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A Simplified Procedure for the Stereospecific Transformation of 1,2-Diols into Epoxides

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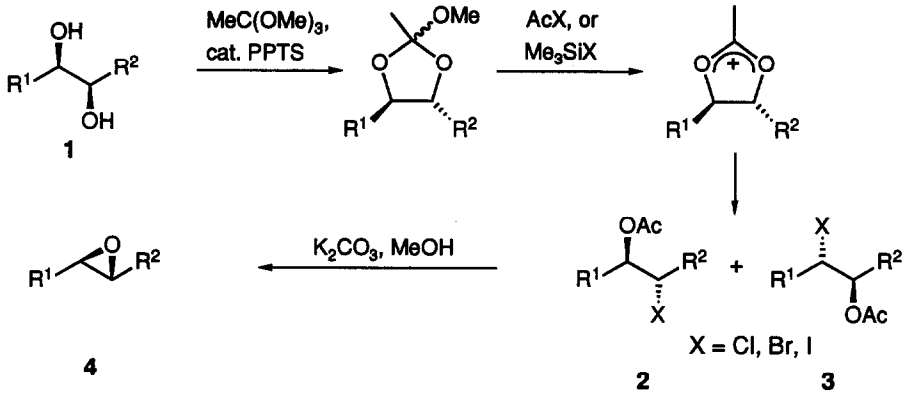
Abstract: A simple, 'one-pot' procedure for the conversion of vicinal diols into epoxides *via* halohydrin ester intermediates has been developed. This method tolerates a wide range of functionality including acid sensitive functional groups. The transformation proceeds *via* a, usually highly regioselective, nucleophilic opening of a cyclic acetoxonium intermediate, generated from a cyclic orthoacetate and Me_3SiCl, acetyl bromide or acetyl chloride/NaI to form 1-acetoxy-2-chloride, 1-acetoxy-2-bromide or 1-acetoxy-2-iodide intermediates, respectively. No epimerization occurs, even with benzylic substrates. Subsequent base mediated methanolysis furnishes epoxides in excellent overall yield. Application of this method led to an efficient formal synthesis of the leukotriene antagonist SKF 104353, commencing with the highly enantioselective *cis*-dihydroxylation of methyl 3-[2-(8-phenyloctyl)phenyl]propenoate.

Enantiomerically pure epoxides have found widespread use as chiral building blocks in organic synthesis.[1] However, there are currently only few methods for the direct enantioselective epoxidation of olefins bearing no directing functional groups in close proximity to the double bond.[2] In contrast, the asymmetric dihydroxylation (AD) of unfunctionalized olefins has reached a high level of efficiency, due to recent progress in the optimization of reaction conditions and ligands.[3] Thus, enantiomeric excesses of greater than 90% ee can now be achieved with a number of olefins representing four of the six olefin substitution classes.

In our efforts to convert vicinal diols into synthetically more valuable intermediates, we have previously shown that cyclic sulfates can act as epoxide-like building blocks.[4] We now wish to report a high yielding and convenient 'one-pot' method for the stereospecific conversion of 1,2-diols into epoxides. This process is based on the acetoxonium ion mediated formation of acetate esters of halohydrins and proceeds with inversion at the halide receiving stereocenter. Subsequent base mediated ester saponification and cyclization with a second inversion at the halide center gives the epoxide (Scheme I). Thus, the transformation results in overall retention of configuration, and therefore the regioselectivity of the initial acetoxy halide formation is inconsequential.

Scheme I

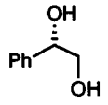
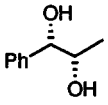
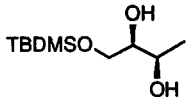
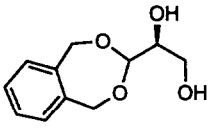
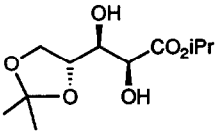
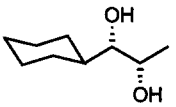
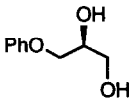
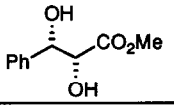


A variety of reagents for the conversion of diols into halohydrin esters have been reported in the literature.[5] These methods all depend on the nucleophilic opening of an intermediate 1,3-dioxolan-2-ylium cation by a halide anion. However, the reagents involved are usually not readily available or are relatively expensive and often require vigorous reaction conditions. In 1958, Baganz and Domaschke reported the formation of 2-haloethyl acetate by treatment of 2-ethoxy-1,3-dioxolane, derived from 1,2-ethanediol and orthoformate, with acetyl halides under reflux conditions.[6] Later, Newman *et al.* showed that the same transformation could be achieved by reacting orthoesters of 1,2-diols with trityl chloride[7] or trimethylsilyl chloride.[8] Surprisingly, this attractive entry into acetoxonium ion chemistry has scarcely been applied in organic synthesis.[9] We set out to better determine the scope and limitations of the method, and along the way managed to further simplify the procedure.

Activated diols, i.e. the benzylic diols **1a** and **1b** (Table I, entries a and b), were cleanly converted into acetoxy chlorides simply by addition of a small excess of trimethyl orthoacetate and trimethylsilyl chloride to a solution of the diol in CH_2Cl_2. The work up of the reaction is extremely simple and consists of evaporating the volatiles to obtain a virtually pure product. Base mediated saponification of the acetate in methanol results in spontaneous cyclization to furnish the epoxide in excellent overall yield. Both steps are performed in the same reaction vessel, thereby making this transformation easy to carry out.[10]

All unactivated diols (entries c-h) are converted into epoxides by the following procedure, consisting of three operations:[11] 1) Formation of the cyclic orthoester at room temperature by acid catalyzed transesterification with a small excess of trimethyl orthoacetate and subsequent evaporation of the volatiles to remove most of the methanol formed (a small amount of methanol is actually needed to catalyze the subsequent transformation); 2) The residue is taken up in a solvent (usually CH_2Cl_2, but MeCN or benzene can also be used) and the reagent (Me_3SiCl, acetyl chloride or acetyl bromide) is added at ambient temperatures. Evaporation of the volatiles upon completion of the reaction gives a mixture of virtually pure acetoxy halides **2** and **3**. The reaction proceeds relatively fast with trimethylsilyl chloride and acetyl bromide, while acetyl chloride requires longer reaction times and in certain cases heating. 3) Addition of methanol and potassium carbonate leads to formation of the epoxide **4** in yields commonly above 90% (see Table I). All three operations are carried out in one reaction vessel without isolation of any intermediates.

Table I. One-Pot Synthesis of Epoxides **4**[a]

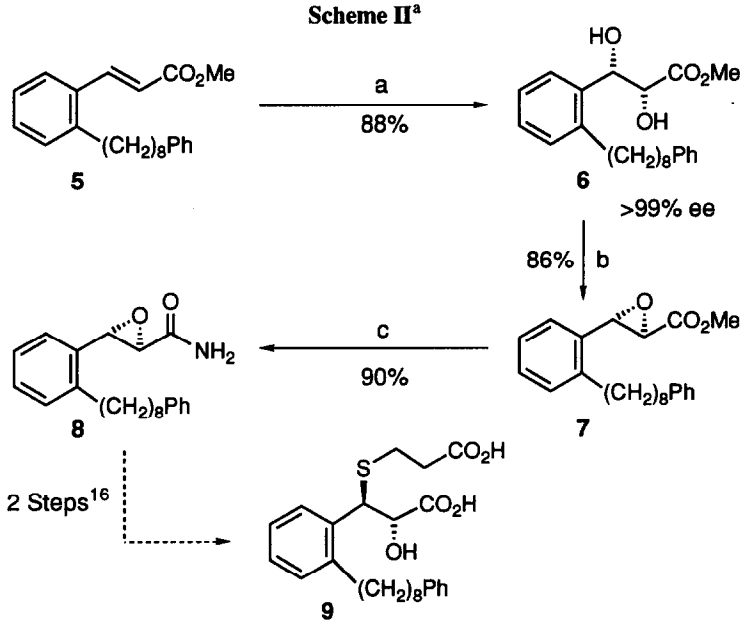
entry	diol **1**	% ee[b]	Ratio of acetoxy halides **2** : **3**[c] (X)	Yield of epoxide **4**[d] (%)
a		97	< 4 : 96 (Cl)	84[e]
b		97	0 : 100 (Cl)	92
c		59	85 : 15 (Br)	83[f,g]
d		96	100 : 0 (Br)	98[e,h]
e		100[i]	100 : 0 (Br)	(77)[f,j]
f		97[k]	86 : 14 (Cl) 88 : 12 (Br) 87 : 13 (I)	89 91 (50)[l]
g		89	100 : 0 (Br)	97[e]
h		99	14 : 86 (Br)	82[m]

