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Synthesis of a 3-ether analogue of lipid A

Masao Shiozaki*, Yoshiyuki Kobayashi, Masami Arai, Noboru Ishida, Tetsuo Hiraoka,
New Lead Research Laboratories, Sankyo Co., Ltd., Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140 (Japan)
Masahiro Nishijima, Sayuri Kuge, Toshiaki Otsuka, and Yuzuru Akamatsu
Department of Chemistry, National Institute of Health, Kamiosaki 2-10-35, Shinagawa-ku, Tokyo 141 (Japan)

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ABSTRACT

Lipid A 3-ether analogues were synthesized from allyl 2-deoxy-4,6-*O*-isopropylidene-2-trifluoroacetamido-α-D-glucopyranoside and 3,4,6-tri-*O*-acetyl-2-trifluoroacetamido-α-D-glucopyranosyl bromide. The compound lost completely the endotoxic activity.

INTRODUCTION

In a continuation[1] of our studies on the synthesis and evaluation of analogues of lipid A, herein is described a synthesis of 3-*O*-alkyl lipid A derivatives. Lipid A, while it may vary slightly in structure from species to species and even within species, is basically a peracylated (1→6)-β-linked disaccharide of D-glucosamine 1,4′-bisphosphate[2,3] as shown in Fig. 1. Ether derivatives are principally designed to resist acyl-group cleavage by macrophage enzymes. Such compounds should be stable and lipophilic, and could possibly retain much of the biological activity of lipid A and its analogues.

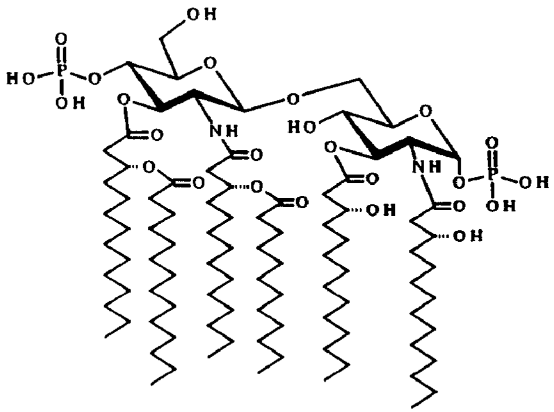

Fig. 1. Structure of lipid A of *E. coli*.

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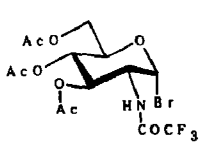

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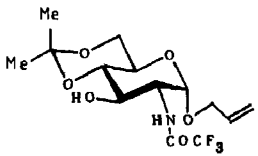

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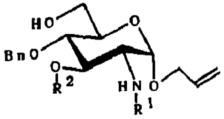
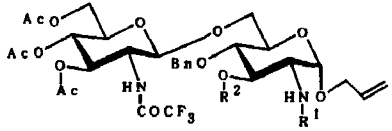


3a R^1 = trifluoroacetyl
R^2 = (RS)-3-(benzyloxy)decanyl

3b R^1 = (R)-3-(benzyloxy)tetradecanoyl
R^2 = (R)-3-(benzyloxy)tetradecanyl



4a R^1 = trifluoroacetyl
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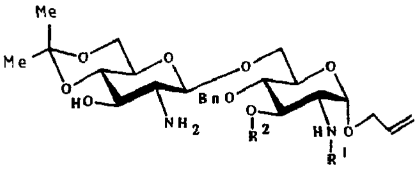
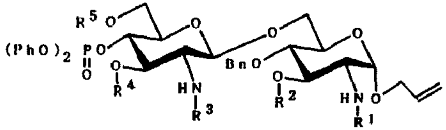


5a R^1 = H
R^2 = (RS)-3-(benzyloxy)decanyl

5b R^1 = (R)-3-(benzyloxy)tetradecanoyl
R^2 = (R)-3-(benzyloxy)tetradecanyl



6a R^1 = R^3 = R^4 = (R)-3-(benzyloxy)tetradecanoyl
R^2 = (RS)-3-(benzyloxy)decanyl
R^5 = benzyloxycarbonyl

6b R^1 = (R)-3-(benzyloxy)tetradecanoyl
R^2 = (R)-3-(benzyloxy)tetradecanyl
R^3 = (R)-3-(dodecanoyloxy)tetradecanoyl
R^4 = (R)-3-(tetradecanoyloxy)tetradecanoyl
R^5 = benzyloxymethyl

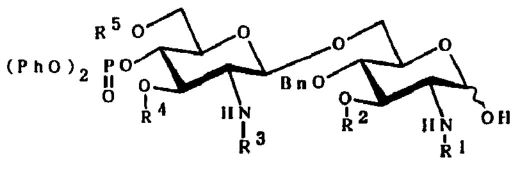
RESULTS AND DISCUSSION

Synthesis. — As demonstrated in the preceeding paper[1], allyl 2-deoxy-4,6-*O*-isopropylidene-2-trifluoroacetamido-α-D-glucopyranoside proved to be a useful intermediate for O-3 alkylation[1]. The trifluoroacetamido group was stable towards base required in the alkylation step, producing none of the undesired elimination products on the acyl group as had been observed with a 2-[(*R*)-3-(benzyloxy)tetradecanamido] intermediate[1]. Furthermore, the *N*-trifluoroacetyl group was easily removed using methanolic sodium hydroxide. Thus for the synthesis of analogues of lipid A, a glycosyl donor 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl bromide (**1**) was prepared from 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside[4] by the sequence of (*i*) *N*-trifluoroacetylation with trifluoroacetic anhydride in pyridine and (*ii*) subsequent reaction with 30% HBr in HOAc.

The glycosyl acceptors **3a** and **3b** were prepared from the α-glycoside intermediate **2** which was described in the preceding paper[1]. Compound **2** was converted to **3a** as follows: (*i*) Alkylation of **2** at O-3 with (*RS*)-3-benzyloxy-1-methanesulfonyloxydecane–NaH in *N,N*-dimethylformamide (DMF); (*ii*) removal of the 4,6-*O*-isopropylidene group with 80% AcOH at 60°; (*iii*) monoacetylation of the diol at O-6 with pyridine–Ac_2O in THF at 5°; (*iv*) benzylation at O-4 with trichloroacetimidate and trifluoromethanesulfonic acid in CH_2Cl_2; (*v*) deacetylation at O-6 with NH_4OH in MeOH to give **3a**. By a similar process, **2** was converted to **3b** as in the following: (*i*) Alkylation of **2** at O-3 with (*R*)-3-benzyloxy-1-methanesulfonyloxytetradecane in DMF using NaH as a base; (*ii*) removal of the 4,6-*O*-isopropylidene group with 80% AcOH at 60°; (*iii*) monoacetylation at O-6 of the diol with pyridine–Ac_2O in THF at 5°; (*iv*) benzylation at O-4 with $PhCH_2Br$–NaH in DMF; (*v*) deacetylation at O-6 with NH_4OH–MeOH; (*vi*) *N*-detrifluoroacetylation with M NaOH in EtOH; and (*vii*) *N*-acylation of the resulting 2-amino-6-hydroxy sugar derivative with (*R*)-3-(benzyloxy) tetradecanoic acid and DCC to give **3b**.

