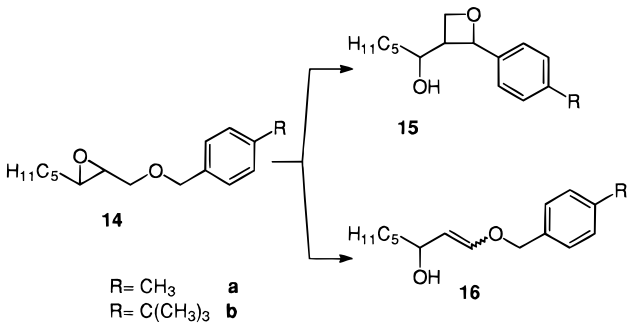
At a first sight one might then argue that electron-donating groups favor deprotonation of the methylene group adjacent to the oxiranyl ring, while electron-withdrawing substituents should enhance the acidity of the benzylic position, thus increasing the chances for a nucleophilic attack on the oxiranyl ring. On this basis, we repeated the base-induced rearrangement on 1-[(4-fluorobenzyl)oxy]-2,3-epoxyoctane (**10**), expecting results similar to those obtained with the benzyl oxiranyl ether **7**. Inversely, a 44:56 mixture of products **11** and **12** was found, the former as a pure *anti*-stereoisomer and the latter as a 30:70 *Z*:*E* mixture (Scheme 5).

Scheme 5



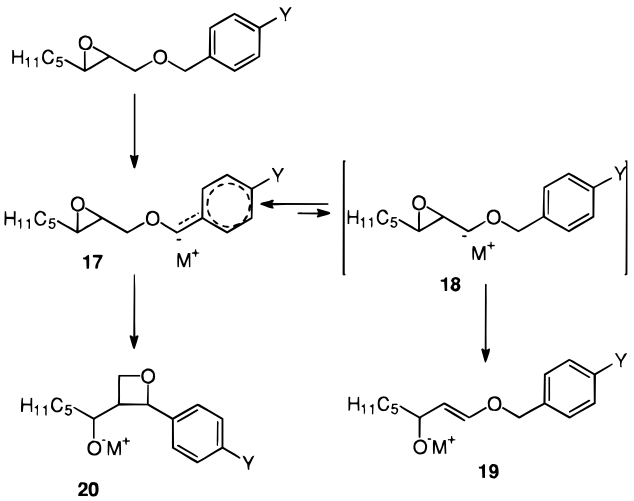
Furthermore we have studied 1-[(4-nitrobenzyl)oxy]- and 1-[(4-methylbenzyl)oxy]-2,3-epoxyoctane (**13** and **14a**). The former remained unchanged after treatment with bases regardless of the reaction conditions used, and the latter underwent decomposition to the original epoxy alcohol. The *p*-nitro-substituted compound is actually deprotonated on the benzylic position, and the benzylmetallic intermediate does not react intramolecularly with the oxirane ring as shown by the formation of the deuterated derivatives upon addition of deuterium oxide. The *p*-methyl substituted ether **14a** could be partially isomerized in a 38% overall yield to both the oxetane **15a** and the hydroxy enether **16a**, in a 56:44 ratio, when the superbasic mixture was used in pentane (Scheme 6). In addition, 52% of the starting material was recovered. The recovery of epoxy alcohol may be due to deprotonation of the benzylic methyl group followed by carbon−oxygen bond cleavage. For this reason we then turned our attention to the 1-[(4-*tert*-butylbenzyl)oxy]-2,3-epoxyoctane (**14b)** which, upon treatment with the LIDAKOR base in THF at −50 °C, gave then a mixture of oxetane **15b** and hydroxy enether **16b** in a 37:63 ratio, the latter as a 48:52 *Z*:*E* mixture (66% overall yield). When the reaction was performed at −100 °C, a similar isomeric ratio (**15b**:**16b** = 25:75) was found, with a very low overall yield (27%).

Scheme 6



In an attempt to rationalize the above results we have created Scheme 7. We presume that the first deprotonation occurs on the benzylic position to form the benzylmetallic intermediate **17** which is in equilibrium with the transmetalated species **18**, unstable and hence irreversibly transformed into alcoholate **19**. The benzylmetallic species may lead to the oxetane **20** via intramolecular nucleophilic attack on the oxirane ring. The **19**:**20** ratio is related to the equilibrium between the species **17** and **18**. When an electron-donating group is present on the aromatic ring (Y = OCH_3), the equilibrium is shifted toward **18** and hence **19** is formed as exclusive product. If Y is hydrogen or fluorine, **17** is predominant and undergoes nucleophilic attack on the oxirane ring in the former case, while it looks not reactive enough toward the epoxide ring and then is slowly transformed into the alcoholate **19**, in the latter.

