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Inversion of configurations of contiguous carbinol centres: application to the synthesis of both enantiomers of natural products from the same enantiomerically pure starting material

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ABSTRACT

A novel method for effecting the inversion of configuration of two and three contiguous carbinol centers in a diol, triol, and tetraol chain, thus affording the opposite enantiomer with ⩾98% e.e., has been developed. The method is based on the sequential formation of a terminal epoxide, Payne rearrangement, and intramolecular lactonization. Application of this methodology to the synthesis of a leukotriene A_4 intermediate and its enantiomer, and the oviposition attractant pheromone of the mosquito *Culex pipiens fatigans* and its enantiomer, from the same enantiomerically pure starting material is described[1].

INTRODUCTION

The epoxide moiety is without question one of the most important functional groups in organic chemistry, especially in the light of the availability of enantiomerically pure 2,3-epoxyalcohols[2–4]. Indeed, the literature confirms that much effort has been expended on the investigation of epoxide chemistry in the past[5]. A large number of syntheses of natural products have been designed solely around epoxide-containing intermediates. Recently, Sharpless and coworkers[5,6] have systematically explored nucleophilic substitution at C-3 or C-2 of acyclic 2,3-epoxyalcohols under both isomerising and non-isomerising conditions. Hoye[7] and Nicolaou[8] described a "zip-type" reaction of a triepoxide to give bistetrahydrofurans and more recently, Still[9] and Schreiber[10] have demonstrated that polyepoxymacrocyclic lactones undergo polyepoxide cyclisation to give tris- and bis-tetrahydrofuranoid materials under acidic conditions.

In the course of our work on lipoxygenase-derived metabolites of arachidonic acid, we had an opportunity[11] to prepare both enantiomers of leukotriene A_4. Both compounds were prepared from 2-deoxy-D-*erythro*-pentose but, however, the unnatural isomer was made by a less-direct route that required protecting-group chemistry in order to invert the desired stereocentre. Although it was possible to start the synthesis of the unnatural enantiomer from the rare 2-deoxy-L-*erythro*-pentose, we sought to

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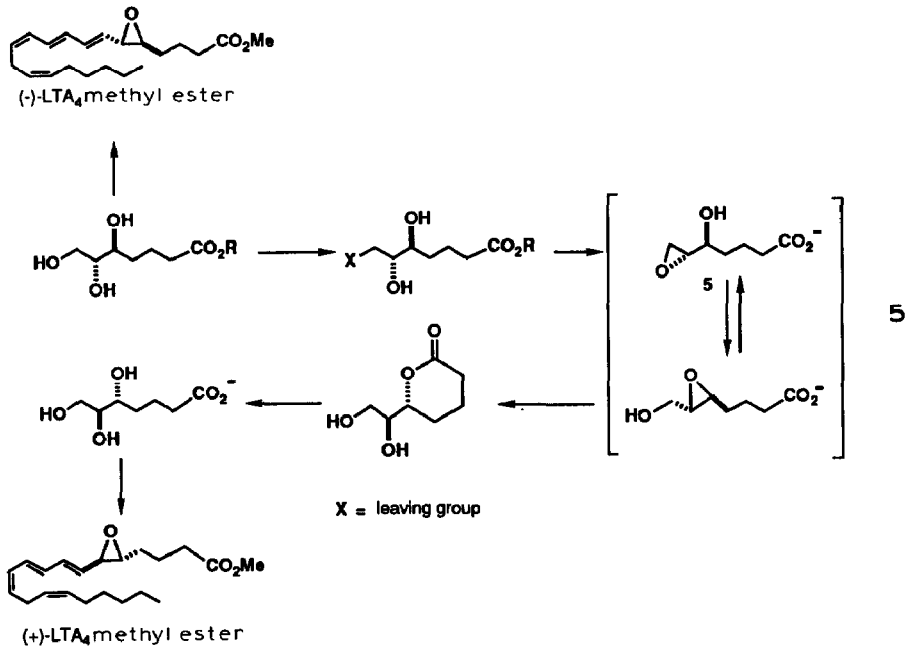
convert 2-deoxy-D-*erythro*-pentose into its L enantiomer or a derivative thereof, that is, by inverting the configuration of both carbinol centres with minimal manipulations.

RESULTS AND DISCUSSION

It was envisaged that the inversion of configuration of several contiguous carbinol centers should be possible *via* sequential epoxide formation, Payne rearrangement[12], and lactonization, as illustrated in Scheme 1. In principle this should be a one-pot process. The equilibrating epoxides would be intercepted by the anticipated irreversible lactonization, followed by hydrolysis to yield the enantiomer of the starting triol (see ref. 13 for related work).



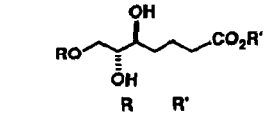
Scheme 1.