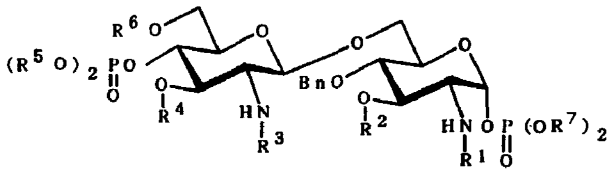
Glycosidation of **1** with both **3a** and **3b**, using $Hg(CN)_2$–$CaSO_4$[3,5] in $CHCl_3$, gave **4a** and **4b**, respectively. Compounds **4a** and **4b** were further converted to **5a** and **5b** in three steps as follows: (*i*) Treatment of **4a** in MeOH and NH_4OH gave a triol, (*ii*) the triol was converted to the 4,6-*O*-isopropylidene compound with 2,2-dimethoxypropane in DMF containing a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS), and the two *N*-trifluoroacetyl groups were removed with M NaOH in EtOH to give diamine **5a**. Compound **4b** was also converted to the amino compound **5b** by the same procedure.

Compounds **5a** and **5b** were converted to **6a** and **6b**, respectively, in five steps, as follows: For **6b**, (*i*) *N*-Diacylation of **5a** with (*R*)-3-(benzyloxy)tetradecanoic acid, using DCC and DMAP; (*iii*) removal of the 4,6-*O*-isopropylidene group with 90% AcOH; (*iv*) benzyloxycarbonylation at O-6 with benzyl chloroformate and DMAP in CH_2Cl_2; and, finally, (*v*) diphenylphosphorylation at O-4 with diphenyl chlorophosphate and DMAP in CH_2Cl_2 to give **6a**. For **6b** treatment of **5b** with (*R*)-3-(dodecanoyloxy)tetradecanoic acid using DCC in CH_2Cl_2 to give the *N*-acyl compound; (*ii*) *O*-acylation of the resulting *N*-acylated compound with (*R*)-3-(tetradecanoyloxy)tetradecanoic acid using DCC



7a $R^1 = R^3 = R^4 =$ (*R*)-3-(benzyloxy)tetradecanoyl
$R^2 =$ (*RS*)-3-(benzyloxy)decanyl
$R^5 =$ benzyloxycarbonyl

7b $R^1 =$ (*R*)-3-(benzyloxy)tetradecanoyl
$R^2 =$ (*R*)-3-(benzyloxy)tetradecanyl
$R^3 =$ (*R*)-3-(dodecanoyloxy)tetradecanoyl
$R^4 =$ (*R*)-3-(tetradecanoyloxy)tetradecanoyl
$R^5 =$ benzyloxymethyl



8a $R^1 = R^3 = R^4 =$ (*R*)-3-(hydroxy)tetradecanoyl
$R^2 =$ (*RS*)-3-(hydroxy)decanyl
$R^5 = R^6 = R^7 = H$

8b $R^1 =$ (*R*)-3-(benzyloxy)tetradecanoyl
$R^2 =$ (*R*)-3-(benzyloxy)tetradecanyl
$R^3 =$ (*R*)-3-(dodecanoyloxy)tetradecanoyl
$R^4 =$ (*R*)-3-(tetradecanoyloxy)tetradecanoyl
$R^5 =$ phenyl, $R^6 =$ benzyloxymethyl, $R^7 =$ benzyl

9b $R^1 =$ (*R*)-3-(hydroxy)tetradecanoyl
$R^2 =$ (*R*)-3-(hydroxy)tetradecanyl
$R^3 =$ (*R*)-3-(dodecanoyloxy)tetradecanoyl
$R^4 =$ (*R*)-3-(tetradecanoyloxy)tetradecanoyl
$R^5 = R^6 = R^7 = H$

and DMAP in CH_2Cl_2; (*iii*) removal of the 4,6-*O*-isopropylidene group with 80% AcOH; (*iv*) benzyloxymethylation[6] at O-6 with benzyl chloromethyl ether using *N,N*-tetramethylurea as a condensing agent in CH_2Cl_2; (*v*) diphenylphosphorylation at O-4 with diphenyl chlorophosphate and DMAP in CH_2Cl_2 to give **6b**.

Treatment of the allyl glycosides **6a** and **6b** with bis(methyldiphenylphosphine) cyclo-octadieneiridium(I) hexafluorophosphate[7], followed by hydrolysis with pyridine–H_2O–I_2[8], gave **7a** and **7b**, respectively.

Treatment of **7a** with BuLi and dibenzyl chlorophosphate[9] in THF at −78° gave the α anomer of the dibenzyl phosphate[10], which was hydrogenolyzed with 10% Pd/C, then with PtO_2[11] to give **8a**. Similar treatment of **7b** with BuLi and $Cl(O)P(OBn)_2$ gave **8b**. However, attempted debenzylation of **8b** with 10% Pd/C and removal of the phenyl groups with PtO_2 gave, instead of **9b**, a markedly less polar, unknown compound.

Biological activity. — The biological activity of lipopolysaccharides (LPS), lipid A, and many related compounds, which induce morphological changes (spreading), prostaglandin synthesis, and killing of tumor cells by mouse peritoneal macrophages *in vitro, etc.*, have been investigated[12]. However, the C-3 ether **8a** completely lost these activities in an assay in the macrophage-like mouse cell line J774.1.

EXPERIMENTAL

General methods. — See preceding paper[1]. ^{1}H-N.m.r. spectra at 60 MHz were recorded on a Varian EM-360L instrument.

