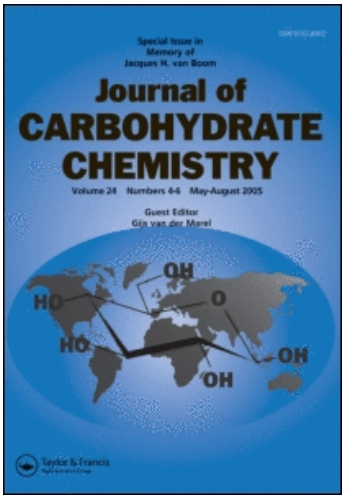

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Kenji Hotta[a]; Hideharu Ishida[a]; Makoto Kiso[a]; Akira Hasegawa[a]
[a] Department of Applied Bioorganic Chemistry, Gifu University, Gifu, Japan

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 66: FIRST TOTAL SYNTHESIS OF A CHOLINERGIC NEURON-SPECIFIC GANGLIOSIDE GQ1bα[1]

Kenji Hotta, Hideharu Ishida, Makoto Kiso, and Akira Hasegawa*

Department of Applied Bioorganic Chemistry, Gifu University, Gifu 501-11, Japan

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ABSTRACT

A first total synthesis of a cholinergic neuron-specific ganglioside, GQ1bα (IV^{3}Neu5Acα, III^{6}Neu5Acα, II^{3}Neu5Acα2-Gg4Cer) is described. Regio- and stereoselective monosialylation of the hydroxyl group at C-6 of the GalNAc residue in 2-(trimethylsilyl)ethyl *O*-(2-acetamido-2-deoxy-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-*O*-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**4**) with methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**5**), and subsequent dimericsialylation of the hydroxyl group at C-3 of the Gal residue with methyl [phenyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid]onate (**7**), using *N*-iodosuccinimide (NIS)-trifluoromethanesulfonic acid (TfOH) as a promoter, gave the desired hexasaccharide **8** containing α-glycosidically-linked mono- and dimeric sialic acids. This was transformed into the acceptor **9** by removal of the isopropylidene group. Condensation of methyl *O*-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-2,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside (**10**) with **9**, using dimethyl(methylthio)sulfonium triflate (DMTST) as a promoter, gave the desired octasaccharide derivative **11** in high yield. Compound **11** was converted into α-trichloroacetimidate **14**, *via* reductive removal of the benzyl groups, *O*-acetylation, removal of the 2-(trimethylsilyl)ethyl group, and treatment with trichloroacetonitrile, which, on coupling with (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (**15**), gave the β-glycoside **16**. Finally, **16** was transformed, *via* selective reduction of the azido group, coupling with octadecanoic acid, *O*-deacylation, and hydrolysis of the methyl ester group, into the title ganglioside **18** in good yield.

INTRODUCTION

Recently, it has been widely recognized[2] that sialoglycoconjugates, so-called gangliosides and glycoproteins, have important roles in biological processes such as cell growth, differentiation, adhesion, oncogenesis, receptor functions for viruses and bacterial toxins, and ligand activities of the selectin family. In particular, α-series gangliosides, which contain α-glycosidically-linked sialic acid at HO-6 of the *N*-acetylgalactosamine residue in the oligosaccharide chain, have been isolated[3,4] as the components in tissues of the central nervous system of mouse and adult bovine brains. Especially, two α-series gangliosides, GT1aα and GQ1bα, have been recognized[5,6] as the cholinergic neuron-specific antigen of bovine brain by Whittaker *et al.* We have reported[7] the first synthesis of α-series gangliosides, GM1α and GD1α, during the course of the structure-function relationship study of sialoglycoconjugates at the molecular level, using our newly developed methods for the regio- and stereoselective synthesis of gangliosides.[8] Here we will report the first total synthesis of α-series ganglioside GQ1bα which is one of the most complex structures among gangliosides.

RESULTS AND DISCUSSION

For the synthesis of an α-series ganglioside GQ1bα, a well designed trisaccharide derivative **4**, which provides two free hydroxyl groups at HO-6 of the *N*-acetylgalactosamine residue and HO-3 of the galactose residue for glycosylation with the sialyl residue **5** and sialyl α(2→8) sialyl residue **7** as the donors, was selected as the key glycosyl acceptor considering the different reactivity of these glycosyl donors.

