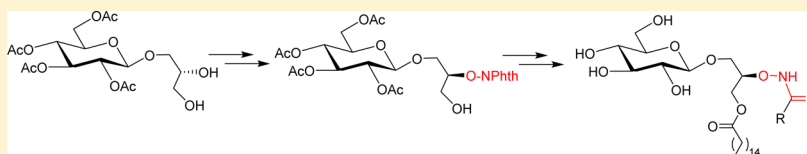


Synthesis of *N*-Oxyamide-Linked Neoglycolipids

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S Supporting Information



ABSTRACT: *N*-Oxyamide-containing compounds have shown improved metabolic stability and interesting secondary structures due to the good hydrogen bond-donating property of *N*-oxyamide. β -Glucolipids linked by the *N*-oxyamide bond have been successfully synthesized as novel mimics of glyco glycerolipids and glycosphingolipids.

As part of the glycoconjugate family, glycolipids are implicated in a variety of important biological phenomena such as cell–cell interactions, viral and bacterial infections, immune response, signal transduction, cell proliferation, etc. Glycolipids are composed of one or several monosaccharide residues bound by a glycosidic linkage to a hydrophobic moiety like an acylglycerol (termed glyco glycerolipids, GGLs) or a ceramide (glycosphingolipids, GSLs). GGLs and mammalian GSLs begin with either glucose or galactose attached in α - or β -linkage to the 1-hydroxyl of mono/diacylglycerol or ceramide. Ceramides consist of fatty-amide-linked sphingosine (a long-chain amino alcohol). GGLs mainly exist in plants, algae, and bacteria. They have shown interesting anti-tumor-promoting activities.¹ Inhibitory effects on DNA polymerase, human Myt1-kinase, human lanosterol synthase, and antitumor activities have also been reported.² Bacterial glyco glycerolipid BbGL2 has been shown to induce natural killer T cell (NKT cell) proliferation and cytokine production,³ an important property known for GSL agelashins.⁴ As a most abundant and diverse class of glycolipids in animals, GSLs are found in the plasma membrane of cells and play key roles in cell–cell interactions and protein activities.⁵ As immunostimulating agents,⁶ these glycolipids have attracted intensive research interest, in particular, since the discovery of a potent NKT immune cell activation effect of synthetic α -galactosyl ceramide (α -GalCer or KRN7000).⁷ The design of glycolipid mimics has become a useful strategy in drug discovery. Modifications have been made on the sugar part, on the configuration and nature of the anomeric bond (C-, S-glycoside), on the polar moiety of the ceramide or glycerol, or on the lipid chains.⁷ Triazole-containing glycolipids have also been reported, showing a comparable stimulatory effect on cytokine production as α -GalCer.⁸ The ability to undergo extensive interlipid hydrogen bonding has been considered to be fundamental for the functions of glycolipids in membranes, through imparting structural integrity to the membranes of the organisms.⁹ *N*-Oxyamide bonds in peptide¹⁰ and sugar derivatives¹¹ have been found to be good hydrogen-bond-donating groups due to lone pair repulsion between adjacent nitrogen and oxygen. They can

easily organize into turns and helices through intramolecular hydrogen bond formation. This unique property makes *N*-oxyamide linkage attractive for the modification of biomolecules. Furthermore, *N*-oxyamides are resistant to chemical and enzymatic hydrolysis.¹² With a continuing interest in *N*-oxyamide-containing biomolecules,¹³ we designed the *N*-oxyamide-linked glycolipids, by replacing the ester function in GGLs by a *N*-oxyamide (Figure 1). These kinds of glycolipids,

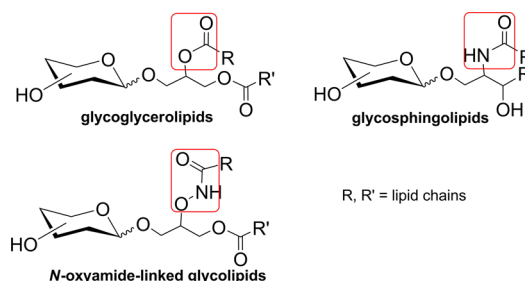
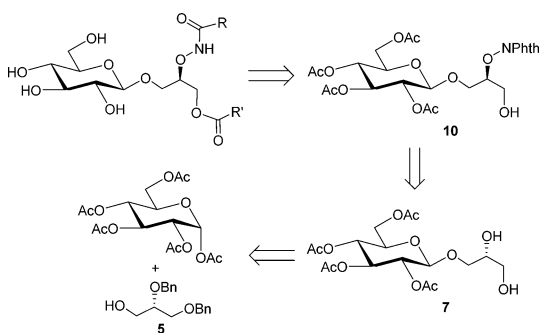
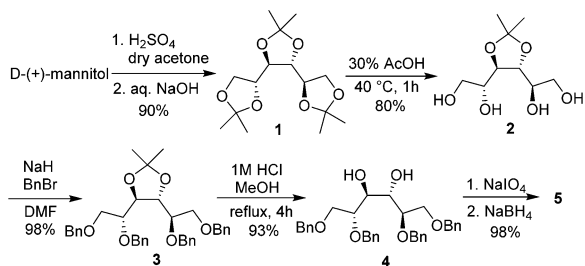


Figure 1. Structure of GGLs, GSLs, and *N*-oxyamide-linked glycolipids.

never reported in the literature, could be considered as analogues of both GGL and GSL (Figure 1). Only one *N*(OMe)-glycoceramide has very recently been reported showing potent inhibitory activity against recombinant endoglycoceramidase II.¹⁴ Because the β -linked glucose unit widely exists in natural glycolipids, we investigated first the synthesis of *O*-amino β -glucoglycerol and its application to *N*-oxyamide-containing glycolipids.

The synthetic strategy toward *N*-oxyamide-containing glycolipids would be the stereoselective synthesis of *O*-amino β -glucoglycerol **10** through Mitsunobu reaction on glycosylglycerol **7**, which can be obtained via glycosylation with

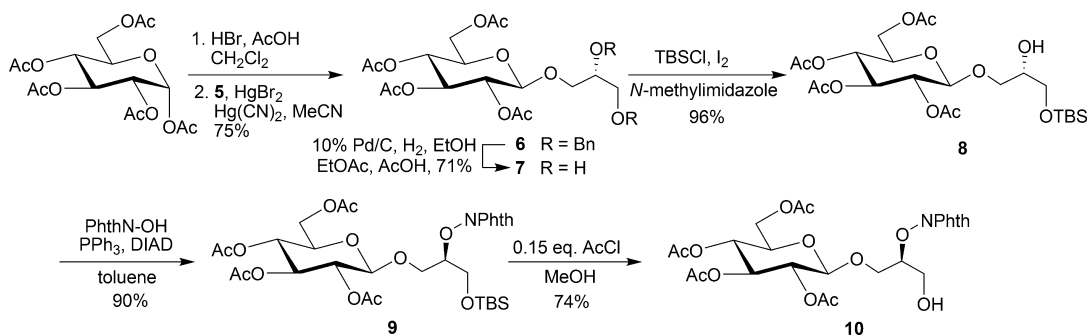
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Scheme 1. Retrosynthesis of *N*-Oxyamide-Linked GlycolipidsScheme 2. Preparation of 1,2-Di-*O*-benzyl-*sn*-glycerol 5

dibenzylated glycerol **5**, followed by introduction of lipid chains and final deprotection (Scheme 1).