3,4,6-Tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl bromide (**1**). — To a solution of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside[4] (4.5 g, 13 mmol) in pyridine (30 mL) was added trifluoroacetic anhydride (6 mL). After 10 min at 20°, the mixture was concentrated *in vacuo*, and diluted with EtOAc. The solution was washed with dil. aq. HCl, H_2O, aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a crystalline solid (5.6 g) which was washed with EtOAc–hexane. The solid thus obtained was dissolved in AcOH (10 mL), and to this solution was added 30% HBr in AcOH (13 mL). After 5 min at 20°, the mixture was diluted with EtOAc, washed with aq. $NaHCO_3$ (several times) and brine, and concentrated *in vacuo* to give an oily product which was chromatographed on a silica gel column. Elution with 2:1 cyclohexane–EtOAc gave 4.3 g (72%) of **1** as a gum. This compound was shown to gradually decompose at room temperature during a few days. ^{1}H-N.m.r. (60 MHz, $CDCl_3$): δ 2.05 (s, 6 H), 2.10 (s, 3 H), 4.1–4.6 (m, 4 H), 5.0–5.7 (m, 2 H), 6.54 (d, 1 H, *J* 4 Hz, H-1), 6.86 (d, 1 H, *J* 8 Hz, NH); i.r. ν_{max}^{film} 3300, 1780–1700 cm^{-1}; m.s. *m/z* 384 (M^+ − HBr), 264, 222.

Anal. Calc. for $C_{14}H_{17}BrF_3NO_8$: C, 36.23; H, 3.69; N, 3.02. Found: C, 36.44; H, 3.47; N, 3.30.

(RS)-3-Benzyloxy-1-methanesulfonyloxydecane. — (*i*) To a solution of $HN(SiMe_3)_2$ (101 g, 0.626 mol) in THF (1.0 L) was added a solution of BuLi (1.6M, in hexane, 391 mL, 0.626 mol) at 0–15° with stirring. To this solution was added a solution of trimethyl phosphonoacetate (95 g, 0.522 mol) in THF (500 mL) with stirring under

nitrogen at -60 to $-50°$. After 10 min, a solution of octanal (66.9 g, 0.522 mol) in THF (300 mL) was added, and the temperature of the reaction mixture was elevated gradually to $-10°$, and then the reaction mixture was quenched with a solution of AcOH (40 g, 0.666 mol) in THF (200 mL), concentrated *in vacuo*, diluted with EtOAc (2 L), washed with H_2O, satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give 96 g of a 1:1 mixture of (*E*)- and (*Z*)-methyl deca-2-enoate, (*E*-isomer, R_F = 0.39; *Z*-isomer, R_F = 0.54; 1:1 cyclohexane–benzene). This mixture was employed for the next reaction without purification. (*ii*) To a solution of the α,β-unsaturated decanoate (96 g, 0.521 mol) in benzyl alcohol (240 mL) was added a catalytic amount of 70% $HClO_4$ (1.8 mL), then $Hg(OAc)_2$ (200 g, 0.628 mol) at 20–25°. After 30 min, the reaction mixture was diluted with absolute EtOH (1.4 L), and $NaBH_4$ (60 g, 1.58 mol) was added gradually to this solution at 15–20° with stirring. After 1 h at 15°, the reaction mixture was quenched with 10% HCl (540 mL), concentrated *in vacuo*, extracted with EtOAc (2 L), washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* (finally at 100°/0.5 mm Hg to remove benzyl alcohol) to give 145 g of an oily residue, which was chromatographed on a silica gel (1.45 kg) column. Elution with 9:1 cyclohexane–EtOAc gave 111 g (73%) of ($\pm$)-methyl 3-benzyloxydecanoate (R_F = 0.48). (*iii*) To a solution of the product obtained above (111 g, 0.380 mol) in THF (730 mL) was added gradually $LiAlH_4$ (14.4 g, 0.379 mol) at 10–15° with stirring. The reaction mixture was poured into ice water (4 L) containing conc. HCl (48 mL). The mixture was extracted with EtOAc. This solution was washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 97.4 g (97%) of ($\pm$)-3-benzyloxy-1-hydroxydecane, which was employed for the next reaction without further purification. (*iv*) To a solution of the alcohol obtained above (97 g, 0.367 mol) in CH_2Cl_2 (1.5 L) was added Et_3N (59 g, 0.583 mol) and a solution of $MeSO_2Cl$ (58 g, 0.506 mol) in CH_2Cl_2 (300 mL) at 20–24° with stirring. After 1 h at room temperature, the reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The solution was washed with 10% HCl, H_2O, satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a residue, which was chromatographed on a silica gel column. Elution with 7:3 cyclohexane–EtOAc gave 115 g (91%) of ($\pm$)-3-benzyloxy-1-methanesulfonyloxydecane: (R_F = 0.60); ^{1}H-n.m.r. (60 MHz, $CDCl_3$): δ 0.8–1.0 (m, 3 H), 1.0–1.7 (m, 12 H), 1.7–2.1 (m, 2 H), 2.91 (s, 3 H), 3.56 (m, 1 H), 4.2–4.7 (m, 4 H), 7.33 (s, 5 H); i.r. ν_{max}^{film} 2940, 2860, 1720–1700 (w) cm^{-1}; m.s. *m/z* 342 (M^+), 246, 203, 147.

*Allyl 4-O-benzyl-3-O-[(3*RS*)-3-(benzyloxy)decanyl]-2-deoxy-2-trifluoroacetamido-α-D-glucopyranoside* (**3a**). — (*i*) To a stirred solution of **2** (8.00 g, 22.5 mmol; for preparation, see ref. 1) and ($\pm$)-3-benzyloxy-1-methanesulfonyloxydecane (7.7 g, 22.5 mmol) in DMF (50 mL) was gradually added NaH (55% oil dispersion, 3.3 g, 250 mmol) at 0–5°. After stirring for 3 h at 20–25°, the mixture was diluted with EtOAc, and the excess NaH was quenched (caution!) with AcOH (24 mL). The whole was washed with aq. $NaHCO_3$ and brine, dried over $MgSO_4$, decolorized with activated charcoal, filtered through Celite, and concentrated *in vacuo* to give an oily mixture, which was purified on a silica gel column. Elution with 5:1 cyclohexane–EtOAc yielded 6.7 g (49%) of the 3-*O*-[3-(benzyloxy)decanyl] ether.

(*ii*) A solution of the ether (6.7 g) in 80% AcOH (70 mL) was kept for 30 min at 60°, then concentrated *in vacuo* to give 6.2 g (99%) of diol as a solid, which was used in the next reaction without purification.

(*iii*) To a solution of the crude diol (6.2 g) in THF (40 mL) and pyridine (2.5 mL) was added with stirring Ac_2O (1.2 g, 1.1 equiv.) at 0–5°. The mixture was maintained for 30 min at this temperature, then at 25° for 15 h. The solution was then concentrated *in vacuo* to give a mixture that was chromatographed on a silica gel column. Elution with 2:1 cyclohexane–EtOAc gave a small amount of diacetate (R_F = 0.47) and 5.8 g (87%) of the 6-*O*-acetyl compound (R_F = 0.40).

