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Synthesis of GLA-60 type pyran carboxylic acids with an alkyl chain instead of an ester chain as LPS-antagonists

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Abstract

Synthesis of GLA-60 type pyran carboxylic acid analogues with an alkyl chain instead of an ester chain and their LPS-antagonist activity toward human U937 cells are described.

Keywords: Lipid A; Endotoxin; LPS-antagonist; TNFα production inhibitor

1. Introduction

Lipopolysaccharides (LPS)[1] cover the outer surface membrane of gram-negative bacteria such as *Escherichia coli* and are highly potent stimulators of the immune system.[2] A variety of responses, both beneficial and harmful, can be elicited by LPS. One of these harmful responses is fatal endotoxic shock (bacterial sepsis) caused as a consequence of acute inflammatory response, which has precluded the clinical use of LPS.

Most of the biological activities of LPS reside in a relatively small portion of the molecule, that is, in the terminal disaccharide phospholipid subunit known as lipid A, which is a hydrophobic anchor substance holding an essentially linear polysaccharide chain to the cell wall. In recent years, endotoxin-related compounds have been studied as LPS-antagonists that may have potential as immunosuppressants,[3] or in the treatment of inflammation, autoimmune diseases[3] and septicemia[4], by deactivating LPS-induced aggressive macrophages. For example, Lipid IVa, which is a biosynthetic precursor of Lipid A, acts as an LPS-antagonist in the human body.[5] Furthermore, Qureshi's group[6] isolated a lipid A-related compound from *Rhodobacter sphaeroides* that showed potent LPS antagonist activity, and recently the Eisai group developed a related compound, E5564,[4,7] as a highly potent anti-septicemia drug.

During our investigation of the biological activities of compounds related to GLA-60,[8] which is a non-reducing monosaccharide ana-

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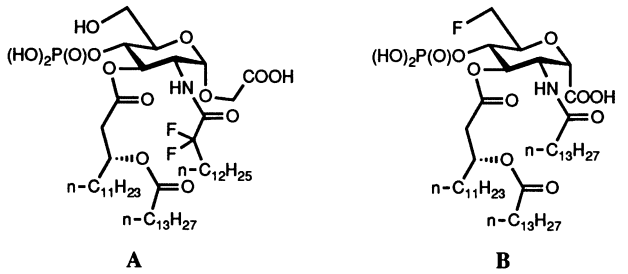


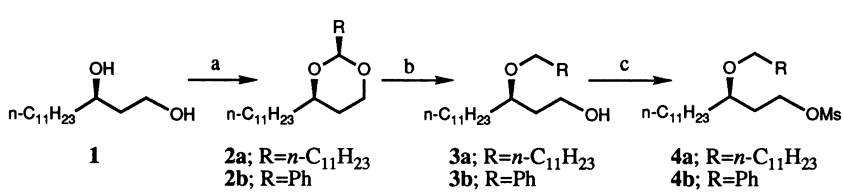
Fig. 1. Monosaccharide LPS-antagonists toward human U937 cells.

logue of Lipid A, we also found that most of them had LPS-agonistic activity, but a few of them behaved as LPS antagonists. The anomeric carboxymethyl GLA-60 analogue **A** and the pyran carboxylic acid **B** exhibited fairly strong LPS-antagonistic activity[9] toward human U937 cells. By using this information on the characteristics of **A** and **B**, we synthesized nine compounds in which the ester bonds were replaced by ether bonds10a in order to stabilize the compounds and to aim at increasing their activities. In this paper, we report the synthesis of these compounds as LPS-antagonists and their activities (Fig. 1).

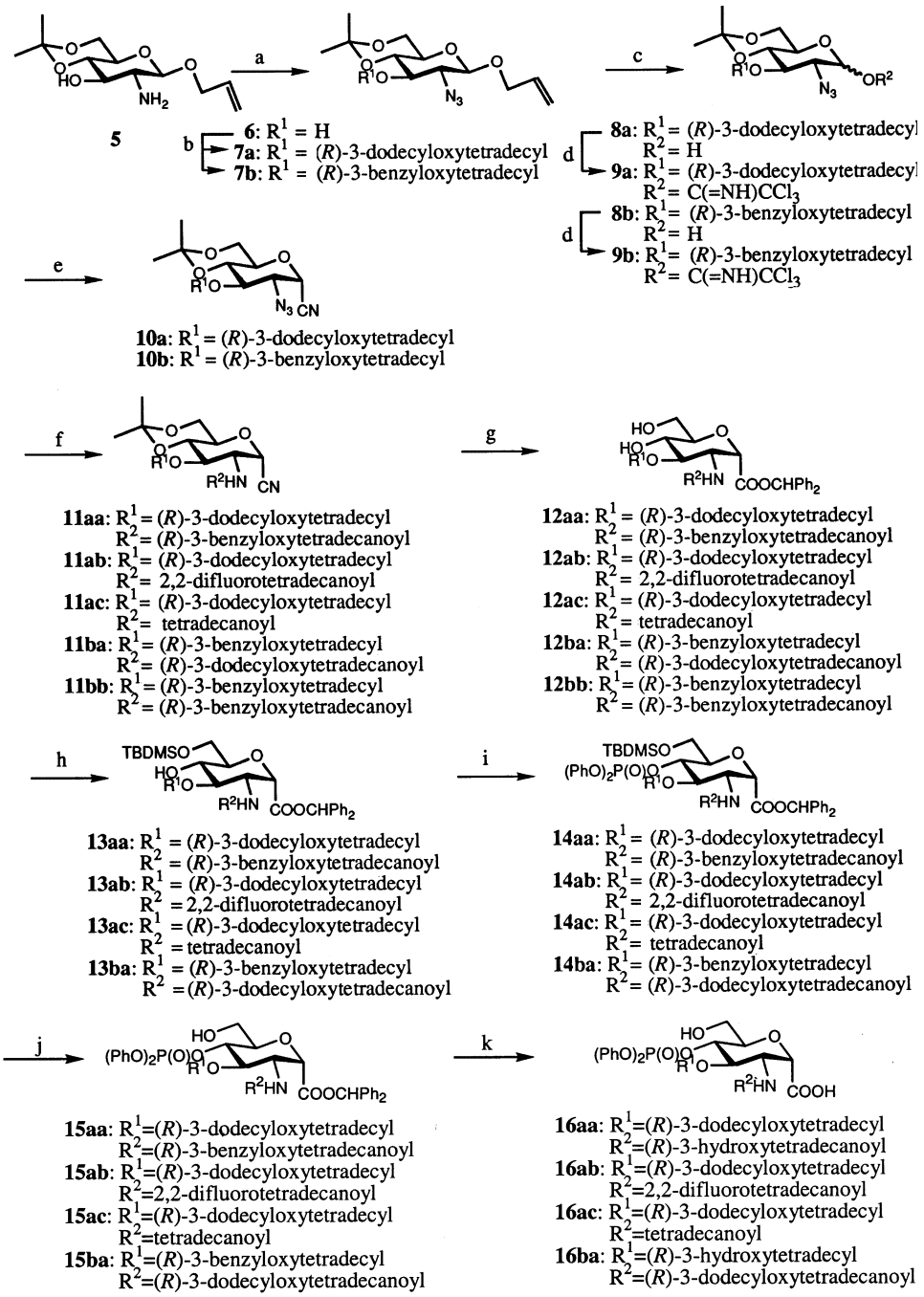
2. Results and discussion

Synthesis.—First, in Scheme 1, two mesylates **4a** and **4b** as side chain materials were prepared from chiral starting diol **1**. The starting diol **1**, easily obtained by lithium aluminum hydride reduction[10b] in THF of commercially available (*R*)-3-hydroxytetradecanoic acid, was treated with dodecyl aldehyde or benzaldehyde dimethyl acetal using *p*-TsOH·water as a catalyst to yield single acetal **2a** or **2b**, respectively. The configurations of all substituents of compounds **2a** and **2b** should be equatorial toward the 1,3-dioxane ring, because the equatorial configuration should be more stable than the axial. DIBAL reduction of compounds **2a** and **2b** in CH_2Cl_2 gave **3a** and **3b**, respectively. Mesylation of **3a** and **3b** yielded **4a** and **4b**, respectively.

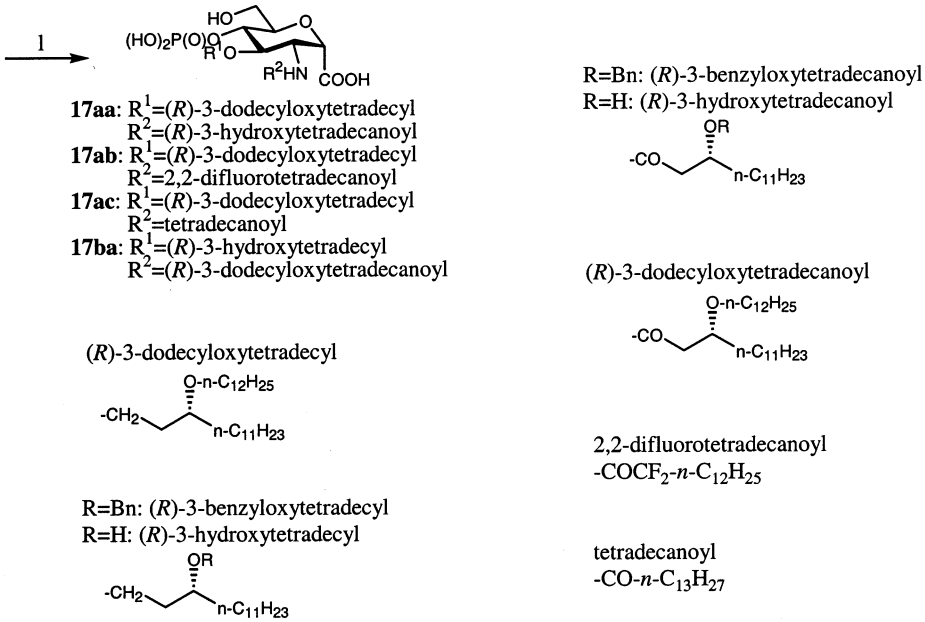
Next, in Scheme 2, C-7 hydroxy compounds **17aa**, **17ab**, **17ac**, and **17ba** were synthesized from **5**. The starting amine **5**[11] was converted to an azide **6** by the reported method.[12] Alkylation of the alcohol of **6** with (*R*)-3-dodecyloxy-1-(methanesulfonyloxy)tetradecane or (*R*) - 3 - benzyloxy - 1 - (methanesulfonyloxy)-tetradecane and sodium hydride gave an ether **7a** or **7b**, respectively. The anomeric allyl protecting groups of **7a** and **7b** were deprotected to give **8a** and **8b**, respectively, by treatment with SeO_2 for **8a** from **7a**, or by treatment with 1,5-cyclooctadienebis(methyldiphenylphosphine)iridium hexafluorophosphate[13] as a catalyst, and successive treatment with water–pyridine–iodine for **8b** from **7b**. The reaction of **8a** and **8b** with trichloroacetonitrile and a catalytic amount of 1,8-diazobicyclo[5.4.0]-undec-7-ene (DBU) gave an anomeric mixture of trichloroacetimidates **9a** and **9b**, respectively.[14] The anomeric α-cyanation was performed by a previously reported method.[15] Treatment of **9a** and **9b** with trimethylsilyl cyanide using 4 Å molecular sieves (4AMS) and trifluoromethanesulfonate as a catalyst stereospecifically gave the nitriles **10a** and **10b**, respectively. Reduction of the azides of **10a** and **10b** with triphenylphosphine and aqueous ammonia, and successive acylation of the amines thus obtained with (*R*)-3-benzyloxytetradecanoic acid, 2,2-difluorotetradecanoic acid[16] or (*R*)-3-dodecyloxytetradecanoic acid using dicyclohexylcarbodiimide (DCC)-dimethylaminopyridine (DMAP), or acylation with tetradecanoyl chloride and triethylamine gave amides **11aa**–**11bb**. Hydration of the nitrile parts of **11aa**–**11bb** with water and 4 M



Scheme 1. Reagents and conditions: (a) *n*-$C_{11}H_{23}CHO$ or $PhCH(OMe)_2$, *p*-TsOH, $PhCH_3$, 60 °C, 30 min, 96% (**2a**) or 97% (**2b**); (b) DIBAL, CH_2Cl_2, rt, 5 h, 89% (**3a**) and 95% (**3b**), respectively; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 98% (**4a**) and 96% (**4b**), respectively.



Scheme 2. Reagents and conditions: (a) 0.4 M TfN_3 in CH_2Cl_2, DMAP, MeOH, rt, 18 h, 91%; (b) (*R*)-3dodecyloxy-1-(methanesulfonyloxy)tetradecane or (*R*)-3-benzyloxy-1-(methanesulfonyloxy)tetradecane, NaH, DMF, 73–74%; (c) SeO_2, cat. AcOH, dioxane, reflux, 1 h, 70% (**8a** from **7a**); or $[C_8H_{12}Ir(PMePh_2)_2]PF_6$, THF, rt, 3 h, then water, I_2, pyridine, rt, 12 h, 65% (**8b** from **7b**); (d) Cl_3CCN, cat. DBU, CH_2Cl_2, 0 °C, 1 h, 91% (**9a** from **8a**); 0 °C, 2 h, 88% (**9b** from **8b**); (e) TMSCN, cat. TMSOTf, 4AMS, CH_2Cl_2, rt, 3 h, 75% (**10a** from **9a**); rt, 2 h, 93% (**10b** from **9b**); (f) (1) Ph_3P, THF, 28% NH_3 in water, 60 °C, 24 h, (2) (*R*)-3-(benzyloxy)tetradecanoic acid, DCC, DMAP, CH_2Cl_2, rt, 18 h, 79% (**11aa** from **10a**) and 63% (**11bb** from **10b**), or 2,2-difluorotetradecanoic acid, DCC, DMAP, CH_2Cl_2, rt, 18 h, 94% (**11ab** from **10a**), or tetradecanoyl chloride, Et_3N, CH_2Cl_2, rt, 1 h, 84% (**11ac** from **10a**), or (*R*)-3-(dodecyloxy)tetra-decanoic acid, DCC, DMAP, rt, 2 h, 74% (**11ba** from **10b**); (g) 4 M HCl dioxane, water, 60 °C (80 °C in the case of **11bb**), 3–4 h (72 h in the case of **11bb**), then Ph_2CN_2, DMF, 60 °C, 1–2 h, 50% (**12aa** from **11aa**), 41% (**12ab** from **11ab**), 46% (**12ac** from **11ac**), 26% (**12ba** from **11ba**), 43% (**12bb** from **11bb**); (h) TBDMSCl, DMAP, CH_2Cl_2, rt, 3 h, 87% (**13aa** from **12aa**), 88% (**13ab** from **12ab**), 89% (**13ac** from **12ac**), and 62% (**13ba** from **12ba**); (i) $(PhO)_2P(O)Cl$, DMAP, CH_2Cl_2, rt, 2 h, 95–97% (> 80% in **14ba**); (j) 3 M HCl aq, THF, rt, 6 h, 88–93% (**15ba**, two steps 80% from **13ba**); (k) H_2, 20% $Pd(OH)_2/C$ in the case of **15aa** and **15ba**, or 10% Pd/C in the case of **15ab** and **15ac**, EtOH, rt, 2–16 h, **16aa**: 82%, **16ab**: 78%, **16ac**: 69%, **16ba**: 58%; (l) H_2, PtO_2, THF, rt, 18 h, **17aa**: 74%, **17ab**: 96%, **17ac**: 99%, and **17ba**: 86%.