In order to test the viability of this approach, ester **1a** was treated with aqueous NaOH in various solvents (EtOH, THF, Me_2SO) at various temperatures, conditions which allowed simultaneous hydrolysis of the ester and rearrangement. The product was isolated as its acetate **3a** and **3b** after neutralization and acetylation. The enantiomeric purity of the product obtained under a variety of conditions was found to be in the range 50–60% e.e., with **3b** predominating as determined by analysis of the 250- and 300-MHz ^{1}H-n.m.r. and ^{19}F-n.m.r. spectra of the corresponding (−)-MTPA [α-methoxy-α(trifluoromethyl)phenylacetic acid] esters[14] **4a** and **4b***. Compounds **4a** and **4b**

* The conversion of **3** into **4** was accomplished by deacetylation, sulfonylation, and lactonization to give **7**, which was then treated with [(−)-MTPACl] in CH_2Cl_2 in the presence of 4-dimethylaminopyridine.

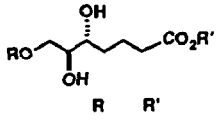
exhibited methoxy resonances at δ 3.58 and 3.46, respectively, in ^{1}H-n.m.r. and trifluoromethyl resonances at δ 4.04, and 4.42, respectively, in ^{19}F-n.m.r. ($CDCl_3$ with CF_3CO_2H as the internal standard). The separation of these signals allowed an accurate measurement of ratio of the two diastereomers.

The loss of optical purity presumably comes from a competing hydroxide anion opening at C-1 of the 1,2-epoxy alcohol **5** in the equilibrium. This hypothesis was substantiated when the protected 2,3-epoxy alchol **8** was used as a substrate under the same conditions[13b]. After the base treatment, removal of the tetrahydropyranyl ether and acetylation, the isolated product had >98% e.e., whereas the e.e. of the product derived from the unprotected alchol **9** was found to be only 68%. It is evident then that anhydrous conditions are essential in order to eliminate side reactions and to obtain high enantiomeric purity. Consequently the acid **2a** was treated with freshly prepared NaOEt in ethanol for 18 h and the product acetylated to afford the diacetate **3b** in 88% yield, $[\alpha]_D$ −55°, (*c* 0.9, $CHCl_3$) whose optical purity was determined to be >98% after conversion into its MTPA ester **4b**. The acid **2a** was conveniently prepared from the unsaturated ester **10**, by hydrogenolysis; **10** was in turn prepared from 2-deoxy-D-*erythro*-pentose[11]. In practice the acid was not islated, but was used directly in the next step after removal of the catalyst under nitrogen. The presence of the catalyst in the next operation caused substantial hydrogenolysis of the epoxide at the terminal position. Thus a simple procedure for effecting the inversion of configuration of two contiguous carbinol centers was achieved in high yield with high optical purity.



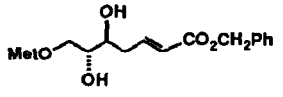
R R'

1a Met Et
2a Met H



R R'

1b Met Et



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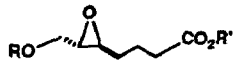
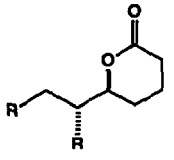


R R'

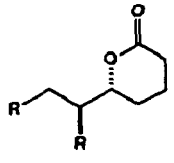
8 OTHP Et
9 OH Et

Met = (i-C_3H_7)$C_6H_2SO_2$ —



R R'

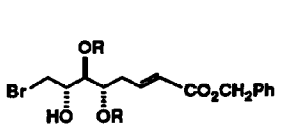
3a OAc OAc
4a OMet OMTPA
7a OMet OH



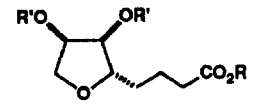
R R'

3b OAc OAc
4b OMet OMTPA
7b OMet OH

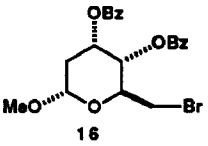
This concept was extended to three contiguous carbinol centers (Scheme 2). When the acid **11a** was treated with freshly prepared NaOEt in ethanol for 18 h, two products were obtained. The expected lactone **13a** and the tetrahydrofuran **14b**, in the ratio of ~1:2–1:3, respectively, were isolated after hydrolysis, acetylation, and diazomethane treatment. Formation of the tetrahydrofuran **14a** came from a surprisingly competitive



12 R = Bz



14a R = H, R' = Ac
14b R = Me, R' = Ac



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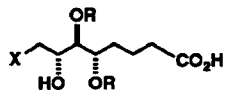
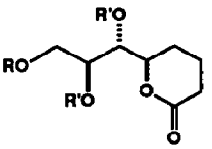
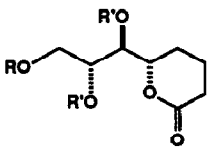