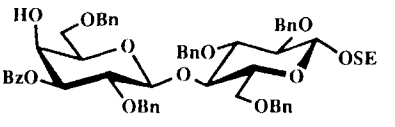
The glycosylation of 2-(trimethylsilyl)ethyl *O*-(3-*O*-benzoyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[9] (**1**) with methyl 6-*O*-benzoyl-2-deoxy-3,4-*O*-isopropylidene-2-phthalimido-1-thio-β-D-galactopyranoside[10] (**2**) in dichloromethane for 12 h at room temperature in the presence of *N*-iodosuccinimide (NIS)-trifluoromethanesulfonic acid (TfOH) and powdered molecular sieves 4Å (MS-4Å) afforded the desired β-glycoside **3** in 66% yield. Significant signals of the galactosamine unit in the ^{1}H NMR spectrum of **3** were two three-proton

singlets at δ 1.30 and 1.62 (Me_2C) and a one-proton doublet at δ 5.42 ($J_{1,2}$ = 8.4 Hz, H-1) indicating the structure assigned. *O*-Debenzoylation of **3** and subsequent conversion of the phthalimide to the acetamide by heating with ethylenediamine in 1-butanol, followed by *N*-acetylation with acetic anhydride afforded gangliotriose acceptor **4**.

The condensation of **4** with methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate[11] (**5**) in acetonitrile for 2 h at -30 °C in the presence of NIS-TfOH and powdered molecular sieves 3Å (MS-3Å) gave the α-glycoside **6** solely at the desired position in 45 % yield. The observed chemical shifts and coupling constants of the sialic acid residue were a one-proton doublet of doublets at δ 2.60 (J_{gem} = 12.5 Hz, $J_{3eq,4}$ = 4.4 Hz, H-3*eq*), a three-proton singlet at δ 3.75 (MeO), a one-proton multiplet at δ 4.88 (H-4), a one-proton multiplet at δ 5.28 (H-8), and a one-proton doublet of doublets at δ 5.30 ($J_{6,7}$ = 1.7 Hz, $J_{7,8}$ = 7.8 Hz, H-7d) indicating the newly formed glycosidic linkage to be α.[12] The regio-chemistry was deduced from ^{1}H NMR spectrum of the acetylation compound of **6**; the observed chemical shift of the galactose residue for H-3 (δ 4.94), indicating the glycosylated position to be HO-6 of the GalNAc residue. The glycosylation of this tetrasaccharide acceptor **6** with methyl [phenyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid]onate[13] (**7**) in a similar condition as described for **6** gave the expected hexasaccharide derivative **8** in 42% yield; significant signals of **8** in the ^{1}H NMR spectrum were a one-proton doublet of doublets at δ 1.72 (J_{gem} = 11.7 Hz, $J_{3ax,4}$ = 13.4 Hz, H-3d*ax*), a one-proton doublet of doublets at δ 2.22 ($J_{3eq,4}$ = 4.4 Hz, H-3d*eq*), and a one-proton multiplet at δ 5.40 (H-4d), indicating the structure assigned.[13]

It is noteworthy for the systematic synthesis of α-seriesgangliosides that the hexasaccharide derivative **8** containing both mono- and dimeric sialic acids at the desired positions in **4** was easily obtained by applying the different reactivity of the mono- and dimeric sialyl donors.

By removal of the isopropylidene group, the hexasaccharide acceptor **9** was formed from **8** in 78% yield. Dimethyl(methylthio)sulfonium triflate[14] (DMTST)-promoted glycosylation of **9** with methyl *O*-(methyl 5-acetamido-4,7,8,9-tetra-*O*-



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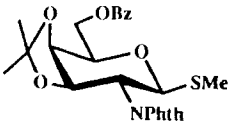

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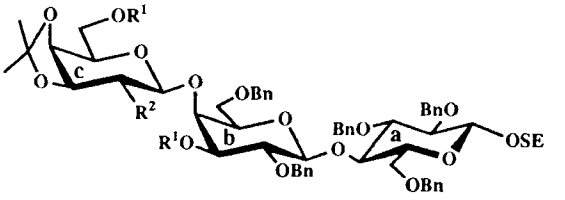
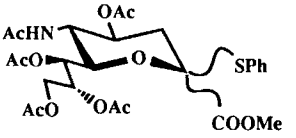


