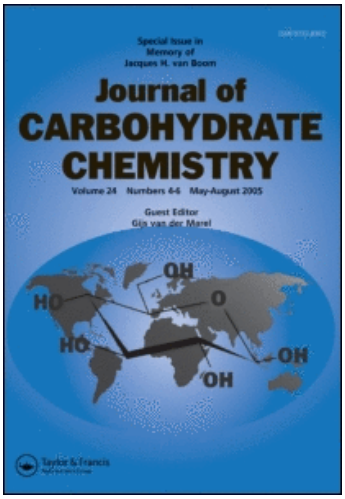

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Synthetic Studies on Sialoglycoconjugates 91: Total Synthesis of Gangliosides GD1C and GT1A

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 91: TOTAL SYNTHESIS OF GANGLIOSIDES GD1c AND GT1a

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ABSTRACT

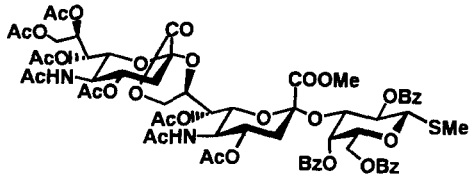
A first total synthesis of gangliosides GD1c and GT1a containing Neu5Acα(2→8) Neu5Acα(2→3)Gal residue in their non-reducing terminal is described. Condensation of methyl *O*-[methyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone) -4,7- di-*O*-acetyl-3,5 -dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate]-(2→ 3)-2,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside (**1**) with 2-(trimethylsilyl)ethyl *O*-(2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranosyl) - (1→4) -*O* -(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**2**) or 2-(trimethylsilyl)ethyl *O*-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-[methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2 → 3)]-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl) - (1→4) - 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**3**) in the presence of dimethyl(methylthio)sulfonium triflate (DMTST) gave the corresponding hexa- and heptasaccharide derivatives **4** and **5**, respectively. These oligosaccharides were converted into the α-trichloroacetimidates **10** and **11** *via* reductive removal of the benzyl groups and/or benzylidene group, *O*-acetylation, selective removal of the 2-(trimethylsilyl)ethyl group and treatment with trichloroacetonitrile, which, on coupling with 2-azidosphingosine derivatives **12** or **13**, gave the β-glycosides **14** and **15**, respectively. Finally, **14** and **15** were transformed, via selective reduction of the azido group, coupling with octadecanoic acid and removal of all protecting groups, into the title gangliosides GD1c **18** and GT1a **19**.

INTRODUCTION

Ganglio-series gangliosides are distinguished from other gangliosides in that they contain gangliotriosylceramide [GalNAcβ(1→4)Galβ(1→4)Glcβ(1→1)Cer] or gangliotetraosylceramide [Galβ(1→3)GalNAcβ(1→4)Galβ(1→4)Glcβ(1→1)Cer] as the neutral sugar chain backbones in their molecules, and sialic acids link at C-3 of Gal, C-6 of GalNAc and/or C-8 of Neu5Ac. These gangliosides are found in the central nervous system,[2-5] and are considered to play various important roles in biological systems.[6-12] In order to elucidate the functions of gangliosides in detail the pure compounds are required, because biologically derived gangliosides are polymorphous at the ceramide unit and available only in very limited quantity. Therefore, it is important to develop a facile chemical synthesis of these complex glycolipids. We have reported systematic syntheses[13-23] of various types of gangliosides and their analogs in order to elucidate structure-function relationships at the molecular level. We describe herein the synthesis of gangliosides GD1c and GT1a which contain the Neu5Acα(2→8)Neu5Acα(2→3)Gal residue in their non-reducing terminal. Gangliosides GD1c and GT1a were first isolated from murine thymoma by Bartoszewicz et al.[24] and from human brain by Ando et al.,[25] respectively. The biological functions of these gangliosides have not been reported yet because of the reason described above.

