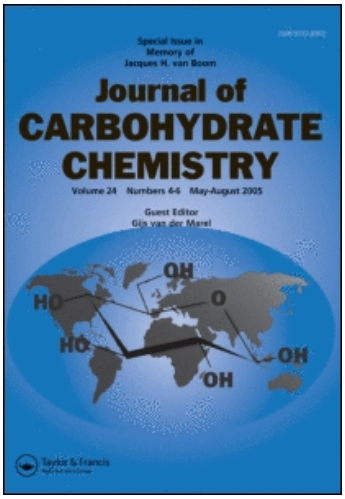

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 40: STEREOCONTROLLED SYNTHESIS OF SIALYL LEWIS X EPITOPE AND ITS CERAMIDE DERIVATIVE

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ABSTRACT

Stereocontrolled synthesis of sialyl Le^x epitope and its ceramide derivative with regard to the introduction of galactose or β-D-galactosyl ceramide into the terminal *N*-acetylglucosamine residue of sialyl Le^x determinant is described. Königs-Knorr condensation of 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**4**) with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl bromide (**5**) gave the desired β-glycoside **6**, which was converted into 2-(trimethylsilyl)ethyl *O*-(2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**8**) *via* removal of the phthaloyl and *O*-acetyl groups, followed by *N*-acetylation and 4,6-*O*-benzylidenation. Glycosylation of **8** with methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**9**) gave the α-glycoside (**10**), which was transformed by reductive ring-opening of the benzylidene acetal into the acceptor (**11**). Dimethyl(methylthio)sulfonium triflate (DMTST)-promoted coupling of **11** with 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 (**12**) afforded the desired pentasaccharide (**13**), which was converted into the α-trichloroacetimidate **16** *via* reductive removal of the benzyl groups, then *O*-acetylation, removal of the 2-(trimethylsilyl)ethyl group and treatment with trichloroacetonitrile. Condensation of **16** with (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (**18**) gave the β-glycoside **19**, which was transformed into the title compound **21**, *via* reduction of the azido group, coupling with octadecanoic acid, *O*-deacylation and hydrolysis of the methyl ester group. On the other hand, *O*-deacylation of **13** and subsequent hydrolysis of the methyl ester group gave the pentasaccharide epitope **17**.

INTRODUCTION

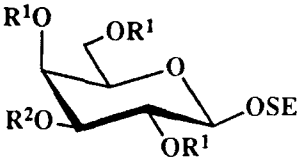
Sialyl Le^x ganglioside was first isolated[1] from human kidney and found[2] to be widespread as the tumor-associated ganglioside antigen. Recently, it has been reported[3] that selectin family (E-, P- or L-selectin) recognizes not only sialyl Le^x determinant, Neu5Acα(2→3)Galβ(1→4) [Fucα(1→3)]GlcNAc-, which is found as the terminal carbohydrate structure in both glycolipids and glycoproteins, but also sialyl Le^a and sialyl Le^x ganglioside. Sialyl-α(2→6)-Le^x ganglioside,[4] however, is not recognized[3C] at all by the selectin family. In view of these facts, it is of interest to elucidate the structural requirements for the recognition by selectin family.

Previously, we have synthesized sialyl Le^x ganglioside and the analogs[5] by use of the methyl β-thioglycosides of sialyl α(2→3)- and sialyl α(2→6)-galactose derivatives[6,7] as the glycosyl donors which are easily prepared according to our newly developed α-glycosylation of sialic acid.[8,9] We describe here the stereocontrolled synthesis of sialyl Le^x oligosaccharide epitope (pentasaccharide), Neu5Acα(2→3)-Galβ(1→4) [Fucα(1→3)]Glc-NAcβ(1→3)Gal, and its ceramide derivative.