	R^1	R^2
3	Bz	NPhth
4	H	NHAc



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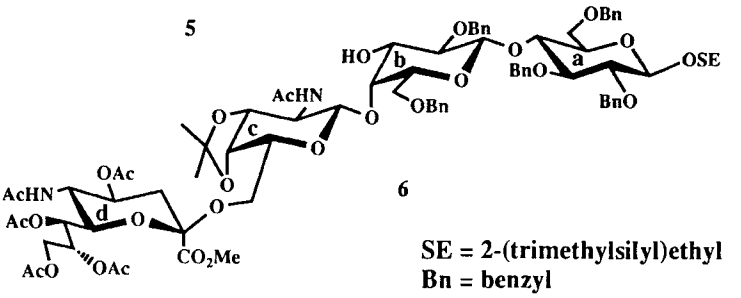
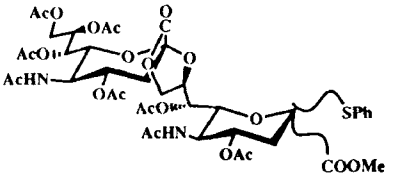


6

SE = 2-(trimethylsilyl)ethyl
Bn = benzyl
Bz = benzoyl

acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-2,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside[15] (**10**) in dichloromethane for 2 days at 0 °C gave the desired octasaccharide **11** in 85% yield. The regio-chemistry of compound **11** was deduced from the ^{1}H NMR spectrum of the acetylated compound **12**. The observed chemical shift of GalNAc unit for H-4 (δ 5.22) indicated the position of glycosylation to be HO-3. Catalytic hydrogenolysis (10% Pd-C) of the benzyl groups of **11** in ethanol-acetic acid for 2 days at 40 °C and subsequent *O*-acetylation gave the per-*O*-acyl derivative **12** in 71% yield. Treatment[16] of **12** with trifluoroacetic acid in



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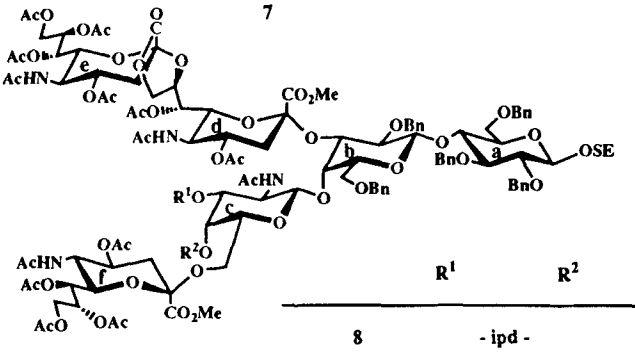
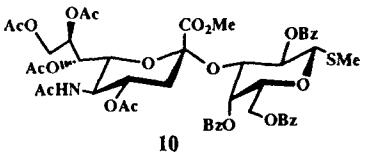


	R^1	R^2
8	- ipd -	
9	H	H



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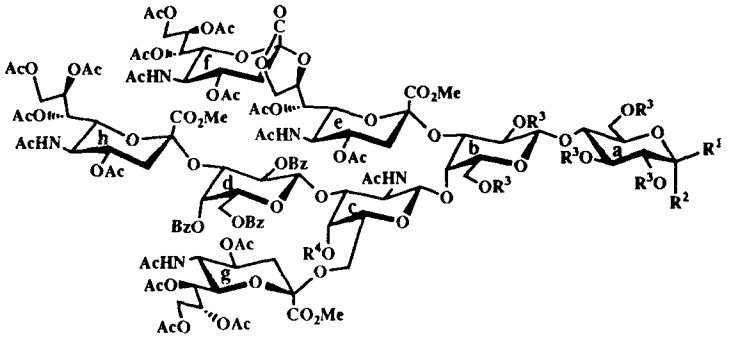
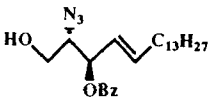


	R^1	R^2	R^3	R^4
11	OSE	H	Bn	H
12	OSE	H	Ac	Ac
13	OH , H		Ac	Ac
14	H	$OC(=NH)CCl_3$	Ac	Ac