RESULTS AND DISCUSSION

For the synthesis of the desired gangliosides GD1c and GT1a we have employed methyl *O*-[methyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonuropyranosylono-1,9'-lactone)-4,7-di-*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[20] (**1**) as a key glycosyl donor, and 2-(trimethylsilyl)ethyl *O*-(2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[26] (**2**) and 2-(trimethylsilyl)ethyl *O*-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-[methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonuropyrano-



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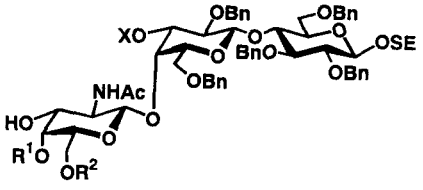
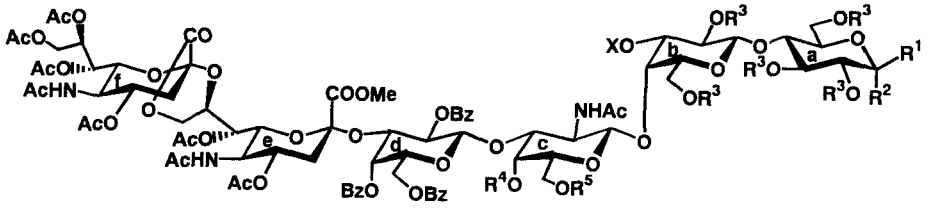
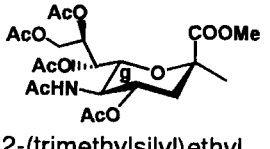


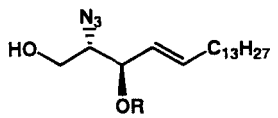
	R^1	R^2	X
2	benzylidene		Bn
3	H	Bn	SA



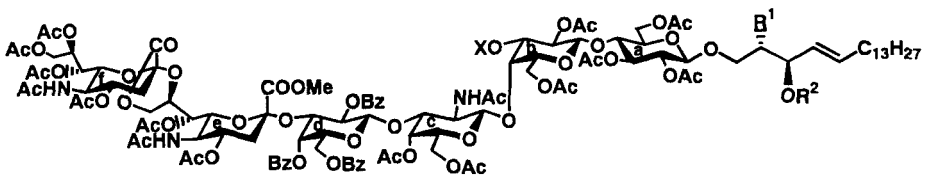
	R^1	R^2	R^3	R^4	R^5	X
4	OSE	H	Bn	benzylidene		Bn
5	OSE	H	Bn	H	Bn	SA
6	OSE	H	Ac	Ac	Ac	Ac
7	OSE	H	Ac	Ac	Ac	SA
8	H, OH		Ac	Ac	Ac	Ac
9	H, OH		Ac	Ac	Ac	SA
10	H	$OC(=NH)CCl_3$	Ac	Ac	Ac	Ac
11	H	$OC(=NH)CCl_3$	Ac	Ac	Ac	SA

SA = 

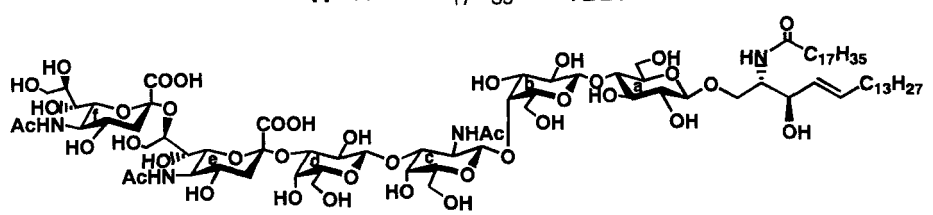
SE = 2-(trimethylsilyl)ethyl
Bn = benzyl
Bz = benzoyl



