Biological. The compounds were evaluated in a purified preparation of cholinergic synaptic vesicles isolated from the electric organ of *Torpedo californica*. A full description of this assay was described earlier.[8] However, the present study was carried out in the absence of ATP and acetylcholine, with a trace amount of [^{3}H]vesamicol. The data reported are averages of duplicates, which exhibit a relative range of less than 5%. Nonlinear regression analysis was carried out with MINSQ (MicroMath Scientific Software, Salt Lake City, UT). Protein content was determined by the method of Bradford,[11] using a bovine serum albumin standard.

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Synthesis of 2-Deoxy-2-[(2,2-difluoro-3-hydroxytetradecanoyl)amino]-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-Phosphate

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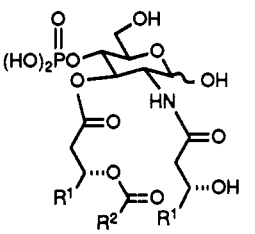
2-Deoxy-2-[(2,2-difluoro-3-hydroxytetradecanoyl)amino]-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-phosphates (**9H,L**) were synthesized from allyl 2-amino-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (**1**), (±)-3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoic acid, and (*R*)-3-(tetradecanoyloxy)tetradecanoic acid. Both compounds **9H** and **9L** were more active than GLA-60 for the prostaglandin D_2 releasing test on macrophages.

Lipopolysaccharide (LPS), an outer-membrane component of Gram-negative bacterial cells, causes fever and lethal shock in higher animals. This toxic principle is called "endotoxin". Westphal et al.[1] isolated lipid A, which is the lipophilic part of LPS. Lipid A shows most of the endotoxic activities of LPS, and it was first chemically synthesized by Shiba et al.[2] Also, Raetz et al.[3] isolated lipid X from a mutant of *Escherichia coli*. Lipid X, which is the reducing sugar part of lipid A, is also one biosynthetic precursor of lipid A. In a series of investigations on the active center of the biological activities of LPS, Hasegawa and Kiso have demonstrated that the nonreducing-sugar subunit analogues of lipid A (namely, some 4-*O*-phosphonoglucosamine derivatives)[4] expressed several kinds of biological activities of endotoxin and was the least active center of LPS. In particular, 2-deoxy-2-[(*R*)-3-hydroxytetradecanoyl)amino]-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-phosphate (GLA-60) (Chart I), one of the 4-phosphonoglucosamine analogues, possesses potent features as a therapeutic agent. In view of this result, we synthesized some compounds related to GLA-60. In this paper, we would like to describe the syntheses of 2-deoxy-2-[((3*R* and 3*S*)-2,2-difluoro-3-hydroxytetradecanoyl)amino]-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-phosphates **9**.

Chart I



$R^1 = n\text{-}C_{11}H_{23}$
$R^2 = n\text{-}C_{13}H_{27}$
GLA-60

Chemistry

The starting allyl 2-amino-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (**1**), which was obtained from allyl 2-deoxy-4,6-*O*-isopropylidene-2-trifluoroacetamido-β-D-glucopyranoside,[5] was treated with (±)-3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoyl chloride, which was obtained from the corresponding carboxylic