Scheme 2. (*Continued*)

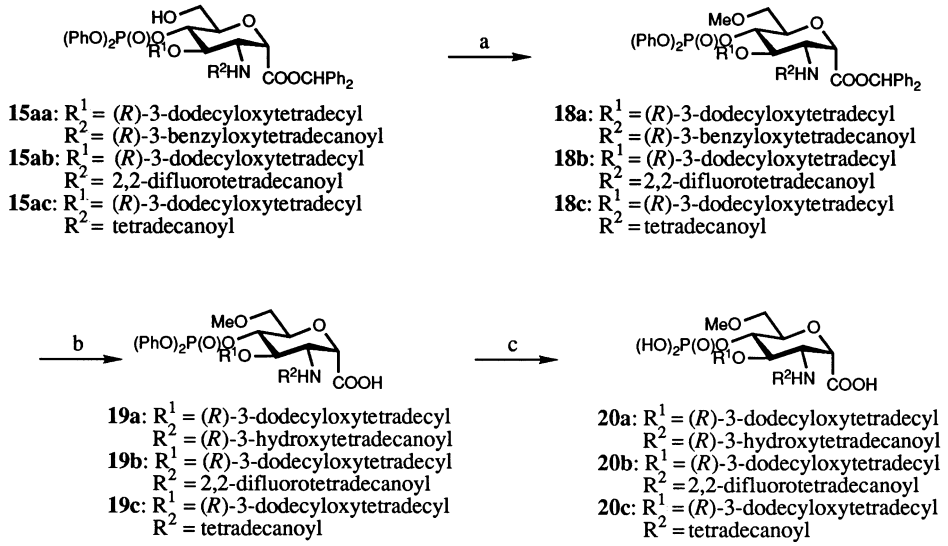
HCl in dioxane, and successive esterification of the acid thus obtained with diphenyldiazomethane gave esters **12aa**–**12bb**, respectively. Selective protection of the C-7 alcohol in diols **12aa**–**12ba** with *tert*-butyldimethylsilyl chloride (TBDMSCl) in dichloromethane using DMAP as a base gave silyl ethers **13aa**–**13ba**, respectively. Phosphorylation of the C-5 alcohol of **13aa**–**13ba** with diphenyl chlorophosphate and DMAP yielded phosphates **14aa**–**14ba**, respectively. Desilylation of **14aa**–**14ba** by aqueous 3 M HCl in THF gave alcohols **15aa**–**15ba**, respectively. Deprotection of the benzhydryl esters and benzyl ethers of both **15aa** and **15ba** by hydrogenolysis using $Pd(OH)_2$-on-carbon as a catalyst, or that of the benzhydryl esters of both **15ab** and **15ac** using Pd/C as a catalyst produced the carboxylic acids **16aa**–**16ba**. Finally, hydrogenolysis of four phosphates **16aa**–**16ba** using PtO_2 as a catalyst yielded 5-*O*-phosphono carboxylic acids **17aa**–**17ba**, respectively.

Thirdly, in Scheme 3, 7-*O*-methyl derivatives **20a**, **20b** and **20c** were synthesized from **15aa**, **15ab** and **15ac**, respectively. Methylation of the C-7 primary alcohol of **15aa**–**15ac** with trimethyloxonium tetrafluoroborate gave **18a**–**18c**, respectively. Deprotection of the benzhydryl ester and benzyl ether of **18a** by hydrogenolysis using $Pd(OH)_2$-on-carbon as a catalyst, or that of the benzhydryl esters of **18b** and **18c** using Pd/C as a catalyst produced carboxylic acids **19a**–**c**. Hydrogenolysis of the phosphates **19a**–**c** using PtO_2 as a catalyst yielded 5-*O*-phosphono carboxylic acids **20a**–**c**, respectively.

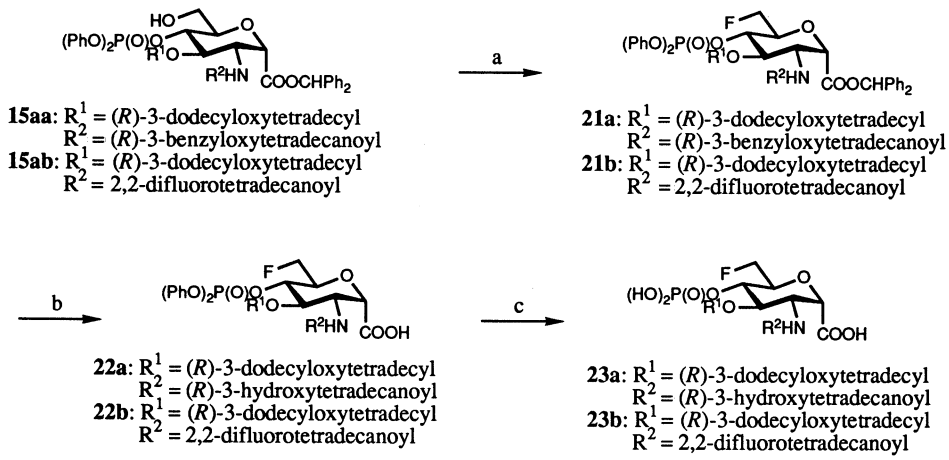
Last, in Scheme 4, 7-C-fluoro derivatives **23a** and **23b** were synthesized from **15aa** and **15ab**, respectively. Fluorination of the C-7 primary alcohol of **15aa** and **15ab** with diethylaminosulfur trifluoride (DAST) gave **21a** and **21b**, respectively. Deprotection of the benzhydryl ester and benzyl ether of **21a** by hydrogenolysis using $Pd(OH)_2$-on-carbon as a catalyst, and that of the benzhydryl ester of **21b** using Pd/C as a catalyst produced carboxylic acids **22a** and **22b**. Hydrogenolysis of the phosphates **22a** and **22b** using PtO_2 as a catalyst yielded 5-*O*-phosphono carboxylic acids **23a** and **23b**, respectively.

Thus, we were able to synthesize a total of nine compounds, **17aa**, **17ab**, **17ac**, **17ba**, **20a**, **20b**, **20c**, **23a** and **23b**.

Biological activities.—The inhibitory activity of the nine synthesized compounds, **17aa**, **17ab**, **17ac**, **17ba**, **20a**, **20b**, **20c**, **23a** and **23b**, on LPS-induced TNFα production was investigated in vitro using human monoblastic U937 cells. The IC_{50} values (nM) of these nine



Scheme 3. Reagents and conditions: (a) Me_3OBF_4, DTBMP, CH_2Cl_2, rt, 3 h, **18a**: 92%, **18b**: 70%, and **18c**: 87%; (b) H_2, 20% $Pd(OH)_2$/C in the case of **18a**, and 10% Pd/C in the case of **18b** and **18c**, EtOH, rt, 2–8 h, **19a**: 83%, **19b**: 69%, and **19c**: 62%; (c) H_2, PtO_2, THF, rt, 18 h, **20a**: 92%, **20b**: 98%, and **20c**: 92%.



Scheme 4. Reagents and conditions: (a) DAST, DME, CH_2Cl_2, 0 °C, 2 h, **21a**: 52%, and **2b**: 77%; (b) H_2, 20% $Pd(OH)_2$/C, EtOH, rt, 8 h, 72% (**22a**), or 10% Pd/C, EtOH, rt, 2 h, 62% (**22b**); (f) H_2, PtO_2, THF, rt, 18 h, **23a**: 69%, and **23b**: 93%.

compounds, **17aa**, **17ab**, **17ac**, **17ba**, **20a**, **20b**, **20c**, **23a** and **23b**, were 32, 3.6, 12, 98, 70, 1.5, 360, 21, and 5.7 nM, respectively. The IC_{50} values of compounds **17ab** and **20b** were stronger than those of compounds **A** and **B** (5 and 5.7 nM, respectively).[9a,9b] The activity of compound **23b** was equal to that of compound **B**. These three active compounds **17ab**, **20b**, and **23b** coincidentally have the 2,2-difluorotetradecanoylamino group as an amide at the C-3 position. The IC_{50} values of ether **17ac** and its ester ((*R*)-3-tetradecanoyloxytetradecanoyl) derivative[9b] were 12 and 7.9 nM, respectively. Therefore, the difference of inhibitory activity between ester and ether compounds in this series may not be so large.

3. 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. ^1H NMR spectra were recorded with a JEOL JNM-270 or a JEOL-GSX 400 spectrometer using Me_4Si as the internal standard. IR absorption spectra were determined with an IR A-2 spectrophotometer, and mass spec-

tra were obtained with a JMS-700 mass spectrometer. Elemental analyses were performed by the Institute of Science and Technology. Column chromatography was carried out 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. Analytical chromatography was performed on E. Merck No. 5715 Silica Gel 60-F_{254} plates. THF was distilled in the presence of radical anions generated by sodium-benzophenone ketyl. Dichloromethane was dried by being passed through an ICN Alumina B-Super I, and DMF and pyridine were dried by storage over 4 Å molecular sieves.

(R)-3-Dodecyloxy-1-(methanesulfonyloxy)-tetradecane (**4a**).—(i) To a solution of (*R*)-1,3-dihydroxytetradecane (**1**) (9.91 g, 43.0 mmol) in toluene (150 mL) were added dodecyl aldehyde (8.73 g, 47.4 mmol) and *p*-TsOH·water (1.64 g, 8.62 mmol). After stirring at 60 °C for 1 h, the reaction mixture was diluted with EtOAc, washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture that was chromatographed on a silica gel column. Elution with 19:1 hexane–EtOAc gave (4*R*)-2,4-diundecyl-1,3-dioxane (**2a**) (16.3 g, 96%) as an oil. IR $\nu_{max}(CHCl_3)$: 2927, 2855, 1467, 1142, 1120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (6 H, t, *J* 6.6–7.3 Hz), 1.26–1.43 (38 H, m), 1.54–1.68 (4 H, m), 3.55 (1 H, m), 3.72 (1 H, dt, *J* 2.2, 11.7 Hz), 4.09 (1 H, dd, *J* 5.1, 11.7 Hz), 4.48 (1 H, t, *J* 5.1 Hz). FABMS, (positive-ion): *m/z* 419 $(M+Na)^+$, 397 $(M+H)^+$; FABMS, (negative-ion): *m/z* 395 $(M-H)^-$. HRFABMS (positive-ion): Calcd for $C_{26}H_{53}O_2$: 397.4046; Found: 397.4054. Anal. Calcd for $C_{26}H_{52}O_2$ (396.7): C, 78.72; H, 13.21. Found: C, 78.53; H, 13.07.

(ii) To a solution of the above obtained **2a** (16.1 g, 40.6 mmol) in CH_2Cl_2 (50 mL) was added DIBAL (1.0 M solution in CH_2Cl_2, 100 mL, 100 mmol) at 0 °C under N_2. After stirring for 5 h at rt the reaction mixture was quenched with satd NH_4Cl at 0 °C, and 0.5 M aq Rochelle salt was added to this mixture. After stirring for 1 h at rt, the mixture was extracted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture that was chromatographed on a silica gel column. Elution with 3:1 hexane–EtOAc gave (*R*)-3-dodecyloxy-1-hydroxytetradecane (**3a**) (14.4 g, 89%) as an oil. IR $\nu_{max}(CHCl_3)$: 3003, 2928, 2855 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (6 H, t, *J* 6.6–7.3 Hz), 1.26–1.81 (42 H, m, containing 38 H, broad s, at δ 1.26), 2.83 (1 H, brs, OH), 3.40 (1 H, m), 3.46–3.54 (2 H, m), 3.71–3.83 (2 H, m). FABMS, (positive-ion): *m/z* 399 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{26}H_{55}O_2$: 399.4202; Found: 399.4221. Anal. Calcd for $C_{26}H_{54}O_2$ (398.7): C, 78.32; H, 13.65. Found: C, 78.48; H, 13.88.

(iii) To a solution of the above obtained **3a** (14.2 g, 35.6 mmol) in CH_2Cl_2 (70 mL) were added Et_3N (7.4 mL, 53.1 mmol) and methanesulfonyl chloride (4 mL, 51.7 mmol) at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo and chromatographed on a silica gel column. Elution with 4:1 hexane–EtOAc gave (*R*)-3-dodecyloxy-1-(methanesulfonyloxy)tetradecane (**4a**) (16.7 g, 98%) as an oil. IR $\nu_{max}(CHCl_3)$: 2928, 2855, 1359 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (6 H, t, *J* 6.6 Hz), 1.26 (38 H, broad s), 1.40–1.57 (2 H, m), 1.79–1.97 (2 H, m), 3.00 (3 H, s), 3.32–3.40 (2 H, m), 3.48 (1 H, m), 4.29–4.39 (2 H, m). FABMS, (positive-ion): *m/z* 515 $(M+K)^+$ (on addition of KI); 477 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{27}H_{56}O_4SK$: 515.3536; Found: 515.3561. Anal. Calcd for $C_{27}H_{56}O_4S$ (476.8): C, 68.02; H, 11.84; S, 6.73. Found: C, 68.06; H, 11.60; S, 6.21.

(R)-3-Benzyloxy-1-(methanesulfonyloxy)-tetradecane (**4b**).—(i) To a solution of (*R*)-1,3-dihydroxytetradecane (1) (5.10 g, 22.1 mmol) in DMF (40 mL) were added benzaldehyde dimethyl acetal (10 mL, 66.6 mmol) and *p*-TsOH·water (845 mg, 4.40 mmol). After stirring at rt for 1 h, the reaction mixture was diluted with EtOAc, washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture that was chromatographed on a silica gel column. Elution with 49:1 cyclohexane–

EtOAc gave (4*R*)-2-phenyl-4-undecyl-1,3-dioxane (**2b**) (6.85 g, 97%) as an oil. IR ν_{max}($CHCl_3$): 2927, 2856, 1602, 1114 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.6 Hz), 1.26–1.53 (20 H, m), 1.61–1.88 (2 H, m), 3.81 (1 H, m), 3.96 (1 H, dt, *J* 2.6, 11.9 Hz), 4.27 (1 H, dd, *J* 4.5, 11.2 Hz), 5.51 (1 H, s), 7.29–7.52 (5 H, m). FABMS, (positive-ion): *m*/*z* 318 ($M^{+\bullet}$). FABMS, (negative-ion): *m*/*z* 317 $(M-H)^-$. HRFABMS (positive-ion): Calcd for $C_{21}H_{34}O_2$: 318.2559; Found: 318.2549. Anal. Calcd for $C_{21}H_{34}O_2$ (318.5): C, 79.19; H, 10.76. Found: C, 79.14; H, 10.57.

(ii) To a solution of the above obtained **2b** (6.74 g, 21.2 mmol) in CH_2Cl_2 (40 mL) was added DIBAL (1.0 M solution in CH_2Cl_2, 65 mL, 65.0 mmol) at −78 °C under N_2. After stirring for 2 h at 0 °C, the reaction mixture was quenched with satd NH_4Cl at 0 °C, and 0.5 M aq Rochelle salt was added to this mixture. After stirring for 30 min at rt, the mixture was extracted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture that was chromatographed on a silica gel column. Elution with 4:1 cyclohexane–EtOAc gave (*R*)-3-benzyloxy-1-hydroxytetradecane (**3b**) (6.47 g, 95%) as an oil. IR ν_{max}($CHCl_3$): 3626, 3505, 2928, 2856 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.6 Hz), 1.27–1.84 (22 H, m), 2.42 (1 H, brs, OH), 3.60–3.85 (3 H, m), 4.48, 4.61 (2 H, ABq, *J* 11.3 Hz), 7.25–7.35 (5 H, m); FABMS, (positive-ion): *m*/*z* 321 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{21}H_{37}O_2$: 321.2794; Found: 321.2789. Anal. Calcd for $C_{21}H_{36}O_2$ (320.5): C, 78.70; H, 11.32. Found: C, 79.77; H, 11.80.

