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Syntheses of 2,6-dideoxy-6-fluoro-2-[(3*R* and 3*S*)-3-hydroxytetradecanamido]-3-*O*-[(3*R*)-3-(tetradecanoyloxy)-tetradecanoyl]-D-glucopyranose 4-(dihydrogen phosphate) and 2-deoxy-2-[(3*R* and 3*S*)-3-hydroxytetradecanamido]-3-*O*-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranosyl fluoride 4-(dihydrogen phosphate): fluorosugar analogues of GLA-60

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ABSTRACT

Both 2,6-dideoxy-6-fluoro-2-[(3*R*)- and (3*S*)-3-hydroxytetradecanamido]-3-*O*-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-phosphate, **11** and **11'** (6-fluoro GLA-60 and its 3'-epimer), and 2-deoxy-2-[(3*R*)- and (3*S*)-(3-hydroxytetradecanamido]-3-*O*-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranosyl fluoride 4-(dihydrogen phosphate), **18** and **18'** (1-fluoro GLA-60 and its 3'-epimer), were synthesized from allyl 2-deoxy-4,6-*O*-isopropylidene-2-trifluoroacetamido-α-D-glucopyranoside.

INTRODUCTION

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 and Luderitz[1] isolated lipid A, which is the lipophilic part of LPS. Lipid A shows most of the endotoxic activities of LPS, and was first chemically synthesized by Shiba and coworkers[2]. Nishijma and Raetz[3] isolated lipid X from a mutant of *E. coli*. Lipid X is really the reducing sugar part of lipid A and is also a biosynthetic precursor of lipid A[4]. It has the ability to activate, albeit weakly, the macrophage-like mouse cell line J774[†]. Hasegawa, Kiso, and coworkers[6], who synthesized various non-reducing sugar parts of lipid A, to say nothing of lipid X ana-

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[†] Recently it has been reported that lipid X is devoid of biological activity. See ref. 5.

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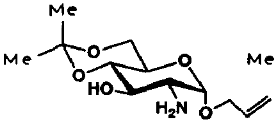
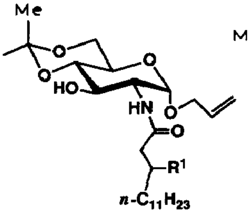
logues, discovered that a lipid A subunit homologue, D-glucosamine 4-(dihydrogen phosphate) derivatives [for example, 2-deoxy-2-[(3*R*)-3-hydroxytetradecanamido]-3-*O*-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-(dihydrogen phosphate), GLA-60][6], elicited some distinct and beneficial biological activities of LPS. As we are interested in the biological activities of the fluorinated compounds related to lipid A, lipid X, or GLA-60, we attempted to synthesize the 1-fluoro and 6-fluoro analogues of GLA-60. Herein we describe details of the syntheses of the title compounds.

RESULTS AND DISCUSSION

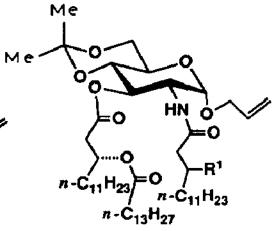
Allyl 2-amino-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside (**1**) obtained from the saponification of allyl 2-deoxy-4,6-*O*-isopropylidene-2-trifluoroacetamido-α-D-glucopyranoside[7] was converted to compounds **2** and **2′** by treatment with (±)-3-



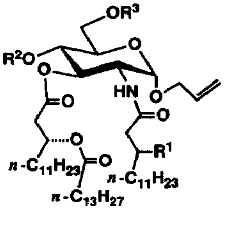
1



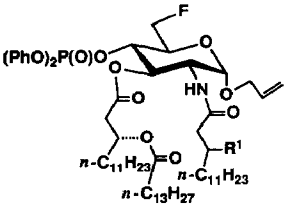
2 : R^1 = ---OCH$_2$Ph
2′: R^1 = —OCH$_2$Ph



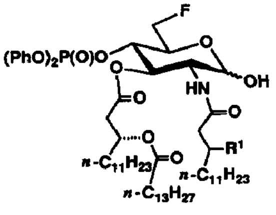
3 : R^1 = ---OCH$_2$Ph
3′: R^1 = —OCH$_2$Ph



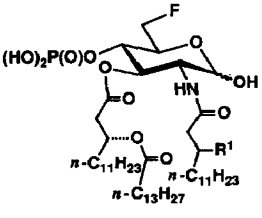
4 : R^1 = ---OCH$_2$Ph, R^2=R^3=H
4′: R^1 = —OCH$_2$Ph, R^2=R^3=H
5 : R^1 = ---OCH$_2$Ph, R^2=H, R^3=SiMe$_2$Bu^t
5′: R^1 = —OCH$_2$Ph, R^2=H, R^3=SiMe$_2$Bu^t
6 : R^1 = ---OCH$_2$Ph, R^2=P(O)(OPh)$_2$, R^3=SiMe$_2$Bu^t
6′: R^1 = —OCH$_2$Ph, R^2=P(O)(OPh)$_2$, R^3=SiMe$_2$Bu^t
7 : R^1 = ---OCH$_2$Ph, R^2=P(O)(OPh)$_2$, R^3=H
7′: R^1 = —OCH$_2$Ph, R^2=P(O)(OPh)$_2$, R^3=H



8 : R^1 = ---OCH$_2$Ph
8′: R^1 = —OCH$_2$Ph



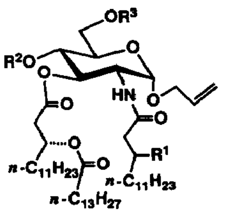
9 : R^1 = ---OCH$_2$Ph
9′: R^1 = —OCH$_2$Ph
10 : R^1 = ---OH
10′: R^1 = —OH



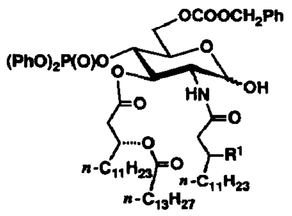
11 : R^1 = ---OH
11′: R^1 = —OH

(benzyloxy)tetradecanoic acid and *N,N'*-dicyclohexylcarbodiimide (DCC). Compounds **2** and **2'** were further converted to **4** and **4'** *via* **3** and **3'**, respectively.

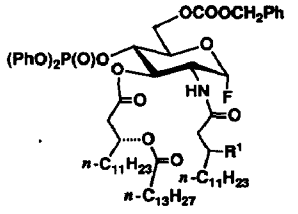
6-Fluoro GLA-60 (**11**) and its (3'*S*)-epimer (**11'**) were prepared as follows. The primary alcoholic group of **4** was silylated with *tert*-butyldimethylsilyl chloride–DMAP to give the monosilylated compound **5**. Phosphorylation of the secondary alcohol of **5** with diphenylphosphoryl chloride–DMAP gave the phosphate **6**. The silyl group of **6** was then removed with 3M HCl–THF to give the alcohol **7**. Treatment of **7** with diethylaminosulfur trifluoride (DAST) gave the 6-fluoro compound **8**. Removal of the *O*-allyl group by reaction of 1,5-cyclooctadiene-bis(methyldiphenylphosphine)iridium hexafluorophosphate[8], $[C_8H_{12}Ir(PMePh_2)_2]PF_6$, followed by hydrolysis with I_2–H_2O–pyridine[9], gave **9**. Debenzylation of **9**, achieved by catalytic hydrogenolysis in MeOH–THF using 10% Pd/C, gave **10**. Finally, the diphenyl groups of **10** were hydrogenolyzed using platinum as catalyst to give **11**. The (3'*S*)-epimer (**11'**) of **11** was obtained from **4'** by the exactly the same procedures for the synthesis of **11** from **4**.