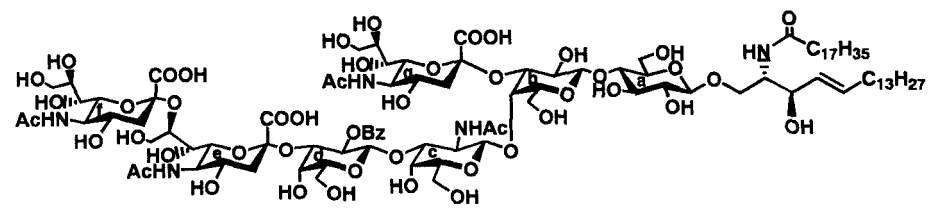
12 R = Bz
13 R = TBDPS



	R^1	R^2	X
14	N_3	Bz	Ac
15	N_3	TBDPS	SA
16	$NHCOC_{17}H_{35}$	Bz	Ac
17	$NHCOC_{17}H_{35}$	TBDPS	SA



18 ganglioside GD1c



19 ganglioside GT1a

TBDPS = *tert*-butyldiphenylsilyl

sylonate)-(2→3)]-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**3**) as the well designed, glycosyl acceptors, suitable for the preparation of the hexa- and heptasaccharide derivatives **4** and **5**.

By further processing, according to our usual procedure,[13] the resulting oligosaccharide intermediates **4** and **5** could be transformed into the end products by introduction of a ceramide moiety.

Glycosylation of **2** or **3** with **1** in the presence of dimethyl(methylthio)sulfonium triflate[13,23] (DMTST) and molecular sieves 4Å (MS-4Å) gave the desired hexasaccharide **4** (56%) and heptasaccharide **5** (31%), respectively. Reductive removal (10% Pd-C) of the benzyl and/or benzylidene groups of **4** and **5** in ethanol-acetic acid, and subsequent *O*-acetylation gave the corresponding per-*O*-acyl-oligosaccharides **6** and **7** in good yields, respectively. The observed chemical shift and coupling constants for H-4c of the GalNAc residue (δ 5.53, $J_{3,4}$ = 3.5 Hz for **6**; δ 5.50, $J_{3,4}$ = 3.4 Hz for **7**) in **6** and **7** indicated the glycosylated position to be the 3-OH. Treatment[27] of **6** and **7** with trifluoroacetic acid in dichloromethane for 30 min at room temperature gave the 1-hydroxy compounds **8** (75%) and **9** (83%). When treated[28] with trichloroacetonitrile in dichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 1 h at 0 °C, compounds **8** and **9** gave the corresponding α-trichloroacetimidates **10** (96%) and **11** (89%); significant signals of the Glc residue in the ^{1}H NMR spectra were a one-proton doublet (δ 6.43, $J_{1,2}$ = 3.7 Hz, for **10**; δ 6.48, $J_{1,2}$ = 3.7 Hz, for **11**), indicating the anomeric configuration of the imidates to be α.

Glycosylation of (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol[29] (**12**) with **10**, in dichloromethane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and molecular sieves 4Å (AW-300 type) for 10 h at 0 °C gave the desired β-glycoside **14** in 53% yield. Selective reduction[29b,30] of azido group in **14** with hydrogen sulfide in aq 83% pyridine and subsequent condensation with octadecanoic acid, using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) in dichloromethane, for 12 h at room temperature gave the protected ganglioside GD1c **16** in 82% yield. Finally, *O*-deacylation of **16** with sodium methoxide in methanol and subsequent saponification of the methyl ester and lactone group, yielded ganglioside GD1c (**18**) in almost quantitative yield.

On the other hand, condensation of **11** with (2*S*,3*R*,4*E*)-2-azido-3-*O*-(*tert*-butyldiphenylsilyl)-4-octadecene-1,3-diol[31] (**13**) in dichloromethane, in the presence of TMSOTf, gave the desired β-glycoside **15** in 65% yield. Selective reduction[32] of the azido group in **15** with triphenylphosphine in benzene-water for 24 h at 30 °C gave the amine, which was treated with octadecanoic acid in the presence of WSC in dichloromethane to give the protected ganglioside GT1a **17** in 95% yield. Finally, removal[33] of the *tert*-butyldiphenylsilyl group in **17** with M tetrabutylammmonium fluoride, *O*-deacylation, and saponification of the methyl ester and lactone group, yielded the desired ganglioside GT1a (**19**) in 75% yield after chromatography on a column of Sephadex LH-20. The ^{1}H NMR data of the products thus obtained are consistent with the structures assigned.