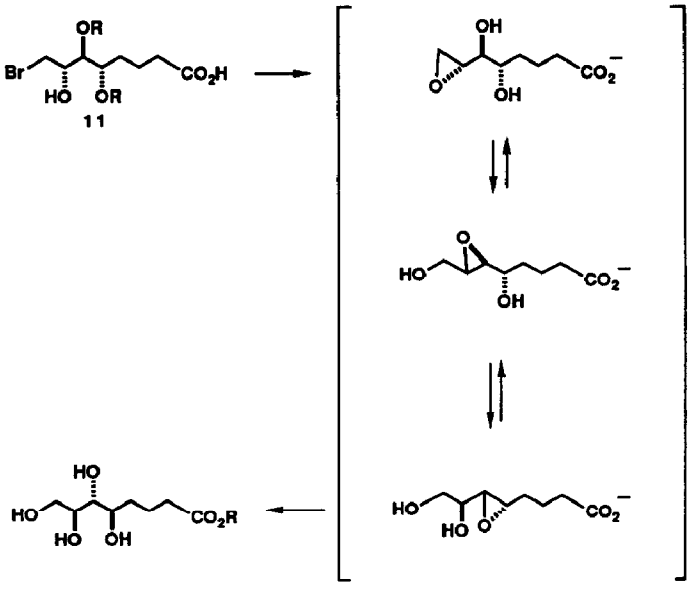
11a X = OTs, R = H
11b X = Br , R = Bz



13a R = R' = Ac
15a R = Met, R '= MTPA



13b R = R' = Ac
15b R = Met, R' = MTPA



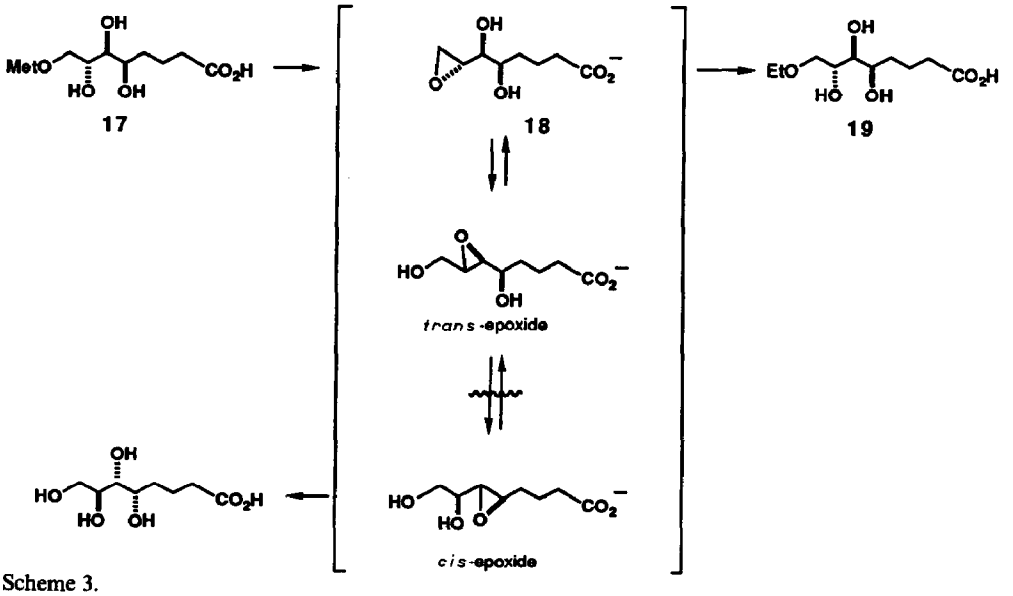
Scheme 2.

SN2 substitution by the C-5 hydroxyl group. It was not clear whether the tetrahydrofuran was formed by a direct displacement of the bromide or by a disfavoured *endo*-opening of the epoxide. Should the former be the case, we envisaged that this side reaction may be suppressed by simply attaching a "transient" protecting group at both C-5 and C-6. The ideal protecting group for this purpose is the benzoyl group, which while allowing the terminal epoxide to be formed preferentially, would later be hydrolysed and allow the "double-Payne rearrangement" to take place (Scheme 2). Indeed this strategy proved successful. When acid **11b** was used the lactone **13a** could be isolated in 68% yield. This lactone had identical spectral properties, but equal and opposite optical rotation to its enantiomer **13b** prepared from D-ribose. Its enantiomeric

purity was determined to be >98% e.e. by conversion into its di-(−)-MTPA esters **15**. Compounds **15a** and **15b** exhibited trifluoromethyl resonances at δ 4.03, 4.43, and δ 4.25, 4.76, respectively, in the ^{19}F-n.m.r. relative to CF_3CO_2H in $CDCl_3$. The acid **11b** was readily prepared by hydrogenolysis of the benzyl ester **12** which was in turn prepared from the known[15] pyranoside **16**. Thus an inversion of configuration of three contiguous carbinol centres was achieved in essentially a one-pot protocol. It is worth noting that several efficient steps took place in this "one-pot": (*a*) carboxylate anion formation, (*b*) epoxide formation, (*c*) ethanolysis of two benzoyloxy groups, (*d*) double-Payne rearrangement, (*e*) lactonization and finally (*f*) ring-opening of the resultant lactone.

We have observed that the stereochemistry of the carbinol centre has a profound effect on the outcome of the reaction[13]. When the acid **17** (Scheme 3), which differed from the acid **11** at the configuration of C-5, was treated with NaOEt in EtOH, none of the expected inverted product was obtained. However the ethyl ether **19** was obtained as the major product. The formation of **19** from **17** must proceed by the attack of ethoxide ion on the 1,2-epoxide **18** of the equilibrating epoxide mixtures. The pathway leading to the inverted product, which required the formation of a *cis*-epoxide, is apparently less favourable. The use of a more-hindered base such as KOBu^t in Bu^{t}OH offered no improvement, as the corresponding butyl ether was isolated as the major product.