Scheme 7



Oxetane **8** was prepared in an optically pure form as well. Treatment of 1-hydroxy-2-octene with *tert*-butyl

hydroperoxide, titanium isopropoxide, and L-(+)-diethyl tartrate[9] led to (2*S*,3*S*)-1-hydroxy-2,3-epoxyoctane in a 68% chemical yield and 96% enantiomeric excess which was then benzylated with benzyl bromide and sodium hydride to (*S*,*S*)-**7**. The latter was submitted to treatment with LIDAKOR to afford (2*S*,3*R*,1′*S*)-2-phenyl-3-(1′-hydroxyhexyl)oxetane (**8**) in a 70% yield and 96% diastereomeric excess.

The results illustrated above show that a subtle change in the stereoelectronic structure of benzyl oxiranyl ethers may lead to different rearranged products. In particular, the stereospecific formation of a disubstituted oxetane[10] deserves attention, and a careful study on a wide range of oxiranyl ethers will be undertaken.

Experimental Section

General. Air and moisture sensitive compounds were stored in Schlenk tubes or in Schlenk burettes. They were protected by and handled under an atmosphere of 99.99% pure nitrogen. Ethereal extracts were dried with sodium sulfate. The temperature of dry ice−ethanol baths is consistently indicated as −78 °C, that of ice bath as 0 °C, and "room temperature" as 25 °C. If no reduced pressure is specified, boiling ranges were determined under ordinary atmospheric conditions (720 ± 35 mmHg). Purifications by flash column chromatography[11] were performed using glass columns (10−50 mm wide), silica gel 230−400 mesh was chosen as stationary phase (15 cm high), with an elution rate of 5 cm/min. Nuclear magnetic resonance spectra of hydrogen and carbon-13 nuclei were recorded at 200 or 300 MHz and at 50.3 or 75.5 MHz, respectively. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$:7.26 and 77.0 ppm, respectively). Mass spectra were obtained at a 70 eV ionization potential.

Materials. Starting materials are commercially available unless otherwise stated. All commercial reagents were used without further purification except diisopropylamine which was distilled over calcium hydride. Tetrahydrofuran was obtained anhydrous by distillation over sodium wire after the characteristic blue color of in situ generated sodium diphenylketyl[12] was found to persist. Dimethylformamide was distilled over calcium hydride and then stored over 4 Å molecular sieves. Methylene chloride was purified by the standard procedure, dried over calcium chloride, and stored over 4 Å molecular sieves. Petroleum ether, unless specified, is the 40−70 °C boiling fraction.

Preparation of the Benzyloxy Oxiranyl Ethers. (*E*)-2-Octen-1-ol. A suspension of $LiAlH_4$ (96 mg, 25.3 mmol) in ether (70 mL) was added, during a period of 40 min, to a stirred solution of (*E*)-2-octenal (12.6 g, 100.0 mmol) in ether (30 mL), cooled to −10 °C. The reaction mixture was stirred for 1 h at 25 °C and then treated with H_2O (50 mL) and 10% H_2SO_4 (50 mL). The two phases were separated, the aqueous phase was extracted with ether (2 × 50 mL), and the organic exctracts were collected and dried. After solvent removal, 12.0 g of crude (*E*)-2-octen-1-ol[13] were obtained and not submitted to further purification: ^{1}H-NMR ($CDCl_3$)δ 5.70 (1H, dt, J = 15.3, 4.8), 5.60 (1H, dt, J = 15.3, 5.3), 4.05 (2H, d, J = 4.8), 2.04 (2H, dt, J = 7.8, 5.3), 1.3 (7H, m), 0.89 (3H, t, J = 6.3).

(*E*)-2,3-Epoxyoctan-1-ol. *m*-CPBA (1.72 g, 10.0 mmol) in CH_2Cl_2 (15 mL) was added, during a period of 20 min, to a solution of (*E*)-2-octen-1-ol (6.4 g, 5.0 mmol) in CH_2Cl_2 (8 mL) under N_2 at 0 °C. The reaction mixture was stirred for 15 h at 25 °C and then cooled to 0 °C. The precipitated *m*-chlorobenzoic acid was rapidly filtered off and washed with cold CH_2Cl_2 (2 × 3 mL). The organic solution was then washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), saturated aqueous $Na_2S_2O_3$ (2 × 10 mL), and brine (10 mL) and dried. After evaporation of the solvent the residue was purified by column chromatography (petroleum ether/ether 1:2), affording 5.8 g (81%) of (*E*)-2,3-epoxyoctan-1-ol, which directly crystallized as a white solid:[14] mp 33−34 °C; ^{1}H-NMR ($CDCl_3$)δ 3.90 (1H, dd, J = 12.6, 4.4), 3.60 (1H, dd, J = 12.6, 4.4), 2.92 (2H, m), 2.68 (1H, bs), 1.54 (2H, m), 1.3 (6H, m), 0.88 (3H, t, J = 6.6); ^{13}C-NMR ($CDCl_3$)δ 61.6, 58.6, 56.0, 31.5, 31.5, 25.6, 22.5, 14.0; MS m/z 101 ($M^+ - C_3H_7$, 4), 83 (95), 71 (10), 69 (12), 61 (11), 57 (67), 56 (44), 55 (100).