RESULTS AND DISCUSSION

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[6] (**12**) was selected as the glycosyl donor, and 2-(trimethylsilyl)ethyl *O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-*O*-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**11**) as the glycosyl aceptor in the synthesis of sialyl Le^x epitope. Coupling of **12** with **11**, and the intermediate obtained could then, by removal of the protecting groups or introduction of the ceramide moiety, be transformed to the end products. 2-(Trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**4**) was obtained in good yield from 2-(trimethylsilyl)ethyl β-D-galactopyranoside[10] (**1**) *via* dibutyltin oxide-mediated selective 3-*O*-4-methoxybenzylation using 4-methoxybenzyl chloride and tetrabutylammonium bromide, *O*-benzylation, and oxidative removal of the 4-methoxybenzyl group with 2,3-dichloro-5,6-dicyanobenzoquinone.[11]

The glycosylation of **4** with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl bromide[12] (**5**) in dichloromethane in the presence of silver carbonate and silver perchlorate gave the desired β-glycoside **6** in 76% yield. Significant signals of the GlcN unit in the ^1H NMR spectrum of **6** were at δ 5.81 (d, $J_{1,2}$ = 8.4 Hz, H-1), 5.26 (t, $J_{2,3} = J_{3,4}$ = 9.3 Hz, H-3), and 5.94 (dd, $J_{4,5}$ = 10.7 Hz, H-4), indicating the

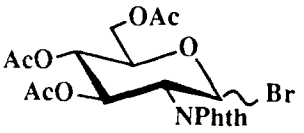


1 $R^1=R^2=H$

2 $R^1=H$, $R^2=MPM$

3 $R^1=Bn$, $R^2=MPM$

4 $R^1=Bn$, $R^2=H$



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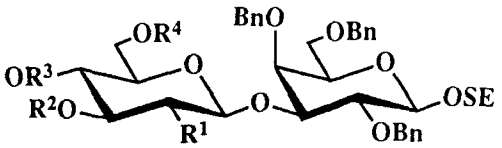
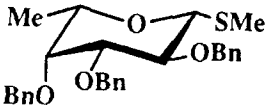


	R^1	R^2	R^3	R^4
6	NPhth	Ac	Ac	Ac
7	NHAc	H	H	H
8	NHAc	H	-benzylidene-	



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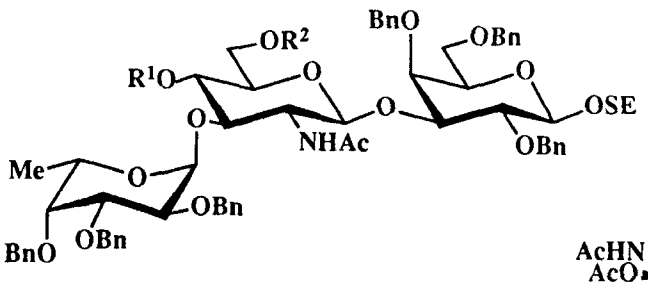
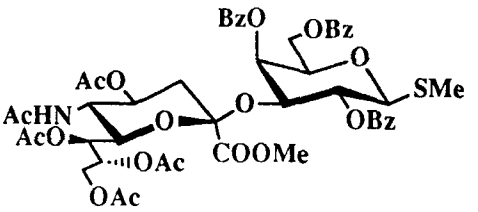


