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Practical stereoselective synthesis of α-linked *C*-glucosamine propionic acid esters: conversion to GLA-60 derivatives

Takanori Wakabayashi, Masao Shiozaki,* Shin-ichi Kurakata

Exploratory Chemistry Research Laboratories, Sankyo Co. Ltd., Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140-8710, Japan

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Abstract

Radical C-glycosylation of glucosamine derivatives by acrylic acid esters gave the corresponding 3-(α-*C*-glucosyl)-propionate derivatives in moderate yields. One of them was used as a versatile synthon for GLA-60 derivatives. However, the biological activity of these compounds as LPS-antagonists was disappointing.

Keywords: GLA-60 derivatives; α-Linked C-glycosylation of glucosamine; LPS-antagonist

1. Introduction

In our investigation of LPS-antagonists, the α anomer **A** (a GLA-60 derivative) showed LPS-antagonist activity toward human monoblastic cells in spite of its β anomer lacking in this activity.[1] This result made us interested in the biological activity of methylene derivatives of **A** such as **15** (Fig. 1).

Syntheses of α-*C*-glycopyranosides have been studied extensively, and many methods to control the stereochemistry at the anomeric position have been reported.[2,3] Among these studies, we thought that the radical α-C-glucosylation method should be one of choice for our purposes, because of the stability and reactivity of α-oriented anomeric radical on the glucose ring.[2c] Actually, the radical α-C-glucosylation reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with Bu_3SnH and methyl acrylate using light or V-70[4] as a radical starter gave a corresponding α-linked *C*-glucopyranoside in moderate yield.[2l] In the case of *N*-acylglucosamines, this radical α-C-glucosylation was carried out using allyltributyltin, vinyl phosphonate, or acrylphosphonate to yield corresponding α-linked *C*-glycosidic adducts in moderate yield.[2j,2m,2o,2p] However, in these attempts, the amide groups such as the acetylamino group derived from the starting glucosamines were too stable to further modifications and functionalizations for the access to the proposed compounds. One of the serious problems is stable intramolecular δ-lactam formation. This prevents further conversion of 3-(α-*C*-glucosyl)-propionate derivatives produced. Therefore, we also attempted another radical α-C-glucosylation reaction of D-glucosamine analogues to solve these restrictions. Herein we describe the results that were applied for the further conversion to α-linked *C*-glucosamine propionic acid derivatives of GLA-60 to give an example.

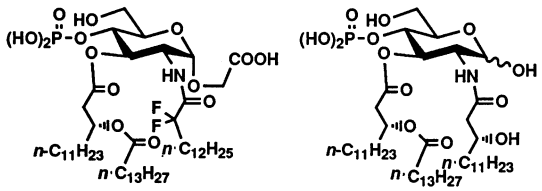

Fig. 1. Structures of compound **A** and GLA-60.

2. Results and discussion

As substrates, we used three kinds of glucosamine analogues, that is, 2-deoxy-2-trifluoroacetamido-, 2-

* Corresponding author. Tel.: +81-3-3492-3131; fax: +81-3-54368570.

E-mail address: shioza@shina.sankyo.co.jp (M. Shiozaki).

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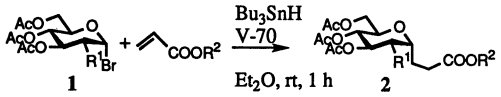
Table 1
Anomeric α-*C*-propionylation of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide analogues (**1**) with acrylic acid esters



Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**1a**	$NHCOCF_3$	Bn	**2a**	84
2	**1a**	$NHCOCF_3$	Bu^t	**2b**	58
3	**1b**	NHCOOBn	Bu^t	**2c**	60
4	**1c**	N=CH–PMP	Bn	**2d**	50

V-70 = 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile); PMP = 4-methoxyphenyl.

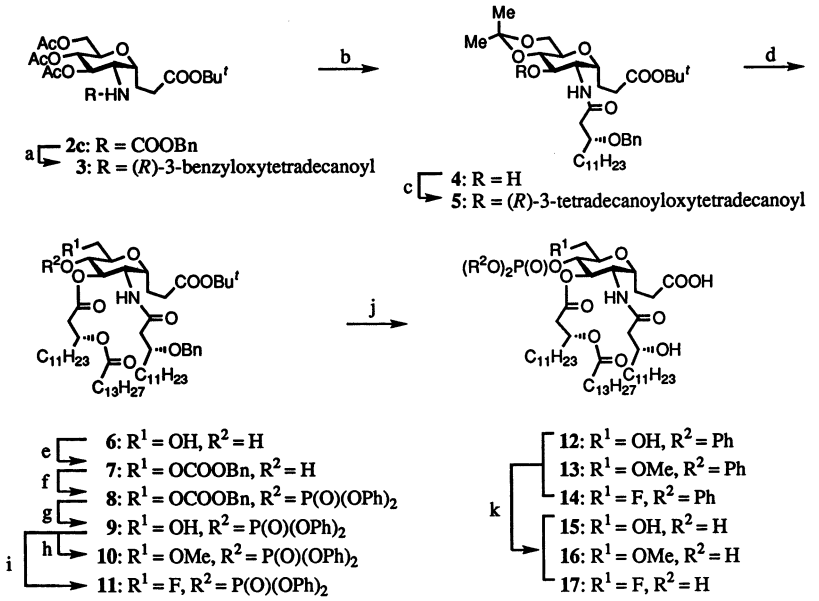
(benzyloxycarbonyl)amino-2-deoxy-, and 2-deoxy-2-(4-methoxybenzyl)imino-α-D-glucopyranosyl bromides (**1a**, **1b**, and **1c**, respectively), which were anticipated to be possible for further conversion. According to the reported procedure of Kita et al.[21] treatment of each compound **1a**,**b**,**c** with benzyl or *tert*-butyl acrylate in the presence of tributyltin hydride using 2,2′-azobis-(2,4-dimethyl-4-methoxyvaleronitrile) (V-70) as a radical initiator gave the corresponding α-linked 5-amino *C*-glucosides **2a**,**b**,**c**,**d**, without detection of β-linked epimers (Table 1). In this series, the yield of trifluoroacetamido-benzyl ester **2a** was 84%, and that of 4-methoxybenzylimino benzyl ester **2d** was 50%. This reaction generally proceeds in moderate yield and thus may have application for other 5-N substitution groups in general.