In conclusion, an efficient total synthesis of gangliosides GD1c and GT1a containing the Neu5Acα(2→8)Neu5Acα(2→3)-Gal residue at their non-reducing terminal was achieved by use of the key glycosyl donor **1**, indicating its usefulness for the syntheses of polysialoglycoconjugates.

EXPERIMENTAL

General procedures. 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 a Jeol JNM-GX 270 spectrometer and at 200 MHz with a Varian VXR spectrometer, and the NMR data were confirmed by use of decoupling techniques. 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*-[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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-

tri-*O*-benzyl-β-D-glucopyranoside (4). To a solution of 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)-2,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside[20] (**1**; 500 mg, 0.37 mmol) and 2-(trimethylsilyl)ethyl *O*-(2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**2**; 300 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) were added molecular sieves 4Å (1.2 g) and the mixture was stirred for 5 h at room temperature and cooled to 0 °C. Dimethyl(methylthio)sulfonium triflate (DMTST; 370 mg, 0.74 mmol) was added, with stirring, to the mixture, and the stirring was continued for 2 days. After reaction was over, the precipitates were filtered off and washed 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 (40:1 CH_2Cl_2-MeOH) of the residue on silica gel (30 g) gave **4** (330 mg, 56%) as an amorphous mass: $[\alpha]_D$ +10.9° (*c* 1.3, $CHCl_3$); IR (KBr) 3400-3100 (OH and NH), 1730 and 1230 (ester), 1650 and 1540 (amide), 860 and 840 (Me_3Si), 710 and 700 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 1.00 (m, 2 H, $Me_3SiCH_2CH_2$), 1.60 (t, 1H, J_{gem} = 13.0 Hz, H-3f*ax*), 1.86-2.11 (9s, 27H, 6AcO, 3AcN), 2.45 (m, 1H, H-3e*eq*), 3.19 (s, 3H, MeO), 4.98 (t, 1H, $J_{1,2} = J_{2,3}$ = 7.9 Hz, H-2d), 5.12 (m, 1H, H-4e), 5.18 (d, 1H, $J_{7,8}$ = 8.5 Hz, H-7e), 5.35 (dd, 1H, $J_{6,7}$ = 1.4 Hz, $J_{7,8}$ = 9.1 Hz, H-7f), 5.56 (m, 1H, H-4f), 5.72 (d, 1H, $J_{3,4}$ = 3.5 Hz, H-4d), 7.12-8.12 (m, 50H, 10Ph).

Anal. Calcd for $C_{136}H_{155}N_3O_{45}Si$ (2579.8): C, 63.32; H, 6.06; N, 1.63. Found: C, 63.25; H, 5.86; N, 1.51.

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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-[methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)]-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (5).

Glycosylation of 2-(trimethylsilyl)ethyl *O*-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-[methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonuropyranosylonate)-(2→3)]-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**3**; 175 mg, 0.12 mmol) with **1** (250 mg, 0.18 mmol), as described for **4**, gave **5** (103 mg, 31%) as an amorphous mass: $[\alpha]_D$ +4.0° (*c* 1.0, $CHCl_3$); IR (KBr) 3400-3100 (OH and NH), 1730 and 1230 (ester), 1650 and 1540 (amide), 860 and 840 (Me_3Si), 710 and 700 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 1.00 (m, 2H, $Me_3SiCH_2CH_2$), 1.83-2.17 (14s, 42H, 10AcO, 4AcN), 2.36-2.60 (m, 3H, H-3e-g*eq*), 3.60 (s, 3H, MeO), 7.18-8.10 (m, 45H, 9Ph).

Anal. Calcd for $C_{149}H_{178}N_4O_{58}Si$ (2965.1): C, 60.36; H, 6.05; N, 1.89. Found: C, 60.18; H, 5.79; N, 1.85.