Footnotes: [a] For diols **1a** and **1b** the reactions were performed according to the procedure for acvivated diols,[10] all other diols were converted into epoxides using the 3 step procedure for unactivated diols.[11] [b] The enantiomeric excesses were determined by HPLC or GC analysis of the free diols or the bis-MTPA esters (see table II). [c] Determined by integration of the ^{1}H-NMR spectra of the crude products. [d] Isolated yields. [e] The enantiomeric excess of the epoxide was found to be identical within the experimental error to that of the diol by HPLC analysis (see table II). [f] The preparation of the acetoxy bromides was performed at 0°C in the presence of 10 mole % of Et_3N. [g] Methanolysis of the acetoxy bromide was performed with Amberlite® IRA 410 (OH^-) as base, since K_2CO_3 gave inferior yields due to partial cleavage of the silyl ether. [h] The preparation of the acetoxy bromide was performed in the presence of 2 mole % of Et_3N. [i] The diol was prepared by Kouhei Morikawa from *D*-glyceraldehyde acetonide. [j] Yield of the acetoxy bromide. This compound decomposed on treatment with K_2CO_3, presumably due to β-elimination of acetate. [k] Prepared by hydrogenation of **1b**. [l] Yield of acetoxy iodide. [m] Treatment of the pure acetoxy bromide **3h** with K_2CO_3 in methanol provided the epoxide **4h** in 91 % yield.

Our investigations show that the reaction tolerates a wide range of functionality (Table I) and even acid sensitive functional groups are compatible when the reaction mixture is buffered with 2 to 10 mole-% of triethylamine (entries c, d and e). The nucleophilic opening of the cyclic acetoxonium ion occurs without epimerization even with benzylic substrates (entries a and b). Acetoxy chlorides and acetoxy bromides are obtained by using trimethylsilyl chloride and acetyl bromide, respectively. The reaction with acetyl iodide, formed *in situ* from acetyl chloride and NaI, provides acetoxy iodides, albeit in only 50 % isolated yield (entry f). In most cases, the opening of the intermediate acetoxonium ion is highly regioselective, the halide being introduced mainly at the least hindered position (entry f), and/or away from an inductively electron withdrawing functional group (entries c, d and g), or in the benzylic position (entries a, b and h). The resultant acetoxy halides are themselves useful synthetic intermediates.[12] Unfortunately, this procedure does not give satisfactory results with the more sterically crowded diols derived from trisubstituted double bonds or with very acid sensitive substrates such as 1,2:5,6-di-*O*-isopropylidene-*D*-mannitol, probably due to the instability of the intermediate orthoacetate and/or decomposition during its formation.

3-Phenyl-2,3-dihydroxy esters can also be converted to the corresponding glycidic esters (entry h). To demonstrate the utility of this procedure we have developed a high yielding three step synthesis of oxirane carboxamide **8**, a precursor to the leukotriene antagonist SKF 104353 **9**,[13] starting from cinnamate **5** (Scheme II).

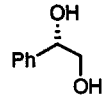
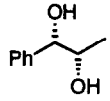
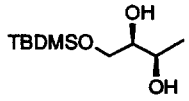
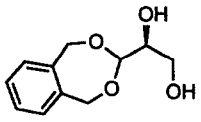
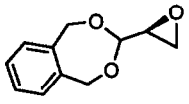
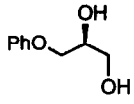
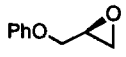
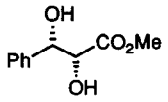
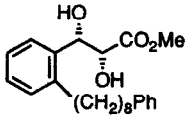
Scheme II[a]



[a] (a) $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $K_2OsO_2(OH)_4$; (b) i) $MeC(OMe)_3$, cat. pTSA, ii) Me_3SiCl, r.t. to 40°C, 3 h, iii) K_2CO_3, MeOH, -17°C, 2 h; (c) NH_3, MeOH, 0°C, 2 h.

Diol **6** was obtained in 88% yield and in greater than 99% ee by dihydroxylation of cinnamate **5** in the presence of 1 mole % of bis(dihydroquinine) phthalazine.[3,14] Transformation of diol **6** into epoxide **7** was accomplished via the corresponding orthoacetate by treatment with trimethylsilyl chloride and subsequently

Table II. Methods for Determinations of Enantiomeric Excesses

Compound No.	Structure	% ee	method (conditions)	derivative	retention times (min)	
1a		97	HPLC (**I**)	bis MTPA ester	16.9 R	18.8 S
4a		96	HPLC (**II**)	——	22.7 S	26.7 R
1b		97	HPLC (**III**)	bis MTPA ester	30.9 R, R	33.0 S, S
1c		59	GLC (**IV**)	bis MTPA ester	20.3 S, S	20.8 R, R
1d		96	HPLC (**V**)	bis MTPA ester	19.9 R	25.2 S
4d		95	HPLC (**VI**)	——	16.2 S	18.7 R
1g		89	HPLC (**VII**)	——	18.9 R	37.6 S
4g		89	HPLC (**VIII**)	——	7.0 R	10.8 S
1h		99	GLC (**IX**)	——	24.9 2R,3S	26.2 2S,3R
6		>99	HPLC (**X**)	——	19.3 2R,3S	23.1 2S,3R

I: Pirkle 1-A, 0.5 % iPrOH- hexane, 3 ml/min. **II**: Chiralcel OD, 0.25 % iPrOH - hexane, 0.4 ml/min.
III: Pirkle 1-A, 0.3 % iPrOH- hexane, 2.5 ml/min. **IV**: 50% cyanopropylsilicone, J&W DB-23, 215°C.
V: Chiralcel OD, 2.5 % iPrOH - hexane, 1 ml/min. **VI**: Chiralcel OD, 20 % iPrOH - hexane, 0.5 ml/min.
VII: Chiralcel OD, 10 % iPrOH - hexane, 0.9 ml/min. **VIII**: Chiralcel OD, 17 % iPrOH - hexane, 0.9 ml/min.
IX: β-cyclodextrin, J &W CDX-B, 165 °C. **X**: Chiralcel OD, 10 % iPrOH - hexane, 0.8 ml/min.

potassium carbonate. Ammonolysis finally provided **8** in 68% overall yield from **5**. Epoxy amide **8** has previously been converted to the leukotriene antagonist SKF 104353 **9** by $Ti(O^iPr)_4$-assisted epoxide opening with thiolate,[15] followed by hydrolysis of both the ester and the amide.[16]

In conclusion, enantiomerically enriched vicinal diols can be converted into the corresponding epoxides in a high yielding two or three step, 'one-pot' procedure. The transformation is of broad scope and should further enhance the utility of 1,2-diols obtained by asymmetric dihydroxylation of unfunctionalized olefins.

Experimental Part. *General* — ^1H NMR spectra were recorded in $CDCl_3$ unless otherwise stated at 250 or 400 MHz respectively. Residual protic solvent $C\underline{H}Cl_3$ (δ_H=7.26 ppm) was used as internal reference. ^{13}C nmr spectra were recorded in $CDCl_3$ unless otherwise stated at 100 MHz using the resonance of $\underline{C}DCl_3$ (δ_C=77.0 ppm, t) as internal reference. Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh). Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}). All reactions were performed at room temperature under an atmosphere of nitrogen in single-necked flasks, sealed with rubber septa, unless otherwise stated. HPLC was performed on Pirkle 1-A Ionic spherical silica (25 cm x 10 mm I.D.) or Chiralcel OD (25 cm x 4.6 mm I.D.) columns respectively (see table II). The detector was set to 254 nm. GLC was performed on β-cyclodextrin, J & W CDX-B (30m x 0.32 mm I.D.) or 50 % cyanopropylsilicone, J & W DB-23 (30 m x 0.32 mm I.D.) columns respectively (see table II).