The required glycerol **5**¹⁵ was prepared in 64% overall yield from D-(+)-mannitol, as outlined in Scheme 2. It is important to control the reaction conditions to convert triacetone **1** to 3,4-isopropylidene-D-mannitol **2**.¹⁵ Deprotection with 70% AcOH at 40 °C¹⁵ gave 50% yield of **2**. The best result (80%) was obtained using 30% AcOH¹⁷ at 40 °C during 1 h.

Glycosylation of glycerol **5** was realized with per-*O*-acetyl- α -D-glucopyranosyl bromide generated from D-glucose pentaacetate (Scheme 3). Dropwise addition of glycosyl bromide in dry acetonitrile into the solution containing compound **5**, HgBr₂, and Hg(CN)₂ is crucial to prepare β -glucoglycerol **6**¹⁵ in good yield (75% for two steps). After debenzylation, regioselective silylation of **7**¹⁸ required the presence of *N*-methylimidazole and iodine¹⁹ as promoter to ensure good reactivity and regioselectivity. The oxyamine function was then introduced via Mitsunobu reaction with PhthNOH to afford compound **9** with inversion of configuration.²⁰ Removal of the TBS group was achieved with catalytic AcCl in MeOH in 72% yield, instead of TBAF which deprotected acetyl groups, leading to a mixture of products.

Scheme 3. Synthesis of *O*-Amino β -Glucoglycerol **10**

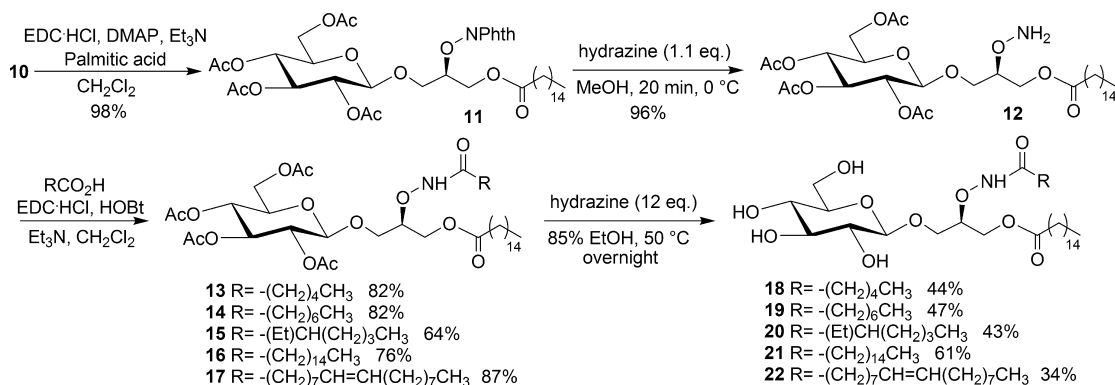
Next, esterification of the *O*-phthaloylamino β -glucoglycerol **10** with palmitic acid using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC) furnished the glucolipid **11** in excellent yield (98%) (Scheme 4). Hydrazinolysis under mild conditions (1.1 equiv, 20 min at 0 °C) deprotected selectively the phthaloyl group. Coupling of the resulting oxyamine **12** with different fatty acids led successfully to the neoglycolipids **13–17** in 64–87% yield. The NH of the *N*-oxyamide bond appeared between 8.81 and 8.87 ppm on the ¹H NMR in CDCl₃. Final deacetylation was realized with hydrazine at 50 °C in EtOH to give the target compounds **18–22**. Due to their amphiphilic nature, some glycolipids are lost during the workup, leading to low yields (34–61%).

In conclusion, we have achieved the first synthesis of *N*-oxyamide-linked β -glucolipids from readily available D-glucose pentaacetate and D-mannitol via the *O*-amino β -glucoglycerol **10** as a versatile intermediate. Different lipid chains could be easily introduced on hydroxyl and oxyamine functions to access a variety of glycolipid structures. Synthesis of 1,2-di-*O*-benzyl-*sn*-glycerol **5** has also been optimized.

EXPERIMENTAL SECTION

3,4-*O*-Isopropylidene-D-mannitol (2). To a stirred solution of 30% aq AcOH (200 mL) was added D-mannitol triacetone **1** (10 g, 33.1 mmol). The mixture was stirred at 40 °C. After 1 h, the solution was evaporated and residual AcOH removed by repeated coevaporation with toluene. Dry acetone was added, and the mixture was thoroughly stirred with excess anhyd K₂CO₃ and then filtered. The insoluble material (remaining mannitol) was washed with acetone, and the combined filtrates were evaporated. The residue was then dissolved in a small volume of EtOAc and allowed to crystallize at rt to give pure product (5.89 g, 80.1%): *R*_f = 0.43 (CH₂Cl₂/MeOH 10/1); ¹H NMR (400 MHz, acetone-*d*₆) δ 4.73 (s, 2H, 2 \times OH), 3.96–3.90 (m, 2H, 2 \times CH), 3.77–3.54 (m, 8H, 2 \times CH, 2 \times CH₂, 2 \times OH), 1.32 (s, 6H, 2 \times CH₃); ¹³C NMR (100 MHz, acetone-*d*₆) δ 109.8 (C_q), 80.8, 74.2 (CH); 64.6 (CH₂), 27.3 (CH₃).

1,2,5,6-Tetra-*O*-benzyl-3,4-*O*-isopropylidene-D-mannitol (3). NaH (60%, 6.36 g, 159 mmol) was added to a stirred solution of **2** (5.88 g, 26.49 mmol) in dry DMF (200 mL). The suspension was stirred for 0.5 h at 0 °C in an ice bath. BnBr (15.11 mL, 127 mmol) was then added, and the stirring continued at rt overnight. Ice was added to destroy the excess NaH, and the solution was then concentrated, diluted with saturated aq NH₄Cl, and the product extracted with EtOAc (200 mL). The extract was washed with water and brine, dried over MgSO₄, and evaporated. Purification by column chromatography (petroleum ether/EtOAc 15/1) afforded compound **3** as a colorless syrup (15.10 g, 98%): *R*_f = 0.31 (petroleum ether/EtOAc 10/1); ¹H NMR (400 MHz, CDCl₃) δ 7.41–7.17 (m, 20H, H-Ph), 4.73 (d, *J* = 11.8 Hz, 2H, 2 \times CH), 4.57 (d, *J* = 11.7 Hz, 2H, 2 \times CH), 4.48–4.46 (m, 4H, 2 \times CH₂), 4.24–4.15 (m, 2H, 2 \times CH), 3.81–3.55 (m, 6H, 2 \times CH₂, 2 \times CH), 1.35 (s, 6H, 2 \times CH₃); ¹³C

Scheme 4. Synthesis of *N*-Oxamide-Linked Neoglycolipids

NMR (100 MHz, CDCl_3) δ 138.6, 138.5 (C_q); 128.5, 128.4, 128.0, 127.7, 127.6 (CH-Ph); 109.9 (C_q); 79.4, 78.6 (CH); 73.4, 72.9, 70.7 (CH_2); 27.3 (CH_3).