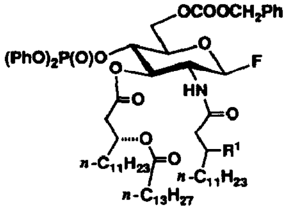
12 : R^1 = ---OCH$_2$Ph, R^2=H, R^3=COOCH$_2$Ph
12': R^1 = —OCH$_2$Ph, R^2=H, R^3=COOCH$_2$Ph
13 : R^1 = ---OCH$_2$Ph, R^2=P(O)(OPh)$_2$, R^3=COOCH$_2$Ph
13': R^1 = —OCH$_2$Ph, R^2=P(O)(OPh)$_2$, R^3=COOCH$_2$Ph



14 : R^1 = ---OCH$_2$Ph
14': R^1 = —OCH$_2$Ph

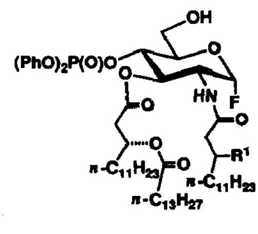


15 : R^1 = ---OCH$_2$Ph
15': R^1 = —OCH$_2$Ph

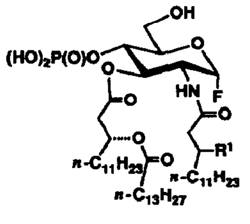


16 : R^1 = ---OCH$_2$Ph
16': R^1 = —OCH$_2$Ph

$$16' \xrightarrow{SiO_2} 15'$$



17 : R^1 = ---OH
17': R^1 = —OH



18 : R^1 = ---OH
18': R^1 = —OH

1-Fluoro GLA-60 (**18**) and its (3′*S*)-epimer (**18′**) were prepared as follows. Compound **4** was treated with benzyloxycarbonyl chloride–DMAP to protect the primary alcohol, and the secondary alcohol of **12** thus obtained was phosphorylated with diphenylphosphoryl chloride–DMAP to give the phosphate **13**. Removal of the *O*-allyl group with $[C_8H_{12}Ir(PMePh_2)_2]PF_6$ (ref. 8), followed by hydrolysis with I_2–H_2O–pyridine[9], gave **14**. Treatment of **14** with diethylaminosulfur trifluoride (DAST) gave the α-D-glycosylfluoride **15** and its β anomer **16**. The $J_{1,2}$ for **15** was 2.4 Hz, a value wich is reasonable for an H-1_e–H-2_a arrangement in the pyranosyl fluoride ($J_{1e,2a}$ 2.5–3.5 Hz)[10], indicating that the fluorine atom is oriented α. Debenzylation of **15** was achieved by catalytic hydrogenolysis in MeOH–THF using 10% Pd/C to give the dihydroxy compound **17**. The β anomer of **17** obtained from an identical reduction of **16** was very unstable, easily decomposing to many products as shown by a multitude of zones on silica gel t.l.c. Finally, the diphenyl group of **17** was hydrogenolyzed using platinum as a catalyst to yield **18**. The (3′*S*)-epimer (**18′**) of **18** was obtained from **4′** by procedures analogous to those used for the synthesis of **18** from **4**. Fluorination of **14′** gave **15′** and **16′**. To our surprise, the β anomer (**16′**) easily epimerized to the α anomer **15′** upon addition of silicic acid to its solution in CH_2Cl_2, in spite of the fact that there was no evidence for the analogous conversion of **15** to **16**. Compound **15′** was converted to **18′** *via* **17′**. We could thus obtain both the 6-fluoro and 1-fluoro analogues of GLA-60.

In order to determine the biological activities of **11**, **11′**, **18**, and **18′**, we examined the effects of those compounds as well as LPS and GLA-60 on the production of $[^{14}C]$prostaglandin-D_2 in the macrophage-like J774.1 cell line, and then the stimulation index was determined[11]. The stimulation indexes of LPS, GLA-60, **11**, **11′**, **18**, and **18′** (LPS: 1 μg/mL; the others: 10 μM) were 60.0, 17.9, 13.3, 4.6, 3.5, and 2.3, respectively. These results indicated that the compounds **11′**, **18**, and **18′** were almost inactive, and **11** was less active than GLA-60 with respect to the induction of prostaglandin-D_2 production, which is an indicator for macrophage activation.

EXPERIMENTAL

General methods. — See previous paper in this series[7]. Palladium-on-charcoal (10% Pd/C) catalyst was the "Type-A" product of Kawaken Chemical Company. Elemental analyses were performed by the Analytical Center of the Analytical and Metabolic Research Laboratories, Sankyo Co., Ltd.

*Allyl 2-amino-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside* (**1**). — A solution of allyl 2-deoxy-2-trifluoroacetamido-α-D-glucopyranoside[7] (40 g, 0.113 mmol) in EtOH (680 mL) and M NaOH (338 mL, 0.338 mmol) was refluxed for 1 h, concentrated to one-third volume, and extracted with EtOAc. The organic extract was washed with H_2O and satd. NaCl, dried over $MgSO_4$, filtered, and concentrated to give 28.1 g of amine **1** (96%), which was used for the next reaction without further purification. For full characterization, 100 mg of this crude amine was chromatographed on a silica gel column: ^{1}H-n.m.r. ($CDCl_3$): δ 1.45 (s, 3 H), 1.53 (s, 3 H), 2.65 (br s, 3 H, NH_2, OH), 2.93 (dd, 1 H, *J* 3.5, 9.8 Hz, H-2), 3.53–4.40 (m, 7 H), 4.91 (d, 1 H, *J* 3.5 Hz, H-1), 5.21–5.39 (m, 2 H), 5.87–6.01 (m, 1 H); m.s. *m/z* 260 (M^+ + 1), 244, 218, 202, 201, 186.

Anal. Calc. for $C_{12}H_{21}NO_5 \cdot 0.33\ H_2O$ (265.3): C, 54.32; H, 8.17; N, 5.27. Found: C, 54.61; H, 7.86; N, 5.30.

*Allyl 2-[(3*R*)-3-(benzyloxy)tetradecanamido]-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside* (**2**) *and allyl 2-[(*3S)-3-(benzyloxy)tetradecanamido]-2-deoxy-4,6-O*-isopropylidene-α-D-glucopyranoside* (**2'**). — To a solution of crude amine **1** (28.0 g, 0.108 mmol) obtained above and (±)-3-(benzyloxy)tetradecanoic acid (37.8 g, 0.113 mmol) in CH_2Cl_2 (570 mL) was added *N,N*-dicyclohexylcarbodiimide (DCC) (26.8 g, 0.130 mmol). The mixture was stirred for 1 h at 25°. The precipitated *N,N'*-dicyclohexylurea was filtered off, the filtrate was concentrated, then diluted with EtOAc. The solution was washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a mixture of products (71 g). Batches (12 g) of this mixture were repeatedly chromatographed on a silica gel (1 kg) column. Elution with 1:1 cyclohexane–EtOAc gave **2** (20.0 g, 32%, R_F = 0.35) as a solid and **2'** (22.0 g, 35%, R_F = 0.21) as a gum.

Compound **2**: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 3 H, *J* 6.8 Hz), 1.15–1.40 [m, 18 H), 1.40–1.77 [m, 8 H, containing two s (3 H) at δ 1.45 and 1.53], 2.42 (dd, 1 H, *J* 6.6, 15.0 Hz), 2.56 (dd, 1 H, *J* 4.0, 15.0 Hz), 3.06 (d, 1 H, *J* 2.9 Hz, OH), 3.55–4.25 (m, 9 H), 4.51, 4.58 (AB-q, 2 H, *J* 11.4 Hz), 4.73 (d, 1 H, *J* 3.7 Hz, H-1), 5.10–5.35 (m, 2 H, olefinic), 5.63–5.86 (m,1 H olefinic), 6.61 (d, 1 H, *J* 8.4 Hz, NH), 7.25–7.40 (m, 5 H); m.s. *m/z* 576 (M^+), 560, 518, 502, 469, 426, 388, 346.

Anal. Calc. for $C_{33}H_{53}NO_7$ (575.8): C, 68.84; H, 9.28; N, 2.43. Found: C, 68.88; H, 9.01; N, 2.52.

Compound **2'**: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 3 H, *J* 6.6 Hz), 1.15–1.42 (m, 18 H), 1.44–1.77 [m, 8 H, containing two s, (3 H) at δ 1.45 and 1.53], 2.36 (dd, 1 H, *J* 7.0, 15.0 Hz), 2.57 (dd, 1 H, *J* 3.7, 15.0 Hz), 3.02 (d, 1 H, *J* 2.6 Hz, OH), 3.55–4.25 (m, 9 H), 4.54, 4.59 (AB-q, 2 H, *J* 11.4 Hz), 4.78 (d, 1 H, *J* 3.7 Hz, H-1), 5.10–5.28 (m, 2 H, olefinic), 5.66–5.84 (m, 1 H, olefinic), 6.77 (d, 1 H, *J* 8.8 Hz, NH), 7.25–7.37 (m, 5 H,); m.s. *m/z* 576 (M^+), 560, 518, 502, 469, 426, 388, 346.