Application to the synthesis of natural products. — Thus with the availability of the lactone **3b**, whose two stereocentres have been inverted, the synthesis of the antipode of leukotriene A_4 became straightforward. Ethanolysis of the lactone **3b** with K_2CO_3 in ethanol followed by selective sulfonylation gave **1b** in 91% yield. Treatment of the sulfonate **1b** with NaOEt in ethanol furnished the enantiomer[11] of **9**, $[\alpha]_D$ +34° ($CDCl_3$) which has previously been converted into the antipode of leukotriene[11] A_4. This com-



Scheme 3.

pound also allows a general entry to the synthesis of the lipoxin A family of compounds in which the stereochemistry of the diol at C-5 and C-6 is critical for biosynthetic studies[16].

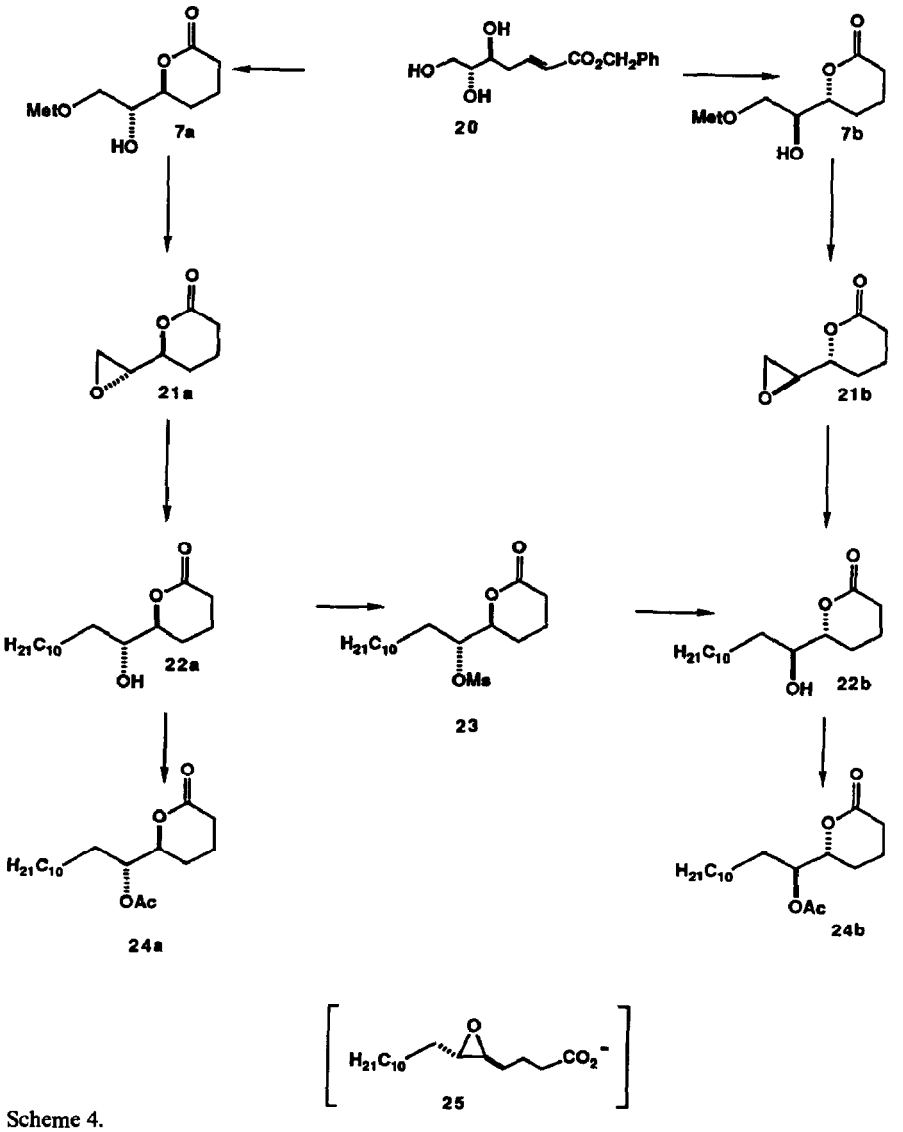
This new methodology was also found to be useful for the synthesis of the oviposition attractant pheromone **24b** of *Culex pipiens fatigans* and its enantiomer **24a** from the same chiral starting material (Scheme 4). In 1982, Lawrence and Picket[17] isolated a substance from the apical droplets that form on the eggs of the mosquito *C. pipiens fatigans* and identified it as 6-acetoxy-5-hexadecanolide by mass-spectral comparison with a synthetic, racemic sample. The substance acts as an oviposition attractant-pheromone in that it attracts other gravid females of the same and related mosquito species and induces them to oviposit in the same spot where the original eggs are found. The amount of the natural material available was too small to determine its optical rotation, but later comparison of the pheromonal activity with that of an optically pure, synthetic specimen proved that the natural substance possessed the (5*R*, 6*S*) stereochemistry[18b].

