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Lipid A-Type Pyrancarboxylic Acid Derivatives, their Synthesis and their Biological Activities

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Abstract—Synthesis of lipid A-type pyrancarboxylic acid derivatives, which have a carboxylic acid group in the anomeric position of the reducing sugar part of the disaccharide instead of the phosphoric acid group in lipid A, is described. We investigated the influence of the substituents in the 2′- and 6′-position of the molecules synthesized on their activities toward human monoblastic U937 cells. It was revealed that a series of compounds, possessing an acetamido group in the 2′-position showed strong LPS-antagonistic activity. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Lipopolysaccharides (LPS)[1] cover the outer surface membrane of Gram-negative bacteria. LPS are known to stimulate the immune system of the host cells, resulting in many pathophysiological events such as fever, depression of blood pressure, platelet aggregation, shock, and organ failure leading to bacterial sepsis.[2] Most of the biological activities of LPS reside in a relatively small portion of the molecule, that is, the terminal disaccharide phospholipid subunit known as lipid A (**1**, Fig. 1),[1,3,4] which is a hydrophobic anchor substance that links an essentially linear polysaccharide chain to the cell wall. In recent years, a lot of lipid A analogues have been investigated to find LPS antagonists as antisepticemia drugs,[5–7] and also LPS agonists as anticancer drugs. Then, a lot of information on the effect of substitutions in the molecules on the biological activities has been reported. It has been revealed that the phosphoric acid group in the 1-position of lipid A can be exchanged with the carboxymethyl group and dicarboxymethyl group without loss of the biological activities of lipid A.[8,9] In addition, the number of fatty acid chains in lipid A-related compounds appear to be important as to whether the molecules show LPS-agonistic or -antagonistic activities.[10]

During our investigation of the biological activities of compounds related to GLA-60 (**2**),[11] a lipid A-related monosaccharide compound which possesses LPS-agonistic activity, we found that the pyrancarboxylic acid derivative

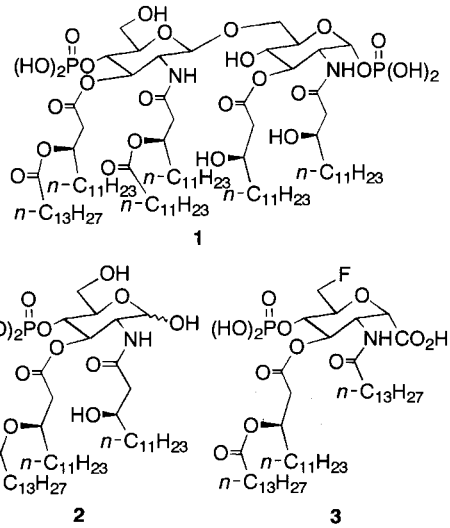

Figure 1. The structures of *E. coli* lipid A (**1**), GLA-60 (**2**), and the pyrancarboxylic acid derivative **3**.

Keywords: antibacterials; biologically active compounds; glycolipids; lipopolysaccharides.

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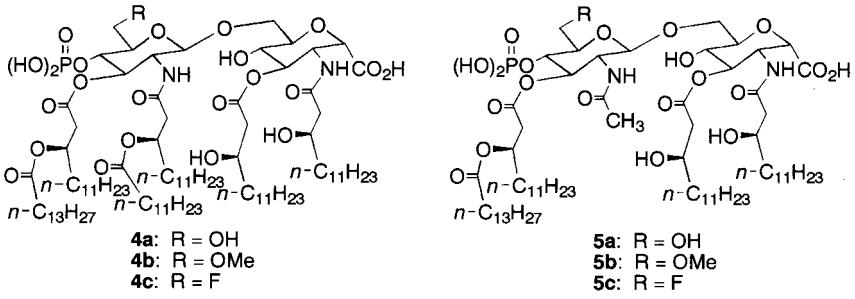


Figure 2. The structures of lipid A-type pyrancarboxylic acids **4a**–**c** and **5a**–**c**.

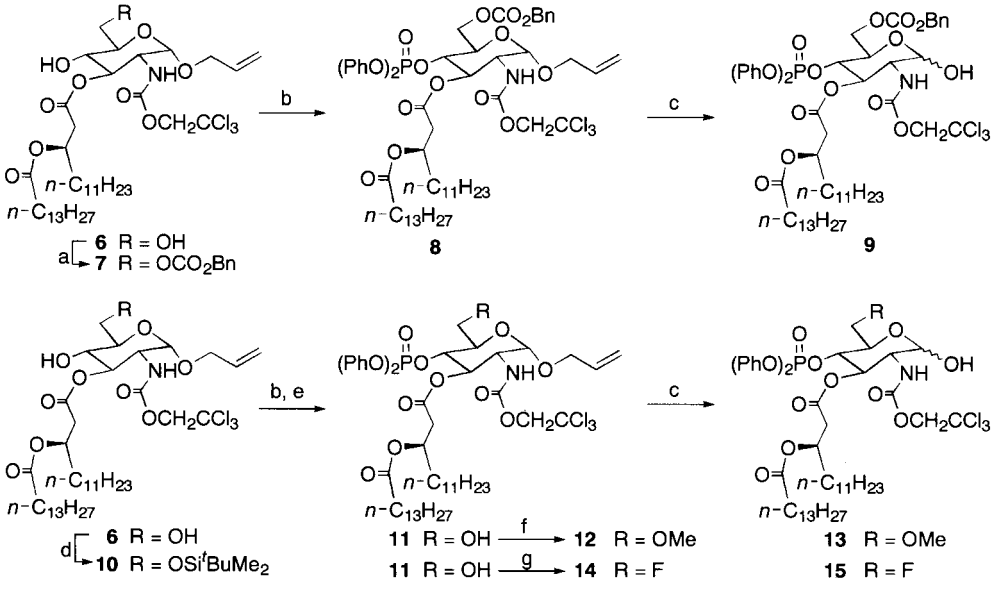
3 showed LPS-antagonistic activity.[12] Then, expecting that disaccharide derivatives like lipid A molecules should have more potent LPS-antagonistic activity, we investigated the synthesis and biological activities of lipid A-type (disaccharide) pyrancarboxylic acid derivatives (Fig. 2).[13] Herein, we disclose the full details of our study of lipid A-type pyrancarboxylic acid derivatives.

We first wanted to examine whether the carboxy group attached directly to the pyran in the anomeric position in the α-configuration plays a decisive role in LPS-agonism or -antagonism of lipid A-type pyrancarboxylic acid derivatives. If not as such, we also wanted to know whether the phosphate group in the anomeric position of lipid A could be exchanged to a carboxy group, which would be more stable than the former, without loss of biological activities. Further, we tried to investigate the effect of the number of fatty acid chains in the pyrancarboxylic acid derivatives upon the biological activities by changing the substituent in the 2′-position in the molecules from (*R*)-3-(dodecanoyloxy)tetradecanamido groups (**4a**–**c**) to acetamido groups (**5a**–**c**). In addition, the effect of a substituent in the 6′-position of the compounds was also examined by comparing the biological activities of 6′-hydroxyl (**4a**, **5a**), 6′-methoxy (**4b**, **5b**), and 6′-fluoro derivatives (**4c**, **5c**).

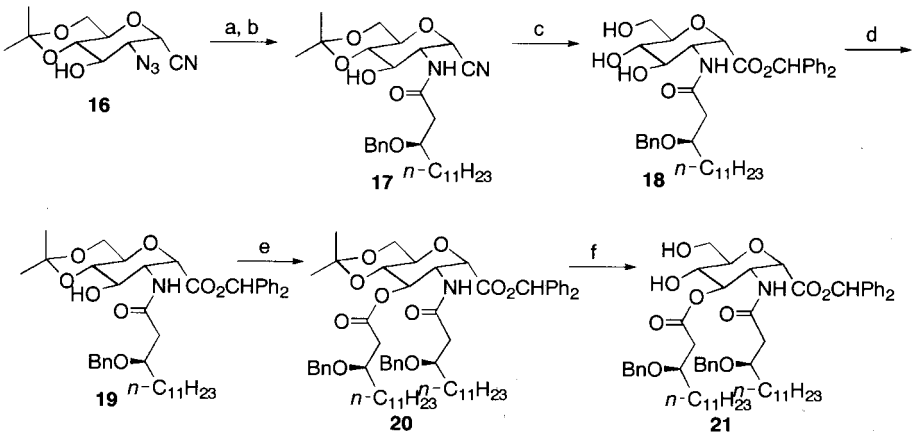
Results

Synthesis

At first, the starting allyl 2-deoxy-3-*O*-[(*R*)-3-tetradecanoyloxytetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (**6**)[3b] was converted to the three different 6-substituted glycosyl donors **9**, **13**, and **15** as shown in Scheme 1. The 6-hydroxyl group of the diol **6** was selectively protected as a benzyloxycarbonate **7** by treatment with benzylchloroformate and pyridine according to the reported method.[14] After 4-*O*-phosphorylation of **7** with diphenyl chlorophosphate and *N*,*N*-dimethylaminopyridine (DMAP), the allyl group in the anomeric position of the thus-obtained **8** was deprotected by treatment with (1,5-cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) hexafluorophosphate in THF and successive hydrolysis with H_2O–I_2, affording a 6-*O*-benzyloxycarbonated intramolecular hemiacetal **9**.[15] On the other hand, the synthesis of 6-methoxy and 6-fluoro derivatives commenced with selective silylation of the 6-hydroxyl group of **6** with *tert*-butyldimethylsilyl chloride and imidazole in DMF to give the 6-*O*-monosilylated compound **10**. Subsequently, 4-*O*-phosphorylation of **10** with diphenyl chlorophosphate and DMAP, and successive deprotection of the 6-*O*-silyl group



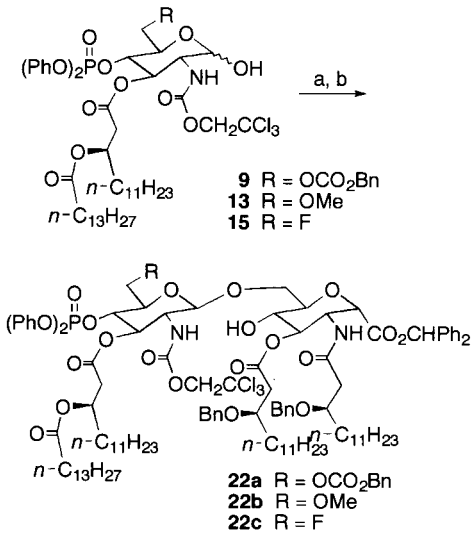
Scheme 1. Reagents and conditions: (a) $ClCO_2Bn$, Py, rt, 1 h, 60%; (b) $ClPO(OPh)_2$, DMAP, CH_2Cl_2, rt, 2 h for **7**, **8**: 98%, 30 min for **10**; (c) [Ir(COD)(P-$MePh_2)_2$]PF_6, THF, rt, 1 h, then H_2O–I_2, 60°C, 1 h, **9**: 77%, **13**: 73%, **15**: 79%; (d) *t*-$BuMe_2SiCl$, imidazole, DMF, rt, 1 h, 84%; (e) 3 M HCl aq., THF, 50°C, 1 h, 96% in 2 steps from **10**; (f) Me_3OBF_4, 2,6-di(*tert*-butyl)-4-methylpyridine, CH_2Cl_2, rt, 24 h, 68%; (g) DAST, CH_2Cl_2, 0°C, 3 h, 29%.