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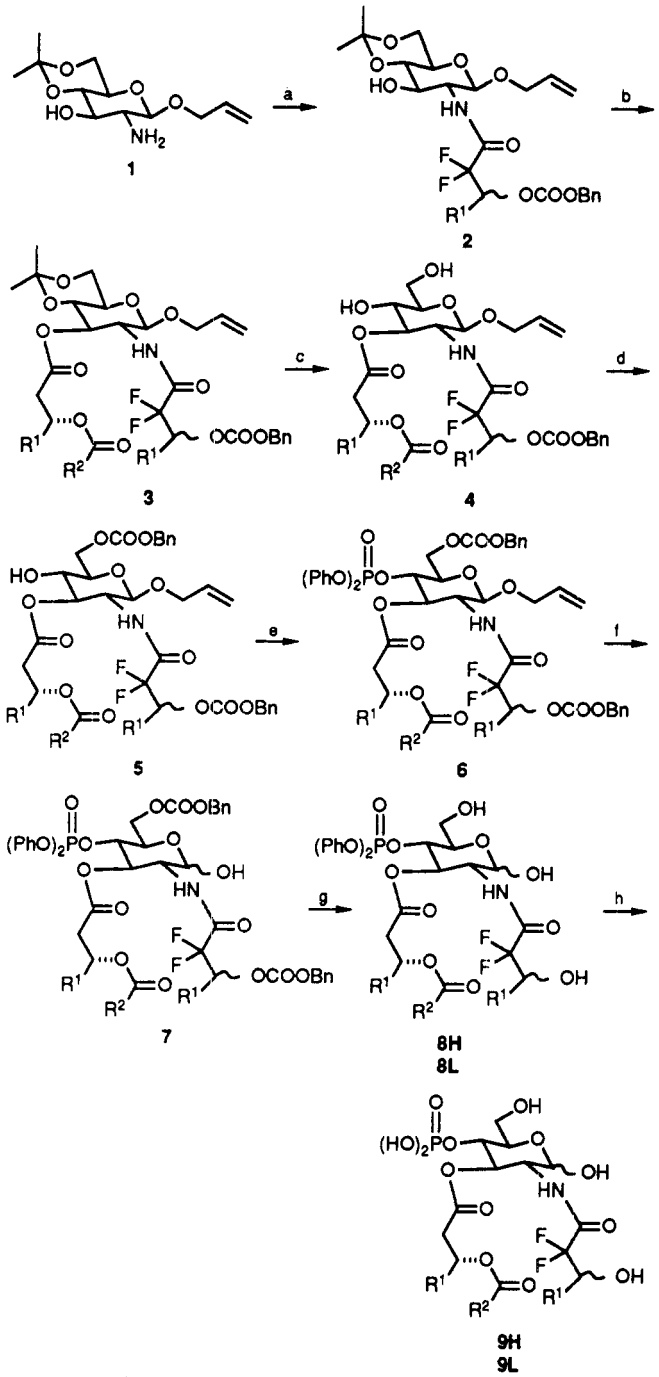
Scheme I[a]



[a] (a) (±)-*n*-$C_{11}H_{23}CH(OCOOBn)CF_2COCl$, Et_3N–CH_2Cl_2, 25 °C, 1 h, 72%; (b) (3*R*)-*n*-$C_{11}H_{23}CH(OCOC_{13}H_{27})CH_2COOH$, DCC, DMAP–$CH_2Cl_2$, 25 °C, 1 h, 68%; (c) aqueous 85% AcOH, 60 °C, 1 h, 50%; (d) ClCOOBn, DMAP–CH_2Cl_2, 0 → 25 °C, 1 h, 36%; (e) $ClP(O)(OPh)_2$, DMAP–THF, reflux, 3 h, 95%; (f) $[C_8H_{12}Ir(PMePh_2)_2]PF_6$–THF, 20 °C, 2 h; then concentrated HCl–THF, 50 °C, 3 h, 79%; (g) H_2, 10% Pd/C–THF, 25 °C, 16 h, **8H**, 31%, **8L**, 35 %; (h) H_2, PtO_2–THF, 25 °C, 3–8 h, 96%.
[b] R^1 = *n*-$C_{11}H_{23}$; R^2 = *n*-$C_{13}H_{27}$.

acid, in dichloromethane using 4-(dimethylamino)pyridine (DMAP) as a base to give a diastereomeric mixture of amides (**2**) (Scheme I). However, the condensation of (±)-3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoic acid, prepared by Hallinan's method,[6] and **1** using 1,3-dicyclohexylcabodiimide (DCC)–DMAP was not effective in yielding **2**. Treatment of **2** with (*R*)-3-(tetradecanoyloxy)tetradecanoyl chloride and Et_3N gave **3**. In this reaction, the use of the corresponding acid and DCC–DMAP made the yield of **3** much lower. Treatment of **3** with 85% AcOH at 60 °C gave 4,6-deprotected diol **4**. Protection of the primary alcohol of **4** with benzyl chloroformate and DMAP gave **5**. Phosphorylation of **5** with diphenylphosphoryl chloride and DMAP gave **6**. Deprotection of the allyl group of **6** with 1,5-cyclooctadiene–bis[methyldiphenylphosphine]iridium hexafluorophosphate ($[C_8H_{12}Ir(PMePh_2)_2]PF_6$)[7] and then pyridine–$H_2O$–$I_2$[8] in THF was not effective because the α,α-difluorinated amide bond was very sensitive to the basic condition. Therefore, **6** was treated with $[C_8H_{12}Ir(PMePh_2)_2]PF_6$ and then addition of concentrated HCl in THF gave **7**. The compounds **2**, **3**, **4**, **5**, **6**, and **7** were each a mixture of diastereomers, which was unseparable chromatographically. Hydrogenolysis of **7** using 10% Pd/C in THF gave two compounds, **8H** and **8L**, which were separated chromatographically. The R_f values of **8H** and **8L** were 0.442 and 0.279 (cyclohexane/EtOAc = 1/1), respectively. The configurations of the 3-hydroxy on the tetradecanoyl group of **8H** and **8L** are not clear. Hydrogenolysis of **8H** and **8L** in THF using Pt as a catalyst gave **9H** and **9L**, respectively.

