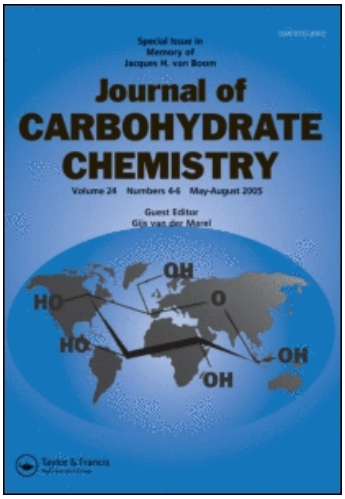

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Synthesis of 2-Deoxy-2-[(3R)-3-Hydroxyacyl]Amino-4-O-Phosphono-3-O-[(3R)-3-Tetradecanoyloxytetradecanoyl]-D-Glucopyranose Derivatives Related to Bacterial Lipid A

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SYNTHESIS OF 2-DEOXY-2-[(3R)-3-HYDROXYACYL]AMINO-4-O-PHOSPHONO-3-O-[(3R)-3-TETRADECANOYLOXYTETRADECANOYL]-D-GLUCOPYRANOSE DERIVATIVES RELATED TO BACTERIAL LIPID A

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ABSTRACT

Lipid A subunit analogs, the 4-O-phosphono-D-glucosamine derivatives (14-16: GLA 93-95) which carry 2-N-linked 3-hydroxyacyl groups, were synthesized. 2-(Trimethylsilyl)ethyl 2-amino-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside (1) was transformed into 2-(trimethylsilyl)ethyl 2-amino-6-O-tert-butyldimethylsilyl-2-deoxy-4-O-diphenylphosphono-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside (7) through several steps. N-Acylation of 7 with 3-hydroxyl fatty acids gave the corresponding 8-10, which were converted, via the cleavage of protecting groups, into a series of desired compounds.

INTRODUCTION

Lipopolysaccharide (LPS),[1] which is an integral component of the outer membrane of gram-negative bacteria, expresses a variety of biological activities such as pyrogenicity and mediator induction.

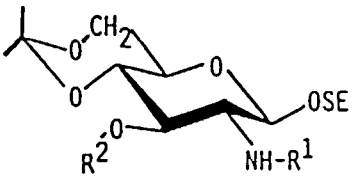
Most of these activities were elucidated in lipid A, a lipid component of LPS. In order to clarify the structure-bio function relationship of lipid A analogs, a series of 4-O-phosphono-D-glucosamine derivatives, composed of different fatty acyl groups, were synthesized[2] and their biological activities were investigated.[3] In the course of such investigations, we have found that the chain-length of the acyloxytetradecanoyl group and the presence of 3-hydroxytetradecanoyl group in the analogs are very important for expression of the immunopharmacological activities.

However, the biological influence of the chain-length of the 3-hydroxyacyl group at C-2 in the sugar moiety was not investigated. We now describe the synthesis of some 2-deoxy-2-[(3R)-3-hydroxyacyl]amino-4-O-phosphono-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucose derivatives (14-16 : GLA 93-95) which are homologous to GLA-60,[2a] possessing some distinct and beneficial immunomodulating activities of bacterial lipid A.

RESULTS AND DISCUSSION

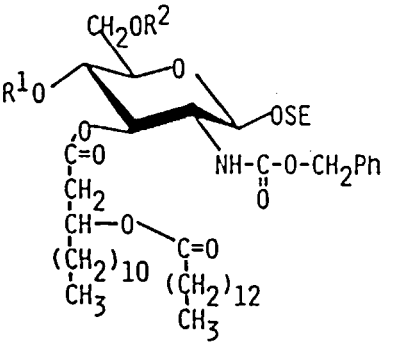
Treatment of 2-(trimethylsilyl)ethyl 2-amino-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside (1) with benzyloxycarbonyl chloride gave 2-(benzyloxycarbonyl)amino derivative (2) in 91% yield. Compound 2 was esterified with (3R)-3-tetradecanoyloxytetradecanoic acid and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSC) in the presence of 4-dimethylaminopyridine (DMAP) to afford 3. Hydrolytic removal of the isopropylidene group with aqueous acetic acid gave 4. Introduction of tert-butyldimethylsilyl group at O-6 and diphenyl phosphono group at O-4 was performed by the usual methods to give compound 6.