(*S*)-(+)-2-Phenyloxirane (4a). Trimethylsilyl chloride (152 μL, 1.2 mmol) was added to a solution of diol **1a** (97 % ee, 133 mg, 1.0 mmol) and trimethyl orthoacetate (150 μL, 1.19 mmol) in CH_2Cl_2 (3 mL) at 0°C. The solution was stirred for 60 min, then evaporated to obtain crude (2*R*) 2-chloro-2-phenylethyl acetate (**3a**) (regioisomeric purity greater than 96% by ^1H NMR). ^1H NMR ($CDCl_3$, 250 MHz) δ 7.46-7.30 (5H, m, Ph), 5.07 (1H, dd, *J* = 6.3, 7.4 Hz, H-2), 4.48 (1H, dd, J = 7.4, 11.7 Hz, H-1), 4.42 (1H, dd, J = 6.3, 11.7, H-1), 2.07 (3H, s, Me). The crude product was dissolved in dry methanol (2 mL) and K_2CO_3 (340 mg, 2.46 mmol) was added. The suspension was stirred vigorously for 105 min, then filtered and the residue washed with CH_2Cl_2. The filtrate was evaporated in a rotary evaporator at room temperature under vacuum (water aspirator) and the residue purified by flash chromatography on silica gel (10% ether/pentane) to obtain oxirane **4a** as a colorless liquid (101 mg, 84 %); $[\alpha]_D^{22}$ +24.1 (*c* 1.67, $CHCl_3$). Lit.:[17] $[\alpha]_D^{22}$ +24.6 (*c* 1.37, $CHCl_3$). The enantiomeric purity was determined to be 96 % ee by HPLC (table II).

(2*S*, 3*S*)-(-)-3-Methyl-2-phenyloxirane (4b). Trimethylsilyl chloride (330 μL, 2.6 mmol) was added to a solution of (1S, 2S)-1-phenyl-1,2-propanediol (97% ee, 304 mg, 2.0 mmol) and trimethyl orthoacetate (325 μL, 2.59 mmol) in CH_2Cl_2 (5 mL) at room temperature. The progress of the reaction was monitored by TLC (silica gel plates, 35% ethyl acetate - hexane), the disappearance of polar compounds (diol, hydroxyacetates, R_f 0.13-0.35) being indicative of the consumption of the starting material. After 60 min, the volatiles were evaporated and the residue was dissolved in methanol (8 mL). K_2CO_3 (345 mg, 2.5 mmol) was added and the mixture stirred vigorously at room temperature for 2 h. The suspension was poured into saturated aqueous NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 X 15 mL). The combined organic layers

were dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (silica gel, 10% ether/pentane) to obtain the epoxide **4b** as a colorless liquid (246 mg, 92%). Physical data of the crude acetoxy chloride intermediate **3b**: IR (neat film): ν 3091 (w), 3066 (m), 3033 (m), 2991 (m), 2941 (m), 1748 (s), 1602 (w), 1588 (w), 1374 (m), 1237 (s), 1061 (s), 764 (m), 700 (m) cm^{-1}; ^1H NMR (400MHz): δ 7.47 - 7.27 (5H, m, Ph), 5.28 (1H, quin, J = 6.2 Hz, H-2), 4.98 (1H, d, $J_{1,2}$ = 5.7 Hz, H-1), 1.97 (3H, s, CH_3CO_2), 1.32 (3H, d, $J_{2,3}$ = 6.3 Hz, 3 x H-3); MS (FAB, NBA/NaI) m/z 235, 237 ($M+Na^+$, 27, 9.4 %), 213 (MH^+, 9.3), 153 ($MH^+-C_2H_3O_2$, 61%); calculated for $C_{11}H_{13}ClO_2Na^+$: 235.0502, found: 235.0509. The physical data of oxirane **4b** were in accord with the literature:[18a] $[\alpha]_D^{22}$ -50.1° (c 3.71, $CHCl_3$) [lit.:[18b] $[\alpha]_D^{20}$ +47.5° (c 1.17, $CHCl_3$) for the *R, R* enantiomer]; IR (neat film): ν 3089 (w), 3066 (w), 3035 (m), 2989 (m), 2929 (m), 1605 (w), 1497 (m), 1463 (m), 1021 (m), 861 (s), 766 (s), 743 (s), 698 (s) cm^{-1}; ^1H NMR (250MHz): δ 7.40 - 7.20 (5H, m, Ph), 3.58 (1H, d, $J_{2,3}$ = 2.0 Hz, H-2), 3.04 (1H, dq, $J_{2,3}$ = 2.1, $J_{3,Me}$ = 5.1 Hz, H-3), 1.46 (3H, d, $J_{3,Me}$ = 5.1 Hz, CH_3).

(2*R*, 3*R*)-(+)-1-(*tert*-Butyldimethylsilyloxy)butane-2,3-diol (1c). Compound **1c** was prepared using AD-mix-β and 1.0 equivalent of methanesulfonamide under the reaction conditions described in reference 3. The optical purity was determined to be 59 % by GLC (table II). $[\alpha]_D^{22}$ +0.95° (c 1.89, $CHCl_3$); IR (neat film): ν 3400 (bs), 2956 (s), 2935 (s), 2887 (m), 2860 (s), 1258 (s), 1121 (s), 1098 (s), 837 (s), 780 (m) cm^{-1}; ^1H NMR (250MHz): δ 3.89 - 3.78 (1H, m, H-3), 3.77 (1H, dd, $J_{1,2}$ = 3.6 Hz, J_{gem} = 10.3 Hz, H-1), 3.66 (1H, dd, $J_{1,2}$ = 5.1 Hz, J_{gem} = 10.2 Hz, H-1), 3.45 - 3.35 (1H, m, H-2), 1.21 (3H, d, $J_{3,4}$ = 6.4 Hz, 3 x H-4), 0.90 (9H, s, Me_3C), 0.09 (6H, s, Me_2Si); MS (FAB, NBA/NaI) m/z 243 ($M+Na^+$, 100 %), 221 (MH^+, 3); calculated for $C_{10}H_{24}O_3SiNa^+$: 243.1392, found: 243.1397. $C_{10}H_{24}O_3Si$ requires: C, 54.50 and H, 10.98 %. Found: C, 54.31 and H, 11.11 %.

(2*R*, 3*R*)-(+)-2-*tert*-Butyldimethylsilyloxymethyl-3-methyloxirane (4c). Trimethyl orthoacetate (325 μL, 2.59 mmol) was added to a solution of the diol **1c** (440 mg, 2 mmol) in CH_2Cl_2 (3 mL), followed by PPTS (5 mg, 0.02 mmol). After 15 min, the volatiles were evaporated and residual MeOH was removed under high vacuum (0.1 mmHg) for 2 min. Triethylamine (30 μL, 0.215 mmol) and CH_2Cl_2 (4 mL) were added, the solution was cooled to 0°C and acetyl bromide (180 μL, 2.42 mmol) introduced dropwise via syringe. After 90 min, a TLC test (20% ethyl acetate - hexane, SiO_2) indicated absence of hydroxyacetates [i.e. the hydrolysis products of the orthoacetate intermediate, R_f 0.17 - 0.29, R_f (**2c**, **3c**) 0.63] and saturated aqueous $NaHCO_3$ solution (2 mL) was added at 0°C to the vigorously stirred solution. The mixture was poured into a separation funnel, diluted with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. Filtration through a silica gel pad (10 % ether - pentane) furnished the acetoxy bromide (600 mg, 92 %, 85 : 15 mixture of **2c** and **3c** by ^1H NMR). IR (neat film): ν 2954 (m), 2933 (m), 2887 (w), 2860 (m), 1748 (s), 1372 (m), 1233 (s), 1125 (m), 839 (s), 780 (m) cm^{-1}; ^1H NMR (400MHz, major isomer): δ 5.02 (1H, dt, J_d = 5.0 Hz, J_t = 5.4 Hz, H-2), 4.31 (1H, dq, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 6.9 Hz, H-3), 3.85 (1H, dd, $J_{1,2}$ = 5.3 Hz, J_{gem} = 11.0 Hz, H-1), 3.78 (1H, dd, $J_{1,2}$ = 4.7 Hz, J_{gem} = 11.0, H-1), 2.10 (3H, s, $MeCO_2$), 1.69 (3H, d, $J_{3,4}$ = 6.9 Hz, 3 x H-4), 0.88 (9H, s, Me_3C), 0.06 (3H, s, MeSi), 0.05 (3H, s, MeSi); ^1H NMR (400MHz, minor isomer, signals partially obscured by major isomer): δ 5.19 (1H, dq, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 6.4 Hz, H-3), 4.18 (1H, ddd, $J_{2,3}$ = 4.2 Hz, $J_{1,2}$ = 5.5 Hz, $J_{1,2}$ = 7.5 Hz, H-2), 3.88 (1H, dd, $J_{1,2}$ = 5.6 Hz, J_{gem} = 11.0, H-1), 3.80 (1H, obscured by major isomer,