1,2,5,6-Tetra-O-benzyl-D-mannitol (4). Compound 3 (15.10 g, 25.96 mmol) was treated with 1 M aq HCl/MeOH (1:9, v/v, 250 mL) under reflux for 4 h, when TLC showed a new single spot. Excess solid NaHCO_3 was added, and the solution evaporated to give an oil which was dissolved in EtOAc (300 mL), dried over MgSO_4 , and evaporated. Purification by column chromatography (petroleum ether/EtOAc 5/1) afforded compound 4 (13.08 g, 93%) as a colorless syrup: R_f = 0.12 (petroleum ether/EtOAc 5/1); ^1H NMR (400 MHz, CDCl_3) δ 7.34–7.26 (m, 20H, H-Ph), 4.72 (d, J = 11.5 Hz, 2H, 2 \times CH), 4.59 (d, J = 11.5 Hz, 2H, 2 \times CH), 4.54 (s, 4H, 2 \times CH_2), 3.96 (m, 2H, 2 \times CH), 3.80–3.65 (m, 6H, 2 \times CH_2 , 2 \times CH), 3.04 (s, 1H, OH), 3.02 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl_3) δ 138.3, 138.1 (C_q); 128.5, 128.1, 127.9, 127.8 (CH-Ph); 79.3 (CH); 73.6, 73.2, 70.3 (CH_2); 70.1 (CH).

1,2-Di-O-benzyl-sn-glycerol (5). To a solution of 4 (14.10 g, 26 mmol) in MeOH (250 mL) was added an aq solution of NaIO_4 (8.56 g, 40 mmol in 150 mL of water). The reaction mixture was stirred for 3 h at rt, after which time TLC analysis revealed the oxidation to be complete (R_f = 0.52, petroleum ether/EtOAc 3/1). The reaction mixture was diluted with MeOH (200 mL) and cooled. The precipitate was filtered off, and to the filtrate was added NaBH_4 (9.84 g, 260 mmol). After 1 h, the reaction mixture was treated with AcOH, and the solution evaporated to a small volume which was diluted in CH_2Cl_2 (300 mL), dried over MgSO_4 , and concentrated. Purification by column chromatography (petroleum ether/EtOAc 3/1) afforded compound 5 (13.87 g, 98%) as a colorless syrup: R_f = 0.24 (petroleum ether/EtOAc 3/1); ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.26 (m, 10H, H-Ph), 4.74–4.53 (m, 4H, 2 \times CH_2), 3.79–3.57 (m, 5H, 2 \times CH_2 , CH), 2.05 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl_3) δ 138.4, 138.1 (C_q); 128.6, 128.6, 128.0, 127.9, 127.8 (CH-Ph); 78.1 (CH); 73.7, 72.3, 70.3, 63.0 (CH_2).

(2R)-1,2-Di-O-benzyl-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (6). To a solution of α -D-glucose pentaacetate (2 g, 5.12 mmol) in CH_2Cl_2 (15 mL) was added HBr (33% in AcOH, 7 mL, 41 mmol) at 0 °C. The mixture was stirred at rt under Ar for 6 h, and then the solution was neutralized with aq NaHCO_3 . The resulting 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide was extracted with CH_2Cl_2 (100 mL), dried over MgSO_4 , and evaporated to give a syrup. To a solution of 1,2-di-O-benzyl-sn-glycerol (5) (1.41 g, 5.2 mmol), HgBr_2 (0.94 g, 2.6 mmol), and $\text{Hg}(\text{CN})_2$ (0.66 g, 2.6 mmol) in dry MeCN (20 mL) was added dropwise over a period of 1 h a solution of glycosyl bromide in MeCN (10 mL). The reaction solution was stirred at rt overnight and then concentrated to an oil which was dissolved in CH_2Cl_2 (100 mL) and washed with saturated aq KBr (2 \times 30 mL) and water (30 mL). The dried (MgSO_4) organic layer was concentrated. Purification by column chromatography (petroleum ether/EtOAc 3/1) afforded compound 6 (2.30 g, 75%) as a colorless paste: R_f = 0.39 (petroleum ether/EtOAc 2/1); ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.28 (m, 10H, H-Ph), 5.18 (t, J = 9.4 Hz, 1H, H-3'), 5.09 (t, J = 9.7 Hz, 1H, H-4'), 5.00 (dd, J = 9.5, 8.2 Hz, 1H, H-2'), 4.65 (s, 2H, CH_2), 4.57–4.50 (m, 3H, H-1', CH_2), 4.28–4.09

(m, 2H, H-6'), 3.99–3.69 (m, 3H, H-2,3), 3.65 (ddd, J = 10.0, 4.5, 2.3 Hz, 1H, H-5'), 3.59–3.57 (m, 2H, H-1), 2.07, 2.04, 2.03, 2.01 (4 \times s, 12H, 4 \times OAc); ^{13}C NMR (100 MHz, CDCl_3) δ 170.9, 170.5, 169.6, 169.5 ($\text{C}=\text{O}$); 138.5, 138.3 (C_q); 128.6, 128.5 (CH-Ph); 101.2 (C-1'), 76.8 (CH), 73.6 (CH_2), 72.9 (C-3'), 72.3 (CH_2), 71.9 (C-5'), 71.4 (C-2'), 69.8, 69.4 (CH_2); 68.5 (C-4'), 62.0 (C-6'), 20.9, 20.8 (OAc).

(2R)-1-O-(2',3',4',6'-Tetra-O-acetyl- β -D-glucopyranosyl)-glycerol (7). A mixture of 6 (12 g, 20 mmol) and 10% Pd/C (1.8 g) in EtOAc (100 mL) containing 5 mL each of EtOH and AcOH was vigorously shaken under H_2 at rt overnight. The catalyst was filtered off, and the filtrate evaporated. Purification by column chromatography (CH_2Cl_2 /MeOH 25/1) afforded compound 7 (6 g, 71%) as a white solid: R_f = 0.12 (CH_2Cl_2 /MeOH 25/1); ^1H NMR (400 MHz, CDCl_3) δ 5.22 (t, J = 9.6 Hz, 1H, H-3'), 5.11–5.04 (m, 1H, H-4'), 5.04–4.97 (m, 1H, H-2'), 4.55 (d, J = 7.8 Hz, 1H, H-1'), 4.25–4.16 (m, 2H, H-6'), 3.89–3.79 (m, 3H, H-2,3), 3.77–3.57 (m, 3H, H-1,5'), 2.32 (s, 2H, 2 \times OH), 2.11, 2.07, 2.04, 2.01 (4 \times s, 12H, 4 \times OAc); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 170.3, 169.7, 169.5 ($\text{C}=\text{O}$); 101.4 (C-1'), 72.6 (C-3'), 72.0 (C-5'), 71.3 (C-2'), 70.5 (CH), 68.4 (C-4'), 63.4, 61.9 (CH_2); 20.8, 20.7 (OAc).

1-O-tert-Butyldimethylsilyl-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)-sn-glycerol (8). To a solution of 7 (2 g, 4.74 mmol), *N*-methylimidazole (1.14 mL, 14.22 mmol), and iodine (3.61 g, 14.22 mmol) in anhyd THF (20 mL) under Ar at 0 °C was added TBSCl (0.86 g, 5.69 mmol). The reaction mixture was stirred for 20 min at 0 °C and then quenched with saturated aq $\text{Na}_2\text{S}_2\text{O}_3$ and diluted with EtOAc (50 mL). The aqueous layers were extracted with EtOAc (2 \times 50 mL). The combined organic layers were dried over MgSO_4 , filtered, concentrated, and purified by column chromatography over silica gel (CH_2Cl_2 /MeOH 100/1) to afford 8 (2.43 g, 95.7%) as a yellowish paste: R_f = 0.74 (CH_2Cl_2 /MeOH 100/3); $[\alpha]_D^{25}$ –9.7 (c 0.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 5.20 (dd, J = 12.0, 6.9 Hz, 1H, H-3'), 5.05 (t, J = 9.7 Hz, 1H, H-4'), 4.98 (dd, J = 9.6, 8.1 Hz, 1H, H-2'), 4.54 (d, J = 7.9 Hz, 1H, H-1'), 4.25–4.11 (m, 2H, H-6'), 3.82–3.68 (m, 4H, H-2,3,5'), 3.62–3.58 (m, 2H, H-1), 2.08, 2.04, 2.01, 1.99 (4 \times s, 12H, 4 \times OAc), 0.88 (s, 9H, *t*-Bu), 0.05 (s, 6H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 170.7, 170.3, 169.5, 169.4 ($\text{C}=\text{O}$); 101.4 (C-1'), 72.8 (C-3'), 71.9 (C-5'), 71.7 (CH_2), 71.4 (C-2'), 70.5 (CH), 68.5 (C-4'), 63.7, 62.0 (CH_2); 25.9, 20.8, 20.7 (CH_3); 18.3 (C_q , *t*-Bu), –5.4 (CH_3 , $\text{Si}(\text{CH}_3)_2$); HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{41}\text{O}_{12}\text{Si}$ 537.2367; found 537.2362 (all HRMS spectra were recorded on a Q-TOF MaXis using standard conditions).