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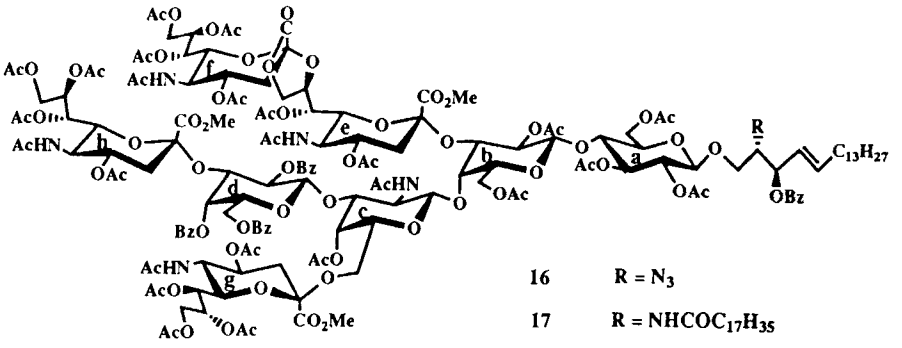
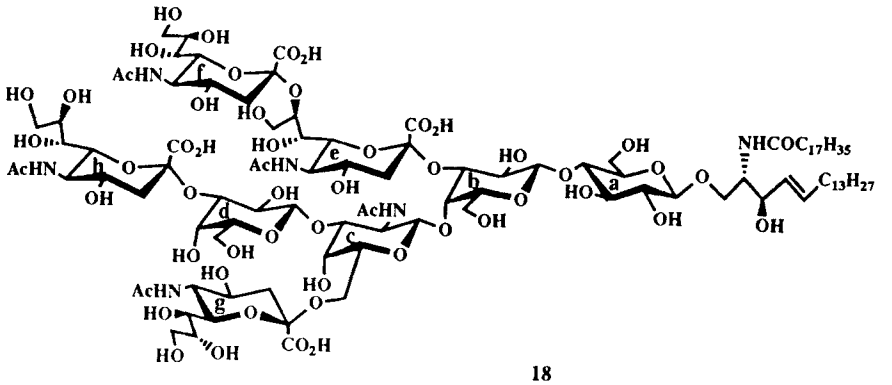


16 R = N_3

17 R = $NHCOC_{17}H_{35}$



18

dichloromethane for 1 h at 0 °C gave the 1-hydroxy compound **13**. When treated with trichloroacetonitrile in dichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 1 h at 0 °C, **13** gave the α-trichloroacetimidate **14** in quantitative yield. The ^{1}H NMR data for Glc unit in **14** [δ 6.50 ($J_{1,2}$ = 3.4 Hz, H-1a), 8.64 (C = NH)] indicated the imidate to be α.

The final glycosylation of (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol[17] (**15**) with **14** in dichloromethane in the presence of boron trifluoride etherate[18] for 8 h at 0 °C afforded the desired β-glycoside **16** in 46% yield. Selective reduction[17a,19] of azido group in **16** with hydrogen sulfide in aqueous 83% pyridine for 3 days at 0 °C gave the amine and this, on condensation with octadecanoic acid using 1-

ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) in dichloromethane, gave the acylated GQ1bα ganglioside **17** in 36% yield after chromatography.

Finally, *O*-deacylation of **17** with sodium methoxide in methanol, and subsequent saponification of the methyl ester group, yielded the desired cholinergic neuron-specific ganglioside GQ1bα **18** in 84% yield after chromatography on a column of Sephadex LH-20. The ^{1}H NMR data of the product thus obtained are consistent with the structure assigned.

EXPERIMENTAL

General methods. Optical rotations were determined with a Union PM-201 polarimeter at 25 °C and IR spectra were recorded with a Jasco IRA-100 spectrophotometer. ^{1}H NMR spectra were recorded at 270 MHz with Jeol JNM-GX 270 and at 500 MHz with a Varian VXR-500S spectrometers. Preparative chromatography was performed on silica gel (Fuji Silysia Co., 300 mesh) with the solvent systems specified. Concentrations were conducted *in vacuo*.

2-(Trimethylsilyl)ethyl *O*-(6-*O*-Benzoyl-2-deoxy-3,4-*O*-isopropylidene-2-phthalimido-β-D-galactopyranosyl)-(1→4)-*O*-(3-*O*-benzoyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (3). To a solution of 2-(trimethylsilyl)ethyl *O*-(3-*O*-benzoyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[9] (**1**; 5.70 g, 11.4 mmol) and methyl 6-*O*-benzoyl-2-deoxy-3,4-*O*-isopropylidene-2-phthalimido-1-thio-β-D-galactopyranoside[10] (**2**; 5.53 g, 5.7 mmol) in CH_2Cl_2 (100 mL) were added 4Å molecular sieves (11 g), and the suspension was stirred for 5 h at room temperature. To the mixture were then added, with stirring, *N*-iodosuccinimide (NIS; 5.14 g, 22.8 mmol) and trifluoromethanesulfonic acid (TfOH; 83 μL, 2.8 mmol), and the stirring was continued for 12 h at room temperature; the progress of the reaction was monitored by TLC. The solids were filtered off and washed thoroughly with CH_2Cl_2. The combined filtrate and washings was washed with M Na_2CO_3 and M $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated. Column chromatography (1:1 hexane-ethyl acetate) of the residue on silica gel (800 g) gave **3** (5.40 g, 66%) as an amorphous mass; $[\alpha]_D$ +28.4° (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.01 (m, 2H,

$Me_3SiCH_2CH_2$), 1.30 and 1.62 (2s, 6H, Me_2C), 5.42 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1c), and 6.94, 8.03 (m, 39H, 8Ph).