Next, we used compound **2c** for the conversion of **2** to propionic acid analogues of GLA-60 (**15**–**17**) according to the modified procedure of the reported method.[1] Deprotection of the benzyloxycarbonyl group from the C-5 carbamate of **2c** by hydrogenolysis using Pd-on-carbon as a catalyst, and successive amide formation with (*R*)-3-benzyloxytetradecanoic acid using 3-(3-dimethylaminopropyl)-1-ethyl-carbodiimide hydrochloride (WSCDI) as a condensing agent, gave the C-5 amide which was treated with NaOMe in MeOH to give the C-6,-7,-9-triol, and successive treatment of the triol with 2,2-dimethoxypropane using catalytic amount of TsOH as a catalyst gave the 7,9-*O*-isopropylidene compound **4**. The 6-OH group of **4** was esterified with (*R*)-3-(tetradecanoyloxy)tetradecanoic acid using DCC–DMAP as condensing reagents to give the C-6 ester **5** in 64% yield in five steps from **2c**. Deblocking of the 7,9-*O*-isopropylidene group of **5** in MeOH solution using TsOH to give a diol **6**, protection of the 9-OH group of **6** with benzyl chloroformate using pyridine as a base gave **7**, diphenylphosphonate ester formation of the 7-OH group of **7** with diphenyl chlorophosphate using DMAP as a base gave **8**, and regioselective deprotection of the 9-benzylcarbonate by chemoselective hydrogenolysis using the ethylenediamine-deactivated Pd (Pd–C(en))[5] as a catalyst gave the 9-OH phosphonate **9** in 76% yield in four steps from **5**. Treatment of **9** with $Me_3O{\cdot}BF_4$ and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at room temperature gave 9-OMe **10** in 92% yield. On the other hand, treatment of **9** with diethylaminosulfur trifluoride (DAST) gave **11** in 71% accompanying with a small amount of an intramolecular cyclic 7,9-*O*-phenylphosphate. Finally, the protective groups were removed from these compounds to afford the objective compounds. Treatment of compounds **8**, **10**, and **11** with CF_3COOH in CH_2Cl_2, and successive treatment of the resulted compounds with hydrogen using $Pd(OH)_2$-on-carbon as a catalyst gave **12**, **13**, and **14**, respectively, and these compounds were further hydrogenolyzed using PtO_2 as a catalyst to afford **15**, **16**, and **17**, respectively (Scheme 1).

Biological activity.—The biological activity of compounds **15**, **16**, and **17** on LPS-induced TNFα production was investigated in vitro using human monoblastic U937 cells. Compound **15** showed weak LPS-antagonistic activity (IC_{50} 50 nM), and compound **17** even showed faint LPS-agonistic activity at a concentration of 50 μM. But both compounds **16** and **17** were almost inactive.

3. Conclusions

Thus, in this study we were able to explore a practical stereoselective synthesis for 5-amino-4,8-anhydro-2,3,5-trideoxy-D-*glycero*-D-*ido*-nononic acid equivalents, and we were able to apply this result to the synthesis of GLA-60 derivatives. However, the biological activity of these compounds as LPS-antagonists was disappointing.



Scheme 1. Reagents and conditions: (a) (1) H_2, $Pd(OH)_2$–C, EtOH, rt, 20 min; (2) (*R*)-3-benzyloxytetradecanoic acid, WSCDI, rt, 16 h, two steps 83%; (b) (1) NaOMe, MeOH, rt, 20 min; (2) 2,2-dimethoxypropane, $TsOH·H_2O$, DMF, rt, 1 h, two steps 88%; (c) (*R*)-3-(tetradecanoyloxy)tetradecanoic acid, DCC, DMAP, 88%; (d) TsOH, MeOH, rt, 2 h, 95%; (e) BnOOCCl, pyridine, CH_2Cl_2, rt, 5 h, 93%; (f) diphenyl chlorophosphate, DMAP, CH_2C1_2, rt, 4 h, 94%; (g) H_2, Pd–C(en), THF, rt, 92%; (h) $Me_3O·BF_4$, DTBMP, CH_2Cl_2, rt, 5 h, 92%; (i) DAST, CH_2Cl_2, 0 °C–rt, 16 h, 71%; (j) CF_3COOH, CH_2Cl_2, rt, 4 h, then H_2, $Pd(OH)_2$–C, EtOH, rt, 2 h, **12** in 73% (from **8**), **13** in 76% (from **10**), and **14** in 56% (from **11**), respectively; (k) H_2, PtO_2, THF, rt, 16 h, 93% (**15**), quant (**16**), and 94% (**17**), respectively.

4. Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were obtained by the use of a JASCO P-1030 polarimeter. ^{1}H NMR spectra were recorded with a JEOL-GSX 400 spectrometer using TMS as the internal standard, and ^{13}C NMR spectra were recorded at 100 MHz using TMS as the internal standard. IR absorption spectra were determined with an IR A-2 spectrophotometer, and mass spectra were obtained with a JMS-700 mass spectrometer. Elemental analyses were performed by the Institute of Science and Technology, Inc. Separation of the compounds by column chromatography was done with Silica Gel 60 (230–400 mesh ASTM, E. Merck) under a slightly elevated pressure (1.1–1.5 atm) for easy elution, and the quantity of silica gel used was 50–100 times the weight charged on the column. THF was distilled in the presence of radical anions generated by sodium–benzophenone ketyl. DMF and pyridine were dried by storage over 4 Å molecular sieves.

6,7,9-Tri-O-*acetyl-4,8-anhydro-2,3,5-trideoxy-5-trifluoroacetylamino*-D-glycero-D-ido-*nononic acid benzyl ester* (**2a**).—To a suspension of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide (**1a**) (194 mg, 0.42 mmol), 2,2′-azobis-(2,4-dimethyl-4-methoxyvaleronitrile) (V-70) (160 mg, 0.52 mmol) and benzyl acrylate (680 mg, 4.2 mmol) in Et_2O (4 mL), a solution of tributyltinhydride (151 mg, 0.52 mmol) in Et_2O (4 mL) was slowly added at rt with stirring. After 1 h, the reaction mixture was filtered, concentrated in vacuo, and chromatographed on a silica gel column. Elution with 1:9, then 1:1 EtOAc–hexane gave **2a** (192 mg, 84% yield). R_f 0.20 (3:7 EtOAc–hexane). IR ν_{max}($CHCl_3$) 3425, 2960, 1738, 1542, 1371, 1249, 1171, 1046 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.39–7.31 (m, 5 H), 7.00 (d, 1 H, *J* 8.7 Hz, N*H*, D_2O exchanged), 5.14, 5.12 (AB-q, 2 H, *J* 12.4 Hz), 5.04 (t, 1 H, *J* 5.5 Hz), 4.91 (t, 1 H, *J* 4.9 Hz), 4.45 (dd, 1 H, *J* 12.1 and 7.3 Hz, C9-*H*), 4.23–4.16 (m, 2 H, C5-*H* and C4-*H* or C8-*H*), 4.09 (dd, 1 H, *J* 12.1 and 4.5 Hz, C9-*H*), 3.99 (m, 1 H, C4-*H* or C8-*H*), 2.48–2.43 (m, 2 H), 2.11 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H), 1.93 (m, 1 H), 1.79 (m, 1 H). FABMS (positive-ion): *m*/*z* 548 $[M + H]^+$, 570 $[M + Na]^+$. HR-FABMS (positive-ion): Calcd for $C_{24}H_{29}F_3NO_{10}$: 548.1744. Found: 548.1738. Anal. Calcd for $C_{24}H_{28}F_3NO_{10}$ (547.5): C, 52.65; H, 5.15; N, 2.56; F, 10.41. Found: C, 52.54; H, 5.10; N, 2.43; F, 10.32.