H-1), 2.07 (3H, s, $MeCO_2$), 1.32 (3H, d, $J_{3,4}$ = 6.3 Hz, 3 x H-4), 0.89 (9H, s, Me_3C), 0.07 (6H, s, Me_2Si); ^{13}C NMR (100 MHz, major isomer): δ 170.14, 76.88, 62.22, 46.50, 25.74, 21.28, 20.93, -5.46, -5.50; MS (FAB, NBA/CsI) m/z 457, 459 ($M+Cs^+$, 100, 88 %); calculated for $C_{12}H_{25}BrO_3SiCs^+$: 456.9811, found: 456.9834.. A mixture of the acetoxy bromides **2c**, **3c** (260 mg, 0.8 mmol), Amberlite IRA410 (OH^- form, 600 mg, prepared from the Cl^- form by washing with 2 M NaOH, water and MeOH, then dried under vacuum and used immediately) and MeOH (1.0 mL) was stirred vigorously at room temperature. After 5 h, the mixture was filtered, the filtrate concentrated at room temperature under vacuum and the residue purified by filtration through a pad of silica (10% ether - pentane) to obtain oxirane **4c** (145 mg, 90 %) as a colorless liquid. The physical data of oxirane **4c** were in accord with the literature.[19] $[\alpha]_D^{22}$ +8.04° (c 3.2, $CHCl_3$) [lit.:[19] $[\alpha]_D^{25}$ +13.12° (c 7.53, $CHCl_3$), 92 % ee]; IR (neat film): ν 2958 (s), 2931 (s), 2887 (m), 2860 (s), 1474 (m), 1256 (s), 1133 (s), 1088 (s), 837 (s), 780 (s) cm^{-1}; ^1H NMR (400MHz): δ 3.78 (1H, dd, J_{vic} = 3.6 Hz, J_{gem} = 11.9 Hz, CH_2OSi), 3.67 (1H, dd, J_{vic} = 4.7 Hz, J_{gem} = 11.9 Hz, CH_2OSi), 2.91 (1H, dq, $J_{2,3}$ = 2.2 Hz, $J_{3,Me}$ = 5.2 Hz, H-3), 2.80 (1H, ddd, $J_{2,3}$ = 2.2 Hz, J_{2,CH_2} = 3.6 Hz, J_{2,CH_2} = 4.7 Hz, H-2), 1.32 (3H, d, $J_{3,Me}$ = 5.2 Hz, Me), 0.89 (9H, s, Me_3C), 0.07 (3H, s, MeSi), 0.06 (3H, s, MeSi); ^{13}C NMR (100 MHz): δ 63.45 (CH_2), 59.62 (CH), 52.25 (CH), 25.86 (3 x CH_3), 18.35 (C_q), 17.32 (CH_3), -5.30 (CH_3), -5.34 (CH_3); MS (EI) m/z 145 (M^+-^{t}Bu, 100 %), 115 (^{t}BuMe$_2$Si$^+$, 100), 75 (Me_2SiOH^+, 50); calculated for M^+-^{t}Bu, $C_6H_{13}O_2Si^+$: 145.0685, found: 145.0688.

(*S*)-(-)-3-(1,2-Epoxyethyl)-1,5-dihydro-3H-2,4-benzodioxepine (4d). Trimethyl orthoacetate (760 µL, 6.05 mmol) was added to a mixture of the diol **1d**[20] (96 % ee, 1050 mg, 4.99 mmol), PPTS (12 mg, 0.048 mmol) and CH_2Cl_2 (6 mL) at room temperature. The mixture was stirred for 15 min, then evaporated and residual methanol was removed under high vacuum (0.1 mmHg) for 2 min. The residue was taken up in CH_2Cl_2 (6 mL) and triethyl amine (14 µL, 0.1 mmol) was added as a pH-buffer (no addition of base is required for the reactions of diols **1f-1h**; the reactions of diols **1c** and **1e** require the presence of 10 mole % of base). Acetyl bromide (450 µL, 6.04 mmol) was added, while the solution was cooled occasionally to maintain the temperature below 40°C. After 30 min, TLC (silica gel plates, 35 % ethyl acetate - hexane) showed absence of polar compounds [hydroxyacetates, formed by hydrolysis of the orthoacetate intermediate on the TLC plate, R_f 0.15, R_f (**2d**) 0.64] and the mixture was evaporated. The residue was dissolved in methanol (20 mL) and K_2CO_3 (1.2 g, 8.68 mmol) was added to the vigorously stirred solution. After 70 min, the mixture was poured into saturated aqueous NH_4Cl (40 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was purified by filtration through a pad of silica gel (65 x 25 mm) and the pad was washed with 20 % ethyl acetate - hexane. Evaporation of the filtrate *in vacuo* gave the epoxide **4d** (945 mg, 98%) as a colorless solid. Physical data of the crude acetoxy bromide intermediate **2d**: ^1H NMR (250MHz): δ 7.29 - 7.13 (4H, m, Ph), 5.18 (1H, ddd, J = 5.4, 3.6, 6.4 Hz, CHR_2OAc), 5.05 (1H, d, J 5.5 Hz, CHO_2), 5.01 - 4.80 (4H, m, 2 x OCH_2), 3.67 (1H, dd, J_{vic} = 3.6 Hz, J_{gem} = 11.2 Hz, CH_2Br), 3.59 (1H, dd, J_{vic} = 6.4 Hz, J_{gem} = 11.1 Hz, CH_2Br), 2.17 (3H, s, $MeCO_2$). The physical data of oxirane **4d** were in accord with the literature:[20] $[\alpha]_D^{22}$ -10.4° (c 3.2, $CHCl_3$) [lit.[20] $[\alpha]_D^{23}$ -11.0° (c 2.97, $CHCl_3$)]; mp 73 - 74°C (lit.[20] 71 - 73°C). The enantiomeric excess was found to be 95 % ee by HPLC (table II).