Anal. Calcd for $C_{83}H_{89}NO_{19}Si$ (1432.7): C, 69.58; H, 6.26; N, 0.98. Found: C, 69.43; H, 6.11; N, 0.74.

2-(Trimethylsilyl)ethyl *O*-(2-Acetamido-2-deoxy-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (4). A solution of **3** (1.74 g, 1.2 mmol) in 1-butanol (50 mL) and ethylenediamine (1.62 mL) was heated for 5 h under reflux. After cooling, insolubles were filtered off and washed with ethanol. The filtrate and washings were combined and concentrated to dryness, the residue was treated with acetic anhydride (8 mL) and methanol (50 mL) for 8 h at room temperature, and the solution was concentrated. Column chromatography (50:1 CH_2Cl_2-MeOH) of the residue on silica gel (200 g) gave **4** (1.17 g, 85%) as an amorphous mass; $[\alpha]_D$ +19.2° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.03 (m, 2H, $Me_3SiCH_2CH_2$), 1.31 and 1.49 (2s, 6H, Me_2C), 1.84 (s, 3H, AcN), 5.18 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1c), 5.78 (d, 1H, 6.2 Hz, N*H*), and 7.23-7.46 (m, 25H, 5Ph).

Anal. Calcd for $C_{63}H_{81}NO_{16}Si$ (1136.42): C, 66.59; H, 7.18; N, 1.23. Found: C, 66.48; H, 7.07; N, 1.05.

2-(Trimethylsilyl)ethyl *O*-[Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→6)-*O*-(2-acetamido-2-deoxy-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-*O*-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (6). To a solution of **4** (300 mg, 0.26 mmol) and methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate[11] (**5**; 308 mg, 0.53 mmol) in MeCN (5 mL) were added 3Å molecular sieves (1.0 g) and the mixture was stirred for 5 h at room temperature, then cooled to -30 °C. To the mixture were added with stirring, NIS (240 mg, 1.1 mmol) and TfOH (5 μL, 0.06 mmol), and the stirring was continued for 2 h at -30 °C. The solids were removed by filtration and washed with CH_2Cl_2. The combined filtrate and washings was successively washed with M Na_2CO_3 and M $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated. Column chromatography (50:1 CH_2Cl_2-MeOH) of the residue on silica gel (50 g) gave **6** (191 mg, 45%) as

an amorphous mass; $[\alpha]_D$ +13.8° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.01 (m, 2H, $Me_3SiCH_2CH_2$), 1.36 and 1.54 (2s, 6H, Me_2C), 1.85-2.13 (6s, 18H, 2AcN and 4AcO), 2.60 (dd, 1H, J_{gem} = 12.5 Hz, $J_{3eq,4}$ = 4.4 Hz, H-3d*eq*), 3.75 (s, 3H, MeO), 4.88 (m, 1H, H-4d), 5.11 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1c), 5.28 (m, 1H, H-8d), 5.30 (dd, 1H, $J_{6,7}$ = 1.7 Hz, $J_{7,8}$ = 7.8 Hz, H-7d), and 7.25-7.49 (m, 2H, 5Ph).

Anal. Calcd for $C_{83}H_{108}N_2O_{28}Si$ (1609.85): C, 61.93; H, 6.76; N, 1.74. Found: C, 61.67; H, 6.48; N, 1.57.