(*E*)-(2*S*,3*S*)-2,3-Epoxyoctan-1-ol. After a suspension of powdered 4 Å molecular sieves (3.0 g) and CH_2Cl_2 was cooled to −20 °C, L-(+)-diethyl tartrate (DET, 1.24 g, 6.0 mmol) and titanium isopropoxide (1.42 g, 5.0 mmol) were consecutively added. *tert*-Butyl hydroperoxide (67.0 mL of a 3 M solution in isooctane, 200 mmol; dried by treatment with 4 Å molecular sieves immediately before the use) was then added and the mixture kept under stirring at −20 °C for 30 min. (*E*)-2-Octenol (12.8 g, 100 mmol) was then slowly (20 min) added, and the suspension was stirred for 4 h at −20 °C. After that time it was poured into a solution of iron(II) sulfate heptahydrate (33.0 g, 120 mmol) and citric acid monohydrate (11.0 g, 60.0 mmol) at 0 °C. The phases were separated, and the aqueous layer was extracted with ether (2 × 30 mL). The organic phase was then stirred for 1 h at 0 °C with a 30% solution of NaOH in brine and extracted again with ether (2 × 50 mL) after diluting with water (50 mL). The residue (12.8 g) after evaporation of the solvent was purified by recrystallization from petroleum ether, giving 10.1 g (70%) of (*E*)-(2*S*,3*S*)-2,3-epoxyoctan-1-ol: mp 37−38 °C (lit.[9b] mp, 38−39.5 °C); $[\alpha]^{20}_D$ −40.5 (*c* 4.04, $CHCl_3$).

Preparation of the Benzyl Ethers. General Procedure: Method A. NaH (0.24 g, 10.0 mmol) suspended in THF (10 mL) was added to a precooled (−5 °C) solution of (*E*)-2,3-epoxyoctan-1-ol (1.4 g, 10.0 mmol) in THF (10 mL). After 1 h at −5 °C the benzyl halide (12.0 mmol) in THF (10 mL) was added and the mixture stirred for 14 h at 25 °C before it was treated with water−ice (25 mL) and extracted with ether (3 × 15 mL). The organic phase was washed with brine (30 mL) and dried.

Method B. NaH (0.22 g, 9.0 mmol) in DMF (8 mL) was added to a precooled (−5 °C) solution of (*E*)-2,3-epoxyoctan-1-ol (0.9 g, 7.0 mmol) in DMF (8 mL). After 30 min at −5 °C the benzyl halide (8.5 mmol) in DMF (8 mL) was added and the mixture warmed up to 25 °C. After 4 h water−ice (5 mL) was added, the mixture was extracted with ether (3 × 10 mL), and the organic phase was washed with water (4 × 10 mL) and brine (2 × 20 mL) and dried.

(*E*)-1-[(4-Methoxybenzyl)oxy]-2,3-epoxyoctane (4). (*E*)-1-[(4-Methoxybenzyl)oxy]-2,3-epoxyoctane was prepared according to procedure A, giving 6.14 g of crude which was then purified by column chromatography (petroleum ether/ether, 3:1), affording 3.12 g (59%) of **4**: ^{1}H-NMR ($CDCl_3$)δ 7.3−7.2 (2H, m), 6.9−6.8 (2H, m), 4.50 (2H, AB system), 3.80 (3H, s), 3.68 (1H, dd, J = 11.4, 3.4), 3.43 (1H, dd, J = 11.4, 5.6), 2.93 (1H, dd, J = 5.6, 3.4, 2.2), 2.81 (1H, app td, J = 5.4, 2.2), 1.6−1.2 (8H, m), 0.89 (3H, t, J = 6.6); ^{13}C-NMR ($CDCl_3$)δ 159.21, 130.01, 129.35, 113.74, 72.87, 70.16, 57.00, 56.16, 55.24, 31.62, 31.54, 25.59, 22.54, 13.96; MS m/z 138 (10), 137 (100), 136 (27), 135 (25), 121 (83), 109 (12), 78 (14), 77 (17), 55 (10).

(*E*)-1-(Benzyloxy)-2,3-epoxyoctane (7). (*E*)-1-(Benzyloxy)-2,3-epoxyoctane was prepared according to procedure A, giving 4.42 g of crude product which was then purified by column chromatography (petroleum ether/ethyl acetate, 10:1), affording 2.81 g (60%) of **7**: ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (5H, m), 4.58 (2H, AB system), 3.72 (1H, dd, J = 11.4, 3.4), 3.47 (1H, dd, J = 11.4, 5.8), 2.95 (1H, ddd, J = 5.8, 3.4, 2.6), 2.82 (1H, app td, J = 5.6, 2.6), 1.6−1.2 (8H, m), 0.89 (3H, t, J = 6.6); ^{13}C-NMR ($CDCl_3$)δ 137.96, 128.39, 127.70, 73.21, 70.47, 56.98, 56.15,

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31.63, 31.54, 25.61, 22.55, 13.98; MS *m/z* 233 (2), 108 (17), 107 (100), 105 (20), 104 (21), 92 (26), 91 (95), 89 (12), 86 (16), 84 (26), 79 (39), 77 (22), 71 (14), 65 (38), 57 (41), 56 (12), 55 (43), 51 (17), 47 (10), 44 (11), 43 (48), 42 (20), 41 (78).