Anal. Calc. for $C_{33}H_{53}NO_7$ (575.8): C, 68.84; H, 9.28; N, 2.43. Found: C, 68.71; H, 9.31; N, 2.22.

*Allyl 2-[(3*R*)-3-(benzyloxy)tetradecanamido]-2-deoxy-4,6-*O*-isopropylidene-3-*O*-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside* (**3**). — To a solution of **2** (18.8 g, 32.7 mmol) and (*R*)-3-(tetradecanoyloxy)tetradecanoic acid (16.4 g, 36.0 mmol) in THF (380 mL) was added DCC (8.8 g, 42.5 mmol) and DMAP (4.4 g, 36.0 mmol) with stirring at 25°. After 4 h, the precipitate was filtered off, and the filtrate was concentrated and diluted with EtOAc (1.2 L), which was then washed with satd. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to give a residue, which was chromatographed on a silica gel (1 kg) column. Elution with 17:3 cyclohexane–EtOAc gave 24.3 g of **3** (74%) as a gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.80–1.00 (m, 9 H), 1.00–1.80 (m, 68 H), 2.10–2.70 (m, 6 H), 3.60–4.40 (m, 8 H), 4.49, 4.54 (AB-q, 2 H, *J* 11.7 Hz), 4.65–4.90 (m, 1 H), 5.03–5.35 (m, 4 H), 5.60–5.95 (m, 1 H), 6.25 (d, 1 H, *J* 9.5 Hz, NH), 7.25–7.65 (m, 5 H); i.r. (neat) 3350, 1730, 1650 cm^{-1}.

Anal. Calc. for $C_{61}H_{105}NO_{10}$ (1012.5): C, 72.36; H, 10.45; N, 1.38. Found: C, 72.23; H, 10.13; N, 1.50.

*Allyl 2-[(3*S*)-3-(benzyloxy)tetradecanamido]-2-deoxy-4,6-*O*-isopropylidene-3-*O*-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-*D*-glucopyranoside* (**3′**). — Compound **2′** was treated as described above to give **3′** in 73% yield: ^{1}H-n.m.r. ($CDCl_3$): δ 0.80–0.97 (m, 9 H), 1.10–1.70 (m, 68 H), 2.12–2.64 (m, 6 H), 3.63–3.90 (m, 6 H), 3.95–4.05 (m, 1 H), 4.22–4.34 (m, 1 H), 4.49, 4.60 (AB-q, 2 H, J 11.4 Hz), 4.78 (d, 1 H, J 3.7 Hz), 5.05–5.23 (m, 4 H), 5.60–5.77 (m, 1 H), 6.85 (d, 1 H, J 9.2 Hz, NH), 7.25–7.40 (m, 5 H); i.r. (neat) 3400, 1730, 1650 cm^{-1}.

Anal. Calc. for $C_{61}H_{105}NO_{10}$ (1012.5): C, 72.36; H, 10.45; N, 1.38. Found: C, 72.41; H, 10.00; N, 1.54.

*Allyl 2-[(3*R*)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-*O*-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-*D*-glucopyranoside* (**4**). — A suspension of **3** (1.1 g, 3.27 mmol) in 90% aq. AcOH (22 mL) was warmed for 50 min at 60° with stirring. The suspension dissolved to form a clear solution that was concentrated to give a residue, which was chromatographed on a silica gel column, eluting with 3:2 cyclohexane–EtOAc to give 0.65 g of **4** (62%) as a solid: ^{1}H-n.m.r. ($CDCl_3$): δ 0.82–0.95 (m, 9 H), 1.15–1.70 (m, 64 H, containing two OH), 2.24–2.58 (m, 6 H), 3.62–3.92 (m, 6 H), 4.00–4.10 (m, 1 H), 4.20–4.30 (m, 1 H), 4.50, 4.55 (AB-q, 2 H, J 11.5 Hz), 4.79 (d, 1 H, J 3.3 Hz, H-1), 5.03–5.24 (m, 4 H), 5.65–5.82 (m, 1 H), 6.33 (d, 1 H, J 9.5 Hz, NH), 7.22–7.36 (m, 5 H); i.r. (Nujol) 3480, 3400, 3300, 1735, 1720, 1700, 1650 cm^{-1}.

Anal. Calc. for $C_{58}H_{101}NO_{10}$ (972.4): C, 71.64; H, 10.47; N, 1.44. Found: C, 71.56; H, 10.38; N, 1.47.

*Allyl 2-[(3*S*)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-*O*-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-*D*-glucopyranoside* (**4′**). — Compound **3′** was treated as described above to give **4′** in 69% yield: ^{1}H-n.m.r. ($CDCl_3$): δ 0.82–0.95 (m, 9 H), 1.15–1.72 (m, 62 H), 2.24–2.50 (m, 6 H), 3.62–3.92 (m, 6 H), 4.00–4.10 (m, 1 H), 4.18–4.30 (m, 1 H), 4.50, 4.57 (AB-q, 2 H, J 11.4 Hz), 4.86 (d, 1 H, J 3.3 Hz, H-1), 5.02–5.27 (m, 4 H), 5.64–5.81 (m, 1 H), 6.80 (d, 1 H, J 8.8 Hz, NH), 7.25–7.40 (m, 5 H); i.r. (Nujol) 3480, 3280, 1737, 1722, 1643 cm^{-1}.

Anal. Calc. for $C_{58}H_{101}NO_{10}$ (972.4): C, 71.64; H, 10.47; N, 1.44. Found: C, 71.61; H, 10.34; N, 1.41.

*Allyl 2-[(3*R*)-3-(benzyloxy)tetradecanamido]-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3-*O*-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-*D*-glucopyranoside* (**5**). — To a solution of **4** (0.49 g, 0.5 mmol) in CH_2Cl_2 (10 mL) were added DMAP (0.15 g, 1.25 mmol) and *tert*-BuMe$_2$SiCl (0.11 g, 0.75 mmol). After 4 h at room temperature, the reaction mixture was concentrated and diluted with EtOAc, washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and again concentrated to give a crude oil. The crude product was chromatographed on a silica gel column, eluting with 85:15 cyclohexane–EtOAc to give **5** (0.53 g, 97%) as an oil: ^{1}H-n.m.r. ($CDCl_3$): δ 0.08 (s, 6 H), 0.82–0.94 (m, 18 H, 3 × Me, *tert*-Bu), 1.16–1.67 (m, 62 H), 2.28 (t, 2 H, J 7.6 Hz), 2.35 (d, 2 H, J 5.9 Hz), 2.42–2.63 (m, 2 H), 3.30 (br s, 1 H, OH), 3.60–4.10 (m, 7 H, H-4, H-5, H-6,6a, OCH_2, H-3′), 4.18–4.30 (m, 1 H, H-2), 4.49, 4.54 (AB-q, 2 H, J 12.0 Hz, CH_2Ph), 4.77 (d, 1 H, J 3.9 Hz, H-1), 5.04–5.22 (m, 4 H, H-3, $H_2C=$, H-3″), 5.65–5.82 (m, 1 H; HC=), 6.72 (d, 1 H, J 9.3 Hz, NH), 7.22–7.35 (m, 5 H, Ph); i.r. (Nujol): 3500–3150, 1730, 1650 cm^{-1}.

Anal. Calc. for $C_{64}H_{115}NO_{10}Si$ (1086.7): C, 70.74; H, 10.67; N, 1.29. Found: C, 70.98; H, 10.51; N, 1.23.

Allyl 2-[(3S)-3-(benzyloxy)tetradecanamido]-6-O-(tert-butyldimethylsilyl)-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside (**5'**). — Compound **4'** was treated as described above to give **5'** in 99% yield: ^{1}H-n.m.r. ($CDCl_3$): δ 0.09 (s, 6 H), 0.80–0.94 (m, 18 H, 3 × Me, *tert*-Bu), 1.15–1.68 (m, 62 H), 2.20–2.56 (m, 6 H), 3.31 (d, 1 H, *J* 2.0 Hz, OH), 3.62–4.08 (m, 7 H, H-4, H-5, H-6,6a, OCH_2, H-3'), 4.15–4.27 (m, 1 H, H-2), 4.49, 4.59 (AB-q, 2 H, *J* 11.2 Hz, CH_2Ph), 4.82 (d, 1 H, *J* 3.4 Hz, H-1), 5.04–5.23 (m, 4 H, H-3, $H_2C=$, H-3''), 5.62–5.80 (m, 1 H, HC=), 6.74 (d, 1 H, *J* 9.3 Hz, NH), 7.22–7.40 (m, 5 H, Ph); i.r. (Nujol): 3600–3150, 1730, 1650 cm^{-1}.