(2R, 3R, 4R)-(+) Isopropyl 3-acetoxy-2-bromo-4,5-dihydroxy-4,5-*O*-isopropylidenepentanoate (2e). PPTS (3 mg, 0.012 mmol) was added to a solution of the diol **1e**[21] (100 mg, 0.403 mmol) and trimethyl orthoacetate (76 µL, 0.6 mmol) in CH_2Cl_2 (0.8 mL). The solution was heated to 38°C until TLC (SiO_2, 35 % ethyl acetate - hexane) showed absence of starting material. After 2h, the volatiles were evaporated and residual MeOH was removed under high vacuum (0.1 mmHg) for 2 min. After addition of triethylamine (6 µL, 0.043 mmol) and CH_2Cl_2 (0.8 mL), the solution was cooled to 0°C and acetyl bromide (36 µL, 0.48 mmol) was introduced via syringe. After 2.5 h, TLC showed absence of hydroxyacetates [SiO_2, 35 % ethyl acetate - hexane, R_f 0.15 - 0.3, R_f (**2e**) 0.57] and the solution was poured into saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL), the combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (SiO_2, 30 % ether - hexane) furnished the acetoxy bromide **2e** (110 mg, 77 %) as a colorless oil. $[\alpha]_D^{22}$ +6.96° (c 1.9, $CHCl_3$); IR (neat film): ν 2987 (s), 2941 (m), 2885 (m), 1756 (s), 1374 (s), 1277 (s), 1223 (s), 1158 (m), 1106 (s), 1065 (s), 851 (m) cm^{-1}; ^1H NMR (400MHz): δ 5.46 (1H, t, J = 5.7 Hz, H-3), 5.05 (1H, sep, J = 6.3 Hz, C<u>H</u>Me_2), 4.50 - 4.44 (2H, m, H-2, H-4), 4.06 (1H, dd, J_{vic} = 6.5 Hz, J_{gem} = 8.5Hz, H-5), 3.89 (1H, dd, J_{vic} = 6.2 Hz, J_{gem} = 8.5 Hz, H-5), 2.09 (3H, s, $MeCO_2$), 1.38 (3H, s, Me_2C), 1.33 (3H, s, Me_2C), 1.28 (3H, d, J = 6.0 Hz, <u>Me_2</u>CH), 1.27 (3H, d, J = 6.1 Hz, <u>Me_2</u>CH); ^{13}C NMR (100 MHz): d 169.23 (C_q), 165.77 (C_q), 109.84 (C_q), 74.62 (CH), 72.46 (CH), 70.47 (CH), 65.60 (CH_2), 45.13 (CH), 26.30 (CH_3), 25.10 (CH_3), 21.48 (CH_3), 21.39 (CH_3), 20.73 (CH_3); MS (FAB, NBA/CsI) m/z 485, 487 ($M+Cs^+$, 100, 99 %), 353, 355 (MH^+, 10, 10); calculated for $C_{13}H_{21}BrO_6Cs^+$: 484.9576, found: 484.9581. $C_{13}H_{21}BrO_6$ requires: C, 44.21 and H, 5.99 %. Found: C, 44.05 and H, 6.13 %.

(1*S*, 2*S*)-(-)-1-Cyclohexylpropane-1,2-diol (1f). A mixture of rhodium on alumina (Degussa type G207 R/D, 5 % Rh, 0.5 g), the diol **1b** (97 % ee, 1.49 g, 9.8 mmol), MeOH (30 mL) and glacial acetic acid (3.0 mL) was shaken for 3 days at room temperature under a 45 - 50 psi hydrogen atmosphere. The reaction mixture was filtered through a small pad of celite and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO_2, 50 % ethyl acetate - hexane) gave diol **1f** (1.44 g, 93 %) as a colorless solid; mp 45 - 46°C, $[\alpha]_D^{22}$ -6.1° (c 1.5, $CHCl_3$); IR (neat film): ν 3390 (bs), 2971 (m), 2929 (s), 2854 (m), 1451 (m), 1133 (m), 1110 (m), 1073 (m), 990 (m) cm^{-1}; ^1H NMR (400MHz): δ 3.82 (1H, dquin, J_d =4.6 Hz, J_{quin} = 6.0 Hz, H-2), 3.09 (1H, q, J = 5.2 Hz, H-1), 2.16 (1H, d, J = 4.5 Hz, OH), 2.10 (1H, d, J = 5.4 Hz, OH), 1.80 - 1.60 (5H, m), 1.51 - 1.40 (1H, m), 1.33 - 1.04 (8H, m, includes: d 1.19, d, $J_{2,3}$ = 6.4 Hz, 3 x H-3); ^{13}C NMR (100 MHz): d 80.10, 67.77, 39.94, 30.10, 26.88, 26.37, 26.09, 19.80; (FAB, NBA/NaI) m/z 181 ($M+Na^+$, 100 %), 159 (MH^+, 1.4), 141 (MH^+-H_2O, 4.5), 123 (MH^+-$2H_2O$, 3); calculated for $C_9H_{18}O_2Na^+$: 181.1205, found: 181.1214.

(2*S*, 3*S*)-(-)-2-Cyclohexyl-3-methyloxirane (4f) *via* (1*S*, 2*R*)-2-chloro-1-cyclohexylpropyl acetate [2f(Cl)] and regioisomer 3f(Cl). Trimethyl orthoacetate (150 µL, 1.19 mmol) was added to a solution of the diol **1f** (158 mg, 1.0 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg) in CH_2Cl_2 (2 mL). After 25 min, the volatiles were evaporated and residual MeOH removed under high vacuum (0.1 mmHg) for 1 min. The residue was dissolved in CH_2Cl_2 (2 mL) and trimethylsilyl chloride (175 µL, 1.38 mmol) was added. After 14 h, TLC (SiO_2, 35 % ethyl acetate - hexane) showed absence of hydroxy acetates [R_f 0.33 - 0.47, R_f [**2f(Cl)**, **3f(Cl)**] 0.77] and the solution was evaporated *in vacuo* to obtain a mixture of acetoxy chlorides [86:14 mixture of **2f(Cl)** and **3f(Cl)** by ^1H NMR]. IR (neat film): ν 2985 (w), 2933 (s), 2856 (m), 1750 (s), 1451 (m), 1372

(m), 1229 (s), 1023 (m) cm^{-1}; ^1H NMR (250MHz, major isomer): δ 4.94 (1H, t, J = 6.0 Hz, H-1), 4.17 (1H, dq, $J_{1,2}$ = 5.7 Hz, $J_{2,3}$ = 6.6 Hz, H-2), 2.11 (3H, s, $MeCO_2$), 1.82 - 1.58 (6H, m), 1.46 (3H, d, $J_{2,3}$ = 6.7 Hz, 3 x H-3), 1.35 - 0.93 (5H, m); ^1H NMR (250MHz, minor isomer, signals partially obscured by major isomer): δ 5.16 (1H, quin, J = 6.1, H-2), 3.84 (1H, t, J = 5.9, H-1), 2.07 (3H, s, $MeCO_2$), 1.32 (3H, d, $J_{2,3}$ = 6.3 Hz, 3 x H-3); MS (FAB, NBA/NaI) m/z 241, 243 ($M+Na^+$, 56, 20 %), 219, 221 (MH^+, 28, 13.5); calculated for $C_{11}H_{19}ClO_2Na^+$: 241.0971, found: 241.0988. K_2CO_3 (275 mg, 1.99 mmol) was added in one portion to a solution of the crude acetoxy chlorides in MeOH (3.5 mL) and the suspension stirred vigorously for 6.5 h, after which time TLC [SiO_2, 40 % CH_2Cl_2 - hexane; R_f [**2f(Cl)**, **3f(Cl)**] 0.54; R_f (**4f**) 0.44] showed absence of acetoxy chlorides **2f(Cl)** and **3f(Cl)**. The mixture was poured into saturated aqueous NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* at room temperature. Purification of the residue by flash chromatography (3 % ether - pentane) afforded the epoxide **4f** (124 mg, 89 %) as a colorless liquid. $[\alpha]_D^{22}$ -29.6° (c 2.53, $CHCl_3$); IR (neat film): ν 2927 (s), 2854 (s), 1451 (m), 1382 (m), 980 (m), 859 (m) cm^{-1}; ^1H NMR (400 MHz) δ 2.79 (1H, dq, $J_{1,2}$ = 2.3 Hz, $J_{2,3}$ = 5.2 Hz, H-2), 2.41 (1H, dd, $J_{1,2}$ = 2.3 Hz, $J_{1,1'}$ = 6.6 Hz, H-1), 1.86 - 1.79 (1H, m), 1.76 - 1.60 (4H, m), 1.26 (3H, d, $J_{2,3}$ = 5.2 Hz, 3 x H-3), 1.28 - 1.00 (6H, m); ^{13}C NMR (100 MHz): d 64.18 (CH), 53.31 (CH), 40.04 (CH), 29.61 (CH_2), 29.02 (CH_2), 26.28 (CH_2), 25.68 (CH_2), 25.51 (CH_2), 17.85 (CH_3); MS (EI) m/z 140 (M^+), 125 (M^+-Me), 96 (M^+-C_2H_4O); calculated for $C_9H_{16}O^+$: 140.1201, found: 140.1204.