Scheme 2. Reagents and conditions: (a) PPh_3, THF, 2 h, then 28% aq. NH_4OH, 60°C, 3 h; (b) (*R*)-3-(benzyloxy)tetradecanoic acid, DCC, CH_2Cl_2, rt, 15 h, 68% in 2 steps from **16**; (c) 4 M HCl, 1,4-dioxane-H_2O, 60°C, 4 h, then Ph_2CN_2, THF, 60°C, 2 h, 33%; (d) $Me_2C(OMe)_2$, *p*-TsOH, DMF, rt, 3 h, 80%; (e) (*R*)-3-(benzyloxy)tetradecanoic acid, DCC, DMAP, CH_2Cl_2, rt, 16 h, 85%; (f) *p*-TsOH, MeOH-THF, rt, 3 h, 87%.

with 3 M aqueous hydrochloric acid in THF provided alcohol **11**. After methylation of the 6-hydroxyl group of **11** with trimethyloxonium tetrafluoroborate and 2,6-di(*tert*-butyl)-4-methylpyridine, deprotection of the anomeric allyl group of the thus-obtained **12** was accomplished by the same procedure as mentioned above, affording 6-methoxy hemiacetal **13**. Furthermore, after fluorination of the 6-hydroxyl group of **11** with diethylaminosulfur trifluoride (DAST), the anomeric allyl group of the thus-obtained **14** was likewise deprotected to yield 6-fluoro hemiacetal **15**.

Glycosyl acceptor **21** was prepared in accordance with the reported procedure (Scheme 2).[12] The 2-azido group of 2,6-anhydro-3-azido-3-deoxy-5,7-*O*-isopropylidene-D-*glycero*-D-*ido*-heptononitrile (**16**)[12] was transformed to the (*R*)-3-(benzyloxy)tetradecanamido group of **17** by successive treatment with triphenylphosphine and aqueous NH_4OH, followed by (*R*)-3-(benzyloxy)tetradecanoic acid and dicyclohexyl carbodiimide (DCC). Acidic hydrolysis of the nitrile **17** with 4 M HCl in dioxane–H_2O, and successive esterification of the resulting carboxylic acid with diphenyl diazomethane gave a triol **18**.[†] After transformation of **18** to 5,7-*O*-isopropylidene **19** by treatment with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH), esterification of the 4-hydroxyl group of **19** with (*R*)-3-(benzyloxy)tetradecanoic acid, DCC, and DMAP yielded compound **20**. Then, deprotection of the isopropylidene group of **20** using *p*-TsOH as a catalyst in MeOH-THF furnished glycosyl acceptor **21**.



Scheme 3. Reagents and conditions: (a) Cl_3CCN, DBU, CH_2Cl_2, 0°C, 30 min; (b) **21**, TMSOTf, MS 4Å, CH_2Cl_2, −50°C, 1 h, **22a**: 56% in 2 steps from **9**, **22b**: 57% in 2 steps from **13**, **22c**: 63% in 2 steps from **15**.

The glycosylation reaction of **9**, **13**, and **15** with **21** was conducted by use of Schmidt's imidate method[16] (Scheme 3). After conversion of the hemiacetals **9**, **13**, and **15** to corresponding trichloroacetimidates with trichloroacetonitrile and a catalytic amount of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU), successive glycosylation with **21** by use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst gave rise to only β-oriented pseudodisaccharides **22a**, **22b**, and **22c**, respectively.

Then, the intermediates **22a**, **22b**, and **22c** were converted into two kinds of lipid A-type pyrancarboxylic acid derivatives; ones with a (*R*)-3-(dodecanoyloxy)tetradecanamido group at the 2′-position in the molecules (Scheme 4) similar to *Escherichia coli* lipid A, and the others with an acetamido group at the same position (Scheme 5). After deprotection of the trichloroethoxycarbonyl (Troc) group at the 2′-position of **22a**–**c** with zinc dust-acetic acid, we treated the thus-obtained amines with (*R*)-3-(dodecanoyloxy)tetradecanoic acid and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl) to afford **23a**–**c**.[‡] Hydrogenolysis of this series of compounds using palladium hydroxide on carbon as a catalyst completed the deprotection of the two benzyl ether groups and the diphenylmethyl ester group of **23a**–**c**, and the benzyloxycarbonyl group of **23a** to furnish **24a**–**c**. Finally, hydrogenolytic deprotection of each diphenyl phosphate ester group of **24a**–**c** using platinum oxide as a catalyst yielded **4a**, **4b**, and **4c**, respectively

[†] This hydrolysis step was thoroughly examined, but gave rise to product **18** in 33% yield at most.

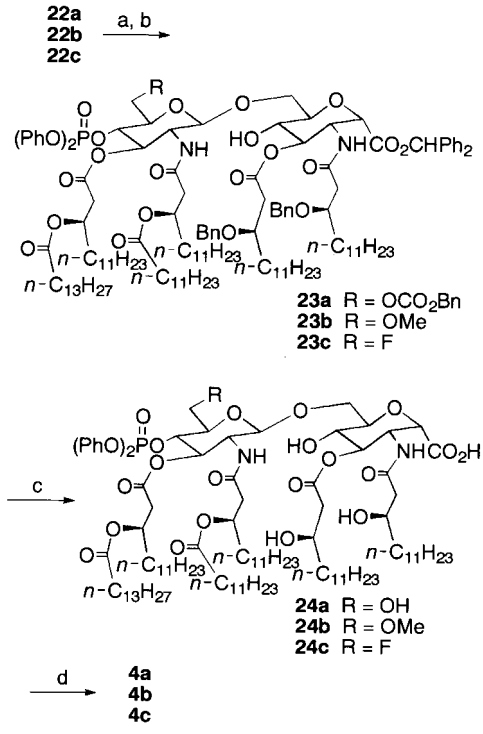
[‡] The given yields of **23a** and **23c** are the results of only one experiment each. Higher yields might be obtained with further investigation.

(Scheme 4). We conducted this 2-step reductive deprotection procedure. So we could avoid the troublesome purification of the very polar products at the last step. We excluded the impurities by reduction after the first deprotection step.

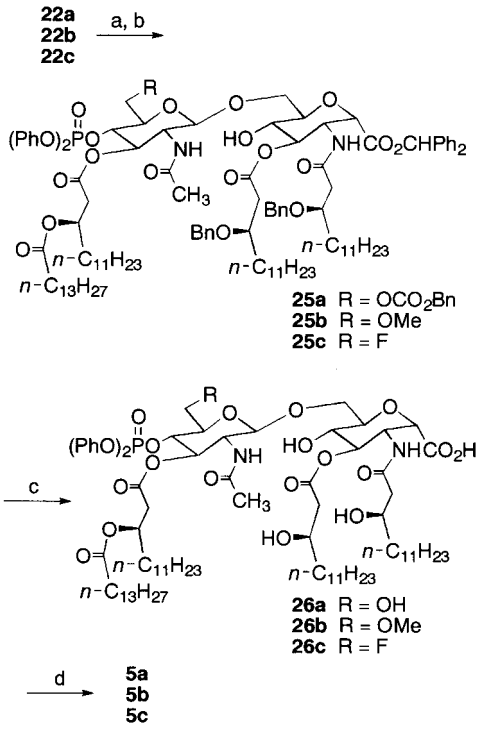
On the other hand, after deprotection of the Troc groups of **22a–c** by the above-mentioned way, we introduced the acetamido group at the 2′-position with acetic acid and EDCI·HCl as a condensing agent, affording **25a–c**. By the same procedure as the synthesis of **4a–c**, the two benzyl ether groups, the diphenylmethyl ester group, and the benzyloxycarbonyl group in the case of **25a** were deprotected, and then the diphenyl phosphate groups of the thus-obtained **26a–c** were deprotected to furnish **5a**, **5b**, and **5c**, respectively (Scheme 5).

Biological activity

The biological activities of the newly synthesized compounds **4a–c** and **5a–c** were investigated by measuring TNFα production in human monoblastic U937 cells, pretreated with TPA, in the absence (LPS agonism) or presence (LPS antagonism) of LPS (30 ng/ml). As shown in Figs. 3 and 4, compounds **4a–c**, which have six fatty acid moieties in each molecule, induced the production of TNFα (LPS-agonistic activity) and showed weak or no inhibitory activity toward LPS-stimulated TNFα production. Compound **4c**, which showed weaker LPS-agonistic activity than compounds **4a** and **4b**, slightly inhibited LPS-induced TNFα production at a higher concentration of 500 nM. On the other hand, compounds **5a–c**, which have four lipids, strongly inhibited the production of TNFα induced by LPS



Scheme 4. Reagents and conditions: (a) Zn, AcOH, rt, 3 h; (b) (*R*)-3-(dodecanoyloxy)tetradecanoic acid, EDCI·HCl, CH_2Cl_2, rt, 16 h, **23a**: 38% in 2 steps from **22a**, **23b**: 59% in 2 steps from **22b**, **23c**: 24% in 2 steps from **22c**; (c) H_2, 20% $Pd(OH)_2$/C, AcOEt or EtOH, rt, 15–20 h, **24a**: 57%, **24b**: 57%, **24c**: 58%; (d) H_2, PtO_2, THF, rt, 15–20 h, **4a**: 88%, **4b**: 49%, **4c**: 73%.



Scheme 5. Reagents and conditions: (a) Zn, AcOH, rt, 5 h; (b) AcOH, EDCI·HCl, CH_2Cl_2, rt, 4 h, **25a**: 47% in 2 steps from **22a**, **25b**: 75% in 2 steps from **22b**, **25c**: 57% in 2 steps from **22c**; (c) H_2, 20% $Pd(OH)_2$/C, AcOEt or EtOH, rt, 7–16h, **26a**: 63%, **26b**: 63%, **26c**: 65%; (d) H_2, PtO_2, THF, rt, 15–20 h, **5a**: 82%, **5b**: 99%, **5c**: 87%.

in a dose-dependent manner (LPS-antagonistic activity, Fig. 4), with an IC_{50} value of 7, 10, 9 nM, respectively, but did not show any LPS-agonistic activity (Fig. 3).

Discussion

The biological activities of the lipid A-type pyrancarboxylic acid derivatives synthesized in this work suggest the following relationships between the structural features of the molecules and their biological activities. Firstly, the LPS-agonistic activity of compounds **4a–c**, which have a similar acyl substitution pattern to *E. coli* lipid A, and have a carboxylic acid group directly attached to the anomeric position of each molecule instead of the phosphate group in lipid A, revealed that the phosphate group can be replaced with the carboxy group without loss of biological activity. The exchangeability of the phosphate group to the stable carboxy group is useful information for development of lipid A-type molecules, in which instability of the molecules in the anomeric position is often encountered.

Secondly, by comparison of the biological activities of compounds **4a–c** with compounds **5a–c**, it appears that the number of lipid chains in the molecule is crucial for whether the lipid A-type molecule has LPS-agonistic or -antagonistic activity. Compounds **5a–c**, which have four lipid chains in the molecules, have strong LPS-antagonistic activities without any LPS-agonistic activity as lipid IVa[5] (Fig. 5), which also has four lipid chains in the molecule and is known as an LPS-antagonist toward human cells. The importance of the number of lipid chains for biological

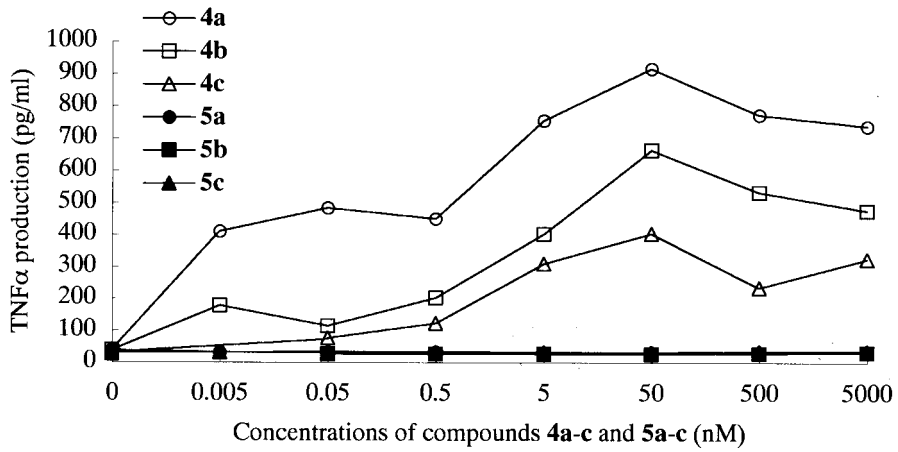


Figure 3. Production of TNFα from TPA-treated U937 cells stimulated by lipid A-type pyrancarboxylic acid derivatives. In this experiment, the dose-dependency of the response by LPS (data not shown) and *E. coli* lipid A[17] was confirmed. As a control, the amounts of TNFα produced by TPA-treated U937 cells stimulated with LPS (30 ng/ml) was 1183 pg/ml.