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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (6). A solution of **4** (300 mg, 0.11 mmol) in AcOH (5 mL) and EtOH (5 mL) was hydrogenated in the presence of 10% Pd-C (300 mg) for 48 h at 45 °C, the catalyst removed by filtration and the solution concentrated. The residue was acetylated with Ac_2O (1 mL) and pyridine (2 mL) for 10 h at 45 °C. The mixture was concentrated, and a solution of the residue in CH_2Cl_2 was successively washed with 2 M HCl and M Na_2CO_3, dried (Na_2SO_4) and concentrated. Column chromatography (25:1 CH_2Cl_2-MeOH) of the residue on the silica gel gave **6** (272 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -6.2° (*c* 1.0, $CHCl_3$); IR (KBr) 3200 (NH), 1730 and 1230 (ester), 1650 and 1540 (amide), 860 and 840 (Me_3Si), and 710 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 1.03 (m, 1H, $Me_3SiCH_2CH_2$), 1.63 (t, 1H, J_{gem} = 12.5 Hz, H-3f*ax*), 1.88-2.22 (17s, 51H, 14AcO, 3AcN), 2.52 (m, 1H, H-3e*eq*), 3.46 (s, 3H, MeO), 5.04 (d, 1H, $J_{7,8}$ = 8.2 Hz, H-7e), 5.07 (m, 1H, H-4e), 5.34 (dd, 1H, $J_{6,7}$ = 2.0 Hz, $J_{7,8}$ = 8.9 Hz, H-7f), 5.53 (d, 1H, $J_{3,4}$ = 3.5 Hz, H-4c), 5.70 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-4d), 7.23-8.10 (m, 15H, 3Ph).

Anal. Calcd for $C_{103}H_{131}N_3O_{53}Si$ (2287.2): C, 54.09; H, 5.77; N, 1.84. Found: C, 53.85; H, 5.73; N, 1.70.

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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-[methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)]-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (7). Removal of benzyl groups and subsequent *O*-acetylation of **5** (100 mg, 0.037 mmol), as described for **6**, gave **7** (70 mg, 76%) as an amorphous mass: $[\alpha]_D$ -13.3° (*c* 1.4, $CHCl_3$); IR (KBr) 3300 (NH), 1750 and 1230 (ester), 1650 and 1540 (amide), 860 and 840 (Me_3Si), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.89 (m, 2H, $Me_3SiCH_2CH_2$), 1.85-2.19 (21s, 63H, 17AcO, 4AcN), 2.52 (m, 1H, H-3f*eq*), 2.84 (m, 1H, H-3g*eq*), 3.45 and 3.80 (2s, 6H, 2MeO), 5.50 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-4c), 5.71 (d, 1H, $J_{3,4}$ = 2.9 Hz, H-4d), 6.03 (d, 1H, $J_{NH,5}$ = 6.4 Hz, NH), 7.15-8.12 (m, 15H, 3Ph).

Anal. Calcd for $C_{121}H_{156}N_4O_{64}Si$ (2718.6): C, 53.46; H, 5.78; N, 2.06. Found: C, 53.22; H, 5.77; N, 2.05.

***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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranose (8).** A solution of **6** (110 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) and trifluoroacetic acid (1 mL) was stirred for 30 min at room temperature. Ethyl acetate (1 mL) was added to the mixture and concentrated. Column chromatography (25:1 CH_2Cl_2-MeOH) of the residue on silica gel (10 g) gave **8** (77 mg, 75%) as an amorphous mass: IR (KBr) 3400-3100 (OH and NH), 1740 and 1230 (ester), 1650 and 1540 (amide), and 710 cm^{-1} (phenyl).

Anal. Calcd for $C_{98}H_{119}N_3O_{53}$ (2187.0): C, 53.82; H, 5.48; N, 1.92. Found: C, 53.54; H, 5.29; N, 1.82.

***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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-[methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)]-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranose (9).** Selective removal of the 2-(trimethylsilyl)ethyl group of **7** (70 mg, 0.028 mmol) with trifluoroacetic acid (1 mL) in CH_2Cl_2 (2 mL) according to the method described for **8** gave **9** (56 mg, 83%) as an amorphous mass: IR (KBr) 3400-3200 (OH and NH), 1750 and 1230 (ester), 1650 and 1540 (amide), and 710 cm^{-1} (Ph).

Anal. Calcd for $C_{116}H_{144}N_4O_{64}$ (2618.4): C, 53.21; H, 5.54; N, 2.14. Found: C, 53.05; H, 5.36; N, 1.97.