6,7,9-Tri-O-*acetyl-4,8-anhydro-2,3,5-trideoxy-5-trifluoroacetylamino*-D-glycero-D-ido-*nononic acid* tert-*butyl ester* (**2b**).—Compound **1b** (237 mg, 0.51 mmol) was treated with *tert*-butyl acrylate as described in the formation of **2a** from **1a** and benzyl acrylate to give **2b** (152 mg, 58% yield) as a gum. R_f 0.35 (7:3 Et_2O–hexane). IR: ν_{max}(film) 3317, 2980, 1747, 1728, 1554, 1370, 1228, 1157, 1094, 1039, 758 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.98 (d, 1 H, *J* 8.7 Hz, N*H*, D_2O exchanged), 5.05 (t,

1 H, *J* 5.9 Hz), 4.94 (t, 1 H, *J* 5.1 Hz), 4.44 (dd, 1 H, *J* 11.9 and 7.1 Hz, C9-*H*), 4.22 (m, 1 H, C5-*H*, changed to dd, *J* 3.5, 6.4 Hz, on addition of D_2O), 4.20–4.14 (m, 2 H, C9-*H* and C4-*H* or C8-*H*), 4.00 (m, 1 H, C4-*H* or C8-*H*), 2.36–2.31 (m, 2 H), 2.12 (s, 3 H), 2.11 (s, 3 H), 2.09 (s, 3 H), 1.88 (m, 1 H), 1.72 (m, 1 H), 1.45 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 170.5, 170.1, 168.7, 156.9, 115.7, 80.8, 71.9, 68.6, 66.8, 60.7, 50.1, 30.9, 28.0, 23.7, 20.7, 20.6. FABMS (positive-ion): *m*/*z* 514 $[M+H]^+$, 512 $[M-H]^+$, 536 $[M+Na]^+$, 552 $[M+K]^+$ (on addition of KI), 590 $[M+2K-H]^+$. HRFABMS (positive-ion): Calcd for $C_{21}H_{30}F_3KNO_{10}$: 552.1459. Found: 552.1477.

6,7,9-Tri-O-*acetyl-4,8-anhydro-2,3,5-trideoxy-5-benzyloxycarbonylamino*-D-glycero-D-ido-*nononic acid* tert-*butyl ester* (**2c**).—Compound **1b** (1.885 g, 3.75 mmol) was treated with *tert*-butyl acrylate as described in the formation of **2a** from **1a** and benzyl acrylate to gave **15** (1.124 g, 54% yield). R_f 0.38 (2:3 EtOAc–hexane). IR ν_{max}(KBr) 3351, 2977, 1746, 1729, 1533, 1330, 1237, 1154, 1039 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.36–7.31 (m, 5 H), 5.15–5.05 (m, 4 H), 4.95 (t, 1 H, *J* 7.0 Hz), 4.32 (dd, 1 H, *J* 12.0 and 6.0 Hz), 4.13–4.00 (m, 3 H), 3.87 (m, 1 H), 2.38–2.25 (m, 2 H), 2.10 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 1.94 (m, 1 H), 1.80 (m, 1 H), 1.45 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.6, 169.1, 155.7, 136.2, 128.5, 128.2, 128.1, 80.6, 71.4, 70.4, 69.9, 67.8, 67.0, 61.6, 52.2, 31.1, 28.0, 22.1, 20.7. FABMS (positive-ion): *m*/*z* 552 $[M+H]^+$, 574 $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{27}H_{38}NO_{11}$: 552,2445. Found: 552.2435. Anal. Calcd for $C_{27}H_{37}NO_{11}$: C, 58.79; H, 6.76; N, 2.54. Found: C, 58.66; H, 6.66; N, 2.48.

6,7,9-Tri-O-*acetyl-4,8-anhydro-2,3,5-trideoxy-5-[(4-methoxybenzylidene)amino]*-D-glycero-D-ido-*nononic acid benzyl ester* (**2d**).—3,4,6-Tri-*O*-acetyl-2-deoxy-2-[(4-methoxybenzylidene)amino]-α-D-glucopyranosyl bromide (**1c**) (1.885 g, 3.75 mmol) was treated as described in the formation of **2a** from **1a** to give **2d** (1.124 g, 54%). R_f 0.38 (2:3 EtOAc–hexane). IR ν_{max}(film) 3030-2840, 1745, 1641, 1605, 1577, 1513 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.17 (s, 1 H), 7.66 (d, 2 H, *J* 8.8 Hz), 7.34 (s, 5 H), 6.90 (d, 2 H, *J* 8.8 Hz), 5.47 (dd, 1 H, *J* 10.2, 9.5 Hz, C6-H), 5.12 (s, 2 H), 5.04 (t, 1 H, *J* 9.5 Hz), 4.29 (dd, 1 H, *J* 11.7, 4.4 Hz), 4.04–3.96 (m, 3 H, C4,6,9-H), 3.84 (s, 3 H), 3.66 (dd, 1 H, 9.5, 5.9 Hz, C8-H), 2.51–2.42 (m, 2 H), 2.37–2.31 (m, 2 H), 2.08 (s, 3 H), 2.03 (s, 3 H), 1.86 (s, 3 H). FABMS (positive-ion): *m*/*z* 570 $[M+H]^+$, $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{30}H_{36}NO_{10}$: 570.2339. Found: 570.2337. Anal. Calcd for $C_{30}H_{35}NO_{10}$: C, 63.26; H, 6.19; N, 2.46. Found: C, 63.16; H, 6.33; N, 2.55.

6,7,9-Tri-O-*acetyl-4,8-anhydro-5-[(R)-3-(benzyloxytetradecanoyl)amino]-2,3,5-trideoxy*-D-glycero-D-ido-*nononic acid* tert-*butyl ester* (**3**).—A solution of **2c** (570 mg, 1.03 mmol) in EtOH (5 mL) containing 20% $Pd(OH)_2$–C (115 mg) was stirred under a hydrogen atmosphere at rt for 20 min. The reaction mixture was filtered and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (10 mL) then (*R*)-3-(benzyloxy)tetradecanoic acid (381 mg, 1.14 mmol) and WSCI (1.16 mmol) were added. After stirring overnight at rt, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 3:7, then 1:1 EtOAc–hexane gave **3** (626 mg, 83% yield). R_f 0.43 (2:3 EtOAc–hexane). IR ν_{max}($CHCl_3$) 3429, 3356, 2928, 2856, 1743, 1671, 1514, 1456, 1369, 1251, 1154, 1045 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.34–7.28 (m, 5 H), 6.64 (d, 1 H, *J* 8.8 Hz), 5.02 (dd, 1 H, *J* 7.8 and 6.9 Hz), 4.89 (t, 1 H, *J* 6.6 Hz), 4.56, 4.52 (ABq, 2 H, *J* 11.3 Hz), 4.35–4.28 (m, 2 H), 4.12–4.06 (m, 2 H), 3.85 (m, 1 H), 3.79 (m, 1 H), 2.46 (dd, 1 H, *J* 15.1 and 3.8 Hz), 2.36 (dd, 1 H, *J* 15.0 and 7.0 Hz), 2.28–2.14 (m, 2 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.89 (s, 3 H), 1.87–1.50 (m, 4 H), 1.44 (s, 9 H), 1.32–1.25 (m, 18 H), 0.88 (t, 3 H, *J* 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 171.1, 170.6, 170.3, 169.3, 138.0, 128.4, 128.1, 127.8, 80.5, 76.2, 71.3, 70.8, 70.5, 69.8, 67.7, 61.5, 49.8, 41.2, 33.6, 31.9, 31.0, 29.61, 29.55, 29.3, 28.1, 25.2, 22.7, 22.4, 20.8, 20.7, 20.5, 14.1. FABMS (positive-ion): *m*/*z* 734 $[M+H]^+$, 756 $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{40}H_{64}NO_{11}$: 734.4479. Found: 734.4498.