(2*S*, 3*S*)-(-)-2-Cyclohexyl-3-methyloxirane (4f) *via* (1*S*, 2*R*)-2-bromo-1-cyclohexylpropyl acetate [2f(Br)] and regioisomer 3f(Br). Trimethyl orthoacetate (150 μL, 1.19 mmol) was added to a solution of the diol **1f** (158 mg, 1.0 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg) in CH_2Cl_2 (2 mL). After 20 min, the volatiles were evaporated and residual MeOH removed under high vacuum (0.1 mmHg) for 1 min. The residue was dissolved in CH_2Cl_2 (2 mL) and acetyl bromide (95 μL, 1.27 mmol) was added. After 45 h, TLC (SiO_2, 35 % ethyl acetate - hexane) showed absence of hydroxy acetates [R_f 0.33 - 0.47, R_f [**2f(Br)**, **3f(Br)**] 0.82] and the solution was evaporated *in vacuo* to obtain a mixture of acetoxy bromides [88:12 mixture of **2f(Br)** and **3f(Br)** by ^1H NMR]. ^1H NMR (250 MHz, major isomer): δ 5.02 (1H, dd, $J_{1,2}$ = 5.5 Hz, $J_{1,1'}$ = 7.1 Hz, H-1), 4.27 (1H, dq, $J_{1,2}$ = 5.5 Hz, $J_{2,3}$ = 6.6 Hz, H-2), 2.11 (3H, s, $MeCO_2$), 1.85 - 1.53 (9H, m, includes δ 1.64, d, $J_{2,3}$ = 6.8 Hz, 3 x H-3), 1.39 - 0.93 (5H, m). ^1H NMR (250 MHz, minor isomer, signals partially obscured by major isomer): δ 5.10 (1H, quin, J = 6.1 Hz, H-2), 3.98 (1H, t, J = 6.1 Hz, H-1), 2.06 (3H, t, $MeCO_2$), 1.36 (3H, d, $J_{2,3}$ = 6.5 Hz, 3 x H-3). K_2CO_3 (275 mg, 1.99 mmol) was added in one portion to a solution of the crude acetoxy bromides in MeOH (3.5 mL) and the suspension stirred vigorously for 6 h. The mixture was filtered, the filtrate evaporated *in vacuo* and the residue purified by flash chromatography (3 % ether - pentane) to obtain the epoxide **4f** (128 mg, 91 %) as a colorless liquid, identical to the previously prepared sample.

(1*S*, 2*R*)-1-Cyclohexyl-2-iodopropyl acetate [2f(I)] and regioisomer 3f(I). Trimethyl orthoacetate (75 μL, 0.597 mmol) was added to a stirred solution of the diol **1f** (97 % ee, 79 mg, 0.5 mmol) and *p*-toluenesulfonic acid monohydrate (1 mg) in CH_2Cl_2 (1.0 mL). After 60 min, the volatiles were evaporated, residual MeOH was removed under high vacuum (0.1 mmHg) and NaI (90 mg, 0.6 mmol) added to the residue. The reaction vessel was sealed, oxygen replaced by argon and dry acetonitrile (1.0 mL) was added at 0°C. Acetyl chloride (40 μL, 0.56 mmol) was introduced dropwise via syringe over 5 min and the reaction

mixture allowed to warm slowly to room temperature. After 75 min, a brown suspension was formed and a TLC test (SiO_2, 35 % ethyl acetate - hexane) showed almost complete absence of hydroxy acetates [R_f 0.35 - 0.47, R_f [**2f(I)**, **3f(I)**] 0.79]. The mixture was poured into a saturated aqueous solution of Na_2SO_3 and $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the colorless residue by flash chromatography (SiO_2, 5 % ether - pentane) furnished the acetoxy iodide [77 mg, 50 %, 87:13 mixture of **2f(I)** and **3f(I)** by ^1H NMR] as a colorless oil. IR (neat film): ν 2925 (s), 2856 (s), 1748 (s), 1449 (m), 1372 (m), 1233 (s), 1021 (m), 616 (m) cm^{-1}; ^1H NMR (400 MHz, major isomer): δ 5.00 (1H, dd, $J_{1,2}$ = 5.4 Hz, J = 7.0 Hz, H-1), 4.37 (1H, dq, $J_{1,2}$ = 5.4 Hz, $J_{2,3}$ = 7.0 Hz, H-2), 2.12 (3H, s, $MeCO_2$), 1.84 (3H, d, $J_{2,3}$ = 7.0 Hz, 3 x H-3), 1.80 - 1.56 (6H), 1.32 - 0.95 (5H); ^1H NMR (400 MHz, minor isomer, signals partially obscured by major isomer): δ 4.75 (1H, quin, J = 6.1 Hz, H-2), 4.15 (1H, t, J = 5.9 Hz, H-1), 2.06 (3H, s, $MeCO_2$), 1.37 (3H, d, $J_{2,3}$ = 6.2 Hz, 3 x H-3); MS (FAB, NBA/NaI) m/z 333 ($M+Na^+$, 100 %), 251 ($M^+-C_2H_3O_2$, 43), 183 (M^+-I, 19); calculated for $C_{11}H_{19}IO_2Na^+$: 333.0328, found: 333.0338.

(2S)-(+)-2-Phenoxymethyloxirane (4g). Trimethyl orthoacetate (450 μL, 3.58 mmol) was added to a solution of the diol **1g** (89 % ee, 505 mg, 3.0 mmol) and PPTS (6 mg, 0.024 mmol) in CH_2Cl_2 (4.5 mL). After 20 min, the reaction mixture was evaporated, the residue subjected to high vacuum (0.1 mmHg) for 1 min and then taken up in CH_2Cl_2 (4.5 mL). Acetyl bromide (270 μL, 3.62 mmol) was added and the solution stirred at room temperature for 30 min. The volatiles were evaporated *in vacuo* to obtain the crude acetoxy bromide **2g** (889 mg) as a yellowish liquid. IR (neat film): ν 3064 (w), 3043 (w), 2935 (m), 2881 (w), 1744 (s), 1600 (m), 1590 (m), 1497 (m), 1229 (s), 1050 (s), 756 (m), 693 (m) cm^{-1}; ^1H NMR (250 MHz): δ 7.36 - 7.23 (2H, m, Ph), 7.04 - 6.87 (3H, m, Ph), 5.32 (1H, quin, J = 5.2 Hz, C<u>H</u>OAc), 4.21 (1H, dd, J_{vic} = 4.8 Hz, J_{gem} = 10.2 Hz, C<u>H</u>$_2$OPh), 4.15 (1H, dd, J_{vic} = 5.2 Hz, J_{gem} = 10.2 Hz, C<u>H</u>$_2$OPh), 3.72 (1H, dd, J_{vic} = 5.4 Hz, J_{gem} = 10.9 Hz, C<u>H</u>$_2$Br), 3.63 (1H, dd, J_{vic} = 5.3 Hz, J_{gem} = 10.9 Hz, H-3), 2.13 (3H, s, $MeCO_2$); MS (FAB, NBA/NaI) m/z 295, 297 ($M+Na^+$, 49.3, 48.6 %), 273, 275 (MH^+, 41, 35), 272, 274 (M^+, 23, 26), 213, 215 ($M^+-C_2H_3O_2$, 30, 29), 179, 181 (M^+-PhO, 100, 98); calculated for $C_{11}H_{13}BrO_3Na^+$: 294.9946, found: 294.9949. K_2CO_3 (540 mg, 3.9 mmol) was added to a solution of the crude acetoxy bromide **2g** in MeOH (10 mL). The mixture was stirred at room temperature for 105 min, then poured into saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification of the residue by flash chromatography (SiO_2, 20 % ether - pentane) afforded the epoxide **4g** (439 mg, 97 %) as a colorless oil. The enantiomeric purity was determined to be 89 % ee by HPLC analysis (table II). $[\alpha]_D^{22}$ +3.48° (c 2.93, $CHCl_3$), $[\alpha]_D^{22}$ +14.4° (c 2.54, MeOH) [lit.:[22] $[\alpha]_D^{25}$ +14.1° (c 2.36, MeOH), 80 % ee]; IR (neat film): ν 3062 (w), 3004 (w), 2927 (w), 2877 (w), 1600 (m), 1588 (m), 1495 (s), 1245 (s), 1040 (m), 754 (s) cm^{-1}; ^1H NMR (400 MHz): δ 7.33 - 7.26 (2H, m, Ph), 7.00 - 6.90 (3H, m, Ph), 4.22 (1H, dd, J_{vic} = 3.2 Hz, J_{gem} = 11.0 Hz, C<u>H</u>$_2$OPh), 3.97 (1H, dd, J_{vic} = 5.6 Hz, J_{gem} = 11.0 Hz, C<u>H</u>$_2$OPh), 3.39 - 3.34 (1H, m, H-2), 2.91 (1H, dd, J_{vic} = 4.2 Hz, J_{gem} = 4.9 Hz, H-3), 2.77 (1H, dd, J_{vic} = 2.7 Hz, J_{gem} = 4.9 Hz, H-3); MS (FAB, NBA/NaI) m/z 150 (M^+), 107 ($PhOCH_2^+$); calculated for $C_9H_{10}O_2^+$: 150.0681, found: 150.0696.