The benzyloxycarbonyl group was cleaved by hydrogenolysis with 10%-palladium on carbon to give the 2-amino derivative (7) in good yield. Because of its instability, compound 7 was immediately treated with (3R)-3-hydroxydecanoic acid, (3R)-3-hydroxydodecanoic acid, and (3R)-3-hydroxyhexadecanoic acid in the presence of WSC to give the corresponding compounds 8, 9, and 10 in 70-73% yields.

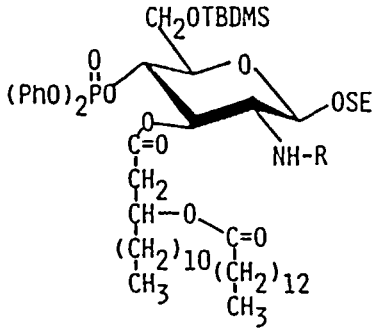


	R^1	R^2
1	H	H
2	$PhCH_2OC(O)$	H
3	$PhCH_2OC(O)$	C_{14}-O-C_{14}

SE = $Me_3SiCH_2CH_2$



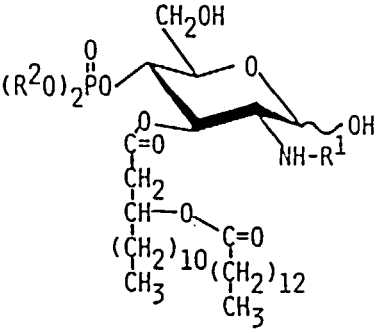
	R^1	R^2
4	H	H
5	H	TBDMS
6	$(PhO)_2P(O)$	TBDMS



	R
7	H
8	C_{10}-OH
9	C_{12}-OH
10	C_{16}-OH

TBDMS = t-$BuMe_2Si$

C_{14}-O-C_{14} = $CH_3(CH_2)_{10}CHCH_2C(O)$
O
$CH_3(CH_2)_{12}C{=}O$



	R^1	R^2
11	C_{10}-OH	Ph
12	C_{12}-OH	Ph
13	C_{16}-OH	Ph
14	C_{10}-OH	H
15	C_{12}-OH	H
16	C_{16}-OH	H

C_n-OH = $CH_3(CH_2)_{n-4}CHCH_2C(O)$
OH

The 2-(trimethylsilyl)ethyl and tert-butyldimethylsilyl groups of 8-10 were simultaneously hydrolyzed with boron trifluoride etherate to give 11-13 in 85-95% yields. These compounds could be assigned the α-D-glucopyranose form based on their ^{1}H-NMR data. Finally, hydrogenolytic deprotection of the phenyl groups from 11-13 with platinum catalyst afforded the desired compounds 14-16 (GLA 93-95) in high yields.

EXPERIMENTAL

General procedures. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Specific rotations were determined with a Union PM-201 polarimeter, and IR spectra were recorded with a Jasco A-100 spectrophotometer. ^{1}H NMR spectra were recorded with a Jeol JNM-GX 270 spectrometer. Preparative chromatography was performed on silica gel (Wako Co., 200 mesh) with the solvent systems specified. Concentrations and evaporations were conducted in vacuo.

2-(Trimethylsilyl)ethyl 2-(Benzyloxycarbonyl)amino-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside (2). To a mixture of 2-(trimethylsilyl)ethyl 2-amino-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside[4] (1, 1.7 g), dichloromethane (50 mL), and M sodium hydrogen carbonate (50 mL) was added benzyloxycarbonyl chloride (2 g). The mixture was stirred vigorously for 2 h at room temperature. The organic layer was separated and washed with water, dried (sodium sulfate) and concentrated. The residue was chromatographed on a column of silica gel with 300:1 dichloromethane-methanol to give 2 (2.25 g, 91%) as an amorphous solid: mp 111-112 °C, $[\alpha]_D$ -30.9° (c 1.3, dichloromethane); IR (film) 3300 (OH, NH), 2950, 2900 (CH), 1700, 1550 (amide), 850, 830 (Me_2C, Si-C) and 750-690 cm^{-1} (Ph); ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9H, Me_3Si), 0.9 (m, 2H, Me_3SiCH_2), 1.43, 1.49 (2s, 6H, Me_2C), 3.25 (m, 1H, H-5), 3.3-4.0 (m, 8H, H-1, 2, 3, 4, 6, and $Me_3SiCH_2CH_2$), 5.11 (s, 2H, $PhCH_2$), and 7.33 (m, 5H, Ph).