(*iv*) To a solution of the monoacetyl compound (5.8 g) and benzyl trichloroacetimidate (4.8 g) in CH_2Cl_2 (50 mL) was added CF_3SO_3H (0.2 g) under nitrogen at 20°. After 15 h, the solution was concentrated to 10 mL and diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and again concentrated to give a mixture to which cyclohexane (25 mL) was added. The mixture was filtered to remove crystalline Cl_3CCONH_2 and concentrated to give a crude product which was chromatographed on a silica gel column. Elution with 4:1 cyclohexane–EtOAc gave 2.0 g (31%) of the 4-*O*-benzyl product.

(*v*) A solution of the 4-*O*-benzyl product (2.0 g) in MeOH (85 mL) and NH_4OH (9.5 mL) was allowed to stand for 15 h. The reaction mixture was concentrated *in vacuo* to give an oily product which was purified on a silica gel column. Elution with 2:1 cyclohexane–EtOAc gave **3a** (1.0 g, 55%, 7.3% over five steps); ^{1}H-n.m.r. (60 MHz, $CDCl_3$): δ 0.8–2.0 (m, 17 H), 3.4–6.2 (m, 20 H), 6.44 (d, 1 H, *J* 10 Hz, NH), 7.32 (s, 10 H); i.r. $\nu_{max}^{CHCl_3}$ 3600, 3420, 1730, 1530, 1495, 1450 cm^{-1}; m.s. *m*/*z* 652 (M^+), 594, 560, 502, 454, 396, 348, 268.

Anal. Calc. for $C_{35}H_{48}F_3NO_7$: C, 64.50; H, 7.42; F, 8.74; N, 2.15. Found: C, 64.79; H, 7.29; F, 8.54; N, 2.27.

*Allyl 4-O-benzyl-2-[(3*R*)-3-(benzyloxy)tetradecanamido]-3-O-[(3*R*)-3-(benzyloxy)tetradecanyl]-2-deoxy-α-*D*-glucopyranoside* (**3b**). — (*i*) To a solution of **2** (18.7 g, 52.7 mmol) and (3*R*)-3-benzyloxy-1-methanesulfonyloxytetradecane (21.0 g, 52.7 mmol; for preparation, see ref. 1) in DMF (150 mL) was gradually added NaH (55% oil dispersion, 6.9 g, 3 equiv.) at 0–5° with stirring. After stirring 3 h at 25°, the mixture was diluted with EtOAc, quenched with AcOH, washed with aq. $NaHCO_3$ and brine, filtered, and concentrated to give 42.1 g of the crude 3-*O*-[3-(benzyloxy)tetradecanyl] ether, which was employed for the next reaction without purification.

(*ii*) A solution of the crude ether (42.1 g) in 80% AcOH (180 mL) was stirred for 1.5 h at 50° and concentrated *in vacuo* to give an oily residue which was chromatographed on a silica gel column. Elution with 3:1, then 1:1 cyclohexane–EtOAc to give 19.6 g (60%, two steps) of the diol as a gum.

(*iii*) To a solution of diol (19.6 g, 31.7 mmol) in THF (150 mL) and pyridine (7.2 mL) was added dropwise a solution of Ac_2O (3.25 mL, 31.7 mmol) in THF (25 mL) at 0–5°. After 15 min, the mixture was allowed to stand overnight at 20°, and then it was concentrated to give a mixture which was chromatographed on a silica gel column. Elution with 3:1 cyclohexane–EtOAc gave 0.82 g (3.7%) of diacetate (R_F = 0.41), 16.5 g

(79%) of the 6-*O*-acetyl compound (R_F = 0.29), and 2.4 g (12%) of recovered starting material.

(*iv*) To a solution of the 4-hydroxy compound (16.5 g, 25.0 mmol) and benzyl bromide (8.5 g, 50.0 mmol) in DMF (300 mL) was added with stirring NaH (55% oil dispersion, 3.3 g, 3 equiv.) at −20°. After 1 h at −10°, the mixture was stirred for 30 min at 25°, quenched with ice water, and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give 17.1 g of a crude oily 4-*O*-benzyl compound, which was employed for the next reaction without purification.

(*v*) A solution of the crude benzylated product (17.1 g) in MeOH (600 mL) and NH_4OH (67 mL) was allowed to stand for 15 h. The reaction mixture was concentrated, diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated to give a crude material which was purified by chromatography on a silica gel column. Elution with 3:1 cyclohexane–EtOAc gave 8.7 g (49%, two steps) of the 6-hydroxy compound (R_F = 0.28) as a gum.

(*vi*) A solution of the material obtained above (8.7 g, 12.3 mmol) in EtOH (140 mL) and M NaOH (60 mL) was heated under reflux for 3 h, and the mixture was then concentrated *in vacuo*, diluted with EtOAc, washed with H_2O and brine, and again concentrated to give a residue which was purified by chromatography on a silica gel column. Elution with EtOAc gave 6.87 g (91%) of the 2-amino-6-hydroxy compound as a gum.

(*vii*) To a solution of the amino sugar (6.85 g, 11.2 mmol) and (3*R*)-3-(benzyloxy)-tetradecanoic acid (4.11 g, 12.3 mmol, 1.1 equiv.) in CH_2Cl_2 (300 mL) was added DCC (2.74 g, 13.4 mmol, 1.2 equiv.) at 25° with stirring. After 30 min, the mixture was filtered to remove *N,N'*-dicyclohexylurea, and the filtrate was concentrated, diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and again concentrated to give a crude gum which was purified by chromatography on a silica gel column. Elution with 2:1 cyclohexane–EtOAc gave **3b** (9.80 g, 94%; 19.9% over seven steps) as a gum; ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 0.85–0.90 (m, 6 H), 1.08–1.90 (m, 42 H), 2.26–2.43 (m, 2 H), 3.41–3.87 (m, 11 H), 4.01 (dd, 1 H, *J* 5.5, 12.8 Hz), 4.16–4.20 (m, 1 H), 4.29, 4.45 (AB-q, 2 H, *J* 11.70 Hz, CH_2Ph), 4.48, 4.54 (AB-q, 2 H, *J* 11.36 Hz, CH_2Ph), 4.61, 4.83 (AB-q, 2 H, *J* 10.99 Hz, CH_2Ph), 4.76 (d, 1 H, *J* 3.66 Hz, H-1), 5.09–5.21 (m, 2 H), 5.68–5.81 (m, 1 H), 6.42 (d, 1 H, *J* 9.16 Hz, NH), 7.23–7.33 (m, 15 H); i.r. ν_{max}^{KBr} 1640, 1548 cm^{-1}; m.s. *m/z* 819, 762, 728, 713, 670, 622, 548, 516, 478, 370.