(*E*)-1-[(4-Fluorobenzyl)oxy]-2,3-epoxyoctane (10). A modified procedure was used in this case. The allylic alcohol was first benzylated and then submitted to the epoxidation reaction.

(a) (*E*)-1-[(4-Fluorobenzyl)oxy]-2-octene. Method B was used, affording 2.36 g (70%) of (*E*)-1-[(4-fluorobenzyl)oxy]-2-octene which was used without further purification in the next step: ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (2H, m), 7.1−7.0 (2H, m), 5.65 (2H, m), 4.46 (2H, s), 3.96 (2H, d, J = 5.8), 2.05 (2H, app q, J = 6.7), 1.5−1.2 (6H, m), 0.89 (3H, t, J = 6.3).

(b) (*E*)-1-[(4-Fluorobenzyl)oxy]-2,3-epoxyoctane (10). *m*-CPBA (3.59 g, 21 mmol) in CH_2Cl_2 (30 mL) was added to (*E*)-1-[(4-fluorobenzyl)oxy]-2-octene (2.36 g, 10 mmol) in CH_2Cl_2 (15 mL) at 0 °C during 20 min. The mixture was then warmed up to 25 °C and stirred for 15 h. After cooling to 0 °C the mixture was filtered to remove *m*-chlorobenzoic acid. The residue was washed with CH_2Cl_2 (2 × 3 mL), and the organic solution thus obtained was washed with saturated $NaHCO_3$ (2 × 25 mL), saturated $Na_2S_2O_3$ (2 × 25 mL), and saturated NaCl (25 mL) and dried. After the solvent was removed under reduced pressure, 2.02 g of crude product was obtained and purified by column chromatography (petroleum ether/ethyl acetate, 10:1), affording 1.55 g (60%) of **10**: ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (2H, m), 7.1−7.0 (2H, m), 4.59 (2H, AB system), 3.72 (1H, dd, J = 11.4, 3.4), 3.44 (1H, dd, J = 11.4, 5.4), 2.94 (1H, ddd, J = 5.4, 3.4, 2.6), 2.81 (1H, app td, J = 5.4, 2.6), 1.6−1.2 (8H, m), 0.89 (3H, t, J = 6.6); ^{13}C-NMR ($CDCl_3$)δ 162.34 (d, J = 244.0), 133.71 (d, J = 2.9), 129.45 (d, J = 8.1), 115.24 (d, J = 20.9), 72.49, 70.49, 56.95, 56.07, 31.60, 31.54, 25.59, 22.54, 13.97; MS *m/z* 125 (94), 110 (11), 109 (100), 83 (13), 57 (15), 55 (10). Anal. Calcd for $C_{15}H_{21}O_2F$: C, 71.40; H, 8.39. Found: C, 71.74; H, 8.29.

(*E*)-1-[(4-Nitrobenzyl)oxy]-2,3-epoxyoctane (13). A modified procedure was used in this case. The allylic alcohol was first benzylated and then submitted to the epoxidation reaction.

***(a)* (*E*)-1-[(4-Nitrobenzyl)oxy]-2-octene.** Ag_2O (4.63 g, 20 mmol) was added to *p*-nitrobenzyl bromide (6.48 g, 30 mmol) in CH_2Cl_2 (30 mL). *(E)*-2-Octenol (2.56 g, 20 mmol) in CH_2Cl_2 (20 mL) was added at −5 °C, refluxed during 60 h and then filtered through a short plug of silica gel to remove Ag_2O. After evaporation of the solvent 7.31 g of crude material were obtained and purified by column chromatography (eluent petroleum ether/ether 4:1) affording 1.72 g (33%) of (*E*)-1-[(4-nitrobenzyl)oxy]-2-octene.

(b) (*E*)-1-[(4-Nitrobenzyl)oxy]-2,3-epoxyoctane (13). *m*-CPBA (1.28 g, 7.4 mmol) in CH_2Cl_2 (11 mL) was added to (*E*)-1-[(4-nitrobenzyl)oxy]-2-octene (0.99 g, 3.7 mmol) in CH_2Cl_2 (4 mL) at 0 °C during 20 min. The mixture was then warmed up to 25 °C and stirred for 15 h. After cooling to 0 °C the mixture was filtered to remove *m*-chlorobenzoic acid. The residue was washed with CH_2Cl_2 (2 × 3 mL), and the organic solution thus obtained was washed with saturated $NaHCO_3$ (2 × 10 mL), saturated $Na_2S_2O_3$ (2 × 10 mL), saturated NaCl (10 mL) and dried. After the solvent was removed under reduced pressure, 0.90 g of crude was obtained and purified by column chromatography (petroleum ether/ethyl acetate, 15:1), affording 0.52 g (50%) of **13**: ^{1}H-NMR ($CDCl_3$)δ 8.21 (2H, app d, J = 8.8), 7.51 (2H, app d, J = 8.8), 4.68 (2H, AB system), 3.84 (1H, dd, J = 11.4, 3.0), 3.47 (1H, dd, J = 11.4, 6.0), 2.98 (1H, m), 2.84 (1H, app td, J = 5.4, 2.2), 1.7−1.2 (8H, m), 0.89 (3H, t, J = 6.6); ^{13}C-NMR ($CDCl_3$)δ 147.34, 145.67, 127.61, 123.54, 71.81, 71.14, 56.80, 55.84, 31.53, 31.49, 25.54, 22.49, 13.90; MS *m/z* 152 (21), 149 (10), 137 (15), 136 (100), 107 (10), 106 (41), 95 (10), 90 (20), 89 (24), 82 (13), 81 (17), 78 (29), 71 (14), 68 (16), 67 (11), 57 (41), 55 (33), 43 (25), 41 (28). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.32; H, 7.62; N, 5.40.

