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SYNTHESIS OF (*S*)- AND (*R*)-3-[(BENZYLOXYCARBONYL)OXY]-2,2-DIFLUOROTETRADECANOIC ACID

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Abstract: Optically active 3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoic acids, (*S*)-**11** and (*R*)-**22** were synthesized from 3,4,6-tri-*O*-acetyl-D-glucal and methyl galactopyranoside via **4** and **15**, respectively. Reaction of **4** and **15** with octylidene triphenylphosphorane followed by Jones oxidation of the alcohols, treatment with DAST, catalytic hydrogenation of double bond and deprotection of benzyl groups yielded 2,2-difluoro-1,3-dihydroxytetradecane (*S*)-**7** and (*R*)-**18**, from which (*S*)-**11** and (*R*)-**22** were obtained in four steps, respectively.

Lipopolysaccharides[1] (LPS), which cover the outer surface membrane of various Gram-negative bacteria such as *Salmonella minnesota*, *Salmonella typhirium*, *Escherichia coli*, etc., are highly potent stimulators of the immune system. A variety of responses, both beneficial and harmful, can be elicited by LPS. One of these harmful responses is fatal endotoxic shock, and this fact has precluded clinical use of LPS. Most of the biological activities of LPS reside in a relatively small portion of the molecule known as lipid A, which is composed of two β (1-6)-linked D-glucosamine units, and a unique hydrophobic anchor substance holding an essentially linear polysaccharide chain to the cell wall. The *S. minnesota* and *E. coli* type Lipid As have two (*R*)-3-hydroxytetradecanoyl groups at the 2- and 3-positions of glucosamine, and (*R*)-acyloxytetradecanoyl groups at the 2'- and 3'-positions of another glucosamine moiety.

Lipid A was chemically synthesized by Shiba *et al.*[2] Nishijima and Raetz[3] found lipid X in certain mutants of *Escherichia coli* defective in phosphatidylglycerol synthesis. Lipid X is a reducing-sugar part of lipid A, and is one of the biosynthetic precursors of lipid A.[4] Lipid X endowed with some of the immunostimulatory properties of LPS, while lacking any endotoxicity. However, Aschauer *et al* [5] have recently demonstrated that the reported immunostimulatory activities of synthetic lipid X in fact resulted from contamination by

small amounts of acylated glucosamine disaccharide formed by Koenigs-Knorr like reactions during the last catalytic hydrogenolysis step of 1-dibenzyl phosphate.

In a series of investigations by Hasegawa and Kiso[6] on relationship between the molecular structure and the biological activity of nonreducing-sugar subunit analogues of lipid A, it has been demonstrated that several kinds of biological activity of LPS can be expressed by some 4-*O*-phosphono-D-glucosamine derivatives, such as GLA-60. (Figure 1).

We have been interested in the biological activity of the compounds related to lipid A, X or GLA-60, containing a fluorinated hydroxytetradecanoyl group. Therefore, we synthesized 2-deoxy-2-[(2,2-difluoro-3-hydroxytetradecanoyl)amino]-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-phosphate (difluoro GLA-60)[7] (Figure 1) using (±)-3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoic acid. This difluoro GLA-60 was more active than GLA-60 with respect to the induction of prostaglandin D_2 production. In this paper, we would like to describe the synthesis of (*S*)- and (*R*)-3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoic acid, **11** and **22**, respectively. (Scheme 1).