Unlike most of the earlier syntheses of the two enantiomeric erythro isomers[18], our synthesis started with the same chiral starting material, 2-deoxy-D-*erythro*-pentose. On heating the ester **1b** in THF containing M HCl and evaporation of the solvent, the liberated acid lactonized to yield the lactone **7b**. Treatment of **7b** with NaH in THF containing a catalytic amount of Me_2SO gave the epoxylactone **21b** as an oil. Selective opening of the epoxide with $C_{10}H_{21}$ MgBr was achieved by using 10 mol % of Li_2CuCl_4 as catalyst to afford the alcohol **22b**, which possessed similar physical data to those reported in the literature[18b].

Finally, acetylation gave the natural product **24b** in 90% yield; its rotation, $[\alpha]_D$ $-38.1°$ ($CHCl_3$), agreed well with literature values[18]. A similar manipulation in the other enantiomeric series starting with the ester **20** gave the antipode of the natural product **24a** without incidents.

Thus far the strategy involved inverting all of the stereocenters of the starting material **1a** to give its enantiomer, which was then further elaborated to give the natural product. An alternative strategy would be to invert the two contiguous asymmetric centres later in the synthetic sequence, after all the structural elements of the desired compound are in place, for example the conversion of **22a** into **22b**. This approach would have the added attraction that both enantiomers **22a** and **22b** may be prepared in fewer steps. This would be particularly useful in cases where long syntheses are involved. Following this strategy, it was anticipated that mesylation of the masked vicinal diol **22a**, followed by saponification should lead directly to its enantiomer **22b**, via the epoxide **25** with carboxylate opening at C-5 competing favorably with random opening by hydroxide anion (compare saponification of **8**)[13,16]. Such a strategy for inverting two carbinol centers have not been fully exploited[19], although the method has been used to invert one carbinol center, (*S*)-4-hydroxymethyl-4-butanolide into its (*R*)-enantiomer[20]. Indeed, when the mesylate **23** was treated with aqueous NaOH followed by acidification with acetic acid, **22b** was obtained in 82% yield and 98% e.e. Acetylation of the alcohol **22b** gave the natural product **24b** as before, $[\alpha]_D$ $-37.5°$ ($CHCl_3$).

In summary, the chemistry described constitutes a convenient way to invert the stereochemistry of two and three contiguous hydroxyl groups in a diol, triol, and tetraol chain, thus affording opposite enantiomers.



Scheme 4.

EXPERIMENTAL

General methods. — All reactions except hydrogenations were carried out under an atmosphere of nitrogen. Conventional processing involved three extractions with the

specied solvent. Organic extracts were then combined, washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under water aspirator pressure. Residues were dried to constant weight under high vacuum or water-aspirator pressure in the case of volatile materials. Unless otherwise noted, column chromatography was performed using EM Silica Gel 60 (0.063–0.2 mm). Thin-layer chromatography (t.l.c.) was performed with EM Silica Gel 60F-254 precoated plates. Spots were detected with u.v. light and/or phosphomolybdic acid and ceric sulfate sprays, followed by heating. Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. ^{1}H-n.m.r. spectra (250 MHz) were obtained in $CDCl_3$ solution unless otherwise noted. Chemical shifts are reported relative to tetramethylsilane as an internal standard. *J* values are in Hz. ^{19}F n.m.r. spectra (300 MHz) were obtained in $CDCl_3$ solution with CF_3CO_2H as the internal standard.

Benzyl (5S,6R)-5,6-dihydroxy-7-(triisopropylbenzensulfonyloxy)-2-heptenoate (**10**). — A mixture of 2-deoxy-D-*erythro*-pentose (5.00 g, 37.31 mmol) and benzyl (triphenylphosphoranylidene) acetate (15.30 g, 1.1 mol. equiv.) in tetrahydrofuran was heated at reflux for 4 h. The resulting solution was evaporated and chromatographed on 200 g of silica gel. Elution with 3:1 EtOAc–hexane afforded 6.42 g (65%) of the adduct as white crystals. After recrystallization from EtOAc–hexane it had m.p. 86–88°, $[\alpha]_D$ −15° (*c* 1, MeOH).

Anal. Calc. for $C_{14}H_{18}O_5$: C, 63.16; H, 6.77. Found: H, 63.34; H, 6.76.

The foregoing triol (5.02 g, 18.187 mmol) was dissolved in pyridine (30 mL) and was added portionwise with stirring triisopropylbenzenesulfonyl chloride (8.58 g, 1.5 mol. eq.) at 0°. The mixture was stirred for 24 h at room temperature and the pyridine was removed under high vacuum. The residue was processed conventionally with EtOAc and the resultant material was chromatographed on 200 g of silica gel. Elution with EtOAc–hexane (1:3–1:2) afforded 9.32 g (93%) of the sulfonate **10** as a white solid. Recrystallized from EtOAc–hexane, it had m.p. 85–86°, $[\alpha]_D$ −1.3° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 7.37 (s, 5 H), 7.20 (s, 2 H), 6.04 (ddd, 1 H, *J* 16, 7), 5.99 (d, 1 H, *J* 16), 5.17 (s, 2 H), 4.23 (d, 2 H, *J* 2), 4.21 (sept, 2 H, *J* 6.4), 3.80 (m, 2 H), 2.92 (sept, 1 H, *J* 6), 2.70–2.10 (m, 4 H), and 1.26 (d, 18 H, *J* 6.4).