***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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl Trichloroacetimidate (10).** To a solution of **8** (250 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) and trichloroacetonitrile (0.4 mL) was added DBU (19 μL, 0.13 mmol) at 0 °C, and the mixture was stirred for 1 h at 0 °C, then concentrated. Column chromatography (30:1 CH_2Cl_2-MeOH) of the residue on silica gel (20 g) gave **10** (240 mg, 96%) as an amorphous mass: $[\alpha]_D$ +18.5° (*c* 1.0, $CHCl_3$); IR (KBr) 3200 (NH), 1740 and 1230 (ester), 1650 and 1540 (amide), and 710 cm^{-1} (phenyl); ^1H NMR MeO), 6.43 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1a), 7.18-8.10 (m, 15H, 3Ph), 8.68 (s, 1H, C=NH).

Anal. Calcd for $C_{100}H_{119}Cl_3N_4O_{53}$ (2331.4): C, 51.52; H, 5.15; N, 2.40. Found: C, 51.46; H, 5.07; N, 2.26.

***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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-[methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)]-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl Trichloroacetimidate (11).** Treatment of **9** (56 mg, 0.023 mmol) with trichloroacetonitrile (0.1 mL) and DBU (4 μL) in CH_2Cl_2 (1 mL), then work up as described for **10** gave **11** (53 mg, 89%) as an amorphous mass: $[\alpha]_D$ +5.7° (*c* 1.1, $CHCl_3$); IR (KBr) 3300 (NH), 1750 and 1230 (ester), 1650 and 1540 (amide), and 710 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 1.85-2.19 (21s, 63H, 17AcO, 4AcN), 2.52 (m, 1H, H-3f*eq*), 2.86 (m, 1H, H-3g*eq*), 3.47 and 3.80 (2s, 6H, 2MeO), 5.71 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4d), 6.06 (d, 1H, $J_{NH,5}$ = 6.4 Hz, NH), 6.48 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1a), 7.27-8.12 (m, 15H, 3Ph) and 8.66 (s, 1H, C=NH).

Anal. Calcd for $C_{118}H_{144}Cl_3N_5O_{64}$ (2762.78): C, 51.30; H, 5.25; N, 2.53. Found: C, 51.29; H, 5.11; N, 2.31.

***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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(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 (14).** To a solution of **10** (240 mg, 0.1 mmol) and (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol[29] (**12**; 87 mg, 0.2 mmol) in CH_2Cl_2 (1.2 mL) were added molecular sieves 4Å (AW-300; 0.85 g), and the mixture was stirred for 5 h at room temperature, then cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (TMSOTf; 40 μL, 0.2 mmol) was added, and the mixture was stirred for 10 h at 0 °C, then filtered. The insoluble materials were washed with M $NaHCO_3$ and H_2O, dried (Na_2SO_4) and concentrated. Column chromatography (30:1 CH_2Cl_2-MeOH) of the residue on silica gel

(30 g) gave **14** (150 mg, 53%) as an amorphous mass: $[\alpha]_D$ -0.6° (*c* 1.0, $CHCl_3$); IR (KBr) 3200 (NH), 3000-2900 (Me, methylene), 2200 (azide), 1730 and 1230 (ester), 1650 and 1540 (amide), and 710 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J_{Me,CH_2} = 7.0 Hz, *Me*CH_2), 1.24 (s, 22H, 11CH_2), 1.65 (t, 1H, J_{gem} = 13.0 Hz, H-3f*ax*), 1.88-2.17 (17s, 51H, 14AcO, 3AcN), 2.52 (m, 1H, H-3e*eq*), 3.27 (s, 3H, MeO), 5,34 (d, 1H, $J_{7,8}$ = 8.6 Hz, H-7f), 5.70 (d, 1H, $J_{3,4}$ = 3.3 Hz, H-4f), 5.86 (m, 1H, H-5 of sphingosine), 7.21-8.11 (m, 20H, 4Ph).

Anal. Calcd for $C_{123}H_{156}N_6O_{55}$ (2598.6): C, 56.85; H, 6.05; N, 3.23. Found: C, 56.81; H, 6.01; N, 3.03.