Biological Activity

To determine the biological activities of **9H** and **9L**, we examined the effects of those compounds as well as LPS and GLA-60 on the production of prostaglandin D_2 in macrophage-like cell line J 774.1 cells. [^{14}C]Prostaglandin release was measured and then the stimulation index was determined as described previously.[9] The stimulation indexes of LPS, GLA-60, **9H**, and **9L** (LPS: 1 μg/mL; others: 10 μM) were 60.0, 17.9, 32.0, and 32.0, respectively. (The values are the means of two independent experiments.) Similar results were obtained by using peptone-induced mouse peritoneal macrophages. These results indicated that both **9H** and **9L** were more active than GLA-60 with respect to the induction of prostaglandin D_2 production, an indicator for macrophage activation.

Experimental Section

^{1}H NMR spectra were recorded on a 270-MHz spectrometer in $CDCl_3$ solution, using tetramethylsilane as internal standard. Preparative TLC was performed on silica gel plates (Merck, silica

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(9) Assay of Released [^{14}C]Prostaglandin D_2. Cells were seeded at approximately 5 × 10^5 cells per well in 12-well dishes containing 1 mL of the culture medium. The cells were cultured overnight and then labeled with 0.1 μCi/mL of [^{14}C]arachidonic acid for 18 h. Each well was then washed with 0.5 mL × 3 of the culture medium. After the addition of the stimulants the cells were incubated at 37 °C for 12 h. The culture media were collected and centrifuged for 5 min. Prostaglandin D_2 that was released into the medium was extracted with $CHCl_3$–EtOH (2/1, v/v) after acidification and analyzed by TLC with a solvent system of EtOAc–$CHCl_3$–EtOH–AcOH (20/20/4/1, v/v/v/v). The radiolabeled prostaglandin D_2 was localized by autoradiography. The regions corresponding to the radioactivity were scraped from the TLC plates and counted with a scintillation counter.

gel 60 F_{254}), and column chromatography was carried out on columns packed with Merck silica gel 60 (230–400 mesh ASTM), using a slightly increased pressure (1.2 atm) for elution. Elemental analyses were performed by the Analytical Center of Analytical and Metabolic Research Laboratories, Sankyo Co., Ltd.

(±)-3-Hydroxy-2,2-difluorotetradecanoic Acid. (i) To a suspension of freshly activated Zn dust (2.66 g)[10] in dry THF (170 mL) was added dropwise a solution of a mixture of *n*-dodecyl aldehyde (6.25 g, 33.9 mmol) and ethyl bromodifluoroacetate (6.88 g, 33.9 mmol) in THF (30 mL) over 30 min at reflux temperature. After an additional 30 min of refluxing, the mixture was cooled to room temperature and was diluted with EtOAc. The organic layer was washed with 1 M $KHSO_4$ and saturated brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give an oily residue that was chromatographed on a silica gel (250 g) column. Elution with cyclohexane/EtOAc (5:1) gave 7.33 g (70%) of (±)-ethyl 2,2-difluoro-3-hydroxytetradecanoate as a solid, mp 33.5 °C: IR ($CHCl_3$) 3600, 2920, 2840, 1765, 1465 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.6–7.0 Hz, CH_3), 1.21–1.75 (m, 23 H, containing 3 H, t, J = 7.0 Hz at δ 1.37), 1.98 (d, 1 H, J = 7.3 Hz, OH), 3.94–4.10 (m, 1 H, C*H*–OH), 4.36 (q, 2 H, J = 7.0 Hz, OCH_2CH_3); MS m/z 309 ($M^+ + 1$). Anal. ($C_{16}H_{30}O_3F_2$) C, H, F.