Anal. Calc. for $C_{58}H_{89}NO_8$: C, 75.04; H, 9.66; N, 1.51. Found: C, 74.70; H, 9.65; N, 1.75.

*Allyl 6-O-[(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido)-β-*D*-glucopyranosyl]-4-O-benzyl-3-O-[(3*RS*)-3-(benzyloxy)decanyl]-2-deoxy-2-trifluoroacetamido-α-*D*-glucopyranoside* (**4a**). — A mixture of the glycosyl bromide **1** (1.93, 4.2 mmol), alcohol **3a** (1.36 g, 2.1 mmol), anhydr. $CaSO_4$ (0.7 g, 5 mmol, powder) and $Hg(CN)_2$ (1.06 g, 4.2 mmol) in $CHCl_3$ (40 mL, freshly passed through Al_2O_3) was refluxed for 15 h, diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated to give an oily mixture which was chromatographed on a silica gel column. Elution with 7:3 cyclohexane–EtOAc gave 1.83 g (85%) of disaccharide **4a** as a gum; ^{1}H-n.m.r. (60 MHz, $CDCl_3$): δ 0.7–2.2 (m, 17 H), 2.03 (m, 9 H), 3.1–6.2 (m, 26 H), 6.3–6.9 (m, 2 H), 7.29 (s, 10 H); i.r. $\nu_{max}^{CHCl_3}$ 1740 cm^{-1}; m.s. *m/z* 1034 (M^+), 943, 870, 779, 605, 544, 502, 454, 384, 264, 180, 91.

Anal. Calc. for $C_{49}H_{64}N_2F_6O_{15}$: C, 56.86; H, 6.23; F, 11.01; N, 2.71. Found: C, 56.55; H, 6.21; F, 10.87; N, 2.75.

Allyl 6-O-[(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido)-β-D-glucopyranosyl]-4-O-benzyl-2-[(3R)-(benzyloxy)tetradecanamido]-3-O-[(3R)-3-(benzyloxy)tetradecanyl]-2-deoxy-α-D-glucopyranoside (**4b**). — A mixture of the glycosyl bromide **1** (8.85 g, 19.1 mmol), alcohol **3b** (5.90 g, 6.36 mmol), anhydr. $CaSO_4$ (2.60 g, 19.1 mmol, powder), and $Hg(CN)_2$ (4.82 g, 19.1 mmol) in $CHCl_3$ (250 mL, freshly passed through Al_2O_3) was heated under reflux for 5 h with stirring. The reaction mixture was filtered, and the filtrate was diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to an oily mixture which was chromatographed on a silica gel column. Elution with 3:2 cyclohexane–EtOAc gave 6.41 g (74%) of disaccharide **4b** as a gum; ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 0.88 (t, 6 H, *J* 6.2–6.9 Hz), 1.17–1.86 (m, 42 H), 2.02 (s, 3 H), 2.03 (s, 3 H), 2.04 (s, 3 H), 2.27–2.43 (m, 2 H), 3.28–3.83 (m, 10 H), 3.96–4.30 (m, 6 H), 4.38, 4.43 (AB-q, 2 H, *J* 11.7 Hz), 4.44–4.56 (m, 3 H), 4.63–4.82 (m, 3 H), 5.06–5.29 (m, 4 H), 5.77 (m, 1 H), 6.46 (d, 1 H, *J* 9.5 Hz, NH), 6.70 (d, 1 H, *J* 8.8 Hz, NH), 7.23–7.32 (m, 15 H); i.r. ν_{max}^{KBr} 1752, 1714, 1643 cm^{-1}.

Anal. Calc. for $C_{72}H_{105}F_3N_2O_{16}$: C, 65.93; H, 8.07; F, 4.35; N, 2.14. Found: C, 65.40; H, 8.02; F, 4.47; N, 2.26.

Allyl 2-amino-6-O-[(2-amino-2-deoxy-4,6-O-isopropylidene)-β-D-glucopyranosyl]-4-O-benzyl-3-O-[(3RS)-3-(benzyloxy)decanyl]-2-deoxy-α-D-glucopyranoside (**5a**). — (*i*) A solution of the acetate **4a** (1.75 g, 1.7 mmol) in MeOH (80 mL) and NH_4OH (8 mL) was allowed to stand for 4 h at 20–25°, concentrated *in vacuo*, and chromatographed on a silica gel column. Elution with EtOAc gave 650 mg (42%) of the triol as a gum.

(*ii*) The triol (650 mg) was dissolved in DMF (4 mL) containing pyridinium *p*-toluenesulfonate (100 mg) and 2,2-dimethoxypropane (6 mL). The mixture was stirred for 5 h at 20–25° and concentrated *in vacuo*, diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a residue which was chromatographed on a silica gel column. Elution with 3:2 cyclohexane–EtOAc gave 577 mg (85%) of an acetonide as a gum.

(*iii*) A solution of the acetonide (560 mg) in EtOH (50 mL) and M NaOH (12 mL) was stirred for 15 h at 20°, concentrated *in vacuo*, diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated to give 402 mg (90%) of diamine **5a** as a viscous oil; ^{1}H-n.m.r. (60 MHz, $CDCl_3$): δ 0.7–1.7 (m, 17 H), 1.42 (s, 3 H), 1.49 (s, 3 H), 1.89 (s, 4 H), 2.5–4.6 (m, 22 H), 4.6–6.2 (m, 5 H), 7.33 (s, 10 H).

Anal. Calc. for $C_{42}H_{64}N_2O_{10}$: C, 66.64; H, 8.52; N, 3.70. Found: C, 66.40; H, 8.25; N, 3.47.

Allyl 6-O-[(2-amino-2-deoxy-4,6-O-isopropylidene)-β-D-glucopyranosyl]-4-O-benzyl-2-[(3R)-3-(benzyloxy)tetradecanamido]-3-O-[(3R)-3-(benzyloxy)tetradeca-

nyl]-2-deoxy-α-D-glucopyranoside (**5b**). — (*i*) A solution of triacetyl compound **4b** (6.1 g, 4.65 mmol) in THF (100 mL), MeOH (270 mL), and NH_4OH (30 mL) was stirred for 15 h at 20° and then concentrated *in vacuo* to give a residue which was chromatographed on a silica gel column. Elution with EtOAc gave 4.33 g (79%) of a triol as a gum.

(*ii*) A solution of the above triol (4.33 g, 3.65 mmol) in DMF (100 mL) and 2,2-dimethoxypropane (50 mL) containing pyridium *p*-toluenesulfonate (1.0 g) was stirred for 15 h. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc, and filtered. The filtrate was washed with H_2O, aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a residue which was chromatographed on a silica gel column. Elution with 1:1 cyclohexane–EtOAc yielded 2.64 g (59%) of the isopropylidene compound as a gum.