(iii) The above obtained **3b** was treated as described in Ref. 17 to give (*R*)-3-benzyloxy-1-(methanesulfonyloxy)tetradecane (**4b**) (7.72 g, 96%) as an oil. IR ν_{max}($CHCl_3$): 2926, 2854 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.6Hz), 1.27 (18 H, brs), 1.47–1.68 (2 H, m), 1.83–2.05 (2 H, m), 2.94 (3 H, s), 3.59 (1 H, m), 4.28–4.42 (2 H, m), 4.45, 4.58 (2 H, ABq, *J* 11.3 Hz), 7.25–7.35 (5 H, m). FABMS, (positive-ion): *m*/*z* 421 $(M+Na)^+$, 399 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{22}H_{38}NaO_4S$: 421.2389; Found: 421.2391.

*Allyl 2-azido-2-deoxy-4,6-*O*-isopropylidene-β-*D*-glucopyranoside* (**6**).—To a solution of **5** (6.35 g, 24.5 mmol) in MeOH (120 mL) was added DMAP (3.07 g, 25.1 mmol) and 0.4 M TfN_3 in CH_2Cl_2 (120 mL, 48.0 mmol). After stirring at rt for 18 h, the reaction mixture was concentrated in vacuo and chromatographed on a silica gel column. Elution with 3:2 cyclohexane–EtOAc gave **6** (6.33 g, 91%) as a solid; mp 67 °C. IR ν_{max}(KBr): 3452, 2996, 2887, 2113 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.37 (3 H, s), 1.51 (3 H, s), 3.21–3.26 (2 H, m), 3.40 (1 H, t, *J* 9.5 Hz), 3.53 (1 H, t, *J* 9.2 Hz), 3.78 (1 H, t, *J* 10.6 Hz), 3.86 (1 H, dd, *J* 5.5, 10.6 Hz), 4.09–4.16 (1 H, m), 4.31–4.36 (1 H, m), 4.45 (1 H, d, *J* 7.3 Hz), 5.17–5.35 (2 H, m), 5.93 (1 H, m). FABMS, (positive-ion): *m*/*z* 286 $(M+H)^+$. HRFABMS (positive-ion): *m*/*z*: Calcd for $C_{12}H_{20}N_3O_5$: 286.1403; Found: 286.1413. Anal. Calcd for $C_{12}H_{19}N_3O_5$ (285.3): C, 50.52; H, 6.71; N, 14.73. Found: C, 50.28; H, 6.70; N, 14.80.

*Allyl 2-azido-2-deoxy-3-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-4,6-O-isopropylidene-β-D-glucopyranoside* (**7a**).—To a solution of **6** (5.15 g, 18.1 mmol) in DMF (50 mL) was gradually added NaH (60% oil dispersion, 1.36 g, 34.0 mmol) at 0 °C with stirring. After 15 min at 0 °C, (*R*)-3-dodecyloxy-1-(methanesulfonyloxy)tetradecane (7.15 g, 15.0 mmol) was added to the mixture. After stirring for 20 h at rt, the reaction mixture was quenched with water, extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 4:1 hexane–EtOAc gave **7a** (7.31 g, 73%) as a gum. IR ν_{max}($CHCl_3$): 2928, 2855, 2114 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (6 H, t, *J* 6.6–7.3 Hz), 1.21–1.56 (46 H, m, containing 3 H, s, at δ 1.39, 3 H, s, at δ 1.49), 1.69–1.74 (2 H, m), 3.15–3.31 (2 H, m), 3.33 (1 H, t, *J* 8.1–9.5 Hz), 3.37–3.47 (3 H, m), 3.60 (1 H, t, *J* 9.5 Hz), 3.69–3.80 (2 H, m), 3.84–3.92 (2 H, m), 4.13 (1 H, dd, *J* 5.9, 13.2 Hz), 4.32 (1 H, d, *J* 8.1 Hz), 4.36 (1 H, dd, *J* 5.1, 13.2 Hz), 5.22–5.36 (2 H, m), 5.92 (1 H, m). FABMS, (positive-ion): *m*/*z* 704 $(M+K)^+$, 666 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{38}H_{72}N_3O_6$: 666.5421;

Found: 666.5444. Anal. Calcd for $C_{38}H_{71}N_3O_6$ (666.0): C, 68.53; H, 10.75; N, 6.31. Found: C, 68.63; H, 10.83; N, 6.53.

*Allyl 2-azido-3-*O*-[(*R*)-3-(benzyloxy)tetradecyl]-2-deoxy-4,6-*O*-isopropylidene-β-*D*-glucopyranoside* (**7b**).—To a solution of **6** (4.52 g, 15.8 mmol) in DMF (60 mL) was gradually added NaH (55% oil dispersion, 963 mg, 22.0 mmol) at 0 °C with stirring. After 15 min at 0 °C, (*R*)-3-benzyloxy-1-(methanesulfonyloxy)tetradecane (5.74 g, 14.4 mmol) was added to the mixture. After stirring for 20 h at rt, the mixture was quenched with water, extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 4:1 cyclohexane–EtOAc gave **7b** (6.23 g, 74%) as an oil. IR $\nu_{max}(CHCl_3)$: 2928, 2856, 2114 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.6 Hz), 1.26–1.62 (26 H, m, containing 3 H, s, at 1.39, 3 H, s, at 1.47), 1.70–1.84 (2 H, m), 3.13–3.23 (2 H, m), 3.33 (1 H, t, *J* 8.0–9.6 Hz), 3.53–3.63 (2 H, m), 3.72–3.81 (2 H, m), 3.82–3.95 (2 H, m), 4.13 (1 H, dd, *J* 6.1, 12.7 Hz), 4.31–4.39 (2 H, m, containing 1 H, d, *J* 8.0 Hz, at δ 4.32), 4.53 (2 H, s), 5.22–5.38 (2 H, m), 5.94 (1 H, m), 7.25–7.45 (5 H, m). FABMS, (positive-ion): *m/z* 588 $(M+H)^+$. HRFABMS (positive-ion): *m/z*: Calcd for $C_{33}H_{54}N_3O_6$: 588.4013; Found: 588.4023. Anal. Calcd for $C_{33}H_{53}N_3O_6$ (587.8): C, 67.43; H, 9.09; N, 7.15. Found: C, 67.33; H, 8.99; N, 7.31.

*2-Azido-2-deoxy-3-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-4,6-*O*-isopropylidene-*D*-glucopyranose* (**8a**).—A suspension of a mixture of **7a** (6.10 g, 9.75 mmol), SeO_2 (1.33 g, 12.0 mmol) and AcOH (0.5 mL) in 1,4-dioxane (40 mL) was heated under reflux for 1 h. The mixture was filtered and insoluble material was washed with 1,4-dioxane. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 7:3 hexane–EtOAc gave **8a** (4.26 g, 70%) as a gum. IR $\nu_{max}(CHCl_3)$: 3599, 2928, 2855, 2114 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (6 H, t, *J* 6.6 Hz), 1.21–1.56 (46 H, m, containing 3 H, s, at δ 1.40, 3 H, s, at δ 1.49), 1.68–1.81 (2 H, m), 2.99 (0.5 H, d, *J* 2.9 Hz, OH), 3.21–3.30 (2 H, m), 3.36–3.48 (4 H, m), 3.50 (0.5 H, d, *J* 5.1 Hz, OH), 3.60–3.97 (5 H, m), 4.60 (0.5 H, dt, *J* 2.2, 5.1–5.9 Hz), 5.24 (0.5 H, t, *J* 3.7 Hz). FABMS, (positive-ion): *m/z* 626 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{35}H_{68}N_3O_6$: 626.5108; Found: 626.5111. Anal. Calcd for $C_{35}H_{67}N_3O_6$ (625.9): C, 67.16; H, 10.79; N, 6.71. Found: C, 66.85; H, 10.46; N, 6.80.

*2-Azido-3-*O*-[(*R*)-3-(benzyloxy)tetradecyl]-2-deoxy-4,6-*O*-isopropylidene-*D*-glucopyranose* (**8b**).—To a solution of **7b** (6.15 g, 10.5 mmol) in THF (120 mL) was added $[C_8H_{12}Ir(PMePh_2)_2]PF_6$ (450 mg). The air in the reaction flask was completely replaced with nitrogen and then further replaced with hydrogen to activate the iridium complex. Immediately after 1 min, when the red-colored solution of the iridium complex had become almost colorless, the hydrogen was completely replaced with nitrogen. This solution was stirred for 3 h at rt. After confirming a double bond shift to an enol ether (as indicated by a slightly higher R_f value) from the 1-allyloxy group by TLC, water (45 mL), pyridine (4.5 mL) and I_2 (2.3 g) were added to this solution. After 12 h stirring at rt, the mixture was concentrated in vacuo, diluted with EtOAc, washed with 10% $Na_2S_2O_3$, satd, aq $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to give a mixture that was purified on a silica gel column. Elution with 3:1 cyclohexane–EtOAc gave an amorphous mixture **8b** (3.71 g, 65%) as a gum. IR $\nu_{max}(CHCl_3)$: 2928, 2855, 2114 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.6 Hz), 1.26–1.60 (26 H, m, containing 1.5 H, s, at δ 1.39, 1.5 H, s, at δ 1.40, 3 H, s, at δ 1.48), 1.71–1.90 (2 H, m), 2.93 (0.5 H, broad, OH), 3.18–3.27 (1.5 H, m, containing 0.5 H, OH), 3.30–3.99 (8 H, m), 4.46–4.60 (2.5 H, m, containing 2 H, s, at δ 4.52), 5.23 (0.5 H, d, *J* 3.3Hz), 7.22–7.37 (5 H, m). FABMS, (positive-ion): *m/z* 548 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{30}H_{50}N_3O_6$: 548.3700; Found: 548.3683. Anal. Calcd for $C_{33}H_{53}N_3O_6$ (547.7): C, 65.79; H, 9.02; N, 7.67. Found: C, 65.43; H, 9.05; N, 7.68.

*2,2,2-Trichloroethylimidoyl 2-azido-2-deoxy-3-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-4,6-*O*-isopropylidene-α-*D*-glucopyranoside* (**9a**).—To a solution of **8a** (4.25 g, 6.79 mmol) and CCl_3CN (7.0 mL, 69.8 mmol) in CH_2Cl_2 (15

mL) was added DBU (211 mg, 1.38 mmol) at 0 °C. After stirring for 1 h at 0 °C, satd $NaHCO_3$ was added to the reaction mixture, and it was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 7:3 hexane–EtOAc gave **9a** (4.77 g, 91%) as a gum. IR $\nu_{max}(CHCl_3)$: 3344, 2928, 2855, 2115, 1674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (6 H, t, *J* 6.6–7.3 Hz), 1.26–1.58 (46 H, m, containing 3 H, s, at δ 1.43, 3 H, s, at δ 1.52), 1.71–1.82 (2 H, m), 3.21–3.30 (2 H, m), 3.36–3.46 (3 H, m), 3.58 (dd, 1 H, *J* 3.7, 9.5 Hz), 3.69–4.01 (7 H, m), 6.31 (1 H, d, *J* 3.7 Hz), 8.70 (1 H, s). FABMS, (positive-ion): *m/z* 791 $(M + Na)^+$. HRFABMS (positive-ion): Calcd for $C_{37}H_{67}Cl_3N_4NaO_6$: 791.4024; Found: 791.4002.

*2,2,2-Trichloroethylimidoyl 2-azido-3-*O*-[(*R*)-3-(benzyloxy)tetradecyl]-2-deoxy-4,6-*O*-isopropylidene-α-*D*-glucopyranoside* (**9b**).—Compound **8b** (3.66 g, 6.70 mmol) was treated as described above to give **9b** (4.08 g, 88%) as a gum. IR $\nu_{max}(CHCl_3)$: 2116, 1676, 1603 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.6 Hz), 1.26–1.65 (26 H, m, containing 3 H, s, at δ 1.41, 3 H, s, at δ 1.50), 1.73–1.95 (2 H, m), 3.52–4.07 (9 H, m), 4,53 (2 H, s), 6.31 (1 H, d, *J* 3.8 Hz), 7.25–7.35 (5 H, m), 8.70 (1 H, s, NH); FABMS, (positive-ion): *m/z* 713 $(M + Na)^+$(on addition of NaI). HRFABMS (positive-ion): Calcd for $C_{32}H_{49}N_4O_6Cl_3Na$: 713.2615; Found: 713.2606. Anal. Calcd for $C_{32}H_{49}Cl_3N_4O_6$ (692.1): C, 55.53; H, 7.14; Cl, 15.37; N, 8.10. Found: C, 55.53; H, 6.78; Cl, 15.45; N, 7.93.

*2,6-Anhydro-3-azido-3-deoxy-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-5,7-*O*-isopropylidene-*D*-glycero-*D*-ido-heptononitrile* (**10a**).—To a solution of **9a** (4.75 g, 6.17 mmol) and Me_3SiCN (1.30 mL, 9.75 mmol) in CH_2Cl_2 (15 mL) was added 4AMS (3.55 g). After stirring for 1 h at rt, TMSOTf (0.35 mL, 1.93 mmol) was added to the suspension. After stirring for 3 h at rt, satd $NaHCO_3$ was added. The reaction mixture was filtered through celite, diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 4:1 hexane–EtOAc gave **10a** (2.95g, 75%) as a gum. IR $\nu_{max}(CHCl_3)$: 2928, 2855, 2119 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (6 H, t, *J* 6.6–7.3 Hz), 1.21–1.59 (46 H, m, containing 3 H, s, at δ 1.42, 3 H, s, at δ 1.49), 1.71–1.79 (2 H, m), 3.34–3.46 (3 H, m), 3.59–3.82 (6 H, m), 3.91–4.00 (2 H, m), 4.78 (1 H, d, *J* 5.9 Hz). FABMS, (positive-ion): 635 $(M + H)^+$. HRFABMS (positive-ion): Calcd for $C_{36}H_{67}N_4O_5$: 635.5133; Found: 635.5111. Anal. Calcd for $C_{36}H_{66}N_4O_5$ (634.9): C, 68.10; H, 10.48; N, 8.82. Found: C, 67.67; H, 10.46; N, 8.93.

*2,6-Anhydro-3-azido-4-*O*-[(*R*)-(benzyloxy)tetradecyl]-3-deoxy-5,7-*O*-isopropylidene-*D*-glycero-*D*-ido-heptononitrile* (**10b**).—Compound **9b** (4.05 g, 5.85 mmol) was treated as described above to give **10b** (3.04 g, 93%) as a gum. IR $\nu_{max}(CHCl_3)$: 2928, 2856, 2119 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.6 Hz), 1.26–1.58 (26 H, m, containing 3 H, s, at δ 1.41, 3 H, s, at δ 1.47), 1.70–1.91 (2 H, m), 3.52–4.05 (9 H, m), 4.54, 4.48 (2 H, ABq, *J* 11.6 Hz), 4.78 (1 H, d, *J* 5.4 Hz), 7.24–7.36 (5 H, m). FABMS, (positive-ion): *m/z* 579 $(M + Na)^+$, 557 $(M + H)^+$. HRFABMS (positive-ion): Calcd for $C_{31}H_{48}NaN_4O_5$: 579.3522; Found: 579.3505. Anal. Calcd for $C_{31}H_{48}N_4O_5$ (556.7): C, 66.88; H, 8.69; N, 10.06. Found: C, 66.79; H, 8.91; N, 10.00.