(ii) To a solution of the ethyl ester (40.8 g, 0.132 mol), prepared by procedure (i) above, in EtOH (300 mL) was added an aqueous solution of 1 M NaOH (140 mL). After 30 min of stirring at room temperature, the mixture was concentrated to half volume under reduced pressure, acidified with concentrated HCl, and extracted with EtOAc. The extract was washed with water and saturated brine, dried ($MgSO_4$), filtered, and concentrated to give a solid that was washed with hexane to give 31.3 g (84%) of (±)-2,2-difluoro-3-hydroxytetradecanoic acid: mp 73.5–74.5 °C; IR ($CHCl_3$) 3600, 2920, 2850, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.6–6.9 Hz, CH_3), 1.21–1.84 (m, 20 H), 4.01–4.13 (m, 1 H, C*H*OH), 5.35 (br s, 2 H, COOH, OH); MS m/z 281 ($M^+ + 1$), 183, 172. Anal. ($C_{14}H_{26}O_3F_2$) C, H, F.

(±)-3-[(Benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoic Acid. (i) To a solution of (±)-2,2-difluorotetradecanoic acid (30.3 g, 0.108 mol), prepared by the procedure above, in THF (300 mL) was added Ph_2CN_2 (23.1 g, 0.119 mol). The mixture was stirred for 1 h at room temperature, quenched with AcOH, and concentrated in vacuo to give a solid that was recrystallized from cold hexane to give 42.5 g (88%) of (±)-benzhydryl 2,2-difluoro-3-hydroxytetradecanoate: mp 44.5 °C; IR ($CHCl_3$) 2930, 2850, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.6 Hz, CH_3), 1.18–1.65 (m, 20 H), 1.93 (d, 1 H, J = 7.0 Hz, OH), 3.98–4.12 (m, 1 H, C*H*OH), 6.99 (s, 1 H, Ph_2CH), 7.27–7.40 (m, 10 H); MS m/z 446 (M^+), 428, 183, 166. Anal. ($C_{27}H_{36}O_3F_2$) C, H, F.

(ii) To a solution of the benzhydryl ester (40.9 g, 91.6 mmol), prepared by procedure (i) above, in CH_2Cl_2 (300 mL) were added $ClCOOCH_2Ph$ (24.3 mL, 137 mmol) and DMAP (22.4 g, 183 mmol) under ice cooling. The mixture was stirred for 30 min at room temperature, concentrated in vacuo, diluted with EtOAc, washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated to give a residue that was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (9:1) gave 53 g (quantitatively) of (±)-benzhydryl 3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoate as a syrup: IR (film) 2925, 2855, 1765, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.6 Hz), 1.19–1.39 (m, 18 H), 1.57–1.75 (m, 2 H, CH_2), 4.99, 5.12 (AB q, 2 H, J = 12.1 Hz, OCH_2Ph), 5.17–5.31 (m, 1 H, C*H*OCOO), 6.94 (s, 1 H, Ph_2CH), 7.25–7.40 (m, 15 H); MS m/z 580 (M^+), 489, 283, 183. Anal. ($C_{35}H_{42}O_5F_2$) C, H, F.

(iii) To a solution of the benzyloxycarbonyl compound (49.5 g, 85.2 mmol), prepared by procedure (ii) above, in $(CH_2Cl)_2$ (100 mL) and anisole (50 mL) was added CF_3COOH (50 mL) under ice cooling. The mixture was stirred for 2 h at room temperature and concentrated in vacuo to give a residue that was chromatographed on a silica gel (75 g) short column. Elution with cyclohexane–EtOAc (5:1) and then EtOAc gave 24.3 g (69%) of (±)-3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoic acid as a viscous oil: IR ($CHCl_3$) 3530, 3400, 2930, 2860, 1735, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.6–7.0 Hz, CH_3), 1.07–1.29 (m, 18 H), 1.55–1.75 (m, 2 H), 5.00–5.35 (m, 3 H, $CHOCOOCH_2Ph$), 7.20–7.35 (m, 5 H, C_6H_5). Anal. ($C_{22}H_{32}O_5F_2$) C, H, F.