(2*R*, 3*S*)-(-) Methyl 2,3-epoxy-3-phenylpropionate (4h). Trimethyl orthoacetate (96 μL, 0.764 mmol) was added to a stirred solution of the diol **1h** (115 mg, 0.586 mmol) and *p*-toluenesulfonic acid monohydrate (1 mg) in CH_2Cl_2 (0.8 mL). After 30 min, the volatiles were evaporated and residual methanol was removed under high vacuum (0.1 mmHg) for 1 min. The residue was taken up in CH_2Cl_2 (0.8 mL), the solution cooled to -20°C and acetyl bromide (52 μL, 0.698 mmol) was added dropwise. After 5 h, further trimethyl orthoacetate (7 μL, 0.056 mmol) and acetyl bromide (7 μL, 0.094 mmol) were added and stirring was continued at -20°C for a further 5 h. The reaction was warmed to room temperature and stirred for a further 1.5 h, after which time TLC (silica gel, 35 % ethyl acetate - hexane) showed absence of polar compounds [*i.e.* diol, hydroxy acetates, R_f 0.11 - 0.27, R_f (**2h**, **3h**) 0.59]. The solvent was evaporated to obtain the crude acetoxy bromide (14 : 86 mixture of **2h** and **3h** by ^1H NMR). Physical data of acetoxy bromide **3h** (obtained from a similar experiment as a colorless solid by recrystallization of the crude mixture from ether - hexane): $[\alpha]_D^{22}$ -110.2° (c 0.95, $CHCl_3$); mp 87°C; IR (KBr): ν 3072 (w), 3035 (w), 2966 (m), 1764 (s), 1748 (s), 1219 (s), 1090 (s), 702 (m) cm^{-1}; ^1H NMR (250 MHz): δ 7.49 - 7.40 (2H, m, Ph), 7.38 - 7.28 (3H, m, Ph), 5.65 (1H, d, $J_{2,3}$ = 6.4 Hz, H-2 or H-3), 5.35 (1H, d, $J_{2,3}$ = 6.4 Hz, H-2 or H-3), 3.71 (3H, s, OMe), 2.11 (3H, s, $MeCO_2$); MS (FAB, NBA/CsI) m/z 433, 435 ($M+Cs^+$, 17.6, 18.2 %), 301, 303 (MH^+, 1.3); calculated for $C_{12}H_{13}BrO_4Cs^+$: 432.9052, found: 432.9056. K_2CO_3 (130 mg, 0.94 mmol) was added in 3 portions to a solution of the crude acetoxy bromides **2h**, **3h** in MeOH (2 mL) at -20°C over 5 min. The suspension was stirred vigorously between -20 and -22°C for 105 min and then poured into saturated aqueous NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL), the combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 13 % ether - pentane, then 20 % ether - pentane) furnished the epoxy ester **4h** (86 mg, 82 %) as a colorless oil. The physical data of oxirane **4h** were in accord with the literature.[23] $[\alpha]_D^{22}$ -179.7° (c 3.63, $CHCl_3$); IR (neat film): ν 3068 (w), 3035 (w), 2956 (m), 1756 (s), 1609 (w), 1588 (w), 1441 (m), 1295 (m), 1212 (s), 1023 (m), 762 (m), 697 (m) cm^{-1}; ^1H NMR (400 MHz): δ 7.41 - 7.34 (3H, m, Ph), 7.32 - 7.27 (2H, m, Ph), 4.10 (1H, d, $J_{2,3}$ = 1.7 Hz, H-3), 3.83 (3H, s, OMe), 3.52 (1H, d, $J_{2,3}$ =1.8 Hz, H-2).

Methyl 3-[2-(8-phenyloctyl)phenyl]propenoate 5. The unsaturated ester **5** was prepared in 99% yield from 2-(8-phenyloctyl)benzenecarbaldehyde[24] by Wadsworth-Horner-Emmons olefination with trimethyl phosphonoacetate under the reaction conditions described by Masamune, Roush *et al.*[25] IR (neat film): ν 3062 (w), 3027 (w), 2929 (s), 2856 (m), 1721 (s), 1632 (m), 1602 (w), 1318 (m), 1171 (s), 766 (m), 749 (m), 698 (m) cm^{-1}; ^1H NMR (400 MHz): δ 8.04 (1H, d, $J_{2,3}$ = 15.9 Hz, H-3), 7.57 (1H, d, J = 7.9 Hz, Ph), 7.36 - 7.15 (8H, m, Ph), 6.39 (1H, d, $J_{2,3}$ = 15.9 Hz, H-2), 3.83 (3H, s, OMe), 2.76 (2H, t, J = 7.8 Hz), 2.62 (2H, t, J = 7.8 Hz), 1.67 - 1.53 (4H, m), 1.34 (8H, s); ^{13}C NMR (100 MHz): δ 167.50 (C_q), 142.89 (C_q), 142.60 (C_q), 142.50 (CH), 132.81 (C_q), 130.03 (CH), 128.39 (CH), 128.22 (CH), 126.51 (CH), 126.32 (CH), 125.55 (CH), 118.85 (CH), 51.68 (CH_3), 35.97 (CH_2), 33.28 (CH_2), 31.60 (CH_2), 31.50 (CH_2), 29.42 (CH_2), 29.38 (CH_2), 29.35 (CH_2), 29.29 (CH_2); MS (FAB, NBA/CsI) m/z 483 ($M+Cs^+$, 55%), 351 (MH^+, 100), 319 (MH^+-CH_4O, 50); calculated for $C_{24}H_{30}O_2Cs^+$: 483.1300, found: 483.1300.

(2*R*, 3*S*)-(+) Methyl 2,3-dihydroxy-3-[2-(8-phenyloctyl)phenyl]propionate 6. A mixture of AD-mix-α[3] (3.7 g), methanesulfonamide (0.25 g, 2.63 mmol) and *tert*-butanol - water (1:1, 26 mL) was stirred vigorously at room temperature for 5 min, before the unsaturated ester **5** (0.91 g, 2.6 mmol) was added. After