(2R)-2-O-Phthalimido-1-O-tert-butyldimethylsilyl-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (9). To a solution of 8 (2.10 g, 3.91 mmol) in toluene (60 mL) were added Ph_3P (3.08 g, 11.7 mmol), PhthNOH (1.91 g, 11.7 mmol), and DIAD (2.30 mL, 11.7 mmol) at 0 °C. The resulting mixture was stirred at rt for 2 h under Ar and then extracted with EtOAc (3 \times 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO_4 , filtered, evaporated, and purified by column chromatography over silica gel (petroleum ether/EtOAc 3/1) to afford 9 (2.39 g, 90%) as a paste: R_f = 0.53 (petroleum ether/EtOAc 1/1); $[\alpha]_D^{25}$ –13.3 (c 0.1,

CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.83–7.70 (m, 4H, Phth), 5.16 (t, J = 9.6 Hz, 1H, H-3'), 5.02 (t, J = 9.8 Hz, 1H, H-4'), 4.92 (dd, J = 9.4, 8.1 Hz, 1H, H-2'), 4.66 (d, J = 7.8 Hz, 1H, H-1'), 4.39–4.41 (m, 1H, H-2), 4.21 (dd, J = 12.3, 4.8 Hz, 1H, H-6'a), 4.15–4.06 (m, 2H, H-3a,6'b), 3.93 (dd, J = 11.7, 6.2 Hz, 1H, H-3b), 3.89 (d, J = 4.7 Hz, 2H, H-1), 3.69 (ddd, J = 10.0, 4.7, 2.2 Hz, 1H, H-5'), 2.06, 2.01, 1.99, 1.96 (4 \times s, 12H, 4 \times OAc), 0.77 (s, 9H, *t*-Bu), –0.02, –0.03 (2 \times s, 6H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 170.4, 169.6, 169.6 (C=O), 163.7 (C=O, Phth); 134.5, 129.0 (C_q), 123.6 (Phth), 100.8 (C-1'), 87.0 (C-2), 73.0 (C-3'), 71.8 (C-5'), 71.2 (C-2'), 68.4 (C-4'), 68.0, 62.0, 61.9 (CH_2); 25.8, 20.8, 20.8, 20.7 (CH_3); 18.2 (C_q , *t*-Bu), –5.6 (CH_3 , $\text{Si}(\text{CH}_3)_2$); HRMS (ESI) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{31}\text{H}_{44}\text{NO}_{14}\text{Si}$ 682.2531; found 682.2526.

2-O-Phthalimido-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)-sn-glycerol (10). To a solution of **9** (1.0 g, 1.47 mmol) in MeOH (30 mL) was added AcCl (16 μL , 0.22 mmol) at 0 $^\circ\text{C}$. The resulting mixture was stirred at rt for 2 h under Ar and then extracted with CH_2Cl_2 (3 \times 30 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, evaporated, and purified by column chromatography over silica gel (petroleum ether/EtOAc 1/1) to give **10** (0.59 g, 72%) as a white powder. mp 72 $^\circ\text{C}$; R_f = 0.23 (petroleum ether/EtOAc 1/1); $[\alpha]_D^{25}$ –17.3 (c 0.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.87–7.74 (m, 4H, Phth), 5.22–5.15 (m, 1H, H-3'), 5.03 (t, J = 10.1 Hz, 1H, H-4'), 4.97 (m, 1H, H-2'), 4.64 (d, J = 7.8 Hz, 1H, H-1'), 4.32–4.26 (m, 1H, H-2), 4.22 (dd, J = 12.3, 4.9 Hz, 1H, H-6'a), 4.14–4.06 (m, 2H, H-3a,6'b), 4.01 (dd, J = 11.6, 6.3 Hz, 1H, H-3b), 3.83–3.66 (m, 3H, H-1,5'), 2.07, 2.04, 1.99, 1.97 (4 \times s, 12H, 4 \times OAc); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 170.3, 169.6, 169.5 (C=O), 164.6 (C=O, Phth); 135.0, 128.8 (C_q); 124.0 (Phth), 100.9 (C-1'), 88.1 (CH), 72.8 (C-3'), 71.9 (C-5'), 71.1 (C-2'), 68.5 (C-4'), 67.8, 61.9, 60.4 (CH_2); 20.8, 20.7, 20.7 (OAc); HRMS (ESI) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{25}\text{H}_{30}\text{NO}_{14}$ 568.1666; found 568.1661.

(2R)-1-O-Palmitoyl-2-O-phthalimido-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (11). To a solution of palmitic acid (0.26 g, 1.02 mmol) in anhyd CH_2Cl_2 (10 mL) were added DMAP (0.25 g, 2.04 mmol), EDC·HCl (0.39 g, 2.04 mmol), and Et_3N (0.28 mL, 2.04 mmol) under Ar at 0 $^\circ\text{C}$. After the mixture was stirred for 20 min, compound **10** (0.58 g, 1.02 mmol) was added. The resulting mixture was stirred at rt overnight. The solution was diluted with EtOAc (30 mL), washed with aq HCl (1 N, 2 \times 15 mL), saturated aq NaHCO_3 (2 \times 15 mL), and brine (15 mL), dried over MgSO_4 , filtered, evaporated, and purified by column chromatography over silica gel (petroleum ether/EtOAc 2/1) to afford **11** (1.05 g, 98.6%) as a white solid: mp 65 $^\circ\text{C}$; R_f = 0.54 (petroleum ether/EtOAc 1/1); $[\alpha]_D^{25}$ –11.0 (c 0.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.87–7.74 (m, 4H, Phth), 5.20 (t, J = 9.5 Hz, 1H, H-3'), 5.06 (t, J = 9.7 Hz, 1H, H-4'), 4.96 (dd, J = 9.2, 7.8 Hz, 1H, H-2'), 4.68 (d, J = 8.2 Hz, 1H, H-1'), 4.62–4.53 (m, 1H, H-2), 4.44–4.31 (m, 2H, H-3), 4.25 (dd, J = 12.3, 4.8 Hz, 1H, H-6'a), 4.18–4.07 (m, 2H, H-1a,6'b), 4.01 (dd, J = 11.8, 5.8 Hz, 1H, H-1b), 3.73 (ddd, J = 9.9, 4.7, 2.4 Hz, 1H, H-5'), 2.38–2.24 (m, 2H, CH_2), 2.10, 2.05, 2.02, 1.99 (4 \times s, 12H, 4 \times OAc), 1.65–1.52 (m, 2H, CH_2), 1.35–1.20 (m, 24H, 12 \times CH_2), 0.88 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 173.5, 170.8, 170.4, 169.6, 169.5, 163.6 (C=O); 134.8, 128.9 (C_q); 123.8 (CH), 100.9 (C-1'), 84.5 (CH), 72.9 (C-3'), 72.0 (C-5'), 71.1 (C-2'), 68.5 (C-4'), 67.8, 62.4, 62.0, 34.1, 32.1, 29.8, 29.8, 29.6, 29.5, 29.4, 29.3, 24.9, 22.8 (CH_2); 20.9, 20.8, 20.7, 14.3 (CH_3); HRMS (ESI) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{41}\text{H}_{60}\text{NO}_{15}$ 806.3963; found 806.3957.