Allyl 2-Amino-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (1). A solution of allyl 2-deoxy-4,6-*O*-isopropylidene-2-trifluoroacetamido-β-D-glucopyranoside[5] (30.0 g, 84.4 mmol) in EtOH (500 mL) and 1 M NaOH (250 mL) was refluxed for 1 h. The reaction mixture was concentrated in vacuo to one-third of its volume and extracted with EtOAc (500 mL × 2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated to give 20.1 g (91%) of 1 as a gum, which was employed for the next reaction without purification and also identical with the reported sample.[11]

Allyl 2-[(*RS*)-[3-[(Benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoyl]amino]-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (2). To a solution of (±)-3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoic acid (7.9 g, 19.1 mmol), obtained by the procedure above, in CH_2Cl_2 (50 mL) were added $(COCl)_2$ (5 mL) and one drop of DMF with stirring at 25 °C. After 1 h the mixture was concentrated and dried with a pump to give a corresponding acid chloride, which was dissolved in CH_2Cl_2 (150 mL). This acid chloride solution was added gradually to a solution of the amine 1[5] (5.44 g, 21 mmol) and Et_3N (2.51 g, 24.8 mmol) in CH_2Cl_2 (50 mL) with stirring at 25 °C. After 1 h the mixture was concentrated in vacuo to give a residue that was dissolved in EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to give a residue that was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (3:1) gave 9.0 g (72%) of 2 as a viscous oil: IR ($CHCl_3$) 3430, 2925, 2850, 1755, 1705, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.2–7.0 Hz), 1.25–1.61 (m, 24 H, containing two methyl singlets at δ 1.45 and 1.52, respectively), 1.72–1.79 (m, 2 H), 2.95 (d, 0.5 H, J = 3.3 Hz, OH of one of diastereomers), 3.11 (d, 0.5 H, J = 3.3 Hz, OH of the other one of diastereomers), 3.21–3.60 (m, 3 H), 3.76–4.13 (m, 4 H), 4.23–4.33 (m, 1 H), 4.70 (d, 0.5 H, J = 8.4 Hz, C1-H of one of diastereomers), 4.81 (d, 0.5 H, J = 8.4 Hz, C1-H of the other one of diastereomers), 5.14–5.31 (m, 5 H), 5.75–5.91 (m, 1 H), 6.47–6.54 (m, 1 H, NH), 7.30–7.40 (m, 5 H); MS m/z 655 (M^+), 640. Anal. ($C_{34}H_{51}NO_9F_2$) C, H, N, F.

Allyl 2-[(*RS*)-[3-[(Benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoyl]amino]-2-deoxy-4,6-*O*-isopropylidene-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranoside (3). (a) To a solution of 2 (8.0 g, 12.2 mmol) in CH_2Cl_2 (150 mL) were added (*R*)-3-(tetradecanoyloxy)tetradecanoic acid (6.1 g, 13.4 mmol), DMAP (1.64 g, 13.4 mmol), and DCC (3.2 g, 15.5 mmol), in this order, with stirring. After 1 h at 25 °C, the mixture was concentrated in vacuo, diluted with EtOAc, washed with H_2O, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and then evaporated to give a residue that was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (5:1) gave 9.1 g (68%) of 3 as a viscous oil: IR (film) 3350 (NH), 2925, 2850, 1760–1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85–0.90 (m, 9 H), 1.20–1.80 (m, 68 H, containing two methyl singlets at δ 1.37 and 1.48, respectively), 2.20–2.31 (m, 2 H, $COCH_2$), 2.43–2.66 (m, 2 H, $COCH_2$), 3.35 (m, 1 H), 3.68–4.07 (m, 5 H), 4.26 (m, 1 H), 4.58 (m, 1 H), 5.11–5.41 (m, 7 H), 5.74 (m, 1 H), 6.50–6.64 (m, 1 H, NH), 7.29–7.38 (m, 5 H). Anal. ($C_{62}H_{103}NO_{12}F_2$) C, H, N, F. (b) To a solution of 2 (8.0 g, 12.2 mmol) in CH_2Cl_2 (100 mL) were added a solution of (*R*)-3-(tetradecanoyloxy)tetradecanoyl chloride (6.33 g, 13.4 mmol) in CH_2Cl_2 (50 mL) and Et_3N (1.5 g, 15 mmol) at room temperature with stirring. The reaction mixture was treated by procedure a above to give 10.5 g (79%) of 3.