(*E*)-1-[(4-Methylbenzyl)oxy]-2,3-epoxyoctane (14a). A modified procedure was used in this case. The allylic alcohol was first benzylated and then submitted to the epoxidation reaction.

(a) (*E*)-1-[(4-Methylbenzyl)oxy]-2-octene. Method B was used leading to 2.36 g (70%) (*E*)-1-[(4-Methylbenzyl)oxy]-2-octene which was used without further purification in the next step: ^{1}H-NMR ($CDCl_3$)δ 7.3−7.0 (4H, m), 5.8−5.5 (2H, m), 4.46 (2H, s), 3.95 (2H, d, J = 6.0), 2.34 (3H, s), 2.1−2.0 (2H, m), 1.5−1.2 (6H, m), 0.89 (3H, t, J = 6.6).

(b) (*E*)-1-[(4-Methylbenzyl)oxy]-2,3-epoxyoctane (14a). *m*-CPBA (2.76 g, 16 mmol) in CH_2Cl_2 (30 mL) was added to (*E*)-1-[(4-methylbenzyl)oxy]-2-octene (1.86 g, 8 mmol) in CH_2Cl_2 (11 mL) at 0 °C during 20 min. The mixture was then warmed up to 25 °C and stirred for 15 h. After cooling to 0 °C the mixture was filtered to remove *m*-chlorobenzoic acid. The residue was washed with CH_2Cl_2 (2 × 3 mL), and the organic solution thus obtained was then washed with saturated $NaHCO_3$ (2 × 25 mL), saturated $Na_2S_2O_3$ (2 × 25 mL), and saturated NaCl (25 mL) and dried. After the solvent was removed under reduced pressure, 1.89 g of crude was obtained and purified by column chromatography (eluent petroleum ether/ether, 6:1), affording 1.12 g (56%) of **14a**: ^{1}H-NMR ($CDCl_3$)δ 7.3−7.0 (4H, m), 4.53 (2H, AB system), 3.68 (1H, dd, J = 11.4, 3.2), 3.45 (1H, dd, J = 11.4, 5.4), 2.93 (1H, ddd, J = 5.4, 3.2, 2.2), 2.81 (1H, app td, J = 5.6, 2.2), 2.34 (3H, s), 1.6−1.2 (8H, m), 0.89 (3H, t, J = 6.6); ^{13}C-NMR ($CDCl_3$)δ 137.40, 134.88, 129.04, 127.82, 73.09, 70.27, 56.98, 56.18, 31.62, 31.54, 25.59, 22.54, 21.15, 13.96; MS *m/z* 248 (2, M^+), 233 (9), 122 (22), 121 (100), 119 (28), 106 (13), 105 (96), 103 (11), 93 (34), 91 (14), 79 (15), 77 (19), 57 (15), 55 (17), 43 (14), 41 (20). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.26; H, 9.72.

(*E*)-1-[(4-*tert*-Butylbenzyl)oxy]-2,3-epoxyoctane (14b). (*E*)-1-[(4-*tert*-Butylbenzyl)oxy]-2,3-epoxyoctane was prepared according to procedure A, giving 3.32 g of crude which was then purified by column chromatography (petroleum ether/ethyl acetate, 10:1), affording 1.88 g (65%) of **14b**: ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (4H, m), 4.54 (2H, AB system), 3.70 (1H, dd, J = 11.4, 3.2), 3.47 (1H, dd, J = 11.4, 5.4), 2.94 (1H, m), 2.82 (1H, app td, J = 5.4, 2.2), 1.6−1.2 (8H, m), 1.31 (9H, s), 0.89 (3H, t, J = 6.6); ^{13}C-NMR ($CDCl_3$)δ 150.70, 134.92, 127.62, 125.33, 73.07, 70.43, 57.02, 56.22, 31.63, 31.56, 31.32, 25.61, 22.55, 13.98; MS *m/z* 289 (1.3, M+), 164 (13), 163 (100), 147 (61), 132 (18), 131 (14), 119 (19), 117 (29), 91 (21), 57 (35), 55 (19), 43 (12), 41 (20). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.56; H, 10.42. Found: C, 78.48; H, 10.82.