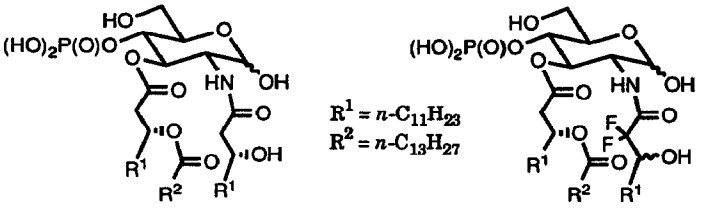
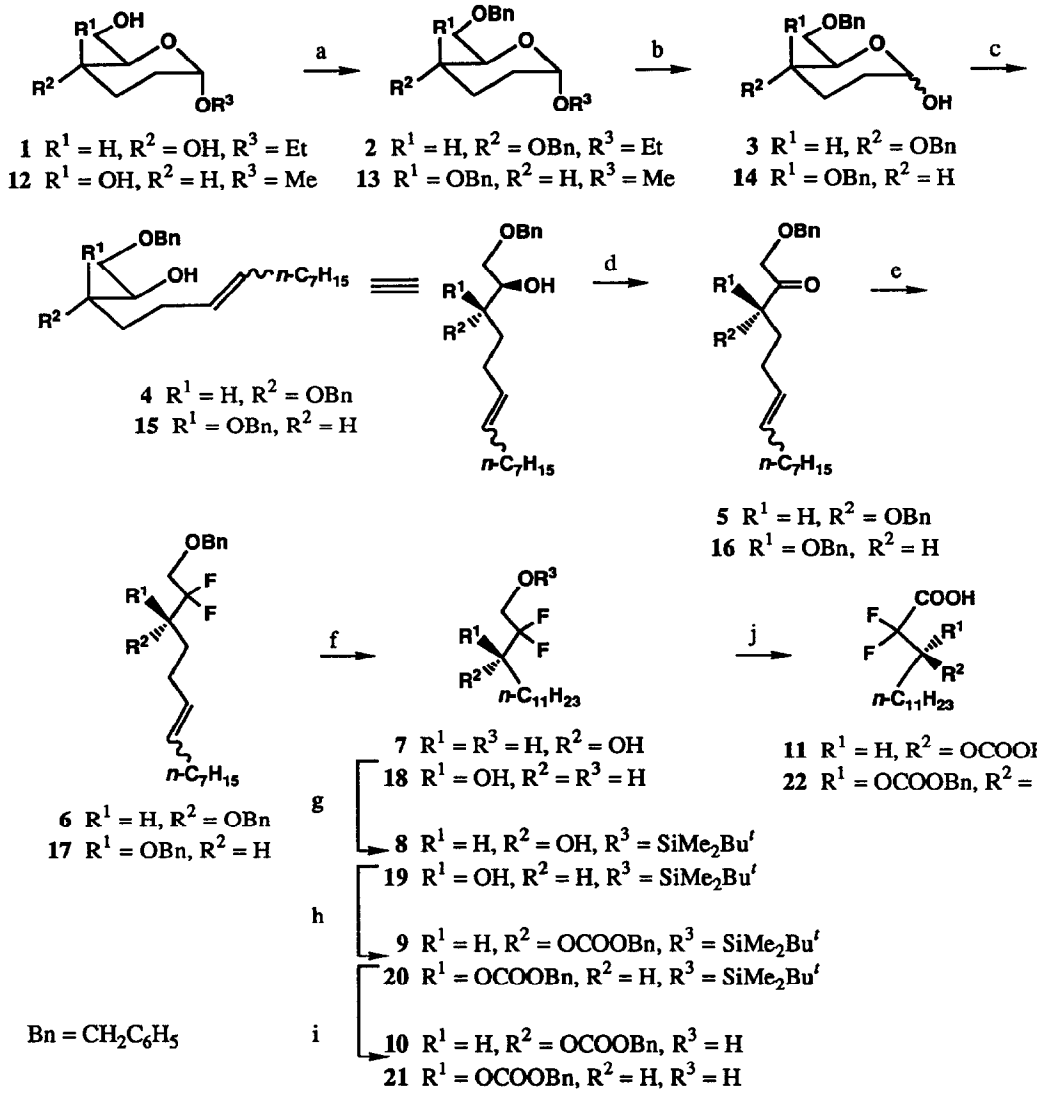


Figure 1.