(2R)-2-O-Amino-1-O-palmitoyl-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (12). To a solution of **11** (0.38 g, 0.47 mmol) in MeOH (3 mL) was added $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (25.2 μL , 0.52 mmol) at 0 $^\circ\text{C}$. The resulting mixture was stirred at 0 $^\circ\text{C}$ for 20 min under Ar and then extracted with CH_2Cl_2 (3 \times 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, evaporated, and purified by column chromatography over silica gel (petroleum ether/EtOAc 3/2) to afford **12** (0.31 g, 96%) as a paste: R_f = 0.40 (petroleum ether/EtOAc 1/1); $[\alpha]_D^{25}$ –46.7 (c 0.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 5.22 (t, J = 8.7 Hz, 1H, H-3'), 5.06 (t, J = 9.6 Hz, 1H, H-4'), 4.96 (dd, J = 9.6, 7.8 Hz, 1H, H-2'), 4.57 (d, J = 7.8 Hz, 1H, H-1'), 4.39–4.06 (m, 4H, H-3,6'), 4.04–3.90

(m, 2H, H-1a,2), 3.79–3.65 (m, 2H, H-1b,5'), 2.32 (t, J = 7.5 Hz, 2H, CH_2), 2.09, 2.07, 2.03, 2.01 (4 \times s, 12H, 4 \times OAc), 1.68–1.57 (m, 2H, CH_2), 1.39–1.20 (m, 24H, 12 \times CH_2), 0.88 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 173.9, 170.8, 170.4, 169.5 (C=O); 101.2 (C-1'), 80.1 (CH), 72.8 (C-3'), 72.0 (C-5'), 71.3 (C-2'), 68.5 (C-4'), 68.0, 62.0, 61.9, 34.3, 32.1, 29.8, 29.6, 29.5, 29.4, 29.3, 25.1, 22.8 (CH_2); 20.9, 20.8, 20.7, 14.2 (CH_3); HRMS (ESI) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{33}\text{H}_{58}\text{NO}_{13}$ 676.3908; found 676.3903.

General Procedure A for N-Oxyamide Formation. Synthesis of (2R)-2-O-Acylamino-1-O-palmitoyl-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (13–17). To a solution of carboxylic acid (0.25 mmol) in anhyd CH_2Cl_2 (4 mL) were added HOBt (0.5 mmol), EDC·HCl (0.5 mmol), and Et_3N (0.5 mmol) under Ar at 0 $^\circ\text{C}$. After being stirred for 20 min, the oxyamine **12** (0.25 mmol) was added. The resulting mixture was stirred at rt overnight. The solution was diluted with EtOAc (25 mL), washed with aq HCl (1 N, 2 \times 10 mL), saturated aq NaHCO_3 (2 \times 10 mL), and brine (10 mL), dried over MgSO_4 , filtered, evaporated, and purified by column chromatography over silica gel (petroleum ether/EtOAc 2/1).

(2R)-2-O-Hexanoylamino-1-O-palmitoyl-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (13). From **12** (153 mg, 0.23 mmol) and hexanoic acid, compound **13** was obtained as a paste (145 mg, 82%); R_f = 0.60 (petroleum ether/EtOAc 1/1); $[\alpha]_D^{25}$ –35.7 (c 0.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.83 (s, 1H, NH), 5.24 (t, J = 9.5 Hz, 1H, H-3'), 5.09 (t, J = 9.7 Hz, 1H, H-4'), 5.02 (dd, J = 9.6, 7.8 Hz, 1H, H-2'), 4.57 (d, J = 8.0 Hz, 1H, H-1'), 4.42 (dd, J = 12.2, 3.2 Hz, 1H, H-3a), 4.32–4.09 (m, 4H, H-2,3b,6'), 4.03–3.96 (m, 1H, H-1a), 3.81–3.68 (m, 2H, H-1b,5'), 2.39–2.33 (m, 2H, CH_2), 2.17–2.01 (m, 14H, 4 \times OAc, CH_2), 1.73–1.57 (m, 4H, 2 \times CH_2), 1.39–1.21 (m, 28H, 14 \times CH_2), 0.96–0.86 (m, 6H, 2 \times CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.4, 170.8, 170.3, 169.6 (C=O); 100.7 (C-1'), 82.2 (CH), 72.5 (C-3'), 72.1 (C-5'), 71.5 (C-2'), 68.4 (C-4'), 67.9, 61.8, 61.4, 34.2, 33.2, 32.1, 31.5, 29.8, 29.8, 29.6, 29.5, 29.4, 29.2, 25.2, 25.0, 22.8, 22.5 (CH_2); 20.9, 20.7, 14.3, 14.1 (CH_3); HRMS (ESI) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{39}\text{H}_{68}\text{NO}_{14}$ 774.4640; found 774.4634.

(2R)-2-O-Octanoylamino-1-O-palmitoyl-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (14). From **12** (151 mg, 0.22 mmol) and octanoic acid, compound **14** was obtained as a paste (147 mg, 82%); R_f = 0.62 (petroleum ether/EtOAc 1/1); $[\alpha]_D^{25}$ –49.3 (c 0.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 1H, NH), 5.24 (t, J = 9.4 Hz, 1H, H-3'), 5.09 (t, J = 9.6 Hz, 1H, H-4'), 5.02 (t, J = 8.8 Hz, 1H, H-2'), 4.57 (d, J = 7.8 Hz, 1H, H-1'), 4.42 (d, J = 10.0 Hz, 1H, H-3a), 4.31–4.09 (m, 4H, H-2,3b,6'), 4.03–3.96 (m, 1H, H-1a), 3.79–3.68 (m, 2H, H-1b,5'), 2.36 (t, J = 7.2 Hz, 2H, CH_2), 2.16–2.00 (m, 14H, 4 \times OAc, CH_2), 1.68–1.58 (m, 4H, 2 \times CH_2), 1.40–1.20 (m, 32H, 16 \times CH_2), 0.93–0.84 (m, 6H, 2 \times CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.4, 170.8, 170.4, 170.3, 169.6 (C=O); 100.7 (C-1'), 82.5 (CH), 72.5 (C-3'), 72.1 (C-5'), 71.5 (C-2'), 68.4 (C-4'), 67.9, 61.8, 61.4, 34.2, 33.2, 32.1, 31.8, 29.8, 29.6, 29.5, 29.4, 29.2, 29.1, 25.5, 25.0, 22.8, 22.7 (CH_2); 20.9, 20.7, 14.3 (CH_3); HRMS (ESI) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{41}\text{H}_{72}\text{NO}_{14}$ 802.4953; found 802.4947.