Anal. Calcd for $C_{22}H_{35}NO_7Si$ (453.61): C, 58.25; H, 7.78; N, 3.09. Found: C, 58.43; H, 7.89; N, 3.13.

2-(Trimethylsilyl)ethyl 2-(Benzyloxycarbonyl)amino-2-deoxy-4,6-O-isopropylidene-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside (3). To a solution of 2 (2.25 g) in dichloromethane (30 mL) were added (3R)-3-tetradecanoyloxytetradecanoic acid (2.93 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC, 1.9 g) and a catalytic amount of 4-dimethylaminopyridine (DMAP). The mixture was stirred overnight at room temperature and concentrated. The residue was chromatographed on a column of silica gel with 500:1 dichloromethane-methanol to afford syrupy 3 (3.8 g, 86%): $[\alpha]_D$ -8.5° (c 0.92, dichloromethane); IR (film) 3400 (NH), 2930, 2850 (CH), 1740 (ester), 1700, 1640 (amide), 860, 840 (Si-C), and 760-690 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.0 (s, 9H, Me_3Si) 0.8-1.0 (m, 8H, Me_3SiCH_2 and Me), 1.0-1.8 (m, 42H, $-CH_2-$), 1.37, 1.47 (2s, 6H, Me_2C), 2.2-2.6 (m, 4H, $-COCH_2-$), 3.15-4.0 (m, 8H, H-1, 2, 4, 5, 6 and $Me_3SiCH_2CH_2$) 4.67 (broad s, 1H, NH), 5.0-5.3 (m, 4H, $PhCH_2$, H-3 of C_{14}-O-C_{14}, and H-3), 7.3-7.5 (m, 5H, Ph).

Anal. Calcd for $C_{50}H_{87}NO_{10}Si$ (890.33): C, 67.45; H, 9.85; N, 1.57. Found : C, 67.32; H, 9.68; N, 1.46.

2-(Trimethylsilyl)ethyl 2-(Benzyloxycarbonyl)amino-2-deoxy-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside (4). A mixture of 3 (3.8 g) and 80% aqueous acetic acid (50 mL) was stirred for 1 h at 50 °C. The mixture was concentrated and then chromatographed on a column of silica gel with 150:1 dichloromethane-methanol to obtain 4 (3.3 g, 91%), which was lyophilized from 1,4-dioxane: mp 47-49 °C, $[\alpha]_D$ -8.6° (c 0.89, dichloromethane); IR (film) 3450 (OH, NH), 2930, 2850 (CH), 1740 (ester), 1700, 1540 (amide), 860, 830 (Si-C), and 780-690 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.0 (s, 9H, Me_3Si), 0.88 (m, 8H, Me_3SiCH_2 and Me), 1.1-1.7 (m, 42H, $-CH_2-$), 2.1-2.6 (m, 4H, $-COCH_2-$), 2.65 (broad s, 2H, OH), 3.4-3.6 (m, 3H, $Me_3SiCH_2CH_2$ and H-5), 3.62 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.3 Hz, H-4), 3.82 (dd, 1H, J_{gem} = 12 Hz, $J_{5,6a}$ = 4.4 Hz, H-6a), 3.92 (dd, 1H, J_{gem} = 12 Hz, $J_{5,6b}$ = 3.3 Hz, H-6b), 3.95 (m, 1H, H-2), 5.04 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 5.1 (m, 4H, $PhCH_2$, H-3 of C_{14}-O-C_{14}, and H-3), and 7.2-7.4 (m, 5H, Ph).

Anal. Calcd for $C_{47}H_{83}NO_{10}Si$ (850.26): C, 66.39; H, 9.84; N, 1.65. Found: C, 66.42; H, 10.01; N, 1.85.