Anal. Calc. for $C_{29}H_{40}O_7 \cdot 0.5\ H_2O$: C, 64.32; H, 7.39; S, 5.91. Found: C, 64.93; H, 7.49; S, 5.89.

(5R,6S)-6,7-Diacetoxy-5-hydroxy heptanoic-1,5-lactone (**3b**). — The benzyl ester **10** (2.00 g, 3.76 mmol) was hydrogenated in the presence of 10% Pd–C (430 mg) in dry EtOH. The catalyst was removed under N_2 and a freshly prepared solution of NaOEt in EtOH (12.20 mL, 1.28M) was added *via* a syringe and the resultant mixture was stirred for 18 h at room temperature. Water (1 mL) was added and after stirring for 1 h at room temperature, the mixture was neutralized with H^+ resin and evaporated. The residue was then acetylated (Ac_2O–pyridine) and the product isolated with CH_2Cl_2 by conventional aqueous extraction. Chromatography of crude material afforded the diacetate **3b** (807 mg, 88% yield) as an oil, $[\alpha]_D$ −55° (*c* 0.9, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 5.15 (m, 1 H), 4.49 (m, 1 H), 4.46 (dd, 1 H, *J* 13, 9), 4.18 (dd, 1 H, *J* 6, 13), 2.38–2.70 (m, 2 H), 2.09 (s, 3 H), 2.09 (s, 3 H), and 2.10–1.68 (m, 4 H).

Anal. Calc. for $C_{11}H_6O_6$: C, 54.10; H, 6.56. Found: C, 54.21; H, 6.50.

Determination of the optical purity of **3**. — The diacetate **3** was converted into its (−)-MTPA derivative, by the following procedure.

Compound **3** was deacetylated with K_2CO_3 in dry EtOH and the resulting triol was sulfonylated with triisopropylbenzenesulfonyl chloride in pyridine to give the diol ester **1**. Heating the ester **1** in THF containing M HCl caused hydrolysis of the ester moiety, which lactonized upon repeated evaporation of the solvent to afford the lactone **7**. Finally esterification of compound **7** with (−)-MTPACl in CH_2Cl_2 containing 4-dimethylaminopyridine afforded **4**. Compounds **4a** and **4b** were indistinguishable by t.l.c. in a variety of solvents. ^{1}H-n.m.r. ($CDCl_3$) for OMe signals; **4a**: δ 3.58; **4b**: δ 3.46. ^{19}F-n.m.r. ($CDCl_3$, CF_3CO_2H as the internal standard) **4a**: δ 4.04; **4b**: δ 4.42.

Benzyl (5S,6S,7S)-8-Bromo-5,6-dibenzoyloxy-7-hydroxy-2-octenoate (**12**). — The glucoside **16** (810 mg, 1.80 mmol) was heated at reflux in 1,4-dioxane (30 mL) containing M HCl (5 mL). When no starting material remained (~5 h), most of the solvent was removed under diminished pressure and the product was extracted into CH_2Cl_2. The organic phase was washed several times with water, dried and evaporated.

The crude lactol was then heated at reflux with benzyl (triphenylphosphoranylidine) acetate (1.12 g, 1.1 mol. eq.) in THF for 5 h. The resulting solution was concentrated and chromatographed on silica gel. Elution with 1:4 EtOAc–hexane afforded the benzyl ester **12** as a syrup, $[\alpha]_D$ −44° (*c* 1, $CDCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 8.10–7.9 (m, 4 H), 7.7–7.25 (m, 11 H), 7.07 (dd, 1 H, *J* 16, 6), 5.99 (d, 1 H, *J* 16), 5.73 (m, 1 H), 5.55 (dd, 1 H, *J* 6, 3), 5.12 (s, 2 H), 4.16 (m, 1 H), 3.70 (dd, 1 H, *J* 11, 3), 3.54 (dd, 7 H, *J* 11), and 2.88 (t, 2 H, *J* 6).

Anal. Calc. for $C_{29}H_{27}BrO_7$: C, 61.39; H, 4.76; Br, 14.09. Found: C, 61.11; H, 4.98; Br, 13.87.

(5R,6R,7S)-6,7,8-Triacetoxy-5-hydroxy-octanoic-1,5-lactone (**13a**). — The benzyl ester **12** (209 mg, 0.37 mmol) was hydrogenated in the presence of 5% Pd–C (50 mg) in EtOAc. After 2.5 h, the catalyst was removed by filtration and the filtrate was evaporated under high vacuum to afford the acid **11b** in virtually quantitative yield. This acid was used directly in the next step without further purification.

The foregoing acid was dissolved in dry EtOH (5 mL) and was treated with a freshly prepared solution of NaOEt in EtOH (1.60M, 1.39 mL, 6 mol. equiv.) for 24 h at room temperature. Water (1 mL) was added and after 1 h at room temperature, the mixture was neutralized with H^+ resin. After the removal of the resin and the solvent under high vacuum the residue was acetylated with Ac_2O in pyridine. The product was isolated by aqueous extraction with CH_2Cl_2 and purified by column chromatography using 1:1 EtOAc–hexane as eluent to afford the title compound **13a**, (80 mg, 68% yield); $[\alpha]_D$ −14.6 (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 5.38 (m, 1 H), δ 5.28 (t, 1 H, *J* 6), 4.48 (m, 1 H), 4.39 (dd, 1 H, *J* 14, 3), 4.25 (dd, 1 H, *J* 14, 7), 2.70–2.40 (m, 2 H), 2.16–1.60 (m, 4 H), 2.12 (s, 3 H), 2.10 (s, 3 H), and 2.09 (s, 3 H).