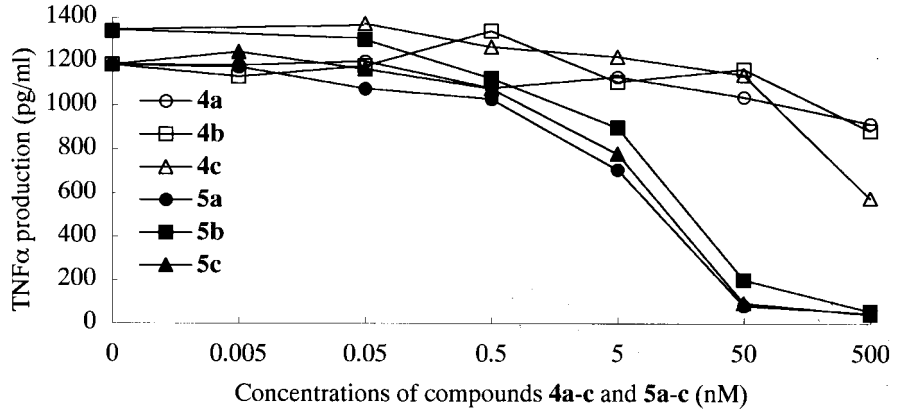


Figure 4. Inhibition of TNFα release from TPA-treated U937 cells stimulated by LPS (30 ng/ml) in the presence of lipid A-type pyrancarboxylic acid derivatives.

activities is obvious. This study provides a new acyl substitution pattern for LPS-antagonistic lipid A-related compounds.

Thirdly, there is no significant difference in LPS-antagonistic activities among the 2′-acetamido derivatives **5a**–**c**. Likewise, compounds **4a**–**c** show almost the same level of LPS-agonistic activity, except for the slight inhibitory activity of a higher concentration of **4c** on LPS-induced TNFα production, the reason for which was not elucidated. Therefore, the substituent in the 6′-position of the molecules appears not to be very important for their biological activities. Further studies are necessary to investigate the slight inhibition of the TNFα production at a higher concentrations of LPS-agonistic compound **4c**.

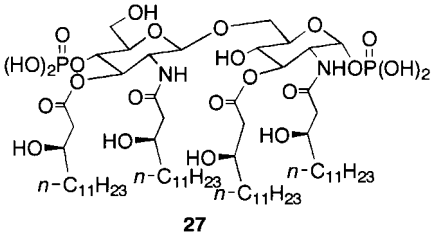


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Figure 5. The structure of lipid IVa (**27**).

Conclusion

In summary, two kinds of lipid A-type pyrancarboxylic acid derivatives were synthesized. One of them, having four lipid chains in the molecules, showed strong LPS-antagonistic activity. The exchangeability of the phosphate group in the anomeric-position to a stable carboxy group and the importance of the lipid chain number suggest an effective acyl substitution pattern for developing LPS-antagonists.

Experimental

General

^{1}H NMR spectra were recorded using tetramethylsilane as the internal reference. IR absorption spectra were recorded on a Jasco IR A-2 spectrophotometer, and mass spectra were obtained with a JMS-700 mass spectrometer. 3-Nitrobenzyl-alcohol was used for a matrix on every measurement.

Elemental analyses were performed by the Institute of Science and Technology, Inc. Separation of the compounds by column chromatography was carried out with silica gel 60 (Merck, 230–400 mesh ASTM).

Allyl 6-*O*-benzyloxycarbonyl-2-deoxy-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (7). To a solution of allyl 2-deoxy-3-*O*-[(*R*)-3-tetradecanoyloxytetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (**6**,[3b] 438 mg, 0.526 mmol) in THF (30 ml), benzyloxycarbonylchloride (125 mg, 0.735 mmol) and pyridine (62.7 mg, 0.790 mmol) were added. After stirring for 2 h at room temperature, the reaction mixture was concentrated in vacuo, diluted with ethyl acetate, washed with 1 M hydrochloric acid, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a mixture. The mixture was chromatographed on a silica gel column. Elution with hexane–EtOAc (1:1) gave **7** (304 mg, 60% yield) as a powder. IR: ν_{max} (KBr) 3472, 1748, 1724, 1540, 1296 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.45–7.29 (5H, m), 5.94–5.79 (1H, m), 5.41–5.05 (7H, m, including 2H, s, at 5.18 ppm), 4.90 (1H, d, *J*=3.5 Hz), 4.76 (1H, AB-q, *J*=12.0 Hz), 4.65 (1H, AB-q, *J*=12.0 Hz), 4.45 (2H, d, *J*=3.3 Hz), 4.20–4.11 (1H, m), 4.01–3.85 (3H, m), 3.66–3.57 (1H, m), 3.40 (1H, d, *J*=3.9 Hz), 2.56–2.45 (2H, m), 2.29 (2H, t, *J*=7.5 Hz), 1.68–1.52 (4H, m), 1.30–1.17 (38 H, m), 0.88 (6H, t, *J*=6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{48}H_{76}NO_{12}Cl_3Na$ $(M+Na)^+$: 986.4331; found: 986.4332. Anal. Calcd for $C_{48}H_{76}NO_{12}Cl_3+H_2O$: C, 58.62; H, 7.99; N, 1.42; Cl, 10.81. Found: C, 58.67; H, 7.90; N, 1.49; Cl, 11.05.

Allyl 6-*O*-benzyloxycarbonyl-2-deoxy-4-*O*-diphenylphosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (8). To a solution of **7** (278 mg, 0.288 mmol) in CH_2Cl_2 (5 ml), DMAP (70.8 mg, 0.58 mmol) and diphenyl chlorophosphate (155 mg, 0.577 mmol) were added. After stirring for 2 h at room temperature, the reaction mixture was concentrated in vacuo, diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, and concentrated in vacuo to give a mixture. The mixture was purified using silica gel chromatography. Elution with hexane–EtOAc (5:1) gave **8** (337 mg, 98% yield) as a viscous oil. IR: ν_{max} (neat) 1751, 1267 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.65–7.14 (15H, m), 5.93–5.79 (1H, m), 5.47–5.38 (2H, m), 5.26 (1H, dd, *J*=28.2, 1.6 Hz), 5.25 (1H, d, *J* =1.1 Hz), 5.13–5.01 (3H, m, including 2H, AB-q, *J*=12.1 Hz, at 5.11, 5.01 ppm), 4.79 (1H, AB-q, *J*=12.0 Hz), 4.74 (1H, q, *J*=9.4 Hz), 4.60 (1H, AB-q, *J*=12.0 Hz), 4.35–4.11 (3H, m), 4.08–3.95 (3H, m), 2.45 (2H, d, *J*=6.3 Hz), 2.14 (2H, t, *J*=7.6 Hz), 1.56–1.40 (4H, m), 1.33–0.92 (38H, m), 0.88 (6H, t, *J*=6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{60}H_{85}NO_{15}Cl_3PK$ $(M+K)^+$: 1234.4359; found: 1234.4381. Anal. Calcd for $C_{60}H_{85}NO_{15}Cl_3P$: C, 60.17; H, 7.15; N, 1.17; Cl, 8.88; P, 2.59. Found: C, 60.29; H, 6.95; N, 1.30; Cl, 8.68; P, 2.57.

6-*O*-Benzyloxycarbonyl-2-deoxy-4-*O*-diphenylphosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranose (9). A solution of **8** (881 mg, 0.735 mmol) and (1,5-cyclooctadiene)bis(diphenylmethylphosphine)iridium(I) hexafluorophosphate (33.9 mg, 0.0401 mmol) in THF (5 ml) was replaced with a hydrogen atmosphere. Stirring for 1 min, the color of the solution turned colorless from red–brown, then immediately the reaction mixture was replaced with a nitrogen atmosphere. After stirring for 1 h at room temperature, H_2O (0.5 ml) and I_2 (280 mg, 1.10 mmol) were added to the mixture, and the mixture was stirred for 1 h at 60°C. The reaction mixture was quenched with aqueous 5% Na_2SO_3, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a mixture. The mixture was purified by silica gel chromatography. Elution with hexane–EtOAc (4:1) gave **9** (656 mg, 77% yield) as a powder. IR: ν_{max} (KBr) 3344 (broad), 1749, 1490, 1269 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.65–7.11 (15H, m), 5.58–5.45 (2H, m), 5.32 (1H, d, *J*=3.4 Hz), 5.13–5.01 (3H, m, including 2H, AB-q, *J*=12.0 Hz, at 5.11, 5.03 ppm), 4.73 (1H, q, *J*=9.2 Hz), 4.64 (1H, AB-q, *J*=12.0 Hz), 4.52 (1H, AB-q, *J*=12.0 Hz), 4.37–4.18 (3H, m), 4.03–3.94 (1H, m), 2.45 (2H, d, *J*=6.3 Hz), 2.16 (2H, t, *J*=7.6 Hz), 1.67–1.33 (4H, m), 1.30–1.11 (38H, m), 0.88 (6H, t, *J*=6.6 Hz). Anal. Calcd for $C_{57}H_{81}NO_{15}Cl_3P+H_2O$: C, 58.24; H, 7.12; N, 1.19; Cl, 9.05; P, 2.63. Found: C, 58.48; H, 7.04; N, 1.23; Cl, 9.32; P, 2.66.

Allyl 6-*O*-*tert*-butyldimethylsilyl-2-deoxy-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (10). To a solution of **6** (2.37 g, 2.86 mmol) in DMF (30 ml), imidazole (398 mg, 5.85 mmol) and *tert*-butyldimethylsilyl chloride (470 mg, 3.12 mmol) were added. After stirring for 1 h at room temperature, the reaction mixture was diluted with diethyl ether, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a mixture. The mixture was chromatographed on a silica gel column. Elution with hexane–EtOAc (10:1) gave **10** (2.27 g, 84% yield) as a viscous oil. IR: ν_{max} (neat) 2926, 2856, 1743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 5.94–5.84 (1H, m), 5.44 (1H, d, *J*=9.5 Hz, NH), 5.32–5.12 (4H, m), 4.89 (1H, d, *J*=3.6 Hz), 4.74, 4.68 (2H, AB-q, *J*=12.5 Hz), 4.19 (1H, dd, *J*=12.5, 5.1 Hz), 3.99 (1H, dd, *J*=12.5, 6.6 Hz), 3.94–3.84 (2H, m), 3.73–3.63 (3H, m), 3.38 (1H, broad s, H), 2.59 (1H, dd, *J*=15.0, 7.7 Hz), 2.50 (1H, dd, *J*=15.4, 4.4 Hz), 2.28 (2H, t, *J*=7.7 Hz), 1.64–1.58 (2H, m), 1.36–1.20 (40H, m), 0.96–0.86 (15H, m), 0.10 (3H, s), 0.07 (3H, s). High Resolution MS (FAB, positive), calcd for $C_{46}H_{84}NO_{10}Cl_3SiNa$ $(M+Na)^+$: 966.4828; found: 966.4811.