Isomerization of the Benzyloxy Oxiranyl Ethers. General Procedure. The solvent was partially evaporated under reduced pressure from a solution of butyllithium in hexane (0.55 mmol) and the residue dissolved at −78 °C in precooled THF (1 mL). Then diisopropylamine (0.56 g, 0.55 mmol) and potassium *tert*-butoxide (0.62 g, 0.55 mmol) were added, and the mixture was stirred for 15 min. After the addition of the substrate (0.55 mmol), the reaction mixture was kept 15 h at −50 °C before it was treated with ether (3 mL) and H_2O (2 mL) and allowed to reach 25 °C. The aqueous phase was then extracted with ether (2 × 3 mL) and the organic solution dried. After evaporation of the solvent the residue was purified.

Isomerization of (*E*)-1-[(4-Methoxybenzyl)oxy]-2,3-epoxyoctane (4). The general procedure was used obtaining 110 mg (84%) of a 40:60 mixture of (*Z*)- and (*E*)-1-[(4-methoxybenzyl)oxy]-1-octen-3-ol (**5**).

(*E*)-1-[(4-Methoxybenzyl)oxy]-1-octen-3-ol [(*E*)-5): ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (2H, m), 7.0−6.8 (2H, m), 6.56 (1H, d, J = 12.8), 4.93 (1H, dd, J = 12.8, 8.6), 4.68 (2H, s), 4.1−4.0 (1H, m), 3.82 (3H, s), 1.6−1.2 (9H, m), 0.89 (3H, t, J = 6.0); ^{13}C-NMR ($CDCl_3$)δ 159.47, 148.46, 129.33, 113.92, 107.92, 70.96, 70.81, 55.27, 55.27, 37.93, 31.69, 25.34, 22.61, 14.04; MS *m/z* 264 (M^+), 121 (100), 91 (14), 78 (26), 77 (34), 55 (11).

(*Z*)-1-[(4-Methoxybenzyl)oxy]-1-octen-3-ol [(*Z*)-5] (diagnostic signals): ^{1}H-NMR ($CDCl_3$)δ 6.09 (1H, d, J = 5.8), 4.6−4.4 (2H, m).

Reaction with 2 equiv of LIDAKOR. The general procedure was followed with BuLi (1.1 mmol), diisopropylamine (11 mg, 1.1 mmol), and KO^{t}Bu (123 mg, 1.1 mmol), obtaining 148 mg of crude material which was then purified by column chromatography (petroleum ether/ether, 1:2) to afford 58 mg of a 23:77 mixture of (*Z*)- and [(*E*)-1-[(4-

methoxybenzyl)oxy]-1-octen-3-ol (**5**) and 22 mg of (*Z*)-1-(4-methoxyphenyl)-2-nonene-1,4-diol (**6**).

(*Z*)-1-(4-Methoxyphenyl)-2-nonene-1,4-diol (6): ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (2H, m), 7.0−6.8 (2H, m), 5.76 (1H, ddd, J = 7.2, 5.6, 0.8), 5.56 (1H, ddd, J = 7.2, 5.6, 0.8), 5.52 (1H, d, J = 5.6), 4.6−4.5 (1H, m), 3.80 (3H, s), 2.8−2.2 (2H, m), 1.4−1.2 (6H, m), 0.86 (3H, t, J = 4.6); ^{13}C-NMR ($CDCl_3$)δ 159.14, 135.30, 134.30, 133.94, 127.39, 114.04, 69.59, 67.76, 55.29, 31.19, 31.67, 25.01, 22.56, 13.98; MS m/z 264 (0.05, M^+), 247 (6), 246 (28), 189 (100), 175 (48), 163 (18), 150 (34), 147 (35), 137 (16), 135 (76), 121 (34), 115 (21), 109 (21), 107 (15), 103 (15), 94 (25), 91 (35), 84 (18), 81 (38), 78 (17), 77 (61), 55 (24), 43 (37).

Isomerization of (*E*)-1-(Benzyloxy)-2,3-epoxyoctane (7). The general procedure was used, obtaining 81 mg (70%) of a crude product which was then purified by column chromatography (petroleum ether/ether, 1:2), giving 38 mg (33%) 2-phenyl-3-(1-hydroxyhexyl)oxetane (**8**): ^{1}H-NMR ($CDCl_3$)δ 7.5−7.2 (5H, m), 5.52 (1H, d, J = 6.6), 4.72 (2H, d, J = 7.6), 4.0−3.9 (1H, m), 2.91 (1H, m), 1.63 (1H, d, J = 5.4), 1.5−1.2 (8H, m), 0.87 (3H, t, J = 6.2); ^{13}C-NMR ($CDCl_3$)δ 142.44, 128.55, 127.99, 125.51, 84.77, 72.21, 70.10, 49.58, 34.93, 31.67, 24.99, 22.54, 13.98; MS m/z 163 (7), 133 (12), 115 (12), 108 (13), 107 (92), 105 (48), 103 (13), 99 (17), 91 (20), 86 (19), 85 (24), 84 (42), 79 (75), 77 (59), 72 (80), 67 (12), 57 (100), 55 (58), 51 (23), 43 (71).