4,8-Anhydro-5-[(R)-3-(benzyloxy)tetradecanoyl-amino]-2,3,5-trideoxy-7,9-O-*isopropylidene*-D-glycero-D-ido-*nononic acid* tert-*butyl ester* (**4**).—A solution of **3** (626 mg, 0.853 mmol) in MeOH (10 mL) was treated with 1 M NaOMe in MeOH (0.1 mL) for 20 min at rt, then evaporated in vacuo. To the residue were added DMF (10 mL), 2,2-dimethoxypropane (5 mL) and $TsOH\cdot H_2O$ (40 mg, 0.21 mmol). After stirring for 1 h at rt, the reaction mixture was quenched with satd aq $NaHCO_3$, extracted with EtOAc, washed with water and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 1:1, then 4:1 EtOAc–hexane gave **4** (485 mg, 88% yield). R_f 0.34 (2:3 EtOAc–hexane). IR ν_{max}(KBr) 3440, 3315, 2925, 2854, 1728, 1630, 1456, 1368, 1156, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.39–7.28 (m, 5 H), 6.50 (d, 1 H, *J* 7.2 Hz), 4.63, 4.51 (ABq, 2 H, *J* 11.3 Hz), 4.16 (m, 1 H), 4.08 (m, 1 H), 3.84–3.77 (m, 2 H), 3.68 (t, 1 H, *J* 10.4 Hz), 3.55–3.45 (m, 2 H), 3.32 (m, 1 H), 2.60 (d, 1 H, *J* 1.9 Hz), 2.53 (dd, 1 H, *J* 15.0 and 3.8 Hz), 2.42 (dd, 1 H, *J* 15.0 and 6.6 Hz), 2.22 (m, 1 H), 2.10 (m, 1 H), 1.84–1.52 (m, 4 H), 1.49 (s, 3 H), 1.44 (s, 9 H), 1.42 (s, 3 H), 1.39–1.25 (m, 18 H), 0.88 (t, 3 H, *J* 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 138.1, 128.5, 127.9, 127.8, 99.8, 80.5, 76.7, 75.4, 74.2, 71.3, 69.9, 64.3, 62.6, 54.0, 40.9, 33.4, 31.9, 31.2, 29.61, 29.55, 29.3, 29.1, 25.2, 22.7, 20.6, 19.1, 14.1. FABMS (positive-ion): *m*/*z* 648

$[M+H]^+$. HRFABMS (positive-ion): Calcd for $C_{37}H_{62}NO_8$: 648.4476. Found: 648.4470.

*4,8 - Anhydro - 5 - [(*R*) - 3 - (benzyloxy)tetradecanoylamino] - 2,3,5 - trideoxy - 7,9 - O - isopropylidene - 6 - O - [(*R*) - 3 - (tetradecanoyloxy)tetradecanoyl] - D - glycero - D - ido-nononic acid* tert-*butyl ester* (**5**).—To a solution of **4** (403 mg, 0.622 mmol), (*R*)-3-(tetradecanoyloxy)-tetradecanoic acid (377 mg, 0.83 mmol) and DMAP (10.6 mg) in CH_2Cl_2 were added DCC (160 mg, 0.776 mmol) at rt. After stirring for 7 h, the reaction mixture was filtered, concentrated in vacuo and chromatographed on a silica gel column. Elution with 3:17, then 1:3 EtOAc–hexane gave **5** (596 mg, 88% yield). R_f 0.39 (1:4 EtOAc–hexane). IR ν_{max}(KBr) 3419, 2921, 2851, 1732, 1661, 1521, 1469, 1368, 1200, 1161, 1111 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.38–7.25 (m, 5 H), 6.34 (d, 1 H, *J* 7.5 Hz), 5.14 (m, 1 H), 5.01 (dd, 1 H, *J* 10.8 and 9.6 Hz), 4.56, 4.51 (ABq, 2 H, *J* 11.8 Hz), 4.29 (m, 1 H), 4.13 (m, 1 H), 3.84–3.78 (m, 2 H), 3.71–3.66 (m, 2 H), 3.42 (m, 1 H), 2.60 (dd, 1 H, *J* 15.1 and 6.9 Hz), 2.50 (dd, 1 H, *J* 14.9 and 5.9 Hz), 2.35–2.25 (m, 4 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.88 (m, 1 H), 1.67–1.52 (m, 5 H), 1.46 (s, 3 H), 1.43 (s, 9 H), 1.36 (s, 3 H), 1.32–1.25 (m, 58 H), 0.88 (t, 9 H, *J* 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 172.1, 171.3, 171.0, 138.5, 128.4, 127.64, 127.58, 99.7, 80.4, 76.1, 74.3, 72.8, 71.2, 70.2, 70.0, 64.7, 62.7, 52.8, 41.6, 39.3, 34.4, 33.9, 33.8, 31.9, 31.1, 29.7, 29.53, 29.46, 29.3, 29.2, 29.0, 28.1, 25.2, 25.0, 22.7, 20.3, 19.1, 14.1. FABMS (positive-ion): *m/z* 1084 $[M+H]^+$. HRFABMS (positive-ion): Calcd for $C_{65}H_{114}NO_{11}$: 1084.8391. Found: 1084.8365.

*4,8 - Anhydro - 5 - [(*R*) - 3 - (benzyloxy)tetradecanoylamino] - 2,3,5 - trideoxy - 6 - O - [(*R*) - 3 - (tetradecanoyloxy)tetradecanoyl] -* D-glycero-D-ido-*nononic acid* tert-*butyl ester* (**6**).—To a suspension of **5** (596 mg, 0.550 mmol) in MeOH (20 mL) were added $TsOH\cdot H_2O$ (10.5 mg) at rt. After stirring for 2 h, the reaction mixture was quenched with NEt_3, evaporated and chromatographed on a silica gel column. Elution with 2:3, then 1:1 EtOAc–hexane gave **6** (546 mg, 95% yield). R_f 0.50 (1:1 EtOAc–hexane). IR ν_{max}(KBr) 3472, 3302, 2922, 2852, 1730, 1649, 1545, 1468, 1368, 1161, 1101 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.36–7.25 (m, 5 H), 6.55 (d, 1 H, *J* 7.5 Hz), 5.09 (m, 1 H), 4.91 (dd, 1 H, *J* 10.4 and 8.3 Hz), 4.56, 4.52 (ABq, 2 H, *J* 11.6 Hz), 4.20 (m, 1 H), 4.12 (m, 1 H), 3.84–3.78 (m, 2 H), 3.59 (m, 1 H), 3.51 (m, 1 H), 3.23 (d, 1 H, *J* 3.7 Hz) 2.50 (d, 2 H, *J* 5.8 Hz), 2.38–2.21 (m, 5 H), 2.11 (m, 1 H), 1.85 (m, 1 H), 1.68–1.53 (m, 5 H), 1.44 (s, 9 H), 1.32–1.26 (m, 58 H), 0.88 (t, 9 H, *J* 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 172.4, 172.2, 171.3, 138.4, 128.4, 127.7, 80.6, 76.2, 74.3, 72.54, 72.47, 71.2, 71.1, 69.8, 62.4, 51.4, 41.4, 40.5, 34.8, 34.5, 34.0, 31.9, 31.2, 29.7, 29.5, 29.3, 29.1, 28.1, 25.3, 25.2, 24.9, 22.7, 20.7, 14.1. FABMS (positive-ion): *m/z* 1044 $[M+H]^+$, 1066 $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{62}H_{109}NNaO_{11}$: 1066.7899. Found: 1066.7874.