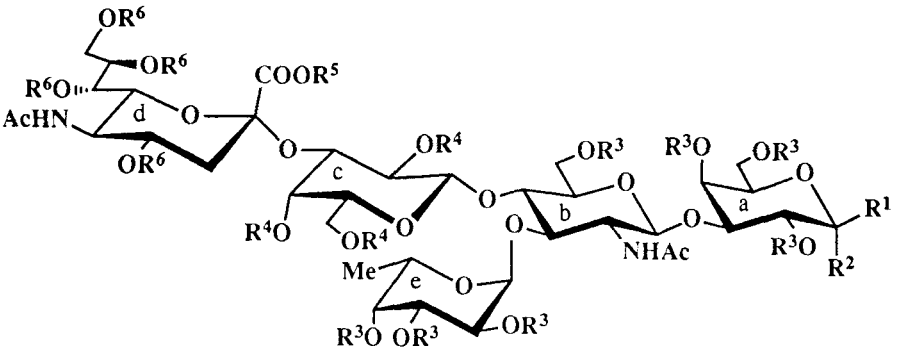
10 $R^1=R^2=$benzylidene

11 $R^1=H$, $R^2=Bn$

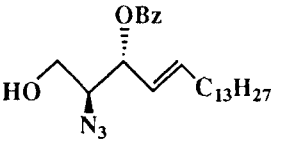


12

SE=2-(trimethylsilyl)ethyl
MPM=*p*-methoxybenzyl
Bn=benzyl
Bz=benzoyl



	R^1	R^2	R^3	R^4	R^5	R^6
13	OSE	H	Bn	Bz	Me	Ac
14	OSE	H	Ac	Bz	Me	Ac
15	OH,H		Ac	Bz	Me	Ac
16	H	$OC(=NH)CCl_3$	Ac	Bz	Me	Ac
17	OSE	H	H	H	H	H



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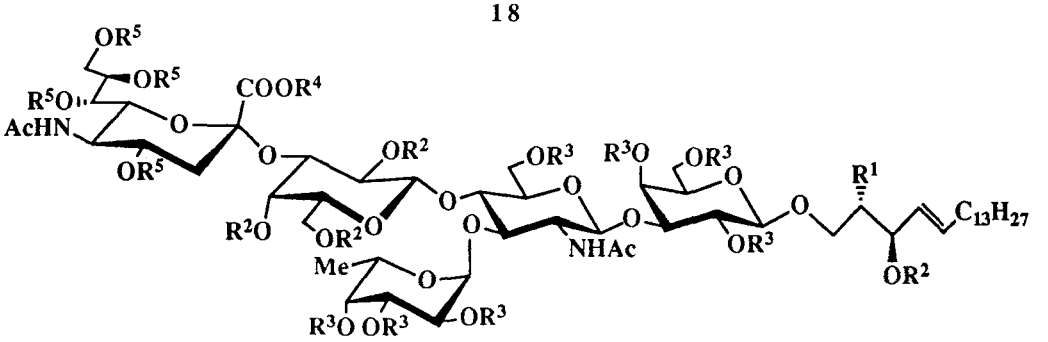

	R^1	R^2	R^3	R^4	R^5
19	N_3	Bz	Ac	Me	Ac
20	$NHCOC_{17}H_{35}$	Bz	Ac	Me	Ac
21	$NHCOC_{17}H_{35}$	H	H	H	H

newly formed glycosidic linkage to be β. *O*-Deacetylation of **6** with sodium methoxide, followed by heating with hydrazine hydrate in aqueous 95% ethanol, and subsequent *N*-acetylation afforded 2-(trimethylsilyl)ethyl *O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**7**) in 82% yield. Treatment of **7** with benzaldehyde dimethyl acetal in *N,N*-dimethylformamide in the presence of *p*-toluenesulfonic acid monohydrate gave the 4,6-*O*-benzylidene derivative **8** in 88% yield.

The glycosylation of **8** with methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside[5b,13] (**9**), in the presence of dimethyl(methylthio)sulfonium triflate[14] (DMTST) as the glycosyl promoter and powdered molecular sieves 4Å (MS-4Å) in benzene for 10 h at 5~10 °C gave the desired α-glycoside **10** in 97% yield; significant signals of the fucose unit in the ^{1}H NMR spectrum were a three-proton doublet at δ 0.87 ($J_{5,6}$ = 6.4 Hz, H-6) and a one-proton doublet at δ 5.07 ($J_{1,2}$ = 3.6 Hz, H-1), indicating the structure assigned. Reductive ring-opening of the benzylidene acetal in **10** with sodium cyanoborohydride-hydrogen chloride according to the method by Garegg et al.[15] afforded compound **11** in 77% yield. Glycosylation of **11** with **12** in dichloromethane for 16 h at 6 °C in the presence of 1.5 equiv. of DMTST to the glycosyl donor and MS-4Å gave the pentasaccharide **13** in 57% yield, which had the expected stereochemistry. The ^{1}H NMR were a three-proton doublet at δ 1.15 ($J_{5,6}$ = 6.4 Hz, H-6e), two three-proton singlets at δ 1.58 and 1.61 (*N*-acetyl), four three-proton singlets at δ 1.80, 1.93, 1.98, and 2.15 (*O*-acetyl), a three-proton singlet at δ 3.79 (*O*-methyl), fifty aromatic protons at δ 7.14-8.22 (10 Ph), and a one-proton doublet of doublets at δ 5.46 ($J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 9.9 Hz, H-2c), indicating the newly formed glycosidic linkage to be β.