The compound **1**, obtained from ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside,[8] was converted to dibenzyl ether (**2**) by treatment with benzyl bromide and sodium hydride (NaH) in tetrahydrofuran (THF). Treatment of **2** with dioxane-aq. 0.5% sulfuric acid (1:1) gave **3** as an anomeric mixture. Treatment of **3** with *n*-octyl triphenylphosphorane, which was prepared from *n*-octyl triphenylphosphonium bromide-*n*-butyl lithium in THF, gave an olefin **4**. The geometry of **4** was not clear. Jones oxidation of **4** afforded a ketone **5**. The compound **5** was found to have a bad smell similar to that of stinkbug. Treatment of **5** with diethylaminosulfur trifluoride (DAST) yielded **6**. Reduction of double bond of **6** using 10% palladium on carbon, and then deprotection of two benzyl groups using Pearlman's catalyst gave 1,3-diol **7**. Protection of primary alcohol of **7** with *tert*-butyldimethylsilyl chloride and 4-dimethylaminopyridine (DMAP) gave **8**, then protection of the remaining secondary alcohol of **8** with benzyl chloroformate and DMAP yielded **9**. Deprotection of silyl group of **9** with dioxane-H_2O-conc. HCl (100:2:5) gave **10**. Jones oxidation of **10** yielded (*S*)-3-



1 R^1 = H, R^2 = OH, R^3 = Et
12 R^1 = OH, R^2 = H, R^3 = Me

2 R^1 = H, R^2 = OBn, R^3 = Et
13 R^1 = OBn, R^2 = H, R^3 = Me

3 R^1 = H, R^2 = OBn
14 R^1 = OBn, R^2 = H

4 R^1 = H, R^2 = OBn
15 R^1 = OBn, R^2 = H

5 R^1 = H, R^2 = OBn
16 R^1 = OBn, R^2 = H

6 R^1 = H, R^2 = OBn
17 R^1 = OBn, R^2 = H

7 R^1 = R^3 = H, R^2 = OH
18 R^1 = OH, R^2 = R^3 = H

8 R^1 = H, R^2 = OH, R^3 = $SiMe_2Bu^t$

19 R^1 = OH, R^2 = H, R^3 = $SiMe_2Bu^t$

9 R^1 = H, R^2 = OCOOBn, R^3 = $SiMe_2Bu^t$

20 R^1 = OCOOBn, R^2 = H, R^3 = $SiMe_2Bu^t$

10 R^1 = H, R^2 = OCOOBn, R^3 = H
21 R^1 = OCOOBn, R^2 = H, R^3 = H

11 R^1 = H, R^2 = OCOOBn
22 R^1 = OCOOBn, R^2 = H

(a) BnBr, NaH-THF, room temperature, 18 h, 96%, 93%; (b) dioxane-aq. 0.5% H_2SO_4 (1:1), 75-80° C, 60 min, 89%, 93%; (c) n-$C_7H_{15}CH{=}PPh_3$-THF, room temperature, 30 min, 95%, 58%; (d) Jones reagent, 0-5° C, 76%, 72%; (e) Et_2NSF_3-CH_2Cl_2/N_2, room temperature, 16 h, 83%, 56%; (f) H_2, 10% Pd/C-AcOH, then H_2-20% $Pd(OH)_2/C$ (H_2O content < 50%)-EtOH, room temperature, 8 h, 80%, 75%; (g) ^{t}BuMe$_2$SiCl, DMAP-CH_2Cl_2, room temperature, 17 h, 81%, 80%; (h) ClCOOBn, DMAP-CH_2Cl_2, 0°C 15 min, room temperature 1 h; (i) dioxane-H_2O-conc. HCl (100:2:5), room temperature, 16 h, two steps 64%, 61%; (j) excess Jones reagent-acetone, 30°C, 5 h, 36%, 32%.

Scheme 1

[(benzyloxycarbonyl)oxy]-2,2-(difluoro)tetradecanoic acid (**11**) as a solid, mp 44-45°C, $[\alpha]_D$ -11.3 (c=1.0, $CHCl_3$).

On the other hand, the compound **12**,[9] obtained from methyl α-D-galactoside, was benzylated with benzyl bromide-NaH in THF to give **13**, which was converted to **14**. Wittig reaction of **14** with $C_7H_{15}CH{=}PPh_3$ gave **15**, which was further converted to (*R*)-3-[(benzyloxycarbonyl)oxy]-2,2-(difluoro)tetradecanoic acid (**22**) mp 43-44°C, $[\alpha]_D$ +11.5 (c=0.9, $CHCl_3$), through the compounds **16**, **17**, **18**, **19**, **20**, and **21**, by the same procedures as used in the conversion of **4** to **11**.