Allyl 2-[(*RS*)-[3-[(Benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoyl]amino]-2-deoxy-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranoside (4). A suspension of 3 (9.0 g) in 85% AcOH (900 mL) was stirred for 1 h at 60 °C. The mixture became a solution, which was concentrated in vacuo to give a residue that was chromatographed on a silica gel column.

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Elution with cyclohexane–EtOAc (2:1) gave 0.92 g of an unknown byproduct (lower R_f value) and 4.33 g (50%) of **4** as a viscous oil: IR (Nujol) 3500, 3450, 3300, 1758, 1715, 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 9 H, J = 6.4–6.8 Hz), 1.18–2.00 (m, 62 H), 2.09 (t, 1 H, J = 5.9–6.4 Hz, OH), 2.25–2.32 (m, 2 H, $COCH_2$), 2.41–2.50 (m, 2 H, $COCH_2$), 3.37–3.53 (m, 1 H), 3.63–3.70 (m, 1 H, OH), 3.78–4.08 (m, 4 H), 4.21–4.34 (m, 1 H), 4.53, 4.59 (d, each 0.5 H, J = 8.3 Hz), 4.92–5.36 (m, 7 H), 5.74–5.88 (m, 1 H), 6.59, 6.69 (d, each 0.5 H, J = 8.8 Hz, NH), 7.35–7.39 (m, 5 H). Anal. ($C_{59}H_{99}NO_{12}F_2$) C, H, N, F.

Allyl 6-*O*-(Benzyloxycarbonyl)-2-[(*RS*)-[3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoyl]amino]-2-deoxy-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranoside (5). To a solution of **4** (4.2 g, 3.99 mmol) and benzyl chloroformate (350 mg, 2.05 mmol) in CH_2Cl_2 (100 mL) was gradually added DMAP (300 mg, 2.45 mmol) with stirring at 0–5 °C. The reaction temperature was slowly elevated to room temperature. After 1 h of stirring at room temperature, the mixture was concentrated in vacuo, diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give a mixture that was chromatographed on a silica gel (120 g) column. Elution with cyclohexane–EtOAc (4:1) gave 1.72 g (36%) of **5** as a gum, and then elution with cyclohexane–EtOAc (1:1) gave 2.52 g of recovered starting **4**. **5**: IR (Nujol) 3480, 3330, 1750–1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 9 H, J = 6.4–6.8 Hz, 3 CH_3), 1.25–1.73 (m, 62 H), 2.24–2.31 (m, 2 H, $COCH_2$), 2.41–2.48 (m, 2 H, $COCH_2$), 3.52–3.69 (m, 4 H), 3.90–4.02 (m, 3 H), 4.18–4.30 (m, 1 H), 4.42–4.57 (m, 3 H), 5.02–5.25 (m, 7 H), 5.68–5.85 (m, 1 H, CH=C), 6.50, 6.61 (d, each 0.5 H, J = 8.8 Hz, NH), 7.32–7.40 (m, 10 H). Anal. ($C_{67}H_{105}NO_{14}F_2$) C, H, N, F.

Allyl 6-*O*-(Benzyloxycarbonyl)-2-[(*RS*)-[3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoyl]amino]-2-deoxy-4-*O*-(diphenylphosphoryl)-3-*O*-[(*R*)-3-(tetradecanoyloxy)-tetradecanoyl]-β-D-glucopyranoside (6). To a solution of **5** (1.6 g, 1.35 mmol) in THF (150 mL) were added diphenyl chlorophosphate (3.2 g, 11.9 mmol) and DMAP (1.6 g, 13.1 mmol). The mixture was refluxed for 3 h, concentrated in vacuo, diluted with EtOAc, washed with dilute HCl, H_2O, and saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to give a residue that was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (3:1) gave 1.82 g (95%) of **6** as a gum: IR (film) 3300, 1750, 1720–1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 9 H, J = 6.4–6.8 Hz), 1.13–1.80 (m, 62 H), 2.12–2.45 (m, 4 H), 3.61–3.83 (m, 3 H), 3.91–4.04 (m, 1 H), 4.13–4.23 (m, 2 H), 4.30–4.38 (m, 1 H), 4.69 (m, 1 H), 4.85 (d, 1 H, J = 7.0 Hz, C1-H), 4.99–5.39 (m, 7 H), 5.47–5.65 (m, 2 H, C=CH_2), 5.67–5.85 (m, 1 H, CH=C), 6.80, 6.95 (d, each 0.5 H, J = 8.8 Hz, NH), 7.10–7.36 (m, 20 H). Anal. ($C_{79}H_{114}NO_{17}F_2P$) C, H, N, F, P.