Allyl 2-deoxy-4-*O*-diphenylphosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (11). To a solution of **10** (2.27 g, 2.40 mmol) in CH_2Cl_2 (30 ml), DMAP (589 mg, 4.82 mmol) and diphenyl chlorophosphate (1.30 g, 4.84 mmol) were added. After stirring for 30 min at room temperature, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a mixture, which was further used without purification. To a solution of the mixture above obtained in THF (30 ml), aqueous 3 M hydrochloric acid was added. After stirring for 1 h at 50°C, the reaction mixture was concentrated in vacuo to give a crude product. The crude product was

purified by silica gel chromatography. Elution with hexane–EtOAc (2:1) gave **11** (2.46 g, 96% yield) as a viscous oil. IR: ν_{max} (neat) 3439, 2926, 2855, 1745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.47–7.12 (10H, m), 5.92–5.83 (1H, m), 5.47 (1H, t, *J*=9.6 Hz), 5.39 (1H, d, *J*=9.7 Hz), 5.31 (1H, dd, *J*=17.3, 1.3 Hz), 5.27–5.23 (1H, m), 5.13 (1H, t, *J*=6.3 Hz), 4.97 (1H, d, *J*=3.5 Hz), 4.80–4.73(1H, m), 4.76 (1H, AB-q, *J*=12.0 Hz), 4.65 (1H, AB-q, *J*=12.0 Hz), 4.21–4.16 (1H, m), 4.08–3.98 (2H, m), 3.75 (1H, d, *J*=9.8 Hz), 3.64–3.62 (2H, m), 3.32–3.28 (1H, m), 2.42–2.40 (2H, m), 2.18 (2H, t, *J*=7.6 Hz), 1.60–1.40 (2H, m), 1.38–1.16 (40H, m), 0.88 (3H, t, *J*=6.8 Hz). High Resolution MS (FAB, positive), calcd for $C_{52}H_{79}NO_{13}Cl_3PNa$ $(M+Na)^+$: 1084.4252; found: 1084.4258.

Allyl 2-deoxy-4-*O*-diphenylphosphono-6-*O*-methyl-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (12). To a solution of **11** (13.1 mg, 0.012 mmol) in CH_2Cl_2 (1 ml), a solution of trimethyloxonium tetrafluoroborate (36.0 mg, 0.243 mmol) and 2,6-di(*tert*-butyl)-4-methylpyridine (9.1 mg, 0.044 mmol) were added. After stirring for 24 h at room temperature, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a mixture. The mixture was chromatographed on a silica gel column. Elution with hexane–EtOAc (5:1) gave **12** (9.0 mg, 68% yield) as a viscous oil. IR: ν_{max} (KBr) 1748, 1516 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.37–7.17 (10H, m), 5.96–5.81 (1H, m), 5.48–5.22 (4H, m), 5.16–5.00 (1H, m), 4.96 (1H, d, *J*=3.5 Hz), 4.84–4.73 (2H, m, including 1H, AB-q, *J*=11.8 Hz at 4.78 ppm), 4.61 (1H, AB-q, *J*=11.8 Hz), 4.25–4.18 (1H, m), 4.05–3.90 (3H, m), 3.52–3.42 (2H, m), 3.20 (3H, s), 2.45 (2H, d, *J*=6.3 Hz), 2.13 (2H, t, *J*=7.5 Hz), 1.61–1.13 (42 H, m), 0.88 (6H, t, *J*=6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{53}H_{81}NO_{13}Cl_3PNa$ $(M+Na)^+$: 1098.4409; found: 1098.4390. Anal. Calcd for $C_{53}H_{81}NO_{13}Cl_3P$: C, 59.08; H, 7.58; N, 1.30; Cl, 9.87; P, 2.87. Found: C, 58.40; H, 7.71; N, 1.26; Cl, 10.15; P, 2.84.

2-Deoxy-4-*O*-diphenylphosphono-6-*O*-methyl-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranose (13). Compound **12** (898 mg, 0.833 mmol) was treated as described in the formation of **9** from **8** to give **13** (629 mg, 73% yield) as a powder. IR: ν_{max} (KBr) 3399 (broad), 1728, 1525 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.37–7.18 (10H, m), 5.66 (1H, d, *J*=9.5 Hz), 5.50 (1H, dd, *J*=10.3, 9.8 Hz), 5.32 (1H, d, *J*=3.1 Hz), 5.15–5.06 (1H, m), 4.79–4.62 (3H, m), 4.32 (1H, broad s, OH), 4.22–4.18 (1H, m), 3.98 (1H, dt, J_d=3.1 Hz, J_t=10.1 Hz), 3.52–3.37 (2H, m), 3.20 (3H, s), 2.44 (2H, d, *J*=6.1 Hz), 2.15 (2H, t, *J*=7.6 Hz), 1.55–1.11 (42 H, m), 0.88 (6H, t, *J*=6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{50}H_{78}NO_{13}Cl_3P$ $(M+H)^+$: 1036.4295; found: 1036.4297.

Allyl 2,6-deoxy-4-*O*-diphenylphosphono-6-fluoro-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (14). To a solution of **11** (2.38 g, 2.24 mmol) in CH_2Cl_2 (100 ml), diethylaminosulfurtrifluoride (2 ml, 15.1 mmol) was added at −35°C. After stirring for 3 h at 0°C, the reaction mixture was quenched with aqueous phosphate buffer (pH 7), extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a mixture. The mixture was chromatographed on a silica gel column. Elution with hexane–EtOAc (2:1) gave **14** (683 mg, 29% yield) as a viscous oil. IR: ν_{max} (KBr) 1747, 1591, 1516, 1491 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.36–7.16 (10H, m), 5.91–5.84 (1H, m), 5.48–5.40 (2H, m), 5.34–5.24 (2H, m), 5.13–5.10 (1H, m), 4.98 (1H, d, *J*=3.7 Hz), 4.80 (1H, AB-q, *J*=12.5 Hz), 4.72 (1H, q, *J*=9.5 Hz), 4.58 (1H, AB-q, *J*=12.5 Hz), 4.46 (2H, dd, *J*=47.2, 2.6 Hz), 4.23–4.18 (1H, m), 4.06–3.95 (3H, m), 2.45 (2H, d, *J*=6.6 Hz), 2.14 (2H, t, *J*=7.3 Hz), 1.60–1.17 (44H, m), 0.88 (6H, t, *J*=7.0 Hz). High Resolution MS (FAB, positive), calcd for $C_{52}H_{78}NO_{12}Cl_3FPNa$ $(M+Na)^+$: 1086.4209; found: 1086.4207. Anal. Calcd for $C_{52}H_{78}NO_{12}Cl_3FP$: C, 58.62; H, 7.38; N, 1.32; F, 1.78; Cl, 9.98; P, 2.91. Found: C, 58.65; H, 7.41; N, 1.24; F, 1.67; Cl, 9.89; P, 3.04.

2,6-Deoxy-4-*O*-diphenylphosphono-6-fluoro-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranose (15). Compound **14** (683.4 mg, 0.641 mmol) was treated as described in the formation of **9** from **8** to give **15** (518 mg, 79% yield) as a powder. IR: ν_{max} (KBr) 3424 (broad), 1728, 1524 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.36–7.17 (10H, m), 5.66 (1H, d, *J*=9.5 Hz), 5.55 (1H, t, *J*=9.9 Hz), 5.37 (1H, d, *J*=3.7 Hz), 5.13–5.09 (1H, m), 4.75 (1H, AB-q, *J*=11.7 Hz), 4.72 (1H, q, *J*=9.5 Hz), 4.64 (1H, AB-q, *J*=11.7 Hz), 4.46 (2H, d, *J*=47.6 Hz), 4.26 (1H, dd, *J*=12.5, 6.2 Hz), 4.03–3.97 (1H, m), 2.45 (2H, d, *J*=6.6 Hz), 2.15 (2H, t, *J*=7.3 Hz), 1.53–1.20 (42 H, m), 0.88 (6H, t, *J*=7.0 Hz). High Resolution MS (FAB, positive), calcd for $C_{49}H_{75}NO_{12}Cl_3FP$ $(M+H)^+$: 1024.4076; found: 1024.4027. Anal. Calcd for $C_{49}H_{74}NO_{12}Cl_3FP$: C, 57.39; H, 7.27; N, 1.37; F, 1.85; Cl, 10.37; P, 3.02. Found: C, 57.11; H, 7.05; N, 1.42; F, 1.96; Cl, 10.74; P, 2.90.

2,6-Anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-3-deoxy-5,7-*O*-isopropylidene-D-*glycero*-D-*ido*-heptononitrile (17). To a solution of 2,6-anhydro-3-azido-3-deoxy-5,7-*O*-isopropylidene-D-*glycero*-D-*ido*-heptononitrile (**16**,[12] 10.1 g, 39.6 mmol) in THF (200 ml), triphenylphosphine (11.4 g, 43.6 mmol) was added at room temperature. After stirring for 2 h, 28% aqueous NH_4OH was added to the reaction mixture, which was further stirred at 60°C for 3 h. Then, the reaction mixture was concentrated in vacuo, and coevaporated with toluene to remove H_2O. The obtained precipitate was dissolved in CH_2Cl_2 (100 ml), and to the solution, a solution of (*R*)-3-(benzyloxy)tetradecanoic acid (13.3 g, 39.8 mmol) in CH_2Cl_2 (70 ml) and a solution of DCC (8.25 g, 40.0 mmol) in CH_2Cl_2 (30 ml) were added. After stirring for 15 h, the resulting white precipitate was removed by filtration, and the solution was concentrated in vacuo to give a mixture. The mixture was purified using silica gel chromatography. Elution with hexane–EtOAc (2:1) gave **17** (14.6 g, 68% yield) as an amorphous film. IR: ν_{max} (neat) 3418, 1644, 1628 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.40–7.32 (10H, m), 7.03 (1H, d, *J*=6.0 Hz), 5.20 (1H, d, *J*=6.0 Hz), 4.64 (1H, AB-q, *J*=11.2 Hz), 4.54 (1H, AB-q, *J*=11.2 Hz), 4.06 (1H, m), 3.91 (1H, dd, *J*=9.7, 4.3 Hz), 3.82 (1H, m), 3.72 (1H, t,

J=10.4–9.8 Hz), 3.65 (1H, m), 3.55–3.44 (2H, m), 2.58–2.41 (2H, m), 1.74–1.50 (2H, m), 1.49 (3H, s), 1.43 (3H, s), 1.26 (18H, m), 0.88 (3H, t, J=7.0–6.2 Hz). High Resolution MS (FAB, positive), calcd for $C_{31}H_{49}N_2O_6$ $(M+H)^+$: 545.3591; found: 545.3579.

Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-3-deoxy-D-*glycero*-D-*ido*-heptonate (18). To a solution of nitrile **17** (3.44 g, 3.99 mmol) in dioxane (22 ml)-H_2O (2.2 ml), 4 M hydrogen chloride dioxane solution was added. After stirring for 4 h at 60°C, the reaction mixture was concentrated in vacuo, giving a precipitate. The precipitate was dissolved in dimethylformamide (DMF, 16 ml), treated with diphenyldiazomethane (3.10 g, 15.9 mmol), and stirred for 2 h at 60°C. The reaction mixture was concentrated in vacuo to give a mixture. The mixture was purified using silica gel chromatography. Elution with EtOAc, and then EtOAc-MeOH (10:1) gave **18** (897 mg, 33% yield) as a powder. IR: ν_{max} (KBr) 3324, 1734, 1645, 1538 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.41–7.21 (15H, m), 6.98 (1H, d, J=9.1 Hz), 6.82 (1H, s), 4.55 (1H, d, J=5.7 Hz), 4.40 (2H, AB-q, J=11.5 Hz), 4.33 (1H, m), 3.81–3.57 (6H, m), 3.28 (1H, m), 2.87 (1H, broad s), 2.42–2.27 (2H, m), 1.65–1.40 (2H, m), 1.30–1.25 (18H, m), 0.88 (3H, t, J=6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{41}H_{56}NO_8$ $(M+H)^+$: 690.4006; found: 690.4016. Anal. Calcd for $C_{41}H_{55}NO_8$: C, 71.37; H, 8.04; N, 2.03. Found: C, 71.25; H, 8.17; N, 2.00.

Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-3-deoxy-5,7-*O*-isopropylidene-D-*glycero*-D-*ido*-heptonate (19). A solution of triol **18** (781 mg, 1.13 mmol) and *p*-TsOH (52 mg) in DMF (8 ml) and 2,2-dimethoxypropane (8 ml) was stirred for 3 h at room temperature, diluted with diethyl ether, extracted with 10% aqueous $NaHCO_3$, washed with brine, and dried over $MgSO_4$. The mixture was filtered, concentrated in vacuo, and purified with silica gel chromatography. Elution with hexane–EtOAc (2:1) gave **19** (660 mg, 80% yield) as a powder. IR: ν_{max} (KBr) 3376, 1728, 1640 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.38–7.24 (15H, m), 6.84 (1H, s), 6.83 (1H, d, J=6.9 Hz), 4.56 (1H, d, J=5.9 Hz), 4.51–4.35 (3H, m, including 1H, d, J=5.9 Hz, at 4.41 ppm), 3.86–3.62 (4H, m), 3.56 (1H, t, J=9.3 Hz), 3.26–3.17 (1H, m), 2.54 (1H, d, J=2.8 Hz), 2.44–2.29 (2H, m), 1.65–1.36 (8H, m, containing two 3H, s, at 1.48 and 1.37 ppm), 1.29–1.23 (18H, m), 0.88 (3H, t, J=6.8–6.4 Hz). High Resolution MS (FAB, positive), calcd for $C_{44}H_{60}NO_8$ $(M+H)^+$: 730.4319; found: 730.4307. Anal. Calcd for $C_{44}H_{59}NO_8$: C, 72.40; H, 8.15; N, 1.92. Found: C, 71.95; H, 7.85; N, 2.22.

Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-5,7-*O*-isopropylidene-D-*glycero*-D-*ido*-heptonate (20). To a solution of alcohol **19** (610 mg, 0.835 mmol) in CH_2Cl_2 (8 ml), (*R*)-3-(benzyloxy)tetradecanoic acid (317 mg, 0.947 mmol), DCC (207 mg, 1.00 mmol), and DMAP (124 mg, 1.01 mmol) were added at 24°C. After stirring for 16 h at 24°C, the reaction mixture was diluted with ethyl acetate, washed with 0.1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine in order, and dried over $MgSO_4$. The mixture was filtered, concentrated in vacuo, and purified using silica gel chromatography. Elution with hexane–EtOAc (10:1) gave **20** (747 mg, 85% yield) as a powder. IR: ν_{max} (KBr) 2920, 1740 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.54–7.08 (20H, m), 6.85 (1H, s), 6.56 (1H, d, J=8.8 Hz), 5.40 (1H, t, J=9.8 Hz), 4.60–4.37 (6H, m), 3.81–3.63 (5H, m), 3.31–3.22 (1H, m), 2.65 (1H, dd, J=15.1, 6.4 Hz), 2.39 (1H, dd, J=15.3, 5.9 Hz), 2.20–2.04 (2H, m), 1.66–1.15 (46H, m), 0.88 (6H, t, J=6.8–6.4 Hz). High Resolution MS (FAB, positive), calcd for $C_{65}H_{91}NO_{10}Na$ $(M+Na)^+$: 1068.6541; found: 1068.6543. Anal. Calcd for $C_{65}H_{91}NO_{10}$: C, 74.61; H, 8.77; N, 1.34. Found: C, 74.89; H, 8.68; N, 1.28.

Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-D-*glycero*-D-*ido*-heptonate (21). To a solution of isopropylidene **20** (1.09 g, 1.04 mmol) in THF (15 ml) and MeOH (15 ml), *p*-TsOH (235 mg) was added at 24°C. After stirring for 3 h at 24°C, the reaction mixture was concentrated in vacuo, and purified with silica gel chromatography. Elution with hexane–EtOAc (2:1) gave **21** (906 mg, 87% yield) as a powder. IR: ν_{max} (KBr) 3350, 1733, 1649, 1536 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.33–7.08 (20H, m), 6.85 (1H, s), 6.61 (1H, d, J=8.8 Hz), 5.27 (1H, t, J=9.9 Hz), 4.63 (1H, d, J=5.8 Hz), 4.50–4.32 (5H, m, including two 2H, s, at 4.48 and 4.37 ppm), 3.99–3.80 (1H, m), 3.73–3.58 (5H, m), 3.37–3.30 (1H, m), 3.14–2.76 (1H, broad s), 2.62–2.42 (2H, m), 2.22–2.14 (2H, m), 1.69–1.14 (40H, m), 0.88 (6H, t, J=6.4 Hz). High Resolution MS (FAB, positive), calcd for $C_{62}H_{88}NO_{10}$ $(M+H)^+$: 1006.6408; found: 1006.6397. Anal. Calcd for $C_{62}H_{87}NO_{10}$: C, 74.00; H, 8.71; N, 1.39. Found: C, 74.19; H, 8.67; N, 1.40.

Diphenylmethyl 2,6-anhydro-7-*O*-[6-*O*-benzyloxycarbonyl-2-deoxy-4-*O*-diphenylphosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-D-*glycero*-D-*ido*-heptonate (22a). To a solution of **9** (249 mg, 0.215 mmol) and trichloroacetonitrile (200 mg, 2.00 mmol) in CH_2Cl_2 (3.0 ml), a solution of DBU (6.8 mg, 0.0446 mmol) in CH_2Cl_2 (1.5 ml) was added at 0°C under nitrogen. After stirring for 30 min at 0°C, the reaction mixture was concentrated in vacuo, and rapidly chromatographed with hexane–EtOAc (2:1). The eluent was concentrated in vacuo to give a crude imidate, which was immediately used for the next reaction without further purification. To a suspension in CH_2Cl_2 (4.0 ml) of the thus-obtained imidate, diol **21** (217 mg, 0.216 mmol) and molecular sieves 4Å dried in advance, TMSOTf (4.8 mg, 0.0217 mmol) in CH_2Cl_2 (50 ml) was added at −50°C. After stirring for 1 h at −50°C, the mixture was quenched with saturated $NaHCO_3$ aqueous solution, extracted with EtOAc, and the extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a mixture. The mixture was purified with silica gel chromatography. Elution with hexane–EtOAc (3:1) gave **22a** (289 mg, 56% yield) as a powder. IR: ν_{max} (KBr) 3343, 1735, 1531, 1268 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.38–7.11 (35H, m), 6.84 (1H, s), 6.51 (1H, d, J=8.9 Hz), 5.71 (1H, d, J=6.8 Hz), 5.55–5.48 (1H, m), 5.32–5.01 (4H, m, including 1H, AB-q, J=12.3 Hz at 5.03 ppm and 1H, AB-q, J=12.3 Hz at 5.12 ppm), 4.99

(1H, d, J=9.7 Hz), 4.75–4.61 (4H, m), 4.57–4.29 (6H, m, including 1H, s at 4.33 ppm, 1H, s, at 4.35 ppm, 1H, s at 4.48 ppm, and 1H, s at 4.49 ppm), 4.22–4.16 (1H, m), 4.01–3.95 (1H, m), 3.85–3.80 (1H, m), 3.74–3.54 (4H, m), 3.45–3.34 (2H, m), 2.82 (1H, broad s), 2.64–2.13 (8H, m), 1.67–1.11 (82H, m), 0.88 (12H, t, J=6.5 Hz). High Resolution MS (FAB, positive), calcd for $C_{119}H_{166}N_2O_{24}Cl_3PNa$ $(M+Na)^+$: 2166.0531; found: 2166.0549. Anal. Calcd for $C_{119}H_{166}N_2O_{24}Cl_3P$: C, 66.61; H, 7.80; N, 1.31; Cl, 4.96; P, 1.44. Found: C, 66.14; H, 7.59; N, 1.29; Cl, 5.16; P, 1.71.

Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-7-*O*-[2-deoxy-4-*O*-diphenylphosphono-6-*O*-methyl-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-D-*glycero*-D-*ido*-heptonate (22b). Compound **13** (21.5 mg, 0.021 mmol) was treated as described in the formation of **22a** from **9** to give **22b** (23.3 mg, 57% yield) as a powder. IR: ν_{max} (KBr) 3550–3360, 1738, 1531 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.36–7.15 (30H, m), 6.84 (1H, s), 6.50 (1H, d, J=8.8 Hz), 5.62 (1H, d, J=6.6 Hz), 5.47 (1H, t, J=9.8 Hz), 5.31–5.17 (2H, m), 4.92 (1H, d, J=8.3 Hz), 4.75–4.61 (4H, m), 4.50–4.34 (5H, m), 4.01–3.97 (1H, m), 3.86–3.73 (2H, m), 3.65–3.47 (3H, m), 3.44–3.38 (4H, m), 3.20 (3H, s), 2.65–2.14 (8H, m), 1.66–1.11 (94H, m), 0.88 (12H, t, J=6.1–6.9 Hz). High Resolution MS (FAB, positive), calcd for $C_{112}H_{162}N_2O_{22}Cl_3PNa$ $(M+Na)^+$: 2046.0320; found: 2046.0288. Anal. Calcd for $C_{112}H_{162}N_2O_{22}Cl_3P$: C, 66.40; H, 8.06; N, 1.38; Cl, 5.25; P, 1.53. Found: C, 66.32; H, 7.85; N, 1.37; Cl, 5.41; P, 1.76.

Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-7-*O*-[2,6-deoxy-4-*O*-diphenylphosphono-6-fluoro-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-D-*glycero*-D-*ido*-heptonate (22c). Compound **15** (312 mg, 0.304 mmol) was treated as described in the formation of **22a** from **9** to give **22c** (385 mg, 63% yield) as a powder. IR: ν_{max} (KBr) 3424, 1732, 1654, 1591, 1491, 1189 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.35–7.14 (30H, m), 6.84 (1H, s), 6.52 (1H, d, J=8.8 Hz), 5.75–5.69 (1H, m), 5.58–5.50 (1H, m), 5.29–5.16 (2H, m), 5.02 (1H, d, J=8.1 Hz), 4.77–4.70 (2H, m), 4.66–4.57 (3H, m), 4.52–4.38 (5H, m), 4.34 (1H, d, J=5.1 Hz), 4.01 (1H, d, J=7.4 Hz), 3.84–3.81 (1H, m), 3.73–3.59 (4H, m), 3.48–3.43 (1H, m), 3.39–3.32 (1H, m), 2.77 (1H, broad s), 2.60 (1H, dd, J=8.1, 15.4 Hz), 2.45 (1H, d, J=5.1 Hz), 2.41 (1H, d, J=4.4 Hz), 2.32 (1H, dd, J=8.1, 15.4 Hz), 2.24–2.13 (4H, m), 1.30–1.08 (82H, m), 0.88 (12H, t, J=6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{111}H_{159}N_2O_{21}Cl_3FPNa$ $(M+Na)^+$: 2034.0120; found: 2034.0135. Anal. Calcd for $C_{111}H_{159}N_2O_{21}Cl_3FP$: C, 66.20; H, 7.96; N, 1.39; Cl, 5.28; F, 0.94; P, 1.54. Found: C, 65.81; H, 7.69; N, 1.49; Cl, 5.32; F, 0.97; P, 1.29.