*2,6-Anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-3-deoxy-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-5,7-*O*-isopropylidene-*D*-glycero-*D*-ido-heptononitrile* (**11aa**).—To a solution of **10a** (1.01 g, 1.59 mmol) in THF (8 mL) was added PPh_3 (438 mg, 1.67 mmol). After stirring for 1 h at rt, 28% NH_3 in water (4 mL) was added to this solution. The mixture was stirred for 24 h at 60 °C, concentrated in vacuo, diluted with toluene, and concentrated in vacuo again. This procedure was repeated three times to completely remove the water. The residual mixture was dissolved in CH_2Cl_2 (10 mL). To this solution, (*R*)-3-(benzyloxy)tetradecanoic acid (640 mg, 1.91 mmol), DCC (496 mg, 2.40 mmol), and DMAP (297 mg, 2.43 mmol) were added with stirring. After 18 h at rt, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give a mixture. The mixture was chromatographed on a silica gel column. Elu-

tion with 4:1 hexane–EtOAc gave **11aa** (1.16 g, 79%) as a gum. IR $\nu_{max}(CHCl_3)$: 3328, 2928, 2855, 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 5.9–7.3 Hz), 1.11–1.70 (68 H, m, containing 3 H, s, at δ 1.40, 3 H, s, at δ 1.47) 2.41 (1 H, dd, *J* 5.9, 15.4 Hz), 2.60 (1 H, dd, *J* 3.7, 15.4 Hz), 3.18–3.33 (5 H, m), 3.58–3.80 (5 H, m), 3.88–4.00 (2 H, m), 4.56, 4.59 (2 H, ABq, *J* 11.0 Hz), 5.27 (1 H, d, *J* 5.9 Hz), 7.20 (1 H, d, *J* 5.1 Hz, NH), 7.26–7.39 (5 H, m). FABMS, (positive-ion): *m/z* 925 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{57}H_{101}N_2O_7$: 925.7609; Found: 925.7619. Anal. Calcd for $C_{57}H_{100}N_2O_7$ (925.4): C, 73.98; H, 10.89; N, 3.03. Found: C, 74.09; H, 10.70; N, 3.12.

*2,6-Anhydro-3-deoxy-3-(2,2-difluorotetradecanamido)-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-5,7-*O*-isopropylidene-*D*-glycero-*D*-ido-heptononitrile* (**11ab**).—To a solution of **10a** (1.06 g, 1.67 mmol)) in THF (5 mL) was added PPh_3 (451 mg, 1.72 mmol). After stirring for 1 h at rt, 28% NH_3 in water (2.5 mL) was added to this solution. The mixture was stirred for 20 h at 60 °C, concentrated in vacuo, diluted with toluene, and concentrated in vacuo again. This procedure was repeated three times to remove the water completely. The residual mixture was dissolved in CH_2Cl_2 (8 mL). To this solution, 2,2-difluorotetradecanoic acid (663 mg, 2.51 mmol), DCC (517 mg, 2.51 mmol), and DMAP (307 mg, 2.51 mmol) were added. After stirring for 18 h at rt, the reaction mixture was filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 4:1 hexane–EtOAc gave **11ab** (1.34 g, 94%) as a gum. IR $\nu_{max}(CHCl_3)$: 3436, 2928, 2856, 1713, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.11–1.86 (68 H, m, containing 3 H, s, at δ 1.43, 3 H, s, at δ 1.51), 2.03–2.15 (2 H, m), 3.31–3.43 (3 H, m), 3.56–3.78 (5 H, m), 3.91–4.00 (2 H, m), 4.05 (1 H, m), 5.27 (1 H, d, *J* 5.9 Hz), 6.82 (1 H, d, *J* 5.1 Hz, NH). FABMS, (positive-ion): *m/z* 855 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{50}H_{93}F_2N_2O_6$: 855.7002; Found: 855.7004.

*2,6-Anhydro-3-deoxy-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-5,7-O-isopropylidene-3-tetradecanamido-*D*-glycero-*D*-ido-heptononitrile* (**11ac**).—Compound **10a** (926 mg, 1.46 mmol) was treated as described above to give a mixture of a product amine and spent reagents, which was dissolved in CH_2Cl_2 (5 mL). To this solution, Et_3N (0.3 mL, 2.13 mmol) and tetradecanoyl chloride (0.6 mL, 2.13 mmol) were added at 0 °C. After stirring for 1 h at rt, the reaction mixture was diluted with EtOAc, washed with water, satd $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 4:1 hexane–EtOAc gave **11ac** (999 mg, 84%) as a gum. IR $\nu_{max}(CHCl_3)$: 3691, 2927, 2855, 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.21–1.72 (70 H, m containing 3 H, s, at δ 1.42, 3 H, s, at δ 1.50), 2.23 (2 H, dt, *J* 3.7, 7.3 Hz), 3.35 (2 H, t, *J* 6.6–7.3 Hz), 3.46–3.76 (6 H, m), 3.91–4.04 (3 H, m), 5.40 (1 H, d, *J* 5.9 Hz), 6.49 (1 H, d, *J* 4.4 Hz, NH). FABMS, (positive-ion): *m/z* 819 $(M+H)^+$. HR-FABMS (positive-ion): Calcd for $C_{50}H_{95}N_2O_6$: 819.7190; Found: 819.7203. Anal. Calcd for $C_{50}H_{94}N_2O_6$ (819.3): C, 73.30; H, 11.57; N, 3.42; Found: C, 73.49; H, 11.10; N, 3.49.

*2,6-Anhydro-4-*O*-[(*R*)-3-(benzyloxy)tetradecyl]-3-deoxy-3-[(*R*)-3-(dodecyloxy)tetradecanamido]-5,7-*O*-isopropylidene-*D*-glycero-*D*-ido-heptononitrile* (**11ba**).—Compound **10b** (1.49 g, 2.67 mmol) was treated as described above to give a mixture of a product amine and spent reagents, which was dissolved in CH_2Cl_2 (10 mL). To this solution, (*R*)-3-dodecyloxytetradecanoic acid (1.32 g, 3.20 mmol), and DCC (0.827 g, 4.01 mmol), DMAP (0.489 g, 4.01 mmol) was added. After stirring for 2 h at rt, the mixture was filtered and concentrated in vacuo to give a mixture. The mixture was chromatographed on a silica gel column. Elution with 7:3 hexane–EtOAc gave **11ba** (1.82 g, 74%) as a gum. IR $\nu_{max}(CHCl_3)$: 3304, 2924, 2854, 1657 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 9 H, *J* 5.9–7.3 Hz), 1.17–1.85 (m, 60 H), 2.26–2.32 (m, 1 H), 2.52–2.48 (m, 1 H), 3.40–3.73 (m, 9 H), 3.90–3.95 (m, 2 H), 4.05–4.09 (m, 1 H), 4.49 (s, 2 H), 5.20 (d, 1 H, *J* 6.6 Hz), 7.17 (d, 1 H, *J* 5.8 Hz), 7.26–7.36 (m, 5 H). HR-FABMS (positive-ion): Calcd for $C_{57}H_{101}N_2O_7$ $(M+H)^+$: 925.7609; Found: 925.7594.

*2,6 - Anhydro - 3 - [(*R*) - 3 - (benzyloxy)tetradecanamido] - 4 -* O *- [(*R*) - 3 - (benzyloxy)tetradecyl]-3-deoxy-5,7-*O*-isopropylidene-*D*-glycero-*D*-ido-heptononitrile* (**11bb**).—(i) Compound **10b** (3.02 g, 5.43 mmol) was treated as described above to give a mixture, which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (9:1, then 3:2) gave an amine ($R^2 = H$ in **11b**, 2.03 g, 71%) as a gum. IR $\nu_{max}(CHCl_3)$: 3691, 2928, 2856, 1602 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.9 Hz), 1.26–1.65 (28 H, m, containing 3 H, s, at δ 1.40, 3 H, s, at δ 1.46), 2.95 (1 H, dd, *J* 6.0, 9.7 Hz), 3.22 (1 H, t, *J* 9.2 Hz), 3.50–3.56 (2 H, m), 3.65–3.76 (3 H, m), 3.91 (1 H, m), 3.99 (1 H, m), 4.46, 4.55 (2 H, ABq, *J* 11.7 Hz), 4.74 (1 H, d, *J* 6.0 Hz), 7.26–7.36 (5 H, m). FABMS, (positive-ion): *m/z* 553 $(M + Na)^+$, 531 $(M + H)^+$. HR-FABMS (positive-ion): Calcd for $C_{31}H_{50}NaN_2O_5$: 553.3617; Found: 553.3603. Anal. Calcd for $C_{31}H_{50}N_2O_5$ (530.7): C, 70.15; H, 9.50; N, 5.28. Found: C, 69.72; H, 9.47; N, 4.52.

(ii) To a solution of the above obtained amine ($R^2 = H$ in **11b**) (1.96 g, 3.71 mmol) in CH_2Cl_2 (30 mL) were added (*R*)-3-(benzyloxy)tetradecanoic acid (1.50 g, 4.48 mmol), DCC (963 mg, 4.67 mmol) and DMAP (574 mg, 4.70 mmol). After stirring for 18 h at rt, the mixture was filtered, diluted with EtOAc, washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture. The mixture was chromatographed on a silica gel column. Elution with 4:1 cyclohexane–EtOAc gave **11bb** (2.79 g, 89%) as a gum. IR $\nu_{max}(CHCl_3)$: 3691, 2928, 2855, 1672, 1603 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.6 Hz), 1.25–1.77 (48 H, m, containing 3 H, s, at δ 1.39, 3 H, s, at δ 1.44), 2.35 (1 H, dd, *J* 6.5, 15.5 Hz), 2.54 (1 H, dd, *J* 3.6, 15.5 Hz), 3.21–3.30 (2 H, m), 3.40 (1 H, m), 3.56–3.81 (5 H, m), 3.86–4.03 (2 H, m), 4.40, 4.45 (2 H, ABq, *J* 11.7 Hz), 4.55 (2 H, s), 5.25 (1 H, d, *J* 6.0 Hz), 7.10 (1 H, d, *J* 5.5 Hz, NH), 7.25–7.40 (10 H, m). FABMS, (positive-ion): *m/z* 869 $(M + Na)^+$, 847 $(M + H)^+$. HRFABMS (positive-ion): Calcd for $C_{52}H_{83}N_2O_7$: 847.6200; Found: 847.6199. Anal. Calcd for $C_{52}H_{82}N_2O_7$ (847.2): C, 73.72; H, 9.76; N, 3.31. Found: C, 73.50; H, 9.82; N, 3.55.

*Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]- 3- deoxy - 4 -* O *- [(*R*)- 3 - (dodecyloxy)tetradecyl]* - D - glycero - D - ido-*heptonate* (**12aa**).—A solution of **11aa** (1.11 g, 1.20 mmol) in 4 M HCl in dioxane (5 mL) and water (1 mL) was stirred at 60 °C for 3 h. The reaction mixture was concentrated and dried in vacuo to give a mixture that was dissolved in DMF (6 mL). Ph_2CN_2 (585 mg, 3.01 mmol) was added to this solution. This solution was warmed at 60 °C for 1 h. The mixture was diluted with EtOAc, washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 1:1 hexane–EtOAc gave **12aa** (642 mg, 50%) as a solid; mp 105.5–106.5 °C. IR ν_{max}(KBr): 3329, 2921, 2851, 1735, 1645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 5.9–7.3 Hz), 1.11–1.65 (62 H, m) 2.08 (1 H, t, *J* 5.9–6.6 Hz, OH), 2.32 (2 H, d, *J* 5.1 Hz), 3.31–3.43 (5 H, m), 3.49–3.83 (8 H, m, containing OH), 4.33, 4.38 (2 H, ABq, *J* 11.3 Hz), 4.65 (1 H, d, *J* 5.1 Hz), 6.85 (1 H, s), 6.89 (1 H, d, *J* 8.8 Hz, NH), 7.22–7.35 (15 H, m). FABMS, (positive-ion): *m/z* 1092 $(M + Na)^+$, 1070 $(M + H)^+$. HRFABMS (positive-ion): Calcd for $C_{67}H_{107}NaNO_9$: 1092.7844; Found: 1092.7838. Anal. Calcd for $C_{67}H_{107}NO_9$ (1070.6): C, 75.17; H, 10.07; N, 1.31. Found: C, 74.95; H, 10.11; N, 1.36

Diphenylmethyl 2,6-anhydro-3-deoxy-3-(2,2 - difluorotetradecanamido) - 4 - O *- [(*R*) - 3-(dodecyloxy)tetradecyl]* - D - glycero - D - ido-*heptonate* (**12ab**).—A solution of **11ab** (1.05 g, 1.23 mmol)) in 4 M HCl in dioxane (5 mL) and concd HCl (1 mL) was stirred at 60 °C for 4 h. The reaction mixture was concentrated and dried in vacuo to give a mixture that was dissolved in DMF (5 mL). Ph_2CN_2 (599 mg, 3.08 mmol) was added to this solution, which was warmed at 60 °C for 2 h. The mixture was diluted with EtOAc, washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 3:2 hexane–EtOAc gave **12ab** (501mg, 41%) as an amorphous solid. IR ν_{max}(KBr): 3394, 3329, 2923, 2853, 1736, 1679 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.21–1.55 (60 H, m),

1.67–1.71 (2 H, m), 1.99–2.03 (3 H, m, containing OH), 3.32–3.40 (4 H, m), 3.48 (1 H, t, *J* 8.8–10.3 Hz), 3.57–3.62 (2 H, m), 3.72–3.79 (3 H, m, containing OH), 3.83 (1 H, m, changed to dd, *J* 3.7, 11.7 Hz, on addition of D_2O), 4.39 (1 H, m), 4.58 (1 H, d, *J* 5.9 Hz), 6.94 (1 H, s), 7.15 (1 H, d, *J* 9.5 Hz, NH), 7.29–7.41 (10 H, m). FABMS, (positive-ion): *m/z* 1038 $(M+K)^+$, 1022 $(M+Na)^+$. HR-FABMS (positive-ion): Calcd for $C_{60}H_{99}F_2NNaO_8$: 1022.7236; Found: 1022.7223. Anal. Calcd for $C_{60}H_{99}F_2NO_8$ (1000.4): C, 72.03; H, 9.98; F, 3.80; N, 1.40. Found: C, 71.64; H, 9.82; F, 3.82; N, 1.58.