2-(Trimethylsilyl)ethyl *O*-[Methyl 5-Acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→3)-*O*-[*O*-(methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-(2-acetamido-2-deoxy-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)]-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (8). To a solution of **6** (1.50 g, 0.93 mmol) and methyl [phenyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid]onate[13] (**7**; 1.75 g, 1.86 mmol) in MeCN (16 mL) were added 3Å molecular sieves (4 g) and the mixture was stirred for 5 h at room temperature, then cooled to -15 °C. To the solution were added NIS (963 mg, 4.4 mmol) and TfOH (40 μL, 0.5 mmol), and the stirring was continued for 2 days at -15 °C. The solids were removed by filtration, and washed with CH_2Cl_2. The combined filtrate and washings was washed with M Na_2CO_3 and M $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated. Column chromatography (20:1 CH_2Cl_2-MeOH) of the residue on silica gel (150 g) gave **8** (1.01 g, 44%) as an amorphous mass; $[\alpha]_D$ -14.0° (*c* 0.4 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.01 (m, 2H, $Me_3SiCH_2CH_2$), 1.26 and 1.39 (2s, 6H, Me_2C), 1.72 (dd, 1H, J_{gem} = 11.7 Hz, $J_{3ax,4}$ 13.4 Hz, H-3d*ax*), 1.84 (t, 1H, J_{gem} = $J_{3ax,4}$ 13.4 Hz, H-3e*ax*), 1.86-2.10 (14s, 42H, 4AcN and 10AcO), 2.22 (dd, 1H, J_{gem} = 11.7 Hz, $J_{3eq,4}$ = 4.4 Hz, H-3d*eq*), 2.45 (dd, 1H, J_{gem} = 13.2 Hz, $J_{3eq,4}$ = 5.4 Hz, H-3e*eq*), 2.59 (dd, 1H, J_{gem} = 12.7 Hz, $J_{3eq,4}$ = 4.6 Hz, H-3f*eq*), 4.82 (m, 1H, H-7f), 5.40 (m, 1H, H-4d), 5.43 (m, 1H, H-4e), 5.65 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1c), and 7.47-7.90 (m, 25H, 5Ph).

Anal. Calcd for $C_{118}H_{154}N_4O_{49}Si$ (2440.60): C, 58.07; H, 6.36; N, 2.30. Found: C, 58.00; H, 6.19; N, 2.21.

2-(Trimethylsilyl)ethyl *O*-[Methyl 5-Acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→3)-*O*-[*O*-(methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→4)]-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (9). To a solution of **8** (550 mg, 0.23 mmol) in MeOH (20 mL) was added *p*-toluenesulfonic acid monohydrate (20 mg), and the mixture was stirred for 1 h at room temperature, then neutralized with Amberlite IRA-410 (OH^-) resin and concentrated. Column chromatography (20:1 CH_2Cl_2-MeOH) of the residue on silica gel (60 g) gave **9** (422 mg, 78%) as an amorphous mass; $[\alpha]_D$ -21.62° (*c* 0.3 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.00 (m, 2H, $Me_3SiCH_2CH_2$), 1.87-2.18 (14s, 42H, 4AcN and 10AcO), 2.34 (m, 1H, H-3d*eq*), 2.57 (dd, 1H, J_{gem} = 13.2 Hz, $J_{3eq,4}$ = 4.4 Hz, H-3e*eq*), 2.69 (dd, 1H, J_{gem} = 13.7 Hz, $J_{3eq,4}$ = 4.2 Hz, H-3f*eq*), 3.42 and 3.49 (2s, 6H, 2MeO), 7.12-7.49 (m, 25H, 5Ph).

Anal. Calcd for $C_{115}H_{150}N_4O_{49}Si$ (2400.53): C, 57.54; H, 6.30; N, 2.33. Found: C, 57.52; H, 6.22; N, 2.13.

2-(Trimethylsilyl)ethyl *O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-[(methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)]-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-{[methyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→3)}-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (11). To a solution of **9** (400 mg, 0.17 mmol) and methyl *O*-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-2,4,6-tri-*O*-ben-

zoyl-1-thio-β-D-galactopyranoside[15] (**10**, 415 mg, 0.42 mmol) in CH_2Cl_2 (20 mL) was added 4Å molecular sieves (2.0 g), and the mixture was stirred for 5 h at room temperature then cooled to 0 °C. To the mixture was added, with stirring, dimethyl-(methylthio)sulfonium triflate[14] (DMTST, 200 mg, 0.68 mmol), and the stirring was continued for 2 days at 0 °C. The precipitates were removed by filtration, and washed thoroughly with CH_2Cl_2. The filtrate and washings were combined, and the solution was successively washed with M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (20:1 CH_2Cl_2-MeOH) of the residue on silica gel (50 g) gave **11** (475 mg, 85%) as an amorphous mass; $[\alpha]_D$ -6.9° (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.00 (m, 2H, $Me_3SiCH_2CH_2$), 1.88-2.10 (19s, 57H, 5AcN and 14AcO), 2.33-2.78 (m, 4H, H-3e*eq*, H-3f*eq*, H-3g*eq*, and H-3h*eq*), 3.47, 3.58, and 3.68 (3s, 9H, 3MeO), 5.62 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-4d), 7.17-8.13 (m, 40H, 8 Ph).