Diphenylmethyl 2,6-anhydro-7-*O*-[6-*O*-benzyloxycarbonyl-2-deoxy-4-*O*-diphenylphosphono-2-[(*R*)-3-(dodecanoyloxy)-tetradecanamido]-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(benzyloxy)-tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-D-*glycero*-D-*ido*-heptonate (23a). To a solution of **22a** (174 mg, 0.080 mmol) in acetic acid (5.0 ml), zinc dust (745 mg, 11.4 mmol) was added. After vigorously stirring for 3 h at room temperature, the solution was filtered through Celite to remove the zinc dust. The filtrate was concentrated in vacuo to give a residue, which was dissolved in $CHCl_3$, washed with saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and dissolved in CH_2Cl_2 (2.0 ml). To this solution, were added (*R*)-3-(dodecanoyloxy)tetradecanoic acid (34.7 mg, 0.081 mmol) and EDCI·HCl (31.0 mg, 0.162 mmol) at room temperature, and the mixture was allowed to stand for 16 h at room temperature. Then, the reaction mixture was concentrated in vacuo, and chromatographed on a silica gel column eluted with hexane–EtOAc (3:1) to give **23a** (71.8 mg, 38%) as a powder. IR: ν_{max} (KBr) 3341, 1732, 1651, 1493 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.58–7.10 (35H, m), 6.83 (1H, s), 6.50 (1H, d, J=8.8 Hz), 6.42 (1H, d, J=7.0 Hz), 5.51–5.47 (1H, m), 5.32–5.28 (1H, m), 5.18–4.99 (5H, m, containing 1H, AB-q, J=12.2 Hz at 5.11 ppm, 1H, AB-q, J=12.2 Hz at 5.01 ppm), 4.64–4.29 (9H, m), 4.24–4.17 (1H, m), 4.10–3.97 (1H, m), 3.83–3.60 (5H, m), 3.43–3.39 (1H, m), 2.61–2.08 (12H, m), 1.66–1.14 (120H, m), 0.88 (18H, t, J=6.2 Hz). High Resolution MS (FAB, positive), calcd for $C_{142}H_{213}N_2O_{25}PNa$ $(M+Na)^+$: 2400.5093; found: 2400.5078. Anal. Calcd for $C_{142}H_{213}N_2O_{25}P+H_2O$: C, 71.15; H, 9.04; N, 1.17; P, 1.29. Found: C, 71.10; H, 8.78; N, 1.13; P, 1.04.

Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-7-*O*-[2-deoxy-4-*O*-diphenylphosphono-2-[(*R*)-3-(dodecanoyloxy)tetradecanamido]-6-*O*-methyl-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-D-*glycero*-D-*ido*-heptonate (23b). Compound **22b** (189 mg, 0.093 mmol) was treated as described in the formation of **23a** from **22a** to give **23b** (123 mg, 59%) as a powder. IR: ν_{max} (KBr) 1736, 1659 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.42–7.14 (30H, m), 6.83 (1H, s), 6.50 (1H, d, J=9.3 Hz), 6.35 (1H, d, J=7.3 Hz), 5.43 (1H, t, J=9.3 Hz), 5.31 (1H, dd, J=10.5, 9.2 Hz), 5.17–5.12 (2H, m), 5.04 (1H, d, J=8.6 Hz), 4.68–4.34 (6H, m), 3.98–3.40 (11H, m), 3.22–3.18 (1H, broad s), 3.18 (3H, s), 2.68–2.04 (12H, m), 1.74–1.23 (120H, m), 0.88 (18H, t, J=6.3 Hz). High Resolution MS (FAB, positive), calcd for $C_{135}H_{209}N_2O_{23}PNa$ $(M+Na)^+$: 2280.4882; found: 2280.4871. Anal. Calcd for $C_{135}H_{209}N_2O_{23}P+H_2O$: C, 71.21; H, 9.34; N, 1.23; P, 1.36. Found: C, 71.21; H, 9.10; N, 1.28; P, 1.13.

Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-7-*O*-[2,6-deoxy-4-*O*-diphenylphosphono-2-[(*R*)-3-(dodecanoyloxy)tetradecanamido]-6-fluoro-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-D-*glycero*-D-*ido*-heptonate (23c). Compound **22c** (123 mg, 0.061 mmol) was treated as described in the formation of **23a** from **22a** to give **23c** (33.1 mg, 24%) as a powder. IR: ν_{max} (KBr) 1737, 1666, 1193 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.33–7.13 (30H, m), 6.84 (1H, s), 6.51 (1H, d, J=8.8 Hz), 6.44 (1H, d, J=6.6 Hz), 5.54 (1H, t, J=9.5 Hz), 5.31 (1H, t, J=9.5 Hz), 5.20 (1H, d, J=8.1 Hz), 5.19–5.13 (2H, m), 4.64 (1H, d, J=5.1 Hz), 4.62–4.31

(7H, m), 4.02 (1H, d, *J*=9.5 Hz), 3.89–3.81 (1H, m), 3.78–3.60 (5H, m), 3.48–3.44 (2H, m), 2.62 (1H, q, *J*=7.7 Hz), 2.47–2.10 (11H, m), 1.81–1.25 (120H, m), 0.88 (18H, t, *J*=7.3–5.1 Hz). High Resolution MS (FAB, positive), calcd for $C_{134}H_{206}N_2O_{22}FPNa$ $(M+Na)^+$: 2268.4682. Found: 2268.4746.

2,6-Anhydro-3-deoxy-7-*O*-[2-deoxy-4-*O*-diphenylphosphono-2-[(*R*)-3-(dodecanoyloxy)tetradecanamido]-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (24a). To a solution of **23a** (73.4 mg, 0.031 mmol) in ethyl acetate (3.0 ml), 20% $Pd(OH)_2$ on carbon (73.6 mg) was added, stirred for 15 h under hydrogen at atmospheric pressure at room temperature, and then, filtered through Celite. The filtrate was concentrated in vacuo, and separated by preparative thin layer chromatography ($CHCl_3$–MeOH, 5:1). The part containing a product was eluted with $CHCl_3$–MeOH (5:1) to give a mixture of **24a** contaminated with silica gel. The mixture was dissolved in $CHCl_3$–MeOH–0.1 M HCl aq. (5:10:4) to remove the silica gel, and extracted with $CHCl_3$. The chloroform layer was concentrated in vacuo to give **24a** (33.5 mg, 57%) as an amorphous film. IR: ν_{max} (KBr) 3372, 1736, 1664, 1490, 1189 cm^{-1}. ^1H NMR (400 MHz, CD_3OD–$CDCl_3$(10:1)) 7.41–7.32 (4H, m), 7.26–7.17 (6H, m), 5.44 (1H, dd, *J*=10.3, 9.5 Hz), 5.24 (1H, dd, *J*=10.3, 9.5 Hz), 5.27–5.18 (2H, m), 4.91 (1H, d, *J*=8.1 Hz), 4.73 (1H, q, *J*=8.8 Hz), 4.25 (1H, dd, *J*=5.9, 5.1 Hz), 4.15 (1H, d, *J*=5.9 Hz), 4.06 (1H, d, *J*=11.0 Hz), 3.68–3.58 (2H, m), 3.45 (1H, t, *J*=9.5 Hz), 2.59–2.40 (6H, m), 2.38–2.22 (4H, m), 2.14 (2H, t, *J*=7.3 Hz), 1.68–1.20 (120H, m), 0.90 (18H, t, *J*=7.3–6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{107}H_{185}N_2O_{23}PNa$ $(M+Na)^+$: 1920.3003; found: 1920.2963.

2,6-Anhydro-3-deoxy-7-*O*-[2-deoxy-4-*O*-diphenylphosphono-2-[(*R*)-3-(dodecanoyloxy)tetradecanamido]-6-*O*-methyl-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (24b). Compound **23b** (29.0 mg, 0.013 mmol) was treated as described in the formation of **24a** from **23a** to give **24b** (12.4 mg, 57%) as a powder. IR: ν_{max} (KBr) 3350 (broad), 1736 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) 7.41–7.36 (4H, m), 7.27–7.18 (6H, m), 5.44 (1H, t, *J*=9.5 Hz), 5.27–5.18 (2H, m), 4.95 (1H, d, *J*=8.8 Hz), 4.71 (1H, q, *J*=9.2 Hz), 4.27–4.22 (1H, m), 4.14 (1H, d, *J*=5.1 Hz), 4.04 (1H, d, *J*=11.0 Hz), 4.02–3.94 (1H, m), 3.93–3.78 (3H, m), 3.77–3.68 (2H, m), 3.53–3.44 (3H, m), 3.21 (3H, s), 2.61–2.40 (6H, m), 2.38–2.21 (4H, m), 2.13 (2H, t, *J*=7.3 Hz), 1.68–1.17 (120H, m), 0.90 (18H, t, *J*=6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{108}H_{187}N_2O_{23}PNa$ $(M+Na)^+$: 1934.3160; found: 1934.3162. Anal. Calcd for $C_{108}H_{187}N_2O_{23}P+2H_2O$: C, 66.55; H, 9.88; N, 1.44; P, 1.59. Found: C, 66.22; H, 9.63; N, 1.47; P, 1.62.

2,6-Anhydro-3-deoxy-7-*O*-[2,6-deoxy-4-*O*-diphenylphosphono-2-[(*R*)-3-(dodecanoyloxy)tetradecanamido]-6-fluoro-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (24c). To a solution of **23c** (16.5 mg, 0.007 mmol) in ethanol (2.0 ml), 20% $Pd(OH)_2$ on carbon (19.0 mg) was added, stirred for 20 h under hydrogen at atmospheric pressure at room temperature, and then, filtered through Celite. The filtrate was concentrated in vacuo, and separated by preparative thin layer chromatography ($CHCl_3$–MeOH, 8:1). The part containing a product was eluted with $CHCl_3$–MeOH (5:1) to give a mixture of **24c** contaminated with silica gel. The mixture was dissolved in $CHCl_3$–MeOH–0.1 M HCl aq. (5:10:4) to remove the silica gel, and extracted with $CHCl_3$. The chloroform layer was concentrated in vacuo to give **24c** (8.1 mg, 58%) as an amorphous film. IR: ν_{max} (KBr) 1736, 1661, 1189 cm^{-1}. ^1H NMR (400 MHz, CD_3OD–$CDCl_3$(10:1)) 7.42–7.35 (4H, m), 7.26–7.16 (6H, m), 5.48 (1H, t, *J*=9.9 Hz), 5.29–5.17 (3H, m), 5.03 (1H, d, *J*=8.1 Hz), 4.72 (1H, t, *J*=9.2 Hz), 4.59–4.47 (2H, m), 4.42–4.33 (1H, m), 4.33–4.23 (1H, m), 4.22–4.12 (1H, m), 4.07 (1H, d, *J*=11.7 Hz), 4.03–3.96 (1H, m), 3.95–3.78 (3H, m), 3.77–3.70 (1H, m), 3.43 (1H, t, *J*=9.9 Hz), 2.61–2.42 (6H, m), 2.36–2.25 (4H, m), 2.18–2.12 (2H, m), 1.68–1.20 (120H, m), 0.90 (18H, t, *J*=7.3–5.9 Hz). High Resolution MS (FAB, positive), calcd for $C_{107}H_{184}N_2O_{22}FPNa$ $(M+Na)^+$: 1922.2960; found: 1922.2898.