***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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-[methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)]-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-2-azido-3-*O*-(*tert*-butyldiphenylsilyl)-4-octadecene-1,3-diol (15).** Glycosylation of (2*S*,3*R*,4*E*)-2-azido-3-*O*-(*tert*-butyldiphenylsilyl)-4-octadecene-1,3-diol[31] (**13**; 23 mg, 40 μmol) with **11** (53 mg, 20 μmol) in CH_2Cl_2 (0.5 mL) in the presence of TMSOTf (15 μL) and MS-4Å (300 mg) for 10 h at 0 °C, then workup as described for **14** gave **15** (40 mg, 65%) as an amorphous mass: $[\alpha]_D$ -1.3° (*c* 0.8, $CHCl_3$); IR (KBr) 3200 (NH), 3100-2950 (Me, methylene), 2200 (azide), 1740 and 1230 (ester), 1650 and 1540 (amide), 710 and 700 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J_{Me,CH_2} = 6.4 Hz, *Me*CH_2), 1.05 (s, 9H, Me_3C), 1.27 (s, 22H, 11CH_2), 1.85-2.19 (21s, 63H, 17AcO, 4AcN), 2.52 (m, 1H, H-3f*eq*), 2.85 (m, 1H, H-3g*eq*), 3.47 and 3.80 (2s, 6H, 2MeO), 5.71 (d, 1H, $J_{3,4}$ = 3.5 Hz, H-4d), 7.27-8.12 (m, 25H, 5Ph).

Anal. Calcd for $C_{150}H_{195}N_7O_{65}Si$ (3164.3): C, 56.94; H, 6.21; N, 3.10. Found: C, 56.83; H, 6.08; N, 2.95.

***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-nonulopyranosyl-**

onate]-(2→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol (16). Hydrogen sulfide was bubbled through a stirred solution of **14** (150 mg, 0.054 mmol) in aq 83% pyridine (10 mL) for 3 days at 0 °C and concentrated. To a solution of the residue in CH_2Cl_2 (2.5 mL) were added octadecanoic acid (33 mg, 0.16 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC; 27 mg, 0.16 mmol) and the mixture was stirred for 12 h at room temperature. After completion of the reaction, CH_2Cl_2 (50 mL) was added and the solution was washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (25:1 CH_2Cl_2-MeOH) of the residue on silica gel gave **16** (84 mg, 52%) as an amorphous mass: $[\alpha]_D$ +8.4° (*c* 1.0, $CHCl_3$); IR (KBr) 3200 (NH), 3000-2900 (Me, methylene), 1740 and 1240 (ester), 1650 and 1540 (amide), and 710 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 0.90 (t, 6H, J_{Me,CH_2} = 6.8 Hz, 2*Me*CH_2), 1.24 (s, 52H, 26CH_2), 1.87-2.18 (17s, 51H, 14AcO, 3AcN), 2.50 (m, 1H, H-3e*eq*), 3.26 (s, 3H, MeO), 5.80 (m, 1H, H-5 of sphingosine), 7.20-8.10 (m, 20H, 4Ph).

Anal. Calcd for $C_{141}H_{192}N_4O_{56}$ (2839.1): C, 59.65; H, 6.82; N, 1.97. Found: C, 59.50; H, 6.68; N, 1.70.

***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*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-[methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)]-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-(*tert*-butyldiphenylsilyl)-2-octadecanamido-4-octadecene-1,3-diol (17).** To a solution of **15** (40 mg, 14 μmol) in benzene (1 mL) and water (0.04 mL) was added triphenylphosphine (7 mg, 28 μmol), and the mixture was stirred for 24 h at 30 °C and concentrated. To a solution of the residue in CH_2Cl_2 (0.8 mL) were added octadecanoic acid (11 mg, 42 μmol) and WSC (9 mg, 42 μmol), and the mixture was stirred for 15 h at