Anal. Calc. for $C_{64}H_{115}NO_{10}Si$ (1086.7): C, 70.74; H, 10.67; N, 1.29. Found: C, 70.93; H, 10.40; N, 1.24.

Allyl 2-[(3R)-3-(benzyloxy)tetradecanamido]-6-O-(tert-butyldimethylsilyl)-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside 4-(diphenyl phosphate) (**6**). — To a solution of **5** (100 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) were added DMAP (34 mg, 0.27 mmol) and a solution of $(PhO)_2P(O)Cl$ (70 mg, 0.27 mmol) in CH_2Cl_2 (1 mL) with stirring. After 1 h at room temperature, the reaction mixture was concentrated and diluted with EtOAc, washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a crude oil. The crude product was chromatographed on a silica gel column, eluting with 9:1 cyclohexane–EtOAc to give **6** (110 mg, 94%) as a gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.01 (s, 6 H), 0.82–0.95 (m, 18 H, 3 × Me, *tert*-Bu), 1.10–1.66 (m, 62 H), 2.14 (t, 2 H), 2.35 (d, 2 H, *J* 5.9 Hz), 2.44 (d, 2 H, *J* 6.8 Hz), 3.65–4.12 (m, 6 H, H-5, H-6,6a, OCH_2, H-3'), 4.23–4.35 (m, 1 H, H-2), 4.53, 4.57 (AB-q, 2 H, *J* 11.5 Hz, CH_2Ph), 4.67 (dd, 1 H, *J* 9.3, 18.6 Hz, H-4), 4.80 (d, 1 H, *J* 3.4 Hz, H-1), 5.05–5.25 (m, 3 H, $H_2C=$, H-3''), 5.43 (dd, 1 H, 1 H, *J* 9.3, 10.7 Hz, H-3), 5.67–5.85 (m, 1 H, HC=), 6.23 (d, 1 H, *J* 9.3 Hz, NH), 7.12–7.40 (m, 15 H, Ph); i.r. (Nujol): 3350 (NH), 1740, 1675 cm^{-1}.

Anal. Calc. for $C_{76}H_{124}NO_{13}PSi$ (1318.9): C, 69.21; H, 9.48; N, 1.06; P, 2.35. Found: C, 69.30; H, 9.26; N, 1.13; P, 2.20.

Allyl 2-[(3S)-3-(benzyloxy)tetradecanamido]-6-O-(tert-butyldimethylsilyl)-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside 4-(diphenyl phosphate) (**6'**). — Compound **5'** was treated as described above to give **6'** in 93% yield: ^{1}H-n.m.r. ($CDCl_3$): δ 0.01 (s, 6 H), 0.80–0.92 (m, 18 H, 3 × Me, *tert*-Bu), 1.05–1.65 (m, 62 H), 2.06–2.16 (m, 1 H), 2.30–2.50 (m, 4 H), 3.62–4.09 (m, 6 H, H-5, H-6,6a, OCH_2, H-3'), 4.22–4.33 (m, 1 H, H-2), 4.49, 4.63 (AB-q, 2 H, *J* 11.5 Hz, CH_2Ph), 4.58–4.72 (m, 1 H, H-4), 4.83 (d, 1 H, *J* 3.4 Hz, H-1), 5.03–5.22 (m, 3 H, $H_2C=$, H-3''), 5.41 (dd, 1 H, 1 H, *J* 9.3, 10.7 Hz, H-3), 5.61–5.78 (m, 1 H, HC=), 6.84 (d, 1 H, *J* 9.3 Hz, NH), 7.10–7.42 (m, 15 H, Ph); i.r. (neat): 3350 (NH), 1735, 1670 cm^{-1}.

Anal. Calc. for $C_{76}H_{124}NO_{13}PSi$ (1318.9): C, 69.21; H, 9.48; N, 1.06; P. 2.35. Found: C, 69.37; H, 9.22; N, 1.05; P, 2.29.

Allyl 2-[(3R)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside 4-(diphenyl phosphate) (**7**). — To a solution of **6** (100 mg, 0.09 mmol) in THF (3 mL) was added 3N HCl (0.4 mL) with stirring. After 1 h at room temperature, the reaction mixture was concentrated and diluted with

EtOAc, washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a crude oil. The crude product was chromatographed on a silica gel column, eluting with 7:3 cyclohexane–EtOAc to give **7** (90 mg, 95%) as a gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.08–1.65 (m, 62 H), 2.15–2.53 (m, 6 H), 3.20–3.32 (m, 1 H, OH), 3.55–4.03 (m, 6 H, H-5, H-6,6a, OCH_2, H-3′), 4.30–4.42 (m, 1 H, H-2), 4.49, 4.55 (AB-q, 2 H, *J* 11.5 Hz, CH_2Ph), 4.75 (dd, 1 H, *J* 9.3, 19.3 Hz, H-4), 4.82 (d, 1 H, *J* 3.4 Hz, H-1), 5.06–5.23 (m, 3 H, $H_2C=$, H-3″), 5.43 (dd, 1 H, 1 H, *J* 9.3, 10.8 Hz, H-3), 5.62–5.78 (m, 1 H, CH=), 6.26 (d, 1 H, *J* 8.8 Hz, NH), 7.12–7.40 (m, 15 H, Ph); i.r. (Nujol): 3470 (OH), 3330 (NH), 1735, 1720, 1650 cm^{-1}.

Anal. Calc. for $C_{70}H_{110}NO_{13}P$ (1204.6): C, 69.80; H, 9.20; N, 1.16; P, 2.57. Found: C, 70.07; H, 9.20; N, 1.21; P, 2.30.

Allyl 2-[(3S)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside 4-(diphenyl phosphate) (**7′**). — Compound **6′** was treated as described above to give **7′** in 89% yield: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.05–1.65 (m, 62 H), 2.18–2.53 (m, 6 H), 3.23 (t, 1 H, *J* 7.3 Hz, OH), 3.51–4.05 (m, 6 H, H-5, H-6,6a, OCH_2, H-3′), 4.30–4.42 (m, 1 H, H-2), 4.50, 4.61 (AB-q, 2 H, *J* 11.5 Hz, CH_2Ph), 4.76 (dd, 1 H, *J* 9.6, 19.3 Hz, H-4), 4.88 (d, 1 H, *J* 3.4 Hz, H-1), 5.05–5.24 (m, 3 H, $H_2C=$, H-3″), 5.42 (dd, 1 H, 1 H, *J* 9.6, 10.5 Hz, H-3), 5.60–5.77 (m, 1 H, HC=), 6.87 (d, 1 H, *J* 8.8 Hz, NH), 7.12–7.40 (m, 15 H, Ph); i.r. (Nujol): 3450 (OH), 3320 (NH), 1730, 1650 cm^{-1}.

Anal. Calc. for $C_{70}H_{110}NO_{13}P$ (1204.6): C, 69.80; H, 9.20; N, 1.16; P, 2.57. Found: C, 70.07; H, 9.13; N, 1.16; P, 2.53.

Allyl 2-[(3R)-3-(benzyloxy)tetradecanamido]-2,6-dideoxy-6-fluoro-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside 4-(diphenyl phosphate) (**8**). — To a solution of DAST (40 mg, 0.23 mmol) in dry CH_2Cl_2 (1 mL) was gradually added a solution of **7** (70 mg, 0.06 mmol) in dry CH_2Cl_2 (1 mL) at 0–5° with stirring under nitrogen. After 3 h at 0°, followed by 30 min at room temperature, water was added to the reaction mixture and it was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a crude oil. The crude product was chromatographed on a silica gel column, eluting with 4:1 cyclohexane–EtOAc to give **8** (61 mg, 87%) as a gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.10–1.65 (m, 62 H), 2.15 (t, 2 H, *J* 7.6 Hz), 2.42 (d, 2 H, *J* 6.3 Hz), 3.70–4.07 (m, 4 H, H-5, OCH_2, H-3′), 4.27–4.55 (m, 3 H, H-2, H-6,6a), 4.49, 4.55 (AB-q, 2 H, *J* 11.5 Hz, CH_2Ph), 4.69 (dd, 1 H, *J* 9.3, 19.0 Hz, H-4), 4.84 (d, 1 H, *J* 3.9 Hz, H-1), 5.03–5.24 (m, 3 H, $H_2C=$, H-3″), 5.43 (dd, 1 H, *J* 9.3, 10.7 Hz, H-3), 5.63–5.80 (m, 1 H, HC=), 6.25 (d, 1 H, *J* 8.8 Hz, NH), 7.12–7.38 (m, 15 H, Ph); i.r. (Nujol): 3330 (NH), 1740, 1730, 1660 cm^{-1}.