*4,8 - Anhydro - 9 - O - benzyloxycarbonyl - 5 - [(*R*) - 3 - (benzyloxy)tetradecanoylamino] - 2,3,5 - trideoxy - 6 - O - [(*R*) - 3 - (tetradecanoyloxy)tetradecanoyl] -* D - glycero - D - ido-*nononic acid* tert-*butyl ester* (**7**).—To a solution of **6** (644 mg, 0.616 mmol) and pyridine (1 mL) in CH_2Cl_2 (12 mL) were gradually added ClCOOBn (1 mL) with stirring at rt. After 5 h, the reaction mixture was concentrated in vacuo, and satd aq $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc, and washed with water and brine, and the organic extract was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with (1:4, then 3:7) EtOAc–hexane gave **7** (676 mg, 93% yield). R_f 0.40 (3:7 EtOAc–hexane). IR ν_{max}(KBr) 3484, 3297, 2921, 2852, 1730, 1650, 1292 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.40–7.27 (m, 5 H), 6.49 (d, 1 H, *J* 7.3 Hz), 5.17 (s, 2 H), 5.09 (m, 1 H), 4.90 (dd, 1 H, *J* 10.6 and 8.4 Hz), 4.55, 4.51 (ABq, 2 H, *J* 11.7 Hz), 4.42–4.36 (m, 2 H), 4.24 (m, 1 H), 4.12 (m, 1 H), 3.81 (m, 1 H), 3.62 (m, 1 H), 3.55 (m, 1 H), 3.27 (d, 1 H, *J* 3.7 Hz) 2.49 (d, 2 H, *J* 5.9 Hz), 2.37–2.20 (m, 5 H), 2.07 (m, 1 H), 1.83 (m, 1 H), 1.63–1.53 (m, 5 H), 1.42 (s, 9 H), 1.36–1.25 (m, 58 H), 0.88 (t, 9 H, *J* 6.6 Hz). FABMS (positive-ion): *m/z* 1178 $[M+H]^+$, 1216 $[M+K]^+$ (on addition of KI). HRFABMS (positive-ion): Calcd for $C_{70}H_{115}NKO_{13}$: 1216.8006. Found: 1216.8030.

*4,8 - Anhydro - 9 - O - benzyloxycarbonyl - 5 - [(*R*) - 3 - (benzyloxy)tetradecanoylamino] - 2,3,5 - trideoxy - 7 - O - diphenylphosphono - 6 - O - [(*R*) - 3 - (tetradecanoyloxy)tetradecanoyl] -* D-glycero-D-ido-*nononic acid* tert-*butyl ester* (**8**).—To a solution of **7** (676 mg, 0.574 mmol) and DMAP (176 mg, 1.441 mmol) in CH_2Cl_2 (6 mL) were added diphenyl chlorophosphate (311 mg, 1.157 mmol) in CH_2Cl_2 (1 mL) with stirring at rt. After 4 h, the reaction mixture was quenched with satd aq $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 1:4, then 3:7 EtOAc–hexane gave **8** (762 mg, 94% yield). R_f 0.40 (1:3 EtOAc–hexane). IR ν_{max}(KBr) 3335, 2922, 2852, 1744, 1729, 1654, 1265, 954 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.37–7.12 (m, 20 H), 6.45 (d, 1 H, *J* 7.4 Hz), 5.23 (dd, 1 H, *J* 10.0 and 8.1 Hz), 5.14–5.07 (m, 3 H), 5.02 (ABq, 1 H, *J* 12.2 Hz), 4.65 (dd, 1 H, *J* 17.1 and 8.4 Hz), 4.56, 4.51 (ABq, 2 H, *J* 11.7 Hz), 4.30–4.16 (m, 4 H), 3.90–3.82 (m, 2 H), 2.51–2.28 (m, 4 H), 2.22–2.15 (m, 3 H), 2.06 (m, 1 H), 1.84 (m, 1 H), 1.67–1.37 (m, 14 H), 1.32–1.25 (m, 58 H), 0.88 (t, 9 H, *J* 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 172.2, 171.4, 170.7, 154.7, 150.3, 138.5, 135.1, 129.8, 128.5, 128.4, 128.3, 128.2, 127.6, 127.5, 125.6, 120.1, 80.5, 76.2, 74.3, 72.3, 71.2, 70.1, 69.9, 69.8, 69.7, 65.3, 51.3, 41.7, 39.2, 34.3, 34.2, 34.1, 31.9, 31.0, 29.7, 29.5, 29.3, 29.2, 28.1, 25.2, 25.1, 25.0, 22.7, 20.7, 14.1. FABMS

(positive-ion): m/z 1410 $[M+H]^+$, 1432 $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{82}H_{125}NO_{16}P$: 1410.8736. Found: 1410.8744. Anal. Calcd for $C_{82}H_{124}NO_{16}P$: C, 69.81; H, 8.86; N, 0.99; P, 2.20. Found: C, 69.64; H, 8.69; N, 0.96; P, 2.00.

*4,8 - Anhydro - 5 - [(*R*) - 3 - (benzyloxy)tetradecanoyl-amino] - 2,3,5 - trideoxy - 7 -* O *- diphenylphosphono - 6 -* O*-[(*R*) - 3 - (tetradecanoyloxy)tetradecanoyl] -* D *- glycero -* D*-ido-nononic acid* tert*-butyl ester* (**9**).—A solution of **8** (305 mg, 0.216 mmol) in THF (2 mL) containing Pd(en)–C (32 mg) was stirred under a hydrogen atmosphere at rt for 1 h. The reaction mixture was filtered, concentrated in vacuo and chromatographed on a silica gel column. Elution with 3:7, then 1:1 EtOAc–hexane gave **9** (254 mg, 92% yield). R_f 0.43 (2:3 EtOAc–hexane). IR ν_{max}(KBr) 2922, 2852, 1736, 1650, 1492, 1197, 1160, 1046, 1026, 968 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.37–7.16 (m, 15 H), 6.42 (d, 1 H, J 7.4 Hz), 5.25 (dd, 1 H, J 10.4 and 8.5 Hz), 5.11 (m, 1 H), 4.66 (dd, 1 H, J 17.7 and 8.7 Hz), 4.57, 4.51 (ABq, 2 H, J 11.7 Hz), 4.30 (m, 1 H), 4.20 (m, 1 H), 3.85 (m, 1 H), 3.69–3.54 (m, 3 H), 3.08 (dd, 1 H, J 7.9 and 6.9 Hz), 2.44–2.03 (m, 8 H), 1.85 (m, 1 H), 1.66–1.21 (m, 72 H) 0.88 (t, 9 H, J 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 172.5, 171.4, 170.8, 150.3, 138.5, 129.9, 128.3, 127.6, 127.5, 125.8, 120.1, 80.6, 76.2, 74.3, 72.4, 71.9, 71.2, 70.4, 69.8, 60.4, 51.8, 41.7, 39.1, 34.4, 34.2, 34.0, 31.9, 31.3, 29.7, 29.6, 29.3, 29.2, 28.1, 25.2, 25.1, 25.0, 22.7, 20.5, 14.1. FABMS (positive-ion): m/z 1276 $[M+H]^+$, 1298 $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{74}H_{118}NNaO_{14}P$: 1298.8188. Found: 1298.8207. Anal. Calcd for $C_{74}H_{118}NO_{14}P$: C, 69.62; H, 9.32; N, 1.10; P, 2.43. Found: C, 69.55; H, 9.15; N, 1.16; P, 2.51.