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR were recorded at 270 MHz using a JEOL JNM-270 with trimethylsilane as an internal standard. The IR absorption spectra were determined on a Jasco IR A-2 spectrophotometer. Mass spectra were obtained on a JMS-O1SG mass spectrometer. Optical rotation was recorded Perkin-Elmer 241 polarimeter. Column chromatography was carried out on silica gel-60 (Merck, 230-400 mesh ASTM), at slightly elevated pressure (1.2 atm) for elution.

Ethyl 4,6-Di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hexopyranoside (2). To a solution of ethyl 2,3-dideoxy-α-D-*erythro*-hexopyranoside[8] (**1**, 4.28 g, 24.3 mmol) in THF (100 mL) was added NaH (55% oil dispersion, 3.18 g, 72.9 mmol, 3 equivalents) and benzyl bromide (8.67 mL, 72.9 mmol). The mixture was stirred for 16 h at 20-25°C. The reaction mixture was diluted with excess ethyl acetate (EtOAc), quenched with H_2O, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oil, which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (9:1) gave 8.50 g of **2** (96%) as an oil. ^1H NMR ($CDCl_3$) δ 1.20 (3H, t, *J*=6.8-7.3 Hz), 1.70-2.10 (4H, m), 4.84 (1H, d, *J*=2.9 Hz), 7.20-7.37 (10H, m). MS *m/z* 356 (M^+), 355, 310, 219, 203, 181. Anal. Calcd. for $C_{22}H_{28}O_4$ (356.46): C, 74.13; H, 7.92. Found: C, 73.83; H, 7.89.

4,6-Di-*O*-benzyl-2,3-dideoxy-D-*erythro*-hexopyranose (3). A solution of **2** (8.10 g, 22.7 mmol) in dioxane-0.5% H_2SO_4 (1:1, 240 mL) was stirred for 60 min at 75-80°C. The mixture was cooled on ice, and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a residue, which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (2:1) gave 6.96 g of **3** (89 %) as a solid; mp 40-52°C (from cyclohexane). ^1H NMR ($CDCl_3$ + D_2O) δ 1.46-2.26 (4H, m), 3.35-4.08 (4H, m), 4.36-4.80 (4H, m), 4.82 (0.4H, dd, *J*=2.0-2.4, 8.3-8.8 Hz), 5.29 (0.6H, d, *J*=2.9 Hz), 7.20-7.38 (10H, m). IR ν_{max}(neat) 3400 cm^{-1}. Anal. Calcd. for $C_{20}H_{24}O_4$·1/3 H_2O (328.4 + 6.0): C, 71.83; H, 7.38. Found: C, 71.83; H, 7.09.

(2*R*,3*S*)-1,3-Dibenzyloxy-2-hydroxytetradec-6-ene (4). Compound **3** (4.40 g, 13.4 mmol) was added to a solution of *n*-$C_7H_{15}CH{=}PPh_3$ in THF-hexane [prepared from a suspension of $(Ph_3P^+C_8H_{17})Br^-$ (15.3 g, 33.6 mmol) in THF (80 mL) and a solution of *n*-BuLi (1.6 M hexane solution, 21 mL, 33.6 mmol) at room temperature for 15 min under nitrogen]. After 30 min at 24°C, the reaction mixture was quenched with 4M-HCl, diluted with EtOAc,

washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue, which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (3:1) gave 5.40 g of **4** (95%) as a gum. The geometry of this compound could not be established clearly. ^1H NMR ($CDCl_3$ + D_2O) δ 0.87 (3H, t, *J*=6.4-6.8 Hz), 1.26 (10H, m), 1.52-1.75 (2H, m), 1.91-2.26 (4H, m), 3.49-3.66 (3H, m), 3.89 (1H, m), 4.49-4.59 (4H, m), 5.29-5.43 (2H, m), 7.27-7.38 (5H, m). IR ν_{max}(neat) 3450, 2930, 2860 cm^{-1}. MS *m/z* 425, 424 (M^+), 333, 316, 315, 303,277. 255. Anal. Calcd. for $C_{28}H_{40}O_3$ (424.6): C, 79.20; H, 9.50. Found: C, 79.04; H, 9.55.