2,6-Anhydro-3-deoxy-7-*O*-[2-deoxy-2-[(*R*)-3-(dodecanoyloxy)tetradecanamido]-4-*O*-phosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (4a). To a solution of **24a** (5.2 mg, 0.0027 mmol) in THF (1.0 ml), PtO_2 (6.3 mg) was added, stirred for 18 h under hydrogen at atmospheric pressure at 50°C, and then filtered. The filtrate was concentrated in vacuo, and separated by preparative thin layer chromatography ($CHCl_3$–EtOH–AcOH–H_2O, 8:5:1:1). The part containing a product was eluted with $CHCl_3$–EtOH–AcOH–H_2O (8:5:1:1) to give a mixture of **4a** contaminated with silica gel. The mixture was dissolved in $CHCl_3$–MeOH–0.1 M HCl aq. (5:10:4) to remove the silica gel, and extracted with $CHCl_3$. The chloroform layer was concentrated in vacuo to give **4a** (4.2 mg, 88%) as a powder. $[\alpha]_D^{26}=-2.6$ (c=0.18, $CHCl_3$). IR: ν_{max} (KBr) 3351, 1734, 1662, 1468 cm^{-1}. ^1H NMR (400 MHz, CD_3OD–$CDCl_3$ (10:1)) 5.32–5.12 (4H, m), 4.68 (1H, d, *J*=8.8 Hz), 4.50 (1H, d, *J*=5.9 Hz), 4.33 (1H, dd, *J*=10.2, 5.1 Hz), 4.21 (1H, q, *J*=9.5 Hz), 4.08 (1H, d, *J*=10.3 Hz), 4.02–3.95 (1H, m), 3.90–3.77 (6H, m), 3.65–3.57 (1H, m), 3.50–3.45 (1H, m), 2.68–2.65 (2H, m), 2.53–2.40 (4H, m), 2.37–2.26 (6H, m), 1.68–1.24 (120H, m), 0.90 (18H, t, *J*=6.6 Hz). High Resolution MS (FAB, negative), calcd for $C_{95}H_{176}N_2O_{23}P$ $(M-H)^-$: 1744.2402; found: 1744.2352.

2,6-Anhydro-3-deoxy-7-*O*-[2-deoxy-2-[(*R*)-3-(dodecanoyloxy)tetradecanamido]-6-*O*-methyl-4-*O*-phosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (4b). Compound **24b** (17.3 mg, 0.009 mmol) was treated as described in the formation of **4a** from **24a** to give **4b** (7.8 mg, 49%) as a powder. $[\alpha]_D^{26}=-4.0$ (c=0.20, $CHCl_3$). IR: ν_{max} (KBr) 3351 (broad), 1734, 1664 cm^{-1}. ^1H NMR (400 MHz, CD_3OD–$CDCl_3$ (5:1)) 5.30–5.20 (4H, m), 4.67

(1H, d, J=8.8 Hz), 4.48 (1H, d, J=5.1 Hz), 4.37–4.33 (1H, m), 4.14–4.05 (2H, m), 4.01–3.96 (1H, m), 3.92–3.87 (2H, m), 3.82–3.76 (3H, m), 3.64–3.55 (3H, m), 3.42 (3H, s), 2.78–2.21 (12H, m), 1.67–1.23 (120H, m), 0.90 (18H, t, J=6.6 Hz). High Resolution MS (FAB, negative), calcd for $C_{96}H_{178}N_2O_{23}P$ $(M-H)^-$: 1758.2558; found: 1758.2534.

2,6-Anhydro-3-deoxy-7-*O*-[2,6-deoxy-2-[(*R*)-3-(dodecanoyloxy)tetradecanamido]-6-fluoro-4-*O*-phosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)-tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (4c). Compound **24c** (7.7 mg, 0.0040 mmol) was treated as described in the formation of **4a** from **24a** to give **4c** (5.2 mg, 73%) as a powder. $[\alpha]_D^{25}=-3.7$ (c=0.20, $CHCl_3$). IR: ν_{max} (KBr) 3362, 1734, 1662, 1467 cm^{-1}. ^1H NMR (400 MHz, CD_3OD–$CDCl_3$ (10:1)) 5.32–5.24 (4H, m), 4.68 (1H, d, J=9.5 Hz), 4.50 (1H, d, J=5.9 Hz), 4.33 (1H, dd, J=10.6, 6.2 Hz), 4.22 (1H, q, J=8.8 Hz), 4.07 (1H, d, J=9.5 Hz), 4.00–3.97 (1H, m), 3.90–3.85 (1H, m), 3.82–3.62 (6H, m), 3.60–3.48 (2H, m, including 1H, t, J=8.8 Hz at 3.60 ppm), 2.72–2.62 (2H, m), 2.55–2.40 (4H, m), 2.37–2.23 (6H, m), 1.67–1.25 (120H, m), 0.90 (18H, t, J=6.6 Hz). High Resolution MS (FAB, negative), calcd for $C_{95}H_{175}N_2O_{22}FP$ $(M-H)^-$: 1746.2358; found: 1746.2345.

Diphenylmethyl 2,6-anhydro-7-*O*-[2-acetamido-6-*O*-benzyloxycarbonyl-2-deoxy-4-*O*-diphenylphosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-D-*glycero*-D-*ido*-heptonate (25a). To a solution of **22a** (99.9 mg, 0.046 mmol) in acetic acid (2.0 ml), zinc dust (310 mg, 4.74 mmol) was added. After vigorously stirring for 5 h at room temperature, the solution was filtered through Celite to remove the zinc dust and concentrated in vacuo to give a crude product. To a solution of this crude product in CH_2Cl_2 (2.0 ml), acetic acid (12 mg) in CH_2Cl_2 (2.0 ml) and EDCI·HCl (17.8 mg, 0.093 mmol) were added at room temperature, and the mixture was allowed to stand for 4 h at room temperature. Then, the reaction mixture was concentrated in vacuo, and chromatographed on a silica gel column eluted with hexane–EtOAc (2:1) to give **25a** (43.5 mg, 47%) as a viscous oil. IR: ν_{max} (KBr) 3360, 1740, 1652, 1531, 1192 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) 7.35–7.11 (35H, m), 6.82 (1H, s), 6.53 (1H, d, J=3.9 Hz), 6.52 (1H, d, J=6.8 Hz), 5.50 (1H, t, J=9.3 Hz), 5.36–5.30 (2H, m), 5.18–5.08 (1H, m), 5.12 (1H, AB–q, J=12.2 Hz), 5.03 (1H, AB-q, J=12.2 Hz), 4.68–4.62 (2H, m, including 1H, AB-q, J=5.9 Hz at 4.62 ppm), 4.54 (1H, AB-q, J=11.7 Hz), 4.49–4.45 (2H, m, including 1H, AB-q, J=10.7 Hz at 4.47 ppm), 4.40–4.33 (3H, m), 4.18 (1H, dd, J=12.2, 4.4 Hz), 4.03 (2H, d, J=9.8 Hz), 3.88–3.81 (1H, m), 3.78–3.73 (1H, m), 3.68–3.55 (4H, m), 3.38–3.31 (2H, m), 2.61 (1H, dd, J=15.4, 7.3 Hz), 2.46–2.38 (2H, m), 2.28–2.11 (5H, m), 1.87 (3H, s), 1.75–1.08 (85H, m), 0.88 (12H, t, J=6.9 Hz). High Resolution MS (FAB, positive), calcd for $C_{118}H_{167}N_2O_{23}PNa$ $(M+Na)^+$: 2034.1595; found: 2034.1606. Anal. Calcd for $C_{118}H_{167}N_2O_{23}P$: C, 70.42; H, 8.36; N, 1.39; P, 1.54. Found: C, 70.14; H, 8.22; N, 1.28; P, 1.27.

Diphenylmethyl 2,6-anhydro-7-*O*-[2-acetamido-2-deoxy-4-*O*-diphenylphosphono-6-*O*-methyl-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecanoyl]-3-deoxy-D-*glycero*-D-*ido*-heptonate (25b). Compound **22b** (23.3 mg, 0.012 mmol) was treated as described in the formation of **25a** from **22a** to give **25b** (15.9 mg, 75%) as a powder. IR: ν_{max} (KBr) 3339, 1742, 1654 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) 7.39–7.13 (30H, m), 6.82 (1H, s), 6.52 (1H, d, J=9.0 Hz), 6.41 (1H, d, J=7.1 Hz), 5.46 (1H, dd, J=10.0, 9.4 Hz), 5.30 (1H, dd, J=10.5, 9.3 Hz), 5.22 (1H, d, J=8.2 Hz), 5.19–5.10 (1H, m), 4.72–4.40 (6H, m), 4.36 (2H, d, J=1.9 Hz), 4.05–3.58 (6H, m), 3.52–3.35 (4H, m), 3.21 (3H, s), 2.65–2.14 (8H, m), 1.87 (3H, s), 1.78–1.11 (82H, m), 0.88 (12H, t, J=6.4 Hz). High Resolution MS (FAB, positive), calcd for $C_{111}H_{163}N_2O_{21}PNa$ $(M+Na)^+$: 1914.1384; found: 1914.1450. Anal. Calcd for $C_{111}H_{163}N_2O_{21}P$: C, 70.45; H, 8.68; N, 1.48; P, 1.64. Found: C, 70.50; H, 8.86; N, 1.45; P, 1.75.

Diphenylmethyl 2,6-anhydro-7-*O*-[2-acetamido-2,6-deoxy-4-*O*-diphenylphosphono-6-fluoro-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)-tetradecanoyl]-3-deoxy-D-*glycero*-D-*ido*-heptonate (25c). Compound **22c** (122 mg, 0.061 mmol) was treated as described in the formation of **25a** from **22a** to give **25c** (65.1 mg, 57%) as a powder. IR: ν_{max} (KBr) 3356, 1733, 1654, 1533, 1193 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.36–7.08 (30H, m), 6.82 (1H, s), 6.55 (1H, d, J=7.3 Hz), 6.52 (1H, d, J=9.5 Hz), 5.53 (1H, t, J=9.5 Hz), 5.38–5.28 (2H, m), 5.15–5.13 (1H, m), 4.67–4.60 (2H, m), 4.57–4.45 (4H, m), 4.39–4.32 (2H, m), 4.07–4.04 (1H, m), 3.86–3.83 (1H, m), 3.73–3.56 (5H, m), 3.40–3.33 (2H, m), 2.61 (1H, dd, J=7.3, 15.4 Hz), 2.41 (2H, dd, J=5.1, 15.4 Hz), 2.25–2.11 (5H, m), 1.87 (3H, s), 1.66–1.25 (82H, m), 0.88 (12H, t, J=6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{110}H_{160}N_2O_{20}FPNa$ $(M+Na)^+$: 1902.1184; found: 1902.1167. Anal. Calcd for $C_{110}H_{160}N_2O_{20}FP$: C, 70.26; H, 8.58; N, 1.49; F, 1.01; P, 1.65. Found: C, 69.98; H, 8.08; N, 1.34; F, 1.12; P, 1.77.

2,6-Anhydro-7-*O*-[2-acetamido-2-deoxy-4-*O*-diphenylphosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-deoxy-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (26a). To a solution of **25a** (15.1 mg, 0.008 mmol) in ethanol (1.0 ml), 20% $Pd(OH)_2$ on carbon (16.0 mg) was added, and the mixture was stirred for 7 h under hydrogen at atmospheric pressure at room temperature, and filtered through Celite. The filtrate was concentrated in vacuo, and separated by preparative thin layer chromatography ($CHCl_3$–MeOH, 5:1). The part containing a product was eluted with $CHCl_3$–MeOH (5:1) to give a mixture of **26a** contaminated with silica gel. The mixture was dissolved in $CHCl_3$–MeOH–0.1 M HCl aq. (5:10:4) to remove the silica gel, and extracted with $CHCl_3$. The chloroform layer was concentrated in vacuo to give **26a** (7.8 mg, 63%) as a powder. IR: ν_{max} (KBr) 3373, 1738, 1662, 1490, 1189 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) 7.41–7.36 (4H, m), 7.26–7.18 (6H, m), 5.41 (1H, t, J=9.9 Hz), 5.30 (1H, t, J=10.3 Hz), 5.11 (1H, t, J=6.2 Hz), 4.76 (1H, d, J=8.8 Hz), 4.71 (1H, q, J=9.2 Hz), 4.49–4.46 (1H, m), 4.36–4.28 (1H, m), 4.11

(1H, d, *J*=11.0 Hz), 3.97–3.75 (6H, m), 3.67–3.58 (2H, m), 3.53 (1H, t, *J*=8.8 Hz), 2.54–2.39 (4H, m), 2.32–2.21 (2H, m), 2.16 (2H, t, *J*=7.3 Hz), 1.94 (3H, s), 1.53–1.18 (82H, m), 0.91–0.88 (12H, m). High Resolution MS (FAB, positive), calcd for $C_{83}H_{139}N_2O_{21}PNa$ $(M+Na)^+$: 1553.9506; found: 1553.9490. Anal. Calcd for $C_{83}H_{139}N_2O_{21}P+2H_2O$: C, 63.58; H, 9.19; N, 1.79; P, 1.98. Found: C, 63.21; H, 8.72; N, 1.77; P, 2.02.