*4,8 - Anhydro - 5 - [(*R*) - 3 - (benzyloxy)tetradecanoyl-amino] - 2,3,5 - trideoxy - 7 -* O *- diphenylphosphono - 9 -* O*-methyl - 6 -* O *-[(*R*) - 3 - (tetradecanoyloxy)tetradecanoyl] -* D*-glycero-*D*-ido-nononic acid* tert*-butyl ester* (**10**).—A solution of **8** (97.9 mg, 0.069 mmol) in THF (1 mL) containing Pd(en)–C (9.8 mg) was stirred under a hydrogen atmosphere at rt for 3 h. The reaction mixture was filtered and concentrated in vacuo to give crude **9** (88.1 mg, 99%). The crude **9** was dissolved in CH_2Cl_2 (2 mL). 2,6-Di-*tert*-butyl-4-methylpyridine (59 mg) and $Me_3O{\cdot}BF_4$ (39 mg) were added portionwise to the solution. After stirring overnight at rt, the reaction mixture was diluted with EtOAc, washed with satd aq $NaHCO_3$, water and brine, and the organic extract was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 1:9, then 2:3 EtOAc–hexane gave **10** (76.3 mg, 85% yield). R_f 0.32 (3:7 EtOAc–hexane). IR ν_{max}(KBr) 3423, 3372, 2927, 2855, 1725, 1674, 1490, 1290, 1161, 1087, 1025, 959 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.35–7.17 (m, 15 H), 6.38 (d, 1 H, J 7.4 Hz), 5.24 (dd, 1 H, J 10.3 and 8.4 Hz), 5.11 (m, 1 H), 4.70 (dd, 1 H, J 17.4 and 8.7 Hz), 4.56, 4.51 (ABq, 2 H, J 11.7 Hz), 4.29 (m, 1 H), 4.20 (m, 1 H), 3.85 (m, 1 H), 3.74 (m, 1 H), 3.44 (d, 2 H, J 3.5 Hz), 3.22 (s, 3 H), 2.49–2.16 (m, 7H), 2.08 (m, 1 H), 1.86 (m, 1 H), 1.68–1.40 (m, 14 H), 1.32–1.25 (m, 58 H), 0.88 (t, 9 H, J 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 172.3, 171.3, 170.9, 150.4, 138.6, 129.8, 128.3, 127.7, 127.5, 125.6, 120.2, 80.4, 76.2, 74.7, 72.5, 71.2, 70.7, 70.2, 69.8, 59.2, 51.7, 41.8, 39.1, 34.3, 34.1, 31.9, 31.1, 29.7, 29.6, 29.4, 29.2, 28.1, 25.2, 25.1, 25.0, 22.7, 20.5, 14.1. FABMS (positive-ion): m/z 1290 $[M+H]^+$, 1312 $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{75}H_{121}NO_{14}P$: 1290.8521. Found: 1290.8525. Anal. Calcd for $C_{75}H_{120}NO_{14}P$: C, 69.79; H, 9.37; N, 1.09; P, 2.40. Found: C, 69.37; H, 9.02; N, 1.12; P, 2.33.

*4,8 - Anhydro - 5 - [(*R*) - 3 - (benzyloxy)tetradecanoyl-amino] - 2,3,5,9 - tetradeoxy - 7 -* O *- diphenylphosphono - 9-fluoro - 6 -* O *-[(*R*) - 3 - (tetradecanoyloxy)tetradecanoyl] -* D*-glycero-*D*-ido-nononic acid* tert*-butyl ester* (**11**).—To a solution of **9** (105 mg, 0.082 mmol) in CH_2Cl_2 (4 mL) was gradually added DAST (200 mL), with stirring at 0 °C. After stirring overnight, the reaction mixture was quenched with satd aq $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 1:4, then 1:1 EtOAc–hexane gave **11** (74.7 mg, 71% yield). R_f 0.58 (3:7 EtOAc–hexane). IR ν_{max}(KBr) 3423, 3371, 2927, 2855, 1724, 1674, 1491, 1292, 1161, 963 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.36–7.16 (m, 15 H), 6.44 (d, 1 H, J 7.2 Hz), 5.26 (dd, 1 H, J 10.2 and 8.4 Hz), 5.10 (m, 1 H), 4.63 (dd, 1 H, J 17.6 and 8.8 Hz), 4.57, 4.51 (ABq, 2 H, J 11.7 Hz), 4.42 (m, 2 H, J_{HF} 46.9 Hz), 4.31–4.19 (m, 2 H), 3.87–3.77 (m, 2 H), 2.50–2.29 (m, 4 H), 2.23–2.15 (m, 3 H), 2.08 (m, 1 H), 1.86 (m, 1 H), 1.67–1.42 (m, 14 H), 1.39–1.25 (m, 58 H), 0.88 (t, 9 H, J 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 172.3, 171.5, 170.9, 150.3, 138.6, 129.9, 128.4, 127.6, 127.5, 125.7, 120.1, 80.9, 80.5, 76.2, 73.9, 72.8, 71.2, 70.6, 70.3, 69.9, 51.6, 41.7, 39.2, 34.3, 34.2, 34.1, 31.9, 31.1, 29.7, 29.6, 29.4, 29.2, 28.1, 25.2, 25.1, 25.0, 22.7, 20.2, 14.1. FABMS (positive-ion): m/z 1278 $[M+H]^+$, 1300 $[M+Na]^+$. HR-FABMS (positive-ion): Calcd for $C_{74}H_{118}FNO_{13}P$: 1278.8325. Found: 1278.8334. Anal. Calcd for $C_{74}H_{117}FNO_{13}P$: C, 69.51; H, 9.22; N, 1.10; F, 1.49; P, 2.42. Found: C, 69.19; H, 8.43; N, 1.03; F, 1.38; P, 2.47

*4,8-Anhydro-2,3,5-trideoxy-7-*O*-diphenylphosphono-5-[(*R*)-3-(hydroxy)tetradecanoylamino]-6-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl] -* D *- glycero -* D *- ido - nononic acid* (**12**).—A solution of **8** (71.5 mg, 0.051 mmol) in CH_2Cl_2 (2 mL) was treated with CF_3COOH (0.2 mL) for 4 h at rt, then evaporated in vacuo to give nononic acid, which was dissolved in EtOH (2 mL). $Pd(OH)_2$–C (21 mg) was added. The mixture was stirred 2 h under a hydrogen atmosphere at rt and was filtered. The filtrate was concentrated in vacuo and chro-