(*S*)-1,3-Dibenzyloxytetradec-6-en-2-one (5). A solution of **4** (5.20 g, 12.2 mmol) in acetone (80 mL) and Jones reagent (8 mL) was stirred for 30 min at 0-5°C. The reaction mixture was diluted with excess EtOAc. The mixture was washed with H_2O, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue, which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (9:1) gave 3.91 g of **5** (76%) as a stinking oil. The geometry of this compound could not be established clearly. ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, *J*=6.6 Hz), 1.55 (10H, m), 1.71-1.77 (2H, m), 1.93-2.05 (2H, m), 2.06-2.18 (2H, m), 3.96-4.00 (1H, m, C3-H), 4.30, 4.37 (2H, AB-q , *J*=17.9 Hz), 4.41-4.54 (2H, AB-q, *J*=17.9 Hz), 5.26-5.43 (2H, m, C1-H_2), 7.29-7.38 (10H, m). IR ν_{max}(neat) 1727 cm^{-1}; MS *m/z* 368 (M^+-54), 331, 273, 270, 255. Anal. Calcd. for $C_{28}H_{38}O_3$-H_2O (422.6 + 18.0): C, 76.33; H, 9.14. Found: C, 76.13; H, 8.84.

(*S*)-2,2-Difluoro-1,3-(dibenzyloxy)tetradec-6-ene (6). A solution of **5** (2.93 g, 6.93 mmol) in CH_2Cl_2 (70 mL) was added Et_2NSF_3 (8.10 g, 50.3 mmol) at 5-10°C. The mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue, which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (19:1) gave 2.56 g of **6** (83%, Rf=0.517, cyclohexane-EtOAc=10:1) as an oil. The geometry of this compound could not be established clearly. ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, *J*=6.4-6.8 Hz), 1.26 (10H, m),1.65-1.74 (2H, m), 1.95-2.24 (4H, m), 3.64-3.92 (3H, m), 4.57, 4.72 (2H, AB-q, *J*=11.2 Hz), 4.61 (2H, s), 5.28-5.42 (2H, m, olefinic), 7.25-7.39 (10H, m). IR ν_{max}(neat) 2940, 2860 cm^{-1}; MS *m/z* 444 (M^+), 353 (M^+-Bn). Anal. Calcd. for $C_{28}H_{38}O_2F_2$ (444.6): C, 75.64; H, 8.62; F, 8.55. Found: C, 75.18; H, 8.73; F, 8.63.

(*S*)-2,2-Difluoro-1,3-(dihydroxy)tetradecane (7). A solution of **6** (2.00 g, 4.50 mmol) in AcOH (40 mL) containing 10% Pd on carbon (1.0 g) was stirred for 5 h under H_2. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give a residue, which was dissolved in EtOH (40 mL) containing 20% $Pd(OH)_2$ on carbon (2.0 g). The mixture was stirred under H_2 for 12 h at 20-24°C. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give a crude solid, which was recrystallized from hexane to give a crystalline solid **7**. The mother liquor was concentrated, and chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (2:1) to give additional **7** (Rf=0.380) as crystals; total 961 mg (80%): mp 79-81°C (from hexane); $[\alpha]_D^{24}$ -17.3 (c=1.4, $CHCl_3$); ^1H NMR ($CDCl_3$+D_2O) δ 0.88 (3H, t, *J*=6.4-6.8 Hz), 1.20-1.80 (20H, m), 3.79-4.05 (3H, m). IR