Anal. Calc. for $C_{70}H_{109}FNO_{12}P$ (1206.6): C, 69.68; H, 9.11; F, 2.57; N, 1.16; P, 1.57. Found: C, 69.74; H, 9.08; F, 2.64; N, 1.03; P, 1.55.

Allyl 2-[(3S)-3-(benzyloxy)tetradecanamido]-2,6-dideoxy-6-fluoro-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside 4-(diphenyl phosphate) (**8′**). — Compound **7′** was treated as described above to give **8′** in 91% yield: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.08–1.60 (m, 62 H), 2.15 (t, 2 H, *J* 7.6 Hz), 2.32–2.52 (m, 4 H), 3.66–4.07 (m, 4 H, H-5, OCH_2, H-3′), 4.26–4.57 (m, 3 H, H-2, H-6,6a), 4.49, 4.61 AB-q, 2 H, *J* 11.5 Hz, C*H*$_2$Ph), 4.70 (dd, 1 H, *J* 9.3, 19.0 Hz, H-4), 4.89 (d, 1 H, *J* 3.4 Hz, H-1), 5.03–5.24 (m, 3 H; $H_2C=$, H-3″), 5.42 (dd, 1 H, 1 H, *J* 9.3, 10.7 Hz, H-3), 5.60–5.76 (m, 1 H; HC=), 6.88 (d, 1 H, *J* 8.8 Hz, NH), 7.12–7.40 (m, 15 H, Ph); i.r. (neat): 3350 (NH), 1740, 1674 cm^{-1}.

Anal. Calc. for $C_{70}H_{109}FNO_{12}P$ (1206.6): C, 69.68; H, 9.11; F, 2.57; N, 1.16; P, 1.57. Found: C, 69.88; H, 9.09; F, 2.58, N, 1.19; P, 1.60.

2-[(3R)-3-(Benzyloxy)tetradecanamido]-2,6-dideoxy-6-fluoro-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-(diphenyl phosphate) (**9**). — To a solution of **8** (460 mg, 0.37 mmol) in dry THF (10 mL, freshly distilled from $LiAlH_4$) was added $[C_8H_{12}Ir(PMePh_2)_2]PF_6$ (16 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 color solution of the iridium complex had become almost colorless, hydrogen was immediately replaced again with nitrogen. This solution was stirred for 2 h at 20°. After confirming the shift of the allylic double bond to that of an enol ether by t.l.c. (a slightly higher R_F is observed), H_2O (1 mL), pyridine (120 mg), and I_2 (190 mg) were added to this solution. After stirring for 30 min at 25°, the reaction mixture was concentrated, diluted with EtOAc, washed with aq. 5% Na_2SO_3, satd. $NaHCO_3$, and brine, dried ($MgSO_4$), and again concentrated to give a mixture that was separated on a silica-gel column. Elution with 3:1 cyclohexane–EtOAc gave **9** (371 mg, 85%) as a gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.07–1.72 (m, 62 H), 2.15 (t, 2 H, *J* 7.6 Hz), 2.25–2.45 (m, 5 H, containing OH), 3.82–4.25 (m, 3 H, H-2, H-5, H-3′), 4.42 (dd, 2 H, *J* 2.4, 46.9 Hz, H-6,6a), 4.39, 4.62 (AB-q, 2 H, *J* 11.2 Hz, C*H*$_2$Ph), 4.67 (dd, 1 H, *J* 9.3, 19.1 Hz, H-4), 5.04 (d, 1 H, *J* 3.4 Hz, H-1), 5.04–5.15 (m, 1 H, H-3″), 5.41 (dd, 1 H, *J* 9.3, 10.7 Hz, H-3), 6.22 (d, 1 H, *J* 8.8 Hz, NH), 7.12–7.40 (m, 15 H, Ph); i.r. (Nujol): 3400 (OH, NH), 1740, 1720, 1665 cm^{-1}.

Anal. Calc. for $C_{67}H_{105}FNO_{12}P$ (1166.5): C, 68.98; H, 9.07; F, 1.63; N, 1.20; P, 2.66. Found: C, 69.09; H, 9.26; F, 1.68; N, 1.15; P, 2.51.

2-[(3S)-3-(Benzyloxy)tetradecanamido]-2,6-dideoxy-6-fluoro-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-(diphenyl phosphate) (**9′**). — Compound **8′** was treated as described above to give **9′** in 90% yield: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.06–1.68 (m, 62 H), 2.15 (t, 2 H, *J* 7.6 Hz), 2.35 (d, 2 H, *J* 6.4 Hz), 2.42 (d, 2 H, *J* 5.9 Hz), 3.20 (d, 1 H, *J* 3.9 Hz, OH), 3.72–3.84 (m, 1 H, H-3′), 4.10–4.70 (m, 4 H, H-2, H-5, H-6,6a), 4.52, 4.58 (AB-q, 2 H, *J* 11.5 Hz, C*H*$_2$Ph), 4.70 (dd, 1 H, *J* 9.3, 19.0 Hz, H-4), 5.27 (d, 1 H, *J* 3.7 Hz, H-1), 5.50 (dd, 1 H, *J* 9.3, 10.7 Hz, H-3), 6.87 (d, 1 H, *J* 8.8 Hz, NH), 7.12–7.40 (m, 15 H, Ph); i.r. (Nujol): 3400 (OH, NH), 1735, 1720, 1665 cm^{-1}.

Anal. Calc. for $C_{67}H_{105}FNO_{12}P$ (1166.5): C, 68.98; H, 9.07; F, 1.63; N, 1.20; P, 2.66. Found: C, 69.04; H, 9.16; F, 1.60; N, 1.12; P, 2.53.

2,6-Dideoxy-6-fluoro-2-[(3R)-3-hydroxytetradecanamido]-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-(diphenyl phosphate) (**10**). — A solution of **9** (370 mg) in THF–MeOH (1:6, 28 mL) containing formic acid (30 mg) was hydrogenolyzed using 10% Pd/C catalyst (370 mg). After 3 h stirring, the reaction mixture was filtered, and the filtrate was concentrated to give a residue, which was chromatographed on a silica gel column. Elution with 13:7 cyclohexane–EtOAc gave **10** (220 mg, 65%) as a gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.10–2.10 (m, 64 H), 2.15–2.55 (m, 6 H), 3.86–3.98 (m, 1 H, H-3′), 4.12–4.30 (m, 2 H, H-2, H-5), 4.46 (dd, 2 H, *J* 2.4, 46.9 Hz, H-6,6a), 4.71 (dd, 1 H, *J* 9.3, 19.1 Hz, H-4), 5.03–5.15 (m, 1 H, H-3″), 5.38 (d, 1 H, 1 H, 3.4 Hz, H-1), 5.52 (dd, 1 H, *J* 9.3, 10.7 Hz, H-3), 6.58 (d, 1 H, *J* 8.3 Hz, NH), 7.12–7.40 (m, 10 H, Ph); i.r. (Nujol): 3450–3200 (OH, NH), 1740, 1642 cm^{-1}.

Anal. Calc. for $C_{60}H_{99}FNO_{12}P$ (1076.4): C, 66.95; H, 9.27; F, 1.76; N, 1.30; P, 2.88. Found: C, 67.00; H, 9.01; F, 1.73; N, 1.39; P, 2.88.