13 h, Na_2SO_3 (1 g) was added, followed by ethyl acetate (45 mL) and stirring was continued for a further 5 min. The mixture was transferred to a separatory funnel, the organic layer separated and the aqueous phase extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with 0.5 M HCl (30 mL) and 2 M KOH (30 mL), then dried ($MgSO_4$) and filtered through a short pad of Celite. The pad was washed thoroughly with ethyl acetate and the combined filtrate and washing liquid were concentrated *in vacuo*. Purification of the resultant yellow oil by filtration through a pad (H 65 mm, D 30 mm) of silica gel (15 % ethyl acetate - hexane, until a non-polar impurity has come off, then 50 % ethyl acetate - hexane) and evaporation of the filtrate gave the diol **6** (876 mg, 88 %) as a colorless solid. The enantiomeric purity was determined to be >99 % ee by HPLC (table II). $[\alpha]_D^{22}$ +10.3° (c 2.15, $CHCl_3$); mp 57-58°C; IR (KBr): ν 3510 (bs), 3062 (w), 3027 (w), 2925 (s), 2854 (m), 1735 (s), 1706 (sh), 1605 (w), 1289 (m), 1233 (s), 1115 (m), 751 (m), 724 (m), 698 (m) cm^{-1}; ^1H NMR (400 MHz): δ 7.57 - 7.50 (1H, m, Ph), 7.32 - 7.14 (8H, m, Ph), 5.29 (1H, bd, $J_{2,3}$ = 2.1 Hz, H-3), 4.31 (1H, bd, $J_{2,3}$ = 2.4 Hz, H-2), 3.82 (3H, s, OMe). 3.19 (1H, bs, OH), 2.80 - 2.55 (5H, m, OH, 2 x CH_2), 1.61 (4H, m), 1.44 - 1.30 (8H, m); ^{13}C NMR (100 MHz): δ 173.30 (C_q), 142.81 (C_q), 139.52 (C_q), 137.43 (C_q), 129.40 (CH), 128.35 (2 x CH), 128.19 (2 x CH), 127.99 (CH), 126.39 (CH), 126.05 (CH), 125.54 (CH), 73.88 (CH), 70.37 (CH), 52.91 (CH_3), 35.92 (CH_2), 32.21 (CH_2), 31.45 (2 x CH_2), 29.67 (CH_2), 29.44 (CH_2), 29.37 (CH_2), 29.27 (CH_2); MS (FAB, NBA/CsI) m/z 517 ($M+Cs^+$, 100 %); MS (FAB, NBA) m/z 367 (MH^+-H_2O), 349 (MH^+-2H_2O); calculated for $C_{24}H_{32}O_4Cs^+$: 517.1355, found: 517.1350. $C_{24}H_{32}O_4$ requires: C, 74.97 and H, 8.39 %. Found: C, 74.97 and H, 8.39 %.

(2*R*, 3*S*)-(-) Methyl 2,3-epoxy-3-[2-(8-phenyloctyl)phenyl]propionate (7). A solution of the diol **6** (3.85 g, 10 mmol), trimethyl orthoacetate (1.5 mL, 11.94 mmol) and *p*-toluenesulfonic acid monohydrate (30 mg, 0.158 mmol) in CH_2Cl_2 (12.5 mL) was allowed to stand at room temperature for 15 min. The solvent was evaporated and residual MeOH removed under high vacuum (0.1 mmHg) for 5 min. The residue was taken up in CH_2Cl_2 (12.5 mL) and Me_3SiCl (1.52 mL, 11.98 mmol) was added. After 105 min, TLC (SiO_2, 25 % ethyl acetate - hexane) showed almost complete absence of hydroxyacetates [R_f 0.22 - 0.36, R_f (acetoxy chloride) 0.62]. The mixture was heated to reflux for 60 min, then allowed to cool and the solvent was evaporated *in vacuo* to obtain crude (2*S*, 3*R*) methyl 2-acetoxy-3-chloro-3-[2-(8-phenyloctyl)phenyl]-propionate as an oil; ^1H NMR (400 MHz): δ 7.57 (1H, m, Ph), 7.30 - 7.12 (8H, m, Ph), 5.56 (1H, d, $J_{2,3}$ = 7.9 Hz, H-2 or H-3), 5.53 (1H, d, $J_{2,3}$ = 8.0 Hz, H-2 or H-3), 3.75 (3H, s, OMe), 2.80 - 2.60 (2H, m), 2.60 (2H, t, J = 7.8 Hz), 2.01 (3H, s, $MeCO_2$), 1.60 (4H, m), 1.34 (8H, s). K_2CO_3 (1.66 g, 12.0 mmol) was added in 2 portions over 10 min to a vigorously stirred solution of the crude acetoxy chloride in MeOH (40 mL) at -17°C. After 135 min, the mixture was poured into saturated aqueous NH_4Cl (60 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO_2, 12 % ether - hexane, then 20 % ether - hexane) afforded the epoxy ester **7** (3.15 g, 86 %) as a colorless oil. $[\alpha]_D^{22}$ -34.7° (c 1.85, $CHCl_3$); IR (neat film): ν 3062 (w), 3027 (m), 2929 (s), 2856 (s), 1756 (s), 1605 (w), 1584 (w), 1441 (m), 1287 (m), 1208 (s), 760 (m), 700 (m) cm^{-1}; ^1H NMR (400 MHz): δ 7.33 - 7.14 (9H, m, Ph), 4.27 (1H, d, $J_{2,3}$ = 1.9 Hz, H-3), 3.84 (3H, s, OMe), 3.42 (1H, d, $J_{2,3}$ = 1.9 Hz, H-2), 2.71 (2H, m), 2.61 (2H, t, J = 7.7 Hz), 1.61 (4H, m), 1.33 (8H, m); ^{13}C NMR (100 MHz): δ 168.80 (C_q), 142.79 (C_q), 141.29 (C_q), 132.70 (C_q), 129.21 (CH), 128.46 (CH), 128.34 (CH), 128.17 (CH), 126.24 (CH), 125.52 (CH), 124.30 (CH), 56.05 (CH), 56.02 (CH), 52.58 (CH_3), 35.91 (CH_2), 32.65 (CH_2), 31.43 (CH_2), 31.03 (CH_2), 29.44 (CH_2), 29.37 (2 x CH_2), 29.24 (CH_2); MS (FAB, NBA/CsI)

m/z 499 (M+Cs$^+$, 100 %); calculated for $C_{24}H_{30}O_3Cs^+$: 499.1249, found: 499.1249. $C_{24}H_{30}O_3$ requires: C, 78.65 and H, 8.25 %. Found: C, 78.28 and H, 8.33 %.

(2*R-trans*)-(+) 3-[2-(8-phenyloctyl)phenyl]oxiranecarboxamide (8). A solution of NH_3 in MeOH (saturated at 0°C, 1.5 mL) was added to a solution of the epoxy ester **7** (121 mg, 0.33 mmol) in MeOH (1.5 mL) at 0°C. After 2 h, the volatiles were evaporated *in vacuo*, the residue taken up in toluene (1 mL) and evaporated again. Purification of the residue by flash chromatography (SiO_2, 35 % ethyl acetate - hexane) afforded the epoxy amide **8** (105 mg, 90 %) as a colorless solid. The physical data of **8** were in accord with the literature:[26] $[\alpha]_D^{22}$ +14.1° (c 1.04, CH_2Cl_2) [lit.:[26] $[\alpha]_D$ +13.2° (c 1.0, CH_2Cl_2)]; mp 81 - 82°C (lit.:[26] 81 - 82°C); IR (KBr): ν 3381 (b), 3195 (b), 3027 (w), 2925 (s), 2854 (m), 1671 (s), 1648 (sh), 1619 (m), 1088 (m), 899 (m), 753 (m), 724 (m), 697 (m) cm^{-1}; ^{1}H NMR (400 MHz): δ 7.32 - 7.12 (9H, m, Ph), 6.21 (1H, bs, NH), 5.84 (1H, bs, NH), 4.12 (1H, d, $J_{2,3}$ = 2.1 Hz, H-2 or H-3), 3.38 (1H, d, $J_{2,3}$ = 1.8 Hz, H-2 or H-3), 2.71 (2H, m), 2.60 (2H, t, J = 7.7 Hz), 1.61 (4H, m), 1.33 (8H, s); ^{13}C NMR (100 MHz): δ 170.29 (C_q), 142.87 (C_q), 141.32 (C_q), 132.66 (C_q), 129.20 (CH), 128.52 (CH), 128.36 (CH), 128.18 (CH), 126.23 (CH), 125.52 (CH), 124.17 (CH), 58.05 (CH), 56.91 (CH), 35.92 (CH_2), 32.56 (CH_2), 31.46 (CH_2), 30.87 (CH_2), 29.41 (CH_2), 29.38 (CH_2), 29.33 (CH_2), 29.25 (CH_2); MS (FAB, NBA) m/z 352 (MH$^+$, 100 %); calculated for $C_{23}H_{30}NO_2^+$: 352.2277, found: 352.2263.

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