Anal. Calcd for $C_{162}H_{199}N_5O_{69}Si$ (3348.43): C, 58.11; H, 5.99; N, 2.09. Found: C, 57.93; H, 5.94; N, 1.94.

2-(Trimethylsilyl)ethyl *O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-[(methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)]-*O*-(2-acetamido-4-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-{[methyl 5-Acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→3)}-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (12). A solution of **11** (580 mg, 0.17 mmol) in EtOH (40 mL) and acetic acid (8 mL) was hydrogenated in the presence of 10% Pd-C (600 mg) for 2 days at 40 °C, the catalyst removed by filtration and the solution concentrated. The residue was acetylated with acetic anhydride (2 mL) and pyridine (3 mL) for 16 h at room temperature. The product was purified by chromatography on a column of silica gel (50 g) with 20:1 CH_2Cl_2-MeOH to give **12** (390 mg, 71%) as an amorphous mass; $[\alpha]_D$ -10.3° (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.98 (m, 2H, $Me_3SiCH_2CH_2$), 1.91-2.14 (25s, 75H, 5AcN and 20AcO), 2.36-2.75 (m, 4H, H-3e*eq*, H-3f*eq*, H-3g*eq*, and H-3h*eq*), 3.46,

3.79, and 3.82 (3s, 9H, 3MeO), 5.22 (d, 1H, $J_{3,4}$ = 3.5 Hz, H-4c), 5.61 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-4d), 7.26-8.16 (m, 15H, 3Ph).

Anal. Calcd for $C_{139}H_{181}N_5O_{75}Si$ (3150.02): C, 53.00; H, 5.79; N, 2.22. Found: C, 52.89; H, 5.59; N, 1.93.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-[(methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)]-*O*-(2-acetamido-4-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-{[methyl 5-Acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→3)}-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranose (13).** To a solution of **12** (110 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (0.8 mL) at 0 °C, and the mixture was stirred for 1 h at 0 °C and concentrated. Column chromatography (20:1 CH_2Cl_2-MeOH) of the residue on silica gel (10 g) gave **13** (80 mg, 75%) as an amorphous mass: IR (KBr) 3600-3300 (OH, NH), 1740 and 1230 (ester), 1670 and 1550 (amide), and 760 and 720 (Ph).

Anal. Calcd for $C_{134}H_{169}N_5O_{75}$ (3049.79.): C, 52.77; H, 5.59; N, 2.30. Found: C, 52.73; H, 5.31; N, 2.29.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-[(methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)]-*O*-(2-acetamido-4-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-{[methyl 5-Acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→3)}-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranosyl Trichloroacetimidate (14).** To a solution of **13** (80 mg, 0.026 mmol) in CH_2Cl_2 (1 mL) and

trichloroacetonitrile (0.13 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 9 mg) at -5 °C, and the mixture was stirred for 1 h at 0 °C, then concentrated. Column chromatography (20:1 CH_2Cl_2-MeOH) of the residue on silica gel (10 g) gave **14** (83 mg, quantitative) as an amorphous mass; $[\alpha]_D$ +4.26° (*c* 1.2 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.85-2.17 (25s, 75H, 5AcN and 20AcO), 2.44-2.69 (m, 4H, H-3e*eq*, H-3f*eq*, H-3g*eq*, and H-3h*eq*), 3.46, 3.80 and 3.83 (3s, 9H, 3MeO), 6.50 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1a), 7.46-8.26 (m, 15H, 3Ph), 8.64 (s, 1H, C=N*H*).