ν_{max}(Nujol) 3300 cm^{-1}. MS *m/z* 267 (M^++1), 266, 265, 248, 228, 220, 197, 185. Anal. Calcd. for $C_{14}H_{28}O_2F_2$.1/3 H_2O (272.4): C, 61.73 H, 10.61; F, 13.95. Found: C, 61.92; H, 10.64; F, 13.68.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,2-difluoro-3-hydroxytetradecane (8). A solution of **7** (232 mg, 0.871 mmol), *t*-BuMe_2SiCl (145 mg, 0.958 mmol, 1.1 equiv.) and DMAP (128 mg, 1.05 mmol, 1.2 equiv.) in CH_2Cl_2 (30 mL) was stirred for 16 h at 25°C. The reaction mixture was diluted with EtOAc, which was washed with H_2O, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily mixture. The mixture was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (9:1) gave 267 mg of **8** (81%, Rf=0.717, cyclohexane-EtOAc=4:1) as an oil. ^1H NMR ($CDCl_3$) δ 0.10 (6H, s), 0.88 (3H, t, *J*=6.8 Hz), 0.91 (9H, s), 1.20-1.40 (18H, m), 1.40-1.75 (2H, m), 2.18 (1H, d, *J*=6.8 Hz, OH), 3.77-4.04 (3H, m). IR ν_{max}(neat) 3400, 2940, 2860 cm^{-1}. MS *m/z* 381 (M^++1), 380, 379, 365, 323, 303. Anal. Calcd. for $C_{20}H_{42}O_2F_2Si$ (380.6): C, 63.11; H, 11.12; F, 9.98. Found: C, 62.83; H, 11.21; F, 9.85.

(*S*)-3-[(Benzyloxycarbonyl)oxy]-1-[(*tert*-butyldimethylsilyl)oxy]-2,2-(difluoro)tetradecane (9). A solution of **8** (248 mg, 0.652 mmol) and ClCOOBn (193 mg, 1.13 mmol) and DMAP (138 mg, 1.13 mmol) in CH_2Cl_2 (5 mL) was stirred for 10 min at 0°C and then for 3 h at room temperature. The reaction mixture was diluted with EtOAc, which was washed with H_2O, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily mixture. The mixture was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (10:1) gave 247 mg of **9** (74%, Rf=0.777) as an oil containing a small amount of dibenzylcarbonate. ^1H NMR ($CDCl_3$) δ 0.05 (3H, s), 0.06 (3H, s), 0.87-0.90 (12H, m, containing 9H, s at δ 0.89), 1.20-1.40 (18H, m), 1.70-1.80 (2H, m), 3.71-3.91 (2H, m), 5.13 (1H, m), 5.16, 5.21 (2H, AB-q, *J*=12.2 Hz), 7.32-7.40 (5H, m). IR ν_{max}(neat) 2935, 2860, 1760 cm^{-1}. MS *m/z* 485 (M^+-F), 457 (M^+-Bu), 321. Anal. Calcd. for $C_{28}H_{48}O_4F_2Si$ (514.8): C, 65.33; H, 9.40; F, 7.38. Found: C, 65.40; H, 9.62; F, 7.23.

(*S*)-3-[(Benzyloxycarbonyl)oxy]-2,2-difluoro-1-hydroxytetradecane (10). A solution of **9** (220 mg, 0.652 mmol) in dioxane-conc. HCl-H_2O (100:5:2, 10.7 mL) was stirred for 16 h at 25-27°C. The reaction mixture was diluted with EtOAc, which was washed with sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily mixture. The mixture was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (4:1) gave 148 mg of **10** (87%, Rf=0.306) as an oil. This compound was gradually decomposed at room temperature during several weeks. ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J=6.4-6.8 Hz), 1.20-1.45 (18H, m), 1.73-1.82 (2H, m), 2.32 (1H, bs, OH), 3.71-3.81 (2H, m), 4.83-5.13 (1H, m), 5.21 (2H, s), 7.34-7.40 (5H, m). IR ν_{max}(neat) 3460, 2930, 2860, 1753 cm^{-1}. MS *m/z* 400 (M^+), 382, 309, 270, 246, 210, 183. Anal. Calcd. for $C_{22}H_{34}O_4F_2$ (400.5): C, 65.98; H, 8.56; F, 9.49. Found: C, 65.43; H, 8.85; F, 9.52.