room temperature. The mixture was diluted with CH_2Cl_2 (50 mL) and the solution 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** (41 mg, 95%) as an amorphous mass: $[\alpha]_D$ -6.3° (*c* 0.8, $CHCl_3$); IR (KBr) 3200 (NH), 3100-2950 (Me, methylene), 1740 and 1240 (ester), 1650 and 1540 (amide), 710 and 700 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, J_{Me,CH_2} = 6.4 Hz, 2*Me*CH_2), 1.05 (s, 9H, Me_3C), 1.26 (s, 52H, 26CH_2), 1.86-2.19 (21s, 63H, 17AcO, 4AcN), 2.51 (m, 1H, H-3e*eq*), 2.83 (m, 1H, H-3g*eq*), 3.47 and 3.82 (2s, 6H, 2MeO), 5.73 (d, 1H, H-4d), 7.29-8.14 (m, 25H, 5Ph).

Anal. Calcd for $C_{168}H_{231}N_5O_{66}Si$ (3404.8): C, 59.27; H, 6.84; N, 2.06. Found: C, 59.03; H, 6.58; N, 1.86.

Ganglioside GD1c (18). To a solution of **16** (84 mg, 28 μmol) in MeOH (5 mL) was added NaOMe (10 mg), and the mixture was stirred for 24 h at 40 °C. Water (0.5 mL) was added and the solution was stirred for 10 h at 40 °C, neutralized with Amberlite IR-120 (H^+) resin and filtered. The resin was washed with MeOH and the combined filtrate and washings were concentrated. Column chromatography (5:5:1 $CHCl_3$-MeOH-H_2O) on Sephadex LH-20 gave **18** (50 mg, quantitative) as an amorphous mass: $[\alpha]_D$ +5.4° (*c* 1.0, 5:5:1 $CHCl_3$-MeOH-H_2O); ^1H NMR ($(CD_3)_2SO$-D_2O) δ 0.88 (t, 6H, J_{Me,CH_2} = 6.4 Hz, 2*Me*CH_2), 1.24 (s, 52H, 26CH_2), 1.78-1.98 (3s, 9H, 3AcN), 2.42 and 2.87 (2m, 2H, H-3e,f*eq*), 5.48 (m, 1H, H-4 of sphingosine), 5.60 (m, 1H, H-5 of sphingosine).

Anal. Calcd for $C_{84}H_{148}N_4O_{39}$ (1838.1): C, 54.89; H, 8.12; N, 3.05. Found: C, 54.60; H, 8.05; N, 3.04.

Ganglioside GT1a (19). To a solution of **17** (41 mg, 13 μmol) in MeCN (1.5 mL) was added M tetrabutylammonium fluoride in tetrahydrofuran (0.3 mL), and the mixture was stirred for 24 h at room temperature, then concentrated. To a solution of the residue in MeOH (2 mL) was added NaOMe (10 mg) and the mixture was stirred for 48 h at 40 °C. Potassium hydroxide (0.2 M, 0.2 mL) was added and the solution was stirred for 10 h at 40 °C, neutralized with Amberlite IR-120 (H^+) resin and filtered. The resin was washed with MeOH, and combined filtrate and washings were concentrated. Column chromatography (5:5:1 $CHCl_3$-MeOH-H_2O) of the residue on Sephadex LH-20 gave **19** (20 mg, 75%) as an amorphous mass: $[\alpha]_D$ +2.0° (*c* 0.6, 5:5:1 $CHCl_3$-MeOH-H_2O); ^1H

NMR ($(CD_3)_2SO$-D_2O) δ 0.88 (t, 6H, J_{Me,CH_2} = 6.3 Hz, 2*Me*CH_2), 1.24 (s, 52H, 26CH_2), 1.76-1.88 (4s, 12H, 4AcN), 2.37-2.84 (m, 3H, H-3-e-g*eq*), 4.16 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1a), 4.28 (m, 2H, H-1b,d), 4.85 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1c), 5.32 (m, 1H, H-4 of sphingosine), 5.58 (m, 1H, H-5 of sphingosine).

Anal. Calcd for $C_{95}H_{165}N_5O_{47}$ (2129.4): C, 53.59; H, 7.81; N, 3.29. Found: C, 53.36; H, 7.79; N, 3.11.

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