Anal. Calcd for $C_{136}H_{169}N_6O_{75}Cl_3$ (3194.17): C, 51.14; H, 5.33; N, 2.63. Found: C, 51.04; H, 5.10; N, 2.39.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-[(methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)]-*O*-(2-acetamido-4-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-{[methyl 5-Acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→3)}-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (16).** To a solution of **14** (83 mg, 0.025 mmol) and (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol[17,18] (**15**, 25 mg, 0.05 mmol) in CH_2Cl_2 (0.8 mL) were added 4Å molecular sieves (AW-300, 0.5 g) and the mixture was stirred for 5 h at room temperature, then cooled to 0 °C. Boron trifluoride etherate (9 μL) was added, and the mixture was stirred for 8 h at 0 °C and then filtered. The insoluble materials were washed with CH_2Cl_2, and the combined filtrate and washings was washed with M $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. Column chromatography (20:1 CH_2Cl_2-MeOH) of the residue on silica gel (10 g) gave **16** (41 mg, 46%) as an amorphous mass; $[\alpha]_D$ -11.9° (*c* 0.8 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, $J_{Me,CH2}$ = 6.8 Hz, *Me*CH_2), 1.25 (s, 22H, 11C*H*$_2$), 1.83-2.17 (25s, 75H, 5AcN and 20AcO), 2.43-2.68 (m, 4H, H-3e*eq*, H-3f*eq*, H-3g*eq*, and H-3h*eq*), 3.47, 3.81 and 3.82 (3s, 9H, 3MeO), 5.58 (d, 1H, $J_{3,4}$ = 3.1 Hz, H-4d), 5.96 (m, 1H, H-5 of sphingosine), 7.39-8.16 (m, 20H, 4Ph).

Anal. Calcd for $C_{159}H_{206}N_8O_{77}$ (3461.38): C, 55.17; H, 6.00; N, 3.24. Found: C, 54.93; H, 5.80; N, 3.16.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-[(methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)]-*O*-(2-acetamido-4-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-{[methyl 5-Acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→3)}-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-acetyl-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol (17).** Hydrogen sulfide was bubbled through a stirred solution of **16** (41 mg, 0.012 mmol) in aqueous 83% pyridine (6 mL) for 3 days at 0 °C. The mixture was concentrated, and the residue was stirred with octadecanoic acid (10 mg, 0.038 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (10 mg, 0.055 mmol) in CH_2Cl_2 (1.5 mL) for 1 day at room temperature. Dichloromethane (20 mL) was added, and the mixture was washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (20:1 CH_2Cl_2-MeOH) of the residue on silica gel (10 g) gave **17** (16 mg, 36%) as an amorphous mass; $[\alpha]_D$ -5.3° (*c* 0.4 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.88 (t, 6H, $J_{Me,CH2}$ = 7.0 Hz, 2*Me*CH_2), 1.26 (s, 52H, 26*CH*$_2$), 1.86-2.18 (25s, 75H, 5AcN and 20AcO), 2.32-2.63 (m, 4H, H-3e*eq*, H-3f*eq*, H-3g*eq*, and H-3h*eq*), 3.48, 3.80 and 3.82 (3s, 9H, 3MeO), 5.85 (m, 1H, H-5 of ceramide), 7.23-8.23 (m, 20H, 4Ph).

Anal. Calcd for $C_{177}H_{242}N_6O_{78}$ (3701.85): C, 57.43; H, 6.59; N, 2.27. Found: C, 57.25; H, 6.47; N, 2.21.

Ganglioside GQ1bα (18). To a solution of **17** (16 mg, 0.0043 mmol) in MeOH (1 mL) was added a catalytic amount of NaOMe, and the mixture was stirred for 24 h at room temperature. Water (0.5 mL) was added and the mixture was again stirred for 24 h at room temperature, then neutralized with Amberlite IR-120 (H^+) resin. The resin was filtered off and washed with 1:1 $CHCl_3$-MeOH, and the combined filtrate

and washings was concentrated. Column chromatography (1:1 $CHCl_3$-MeOH) of the residue on Sephadex LH-20 (10 g) gave **18** (8.8 mg, 84%) as an amorphous solid; $[\alpha]_D$ -13.0° (*c* 0.2, 1:1 $CHCl_3$-MeOH); ^1H NMR (1:1 DMSO-d6-D_2O): δ 0.88 (t, 6H, $J_{Me,CH2}$ = 6.4 Hz, 2*Me*CH_2), 1.24 (s, 52H, 26*CH*$_2$), 1.85-1.90 (5s, 15H, 5AcN), 2.05 (d, $J_{CH2,CH2}$ = 6.0 Hz, CO*CH*$_2$*CH*$_2$), 2.54-2.78 (m, 4H, H-3e*eq*, H-3f*eq*, H-3g*eq*, and H-3h*eq*), 4.19 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1a), 4.31 (m, 2H, H-1b and H-1d), 4.62 (d, 1H, $J_{1,2}$ = 8.9 Hz, H-1c), 5.33 (m, 1H, H-4 of ceramide), and 5.57 (m, 1H, H-5 of ceramide).

Anal. Calcd for $C_{106}H_{182}N_6O_{55}$ (2420.61): C, 52.60; H, 7.58; N, 3.47. Found: C, 52.46; H,7.51; N, 3.30.

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