2-(Trimethylsilyl)ethyl 2-(Benzyloxycarbonyl)amino-6-O-tert-butyldimethylsilyl-2-deoxy-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside (5). To a solution of 4 (2 g) in pyridine (40 mL) was added tert-butyldimethylsilyl chloride (0.53 g). The mixture was stirred overnight at room temperature. Methanol was added to decompose the excess reagent and the solvents were evaporated. The residue was extracted with dichloromethane. The extract was washed with 2M hydrochloric acid and water, dried (sodium sulfate) and concentrated. The residual syrup was chromatographed on a column of silica gel with 400:1 dichloromethane-methanol to give 5 (2.4 g, 98%) as a syrup : $[\alpha]_D$ -10.0° (c 1.0, dichloromethane); IR (film) 3500 (OH), 3350 (NH), 1740 (ester), 1700, 1540 (amide), 830 (Si-C), and 780-680 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.0 (s, 15H, MeSi), 0.8-1.0 (m, 17H, Me_3SiCH_2, tert-Bu, and Me), 1.1-1.7 (m, 42H, $-CH_2-$), 2.15-2.65 (m, 4H, $-COCH_2-$), 3.3-3.6 (m, 4H, $Me_3SiCH_2CH_2$, H-5, and OH), 3.63 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 3.85-4.0 (m, 3H, H-2 and 6), 4.98 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 5.0-5.2 (m, 4H, $PhCH_2$, H-3 of C_{14}-O-C_{14}, and H-3), and 7.2-7.4 (m, 5H, Ph).

Anal. Calcd for $C_{53}H_{97}NO_{10}Si$ (964.53): C, 66.00; H, 10.14; N, 1.45. Found: C, 66.05; H, 10.36; N, 1.23.

2-(Trimethylsilyl)ethyl 2-(Benzyloxycarbonyl)amino-6-O-tert-butyldimethylsilyl-2-deoxy-4-O-diphenylphosphono-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside (6). To a cooled and stirred mixture of 5 (2.2 g), DMAP (0.38 g), and pyridine (10 mL) were added diphenyl phosphorochloridate (1.7 g) and dichloromethane (10 mL); stirring was continued overnight at room temprature. Methanol was added and the solvents were evaporated. The residue was chromatographed on a column of silica gel with 8:1 hexane-ethyl acetate to give syrupy 6 (2.5 g, 93%); $[\alpha]_D$ +2.9° (c 0.96, dichloromethane); IR (film) 3350 (NH), 2940, 2850 (CH), 1740 (ester), 1700, 1540 (amide), 960 (P-O-Ph), 840 (Si-C), and 780-680 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.0 (s, 15H, MeSi), 0.8-1.0 (m, 17H,

MeSiCH$_2$, tert-Bu, and Me), 1.1-1.7 (m, 42H, -CH$_2$-), 2.0-2.5 (m, 4H, -COCH$_2$-), 3.2-4.0 (m, 6H, Me$_3$SiCH$_2$CH$_2$, H-2, 5, and 6), 4.61 (q, 1H, $J_{3,4} = J_{4,5} = J_{4,P} = 9.2$ Hz, H-4), 4.85-5.8 (m, 6H, PhCH$_2$, H-3 of C$_{14}$-O-C$_{14}$, H-1, 3, and NH), and 7.1-7.4 (m, 15H, Ph).

Anal. Calcd for $C_{65}H_{106}NO_{13}PSi_2$ (1196.70): C, 65.24; H, 8.93; N, 1.17. Found: C, 65.45; H, 8.89; N, 1.26.

2-(Trimethylsilyl)ethyl 2-Amino-6-O-tert-butyldimethylsilyl-2-deoxy-4-O-diphenylphosphono-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside (7). To a solution of 6 (1 g) in methanol (50 mL) was added 10%-palladium on carbon (0.5 g), and the mixture was stirred for 1 h in a hydrogen atmosphere. The catalyst was filtered off, and washed with methanol. The filtrate and washings were combined and concentrated to give 7 as a syrup (0.89 g, 98%): $[\alpha]_D$ -2.5° (c 0.4, dichloromethane); IR (film) 2930, 2850 (CH), 1740 (ester), 1600 (amino), 950 (P-O-Ph), 840 (Si-C), and 780-680 cm^{-1} (Ph); ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 15H, Me-Si), 0.8-1.0 (m, 17H, Me$_3$SiCH$_2$, tert-Bu, and Me), 1.1-1.8 (m, 42H, -CH$_2$-), 2.0-2.5 (m, 4H, -COCH$_2$-), 2.9 (m, 1H, H-2), 3.1-4.0 (m, 5H, H-5, 6, and Me$_3$SiCH$_2$CH$_2$), 4.21 (d, 1H, $J_{1,2} = 8$ Hz, H-1), 4.59 (q, 1H, $J_{3,4} = J_{4,5} = J_{4,P} = 9$ Hz, H-4), 5.0-5.1 (m, 2H, H-3 of C$_{14}$-O-C$_{14}$ and H-3), and 7.2-7.4 (m, 10H, Ph).