The determination of the optical purity of compounds was performed as for compounds **3** except that 2 equiv. of (−)-MTPACl was used. ^{1}H-n.m.r. for OMe signals; **15a**: δ 3.44, 3.41; **15b**: 3.55, 3.39. ^{19}F-n.m.r. ($CDCl_3$, CF_3CO_2H as an internal standard): **15a**; δ 4.03, 4.43; **15b**: δ 4.25, 4.76.

Ethyl (5R,6S)-6-hydroxy-7-(triisopropylbenzenesulfonyloxy)heptanoate (**1b**). — The acetate **3b** (443 mg, 1.82 mmol) was dissolved in dry EtOH and the solution was stirred with K_2CO_3 (440 mg). After neutralization with acid resin, the solution was evaporated. The residue was then dissolved in pyridine (4 mL) and treated with triisopropylbenzenesulfonyl chloride (715 mg, 1.3 mol. equiv.) at 0°. After 24 h at room temperature, it was diluted with CH_2Cl_2, washed with M hydrochloric acid and worked up conventionally with CH_2Cl_2. Chromatography of the oily residue on silica gel afforded 781 mg (91%) of the mesitylenesulfonate **16** as a colorless oil; $[\alpha]_D$ −1.8° (*c* 2, $CHCl_3$); ^{1}H-n.m.r.: δ 7.20 (s, 2 H), 4.20 (d, 2 H, *J* 6), 4.15 (q, 2 H, *J* 6), 4.11 (sept, 2 H, *J* 6), 3.79 (ddd, 1 H, *J* 5), 3.68 (m, 1 H), 2.91 (sept, 1 H, *J* 6), 2.35 (dd, 2 H, *J* 7), 1.92–1.36 (m, 4 H), 1.34 (d, 18 H, *J* 6), and 1.24 (t, 3 H, *J* 6).

Anal. Calc. for $C_{24}H_{40}O_7S$: C, 61.02; H, 8.47. Found: C, 61.28; H, 8.64.

(5R,6S)-5,6-Dihydroxy-7-(triisopropylbenzenesulfonyloxy)heptanoic-1,5-lactone (**7b**). — A solution of the ester **1b** (602 mg, 1.28 mmol) in tetrahydrofuran (6 mL) containing M hydrochloric acid (1 mL) was heated under reflux until all of the starting material disappeared (~10 h). Volatile materials were then removed under diminished pressure (water bath 45°). This procedure was repeated by the addition of several portions of tetrahydrofuran until all of the free acid lactonized. Chromatography of the residue afforded 544 mg (78%) of the lactone **7b**, $[\alpha]_D$ −30° (*c* 1, $CHCl_3$) m.p. 131–132° (recrystallized from EtOAc–hexane); ^{1}H-n.m.r.: 4.40–4.03 (m, 5 H), 3.98 (m, 1 H), 2.93 (sept, 1 H, *J* 6), 2.73 (d, 1 H, *J* 5), 2.69–2.39 (m, 2 H), 2.20–1.64 (m, 4 H), and 1.27 (d, 2 H, *J* 6).

Anal. Calc. for $C_{22}H_{34}O_6S$: C, 61.97; H, 7.98; S, 7.51. Found: C, 62.12; H, 7.81; S, 7.40.

(5S,6R)-5,6-Dihydroxy-7-(triisopropylbenzenesulfonyloxy)heptanoic-1,5-lactone (**7a**). — A 2.60-g (4.89 mmol) sample of the benzyl ester **10** was hydrogenated over 100 mg of 10% Pd–C in EtOH at room temperature and atmospheric pressure. The catalyst was filtered and the filtrate evaporated under diminished pressure. The residue was taken up in $CHCl_3$ (50 mL) and heated at refluxing temperature until the lactonization was complete (~24 h). After removal of the solvent, chromatography of the resultant material on silica gel (eluted with 1:1 EtOAc–hexane) afforded the lactone **7a** as a white solid (1.62 g, 78%). After recrystallization from EtOAc–hexane it had m.p. 130–132, $[\alpha]_D$ +29.7° (*c* 1.2, $CHCl_3$).

Anal. Calc. for $C_{22}H_{34}O_6S$: C, 61.97; H, 7.98. Found: C, 61.80; H, 7.62.

(5S,6S)-6,7-Epoxy-5-hydroxypentanoic-1,5-lactone (**21b**). — A solution of the lactone **7b** (1.21 g, 2.84 mmol) in tetrahydrofuran (30 mL) containing Me_2SO (500 μL) at 0° was added 60% NaH (136 mg, 1.2 mol. eq.) in one portion. After stirring overnight at room temperature, aq. NH_4OAc (5 mL) was added. The mixture was then poured into a mixture of brine and CH_2Cl_2. Conventional processing with CH_2Cl_2 gave 450 mg of crude product as an oil. Bulb-to-bulb distillation (175°; bath temperature, 0.1 mmHg) gave 362 mg (90%) of the epoxide **21b** as an oil; $[\alpha]_D$ −41° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: 4.14–4.06 (m, 1 H), 3.14–3.06 (m, 1 H), 2.90–2.84 (m, 1 H), 2.76–2.70 (m, 1 H), 2.70–2.40 (m, 2 H), and 2.20–1.62 (m, 4 H).