(*S*)-3-[(Benzyloxycarbonyl)oxy]-2,2-(difluoro)tetradecanoic acid (11). To a solution of **10** (140 mg, 0.350 mmol) in acetone (10 mL) was added Jones reagent (2.0 mL). The mixture was stirred for 5 h at 30°C, and diluted with EtOAc (100 mL), which was washed with H_2O (20 mL x 2), and sat. $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo* to give a residual mixture. The mixture was chromatographed on a short column of silica gel. Elution with cyclohexane-EtOAc (2:1) to remove the less polar starting material and elution

with EtOAc gave a EtOAc solution of **11**. The solution was washed with dil. HCl and H_2O, and concentrated *in vacuo* to obtain 52 mg of **11** (36%) as a solid; mp 44-45°C (from hexane); $[\alpha]_D^{24}$ - 11.3 (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, *J*=6.8 Hz), 1.20-1.45 (18H, m), 1.73-1.82 (2H, m), 5.14-5.29 (3H, m, containing 2H, s at δ 5.20), 7.37 (5H, s). IR ν_{max}(Nujol) 3540, 3460, 1728 cm^{-1}. Anal. Calcd. for $C_{22}H_{32}O_5F_2$ (414.5): C, 63.75; H, 7.78; F, 9.17. Found: C, 63.29; H, 8.26; F, 9.15.

Methyl 4,6-Di-*O*-benzyl-2,3-dideoxy-α-D-*threo*-hexopyranoside (13). Methyl 2,3-dideoxy-α-D-*threo*-hexopyranoside[9] (**12**, 1.96 g, 12.1 mmol) was treated as described for the preparation of **2** from **1** to give an oil, which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (4:1) gave 3.82 g of **13** (93%) as an oil. ^1H NMR ($CDCl_3$) δ 1.51-1.59 (1H, m), 1.76-1.94 (2H, m), 1.99-2.13 (1H, m), 3.38 (3H, s), 3.54-3.68 (3H, m), 3.99 (1H, dt, *J*=1.3, 6.4 Hz), 4.39-4.66 (4H, m), 4.76 (1H, d, *J*=2.9 Hz), 7.22-7.65 (10H, m). MS *m/z* 342 (M^+), 334, 311, 292, 251, 219. Anal. Calcd. for $C_{21}H_{26}O_4$ (342.4): C, 73.66; H, 7.65. Found: C, 73.29; H, 7.75.

4,6-Di-*O*-benzyl-2,3-dideoxy-α-D-*threo*-hexopyranoside (14). The compound **13** (3.80 g, 11.1 mmol) was treated as described for the preparation of **3** from **2** to give 3.39 g of **14** (93%) as an oil. ^1H NMR ($CDCl_3$) δ 1.54-2.20 (4H, m), 3.45-3.76 (3H, m), 4.24 (0.5H, t, *J*=5.9 Hz), 4.37-4.70 (4.5H, m), 4.78-4.82 (0.5H, m), 5.36 (0.5H, bs), 7.27-7.65 (10H, m). IR ν_{max}(Nujol) 3420 cm^{-1}. MS *m/z* 310 (M^+-18), 292, 279, 235, 219, 202, 177. Anal. Calcd. for $C_{20}H_{24}O_4$ (328.4): C, 73.14; H, 7.37. Found: C, 73.23; H, 7.15.

(2*R*,3*R*)-1,3-Dibenzyloxy-2-hydroxytetradec-6-ene (15). The compound **14** (3.00 g, 9.13 mmol) was treated as described for the preparation of **4** from **3** to give 2.25 g of **13** (58%) as an oil. The geometry of this compound could not be established clearly. ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, *J*=6.3-6.8 Hz), 1.20-1.35 (10H, m), 1.57-1.77 (2H, m), 1.92-2.05 (2H, m), 2.05-2.16 (2H, m), 2.41 (1H, d, *J*=5.4 Hz, OH), 3.49-3.59 (3H, m), 3.84 (1H, m), 4.51, 4.61 (2H, AB-q, J=11.2 Hz), 4.54 (2H, s, CH_2Ph), 5.28-5.43 (2H, m, olefinic), 7.26-7.39 (10H, m). IR ν_{max}(neat) 3440, 2920, 2850 cm^{-1}. MS *m/z* 424 (M^+), 386, 368, 333, 316, 315. Anal. Calcd. for $C_{28}H_{40}O_3$-0.1 H_2O (424.6 + 1.8): C, 78.86; H, 9.50. Found: C, 78.60; H, 9.44.