(2R)-2-O-(2-Ethylhexanoyl)amino-1-O-palmitoyl-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (15). From **12** (151 mg, 0.22 mmol) and 2-ethylhexanoic acid, compound **15** was obtained as a paste (114 mg, 64%); R_f = 0.47 (petroleum ether/EtOAc 1/1); $[\alpha]_D^{25}$ –38.0 (c 0.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.87 (s, 1H, NH), 5.25 (t, J = 9.4 Hz, 1H, H-3'), 5.09 (t, J = 9.7 Hz, 1H, H-4'), 5.01 (t, J = 8.7 Hz, 1H, H-2'), 4.57 (d, J = 7.7 Hz, 1H, H-1'), 4.47–4.39 (m, 1H, H-3a), 4.31–4.10 (m, 4H, H-2,3b,6'), 4.03–3.96 (m, 1H, H-1a), 3.78–3.69 (m, 2H, H-1b,5'), 2.36 (t, J = 7.2 Hz, 2H, CH_2), 2.10, 2.09, 2.04, 2.02 (4 \times s, 12H, 4 \times OAc), 1.95–1.85 (m, 1H, CH), 1.69–1.57 (m, 4H, 2 \times CH_2), 1.52–1.39 (m, 2H, CH_2), 1.37–1.20 (m, 28H, 14 \times CH_2), 0.95–0.84 (m, 9H, 3 \times CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.4, 173.7, 170.8, 170.4, 170.2, 169.6 (C=O); 100.7 (C-1'), 82.2 (CH), 72.5 (C-3'), 72.0 (C-5'), 71.5 (C-2'), 68.3 (C-4'), 67.9, 61.8, 61.3 (CH_2); 45.7 (CH), 34.3, 34.2, 32.2, 32.0, 29.8, 29.6, 29.5, 29.4, 29.2, 25.9, 24.9, 22.8 (CH_2); 20.9, 20.8, 20.7, 14.2, 14.1, 12.1 (CH_3); HRMS (ESI) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{41}\text{H}_{72}\text{NO}_{14}$ 802.4953; found 802.4947.

(2R)-1-O-Palmitoyl-2-O-palmitoylamino-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (16). From **12** (189 mg, 0.28 mmol) and palmitic acid, compound **15** was obtained as a white solid (192 mg, 76%): mp 74 °C: R_f = 0.57 (petroleum ether/EtOAc 1/1); $[\alpha]_D$ –42.3 (c 0.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.86 (s, 1H, NH), 5.24 (t, J = 9.5 Hz, 1H, H-3'), 5.09 (t, J = 9.7 Hz, 1H, H-4'), 5.02 (t, J = 9.6, 7.8 Hz, 1H, H-2'), 4.57 (d, J = 7.9 Hz, 1H, H-1'), 4.42 (dd, J = 12.2, 3.3 Hz, 1H, H-3a), 4.32–4.08 (m, 4H, H-2,3b,6'), 4.03–3.96 (m, 1H, H-1a), 3.78–3.69 (m, 2H, H-1b,5'), 2.36 (t, J = 7.5 Hz, 2H, CH₂), 2.18–2.01 (m, 14H, 4 \times OAc, CH₂), 1.68–1.58 (m, 4H, 2 \times CH₂), 1.40–1.22 (m, 48H, 24 \times CH₂), 0.93–0.81 (m, 6H, 2 \times CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 171.2, 170.8, 170.2, 169.5 (C=O); 100.7 (C-1'), 82.1 (CH), 72.5 (C-3'), 72.1 (C-5'), 71.4 (C-2'), 68.4 (C-4'), 67.8, 61.8, 61.3, 34.2, 33.3, 32.0, 29.8, 29.6, 29.5, 29.4, 29.2, 25.5, 24.9, 22.8 (CH₂); 20.8, 20.7, 14.2 (CH₃); HRMS (ESI) m/z [M + H]⁺ calcd for C₄₉H₈₈NO₁₄ 914.6205; found 914.6199.

(2R)-2-O-Oleoylamino-1-O-palmitoyl-3-O-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)glycerol (17). From **12** (151 mg, 0.22 mmol) and oleic acid, compound **17** was obtained as a white solid (206 mg, 87%): mp 57 °C: R_f = 0.52 (petroleum ether/EtOAc 1/1); $[\alpha]_D$ –35.3 (c 0.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.83 (s, 1H, NH), 5.43–5.32 (m, 2H, CH=CH), 5.24 (t, J = 9.5 Hz, 1H, H-3'), 5.09 (t, J = 9.7 Hz, 1H, H-4'), 5.02 (dd, J = 9.6, 8.0 Hz, 1H, H-2'), 4.57 (d, J = 7.9 Hz, 1H, H-1'), 4.42 (dd, J = 12.2, 3.3 Hz, 1H, H-3a), 4.32–4.08 (m, 4H, H-2,3b,6'), 4.03–3.96 (m, 1H, H-1a), 3.78–3.69 (m, 2H, H-1b,5'), 2.36 (t, J = 7.5 Hz, 2H, CH₂), 2.20–1.98 (m, 16H, 4 \times OAc, 2 \times CH₂), 1.71–1.57 (m, 4H, 2 \times CH₂), 1.39–1.21 (m, 46H, 23 \times CH₂), 0.95–0.82 (m, 6H, 2 \times CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 170.8, 170.4, 170.3, 169.6 (C=O); 130.1, 129.8 (CH=CH); 100.7 (C-1'), 82.2 (CH), 72.5 (C-3'), 72.1 (C-5'), 71.4 (C-2'), 68.4 (C-4'), 67.8, 61.8, 61.3, 34.2, 33.3, 32.0, 29.9, 29.8, 29.6, 29.5, 29.4, 29.2, 27.3, 25.5, 25.0, 22.8 (CH₂); 20.8, 20.7, 14.3 (CH₃); HRMS (ESI) m/z [M + H]⁺ calcd for C₅₁H₉₀NO₁₄ 940.6361; found 940.6356.

General Procedure B for Deacetylation. Synthesis of (2R)-2-O-acylamino-3-O- β -D-glucopyranosyl-1-O-palmitoylglycerol (18–22). To a solution of acetylated compound (0.1 mmol) in 85% EtOH (5 mL) was added N₂H₄·H₂O (1.2 mmol). The mixture was stirred at 50 °C overnight. The solution was poured into ice-cold brine and extracted with CHCl₃ (3 \times 20 mL). The combined CHCl₃ layers were dried over MgSO₄, filtered, evaporated, and purified by column chromatography over silica gel (CH₂Cl₂/MeOH 30/1 to 20/1).

(2R)-3-O- β -D-Glucopyranosyl-2-O-hexanoylamino-1-O-palmitoylglycerol (18). Deacetylation of **13** (105 mg, 0.14 mmol) led to **18** as a white solid (30 mg, 44% yield): mp 94 °C: R_f = 0.43 (CH₂Cl₂/MeOH 8/1); $[\alpha]_D$ –32.0 (c 0.1, MeOH); ¹H NMR (400 MHz, CD₃OD) δ 4.35–4.20 (m, 3H, H-1',3), 4.19–4.12 (m, 1H, H-2), 4.04 (dd, J = 11.4, 3.9 Hz, 1H, H-1a), 3.86 (d, J = 11.7 Hz, 1H, H-6'a), 3.75 (dd, J = 11.4, 6.1 Hz, 1H, H-1b), 3.67–3.61 (m, 1H, H-6'b), 3.40–3.24 (m, 3H, H-3',4',5'), 3.22–3.15 (m, 1H, H-2'), 2.34 (t, J = 7.4 Hz, 2H, CH₂), 2.07 (t, J = 7.4 Hz, 2H, CH₂), 1.70–1.55 (m, 4H, 2 \times CH₂), 1.45–1.22 (m, 28H, 14 \times CH₂), 0.97–0.85 (m, 6H, 2 \times CH₃); ¹³C NMR (100 MHz, CD₃OD) δ 175.2, 173.2 (C=O); 104.9 (C-1'), 83.7, 78.0, 77.9, 75.0, 71.6 (CH); 69.0, 63.3, 62.7, 34.9, 33.7, 33.1, 32.4, 30.8, 30.6, 30.5, 30.2, 26.3, 25.9, 23.7, 23.4 (CH₂); 14.5, 14.3 (CH₃); HRMS (ESI) m/z [M + H]⁺ calcd for C₃₁H₆₀NO₁₀ 606.4217; found 606.4212.