2,6-Anhydro-7-*O*-[2-acetamido-2-deoxy-4-*O*-diphenylphosphono-6-*O*-methyl-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-deoxy-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (26b). To a solution of **25b** (14.6 mg, 0.008 mmol) in EtOAc (3.0 ml), 20% $Pd(OH)_2$ on carbon (15.2 mg) was added, and the mixture was stirred for 16 h under hydrogen at atmospheric pressure at room temperature, and then, filtered through Celite. The filtrate was concentrated in vacuo, and separated by preparative thin layer chromatography ($CHCl_3$–MeOH, 8:1). The part containing a product was eluted with $CHCl_3$–MeOH (5:1) to give a mixture of **26b** contaminated with silica gel. The mixture was dissolved in $CHCl_3$–MeOH–0.1 M HCl aq. (5:10:4) to remove the silica gel, and extracted with $CHCl_3$. The chloroform layer was concentrated in vacuo to give **26b** (7.7 mg, 63%) as a powder. IR: ν_{max} (KBr) 3500–3300 (broad), 1740, 1655 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) 8.16 (1H, d, *J*=10.0 Hz), 7.41–7.37 (4H, m), 7.27–7.19 (6H, m), 5.41 (1H, t, *J*=9.9 Hz), 5.26 (1H, t, *J*=9.5 Hz), 5.10 (1H, t, *J*=5.9 Hz), 4.97 (1H, d, *J*=8.1 Hz), 4.72 (1H, q, *J*=9.2 Hz), 4.27–4.23 (1H, m), 4.16 (1H, d, *J*=5.1 Hz), 4.04 (1H, d, *J*=12.5 Hz), 3.97–3.82 (4H, m), 3.77–3.70 (2H, m), 3.54–3.41 (3H, m), 3.22 (3H, s), 2.50–2.37 (4H, m), 2.34–2.21 (2H, m), 2.15 (2H, t, *J*=7.3 Hz), 2.00 (3H, s), 1.55–1.25 (82H, m), 0.90 (12H, t, *J*=7.3–6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{84}H_{141}N_2O_{21}PNa$ $(M+Na)^+$: 1567.9662; found: 1567.9694. Anal. Calcd for $C_{84}H_{141}N_2O_{21}P$: C, 65.26; H, 9.19; N, 1.81; P, 2.00. Found: C, 64.89; H, 9.04; N, 1.64; P, 1.97.

2,6-Anhydro-7-*O*-[2-acetamido-2,6-deoxy-4-*O*-diphenylphosphono-6-fluoro-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-deoxy-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (26c). Compound **25c** (54.5 mg, 0.029 mmol) was treated as described in the formation of **26a** from **25a** to give **26c** (29.1 mg, 65%) as an amorphous film. IR: ν_{max} (KBr) 3345, 1738, 1662, 1491, 1189 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) 7.41–7.37 (4H, m), 7.27–7.17 (6H, m), 5.46 (1H, t, *J*=9.9 Hz), 5.27 (1H, t, *J*=9.5 Hz), 5.13–5.04 (1H, m), 4.81 (1H, d?, unclear due to overlapping with solvent's peak), 4.70 (1H, q, *J*=9.3 Hz), 4.60 (1H, d, *J*=11.0 Hz), 4.49 (1H, d, *J*=11.0 Hz), 4.40–4.36 (1H, m), 4.27–4.23 (1H, m), 4.18–4.14 (1H, m), 4.04 (1H, d, *J*=12.5 Hz), 3.99–3.81 (4H, m), 3.76–3.68 (1H, m), 3.42 (3H, t, *J*=9.5 Hz), 2.50–2.41 (4H, m), 2.34–2.21 (2H, m), 2.16 (2H, t, *J*=7.3 Hz), 2.01 (3H, s), 1.55–1.20 (82H, m), 0.90 (12H, t, *J*=6.6 Hz). High Resolution MS (FAB, positive), calcd for $C_{83}H_{138}N_2O_{20}FPNa$ $(M+Na)^+$: 1555.9462; found: 1555.9437. Anal. Calcd for $C_{83}H_{138}N_2O_{20}FP+2H_2O$: C, 63.50; H, 9.12; N, 1.78; F, 1.21; P, 1.97. Found: C, 63.37; H, 8.66; N, 1.76; F, 1.41; P, 2.11.

2,6-Anhydro-7-*O*-[2-acetamido-2-deoxy-4-*O*-phosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-deoxy-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (5a). To a solution of **26a** (6.6 mg, 0.004 mmol) in THF (1.0 ml), PtO_2 (8.4 mg) was added, and the mixture was stirred for 20 h under hydrogen at atmospheric pressure at room temperature, and then filtered. The filtrate was concentrated in vacuo, and separated by preparative thin layer chromatography ($CHCl_3$–EtOH–AcOH–H_2O, 8:5:1:1). The part containing a product was eluted with $CHCl_3$-EtOH-AcOH-H_2O (8:5:1:1) to give a mixture of **5a** contaminated with silica gel. The mixture was dissolved in $CHCl_3$–MeOH–0.1 M HCl aq. (5:10:4) to remove the silica gel, and extracted with $CHCl_3$. The chloroform layer was concentrated in vacuo to give **5a** (4.9 mg, 82%) as a powder. $[\alpha]_D^{25}=-7.8$ (c=0.20, $CHCl_3$). IR: ν_{max} (KBr) 3368, 1737, 1664, 1466 cm^{-1}. ^1H NMR (500 MHz, CD_3OD–$CDCl_3$ (10:1)) 5.26–5.12 (3H, m), 4.62 (1H, d, *J*=8.8 Hz), 4.31–4.18 (3H, m), 4.09 (1H, d, *J*=9.5 Hz), 4.03–3.87 (4H, m), 3.82–3.73 (3H, m), 3.50–3.38 (2H, m), 2.74–2.60 (2H, m), 2.52–2.38 (2H, m), 2.36–2.22 (4H, m), 1.98 (3H, s), 1.63–1.58 (4H, m), 1.45–1.41 (6H, m), 1.38–1.23 (72H, m), 0.90 (12H, t, *J*=7.3–6.6 Hz). High Resolution MS (FAB, negative), calcd for $C_{71}H_{130}N_2O_{21}P$ $(M-H)^-$: 1377.8904; found: 1377.8844. Anal. Calcd for $C_{71}H_{131}N_2O_{21}P+H_2O$: C, 61.01; H, 9.59; N, 2.00; P, 2.22. Found: C, 61.24; H, 9.79; N, 2.14; P, 1.94.

2,6-Anhydro-7-*O*-[2-acetamido-2-deoxy-6-*O*-methyl-4-*O*-phosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-deoxy-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (5b). Compound **26b** (7.0 mg, 0.0045 mmol) was treated as described in the formation of **5a** from **26a** to give **5b** (6.8 mg, 99%) as a powder. $[\alpha]_D^{26}=-6.6$ (c=0.20, $CHCl_3$). IR: ν_{max} (KBr) 3362, 1737, 1665 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) 5.30 (1H, dd, *J*=10.7, 8.8 Hz), 5.23–5.15 (2H, m), 4.66 (1H, d, *J*=8.5 Hz), 4.50 (1H, d, *J*=5.7 Hz), 4.34–4.29 (1H, m), 4.22–4.19 (1H, m), 4.10 (1H, d, *J*=1.4 Hz), 4.00–3.94 (1H, m), 3.88–3.73 (5H, m), 3.62–3.57 (2H, m), 3.54 (1H, t, *J*=9.1 Hz), 3.41 (3H, s), 2.72–2.22 (8H, m), 1.94 (3H, s), 1.62–1.56 (4H, m), 1.48–1.40 (6H, m), 1.39–1.23 (72H, m), 0.91 (12H, t, *J*=7.0–6.6 Hz). High Resolution MS (FAB, negative), calcd for $C_{72}H_{132}N_2O_{21}P$ $(M-H)^-$: 1391.9060; found: 1391.9093. Anal. Calcd for $C_{72}H_{133}N_2O_{21}P+H_2O$: C, 61.25; H, 9.64; N, 1.98; P, 2.19. Found: C, 61.53; H, 9.50; N, 1.99; P, 2.23.

2,6-Anhydro-7-*O*-[2-acetamido-2,6-deoxy-6-fluoro-4-*O*-phosphono-3-*O*-[(*R*)-3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-3-deoxy-3-[(*R*)-3-(hydroxy)tetradecanamido]-4-*O*-[(*R*)-3-(hydroxy)tetradecanoyl]-D-*glycero*-D-*ido*-heptonic acid (5c). Compound **26c** (17.1 mg, 0.0111 mmol) was treated as described in the formation of **5a** from **26a** to give **5c** (13.3 mg, 87%) as a powder. $[\alpha]_D^{26}=-18.6$ (c=0.20, $CHCl_3$). IR: ν_{max} (KBr) 3363, 1734, 1662, 1466 cm^{-1}. ^1H NMR (400 MHz, CD_3OD–$CDCl_3$(10:1)) 5.23–5.14 (3H, m), 4.72–4.57 (2H, m), 4.33–4.28 (2H, m), 4.18–4.12 (2H, m), 4.00–3.88 (3H, m), 3.78–3.56 (4H, m), 3.32 (1H, t, *J*=1.5 Hz), 2.74 (1H, d, *J*=9.5, 6.6 Hz), 2.63 (1H, dd, *J*=9.5, 6.6 Hz), 2.52–2.40

(2H, m), 2.36–2.22 (4H, m), 1.99 (3H, s), 1.63–1.58 (4H, m), 1.50–1.42 (6H, m), 1.38–1.22 (72H, m), 0.89 (12H, t, J=7.3–6.6 Hz). High Resolution MS (FAB, negative), calcd for $C_{71}H_{129}N_2O_{20}FP$ $(M-H)^-$: 1379.8860; found: 1379.8854. Anal. Calcd for $C_{71}H_{130}N_2O_{20}FP$: C, 61.72; H, 9.48; N, 2.03; F, 1.38; P, 2.24. Found: C, 61.55; H, 9.36; N, 1.76; F, 1.19; P, 2.11.

Method for biological activity measurement[12]

The sources of the materials used in the study are as follows: lipopolysaccharide (LPS) from *E. coli* serotype 026:B6[18] and 12-*O*-tetradecanoylphorbor acetate (TPA) were from SIGMA, St. Louis, MO; RPMI-1640 medium, fetal bovine serum (FBS), and newborn calf serum (NBCS) were from GIBCO, Grand Island, NY; and 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 (1×10^4/200μl/well) were plated in 96-well plates (Corning, Cambridge, MA), and were cultured in the presence of TPA (30 ng/ml) for 72 h at 37°C. After removing the supernatant, the cells were incubated in 200 μl of fresh RPMI-1640 medium containing 10% NBCS, in the absence or the presence of 30 ng/ml of LPS with graded concentrations of the compounds in a humidified atmosphere of 5% CO_2 for 4.5 h at 37°C. After incubation, the amount of TNFα produced in the culture supernatants was determined using the TNFα ELISA kits. As a control, the amount of TNFα produced by the U937 cells, which were stimulated with 30 ng/ml of LPS in the absence of compounds, was used. The concentrations (nM) of compounds required to inhibit the LPS-induced TNFα production by U937 cells by 50% (IC_{50}) was calculated from the control amount. All experiments were carried out at least twice, showing the data are reproducible. The representative data are shown in Figs. 3 and 4.

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