Anal. Calcd for $C_{57}H_{100}NO_{11}PSi_2$ (1062.57): C, 64.43; H, 9.49; N, 1.32. Found: C, 64.34; H, 9.76; N, 1.25.

2-(Trimethylsilyl)ethyl 6-O-tert-Butyldimethylsilyl-2-deoxy-4-O-diphenylphosphono-2-[(3R)-3-hydroxydecanamido]-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside (8). A mixture of 7 (0.25 g), (3R)-3-hydroxydecanoic acid (0.22 g), and WSC (0.2 g) in dichloromethane (10 mL) was stirred overnight at room temperature. The reaction mixture was directly chromatographed on a column of silica gel with 300:1 dichloromethane-methanol to afford 8 (0.2 g, 70%) as a syrup: $[\alpha]_D$ -3.6° (c 0.44, dichloromethane); IR (film) 3500 (OH), 3300 (NH), 1740 (ester), 1660, 1550 (amide), 960 (P-O-Ph), 840 (Si-C), and 780-680 cm^{-1} (Ph); ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 15H, MeSi), 0.8-1.0 (m, 20H, Me$_3$SiCH$_2$, tert-Bu, and Me), 1.1-1.6 (m, 54H, -CH$_2$-), 2.0-2.7 (m, 7H, OH and -COCH$_2$-), 3.4-4.0 (m, 7H,

$Me_3SiCH_2CH_2$, H-3 of C_{10}-OH, H-2, 5, and 6), 4.60 (q, 1H, $J_{3,4}$ = $J_{4,5}$ = $J_{4,P}$ = 9.2 Hz, H-4), 4.99 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 5.13 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.4 Hz, H-3), 6.42 (d, 1H, J = 7.3 Hz, NH), and 7.1-7.4 (m, 10H, Ph).

Anal. Calcd for $C_{67}H_{118}NO_{13}PSi_2$ (1232.82): C, 65.28; H, 9.65, N, 1.14. Found: C, 65.02; H 9.60; N, 1.02.

2-(Trimethylsilyl)ethyl 6-O-tert-Butyldimethylsilyl-2-deoxy-4-O-diphenylphosphono-2-[(3R)-3-hydroxydodecanamido]-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside (9) and 2-(Trimethylsilyl)ethyl 6-O-tert-Butyldimethylsilyl-2-deoxy-4-O-diphenylphosphono-2-[(3R)-3-hydroxyhexadecanamido]-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside (10). Compounds 9 and 10 were obtained by acylation of 7 with (3R)-3-hydroxydodecanoic acid and (3R)-3-hydroxyhexadecanoic acid, respectively, in 70% and 73% yields, according to the method described for 8. IR and ^1H NMR data were similar to those of 8 except for the number of methylene protons at δ 1.1-1.6 ppm.

Compound 9 had $[\alpha]_D$ -5.5° (c 0.4, dichloromethane).

Anal. Calcd for $C_{69}H_{122}NO_{13}PSi_2$ (1260.87): C, 65.73; H, 9.75; N, 1.11. Found: C, 65.97; H, 9.64; N, 1.04.

Compound 10 had $[\alpha]_D$ -3.5° (c 0.46, dichloromethane).

Anal. Calcd for $C_{73}H_{130}NO_{13}PSi_2$ (1316.98): C, 66.58; H, 9.95; N, 1.06. Found: C, 66.53; H, 10.01; N, 1.12.

2-Deoxy-4-O-diphenylphosphono-2-[(3R)-3-hydroxydecanamido]-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucopyranose (11). To a solution of 8 (0.1 g) in dichloromethane (10 mL) was added boron trifluoride etherate (0.5 mL) at 0 °C. The mixture was stirred for 1 h at the same temperature. The mixture was washed with saturated sodium hydrogen carbonate and water, dried (sodium sulfate) and concentrated. The residue was chromatographed on a column of silica gel with 50:1 dichloromethane-methanol to give 11 (0.75 g, 89%) which was lyophilized from 1,4-dioxane solution: mp 121-122 °C, $[\alpha]_D$ +5.6° (c 1.0, dichloromethane); IR (KBr) 3350 (OH, NH), 1740 (ester), 1650, 1550 (amide), 960 (P-O-Ph), and 780-680 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.88 (t, 9H, Me), 1.0-1.7 (m, 54H, $-CH_2-$), 2.0-2.5 (m,