*2,6-Dideoxy-6-fluoro-2-[(3*S*)-3-hydroxytetradecanamido]-3-O-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-(diphenyl phosphate)* (**10′**). — Compound **9′** was treated as described above to give **10′** in 81% yield: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.10–1.60 (m, 62 H), 2.14–2.50 (m, 6 H), 3.43 (d, 1 H, *J* 3.4 Hz, OH), 3.50 (d, 1 H, *J* 2.9 Hz, OH), 3.85–4.30 (m, 3 H, H-2, H-5, H-3′), 4.45 (dd, 2 H, *J* 2.4, 46.9 Hz, H-6,6a), 4.70 (dd, 1 H, *J* 9.3, 19.0 Hz, H-4), 5.03–5.15 (m, 1 H, H-3″), 5.39 (d, 1 H, 3.4 Hz, H-1), 5.52 (dd, 1 H, *J* 9.3, 10.7 Hz, H-3), 6.61 (d, 1 H, *J* 8.8 Hz, NH), 7.12–7.37 (m, 10 H, Ph); i.r. (Nujol): 3600–3100 (OH, NH), 1730, 1660 cm^{-1}.

Anal. Calc. for $C_{60}H_{99}FNO_{12}P$ (1076.4): C, 66.95; H, 9.27; F, 1.76; N, 1.30; P, 2.88. Found: C, 67.03; H, 9.22; F, 1.71; N, 1.38; P, 2.70.

*2,6-Dideoxy-6-fluoro-2-[(3*R*)-3-hydroxytetradecanamido]-3-O-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-(dihydrogen phosphate)* (**11**). — A solution of **10** (135 mg) in THF (8 mL) was hydrogenolyzed using of PtO_2 (27 mg) as catalyst. After 1 h stirring, the reaction mixture was filtered, and concentrated to give **11** (107 mg, 92%) as a powder: ^{1}H-n.m.r. (C_5D_5N): δ 0.80–0.98 (m, 9 H), 1.12–1.95 (m, 62 H), 2.47 (t, 2 H, *J* 7.3 Hz), 2.79–2.92 (m, 2 H), 2.97–3.36 (m, 2 H), 3.62–3.70 (m, 1 H, H-3′), 4.45–5.80 (m, 7 H, H-1, H-2, H-4, H-5, H-6,6a, H-3″), 6.24 (dd, 1 H, *J* 9.3, 10.8 Hz, H-3), 8.88 (d, 1 H, *J* 9.8 Hz, NH); i.r. (Nujol): 3600–3200 (OH, NH), 1730, 1640 cm^{-1}.

Anal. Calc. for $C_{48}H_{91}FNO_{12}P$ (924.2): C, 62.38; H, 9.92; F, 2.06; N, 1.52; P, 3.35. Found: C, 62.10; H, 10.03; F, 1.99; N, 1.42; P, 3.05.

*2,6-Dideoxy-6-fluoro-2-[(3*S*)-3-hydroxytetradecanamido]-3-O-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-(dihydrogen phosphate)* (**11′**). — Compound **10′** was treated as described in the foregoing section to give **11′** in quantitative yield: ^{1}H-n.m.r. (C_5D_5N): δ 0.80–0.97 (m, 9 H), 1.10–1.90 (m, 62 H), 2.45 (t, 2 H, *J* 7.3 Hz), 2.84 (d, 2 H, *J* 5.9 Hz), 3.11 (dd, 1 H, *J* 6.4, 16.3 Hz), 3.27 (dd, 1 H, *J* 6.4, 16.3 Hz), 3.62–3.70 (m, 1 H, H-3′), 4.38–5.50 (m, 7 H, H-1, H-2, H-4, H-5, H-6,6a, H-3″), 6.25 (dd, 1 H, *J* 9.3, 10.9 Hz, H-3), 8.88 (d, 1 H, *J* 9.8 Hz, NH); i.r. (Nujol): 3600–3200 (OH, NH), 1730, 1700, 1650 cm^{-1}.

Anal. Calc. for $C_{48}H_{91}FNO_{12}P$ (924.2): C, 62.38; H, 9.92; F, 2.06; N, 1.52; P, 3.35. Found: C, 61.95; H, 10.00; F, 1.94; N, 1.49; P, 2.98.

*Allyl 6-O-(benzyloxycarbonyl)-2-[(3*R*)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside* (**12**). — To a solution of **4** (15.8 g, 16.3 mmol) in CH_2Cl_2 (240 mL) were added DMAP (3.0 g, 24.4

mmol) and $ClCOOCH_2Ph$ (3.3 g, 19.5 mmol) with stirring at ice-cooling temperatures. After 3 h at room temperature, the reaction mixture was concentrated and diluted with EtOAc (800 mL), washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a crude oil, which was chromatographed on a silica gel column. Elution with 4:1 cyclohexane–EtOAc gave 2.5 g of the bis(benzyloxycarbonyl)ated product, 1.3 g of starting material **4**, and **12** (11.3 g, 63%) as gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (m, 9 H), 1.10–1.70 (m, 62 H), 2.28 (t, 2 H, *J* 7.7 Hz), 2.35 (d, 2 H, *J* 5.9 Hz), 3.34 (d, 1 H, *J* 4.0 Hz, OH), 3.53–4.52 (m, 7 H), 4.20–4.35 (m, 1 H), 4.49, 4.56 (AB-q, 2 H, *J* 11.7 Hz), 4.77 (d, 1 H, *J* 3.7 Hz), 5.00–5.25 (m, 6 H), 5.62–5.78 (m, 1 H), 6.29 (d, 1 H, *J* 9.5 Hz, NH), 7.22–7.43 (m, 10 H); i.r. (Nujol) 3500 (OH), 3310 (NH), 1730 (ester), 1650 (amide) cm^{-1}.

Anal. Calc. for $C_{66}H_{107}NO_{12}$ (1106.5): C, 71.64; H, 9.75; N, 1.27. Found: C, 71.83; H, 9.80; N, 1.40.

Allyl 6-O-(benzyloxycarbonyl)-2-[(3S)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside (**12′**). — Compound **4′** was treated as described above to give **12′** in 65% yield as a powder: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz); 1.15–1.65 (m, 62 H), 2.28 (t, 2 H, *J* 7.5 Hz), 2.32–2.50 (m, 4 H), 3.33 (d, 1 H, *J* 4.0 Hz, OH), 3.55–4.52 (m, 8 H), 4.49, 4.57 (AB-q, 2 H, *J* 11.4 Hz), 4.83 (d, 1 H, *J* 3.3 Hz, H-1); 5.00–5.22 (m, 6 H), 5.60–5.77 (m, 1 H), 6.76 (d, 1 H, *J* 8.8 Hz, NH), 7.25–7.42 (m, 10 H); i.r. (Nujol): 3500, 3290, 1720, 1647 cm^{-1}.

Anal. Calc. for $C_{66}H_{107}NO_{12}$ (1106.5): C, 71.64; H, 9.75; N, 1.27. Found: C, 71.55; H, 9.81; N, 1.13.

Allyl 6-O-(benzyloxycarbonyl)-2-[(3R)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside 4-(diphenyl phosphate) (**13**). — To a solution of **12** (11.3 g, 10.2 mmol) and DMAP (7.5 g, 61.2 mmol) in CH_2Cl_2 (160 mL) was gradually added a solution of $(PhO)_2P(O)Cl$ (8.2 g, 30.6 mmol) in CH_2Cl_2 (70 mL) with stirring. After 1 h at room temperature, the reaction mixture was concentrated and diluted with EtOAc, washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a crude oil, which was chromatographed on a silica gel column. Elution with 7:3 cyclohexane–EtOAc gave **13** (6.1 g, 45%) as a gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.10–1.60 (m, 62 H), 2.15 (t, 2 H, *J* 7.3 Hz), 2.33 (d, 2 H, *J* 5.9 Hz), 2.42 (d, 2 H, *J* 6.2 Hz), 3.67–4.78 (m, 7 H), 4.48, 4.54 (AB-q, 2 H, *J* 11.4 Hz), 4.72 (dd, 1 H, *J* 9.2, 19.1 Hz, H-4), 4.80 (d, 1 H, *J* 3.3 Hz, H-1), 5.00–5.20 (m, 5 H), 5.40 (dd, 1 H, *J* 9.2, 10.6 Hz), 5.40 (dd, 1 H, *J* 9.2, 10.6 Hz, H-3), 5.62–5.77 (m, 1 H), 6.22 (d, 1 H, *J* 8.8 Hz, NH), 7.10–7.38 (m, 20 H); i.r. (Nujol): 3400, 1735, 1720, 1665 cm^{-1}.