Catalytic hydrogenolysis (10% Pd-C) of the benzyl groups of **13** in ethanol-formic acid for 48 h at 45 °C and subsequent *O*-acetylation gave the per-*O*-acyl compound **14** in 66% yield, which, on *O*-deacylation with sodium methoxide in methanol and subsequent saponification of the methyl ester group, yielded the desired sialyl Le^x oligosaccharide **17** in quantitative yield. Treatment[16] of **14** with trifluoroacetic acid in dichloromethane for 30 min at 0 °C gave the 1-hydroxy compound **15**. When treated with trichloroacetonitrile in dichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 3 h at 0 °C, **15** gave the α-trichloroacetimidate **16** in 85% yield. The ^{1}H NMR data for the Gal unit in **16** [δ 6.46 ($J_{1,2}$ = 3.9 Hz, H-1), 8.65 (C=NH)] indicated the trichloroacetimidate to be α.

The final glycosylation of (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol[17](**18**) with **16** thus obtained, in dichloromethane in the presence of boron trifluoride etherate[17b,18] for 8 h at 0 °C afforded the expected β-glycoside **19** in 71% yield. Selective reduction[17b,19] of the azide group in **19** with hydrogen sulfide in

aqueous pyridine for 3 days at 0 °C gave the amine, which, on condensation with octadecanoic acid, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) in dichloromethane gave the acylated sialyl Le^x **20** in 80% yield, after chromatography.

Finally, *O*-deacylation of **20** with sodium methoxide in methanol, with subsequent saponification of the methyl ester group, yielded the desired sialyl Le^x ceramide **21**, Neu5Acα(2→3)Galβ(1→4) [Fucα(1→3)]GlcNAcβ(1→3)Galβ(1→1)Cer, in quantitative yield after chromatography on a column of Sephadex LH-20. Compound **17** and **21** synthesized here were recognized[3c] by E-selectin (ELAM-1; endotherial leukocyte adhesion molecule-1).

EXPERIMENTAL

General Procedures. Specific rotations were determined with a Union PM-201 polarimeter at 25 °C, and IR spectra were recorded with a Jasco A-100 spectrophotometer. ^1H NMR spectra were recorded with a JEOL JNM-GX 270 spectrometer. Preparative chromatography was performed on silica gel (Wako Chemical Co., 200 mesh) with the solvent systems specified. Concentrations were conducted *in vacuo*.

2-(Trimethylsilyl)ethyl 3-*O*-(4-Methoxybenzyl)-β-D-galactopyranoside (2). A suspension of 2-(trimethylsilyl)ethyl β-D-galactopyranoside (**1**[10]; 17 g, 60.6 mmol) and dibutyltin oxide (20 g) in methanol (170 mL) was stirred and heated for 10 h at 55 °C, then concentrated. To a solution of the residue in benzene (170 mL) were added 4-methoxybenzyl chloride (25 mL) and tetrabutylammonium bromide (10 g), and the mixture was boiled, with stirring, under reflux for 4 h, then concentrated. Column chromatography (3:1 ethyl acetate-hexane) of the residue on silica gel (500 g) gave **2** (15.4 g, 63%). Recrystallization from ethyl acetate-hexane gave needles with mp 69-71 °C: $[\alpha]_D$ -8.5° (*c* 1.1, $CHCl_3$); IR (KBr) 3600-3200 (OH), 860 and 830 (TMS), and 750 and 690 cm^{-1} (Ph).