(*iii*) A solution of the isopropylidene compound obtained above (2.64 g, 2.15 mmol) in EtOH (150 mL) and M NaOH (10 mL) was stirred for 3 h at 25°, concentrated *in vacuo*, diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give a residue which was chromatographed on a short silica gel column. Elution with EtOAc gave 1.34 g (65%) of amine (**5b**) as a gum; overall yield, 30.3%; ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 0.88 (t, 6 H, *J* 6.3–6.9 Hz), 1.18–1.38 (m, 40 H), 1.43 (s, 3 H), 1.49 (s, 3 H), 1.50–2.00 (m, 5 H, containing OH, NH_2), 2.25–2.45 (m, 2 H), 2.79 (dd, 1 H, *J* 8.1, 9.2 Hz, H-2′), 3.23 (m, 1 H), 3.39–3.95 (m, 13 H), 4.00–4.11 (m, 2 H), 4.18 (d, 1 H, *J* 7.7 Hz, H-1′), 4.25 (m, 1 H), 4.40, 4.45 (AB-q, 2 H, *J* 11.7 Hz, CH_2Ph), 4.47, 4.53 (AB-q, 2 H, *J* 11.4 Hz, CH_2Ph), 4.59, 4.85 (AB-q, 2 H, *J* 11.7 Hz, CH_2Ph), 4.76 (d, 1 H, *J* 3.7 Hz, H-1), 5.07–5.21 (m, 2 H, allyl), 5.75 (m, 1 H, allyl), 6.39 (d, 1 H, *J* 9.5 Hz, NH), 7.22–7.32 (m, 15 H); i.r. ν_{max}^{KBr} 1642, 1542 cm^{-1}.

Anal. Calc. for $C_{49}H_{64}F_6N_2O_{15}$: C, 70.25; H, 9.15; N, 2.45. Found: C, 70.52; H, 9.21; N, 2.45.

*Allyl 4-O-benzyl-6-O-{6-O-(benzyloxy)carbonyl-2-[(3*R*)-3-(benzyloxy)tetradecanamido]-2-deoxy-4-O-diphenylphosphono-β-D-glucopyranosyl}-3-O-[(3*RS*)-3-(benzyloxy)decanyl]-2-[(3*R*)-3-(benzyloxy)tetradecanamido]-2-deoxy-α-D-glucopyranoside* (**6a**). — (*i*) To a solution of the diamine **5a** (3.29, 4.35 mmol) and (3*R*)-3-(benzyloxy)tetradecanoic acid (3.64 g, 10.87 mmol, 2.5 equiv.) in CH_2Cl_2 (80 mL) was added dropwise a solution of DCC (2.24 g, 10.87 mmol) in CH_2Cl_2 (10 mL) at 25° with stirring. After 1 h, the reaction mixture was filtered to remove the precipitated *N,N′*-dicyclohexylurea and concentrated *in vacuo* to give an oily mixture which was chromatographed on a silica gel (800 g) column. Elution with 3:2 cyclohexane–EtOAc yielded 0.69 g of unknown material (R_F = 0.29), and 3.85 g (64%) of a diamide (R_F = 0.17) as a gum.

(*ii*) To a solution of the above diamide (3.85, 2.77 mmol), (3*R*)-3-(benzyloxy)tetradecanoic acid (1.38 g, 4.14 mmol, 1.5 equiv.) and DMAP (34 mg, 0.28 mmol) in CH_2Cl_2 (70 mL) was added dropwise with stirring a solution of DCC (0.85 g, 4.14 mmol) in CH_2Cl_2 (10 mL) at 25°. After 1 h, the reaction mixture was filtered to remove the precipitated *N,N′*-dicyclohexylurea and concentrated *in vacuo* to give an oily mixture which was chromatographed on a silica gel (750 g) column. Elution with 3:1 cyclohexane–EtOAc yielded 4.25 g (90%) of an ester (R_F = 0.19) as a gum.

(*iii*) A solution of the ester obtained above (4.25 g, 2.49 mmol) in 90% AcOH (350 mL) was stirred for 1 h at 75°, then concentrated *in vacuo* to give a residue which was chromatographed on a silica gel (600 g) column. Elution with 1:1 cyclohexane–EtOAc yielded 3.72 g (93%) of a diol (R_F = 0.30) as a gum.

(*iv*) To a solution of the diol obtained above (3.72 g, 2.32 mmol) and DMAP (425 mg, 3.48 mmol) in CH_2Cl_2 (60 mL) was added dropwise with stirring a solution of benzyl chloroformate (594 mg, 3.48 mmol) in CH_2Cl_2 (10 mL) at 25°. After 1 h, the reaction mixture was concentrated, diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a mixture which was chromatographed on a silica gel column. Elution with 7:3 cyclohexane–EtOAc gave bis(benzyloxycarbonyl) compound (0.47 g, 11%, R_F = 0.47) and 2.57 g (64%) of the monobenzyloxycarbonyl compound (R_F = 0.24) as a gum. Elution with 2:3 cyclohexane–EtOAc recovered the starting diol (0.48 g, 13%).

(*v*) A solution of the ether obtained above (2.57 g, 1.43 mmol), diphenyl chlorophosphate (1.15 g, 4.28 mmol) and DMAP (1.05 g, 8.58 mmol) in CH_2Cl_2 (50 mL) was stirred for 1 h at 25°, concentrated, diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and again concentrated to give a residue which was purified by chromatography on a silica gel (150 g) column. Elution with 7:3 cyclohexane–EtOAc yielded 2.61 g (90%) of the 4-*O*-diphenylphosphono compound (**6a**) as a gum; overall yield, 31%; ^{1}H-n.m.r. (60 MHz, $CDCl_3$): δ 0.85–1.05 (m, 12 H), 1.1–2.6 (m, 80 H), 3.2–5.5 (m, 34 H), 5.5–6.8 (m, 5 H), 7.1–7.5 (m, 40 H); i.r. $\nu_{max}^{CHCl_3}$ 3450 (w), 3350 (w), 1745, 1665, 960 cm^{-1}.

Anal. Calc. for $C_{122}H_{171}N_2O_{21}P$: C, 72.09; H, 8.48; N, 1.38; P, 1.52. Found: C, 71.90; H, 8.26; N, 1.41; P, 1.33.