Anal. Calc. for $C_{78}H_{116}NO_{15}P$ (1338.8): C, 69.98; H, 8.73; N, 1.05; P, 2.31. Found: C, 69.95; H, 8.71; N, 1.17; P, 2.10.

Allyl 6-O-(benzyloxycarbonyl)-2-[(3S)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranoside 4-(diphenyl phosphate) (**13′**). — Compound **12′** was treated as described above to give **13′** in 95% yield: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.10–1.65 (m, 62 H), 2.15 (t, 2 H, *J*

7.5 Hz), 2.30–2.51 (m, 4 H), 3.65–4.35 (m, 7 H), 4.49, 4.61 (AB-q, 2 H, *J* 11.4 Hz), 4.72 (dd, 1 H, *J* 9.2, 18.7 Hz, H-4), 4.85 (d, 1 H, *J* 3.3. Hz, H-1), 5.01–5.20 (m, 5 H), 5.39 (dd, 1 H, *J* 9.2, 10.6 Hz, H-3), 5.59–5.74 (m, 1 H), 6.86 (d, 1 H, *J* 8.8 Hz, NH), 7.10–7.40 (m, 20 H); i.r. ($CHCl_3$): 3350, 1745, 1650 cm^{-1}.

Anal. Calc. for $C_{78}H_{116}NO_{15}P$ (1338.8): C, 69.98; H, 8.73; N, 1.05; P, 2.31. Found: C, 70.28; H, 8.74; N, 1.00; P, 2.03.

6-O-(Benzyloxycarbonyl)-2-[(3R)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-(diphenyl phosphate) (**14**). — To a solution of **13** (1.05 g, 0.78 mmol) in THF (21 mL) was added $[C_8H_{12}Ir(PMePh_2)_2]PF_6$ (33 mg, 0.04 mmol). 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, at which time the red color solution of the iridium complex became almost colorless, hydrogen was immediately replaced again with nitrogen. This solution was stirred for 3 h at room temperature. After determining that the allylic double bond had shifted to that of an enol ether, as indicated by a slightly higher R_F value, H_2O (2 mL), pyridine (0.25 g, 3.2 mmol), and I_2 (0.4 g, 1.6 mmol) were added to this solution. After 30 min stirring, the reaction mixture was concentrated, diluted with EtOAc (150 mL), washed with 5% aq. Na_2SO_3, satd. $NaHCO_3$, and brine, dried over $MgSO_4$, and again concentrated to give a crude oil, which was chromatographed on a silica gel column. Elution with 7:3 cyclohexane–EtOAc gave **14** (0.92 g, 90%) as a gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.08–1.70 (m, 62 H), 2.10–2.22 (t, 2 H, *J* 7.3 Hz), 2.27–2.35 (m, 2 H), 2.38–2.44 (m, 2 H), 2.50 (dd, 1 H, *J* 1.1, 4.4 Hz, OH), 3.82–3.93 (m, 1 H), 4.10–4.39 (m, 4 H), 4.39, 4.60 (AB-q, 2 H, *J* 11.0 Hz), 4.68 (dd, 1 H, *J* 9.2, 18.3 Hz, H-4), 5.00–5.13 (m, 4 H), 5.39 (dd, 1 H, *J* 9.2, 11.0 Hz, H-3), 6.22 (d, 1 H, *J* 8.8 Hz, NH), 7.09–7.39 (m, 20 H); i.r. (Nujol): 3600–3100, 1735, 1650 cm^{-1}.

Anal. Calc. for $C_{75}H_{112}NO_{15}P$ (1298.6): C, 69.36; H, 8.69; N, 1.08; P, 2.39. Found: C, 69.35; H, 8.63; N, 1.20; P, 2.37.

6-O-(Benzyloxycarbonyl)-2-[(3S)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-D-glucopyranose 4-(diphenyl phosphate) (**14′**). — Compound **13′** was treated as described above to give **14′** in 88% yield as a gum: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.07–1.65 (m, 62 H), 2.16 (t, 2 H, *J* 7.7 Hz), 2.36 (d, 2 H, *J* 7.0 Hz), 2.41 (d, 2 H, *J* 7.7 Hz), 2.99 (dd, 1 H, *J* 1.5, 4.0 Hz, OH), 3.70–3.82 (m, 1 H), 4.13–4.38 (m, 4 H, H-2, H-5, H-6,6a), 4.52, 4.57 (AB-q, 2 H, *J* 11.0 Hz), 4.71 (dd, 1 H, *J* 9.2, 18.7 Hz, H-4), 4.97–5.25 (m, 4 H), 5.46 (dd, 1 H, *J* 9.2, 10.6 Hz, H-3), 6.86 (d, 1 H, *J* 8.4 Hz, NH), 7.08–7.40 (m, 20 H); i.r. (film): 3600–3200, 1748, 1640 cm^{-1}.

Anal. Calc. for $C_{75}H_{112}NO_{15}P$ (1298.6): C, 69.36; H, 8.69; N, 1.08; P, 2.39. Found: C, 69.40; H, 8.73; N, 1.00; P, 2.53.

6-O-(Benzyloxycarbonyl)-2-[(3R)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranosyl fluoride 4-(diphenyl phosphate) (**15**) *and 6-O-(benzyloxycarbonyl)-2-[(3R)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl fluoride 4-(diphenyl phosphate)* (**16**). — To a solution of **14** (2.74 g, 2.11 mmol) in

CH_2Cl_2 (25 mL) was gradually added a solution of DAST (1.36 g, 8.44 mmol) in CH_2Cl_2 (30 mL) at 0–5° with stirring. The mixture was stirred for 1 h at 0°. The reaction mixture was poured into ice–water (130 mL), and the organic layer was separated. The water layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was chromatographed on a silica gel column. Elution with 4:1 cyclohexane–EtOAc gave **15** (1.10 g, 40%, R_F 0.38) and **16** (1.14 g, 42%, R_F 0.28) as a powder, respectively. Compound **16**, as its solution in CH_2Cl_2 was converted to an unknown product (R_F 0.44) by the action of silica gel during a period of 24 h.

Compound **15**: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.10–1.67 (m, 62 H), 2.17 (t, 2 H, *J* 7.6 Hz), 2.30–2.47 (m, 4 H), 3.77–3.88 (m, 1 H), 4.08–4.42 (m, 4 H), 4.48, 4.56 (AB-q, 2 H, *J* 11.5 Hz), 4.81 (dd, 1 H, *J* 8.8, 18.1 Hz), 5.00–5.13 (m, 4 H), 5.01, 5.10 (AB-q, 2 H, *J* 11.7 Hz), 5.04–5.13 (m, 1 H), 5.38 (dd, 1 H, *J* 9.3, 11.2 Hz, H-3), 5.61 (dd, 1 H, *J* 2.4, 52.3 Hz, H-1), 6.51 (d, 1 H, *J* 8.3 Hz, NH), 7.10–7.40 (m, 20 H); i.r. (Nujol): 3380, 1740, 1660 cm^{-1}.

Anal. Calc. for $C_{75}H_{111}FNO_{14}P$ (1300.7): C, 69.26; H, 8.60; F, 1.46; N, 1.08; P, 2.38. Found: C, 69.11; H, 8.62; F, 1.42; N, 1.02; P, 2.35.

Compound **16**: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.10–1.65 (m, 62 H), 2.18 (t, 2 H, *J* 7.6 Hz), 2.32–2.44 (m, 4 H), 3.74–4.45 (m, 5 H), 4.47, 4.59 (AB-q, 2 H, *J* 11.5 Hz), 4.75 (dd, 1 H, *J* 8.8, 18.1 Hz), 5.03, 5.15 (AB-q, 2 H, *J* 12.2 Hz), 5.07–5.15 (m, 1 H), 5.26 (dd, 1 H, *J* 6.8, 51.8 Hz, H-1), 5.30–5.40 (m, 1 H, H-3), 6.56 (d, 1 H, *J* 8.3 Hz, NH), 7.10–7.38 (m, 20 H); i.r. (Nujol): 3320, 1745, 1725, 1662 cm^{-1}.

Anal. Calc. for $C_{75}H_{111}FNO_{14}P$ (1300.7): C, 69.26; H, 8.60; F, 1.46; N, 1.08; P, 2.38. Found: C, 69.25; H, 8.53; F, 1.44; N, 1.07, P, 2.51.