(2R)-3-O- β -D-Glucopyranosyl-2-O-octanoylamino-1-O-palmitoylglycerol (19). Deacetylation of **14** (95 mg, 0.12 mmol) led to **19** as a white solid (35 mg, 47% yield): mp 96 °C: R_f = 0.26 (CH₂Cl₂/MeOH 10/1); $[\alpha]_D$ –21.7 (c 0.1, MeOH); ¹H NMR (400 MHz, CD₃OD) δ 4.37–4.19 (m, 3H, H-1',3), 4.19–4.12 (m, 1H, H-2), 4.04 (dd, J = 11.4, 3.8 Hz, 1H, H-1a), 3.86 (d, J = 11.6 Hz, 1H, H-6'a), 3.75 (dd, J = 11.4, 6.2 Hz, 1H, H-1b), 3.63 (dd, J = 9.8, 7.2 Hz, 1H, H-6'b), 3.40–3.24 (m, 3H, H-3',4',5'), 3.22–3.16 (m, 1H, H-2'), 2.34 (t, J = 7.4 Hz, 2H, CH₂), 2.07 (t, J = 7.4 Hz, 2H, CH₂), 1.69–1.54 (m, 4H, 2 \times CH₂), 1.48–1.22 (m, 32H, 16 \times CH₂), 1.01–0.81 (m, 6H, 2 \times CH₃); ¹³C NMR (100 MHz, CD₃OD) δ 175.2, 173.2 (C=O); 104.9 (C-1'), 83.7, 78.0, 77.9, 75.0, 71.6 (CH); 69.0, 63.3, 62.7,

34.9, 33.8, 33.1, 32.9, 30.8, 30.6, 30.5, 30.2, 30.2, 26.6, 25.9, 23.8, 23.7 (CH₂); 14.5 (CH₃); HRMS (ESI) m/z [M + H]⁺ calcd for C₃₃H₆₄NO₁₀ 634.4530; found 634.4525.

(2R)-2-O-(2-Ethylhexanoyl)amino-3-O- β -D-glucopyranosyl-1-O-palmitoylglycerol (20). Deacetylation of **15** (85 mg, 0.106 mmol) led to **20** as a paste (29 mg, 43% yield): R_f = 0.39 (CH₂Cl₂/MeOH 10/1); $[\alpha]_D$ –29.7 (c 0.1, MeOH); ¹H NMR (400 MHz, CD₃OD) δ 4.37–4.21 (m, 3H, H-1',3), 4.20–4.12 (m, 1H, H-2), 4.05 (dd, J = 11.1, 3.9 Hz, 1H, H-1a), 3.85 (d, J = 11.7 Hz, 1H, H-6'a), 3.75 (dd, J = 11.3, 6.2 Hz, 1H, H-1b), 3.71–3.60 (m, 1H, H-6'b), 3.44–3.24 (m, 3H, H-3',4',5'), 3.22–3.15 (m, 1H, H-2'), 2.34 (t, J = 7.3 Hz, 2H, CH₂), 2.03–1.90 (m, 1H, CH), 1.70–1.50 (m, 4H, 2 \times CH₂), 1.49–1.17 (m, 30H, 15 \times CH₂), 1.06–0.81 (m, 9H, 3 \times CH₃); ¹³C NMR (100 MHz, CD₃OD) δ 175.7, 175.2 (C=O); 104.9 (C-1'), 83.9, 78.0, 77.9, 75.0, 71.5 (CH); 69.0, 63.2, 62.7 (CH₂); 46.6 (CH), 34.8, 33.3, 33.1, 30.8, 30.6, 30.5, 30.2, 26.9, 25.9, 23.7, 23.7 (CH₂); 14.5, 14.4, 12.4 (CH₃); HRMS (ESI) m/z [M + H]⁺ calcd for C₃₃H₆₄NO₁₀ 634.4530; found 634.4525.

(2R)-3-O- β -D-Glucopyranosyl-1-O-palmitoyl-2-O-palmitoylaminoglycerol (21). Deacetylation of **16** (62 mg, 0.068 mmol) led to **21** as a white solid (31 mg, 61% yield): mp 177 °C: R_f = 0.24 (CH₂Cl₂/MeOH 20/1); $[\alpha]_D$ –14.0 (c 0.1, MeOH); ¹H NMR (400 MHz, CD₃OD) δ 4.39–4.22 (m, 3H, H-1',3), 4.22–4.16 (m, 1H, H-2), 4.08 (dd, J = 11.6, 3.5 Hz, 1H, H-1a), 3.90 (d, J = 12.0 Hz, 1H, H-6'a), 3.78 (dd, J = 11.6, 6.3 Hz, 1H, H-1b), 3.69 (dd, J = 11.8, 5.2 Hz, 1H, H-6'b), 3.43–3.23 (m, 4H, H-2',3',4',5'), 2.37 (t, J = 7.5 Hz, 2H, CH₂), 2.10 (t, J = 7.4 Hz, 2H, CH₂), 1.69–1.58 (m, 4H, 2 \times CH₂), 1.49–1.10 (m, 48H, 24 \times CH₂), 0.96–0.86 (m, 6H, 2 \times CH₃); ¹³C NMR (100 MHz, CD₃OD) δ 175.1, 172.9 (C=O); 104.6 (C-1'), 83.4, 77.5, 74.6, 71.2 (CH); 68.9, 63.0, 62.5, 34.7, 33.6, 32.8, 30.5, 30.3, 30.2, 30.0, 26.3, 25.6, 23.4 (CH₂); 14.4 (CH₃); HRMS (ESI) m/z [M + H]⁺ calcd for C₄₁H₈₀NO₁₀ 746.5782; found 746.5777.