Allyl 4-O-benzyl-6-O-{6-O-(benzyloxy)methyl-2-deoxy-4-O-diphenylphosphono-2-[(3R)-3-(dodecanoyloxy)tetradecanamido]-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl)]-β-D-glucopyranosyl}-2-[(3R)-3-(benzyloxy)tetradecanamido]-3-O-[(3R)-3-(benzyloxy)tetradecanyl]-2-deoxy-α-D-glucopyranoside (**6b**). — (*i*) To a solution of amine **5b** (1.30 g, 1.13 mmol) and (3*R*)-3-(dodecanoyloxy)tetradecanoic acid (0.51 g, 1.19 mmol) in CH_2Cl_2 (50 mL) was added *N,N'*-dicyclohexylcarbodiimide (DCC, 0.28 g, 1.36 mmol) with stirring under nitrogen at 25°. After 1 h, the reaction mixture was concentrated, diluted with EtOAc, and filtered. The filtrate was washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a residue which was chromatographed on a silica gel column. Elution with 1:1 cyclohexane–EtOAc gave 1.29 g (74%) of amide as a gum.

(*ii*) A mixture of the amide obtained above (1.29 g, 0.83 mmol), (3*R*)-3-(tetradecanoyloxy)tetradecanoic acid (416 mg, 0.91 mmol), 4-dimethylaminopyridine (112 mg, 0.91 mmol), and DCC (226 mg, 1.0 mmol) in CH_2Cl_2 (50 mL) was stirred for 2 h at 25°, concentrated *in vacuo*, diluted with EtOAc, and filtered to remove *N,N'*-dicyclohexylurea. The filtrate was washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a residue which was chromatographed on a silica gel column. Elution with 3:1 cyclohexane–EtOAc yielded 1.44 (88%) of an ester as a gum.

(*iii*) A solution of the product obtained above (1.44 g, 0.73 mmol) in 80% AcOH

(35 mL) was stirred for 6 h at 50–60°, concentrated *in vacuo* to give a mixture which was chromatographed on a silica gel column. Elution with 1:1 cyclohexane–EtOAc gave 748 mg (53%) of the diol (R_F = 0.50) as a gum.

(*iv*) A solution of the diol (748 mg, 0.387 mmol), benzyl chloromethyl ether (67 mg, 0.416 mmol, 1.1 equiv.) and tetramethylurea (50 mg, 0.416 mmol) in CH_2Cl_2 (10 mL) was heated under reflux for 24 h, and to this mixture was added an additional amount of benzyl chloromethyl ether (34 mg) and tetramethylurea (25 mg) in CH_2Cl_2 (2 mL). The mixture was heated under reflux for another day, concentrated, diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and again concentrated to give a mixture which was chromatographed on a silica gel column. Elution with 2:1 cyclohexane–EtOAc yielded 596 mg (75%) of the 6′-*O*-benzyloxymethyl ether (R_F = 0.45) as a gum.

(*v*) A solution of the ether obtained above (596 mg, 0.290 mmol), diphenyl chlorophosphate (194 mg, 0.722 mmol), and DMAP (43 mg, 0.352 mmol) in CH_2Cl_2 (20 mL) was stirred for 6 h at 25°, concentrated, diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a residue which was purified by chromatography on a silica gel column. Elution with 3:1 cyclohexane–EtOAc yielded 656 mg (99%) of the 4′-*O*-diphenylphosphono compound **6b** as a gum; overall yield 25.6%. ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 0.88 (t, 18 H, *J* 5.5–7.5 Hz), 1.08–1.85 (m, 122 H), 2.14–2.50 (m, 10 H), 3.35–4.25 (m, 18 H), 4.36–4.80 (m, 11 H), 5.06–5.25 (m, 4 H), 5.62–5.80 (m, 2 H), 6.28–6.38 (m, 2 H, 2 × NH), 7.12–7.35 (m, 30 H); i.r. ν_{max}^{KBr} 1735, 1725, 1660, 1642, 1491, 1191, 1025, 953 cm^{-1}.

Anal. Calc. for $C_{138}H_{217}N_2O_{22}P$: C, 72.47; H, 9.56; N, 1.22; P, 1.35. Found: C, 72.09; H, 9.42; N, 1.02; P, 1.28.

*4-*O*-Benzyl-2-[(3*R*)-3-(benzyloxy)tetradecanamido]-3-*O*-[(3*RS*)-3-(benzyloxy)decanyl]-6-*O*-{6-*O*-(benzyloxy)carbonyl-2-[(3*R*)-3-(benzyloxy)tetradecanamido]-3-*O*-[(3*R*)-3-(benzyloxy)tetradecanoyl]-2-deoxy-4-*O*-diphenylphosphono-β-D-glucopyranosyl}-2-deoxy-D-glucopyranose* (**7a**). — To a solution of **6a** (1.70 g, 0.837 mmol) in THF (85 mL, freshly distilled from $LiAlH_4$) was added bis(methyldiphenylphosphine)cyclo-octadieneiridium(I) hexafluorophosphate, $[C_8H_{12}Ir(PMePh_2)_2]PF_6$, (50 mg). The air in the reaction flask was completely replaced with nitrogen, and then further replaced with hydrogen to activate the iridium complex. After 1–2 min, when the red color solution of the iridium complex became almost colorless, hydrogen was immediately replaced with nitrogen. This solution was stirred for 2 h at 20°. After t.l.c. indicated a double-bond shift to an enol ether (a slightly higher R_F value), H_2O (8.5 mL), pyridine (0.26 g), and I_2 (0.43 g) were added. After 20 min stirring at 20°, the mixture was concentrated *in vacuo*, 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 which was separated on a silica gel column. Elution with 7:3 cyclohexane–EtOAc gave 0.17 g (10%) of the starting **6a** (R_F = 0.40) and 1.50 g (90%) of **7a** (R_F = 0.175) as a solid; ^{1}H-n.m.r. (60 MHz, $CDCl_3$): δ 0.8–1.0 (m, 12 H), 1.0–1.8 (m, 74 H), 1.9–2.7 (m, 6 H), 3.0–5.2 (m, 33 H, containing OH), 6.2–6.6 (m, 2 H, NH), 7.1–7.4 (m, 40 H); i.r. $\nu_{max}^{CHCl_3}$ 3350, 1745, 1668, 1595, 1495, 960 cm^{-1}.

Anal. Calc. for $C_{119}H_{167}N_2O_{21}P$: C, 71.73; H, 8.45; N, 1.41; P, 1.55. Found: C, 71.25; H, 8.25; N, 1.55; P, 1.43.