6-*O*-(Benzyloxycarbonyl)-2-[(*RS*)-[3-[(benzyloxycarbonyl)oxy]-2,2-difluorotetradecanoyl]amino]-2-deoxy-4-*O*-(diphenylphosphoryl)-3-*O*-[(*R*)-3-(tetradecanoyloxy)-tetradecanoyl]-D-glucopyranose (7). To a solution of **6** (1.0 g, 0.7 mmol) in THF (40 mL, freshly distilled over $LiAlH_4$) was suspended [C_8H_{12}(Ir(PMePh$_2$)$_2$]PF_6 (20 mg). The air in the reaction flask was completely replaced with nitrogen and then further replaced with hydrogen to activate the iridium complex. After 1 or 2 min, when the red-colored iridium complex becomes colorless and solution, immediately the hydrogen was completely replaced again with nitrogen. This solution was stirred for 2 h at 20 °C. After checking for the double-bond shift to an enol ether (slightly higher R_f value on silica gel TLC), concentrated HCl (10 mL) was added to this mixture, which was stirred for 3 h at 50 °C and then diluted with EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a residue that was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (3:1) gave 0.75 g (79%) of **7** as a gum: IR (film) 3350, 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 9 H, J = 6.4–6.8 Hz), 1.16–1.75 (m, 62 H), 2.09–2.18 (m, 2 H, $COCH_2$), 2.32–2.49 (m, 2 H, $COCH_2$), 2.73, 3.29 (d, each 0.5 H, J = 3.9 Hz, OH), 4.01–4.38 (m, 4 H), 4.70 (m, 1 H), 4.89–5.27 (m, 7 H), 5.33–5.47 (m, 1 H), 6.81, 6.90 (d, each 0.5 H, J = 8.3 Hz, NH), 7.10–7.37 (m, 20 H). Anal. ($C_{76}H_{110}NO_{17}F_2P$) C, H, N, F, P.

2-Deoxy-2-[(*R* and *S*)-(2,2-difluoro-3-hydroxytetradecanoyl)amino]-4-*O*-(diphenylphosphoryl)-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose (8H,L). To a solution of **7** (300 mg, 0.27 mmol) in THF (2 mL) was added 10% Pd on carbon (100 mg). The mixture was hydrogenolyzed at room temperature with vigorous stirring. After completion of the reaction (16 h), the mixture was filtered and then chromatographed on silica gel TLC plates. Development with cyclohexane–EtOAc (1:1) gave 76 mg (31%, R_f = 0.442) of **8H** and 84 mg (35%, R_f = 0.279) of **8L** as gums, respectively. The compounds (**8H** and **8L**) were stable in long-term storage. **8H**: ^1H NMR ($CDCl_3$) δ 0.88 (t, 9 H, J = 6.4–6.8 Hz), 1.20–1.70 (m, 62 H), 2.17–2.23 (m, 2 H, $COCH_2$), 2.34–2.48 (m, 2 H, $COCH_2$), 3.10 (1 H, d, J = 4.5 Hz, OH), 3.18–3.27 (2H, m, 2 OH), 3.60–3.65 (m, 2 H, C6-H_2), 3.90–4.04 (m, 2 H), 4.33 (m, 1 H), 4.78 (m, 1 H, C4-H), 5.10 (m, 1 H, C2-H), 5.36 (t, 1 H, J = 3.4–3.9 Hz, C1-H, changed to a doublet (J = 3.4 Hz) on addition of D_2O), 5.53 (t, 1 H, J = 9.3–10.7 Hz, C3-H), 6.88 (d, 1 H, J = 8.8 Hz, NH), 7.14–7.39 (m, 10 H). Anal. ($C_{80}H_{98}NO_{13}F_2P$) C, H, N, F, P.