(2R)-3-O- β -D-Glucopyranosyl-2-O-oleoylamino-1-O-palmitoylglycerol (22). Deacetylation of **17** (125 mg, 0.133 mmol) led to **22** as a white solid (35 mg, 34% yield): mp 162 °C: R_f = 0.32 (CH₂Cl₂/MeOH 10/1); $[\alpha]_D$ –18.0 (c 0.1, MeOH); ¹H NMR (400 MHz, CD₃OD) δ 5.32 (s, 2H, CH=CH), 4.37–4.20 (m, 3H, H-1',3), 4.19–4.11 (m, 1H, H-2), 4.04 (d, J = 10.0 Hz, 1H, H-1a), 3.85 (d, J = 11.3 Hz, 1H, H-6'a), 3.79–3.71 (m, 1H, H-1b), 3.68–3.58 (m, 1H, H-6'b), 3.40–3.22 (m, 3H, H-3',4',5'), 3.19 (t, J = 7.9 Hz, 1H, H-2'), 2.40–2.28 (m, 2H, CH₂), 2.14–1.94 (m, 4H, 2 \times CH₂), 1.67–1.52 (m, 4H, 2 \times CH₂), 1.48–1.10 (m, 46H, 23 \times CH₂), 0.97–0.80 (m, 6H, 2 \times CH₃); ¹³C NMR (100 MHz, CD₃OD) δ 175.2, 173.2 (C=O); 130.9, 130.8 (CH=CH); 104.9 (C-1'), 83.7, 78.0, 77.9, 75.0, 71.6 (CH); 69.0, 63.4, 62.7, 34.9, 33.8, 33.1, 30.8, 30.7, 30.5, 30.4, 30.2, 28.2, 26.6, 26.0, 23.8 (CH₂); 14.5 (CH₃); HRMS (ESI) m/z [M + H]⁺ calcd for C₄₃H₈₂NO₁₀ 772.5939; found 772.5933.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ¹H, ¹³C, Dept-135, COSY, and HMQC NMR spectra of all described compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Shirahashi, H.; Murakami, N.; Watanabe, M.; Nagatsu, A.; Sakakibara, J.; Tokuda, H.; Nishino, H.; Iwashima, A. *Chem. Pharm. Bull.* **1993**, *41*, 1664–1666.
- (2) (a) Murakami, C.; Kumagai, T.; Hada, T.; Kanekazu, U.; Nakazawa, S.; Kamisuki, S.; Maeda, N.; Xu, X.; Yoshida, H.; Sugawara, F.; Sakaguchi, K.; Mizushima, Y. *Biochem. Pharmacol.* **2003**, *65*, 259–267. (b) Maeda, N.; Hada, T.; Murakami-Nakai, C.; Kuriyama, I.; Ichikawa, H.; Fukumori, Y.; Hiratsuka, J.; Yoshida, H.; Sakaguchi, K.; Mizushima, Y. *J. Nutr. Biochem.* **2005**, *16*, 121–128. (c) Maeda, N.; Matsubara, K.; Yoshida, H.; Mizushima, Y. *Mini-Rev. Med. Chem.* **2011**, *11*, 32–38. (d) Colombo, D.; Scala, A.; Taino, I. M.; Toma, L.; Ronchetti, F.; Tokuda, H.; Nishino, H.; Nagatsu, A.; Sakakibara, J. *Cancer Lett.* **1998**, *123*, 83–86. (e) Sun, Y.; Zhang, J.; Li, C.; Guan, H.; Yu, G. *Carbohydr. Res.* **2012**, *355*, 6–12. (f) Tanaka, R.; Sakano, Y.; Nagatsu, A.; Shibuya, M.; Ebizuka, Y.; Goda, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 159–162.
- (3) Kinjo, Y.; Tupin, E.; Wu, D.; Fujio, M.; Garcia-Navarro, R.; Benhnia, M. R.; Zajonc, D. M.; Ben-Menachem, G.; Ainge, G. D.; Painter, G. F.; Khurana, A.; Hoebe, K.; Behar, S. M.; Beutler, B.; Wilson, I. A.; Tsuji, M.; Sellati, T. J.; Wong, C.-H.; Kronenberg, M. *Nat. Immunol.* **2006**, *7*, 978–986.
- (4) (a) Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771–2784. (b) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J. Med. Chem.* **1995**, *38*, 2176–2187.
- (5) (a) Schnaar, R. L.; Suzuki, A.; Stanley, P. In *Essentials of Glycobiology*, 2nd ed.; Varki, A., Cummings, R. D., Esko, J. D., Freeze, H. H., Stanley, P., Bertozzi, C. R., Hart, G. W., Etzler, M. E., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, 2009; Chapter 10. (b) Schnaar, R. L. *Arch. Biochem. Biophys.* **2004**, *426*, 163–172.
- (6) (a) Long, X.; Deng, S.; Mattner, J.; Zang, Z.; Zhou, D.; McNary, N.; Goff, R. D.; Teyton, L.; Bendelac, A.; Savage, P. B. *Nat. Chem. Biol.* **2007**, *3*, 559–564. (b) Wu, D.; Fujio, M.; Wong, C.-H. *Bioorg. Med. Chem.* **2008**, *16*, 1073–1083.
- (7) Banchet-Cadédu, A.; Hénon, E.; Dauchez, M.; Renault, J.-H.; Monneaux, F.; Haudrechy, A. *Org. Biomol. Chem.* **2011**, *9*, 3080–3104 and references therein.
- (8) Lee, T.; Cho, M.; Ko, S.-Y.; Youn, H.-J.; Baek, D. J.; Cho, W.-J.; Kang, C.-Y.; Kim, S. J. *Med. Chem.* **2007**, *50*, 585–589.
- (9) Malhotra, R. *Biochem. Anal. Biochem.* **2012**, *1*, 108.
- (10) Li, X.; Wu, Y.-D.; Yang, D. *Acc. Chem. Res.* **2008**, *41*, 1428–1438.
- (11) Chandrasekhar, S.; Rao, C. L.; Reddy, M. S.; Sharma, G. D.; Kiran, M. U.; Naresh, P.; Chaitanya, G. K.; Bhanuprakash, K.; Jagadeesh, B. *J. Org. Chem.* **2008**, *73*, 9443–9446.
- (12) Chen, F.; Ma, B.; Yang, Z.-C.; Lin, G.; Yang, D. *Amino Acids* **2012**, *43*, 499–503.
- (13) (a) Malapelle, A.; Ramozzi, R.; Xie, J. *Synthesis* **2009**, 888–890. (b) Gong, Y. C.; Sun, H. B.; Xie, J. *Eur. J. Org. Chem.* **2009**, 6027–6033. (c) Gong, Y.; Peyrat, S.; Sun, H.; Xie, J. *Tetrahedron* **2011**, *67*, 7114–7120. (d) Song, Z.; He, X.-P.; Chen, G.-R.; Xie, J. *Synthesis* **2011**, 2761–2766. (e) Peyrat, S.; Xie, J. *Synthesis* **2012**, *44*, 1718–1724. (f) Noel, O.; Xie, J. *Synthesis* **2013**, *45*, 134–140. (g) Peyrat, S.; Cheng, K.; Xie, J. *Synthesis* **2013**, *45*, 2737–2744. (h) Zhang, H.-L.; Zang, Y.; Xie, J.; Chen, G.-R.; He, X.-P.; Tian, H. *Sci. Rep.* **2014**, *4*, 5513.
- (14) Ishida, J.; Hinou, H.; Naruchi, K.; Nishimura, S.-I. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1197–1200.
- (15) van Boeckel, C. A. A.; Visser, G. M.; van Boom, J. H. *Tetrahedron* **1985**, *41*, 4557–4565.
- (16) Yadav, V. K.; Agrawal, D. *Chem. Commun.* **2007**, 5232–5234.
- (17) Mannock, D. A.; Lewis, R. N.; McElhaney, R. N. *Chem. Phys. Lipids* **1987**, *43*, 113–127.
- (18) Janwitayanuchit, W.; Suwanborirux, K.; Patarapanich, C.; Pummangura, S.; Lipipun, V.; Vilaivan, T. *Phytochemistry* **2003**, *64*, 1253–1264.
- (19) Bartoszewicz, A.; Kalek, M.; Stawinski, J. *Tetrahedron* **2008**, *64*, 8843–8850.
- (20) (a) Schenk, S.; Weston, J.; Anders, E. *J. Am. Chem. Soc.* **2005**, *127*, 12566–12576. (b) But, T. Y. S.; Toy, P. H. *Chem.—Asian J.* **2007**, *2*, 1340–1355.