2-Deoxy-3-O-[(3RS)-3-hydroxydecanyl]-2-[(3R)-3-hydroxytetradecanamido]-6-O-{2-[(3R)-3-hydroxytetradecanamido]-3-O-[(3R)-3-hydroxytetradecanoyl]-2-deoxy-4-O-phosphono-β-D-glucopyranosyl}-α-D-glucopyranosyl phosphate (**8a**). — To a solution of **7a** (0.50 g, 0.25 mmol) in THF (15 mL) was added a solution of BuLi (0.20 mL, 1.6M solution in hexane), and then a solution of $(PhCH_2O)_2P(O)Cl$ (97 mg, 0.325 mmol) at −78°, under nitrogen with stirring. After 10 min, the mixture was hydrogenolyzed by using 10% Pd/C (1.0 g, Type A; Kawaken Fine Chemical Co.) as a catalyst at −78° under nitrogen. After 15 min, the mixture was gradually warmed to room temperature. Hydrogenolysis was continued for 3 h to deprotect the benzyl groups. The mixture was filtered, and the filtrate was further hydrogenolyzed for 2 h to deprotect the phenyl groups of the diphenyl phosphate by use of PtO_2 as a catalyst. The reaction mixture was filtered and concentrated to give a residue which was chromatographed on a silica gel column. Elution with 50:20:3:0.2 $CHCl_3$–MeOH–H_2O–EtOH gave 100 mg of crude product as a powder. The powder (30 mg) was suspended in 0.1M HCl (8 mL), and 1:2 $CHCl_3$–MeOH (30 mL) and dissolved with aid of ultrasound. Another portion of $CHCl_3$ (10 mL) and 0.1M HCl (10 mL) was added to this solution to separate to two phases. The lower chloroform phase was collected and concentrated to give 23 mg of **7a**, which was soluble in 0.1% Et_3N–water (v/v). ^{1}H-N.m.r. (270 MHz, CF_3COOD): δ 0.89–0.93 (m, 12 H), 1.35–2.05 (m, 74 H), 2.6–2.9 (m, 6 H), 3.8–5.0 (m, 19 H), 5.65 (m, 1 H); i.r. $\nu_{max}^{CHCl_3}$ 3300, 2930, 2860, 1735, 1640 cm^{-1}; f.a.b.-m.s. (negative, triethanolamine) *m/z* 1333 (M^-).

Anal. Calc. for $C_{64}H_{124}N_2O_{22}P_2$: C, 57.55; H, 9.36; N, 2.10; P, 4.64. Found: C, 56.98; H, 8.97; N, 2.09; P, 4.45.

4-O-Benzyl-6-O-{6-O-(benzyloxy)methyl-2-deoxy-4-O-diphenylphosphono-2-[(3R)-3-(dodecanoyloxy)tetradecanamido]-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl}-3-O-[(3R)-3-(benzyloxy)tetradecanyl]-2-deoxy-2-[(3R)-3-(benzyloxy)tetradecanamido]-α-D-glucopyranose (**7b**). — Treatment of **6b** (500 mg, 0.219 mmol) in the same manner as described in the formation of **7a** from **6a** gave 355 mg (72%) of **7b**: ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 0.88 (t, 18 H, *J* 6.2–6.9 Hz), 1.13–1.86 (m, 122 H), 2.18–2.46 (m, 10 H), 3.13–4.28 (m, 14 H), 4.36–4.81 (m, 13 H), 5.00–5.21 (m, 2 H), 5.49–5.57 (m, 2 H), 5.35–6.51 (m, 2 H), 7.12–7.35 (m, 30 H); i.r. ν_{max}^{KBr} 3550–3300, 2920, 2850, 1740, 1705, 1660, 1643, 1590, 1555 cm^{-1}.

Anal. Calc. for $C_{135}H_{213}N_2O_{22}P$: C, 72.16; H, 9.55; N, 1.25; P, 1.38. Found: C, 71.59; H, 9.33; N, 1.06; P, 1.22.

Dibenzyl 4-O-benzyl-6-O-{6-O-(benzyloxy)methyl-2-deoxy-4-O-diphenylphosphono-2-[(3R)-3-(dodecanoyloxy)tetradecanamido]-3-O-[(3R)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl}-3-O-[(3R)-3-(benzyloxy)tetradecanyl]-2-deoxy-2-[(3R)-3-(benzyloxy)tetradecanamido]-α-D-glucopyranosyl phosphate (**8b**). — To a solution of **7b** (325 mg, 0.145 mmol) in THF (15 mL) was added gradually a solution of BuLi (0.12 mL, 1.6M in hexane) at −78° under nitrogen with stirring. After 2 min, a solution of $(PhCH_2O)_2P(O)Cl$ (56 mg) in THF (2 mL) was added gradually to this solution. After 5 min, a solution of AcOH (0.1 mL) in THF (1 mL) was added at −78°.

The reaction mixture was diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed on a silica gel column. Elution with 2:1 cyclohexane–EtOAc gave 146 mg (40%) of **8b** (R_F = 0.56) and 100 mg (31%) of recovered starting **7b** (R_F = 0.29); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 0.88 (t, 18 H, *J* 5.9–6.9 Hz), 1.09–1.86 (m, 122 H), 2.12–2.45 (m, 10 H), 3.11–4.21 (m, 13 H), 4.37–4.81 (m, 13 H), 4.93–5.21 (m, 6 H), 5.40–5.69 (m, 2 H), 6.39 (d, 1 H, *J* 7.3 Hz, NH), 6.49 (d, 1 H, *J* 9.9 Hz, NH), 7.12–7.65 (m, 40 H); i.r. ν_{max}^{film} 3320, 2930, 2860, 1735, 1675, 1590 cm^{-1}.

Anal. Calc. for $C_{149}H_{226}N_2O_{25}P_2$: C, 71.37; H, 9.09; N, 1.12; P, 2.47. Found: C, 71.14; H, 8.93; N, 1.03; P, 2.18.

*Attempted synthesis of 2-deoxy-6-O-{2-deoxy-2-[(3*R*)-3-(dodecanoyloxy)tetradecanamido]-4-O-phosphono-3-O-[(3*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl}-2-[(3*R*)-hydroxytetradecanamido]-3-O-[(3*R*)-3-hydroxytetradecanyl]-α-D-glucopyranosyl phosphate* (**9b**). — To a solution of **8b** (125 mg) in 2:3 THF–MeOH (25 mL) was added 10% Pd/C (100 mg). The mixture was stirred for 3 h at 25° under a hydrogen atmosphere to deprotect the benzyl groups, and filtered. To this filtrate was added PtO_2 (55 mg), and the mixture was hydrogenolysed at 25° for 2 h under hydrogen atmosphere to cleave the two oxygen–phenyl bonds on diphenylphosphate to give **9b**, and filtered. The filtrate was concentrated to give 55 mg of a degradated material. On concentration, **9b** changed to a less polar material, as indicated by t.l.c.

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