6-O-(Benzyloxycarbonyl)-2-[(3S)-3-(benzyloxy)tetradecanamido]-2-deoxy-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-α-D-glucopyranosyl fluoride 4-(diphenyl phosphate) (**15'**). — To a solution of **14'** (3.00 g, 2.31 mmol) in CH_2Cl_2 (30 mL) was gradually added a solution of DAST (1.49 g, 9.20 mmol) in CH_2Cl_2 (30 mL) at 0–5° with stirring. The mixture was stirred for 1 h at 0°, and then at room temperature for 30 min. The reaction mixture was poured into ice–water (150 mL), and the organic layer was separated. The water layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a 1:1 mixture of **15'** and **16'** as determined by t.l.c. [R_F 0.52 and R_F 0.46 (3:1 cyclohexane–EtOAc), respectively]. To this mixture, diluted with CH_2Cl_2 (100 mL), was added silica gel powder for chromatography (5.0 g, E. Merck No. 9385). The mixture was stirred for 16 h at room temperature to convert **16'** into **15'**. The silica gel was filtered off and washed with EtOAc. The combined organic layers were then concentrated to give a residue, which was quickly chromatographed on a silica gel column. Elution with 17:3 cyclohexane–EtOAc gave **15'** (2.40 g, 80%), which was not stable at room temperature: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.05–1.65 (m, 62 H), 2.17 (t, 2 H, *J* 7.3 Hz), 2.28–2.34 (m, 2 H), 2.44 (m, 2 H), 3.75–3.83 (m, 1 H), 4.10–4.42 (m, 4 H), 4.51, 4.56 (AB-q, 2 H, *J* 11.2 Hz), 4.82 (dd, 1 H, *J* 8.8, 18.1 Hz), 5.02–5.10 (m, 1 H), 5.02, 5.10 (AB-q, 2 H, *J* 12.0 Hz), 5.37 (dd, 1 H, *J* 9.3, 11.2 Hz, H-3), 5.69 (dd, 1 H, *J* 2.4, 52.7 Hz, H-1), 6.51 (d, 1 H, *J* 8.3 Hz, NH), 7.10–7.40 (m, 20 H); i.r. (Nujol): 3390, 1740, 1650 cm^{-1}.

Anal. Calc. for $C_{75}H_{111}FNO_{14}P$ (1300.7): C, 69.26; H, 8.60; F, 1.46; N, 1.08; P, 2.38. Found: C, 69.87; H, 8.62; F, 0.99; N, 1.10; P, 2.29.

*2-Deoxy-2-[(3*R*)-3-hydroxytetradecanamido]-3-O-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-*D*-glucopyranosyl fluoride 4-(diphenyl phosphate)* (**17**). — To a solution of **15** (400 mg) in THF (6 mL) was added 10% Pd/C (0.4 g) and MeOH (24 mL) containing formic acid (30 mg). The mixture was hydrogenolyzed. After 3 h stirring, the reaction mixture was filtered, and the filtrate was concentrated to give a residue that was rapidly chromatographed on a silica gel column. Elution with 3:2 cyclohexane–EtOAc gave **17** (101 mg, 30%) as a powder, which was unstable at room temperature: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.10–1.70 (m, 62 H), 1.77 (br s, 2 H, OH), 2.20–2.46 (m, 6 H), 3.52–3.96 (m, 4 H), 4.25–4.45 (m, 1 H), 4.83 (dd, 1 H, *J* 9.8, 19.5 Hz), 5.02–5.15 (m, 1 H), 5.44 (dd, 1 H, *J* 9.6, 11.0 Hz, H-3), 5.73 (dd, 1 H, *J* 2.9, 53.0 Hz, H-1), 6.66 (d, 1 H, *J* 7.8 Hz, NH), 7.10–7.42 (m, 10 H); i.r. (Nujol): 3550, 3420, 1732, 1646 cm^{-1}.

Anal. Calc. for $C_{60}H_{99}FNO_{12}P$ (1076.4): C, 66.95; H, 9.27; F, 1.76; N, 1.30; P, 2.88. Found: C, 66.58; H, 8.81; F, 1.59; N, 1.24; P, 2.73.

*2-Deoxy-2-[(3*S*)-3-hydroxytetradecanamido]-3-O-[(3*R*)-3-(tetradecanoyloxy)-tetradecanoyl]-α-*D*-glucopyranosyl fluoride 4-(diphenyl phosphate)* (**17′**). — Compound **15′** was treated as described above to give **17′** in 25% yield as a powder: ^{1}H-n.m.r. ($CDCl_3$): δ 0.88 (t, 9 H, *J* 6.4–6.8 Hz), 1.10–1.65 (m, 62 H), 2.20–2.45 (m, 6 H), 3.17–3.35 (m, 2 H, OH), 3.52–4.00 (m, 4 H), 4.22–4.45 (m, 1 H, H-2), 4.83 (dd, 1 H, *J* 9.5, 19.3 Hz), 5.03–5.17 (m, 1 H), 5.44 (dd, 1 H, *J* 9.5, 11.0 Hz, H-3), 5.73 (dd, 1 H, *J* 2.4, 52.7 Hz, H-1), 6.63 (d, 1 H, *J* 8.3 Hz, NH), 7.12–7.42 (m, 10 H); i.r. (Nujol): 3600–3100, 1740, 1720, 1645 cm^{-1}.

Anal. Calc. for $C_{60}H_{99}FNO_{12}P$ (1076.4): C, 66.95; H, 9.27; F, 1.76; N, 1.30; P, 2.88. Found: C, 67.04; H, 8.98; F, 1.58; N, 1.37; P, 3.06.

*2-Deoxy-2-[(3*R*)-3-hydroxytetradecanamido]-3-O-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-α-*D*-glucopyranosyl fluoride 4-(dihydrogen phosphate)* (**18**). — A solution of **17** (85 mg) in THF (5 mL) was hydrogenolyzed using PtO_2 (17 mg) as catalyst. After 4 h stirring at room temperature, the reaction mixture was filtered at 45° through Celite to give **18** (72 mg, 97%) as a powder: ^{1}H-n.m.r. (C_5D_5N): δ 0.82–0.95 (m, 9 H), 1.15–1.90 (m, 62 H), 2.48 (t, 2 H, *J* 7.3 Hz), 2.80–2.90 (m, 2 H), 3.06–3.30 (m, 2 H), 3.75–4.60 (m, 7 H), 5.00–5.25 (m, 1 H, H-4), 5.65–5.76 (m, 1 H), 5.97 (dd, 1 H, *J* 2.4, 52.5 Hz, H-1), 6.06 (dd, 1 H); i.r. (Nujol): 3250, 1722, 1645 cm^{-1}.

Anal. Calc. for $C_{48}H_{91}FNO_{12}P$ (924.2): C, 62.38; H, 9.92; F, 2.06; N, 1.52; P, 3.35. Found: C, 62.25; H, 9.58; F, 1.83; N, 1.20; P, 3.09.

*2-Deoxy-2-[(3*S*)-3-hydroxytetradecanamido]-3-O-[(3*R*)-3-(tetradecanoyloxy)-tetradecanoyl]-α-*D*-glucopyranosyl fluoride 4-(dihydrogen phosphate)* (**18′**). — Compound **17′** was treated as described above to give **18′** in 87% yield as a powder: ^{1}H-n.m.r. (C_5D_5N): δ 0.80–0.97 (m, 9 H), 1.10–1.90 (m, 62 H), 2.46 (t, 2 H, *J* 7.3 Hz), 2.82 (d, 2 H, *J* 5.9 Hz), 3.04–3.25 (m, 2 H), 3.60–3.70 (m, 1 H), 3.80–4.55 (m, 6 H), 5.65–5.77 (m, 1 H), 6.00–6.10 (m, 1 H, H-3), 6.10 (dd, 1 H, *J* 2.9, 53.7 Hz, H-1); i.r. (Nujol): 3550, 3300, 1730, 1650 cm^{-1}.

Anal. Calc. for $C_{48}H_{91}FNO_{12}P$ (924.2): C, 62.38; H, 9.92; F, 2.06; N, 1.52; P, 3.35. Found: C, 61.81; H, 9.93; F, 1.87; N, 1.34; P, 3.25.

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