*Diphenylmethyl 2,6-anhydro-3-deoxy-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-3-tetradecanamido*-D-glycero-D-ido-*heptonate* (**12ac**).—Compound **11ac** (901 mg, 1.10 mmol) was treated, as described in the formation of **12aa** from **11aa** to give **12ac** (485 mg, 46%) as a white solid; mp 128.5–129.5 °C. IR ν_{max}(KBr): 3406, 3332, 1738, 1646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (6 H, t, *J* 6.6–7.3 Hz), 1.21–1.73 (64 H, m), 2.07 (2 H, t, *J* 7.3–8.1 Hz), 3.35 (2 H, t, *J* 6.6 Hz), 3.39–3.44 (2 H, m), 3.52–3.63 (4 H, m, containing OH), 3.76–3.84 (4 H, m, containing OH), 4.43 (1 H, dt, *J* 5.9, 9.5 Hz), 4.62 (1 H, d, *J* 5.9 Hz), 6.09 (1 H, d, *J* 9.5 Hz, NH), 6.90 (1 H, s), 7.29–7.38 (10 H, m). FABMS, (positive-ion): *m/z* 986 $(M+Na)^+$, 964 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{60}H_{101}NNaO_8$: 986.7425; Found: 986.7424. Anal. Calcd for $C_{60}H_{101}NO_8$ (964.5): C, 74.72; H, 10.56; N, 1.45. Found: C, 74.41; H, 10.27; N, 1.51.

*Diphenylmethyl 2,6-anhydro-4-*O*-[(*R*)-3-(benzyloxy)tetradecyl]-3-deoxy-3-[(*R*)-3-(dodecyloxy)tetradecanamido]-5,7-*O*-isopropylidene*-D-ido-*heptonate* (**12ba**).—Compound **11ba** (146 mg, 0.158 mmol) was treated, as described in the formation of **12aa** from **11aa** to give **12ba** (44.5 mg, 26%) as a gum. IR ν_{max}($CHCl_3$): 2927, 2855, 1734, 1669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.16–1.78 (62 H, m), 2.07–2.35 (2 H, m), 3.18–3.31 (2 H, m), 3.34–3.87 (9 H, m), 4.34–4.49 (3 H, m), 4.63 (1 H, d, *J* 5.9 Hz), 6.88 (1 H, s), 6.96 (1 H, d, *J* 8.8 Hz), 7.24–7.34 (15 H, m). FABMS, (positive-ion): *m/z* 1108 $(M+K)^+$ (on addition of KI). HRFABMS (positive-ion): Calcd for $C_{67}H_{107}KNO_9$ $(M+K)^+$: 1108.7583; Found: 1108.7576.

*Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-4-*O*-[(*R*)-3-(benzyloxy)tetradecyl]-3-deoxy-*D*-glycero-*D*-ido-heptonate* (**12bb**).—Compound **11bb** (2.70 g, 3.19 mmol) was treated, as described in the formation of **12aa** from **11aa** to give **12bb** (1.35 g, 43%) as an amorphous solid. IR ν_{max}($CHCl_3$): 3691, 2928, 2855, 1672, 1603 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.5 Hz), 1.25–1.71 (42 H, m), 1.95 (1 H, broad, OH), 2.29 (2 H, d, *J* 5.3 Hz), 3.30 (1 H, broad, OH), 3.35–3.74 (10 H, m), 4.32, 4.38 (2 H, ABq, *J* 11.3 Hz), 4.43 (2 H, s), 4.62 (1 H, d, *J* 5.6 Hz), 6.84 (1 H, s), 6.87 (1 H, d, *J* 8.8 Hz, NH), 7.23–7.33 (10 H, m). FABMS, (positive-ion): *m/z* 1014 $(M+Na)^+$, 992 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{62}H_{90}NO_9$: 992.6616; Found: 992.6610. Anal. Calcd for $C_{62}H_{89}NO_9$ (992.4): C, 75.04; H, 9.04; N, 1.41. Found: C, 74.62; H, 8.94; N, 1.43.

*Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-3-deoxy-7-*O*-tert-butyldimethylsilyl-4-*O*-[(*R*)-3-(dodecyloxy)-tetradecyl]*-D-glycero-D-ido-*heptonate* (**13aa**).—To a solution of **12aa** (514 mg, 0.480 mmol) in CH_2Cl_2 (3 mL) were added DMAP (88.3 mg, 0.723 mmol) and $^tBuMe_2SiCl$ (109 mg, 0.720 mmol). After stirring for 3 h at rt, the mixture was diluted with EtOAc, washed with water, satd $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and chromatographed on a silica gel column. Elution with 7:3 hexane–EtOAc gave **13aa** (496 mg, 87%) as a gum. IR ν_{max}($CHCl_3$): 3432, 3356, 2928, 2856, 1732, 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.059 (3 H, s), 0.069 (3 H, s), 0.85–0.95 (18 H, m), 1.26–1.62 (62 H, m), 2.30 (2 H, d, *J* 5.9 Hz), 3.29–3.43 (5 H, m), 3.50–3.64 (5 H, m, containing OH), 3.75–3.84 (2 H, m), 4.30–4.38 (3 H, m, containing 2 H, ABq, *J* 11.0 Hz, at δ 4.33, 4.37), 4.64 (1 H, d, *J* 5.1 Hz), 6.82 (1 H, d, *J* 8.8 Hz, NH), 6.84 (1 H, s), 7.22–7.35 (15 H, m). FABMS, (positive-ion): *m/z* 1184 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{73}H_{122}NO_9Si$: 1184.8889; Found: 1184.8903. Anal. Calcd for $C_{73}H_{121}NO_9Si$ (1184.8): C, 74.00; H, 10.29; N, 1.18. Found: C, 74.23; H, 10.32; N, 1.18.

*Diphenylmethyl 2,6-anhydro-7-*O*-tert-butyldimethylsilyl-3-deoxy-3-(2,2-difluorotetradecanamido)-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-*D*-glycero-*D*-ido-heptonate* (**13ab**).—Compound **12ab** (431 mg, 0.430 mmol) was treated as described in the formation of **13aa** from **12aa** to give **13ab** (421 mg, 88%) as a gum. IR ν_{max}($CHCl_3$): 3692, 3607, 3424, 2928, 2856, 1708 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.07 (3 H, s), 0.08 (3 H, s), 0.84–0.89 (18 H, m), 1.26–1.50 (60 H, m), 1.67–1.71 (2 H, m), 1.98–2.06 (2 H, m), 3.31–3.37 (4 H, m), 3.46–3.50 (2 H, m, containing OH, changed to t, 1 H, *J* 8.1–10.3 Hz, at δ 3.48, on addition of D_2O), 3.65–3.71 (3 H, m), 3.78 (1 H, dd, *J* 4.4, 11.0 Hz), 3.83 (1 H, dd, *J* 4.4, 11.0 Hz), 4.37 (1 H, m), 4.57 (1 H, d, *J* 5.1 Hz), 6.94 (1 H, s), 7.11 (1 H, d, *J* 8.8 Hz, NH), 7.28–7.39 (10 H, m). FABMS, (positive-ion): *m/z* 1136 $(M+Na)^+$, 1114 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{66}H_{113}F_2NNaO_8Si$: 1136.8101; Found: 1136.8101. Anal. Calcd for $C_{66}H_{113}F_2NO_8Si$ (1114.7): C, 71.12; H, 10.22; F, 3.41; N, 1.26. Found: C, 70.86; H, 10.02; F, 3.45; N, 1.35.

*Diphenylmethyl 2,6-anhydro-7-*O*-tert-butyldimethylsilyl-3-deoxy-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-3-tetradecanamido-*D*-glycero-*D*-ido-heptonate* (**13ac**).—Compound **12ac** (448 mg, 0.465 mmol) was treated, as described in the formation of **13aa** from **12aa** to give **13ac** (446 mg, 89%) as a gum. IR ν_{max}($CHCl_3$): 2928, 2855, 1728, 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.06 (3 H, s), 0.07 (3 H, s), 0.84–0.89 (18 H, m), 1.23–1.51 (62 H, m), 1.67–1.72 (2 H, m), 2.04 (2 H, t, *J* 6.6–8.8 Hz), 3.33–3.44 (5 H, m, containing OH, 2 H, t, *J* 6.6 Hz, at δ 3.35), 3.54 (1 H, t, *J* 8.8–9.5 Hz), 3.65–3.71 (3 H, m), 3.77 (1 H, dd, *J* 5.1, 11.0 Hz), 3.83 (1 H, dd, *J* 4.4, 10.3 Hz), 4.37 (1 H, m), 4.64 (1 H, d, *J* 5.1 Hz), 6.08 (1 H, d, *J* 8.8 Hz, NH), 6.89 (1 H, s), 7.29–7.37 (10 H, m). FABMS, (positive-ion): *m/z* 1078 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{66}H_{116}NO_8Si$: 1078.8470; Found: 1078.8462. Anal. Calcd for $C_{66}H_{115}NO_8Si$ (1078.7): C, 73.49; H, 10.75; N, 1.30. Found: C, 73.69; H, 10.58; N, 1.37.

*Diphenylmethyl 2,6-anhydro-4-*O*-[(*R*)-3-(benzyloxy)tetradecyl]-7-*O*-tert-butyldimethylsilyl-3-deoxy-3-[(*R*)-3-(dodecyloxy)-tetradecanomido]-D-glycero-D-ido-heptonate* (**13ba**).—Compound **12ba** (38.8 mg, 0.036 mmol) was treated, as described in the formation of **13aa** from **12aa** to give **13ba** (26.8 mg, 62%) as a gum. IR ν_{max}($CHCl_3$): 2919, 2850, 1734, 1650 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 3 H), 0.063 (s, 3 H) 0.82–0.94 (m, 18 H), 1.26–1.83 (m, 62 H), 2.21–2.23 (m, 2 H), 3.17–3.29 (m, 2 H), 3.35–3.42 (m, 2 H), 3.50–3.55 (m, 1 H), 3.60–3.65 (m, 2 H), 3.72–3.80 (m, 4 H), 4.21–4.26 (m, 1 H), 4.33–4.37 (m, 1 H), 4.45–4.50 (m, 2 H), 4.63 (d, 1 H, *J* 5.5 Hz), 6.87–6.89 (m, 2 H), 7.23–7.39 (m, 15 H). FABMS, (positive-ion): *m/z* 1222 $(M+K)^+$ (on addition of KI). HR-FABMS (positive-ion): Calcd for $C_{73}H_{121}KNO_9Si$ $(M+K)^+$: 1222.8448; Found: 1222.8459.

*Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-3-deoxy-7-*O*-tert-butyldimethylsilyl-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-D-glycero-D-ido-heptonate* (**14aa**).—To a solution of **13aa** (436 mg, 0.368 mmol) in CH_2Cl_2 (3 mL) were added DMAP (67.5 mg, 0.553 mmol) and $(PhO)_2P(O)Cl$ (0.115 mL, 0.555 mmol). After stirring for 2 h at rt, the mixture was diluted with EtOAc, washed with satd $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and chromatographed on a silica gel column. Elution with 3:1 hexane–EtOAc gave **14aa** (496 mg, 95%) as a gum. IR ν_{max}($CHCl_3$): 3429, 3347, 2928, 2856, 1754, 1668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.020 (6 H, s), 0.85–0.92 (18 H, m), 1.17–1.47 (58 H, m), 1.59–1.71 (4 H, m), 2.06 (1 H, dd, *J* 3.7, 12.5 Hz), 2.18 (1 H, dd, *J* 8.1, 15.4 Hz), 3.24–3.39 (4 H, m), 3.65–3.92 (5 H, m), 4.02 (1 H, m), 4.27, 4.36 (2 H, ABq, *J* 11.4 Hz), 4.59 (1 H, m), 4.66–4.72 (2 H, m), 6.85 (1 H, s), 6.86 (1 H, d, *J* 8.8 Hz, NH), 7.11–7.32 (25 H, m). FABMS, (positive-ion): *m/z* 1416 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{85}H_{131}NO_{12}PSi$: 1416.9178; Found: 1416.9197.

*Diphenylmethyl 2,6-anhydro-7-*O*-tert-butyldimethylsilyl-3-deoxy-3-(2,2-difluorotetradecanamido)-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-D-glycero-D-ido-heptonate* (**14ab**).—Compound **13ab** (368 mg, 0.330 mmol) was treated as described in the formation of **14aa** from **13aa** to give **14ab**

(425 mg, 96%) as an oil. IR ν_{max}($CHCl_3$): 3691, 3425, 2928, 2856, 1755, 1706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.011 (3 H, s), 0.020 (3 H, s), 0.85–0.91 (18 H, m), 1.17–1.49 (60 H, m), 1.68–1.83 (4 H, m), 3.26 (1 H, m), 3.34 (2 H, t, *J* 6.6 Hz), 3.67–3.72 (3 H, m), 3.83 (1 H, dd, *J* 6.6, 10.3 Hz), 3.89 (1 H, dd, *J* 6.6, 10.3 Hz), 4.12 (1 H, m), 4.56 (1 H, m), 4.67 (1 H, d, *J* 2.9 Hz), 4.73 (1 H, m), 6.97 (1 H, s), 7.07 (1 H, d, *J* 9.5 Hz, NH), 7.16–7.36 (20 H, m). FABMS, (positive-ion): *m/z* 1384 $(M+K)^+$ (on addition of KI). FABMS, (negative-ion): *m/z* 1344 $(M-H)^-$. HRFABMS (negative-ion): Calcd for $C_{78}H_{121}F_2NO_{11}PSi$: 1344.8415; Found: 1344.8405. Anal. Calcd for $C_{78}H_{122}F_2NO_{11}PSi$ (1346.9): C, 69.56; H, 9.13; F, 2.82; N, 1.04; P, 2.30. Found: C, 69.55; H, 9.04; F, 2.82; N, 1.09; P, 2.05.

*Diphenylmethyl 2,6-anhydro-7-*O-tert-*butyldimethylsilyl-3-deoxy-5-*O-*diphenylphosphono-4-*O-*[(*R*)-3-(dodecyloxy)tetradecyl]-3-tetradecanamido-*D-glycero-D-ido-*heptonate* (**14ac**).—Compound **13ac** (425 mg, 0.394 mmol) was treated, as described in the formation of **14aa** from **13aa** to give **14ac** (500 mg, 97%) as a gum. IR ν_{max}($CHCl_3$): 2928, 2855, 1752, 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.07 (3 H, s), 0.018 (3 H, s), 0.83–0.89 (18 H, m), 1.11–1.48 (62 H, m), 1.68–1.82 (4 H, m), 3.28 (1 H, m), 3.34 (2 H, t, *J* 6.6 Hz), 3.66–3.85 (4 H, m), 3.93 (1 H, dd, *J* 2.9 Hz), 4.20 (1 H, m), 4.55 (1 H, m), 4.67 (1 H, d, *J* 2.9 Hz), 4.73 (1 H, m), 6.00 (1 H, d, *J* 9.5 Hz, NH), 6.94 (1 H, s), 7.16–7.35 (20 H, m). FABMS, (positive-ion): *m/z* 1332 $(M+Na)^+$, 1310 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{78}H_{124}NNa{:}O_{11}PSi$ 1332.8579; Found: 1332.8627. Anal. Calcd for $C_{78}H_{124}NO_{11}PSi$ (1310.9): C, 71.47; H, 9.54; N, 1.07; P, 2.36. Found: C, 71.59; H, 9.59; N, 1.38; P, 2.46.

*Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-3-deoxy-5-*O-*diphenylphosphono-4-*O-*[(*R*)-3-(dodecyloxy)tetradecyl]-*D-glycero-D-ido-*heptonate* (**15aa**).—A solution of **14aa** (452 mg, 0.319 mmol) in THF (3 mL) and 3 M HCl aq (0.4 mL) was stirred for 6 h at rt. The reaction mixture was diluted with EtOAc, washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and chromatographed on a silica gel column. Elution with 1:1 hexane–EtOAc gave **15aa** (385 mg, 93%) as an amorphous residue. IR ν_{max}($CHCl_3$): 3433, 2928, 2855, 1731, 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 5.9–7.3 Hz), 1.24–1.61 (62 H, m), 2.26 (2 H, d, *J* 5.9 Hz), 3.15 (1 H, m), 3.22 (2 H, t, *J* 6.6–7.3 Hz), 3.40 (1 H, m), 3.50–3.57 (4 H, m), 3.66 (1 H, m), 3.78 (1 H, dd, *J* 8.1, 9.5 Hz), 4.31, 4.35 (2 H, ABq, *J* 11.7 Hz), 4.49 (1 H, m), 4.57 (1 H, q, *J* 8.8 Hz), 4.73 (1 H, d, *J* 5.1 Hz), 6.82 (1 H, s), 6.83 (1 H, d, *J* 7.3 Hz, NH), 7.12–7.34 (25 H, m). FABMS, (positive-ion): *m/z* 1324 $(M+Na)^+$, 1302 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{79}H_{116}NNaO_{12}P$: 1324.8133; Found: 1324.8129. Anal. Calcd for $C_{79}H_{116}NO_{12}P$ (1302.7): C, 72.84; H, 8.98; N, 1.08; P, 2.38. Found: C, 72,53; H, 8.72; N, 1.04; P, 1.99.

*Diphenylmethyl 2,6-anhydro-3-deoxy-3-(2,2-difluorotetradecanamido)-5-*O-*diphenylphosphono-4-*O-*[(*R*)-3-(dodecyloxy)tetradecyl]-*D-glycero-D-ido-*heptonate* (**15ab**).—Compound **14ab** (390 mg, 0.290 mmol) was treated as described in the formation of **15aa** from **14aa** to give **14ab** (316 mg, 88%) as an amorphous solid. IR ν_{max}(KBr): 3449, 3338, 2922, 2853, 1713 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6 Hz), 1.18–1.45 (60 H, m), 1.63–1.66 (2 H, m), 1.94–1.98 (2 H, m), 3.18 (1 H, m), 3.24–3.35 (4 H, m, containing OH), 3.58–3.66 (3 H, m), 3.72–3.82 (2 H, m), 4.50 (1 H, m), 4.60 (1 H, dd, *J* 8.1, 17.6 Hz), 4.68 (1 H, d, *J* 5.1 Hz), 6.95 (1 H, s), 7.02 (1 H, d, *J* 9.5 Hz, NH), 7.13–7.37 (20 H, m). FABMS, (positive-ion): *m/z* 1254 $(M+Na)^+$, 1232 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{72}H_{108}NNaO_{11}F_2P$: 1254.7526; Found: 1254.7517.

*Diphenylmethyl 2,6-anhydro-3-deoxy-5-*O-*diphenylphosphono-4-*O-*[(*R*)-3-(dodecyloxy)tetradecyl]-3-tetradecanamido-*D-glycero-D-ido-*heptonate* (**15ac**).—Compound **14ac** (471 mg, 0.359 mmol) was treated as described in the formation of **15aa** from **14aa** to give **15ac** (392 mg, 91%) as a white solid; mp 73.5–74.5 °C. $[\alpha]_D^{25}$ +15.4° (*c* 0.15, $CHCl_3$). IR ν_{max}($CHCl_3$): 3435, 2927, 2855, 1728, 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.20–1.47 (60 H, m), 1.62–1.64 (4 H, m), 1.92–1.98 (2 H, m), 3.15 (1 H, brs, OH), 3.26–3.29 (3 H, m, containing 2 H, t, *J* 6.6 Hz, at 3.27), 3.59–3.67 (4 H, m),

3.77–3.82 (2 H, m), 4.49 (1 H, m), 4.59 (1 H, m), 4.78 (1 H, d, *J* 5.1 Hz), 6.04 (1 H, d, *J* 8.8 Hz, NH), 6.91 (1 H, s), 7.15–7.35 (20 H, m). FABMS, (positive-ion): *m/z* 1218 $(M+Na)^+$, 1196 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{72}H_{110}NNaO_{11}P$: 1218.7714; Found: 1218.7747. Anal. Calcd for $C_{72}H_{110}NO_{11}P$ (1196.6): C, 72.27; H, 9.27; N, 1.17; P, 2.59. Found: C, 71.88; H, 8.85; N, 1.18; P, 2.56.

*Diphenylmethyl 2,6-anhydro-4-*O*-[(*R*)-3-(benzyloxy)tetradecyl]-3-deoxy-5-*O*-diphenylphosphono-3-[(*R*)-3-(dodecyloxy)tetradecanamido]-*D*-glycero-*D*-ido-heptonate* (**15ba**).—To a solution of **13ba** (200 mg, 0.168 mmol) in CH_2Cl_2 (2 mL) were added DMAP (41.2 mg, 0.338 mmol) and $(PhO)_2P(O)Cl$ (0.07 mL, 0.338 mmol). After stirring for 2 h at rt, the reaction mixture was diluted with EtOAc, washed with satd $NaHCO_3$ aq, and brine, dried over $MgSO_4$, filtered, and concentrated to give a mixture of **14ba** and spent reagents. This mixture was treated, as described in the formation of **15aa** from **14aa** to give **15ba** (176 mg, 80%). IR $\nu_{max}(CHCl_3)$: 3467, 2920, 2851, 1733, 1649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88(9 H, t, *J* 6.8–7.0 Hz), 1.17–1.77 (6 H, m), 2.14 (2 H, d, *J* 6.1 Hz), 3.13–3.17 (1 H, m), 3.21–3.31 (2 H, m), 3.38–3.42 (2 H, m), 3.55 (2 H, s), 3.73–3.82 (2 H, m), 3.86–3.90 (1 H, m), 4.37 (2 H, s), 4.53 (1 H, dt, *J* 5.4, 9.1 Hz), 4.60 (1 H, dd, *J* 8.2, 17.4 Hz), 4.72 (1 H, d, *J* 5.3 Hz), 6.88 (1 H, s), 6.95 (1 H, d, *J* 9.0 Hz), 7.13–7.34 (25 H, m). HRFABMS, (positive-ion): Calcd for $C_{79}H_{117}NO_{12}P$ $(M+H)^+$: 1302.8313; Found: 1302.8339.

*2,6-Anhydro-3-deoxy-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-3-[(*R*)-3-hydroxytetradecanamido]-*D*-glycero-*D*-ido-heptonic acid* (**16aa**).—A solution of **15aa** (64.5 mg, 0.050 mmol) in EtOH (2 mL) containing 20% $Pd(OH)_2$-on-carbon (31 mg) was stirred vigorously under hydrogen for 8 h at rt. The reaction mixture was filtered and concentrated in vacuo to give a crude product. The crude product was chromatographed on a silica gel short solumn. Elution with 8:1 $CHCl_3$–MeOH gave **16aa** (42.3 mg, 82%) as an amorphous residue. IR ν_{max}(KBr): 3334, 3063, 2955, 2922, 2852, 1742, 1649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.10–1.68 (62 H, m), 2.20–2.32 (2 H, m), 3.28–3.31 (3 H, m, containing 2 H, t, *J* 6.6 Hz, at 3.30), 3.66–3.75 (4 H, m), 3.84 (1 H, t, *J* 6.6–7.3 Hz), 3.97–3.99 (2 H, m), 4.49 (1 H, m), 4.59 (1 H, m), 4.70 (1 H, d, *J* 4.4 Hz), 7.18–7.35 (10 H, m). FABMS, (positive-ion): *m/z* 1068 $(M+Na)^+$, 1046 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{59}H_{100}NNaO_{12}P$: 1068.6881; Found: 1068.6887.

*2,6-Anhydro-3-deoxy-3-(2,2-difluorotetradecanamido)-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-*D*-glycero-*D*-ido-heptonic acid* (**16ab**).—Compound **15ab** (42.5 mg, 0.035 mmol) was treated as described below in the formation of **16ac** from **15ac** to give **16ab** (25.4 mg, 69%) as an amorphous solid. IR $\nu_{max}(CHCl_3)$: 3381, 3309, 2922, 2851, 1717, 1691 cm^{-1}. ^1H NMR (400 MHz, 9:1 CD_3OD–$CDCl_3$): δ 0.89 (9 H, t, *J* 6.6 Hz), 1.13–1.48 (60 H, m), 1.66–1.71 (2 H, m), 2.03–2.07 (2 H, m), 3.27–3.36 (3 H, m), 3.73–3.77 (4 H, m), 3.87 (1 H, t, *J* 6.6–7.3 Hz), 4.07 (1 H, m), 4.44 (1 H, m), 4.60 (1 H, d, *J* 4.4 Hz), 4.67 (1 H, m), 7.20–7.40 (10 H, m), 8.01 (1 H, d, *J* 8.8 Hz, NH). FABMS, (positive-ion): *m/z* 1088 $(M+Na)^+$, 1066 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{59}H_{98}F_2NNaO_{11}P$: 1088.6743; Found: 1088.6752.

*2,6-Anhydro-3-deoxy-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-3-tetradecanamido-*D*-glycero-*D*-ido-heptonic acid* (**16ac**).—A solution of **15ac** (38.1 mg, 0.032 mmol) in EtOH (2 mL) containing 10% Pd/C (18.8 mg) was stirred vigorously under N_2 for 2 h at rt. The reaction mixture was filtered and concentrated in vacuo to give a crude product. The crude product was chromatographed on a short column of silica gel. Elution with 8:1 $CHCl_3$–MeOH gave **16ac** (25.6 mg, 78%) as an amorphous residue. IR $\nu_{max}(CHCl_3)$: 3434, 2927, 2855, 1747, 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.11–1.56 (62 H, m), 1.66–1.68 (2 H, m), 2.08–2.15 (2 H, m), 3.30–3.33 (3 H, m, containing 2 H, t, *J* 6.6–7.3 Hz, at 3.32), 3.68–3.83 (5 H, m), 3.95 (1 H, m), 4.52 (1 H, m), 4.60 (1 H, m), 4.67 (1 H, d, *J* 3.7 Hz), 6.50 (1 H, d, *J* 8.8 Hz, NH), 7.19–

7.37 (10 H, m). FABMS, (positive-ion): *m/z* 1052 $(M+Na)^+$. HRFABMS (positive-ion): Calcd for $C_{59}H_{100}NNaO_{11}P$: 1052.6932; Found: 1052.6930.

2,6-Anhydro-3-deoxy-5-O-diphenylphosphono-3-[(R)-3-(dodecyloxy)tetradecanamido]-4-O-[(R)-3-hydroxytetradecyl]-D-glycero-D-ido-heptonic acid (**16ba**).—A solution of **15ba** (26.0 mg, 0.020 mmol) in EtOH (2 mL) containing 20% $Pd(OH)_2$-on-carbon (30.0 mg) was stirred vigorously under hydrogen for 16 h at rt. The reaction mixture was filtered and concentrated in vacuo to give a crude product. The crude product was chromatographed on a silica gel TLC plate. Elution with 4:1 $CHCl_3$–MeOH gave **16ba** (12.2 mg, 58%). IR ν_{max}(KBr): 3412, 2919, 2850, 1645 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.88–0.91 (m, 9 H), 1.19–1.70 (m, 62 H), 2.32–2.45 (m, 2 H), 3.31 (s, 3 H), 3.41–3.44 (m, 1 H), 3.48–3.54 (m, 1 H), 3.60–3.62 (m, 1 H), 3.65–3.76 (m, 4 H), 3.83 (dd, 1 H, *J* 6.2 Hz, 8.2 Hz), 3.87–3.94 (m, 2 H), 4.32 (d, 1 H, *J* 4.5 Hz), 4.37–4.41 (m, 1 H), 4.61 (dd, 1 H, *J* 1.8, 7.4 Hz), 7.21–7.40 (m, 10 H). HRFABMS (positive-ion): Calcd for $C_{59}H_{101}NO_{12}P$ $(M+H)^+$: 1046.7061; Found:1046.7063.

2,6-Anhydro-3-deoxy-4-O-[(R)-3-(dodecyloxy)tetradecyl]-3-[(R)-3-hydroxytetradecanamido]-5-O-phosphono-D-glycero-D-ido-heptonic acid (**17aa**).—A solution of **16aa** (37.5 mg, 0.036 mmol) in THF (2 mL) containing PtO_2 (20.1 mg) was stirred vigorously under hydrogen for 18 h at rt. The reaction mixture was filtered and concentrated in vacuo to give a residue. The residue was dissolved in $CHCl_3$ (4 mL), MeOH (8 mL) and aq 0.1M HCl (4 mL). To this solution was added another volume of $CHCl_3$ (4 mL) and aq 0.1 M HCl (4 mL) to separate the solution into two phases. The lower $CHCl_3$ phase was collected and concentrated to give **17aa** (23.8 mg, 74%) as a white powder; mp. 129.5–130.5 °C. $[\alpha]_D^{24}$ +11.2° (*c* 0.15, $CHCl_3$). IR ν_{max}(KBr): 3313, 2956, 2922, 2853, 1734, 1646 cm^{-1}. ^1H NMR (400 MHz, 5:1 CD_3OD–$CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.16–1.58 (60 H, m), 1.75–1.78 (2 H, m), 2.31 (1 H, dd, *J* 8.1, 14.6 Hz), 2.39 (1 H, dd, *J* 4.4, 14.6 Hz), 3.42–3.49 (3 H, m), 3.71–3.80 (4 H, m), 3.90–3.99 (3 H, m), 4.22 (1 H, m), 4.39 (1 H, m), 4.57 (1 H, d, *J* 4.4 Hz). FABMS, (positive-ion): *m/z* 916 $(M+Na)^+$. FABMS, (negative-ion): *m/z* 892 $(M-H)^-$. HRFABMS (positive-ion): Calcd for $C_{47}H_{92}NO_{12}PNa$: 916.6225; Found: 916.6227. Anal. Calcd For $C_{47}H_{92}NO_{12}P$ (894.2): C. 63.13; H, 10.37; N, 1.57; P, 3.46. Found: C, 62.12; H, 9.91; N, 1.58; P, 3.35.

2,6-Anhydro-3-deoxy-3-(2,2-difluorotetradecanamido)-4-O-[(R)-3-(dodecyloxy)tetradecyl]-5-O-phosphono-D-glycero-D-ido-heptonic acid (**17ab**).—Compound **16ab** (21.5 mg, 0.020 mmol) was treated as described in the formation of **17aa** from **16aa** to give **17ab** (17.8 mg, 96%) as a white powder; mp 133.0–135.5 °C. $[\alpha]_D^{23}$ +4.1° (*c* 0.60, $CHCl_3$). IR ν_{max}(KBr): 3338, 2922, 2852, 1688 cm^{-1}. ^1H NMR (400 MHz, 5:1 CD_3OD–$CDCl_3$): δ 0.89 (9 H, t, *J* 6.6–7.3 Hz), 1.20–1.58 (60 H, m), 1.74–1.79 (2 H, m), 1.99–2.08 (2 H, m), 3.39 (1 H, m), 3.45 (2 H, t, *J* 6.6 Hz), 3.70–3.76 (3 H, m), 3.82 (1 H, m), 3.94–3.97 (2 H, m), 4.27 (1 H, m), 4.42 (1 H, dd, *J* 4.4, 6.6 Hz), 4.59 (1 H, d, *J* 3.7 Hz). FABMS, (positive-ion): *m/z* 936 $(M+Na)^+$, 914 $(M+H)^+$. FABMS, (negative-ion): *m/z* 912 $(M-H)^-$. HRFABMS (positive-ion): Calcd for $C_{47}H_{90}NNaO_{11}F_2P$: 936.6117; Found: 936.6133. Anal. Calcd for $C_{47}H_{90}NO_{11}F_2P$ (914.2): C, 61.75; H, 9.92; N, 1.53; F, 4.16; P, 3.39. Found: C, 61.70; H, 9.51; N, 1.38; F, 3.88; P, 3.02.