(*R*)-1,3-Dibenzyloxytetradec-6-en-2-one (16). The compound **15** (2.20 g, 5.18 mmol) was treated as described for the preparation of **5** from **4** to give 1.58 g of **16** (72%) as a stinking oil. The geometry of this compound could not be established clearly. The ^1H NMR, IR and MS spectra were identical with those of **5**. Anal. Calcd. for $C_{28}H_{38}O_3$-H_2O (422.6 + 18.0): C, 76.33; H, 9.14. Found: C, 76.01; H, 8.95.

(*R*)-2,2-Difluoro-1,3-(dibenzyloxy)tetradec-6-ene (17). The compound **16** (1.40 g, 3.31 mmol) was treated as described for the preparationin of **6** from **5** to give 825 mg of **17** (56%) as an oil. The ^1H NMR, IR and MS spectra were identical with those of **6**. Anal. Calcd. for $C_{28}H_{38}O_2F_2$ (444.6): C, 75.64; H, 8.62; F, 8.55. Found: C, 75.25; H, 8.16; F, 8.09.

(*R*)-2,2-Difluoro-1,3-(dihydroxy)tetradecane (18). The compound **17** (400 mg, 0.90 mmol) was treated as described for the preparation of **7** from **6** to give 180 mg of **18** (75%) as a solid; mp 80-81°C (from hexane). $[\alpha]_D^{24}$ +17.9 (c=1.5, $CHCl_3$). The ^1H NMR, IR and MS

spectra were identical with those of **7**. Anal. Calcd. for $C_{28}H_{38}O_2F_2$ (444.6): C, 75.64; H, 8.62; F, 8.55. Found: C, 75.25; H, 8.16; F, 8.09.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,2-difluoro-3-hydroxytetradecane (19). The compound **18** (282 mg, 1.06 mmol) was treated as described in the formation of **8** from **7** to give 214 mg of **19** (80%) as an oil. The ^1H NMR, IR and MS spectra were identical with those of **8**. Anal. Calcd. for $C_{20}H_{42}O_2F_2Si$ (380.6): C, 63.11 H, 11.12; F, 9.98. Found: C, 62.99; H, 11.26; F, 9.73.

(*R*)-3-[(Benzyloxycarbonyl)oxy]-2,2-difluoro-1-hydroxytetradecane (21). The crude **20** (306 mg), obtained by the benzyloxycarbonylation of **19** (190 mg, 0.50 mmol), was treated as described for the preparation of **10** from **9** to give 122 mg of **21** (two steps 61%) as an oil. The ^1H NMR, IR and MS spectra were identical with those of **10**. Anal. Calcd. for $C_{22}H_{34}O_4F_2$-1/6.H_2O (400.5 + 3.0): C, 65.49 H, 8.58; F, 9.42. Found: C, 652; H, 8.69; F, 9.43.

(*R*)-3-[(Benzyloxycarbonyl)oxy]-2,2-(difluoro)tetradecanoic acid (22). The compound **21** (91 mg, 0.23 mmol) was treated as described for the preparation of **11** from **10** to give 30 mg of **22** (32%) as a solid; mp 43-44°C (from hexane). $[\alpha]_D^{24}$ +11.5 (c=0.9, $CHCl_3$); The ^1H NMR, IR and MS spectra were identical with those of **11**. Anal. Calcd. for $C_{22}H_{32}O_5F_2$ (414.5): C, 63.75; H, 7.78; F, 9.17. Found: C, 63.30; H, 8.06; F, 9.61.

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