8L: IR (Nujol) 3510, 3450, 3375, 1735, 1728, 1685, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 9 H, J = 6.4–6.8 Hz), 1.13–1.72 (m, 62 H), 2.12–2.29 (m, 2 H, $COCH_2$), 2.39–2.42 (m, 2 H, $COCH_2$), 2.91 (br s, 1 H, OH), 3.30 (br s, 1 H, OH), 3.54 (br s, 1 H, OH), 3.61 (m, 2 H, C6-H_2), 3.93–4.06 (m, 2 H), 4.32 (m, 1 H), 4.78 (q, 1 H, J = 9.3–9.7 Hz, C4-H), 5.14 (m, 1 H, C2-H), 5.36 (t, 1 H, J = 3.4 Hz, C1-H, changed to a doublet (J = 3.4 Hz) on addition of D_2O), 5.55 (t, 1 H, J = 10.2 Hz, C3-H), 6.93 (d, 1 H, J = 8.8 Hz, NH), 7.14–7.40 (m, 10 H). Anal. ($C_{60}H_{98}NO_{13}F_2P$) C, H, N, F, P.

2-Deoxy-2-[(2,2-difluoro-3-hydroxytetradecanoyl)-amino]-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-Phosphate (9H or 9L). A solution of **8H** (30 mg) or **8L** (30 mg) in THF (3 mL) containing PtO_2 (3 mg) was stirred for 3–8 h under hydrogen at 25 °C. Platinum metal was filtered off, and the filtrate was concentrated to give 25 mg (96%) of **9H** or **9L** as a powder. Both **9H** and **9L** were changed gradually to corresponding less polar materials during storage for several months at room temperature.

9H: IR (Nujol) 3500–3300, 1720 (shoulder), 1685 cm^{-1}; ^1H NMR (pyridine-d_5) δ 0.81–0.94 (m, 9 H), 1.15–2.05 (m, 62 H), 2.40–2.49 (m, 2 H, $COCH_2$), 3.03–3.14 (m, 1 H, COCH), 3.20–3.36 (m, 1 H, COCH), 4.08–4.21 (m, 1 H, C5-H), 4.46–4.68 (m, 2 H, C6-H_2), 4.93–5.08 (m, 1 H), 5.17–5.30 (m, 1 H), 5.68–5.83 (m, 2 H), 6.32 (t, 1 H, J = 9.3 Hz, C3-H), 8.96 (d, 1 H, J = 9.3 Hz, NH, disappear on addition of D_2O). Anal. ($C_{48}H_{90}NO_{13}F_2P$) C, H, N, F, P.

9L: IR (Nujol) 3500–3300, 1720 (shoulder), 1685 cm^{-1}; ^1H NMR (C_5D_5N + D_2O) δ 0.85–0.90 (m, 9 H), 1.14–2.04 (m, 62 H), 2.39–2.50 (m, 2 H, $COCH_2$), 3.14 (dd, 1 H, J = 6.4, 16.6 Hz), 3.38 (dd, 1 H, J = 6.4, 16.6 Hz), 4.07–4.14 (m, 1 H, C5-H), 4.51–4.66 (m, 2 H, C6-H_2), 4.95 (dd, 1 H, J = 3.4, 10.7 Hz), 5.18–5.29 (m, 1 H), 5.52 (m, 1 H), 5.72 (d, 1 H, J = 3.4 Hz, C1-H), 5.76–5.82 (m, 1 H), 6.29 (t, 1 H, J = 9.3–10.7 Hz, C3-H), 8.96 (d, 1 H, J = 9.8 Hz, NH, disappear on addition of D_2O). Anal. ($C_{48}H_{90}NO_{13}F_2P$) C, H, N, F, P.

Procedure for Triethylamine Solution of 9H and 9L. The powder (**9H** or **9L**) (15 mg) was suspended in 0.1 M HCl (4 mL) and $CHCl_3$–MeOH (1:2, 15 mL) and dissolved by ultrasound. Additional $CHCl_3$ (5 mL) and 0.1 M HCl (5 mL) were added to this solution to separate to two phases. The lower chloroform phase was collected and concentrated to give 13 mg of **9H** or **9L**, which was dissolved in a 0.1% triethylamine (v/v) water solution.

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