(2*S*,3*R*,1′*S*)-2-Phenyl-3-(1′-hydroxyhexyl)oxetane 8: $[\alpha]^{20}_D$ −31.0 (*c* 0.98, $CHCl_3$).

Isomerization of (*E*)-1-[(4-Fluorobenzyl)oxy]-2,3-epoxyoctane (10). The general procedure was used obtaining 79 mg (63%) of a 56:44 mixture of the two isomeric 1-[(4-fluorobenzyl)oxy]-1-octen-3-ol (**12**) (*Z*:*E* = 30:70) and 2-(4-fluorophenyl)-3-(2-hydroxyhexyl)oxetane (**11**). After a further purification by column chromatography (petroleum ether/ethyl acetate, 3:2), **12** (42 mg) and **11** (32 mg) were obtained.

2-(4-Fluorophenyl)-3-(2-hydroxyhexyl)oxetane (11): ^{1}H-NMR ($CDCl_3$)δ 7.5−7.3 (2H, m), 7.1−7.0 (2H, m), 5.50 (1H, d, J = 6.6), 4.70 (2H, app d, J = 7.6), 4.0−3.9 (1H, m), 2.89 (1H, m), 1.57 (1H, d, J = 5.4), 1.5−1.2 (8H, m), 0.87 (3H, t, J = 6.6); ^{13}C-NMR ($CDCl_3$)δ 162.50 (d, J = 246.7), 138.28 (d, J = 3.0), 127.38 (d, J = 7.5), 115.45 (d, J = 21.9), 84.16, 72.08, 69.94, 49.81, 34.96, 31.69, 24.96, 22.53, 13.96; MS m/z 251 (0.1, $M^+ - 1$), 125 (100), 123 (17), 97 (12), 86 (13), 84 (25), 72 (19), 57 (41), 55 (12), 43 (15). Anal. Calcd for $C_{15}H_{21}O_2F$: C, 71.40; H, 8.39. Found: C, 71.11; H, 8.63.

(*E*)-1-[(4-Fluorobenzyl)oxy]-1-octen-3-ol [(*E*)-12]: ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (2H, m), 7.1−7.0 (2H, m), 6.55 (1H, d, J = 12.8), 4.93 (1H, dd, J = 12.8, 8.6), 4.72 (2H, s), 4.1−4.0 (1H, m), 1.6−1.2 (9H, m), 0.89 (3H, t, J = 6.8); MS m/z 251 (0.2, $M^+ - 1$), 110 (18), 109 (100), 83 (14), 43 (14), 41 (12). Anal. Calcd for $C_{15}H_{21}O_2F$: C, 71.40; H, 8.39. Found: C, 71.36; H, 8.37.

(*Z*)-1-[(4-Fluorobenzyl)oxy]-1-octen-3-ol [(*Z*)-12]: ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (2H, m), 7.1−7.0 (2H, m), 6.07 (2H, d, J = 5.4), 4.77 (2H, s), 4.6−4.5 (2H, m), 1.6−1.2 (9H, m), 0.9−0.8 (3H, m).

Isomerization of (*E*)-1-[(4-Methylbenzyl)oxy]-2,3-epoxyoctane (14a). A solution of butyllithium in hexane (0.55 mmol), diisopropylamine (56 mg, 0.55 mmol), and potassium *tert*-butoxide (62 mg, 0.55 mmol) was mixed together in pentane (3 mL). After 15 min, **14a** (124 mg, 0.50 mmol) was added and the mixture stirred for 15 h at 25 °C before it was treated with ether (3 mL) and H_2O (2 mL). The aqueous phase was then extracted with ether (2 × 3 mL) and the organic solution dried. After evaporation of the solvent 44 mg of a mixture of (*E*)-1-[(4-methylbenzyl)oxy]-2,3-epoxyoctane (**14a**) (52%), 1-[(4-methylbenzyl)oxy]-1-octen-3-ol (**16a**) (21%, *Z*/*E* 84:16), and 2-(4-methylphenyl)-3-(1-hydroxyhexyl)oxetane (**15a**) (27%) was obtained, which after purification by column chromatography (petroleum ether/ethyl acetate, 3:1) gave 9 mg of **15a** and 7 mg of **16a.**

2-(4-Methylphenyl)-3-(1-hydroxyhexyl)oxetane (15a): ^{1}H-NMR ($CDCl_3$)δ 7.2−7.1 (4H, m), 5.48 (1H, d, J = 6.2), 4.71 (2H, d, J = 7.4), 4.0−3.8 (1H, m), 2.91 (1H, m), 2.36 (3H, s), 1.59 (1H, bs), 1.6−1.0 (8H, m), 0.88 (3H, t, J = 4.4); ^{13}C-NMR ($CDCl_3$)δ 139.49, 137.83, 129.23, 125.64, 84.80, 72.35, 70.02, 49.74, 34.96, 31.69, 25.00, 22.54, 21.19, 13.97; MS m/z 167 (9), 149 (100), 121 (36), 119 (14), 105 (12), 97 (15), 94 (11), 93 (13), 91 (13), 85 (22), 84 (24), 83 (19), 71 (27), 70 (13), 69 (28), 57 (49), 55 (39). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.14. Found: C, 77.10; H, 10.00.