2,6-Anhydro-3-deoxy-4-O-[(R)-3-(dodecyloxy)tetradecyl]-5-O-phosphono-3-tetradecanamido-D-glycero-D-ido-heptonic acid (**17ac**).—Compound **16ac** (23.8 mg, 0.023 mmol) was treated as described in the formation of **17aa** from **16aa** to give **17ac** (20.0 mg, 99%) as a white powder; mp. 119.5–121.0 °C. $[\alpha]_D^{26}$ +8.3° (*c* 0.41, $CHCl_3$). IR ν_{max}(KBr): 3307, 2922, 2852, 1733, 1650 cm^{-1}. ^1H NMR (400 MHz, 9:1 CD_3OD–$CDCl_3$): δ 0.90 (9 H, t, *J* 6.6–7.3 Hz), 1.20–1.78 (64 H, m), 2.23 (2 H, t, *J* 7.3–8.1 Hz), 3.42–3.48 (3 H, m, containing 2 H, t, *J* 6.6 Hz, at δ 3.46), 3.70–3.81 (4 H, m), 3.90 (1 H, m), 4.04 (1 H, m), 4.20 (1 H, m), 4.34 (1 H, m), 4.56 (1 H, d, *J* 4.4 Hz). FABMS, (positive-ion): *m/z* 900 $(M+Na)^+$. HRFABMS (positive-ion): Calcd for $C_{47}H_{92}NNaO_{11}P$: 900.6306; Found: 900.6315. Anal. Calcd for $C_{47}H_{92}NO_{11}P$ (878.2): C,

64.28; H, 10.56; N, 1.60; P, 3.53. Found: C, 62.62; H, 10.45; N, 1.24; P, 3.45.

*2,6-Anhydro-3-deoxy-3-[(*R*)-3-(dodecyloxy)-tetradecanamido]-4-*O*-[(*R*)-3-hydroxytetradecyl]-5-*O*-phosphono*-D-glycero-D-ido-*heptonic acid* (**17ba**).—A solution of **16ba** (8.7 mg, 0.008 mmol) in THF (2 mL) containing PtO_2 (21.3 mg, 0.094 mmol) was stirred vigorously under hydrogen for 18 h at rt. The reaction mixture was filtered and concentrated in vacuo to give a residue. The residue was dissolved in $CHCl_3$ (4 mL), MeOH (8 mL) and aq 0.1 M HCl (4 mL). To this solution was added another volume of $CHCl_3$ (4 mL) and aq 0.1 M HCl (4 mL) to separate the solution into two phases. The lower $CHCl_3$ phase was collected and concentrated to give **17ba** (6.4 mg, 86%). $[\alpha]_D^{24}$ −6.9° (*c* 0.30, $CHCl_3$). IR ν_{max}(KBr): 3370, 2957, 2919, 2850, 1646 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 0.90 (9 H, t, *J* 6.8 Hz), 1.16–1.78 (62 H, m), 2.28–2.30 (2 H, m), 3.41–3.48 (1 H, m), 3.50–3.56 (1 H, m), 3.66–3.69 (2 H, m), 3.73–3.92 (6 H, m), 4.24–4.25 (1 H, m), 4.33–4.35 (1 H, m), 4.52 (1 H, d, *J* 4.9 Hz). HRFABMS (positive-ion): Calcd for $C_{49}H_{93}NO_{12}P$ $(M+H)^+$: 894.6435; Found: 894.6436.

*Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-3-deoxy-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)-tetradecyl]-7-*O*-methyl*-D-glycero-D-ido-*heptonate* (**18a**).—To a solution of **15aa** (86.0 mg, 0.066 mmol) in CH_2Cl_2 (3 mL) were added 2,6-di-*tert*-butyl-4-methyl-pyridine (44.8 mg, 0.218 mmol) and Me_3OBF_4 (30.1 mg, 0.204 mmol). After stirring for 3 h at rt, the mixture was diluted with EtOAc, washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and chromatographed on a silica gel column. Elution with 7:3 hexane–EtOAc gave **18a** (80.2 mg, 92%) as an amorphous residue. IR ν_{max}($CHCl_3$): 3691, 2928, 2855, 1732, 1669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 5.9–7.3 Hz), 1.24–1.66 (62 H, m), 2.11 (1 H, dd, *J* 3.7, 15.4 Hz), 2.20 (1 H, dd, *J* 8.1, 15.4 Hz), 3.19–3.29 (6 H, m, containing 3 H, s, at δ 3.26), 3.44–3.64 (5 H, m), 3.78 (1 H, m), 3.94 (1 H, m), 4.28, 4.38 (2 H, ABq, *J* 11.7 Hz), 4.53–4.63 (2 H, m), 4.70 (1 H, d, *J* 4.4 Hz), 6.84 (1 H, s), 6.85 (1 H, d, *J* 8.8 Hz, NH), 7.12–7.33 (25 H, m). FABMS, (positive-ion): *m/z* 1316 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{80}H_{119}NO_{12}P$: 1316.8470; Found: 1316.8475.

*Diphenylmethyl 2,6-anhydro-3-deoxy-3-(2,2-difluorotetradecanamido)-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-7-*O*-methyl*-D-glycero-D-ido-*heptonate* (**18b**).—Compound **15ab** (78.9 mg, 0.064 mmol) was treated as described in the formation of **18a** from **15aa** to give **18b** (56.1 mg, 70%) as an amorphous solid. IR ν_{max}($CHCl_3$): 2927, 2855, 1709 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 5.9–7.3 Hz), 1.20–1.46 (60 H, m), 1.66 (2 H, q, *J* 6.6 Hz), 1.69–1.83 (2 H, m), 3.22 (1 H, m), 3.27 (3 H, s), 3.29 (2 H, t, *J* 7.3 Hz), 3.52–3.70 (5 H, m), 4.01 (1 H, m), 4.53 (1 H, m), 4.63 (1 H, d, *J* 5.1 Hz), 4.67 (1 H, d, *J* 4.4 Hz), 6.96 (1 H, s), 7.03 (1 H, d, *J* 8.8 Hz, NH), 7.16–7.37 (20 H, m). FABMS, (positive-ion): *m/z* 1268 $(M+Na)^+$, 1246 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{73}H_{110}NNaO_{11}F_2P$: 1268.7682; Found: 1268.7653.

*Diphenylmethyl 2,6-anhydro-3-deoxy-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)-tetradecyl]-7-*O*-methyl-3-tetradecanamido*-D-glycero-D-ido-*heptonate* (**18c**).—Compound **15ac** (73.2 mg, 0.061 mmol) was treated as described in the formation of **18c** from **15ac** to give **18c** (64.1 mg, 87%) as a white solid; mp. 70.5–71.0 °C. $[\alpha]_D^{26}$ +4.4° (*c* 0.18, $CHCl_3$). IR ν_{max}(KBr): 3349, 2922, 2852, 1741, 1648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6 Hz), 1.13–1.47 (62 H, m), 1.65–1.70 (2 H, m), 1.77–1.83 (2 H, m), 3.26 (1 H, m), 3.29 (3 H, s), 3.32 (2 H, t, *J* 6.6 Hz), 3.56 (1 H, dd, *J* 5.9, 10.3 Hz), 3.77 (1 H, t, *J* 5.1 Hz), 4.16 (1 H, m), 4.53 (1 H, m), 4.63 (1 H, m), 4.72 (1 H, d, *J* 3.7 Hz), 5.98 (1 H, d, *J* 8.8 Hz, NH), 6.93 (1 H, s), 7.17–7.37 (20 H, m). FABMS, (positive-ion): *m/z* 1232 $(M+Na)^+$, 1210 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{73}H_{112}NNaO_{11}P$: 1232.7833; Found: 1232.7871.

*2,6-Anhydro-3-deoxy-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-3-[(*R*)-3-hydroxytetradecanamido]-7-*O*-methyl*-D-glycero-D-ido-*heptonic acid* (**19a**).—Compound **18a** (75.5 mg, 0.0573 mmol) was treated as described in the formation of **16aa** from **15aa** to give **19a** (50.3 mg, 83%) as an

amorphous residue. IR ν_{max}(KBr): 3343, 3069, 2922, 2852, 1734, 1651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.25–1.53 (60 H, m), 1.67–1.72 (2 H, m), 2.15 (1 H, dd, *J* 9.5, 15.4 Hz), 2.26 (1 H, m), 3.26–3.38 (6 H, m, containing 3 H, s, at δ 3.31), 3.59–3.78 (6 H, m), 3.94 (1 H, m), 4.31 (1 H, m), 4.58 (1 H, d, *J* 4.4 Hz), 4.65 (1 H, m), 7.06 (1 H, d, *J* 9.5 Hz, NH), 7.18–7.37 (10 H, m). FABMS, (positive-ion): *m/z* 1082 $(M+Na)^+$, 1060 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{60}H_{102}NNaO_{12}P$: 1082.7037; Found: 1082.7019.

*2,6-Anhydro-3-deoxy-3-(2,2-difluorotetradecanamido)-5-*O*-diphenylphosphono-4-*O*-[(*R*)3-(dodecyloxy)tetradecyl]-7-*O*-methyl-*D*-glycero-*D*-ido-heptonic acid* (**19b**).—Compound **15ab** (39.5 mg, 0.032 mmol) was treated as described in the formation of **16ac** from **15ac** to give **19b** (23.6 mg, 69%) as an amorphous solid. IR ν_{max}(KBr): 3352, 2922, 2852, 1733, 1695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6 Hz), 1.23–1.49 (60 H, m), 1.69 (2 H, q, *J* 6.6 Hz), 1.98–2.05 (2 H, m), 3.25–3.35 (6 H, m, containing 3 H, s, at δ 3.30), 3.52 (1 H, dd, *J* 4.4, 11.0 Hz), 3.67–3.75 (4 H, m), 4.23 (1 H, m), 4.54–4.62 (3 H, m, containing 1 H, d, *J* 3.7 Hz, at δ 4.60), 7.18–7.36 (11 H, m, containing NH). FABMS, (positive-ion): *m/z* 1102 $(M+Na)^+$, 1080 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{60}H_{100}F_2NNaO_{11}P$: 1102.6900; Found: 1102.6884.

*2,6-Anhydro-3-deoxy-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-7-*O*-methyl-3-tetradecanamido-*D*-glycero-*D*-ido-heptonic acid* (**19c**).—Compound **18c** (58.1 mg, 0.0480 mmol) was treated as described in the formation of **16ac** from **15ac** to give **19c** (31.2 mg, 62%) as an amorphous residue. IR ν_{max}($CHCl_3$): 3436, 2927, 2855, 1774, 1753, 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.20–1.52 (62 H, m), 1.67–1.72 (2 H, m), 2.00–2.17 (2 H, m), 3.26–3.37 (6 H, m, containing 3 H, s, at δ 3.31), 3.59 (1 H, m), 3.66–3.75 (4 H, m), 4.31 (1 H, m), 4.57–4.62 (3 H, m, containing 1 H, d, *J* 4.4 Hz, at δ 4.61), 6.49 (1 H, d, *J* 8.8 Hz, NH), 7.20–7.36 (10 H, m). FABMS, (positive-ion): *m/z* 1066 $(M+Na)^+$. HRFABMS (positive-ion): Calcd for $C_{60}H_{102}NNaO_{11}P$: 1066.7088; Found: 1066.7092.

*2,6-Anhydro-3-deoxy-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-3-[(*R*)-3-hydroxytetradecanamido]-7-*O*-methyl-5-*O*-phosphono-*D*-glycero-*D*-ido-heptonic acid* (**20a**).—Compound **19a** (46.5 mg, 0.0439 mmol) was treated as described in the formation of **17aa** from **16aa** to give **20a** (36.7 mg, 92%) as a white powder; mp 102.5–103.0 °C. $[\alpha]_D^{25}$ +6.7° (*c* 0.14, $CHCl_3$). IR ν_{max}(KBr): 3310, 2956, 2923, 2853, 1733, 1648 cm^{-1}. ^1H NMR (400 MHz, 5:1 CD_3OD–$CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.18–1.58 (60 H, m), 1.76–1.77 (2 H, m), 2.31 (1 H, dd, *J* 8.1, 14.6 Hz), 2.39 (1 H, dd, *J* 4.4, 14.6 Hz), 3.32–3.49 (6 H, m, containing 3 H, s, at δ 3.39), 3.65–3.78 (5 H, m), 3.93 (1 H, m), 4.19–4.27 (2 H, m), 4.43 (1 H, m), 4.57 (1 H, d, *J* 3.7 Hz). FABMS, (positive-ion): *m/z* 930 $(M+Na)^+$. FABMS, (negative-ion): *m/z* 906 $(M-H)^-$. HRFABMS (positive-ion): Calcd for $C_{48}H_{94}NNaO_{12}P$: 930.6411; Found: 930.6417. Anal. Calcd for $C_{48}H_{94}NO_{12}P$ (908.2): C, 63.48; H, 10.43; N, 1.54; P, 3.41. Found: C, 61.81; H, 10.45; N, 1.49; P, 3.45.

*2,6-Anhydro-3-deoxy-3-(2,2-difluorotetradecanamido)-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-7-*O*-methyl-5-*O*-phosphono-*D*-glycero-*D*-ido-heptonic acid* (**20b**).—Compound **19b** (20.8 mg, 0.0193 mmol) was treated as described in the formation of **17aa** from **16aa** to give **20b** (17.6 mg, 98%) as a white powder; mp 124.5–125.5 °C. $[\alpha]_D^{26}$ +3.0° (*c* 0.65, $CHCl_3$). IR ν_{max}(KBr): 3348, 2923, 2853, 1718, 1693 cm^{-1}. ^1H NMR (400 MHz, 9:1 CD_3OD–$CDCl_3$): δ 0.90 (9 H, t, *J* 5.9–7.3 Hz), 1.20–1.56 (60 H, m), 1.76–1.77 (2 H, m), 2.01–2.07 (2 H, m), 3.39 (3 H, s), 3.42–3.48 (3 H, m), 3.66–3.80 (5 H, m), 4.24–4.31 (2 H, m), 4.44 (1 H, m), 4.84 (1 H, d, *J* 3.7 Hz). FABMS, (positive-ion): *m/z* 950 $(M+Na)^+$. HRFABMS (positive-ion): Calcd for $C_{48}H_{92}NO_{11}F_2PNa$: 950.6274; Found: 950.6270. Anal. Calcd for $C_{48}H_{92}F_2NO_{11}P$ (928.2): C, 62.11; H, 9.99; F, 4.09; N, 1.51; P, 3.34. Found: C, 61.77; H, 10.14; F, 3.84; N, 1.54; P, 3.61.