matographed on a silica gel column. The crude product was purified by preparative TLC to give **12** (42.1 mg, 73% yield). R_f 0.60 (1:9 MeOH–CH_2Cl_2). IR ν_{max}(KBr) 3414, 2924, 2854, 1738, 1648, 1664, 1490, 1457, 1275, 1189, 1025, 964 cm^{-1}. ^1H NMR (CD_3OD): δ 7.41-7.19 (m, 10 H), 5.42 (dd, 1 H, *J* 10.4 and 8.7 Hz), 5.14 (m, 1 H), 4.68 (dd, 1 H, *J* 17.7 and 8.9 Hz), 4.33 (dd, 1 H, *J* 10.6 and 5.7 Hz), 4.08 (m, 1 H), 3.93 (m, 1 H), 3.75 (m, 1 H), 3.68 (dd, 1 H, *J* 12.0 and 1.6 Hz), 3.59 (dd, 1 H, *J* 12.2 and 4.9 Hz), 2.55–2.23 (m, 6 H), 2.19 (t, 2 H, *J* 7.3 Hz), 2.10 (m, 1 H), 1.90 (m, 1 H), 1.59–1.28 (m, 62 H) 0.89 (t, 9 H, *J* 6.6 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 173.4, 173.0, 170.2, 150.3, 129.6, 125.5, 119.8, 75.5, 72.7, 71.5, 70.7, 69.5, 68.2, 60.2, 51.2, 43.3, 38.4, 37.1, 33.8, 33.6, 31.6, 29.4, 29.3, 29.0, 28.8, 28.7, 25.3, 24.7, 22.3, 20.6, 13.0. FABMS (positive-ion): *m*/*z* 1131 $[M+H]^+$, 1153 $[M+Na]^+$, 1169 $[M+K]^+$ (on addition of KI), 1207 $[M+2K-H]^+$. HRFABMS (positive-ion): Calcd for $C_{63}H_{104}NNaO_{14}P$: 1152.7092. Found: 1152.7097. Anal. Calcd for $C_{63}H_{104}NO_{14}P$: C, 66.94; H, 9.27; N, 1.24; P, 2.74. Found: C, 66.40; H, 8.79; N, 1.17; P, 2.95.

*4,8-Anhydro-2,3,5-trideoxy-7-*O*-diphenylphosphono-5-[(*R*)-3-(hydroxy)tetradecanoylamino]-9-*O*-methyl-6-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-*D*-glycero-*D*-ido-nononic acid* (**13**).—Compound **10** (67.4 mg) was treated as described in the formation of **12** from **8** to give **13** (49.8 mg, 83% yield). R_f 0.54 (1:9 MeOH–CH_2Cl_2). IR ν_{max}(neat) 3307, 2922, 2852, 1737, 1654, 1491, 1290, 1192, 1094, 1025, 960 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.36–7.17 (m, 10 H), 6.85 (d, 1 H, *J* 7.4 Hz), 5.30 (dd, 1 H, *J* 10.0 and 8.7 Hz), 5.08 (m, 1 H), 4.70 (dd, 1 H, *J* 17.5 and 8.8 Hz), 4.36–4.26 (m, 2 H), 3.94 (m, 1 H), 3.78 (m, 1 H), 3.46 (d, 2 H, *J* 3.5 Hz), 3.24 (s, 3 H), 2.54–2.20 (m, 8 H), 2.03–1.88 (m, 2 H), 1.58–1.22 (m, 62 H) 0.88 (t, 9 H, *J* 6.6 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 175.8, 173.9, 172.9, 171.2, 150.4, 129.9, 125.7, 120.2, 74.8, 72.3, 70.8, 70.7, 70.3, 70.0, 68.7, 59.2, 51.5, 42.8, 39.4, 37.2, 34.4, 34.3, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 25.5, 25.1, 25.0, 22.7, 20.6, 14.1. FABMS (positive-ion): *m*/*z* 1144 $[M+H]^+$, 1166 $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{64}H_{106}NNaO_{14}P$: 1166.7248. Found: 1166.7263. Anal. Calcd for $C_{64}H_{106}NO_{14}P$: C, 67.16; H, 9.34; N, 1.22; P, 2.71. Found: C, 67.32; H, 9.43; N, 1.14; P, 2.98.

*4,8-Anhydro-2,3,5,9-tetradeoxy-7-*O*-diphenylphosphono-9-fluoro-5-[(*R*)-3-(hydroxy)tetradecanoylamino]-6-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-*D*-glycero-*D*-ido-nononic acid* (**14**).—Compound **11** (52.9 mg) was treated as described in the formation of **12a** from **8** to give **12c** (35.6 mg, 76% yield). R_f 0.55 (1:9 MeOH–CH_2Cl_2). IR ν_{max}(neat) 3307, 2925, 2854, 1736, 1655, 1490, 1189, 961 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.36–7.16 (m, 10 H), 6.93 (d, 1 H, *J* 6.4 Hz), 5.32 (t, 1 H, *J* 9.3 Hz), 5.07 (m, 1 H), 4.64 (dd, 1 H, *J* 17.8 and 9.0 Hz), 4.46 (dd, 2 H, *J* 2.5, J_{FH} 47.0 Hz), 4.34–4.29 (m, 2 H), 3.95 (m, 1 H), 3.83 (m, 1 H, *J* 9.0, J_{FH} 23.3 Hz) 2.51–2.21 (m, 8 H), 2.01–1.91 (m, 2 H), 1.58–1.25 (m, 62 H) 0.88 (t, 9 H, *J* 6.7 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 176.1, 174.1, 173.1, 171.1, 150.3, 129.9, 125.7, 120.1, 80.9, 74.0, 72.6, 70.6, 70.4, 70.1, 68.7, 51.6, 42.8, 39.5, 37.2, 34.4, 34.3, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 25.5, 25.1, 25.0, 22.7, 20.2, 14.1. FABMS (positive-ion): *m*/*z* 1132 $[M+H]^+$, 1154 $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{63}H_{104}FNO_{13}P$: 1132.7229. Found: 1132.7230. Anal. Calcd for $C_{63}H_{103}FNO_{13}P$: C, 66.82; H, 9.17; F, 1.68; N, 1.24; P, 2.74. Found: C, 66.63; H, 9.01; F, 1.70; N, 1.17; P, 2.62.

*4,8-Anhydro-2,3,5-trideoxy-5-[(*R*)-3-(hydroxy)tetradecanoylamino]-7-*O*-phosphono-6-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-*D*-glycero-*D*-ido-nononic acid* (**15**).—A solution of **12** (18.8 mg, 0.017 mmol) in THF (2 mL) containing PtO_2 (9.8 mg) was stirred under a hydrogen atmosphere at rt for 16 h. The reaction mixture was filtered and concentrated in vacuo. The residue were dissolved in $CHCl_3$ (6 mL), MeOH (12 mL) and 0.1 M aq HCl (4.8 mL). To the solution was added another volume of $CHCl_3$ (6 mL) and 0.1 M aq HCl (6 mL) to separate the solution into two phases. The lower $CHCl_3$ phase was collected and concentrated to give **15** (16.0 mg, 98%), mp 211–213 °C. $[\alpha]_D^{25}$ + 49.5° (*c* 0.20, $CHCl_3$). IR ν_{max}(KBr) 3304, 2921, 2852, 1732, 1649, 1649, 1545, 1468, 1261, 1182, 1097, 1056 cm^{-1}. ^1H NMR (4:1 CD_3OD–$CDCl_3$): δ 5.27–5.18 (m, 2 H), 4.30–4.22 (m, 2 H), 4.08 (m, 1 H), 3.94 (m, 1 H), 3.78 (br, 2 H), 3.64 (m, 1 H), 2.65 (d, 2 H, *J* 6.3 Hz), 2.49–2.24 (m, 6 H), 2.06 (m, 1 H), 1.87 (m, 1 H), 1.61–1.60 (m, 4 H), 1.45–1.29 (m, 58 H), 0.89 (m, 9 H). ^{13}C NMR (100 MHz, CD_3OD): δ 176.8, 175.0, 174.2, 171.6, 74.0, 73.9, 73.4, 72.0, 71.2, 69.5, 61.8, 52.2, 44.4, 38.4, 35.2, 35.0, 32.8, 30.6, 30.2, 30.0, 29.9, 26.5, 26.5, 26.1, 25.9, 23.5, 21.6, 14.4. FABMS (positive-ion): *m*/*z* 978 $[M+H]^+$, 1000 $[M+Na]^+$. HRFABMS (positive-ion): Calcd for $C_{51}H_{97}NO_{14}P$: 978.6647. Found: 978.6631. Anal. Calcd for $C_{51}H_{96}NO_{14}P$: C, 62.62; H, 9.89; N, 1.43; P, 3.17. Found: C, 62.61; H, 10.14; N, 1.24; P, 2.96.