(*Z*)-1-[(4-Methylbenzyl)oxy]-1-octen-3-ol [(*Z*)-16a]: ^{1}H-NMR ($CDCl_3$)δ 7.2−7.0 (4H, m), 6.08 (1H, d, J = 5.6), 4.77 (2H, s), 4.53 (1H, m), 4.6−4.4 (1H, m), 2.35 (3H, s), 1.7−1.1 (9H, m), 0.88 (3H, t, J = 6.2); ^{13}C-NMR ($CDCl_3$)δ 145.86, 137.91, 134.00, 129.23, 127.59, 110.91, 74.06, 66.45, 37.33, 31.80, 30.94, 25.08, 22.65, 21.18, 14.06; MS m/z 167 (5), 149 (39), 121 (12), 105 (100), 85 (13), 84 (18), 69 (14), 57 (20), 55 (20).

(*E*)-1-[(4-Methylbenzyl)oxy]-1-octen-3-ol [(*E*)-16a]: ^{1}H-NMR ($CDCl_3$)δ 7.2−7.0 (4H, m), 6.55 (1H, d, J = 12.4), 4.92 (1H, dd, J = 12.4, 8.0), 4.71 (2H, s), 4.2−4.0 (1H, m), 2.35 (1H, s), 1.7−1.1 (9H, m), 0.88 (3H, J = 6.2). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.56; H, 9.71.

Isomerization of (*E*)-1-[(4-*tert*-Butylbenzyl)oxy]-2,3-epoxyoctane (14b). (a) Reaction with 1 equiv of LIDAKOR. The general procedure was used, obtaining 96 mg (66%) of a 63:37 mixture of the two isomeric 1-[(4-*tert*-butylbenzyl)-oxy]-1-octen-3-ol (**16b**) (*Z*:*E* = 48:52) and 2-(4-*tert*-butylphenyl)-3-(2-hydroxyhexyl)oxetane (**15b**). After a further purification by column chromatography (eluent petroleum ether/ethyl acetate, 3:1), **16b** (32 mg) and **15b** (30 mg) were obtained.

2-(4-*tert*-Butylphenyl)-3-(2-hydroxyhexyl)oxetane (15b): ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (4H, m), 5.49 (1H, d, J = 6.2), 4.70 (2H, app d, J = 7.8), 4.0−3.9 (1H, m), 2.94 (1H, m), 1.63 (1H, d, J = 5.2), 1.5−1.2 (8H, m), 1.33 (9H, s), 0.87 (3H, t, J = 6.0); ^{13}C-NMR ($CDCl_3$)δ 151.06, 139.40, 125.48, 125.40, 84.70, 72.32, 70.01, 49.41, 34.96, 34.58, 31.69, 31.32, 25.01, 22.54, 13.96; MS m/z 290 (0.1, M^+), 163 (100), 147 (79), 115 (11), 91 (26), 86 (11), 84 (18), 57 (58), 55 (17). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.33; H, 10.58.

(*E*)-1-[(4-*tert*-Butylbenzyl)oxy]-1-octen-3-ol [(*E*)-16b]: ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (4H, m), 6.57 (1H, d, J = 12.4), 4.93 (1H, dd, J = 12.4, 8.4), 4.72 (2H, s), 4.1−4.0 (1H, m), 1.6−1.2 (9H, m), 1.32 (9H, s), 0.88 (3H, t, J = 6.2); ^{13}C-NMR ($CDCl_3$)δ 151.12, 145.99, 133.59, 127.53, 125.46, 107.88, 73.98, 71.07, 37.93, 34.56, 31.69, 31.29, 25.34, 22.64, 14.04; MS m/z 149 (10), 148 (19), 147 (100), 132 (25), 131 (13), 119 (13), 117 (39), 115 (15), 105 (12), 91 (25), 57 (11), 55 (11). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.77; H, 10.32.

(*Z*)-1-[(4-*tert*-Butylbenzyl)oxy]-1-octen-3-ol [(*Z*)-16b]: ^{1}H-NMR ($CDCl_3$)δ 7.4−7.2 (4H, m), 6.10 (1H, d, J = 5.8), 4.78 (2H, s), 4.7−4.5 (2H, m), 1.6−1.2 (9H, m), 1.32 (9H, s), 0.88 (3H, t, J = 6.2); ^{13}C-NMR ($CDCl_3$)δ 148.59, 145.99, 134.03, 127.28, 125.46, 110.79, 73.98, 66.45, 37.33, 34.56, 31.78, 31.29, 25.08, 22.64, 14.04.

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