6H, $-COCH_2-$), 3.0-4.2 (m, 7H; H-3 of C_{10}-OH, H-5, 6, and OH), 4.21 (m, 1H, H-2), 4.71 (q, 1H, $J_{3,4} = J_{4,5} = J_{4,P} = 9.5$ Hz, H-4), 5.10 (m, 1H, H-3 of C_{14}-O-C_{14}), 5.28 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1), 5.48 (t, 1H, $J_{2,3} = J_{3,4} = 9.8$ Hz, H-3), 6.54 (d, 1H, J = 8.8 Hz, NH), and 7.2-7.4 (m, 10H, Ph).

Anal. Calcd for $C_{56}H_{92}NO_{13}P$ (1018.32): C, 66.05; H, 9.11; N, 1.38. Found: C, 65.78; H, 8.96; N, 1.64.

2-Deoxy-4-O-diphenylphosphono-2-[(3R)-3-hydroxydodecanamido]-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucopyranose (12) and 2-Deoxy-4-O-diphenylphosphono-2-[(3R)-3-hydroxyhexadecanamido]-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucopyranose (13). Cleavage of the silyl groups of 9 and 10 as described for 11, gave 12 (85%) and 13 (95%) respectively. IR and ^1H NMR spectra were consistent with the structures assigned.

Compound 12 had mp 117-119 °C, $[\alpha]_D$ +12.6° (c 0.87, dichloromethane).

Anal. Calcd for $C_{58}H_{96}NO_{13}P$ (1046,37): C, 66.58; H, 9.25; N, 1.34. Found: C, 66.75; H, 9.40; N, 1.56.

Compound 13 had mp 116-118 °C, $[\alpha]_D$ +5.8° (c 1.29, dichloromethane).

Anal. Calcd for $C_{62}H_{104}NO_{13}P$ (1102,48): C, 67.55; H, 9.51; N, 1.27. Found: C, 67.61; H, 9.26; N, 1.49.

2-Deoxy-2-[(3R)-3-hydroxydecanamido]-4-O-phosphono-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucopyranose (14: GLA-93). To a solution of 11 (75 mg) in ethanol (60 mL) was added Adams' platinum catalyst (80 mg), and the mixture was stirred overnight in a hydrogen atmosphere. The catalyst was filtered off and washed with ethanol. The filtrate and washings were combined and concentrated to afford 14 (64 mg, quantitative) which was lyophilized from 1,4-dioxane suspension. It was positive to the specific spray-reagent[5] for the phosphono group: mp 157-159 °C, $[\alpha]_D$ +14.3° (c 0.14, 3:1 chloroform-methanol); IR (KBr) 3400 (OH, NH), 2940, 2850 (CH), 1720 (ester), and 1640, 1550 cm^{-1} (amide).

Anal. Calcd for $C_{44}H_{84}NO_{13}P$ (866.12): C, 61.02; H, 9.78; N, 1.62. Found: C, 61.30; H, 9.90; N, 1.57.

2-Deoxy-2-[(3R)-3-hydroxydodecanamido]-4-O-phosphono-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucopyranose (15: GLA-94) and 2-Deoxy-2-[(3R)-3-hydroxyhexadecanamido]-4-O-phosphono-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucopyranose (16: GLA-95). Compounds 12 and 13 were hydrogenolyzed as described for 11, to afford the corresponding 15 and 16.

Compound 15 was obtained in 95% yield: mp 158-159 °C, $[\alpha]_D$ +10.0° (c 0.1, 3:1 chloroform-methanol); IR data was similar to that of 11.

Anal. Calcd for $C_{46}H_{88}NO_{13}P$ (894.18): C, 61.79; H, 9.92; N, 1.57. Found: C, 61.71; H, 9.68; N, 1.56.

Compound 16 was obtained in 91% yield: mp 160 °C, $[\alpha]_D$ +19.6° (c 0.15, 3:1 chloroform-methanol); IR spectra was similar to that of 11.

Anal. Calcd for $C_{50}H_{96}NO_{13}P$ (950.29): C, 63.20; H, 10.18; N, 1.47. Found: C, 63.36; H, 10.33; N, 1.50.

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