*4,8-Anhydro-2,3,5-trideoxy-5-[(*R*)-3-(hydroxy)tetradecanoylamino]-7-*O*-phosphono-9-*O*-methyl-6-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-*D*-glycero-*D*-ido-nononic acid* (**16**).—Compound **13** (38.3 mg) was treated as described in the formation of **15** from **12** to give **16** (33.6 mg, quant), mp 157–160 °C. $[\alpha]_D^{23}$ + 18.4° (*c* 0.20, $CHCl_3$). IR ν_{max}(neat) 3298, 2922, 2852, 1734, 1647, 1543, 1468, 1181, 1091 cm^{-1}. ^1H NMR (CD_3OD): δ 5.25–5.17 (m, 2 H), 4.27–4.19 (m, 2 H), 4.03 (m, 1 H), 3.94 (m, 1 H), 3.78 (m, 2 H), 3.69 (dd, 1 H, *J* 10.7 and 2.4 Hz), 3.58 (dd, 1 H, *J* 10.8 and 5.9 Hz), 3.38 (s, 3 H), 2.65 (d, 2 H, *J* 6.2 Hz), 2.47–2.24 (m, 6 H), 2.04 (m, 1 H), 1.85 (m, 1 H), 1.60–1.59 (m, 4 H), 1.45–1.29 (m, 58 H) 0.90 (t, 9 H, *J* 6.8 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 176.9, 175.1, 174.4, 171.7,

74.5, 73.6, 72.8, 72.4, 72.3, 71.4, 69.7, 59.5, 52.2, 44.8, 40.3, 38.6, 35.3, 35.2, 33.1, 30.8, 30.7, 30.5, 30.3, 26.8, 26.4, 26.2, 23.8, 22.3, 14.5. FABMS (positive-ion): m/z 992 $[M+H]^+$, 1014 $[M+Na]^+$, 1036 $[M+2Na-H]^+$. HRFABMS (positive-ion): Calcd for $C_{52}H_{98}NNaO_{14}P$: 1014.6623. Found: 1014.6633. Anal. Calcd for $C_{52}H_{98}NO_{14}P$: C, 62.94; H, 9.96; N, 1.41; P, 3.12. Found: C, 62.98; H, 9.84; N, 1.58; P, 3.11.

*4,8-Anhydro-2,3,5,9-tetradeoxy-9-fluoro-5-[(*R*)-3-(hydroxy)tetradecanoylamino]-7-*O*-p hosphono-6-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-*D*-glycero-*D*-ido-nononic acid* (**17**).—Compound **12c** (33.2 mg) was treated as described in the formation of **15** from **12** to give **17** (27.1 mg, 94% yield), mp 148–167 °C. $[\alpha]_D^{25}$ + 14.2° (*c* 0.21, $CHCl_3$). IR ν_{max}(neat) 3371, 2921, 2852, 1733, 1645, 1544, 1467, 1182, 1098 cm^{-1}. ^1H NMR (CD_3OD): δ 5.28–5.17 (m, 2 H), 4.67–4.55 (m, 2 H, J_{FH} 47.4 Hz), 4.29–4.19 (m, 2 H), 4.06 (m, 1 H), 3.94 (m, 1 H), 3.85 (m, 1 H, J_{FH} 22.5 Hz), 2.66 (d, 2 H, J 6.3 Hz), 2.45–2.25 (m, 6 H), 2.07 (m, 1 H), 1.88 (m, 1 H), 1.61 (br, 4 H), 1.45–1.29 (m, 58 H), 0.90 (t, 9 H, J 6.8 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 176.8, 175.1, 174.5, 171.7, 82.7, 74.1, 73.6, 72.3, 71.4, 69.7, 52.3, 44.8, 40.3, 38.6, 35.3, 35.2, 33.1, 30.8, 30.5, 30.3, 26.8, 26.4, 26.2, 23.8, 22.0, 14.5. FABMS (positive-ion): m/z 980 $[M+H]^+$, 1002 $[M+Na]^+$, 1024 $[M+2Na-H]^+$. HRFABMS (positive-ion): Calcd for $C_{51}H_{95}FNNaO_{13}P$: 1002.6423. Found: 1002.6399. Anal. Calcd for $C_{51}H_{95}FNO_{13}P$: C, 62.49; H, 9.77; N, 1.43; F, 1.94; P, 3.16. Found: C, 62.34; H, 9.69; N, 1.43; F, 1.87; P, 3.09.

Preparation of aqueous solutions of compounds for measurement of biological activities.—Compound **15** was dissolved in aq 0.1% Et_3N (v/v) solution for measurement of the biological activity. Aq 0.1% Et_3N solutions of compounds **16** and **17** were prepared as described above in the preparation of the solution of compound **15**.

Method for biological activity measurement.—The sources of the materials used in the study are as follows: Lipopolysaccharide (LPS) from *Escherichia coli* serotype 026:B6, 12-*O*-tetradecanoylphorbor acetate (TPA) and prednisolone were from Sigma Chemical Co., St. Louis, MO. PRMI-6140 medium, fetal bovine serum (FBS), and newborn calf serum (NBCS) were from GIBCO, Grand Island, NY. Human tumor necrosis factor-α enzyme-linked immunosorbent assay (TNFα ELISA) kit was from Genzyme, Cambridge, MA.

Cell culture.—Human monoblastic U937 cells were maintained in RPMI-1640 medium supplemented with 10% FBS, 100 units/mL of penicillin and 100 μg/mL of streptomycin (growth medium).

Production of TNFα by U937 cells.—U937 cells (1×10^4/200 μL/well) were plated in 96-well plates (Corning, Cambridge, MA) and cultured in the presence of TPA (30 ng/mL) for 72 h at 37 °C. After removal of the supernatant, the cells were incubated in 200 μL of fresh RPMI-1640 medium containing 10% NBCS, 30 ng/mL LPS and graded concentrations of compounds in a humidified atmosphere of 5% CO_2 for 4.5 h at 37 °C. After incubation, the amounts of TNFα produced in the culture supernatants were determined by the TNFα ELISA kits. As a control, the amount of TNFα produced by U937 cells, which were stimulated with 30 ng/mL of LPS in the absence of compounds, was used. TNFα production of U937 cells increased dose-dependently until coming to 10 ng/mL of the LPS concentration, and reached to almost ceiling. Therefore, 30 ng/mL of LPS for stimulation of U937 cells was used. All experiments were carried out at least twice.

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