Anal. Calc. for $C_7H_{15}O_3$: C, 59.15; H, 7.04. Found: C, 59.21; H, 7.12.

(5R,6R)-6,7-Epoxy-5-hydroxypentanoic-1,5-lactone (**21a**). — In the same manner as the foregoing, the lactone **7a** (1.50 g, 3.52 mmol) yielded 435 mg (87%) of the epoxide **21a**; $[\alpha]_D$ +41° (*c* 1, $CHCl_3$).

Anal. Calc. for $C_7H_{15}O_3$: C, 59.15; H, 7.04. Found: C, 59.31; H, 7.24.

(5R,6S)-6-Hydroxy-5-hexadecanolide (**22b**). — To a stirred solution of decylmagnesium bromide (4.05 mL, 0.99 M–ether, 3.66 mmol) in tetrahydrofuran (2 mL) at −30° was added a solution of Li_2CuCl_4 (4.01 mL, 0.1M, 1.1 mmol). After 10 min at −30°, the contents of the flask were transferred via a cannula to a stirred solution of the epoxide **21b** (160 mg, 1.13 mmol) at −78°. After stirring for 30 min, the reaction was quenched by the addition aq. NH_4OAc. The mixture was allowed to warm to room temperature and the product extracted with CH_2Cl_2 and processed conventionally. Chromatography of the resultant residue on silica gel (eluted with 1:2 EtOAc–hexane) afforded 228 mg (75%) of the lactone **22b**. Recrystallized from hexane, it had m.p. 68–69°, $[\alpha]_D$ −13.9° (*c* 0.4, $CHCl_3$) (lit.[18b] m.p. 67–68°, $[\alpha]_D$ −12.5°).

(5S,6R)-Isomer (**22a**). — The epoxide **21a** (190 mg, 1.33 mmol) gave 284 mg of **22a** (75%); m.p. 67–68°, $[\alpha]_D$ +12.9° (*c* 1, $CHCl_3$); lit.[18b] m.p. 66.5–68°, $[\alpha]_D$ +12.7°).

(5R,6S)-6-Acetoxy-5-hexadecanolide (**24b**). — The lactone **22b** (80 mg, 0.30 mmol) was acetylated with Ac_2O (0.2 mL) and 4-dimethylaminopyridine (37 mg) in CH_2Cl_2 (2 mL) at room temperature. Conventional work-up with ether followed by chromatography afforded 84 mg (90%) of the natural product **24b**, $[\alpha]_D$ −38.1° (*c* 0.4, $CHCl_3$) (lit.[18b] −38.5°); ^{1}H-n.m.r.: δ 5.02–4.93 (m, 1 H), 4.39–4.29 (m, 1 H), 2.68–2.36 (m, 2 H), 2.08 (s, 3 H), 2.0–1.6 (m, 6 H), 1.25 (br, s), and 0.88 (t, 3 H, *J* 6).

(5S,6R)-6-Acetoxy-5-hexadecanolide (**24a**). — This product had $[\alpha]_D$ +38.0° (*c* 1, $CHCl_3$), (lit.[18b] $[\alpha]_D$ +38.4°).

(5S,6R)-6-Methylsulfonyloxy-5-hexadecanolide (**23**). — To a solution of the alcohol **22a** (203 mg, 0.715 mmol) in CH_2Cl_2 containing MsCl (89 μL, 1.6 mol eq.) at −78° was added dropwise Et_3N (199 μL, 2 mol. eq.). After stirring for 5 min at −78° the mixture was allowed to warm up to 0° and was quenched with aq. NH_4OAc. Conventional work-up with CH_2Cl_2 followed by chromatography afforded the mesylate **23** (259 mg, 89%); $[\alpha]_D$ −7.0° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: δ 4.72 (m, 1 H), 4.40 (m, 1 H), 3.08 (s, 3 H), 2.68–2.54 (m, 1 H), 2.60–2.34 (m, 1 H), 1.26 (br, s), and 0.88 (t, 3 H, *J* 7); *m/z* calc. for ($C_{18}H_{34}O_5S$ + NH_4^+) 380.2471, found 380.2471.

Reaction of the mesylate **23** *with base.* — The mesylate **23** (80 mg, 0.21 mmol) in MeOH (3 mL) was treated with 0.1M aq. NaOH and stirred for 5 h. Acetic acid (3 mL) was added and the mixture was stirred for 18 h. Volatile components were then removed under diminished pressure and the residue was chromatographed on silica gel to afford the alcohol **22b**, whose spectral properties were identical to those of the sample prepared earlier. Recrystallized from hexane, it has m.p. 68–69; $[\alpha]_D$ −13° (*c* 0.4, $CHCl_3$). The optical purity as ascertained by conversion into its MTPA ester was 98% e.e.

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