*2,6-Anhydro-3-dzeoxy-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-7-*O*-methyl-5-*O*-phosphono-3-tetradecanamido-*D*-glycero-*D*-ido-heptonic acid* (**20c**).—Compound **19c** (28.6 mg, 0.027 mmol) was treated as described in the forma-

tion of **17aa** from **16aa** to give **19c** (22.5 mg, 92%) as a white powder; mp 95.5–96.0 °C. $[\alpha]_D^{26}$ +9.4° (*c* 0.54, $CHCl_3$). IR ν_{max}(KBr): 3333, 2922, 2852, 1734, 1650 cm^{-1}. ^1H NMR (400 MHz, 9:1 CD_3OD–$CDCl_3$): δ 0.90 (9 H, t, *J* 6.6–7.3 Hz), 1.29–1.60 (62 H, m), 1.75–1.77 (2 H, m), 2.22 (2 H, t, *J* 7.3–8.1 Hz), 3.38 (3 H, s), 3.42–3.48 (3 H, m), 3.66–3.79 (5 H, m), 4.23 (1 H, m), 4.39 (1 H, m), 4.56 (1 H, d, *J* 3.7 Hz). FABMS, (positive-ion): *m/z* 914 $(M+Na)^+$, 892 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{48}H_{94}NNaO_{11}P$: 914.6462; Found: 914.6450.

*Diphenylmethyl 2,6-anhydro-3-[(*R*)-3-(benzyloxy)tetradecanamido]-3,7-dideoxy-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-7-fluoro*-D-glycero-D-ido-*heptonate* (**21a**).—To a solution of **15aa** (101 mg, 0.078 mmol) in DME (2 mL) was gradually added a solution of DAST (0.03 mL, 0.227 mmol) in DME (1 mL) at 0 °C with stirring under N_2. After stirring for 2 h at 0 °C, the reaction mixture was quenched with water, extracted with EtOAc, washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and chromatographed on a silica gel column. Elution with 3:1 hexane–EtOAc gave **21a** (52.2 mg, 52%) as an amorphous residue. IR ν_{max}($CHCl_3$): 2928, 2855, 1755, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 5.9–7.3 Hz), 1.24–1.65 (62 H, m), 2.12 (1 H, dd, *J* 3.7, 15.4 Hz), 2.20 (1 H, dd, *J* 8.1, 15.4 Hz), 3.20 (1 H, m), 3.27 (2 H, t, *J* 6.6 Hz), 3.41 (1 H, m), 3.60–3.63 (2 H, m), 3.80 (1 H, t, *J* 6.6 Hz), 4.00 (1 H, m), 4.29, 4.33 (2 H, ABq, *J* 11.0 Hz), 4.36–4.64 (4 H, m), 4.73 (1 H, d, *J* 4.4 Hz), 6.86 (1 H, s), 6.89 (1 H, d, *J* 8.8 Hz, NH), 7.11–7.35 (25 H, m). FABMS, (positive-ion): *m/z* 1326 $(M+Na)^+$, 1304 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{79}H_{116}FNO_{11}P$: 1304.8270; Found: 1304.8263.

*Diphenylmethyl 2,6-anhydro-3,7-dideoxy-3-(2,2-difluorotetradecanamido)-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-7-fluoro*-D-glycero-D-ido-*heptonate* (**21b**).—To a solution of **15ab** (58.4 mg, 0.0474 mmol) in CH_2Cl_2 (2 mL) was gradually added a solution of DAST (0.016 mL, 0.121 mmol) in CH_2Cl_2 (1 mL) at −40 °C with stirring under N_2. After stirring for 2 h at 0 °C, the reaction mixture was quenched with water, extracted with EtOAc, washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and chromatographed on a silica gel column. Elution with 3:1 hexane–EtOAc gave **21b** (45.1 mg, 77%) as an amorphous solid. IR ν_{max}($CHCl_3$): 3691, 2927, 2855, 1756, 1709 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6 Hz), 1.20–1.47 (60 H, m), 1.66 (2 H, q, *J* 6.6 Hz), 1.75–1.83 (2 H, m), 3.21 (1 H, m), 3.25–3.37 (2 H, m), 3.65–3.71 (3 H, m), 4.09 (1 H, m), 4.46 (1 H, ddd, *J* 3.7, 10.3, 46.1 Hz), 4.51–4.57 (2 H, m), 4.61 (1 H, ddd, *J* 6.6, 10.3, 46.1 Hz), 4.71 (1 H, d, *J* 3.7 Hz), 6.97 (1 H, s), 7.02 (1 H, d, *J* 9.5 Hz, NH), 7.16–7.36 (20 H, m). FABMS, (positive-ion): *m/z* 1256 $(M+Na)^+$, 1234 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{72}H_{107}F_3NNaO_{10}P$: 1256.7482; Found: 1256.7454.

*2,6-Anhydro-3,7-dideoxy-5-*O*-diphenylphosphono-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-7-fluoro-3-[(*R*)-3-hydroxytetradecanamido]-*D-glycero-D-ido-*heptonic acid* (**22a**).—Compound **21a** (21.8 mg, 0.017 mmol) was treated as described in the formation of **16aa** from **15aa** to give **22a** (12.6 mg, 72%) as an amorphous residue. IR ν_{max}(KBr): 3350, 2923, 2853, 1736, 1653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6 Hz), 1.21–1.51 (60 H, m), 1.68–1.70 (2 H, m), 2.16 (1 H, dd, *J* 9.5, 15.4 Hz), 2.27 (1 H, m), 3.30–3.41 (3 H, m), 3.67–3.77 (4 H, m), 3.94 (1 H, m), 4.46 (1 H, m), 4.57–4.65 (4 H, m), 7.12 (1 H, d, *J* 9.5 Hz, NH), 7.18–7.38 (10 H, m). FABMS, (positive-ion): *m/z* 1070 $(M+Na)^+$, 1048 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{59}H_{99}FNNaO_{11}P$: 1070.6838; Found: 1070.6848.

*2,6-Anhydro-3,7-dideoxy-3-(2,2-difluorotetradecanamido)-5-*O*-diphenylphosphono-4-*O*-[(*R*)3-(dodecyloxy)tetradecyl]-7-fluoro-*D-glycero-D-ido-*heptonic acid* (**22b**).—Compound **21b** (40.5 mg, 0.033 mmol) was treated as described in the formation of **16ac** from **15ac** to give **22b** (25.1 mg, 72%) as an amorphous solid. IR ν_{max}($CHCl_3$): 3434, 2928, 2855, 1780, 1711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (9 H, t, *J* 6.6–7.3 Hz), 1.25–1.49 (60 H, m), 1.66–1.71 (2 H, m), 1.96–2.05 (2 H, m), 3.23–3.38 (3 H, m), 3.66–3.77 (3 H,

m), 4.32 (1 H, m), 4.49 (1 H, ddd, *J* 3.7, 10.3, 46.1 Hz), 4.56–4.62 (2 H, m), 4.64 (1 H, ddd, *J* 6.6, 10.3, 46.1 Hz), 7.19–7.37 (11 H, m, containing NH). FABMS, (positive-ion): *m/z* 1090 $(M+Na)^+$, 1068 $(M+H)^+$. HR-FABMS (positive-ion): Calcd for $C_{59}H_{97}F_3NNaO_{10}P$: 1090.6700; Found: 1090.6688.

*2,6-Anhydro-3,7-dideoxy-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-7-fluoro-3-[(*R*)-3-hydroxytetradecanamido]-5-*O*-phosphono*-D-glycero-D-ido-*heptonic acid* (**23a**).—Compound of **22a** (10.3 mg, 0.010 mmol) was treated as described in the formation of **17aa** from **16aa** to give **23a** (6.1 mg, 69%) as a white powder; mp 112.5–113.5 °C. $[\alpha]_D^{25}$ +8.1° (*c* 0.10, $CHCl_3$). IR ν_{max}(KBr): 3311, 2956, 2923, 2853, 1730, 1646 cm^{-1}. ^1H NMR (400 MHz, 5:1 CD_3OD–$CDCl_3$): δ 0.89 (9 H, t, *J* 6.6 Hz), 1.29–1.56 (60 H, m), 1.76–1.77 (2 H, m), 2.32 (1 H, dd, *J* 8.1, 14.6 Hz), 2.39 (1 H, dd, *J* 3.7, 14.6 Hz), 3.43–3.48 (3 H, m), 3.76–3.80 (4 H, m), 3.91 (1 H, m), 4.20–4.73 (5 H, m, containing 1 H, d, *J* 3.7 Hz, at 4.60). FABMS, (positive-ion): *m/z* 918 $(M+Na)^+$. FABMS, (negative-ion): *m/z* 894 $(M-H)^-$. HRFABMS (positive-ion): Calcd for $C_{47}H_{91}FNNaO_{11}P$: 918.6211; Found: 918.6232.

*2,6-Anhydro-3,7-dideoxy-3-(2,2-difluorotetradecanamido)-4-*O*-[(*R*)-3-(dodecyloxy)tetradecyl]-7-fluoro-5-*O*-phosphono*-D-glycero-D-ido-*heptonic acid* (**23b**).—Compound **22b** (21.1 mg, 0.020 mmol) was treated as described in the formation of **17aa** from **16aa** to give **23b** (16.7 mg, 93%) as a white powder; mp 72.0–74.0 °C. $[\alpha]_D^{26}$ +3.7° (*c* 0.44, $CHCl_3$). IR ν_{max}(KBr): 3327, 2922, 2852, 1691 cm^{-1}. ^1H NMR (400 MHz, 9:1 CD_3OD–$CDCl_3$): δ 0.90 (9 H, t, *J* 6.6–7.3 Hz), 1.29–1.57 (60 H, m), 1.74–1.79 (2 H, m), 1.99–2.07 (2 H, m), 3.41–3.47 (3 H, m), 3.73–3.83 (3 H, m), 4.23–4.34 (2 H, m), 4.41 (1 H, dd, *J* 3.7, 6.6 Hz), 4.60 (1 H, ddd, *J* 3.7, 10.3, 48.3 Hz), 4.63 (1 H, d, *J* 3.7 Hz), 4.77 (1 H, ddd, *J* 6.6, 10.3, 48.3 Hz). FABMS, (positive-ion): *m/z* 938 $(M+Na)^+$, 916 $(M+H)^+$. HRFABMS (positive-ion): Calcd for $C_{47}H_{89}F_3NNaO_{10}P$: 938.6074; Found: 938.6078. Anal. Calcd for $C_{47}H_{89}F_3NO_{10}P$ (916.2): C, 61.62; H, 9.79; F, 6.22; N, 1.53; P, 3.38. Found: C, 60.94; H, 9.94; F, 5.82; N, 1.50; P, 3.56.

Determination of biological activity.—The sources of the materials used in the study are as follows: lipopolysaccharide (LPS) from *E. coli* serotype 026:B6 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 (1×10^4/200 μL/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.

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References

[1] Westphal, O.; Luderitz, O. *Angew. Chem.* **1954**, *66*, 407–417.

[2] Galanos, C.; Luderitz, O.; Rietschel, E. T.; Westphal, O. *Int. Rev. Biochem.* **1977**, *14*, 239–335.
[3] Fukushima, D.; Shibayama, S.; Tada, H, *Patent WO 9965480*, Ono Pharm Co. Ltd., Dec. 23, 1999.
[4] Rossignol, D. P.; Hawkins, L. D.; Christ, W. J.; Kobayashi, S.; Kawata, T.; Lynn, M.; Yamatsu, I.; Kishi, Y. in: Brade, H.; Opel, S. M.; Vogel, S. N.; Morrison, D. C. (Eds.); *Endotoxin in Health and Disease*; pp. 699–717.
[5] Rietschel, E. T.; Kirikae, T.; Schade, F. U.; Ulmer, A. J.; Holst, O.; Brade, H.; Schmidt, G.; Mamat, U.; Grimmecke, H. D.; Kusumoto, S.; Zahringer, U. *Immunobiology* **1993**, *187*, 169–190.
[6] (a) Qureshi, N.; Honovich, J. P.; Hara, H.; Cotter, R. J.; Takayama, K. *J. Biol. Chem.* **1988**, *263*, 5502–5504;
(b) Qureshi, N.; Takayama, K.; Kurtz, R. *Infect. Immun.* **1991**, *59*, 441–444;
(c) Christ, W. J.; McGuinness, P. D.; Asano, O.; Wang, Y.; Mullarkey, M. A.; Perez, M.; Hawkins, L. D.; Blythe, T. A.; Dubuc, G. R.; Robidoux, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 3637–3638.
[7] Christ, W. J.; Asano, O.; Robidoux, A. L. C.; Perez, M.; Wang, Y.; Dubuc, G. R.; Gavin, W. E.; Hawkins, L. D.; McGuinness, P. D.; Mullarkey, M. A.; Lewis, M. D.; Kishi, Y.; Kawata, T.; Bristol, J. R.; Rose, J. R.; Rossignol, D. P.; Kobayashi, S.; Hishinuma, I.; Kimura, A.; Asakawa, N.; Katayama, K.; Yamatsu, I. *Science* **1995**, *268*, 80–83.
[8] Matsuura, M.; Kojima, Y.; Kubota, Y.; Yamamoto, A.; Kiso, M.; Hasegawa, A. *FEBS Lett.* **1984**, *167*, 226–230.
[9] (a) Shiozaki, M.; Deguchi, N.; Macindoe, W. M.; Arai, M.; Miyazaki, H.; Mochizuki, T.; Tatsuta, T.; Ogawa, J.; Maeda, H.; Kurakata, S. *Carbohydr. Res.* **1996**, *283*, 27–51;
(b) Shiozaki, M.; Kurakata, S.; Tatsuta, T.; Maeda, H.; Nishijima, M. *Tetrahedron* **1997**, *53*, 16041–16060.
[10] (a) Shiozaki, M.; Kobayashi, Y.; Arai, M.; Ishida, N.; Hiraoka, T.; Nishijima, M.; Kuge, S.; Otsuka, T.; Akamatsu, Y. *Carbohydr. Res.* **1991**, *222*, 69–82;
(b) Shiozaki, M.; Kobayashi, Y.; Ishida, N.; Arai, M.; Hiraoka, T.; Nishijima, M.; Kuge, S.; Otsuka, T.; Akamatsu, Y. *Carbohydr. Res.* **1991**, *222*, 57–68.
[11] Shiozaki, M.; Kobayashi, Y.; Arai, M.; Watanabe, T.; Hiraoka, T. *J. Med. Chem.* **1991**, *34*, 2643–2646.
[12] Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Romas, M. *Helv. Chim. Acta* **1991**, *74*, 2073–2077.
[13] (a) Haines, L. M.; Singleton, E. *J. Chem. Soc., Dalton Trans.* **1972**, 1891–1896;
(b) Oltvoort, J. J.; van Boeckel, C. A. A.; de Koning, J. H.; van Boom, J. H. *Synthesis* **1981**, 305–308.
[14] Hoffmann, M. G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 2403–2419.
[15] Shiozaki, M.; Mochizuki, T.; Wakabayashi, T.; Kurakata, S.; Tatsuta, T.; Nishijima, M. *Tetrahedron Lett.* **1996**, *37*, 7271–7274.
[16] Shiozaki, M.; Miyazaki, H.; Arai, M.; Hiraoka, T.; Kurakata, S.; Tatsuta, T.; Ogawa, J.; Nishijima, M.; Akamatsu, Y. *Biosci. Biotech. Biochem.* **1995**, *59*, 501–506.
[17] Shiozaki, M.; Kobayashi, Y.; Ishida, N.; Arai, M.; Hiraoka, T.; Nishijima, M.; Kuge, S.; Otsuka, T.; Akamatsu, Y. *Carbohydr. Res.* **1991**, *222*, 57–68.