Anal. Calcd for $C_{19}H_{32}O_7Si$ (400.5): C, 56.97; H, 8.05. Found: C, 56.83; H, 8.22.

2-(Trimethylsilyl)ethyl 2,4,6-Tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-β-D-galactopyranoside (3). To a solution of **2** (15.4 g, 38.4 mmol) in *N,N*-dimethylformamide (DMF, 150 mL) was added a suspension of sodium hydride in oil (7 g, 60% of sodium hydride by weight). The mixture was stirred for 30 min at 0 °C, benzyl bromide (20 mL, 168 mmol) was added dropwise, and stirring was continued for 3 h at room temperature. The reaction was monitored by TLC and, when complete, methanol (5 mL) was added, and the mixture was concentrated and extracted with dichloro-methane. The extract was washed with water, dried (Na_2SO_4) and concentrated. Column

chromatography (1:5 ethyl acetate-hexane) of the residue on silica gel (600 g) gave **3** (23 g, 89%) as a syrup: $[\alpha]_D$ -5.7° (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.03 (m, 2H, $Me_3SiCH_2CH_2$), 3.78 (s, 3H, MeO), 4.00 (m, 1H, $Me_3SiCH_2CH_2$), 4.35 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), and 6.82-7.38 (m, 19H, 4 Ph).

Anal. Calcd for $C_{40}H_{50}O_7Si$ (670.9): C, 71.61; H, 7.51. Found: C, 71.58; H, 7.69.

2-(Trimethylsilyl)ethyl 2,4,6-Tri-*O*-benzyl-β-D-galactopyranoside (4). To a stirred solution of **3** (13.4 g, 20 mmol) in dichloromethane (180 mL) were added 2,3-dichloro-5,6-dicyanobenzoquinone (6.8 g, 30 mmol) and water (10 mL), and stirring was continued for 1 h at room temperature. The precipitate was collected and washed with dichloromethane, and the combined filtrate and washings were washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (1:6 ethyl acetate-hexane) of the residue on silica gel (500 g) gave **4** (9.5 g, 87%) as an amorphous mass: $[\alpha]_D$ -0.5° (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.01 (m, 2H, $Me_3SiCH_2CH_2$), 2.31 (broad d, 1H, OH), 3.83 (d, 1H, $J_{3,4}$ = 2.9 Hz, H-4), 3.98 (m, 1H, $Me_3SiCH_2CH_2$), 4.34 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1), and 7.21-7.37 (m, 15H, 3Ph).

Anal. Calcd for $C_{32}H_{42}O_6Si$ (550.8): C, 69.78; H, 7.69. Found: C, 69.53; H, 7.65.

2-(Trimethylsilyl)ethyl *O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (6). To a solution of **4** (11.5 g, 21 mmol) in dichloromethane (45 mL) were added silver carbonate (11.5 g, 42 mmol), silver perchlorate (4.3 g, 21 mmol), and powdered molecular sieves 4 Å (20 g), and the mixture was stirred for 20 h at room temperature in the dark (mixture **A**). A solution of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl bromide (**5**[12]; 14 g, 28 mmol) in dichloromethane (28 mL) was treated with powdered molecular sieves 4 Å (15 g) as above and then added to mixture A at room temperature. After vigorous stirring for 24 h in the dark, the precipitate was collected and washed with dichloromethane, and the combined filtrate and washings were concentrated. Column chromatography (1:1 ethyl acetate-hexane) of the residue on silica gel (500 g) afforded **6** (15.4 g, 76%). Recrystallization from ethyl acetate-hexane gave needles: mp 140-142 °C, $[\alpha]_D$ -4.5° (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (m, 2H, $Me_3SiCH_2CH_2$), 1.95, 2.11, 2.13 (3s, 9H, 3AcO), 3.88 (dd, 1H, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 3.1 Hz, H-3 for Gal), 4.04 (d, 1H, H-4 for Gal), 4.35 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1 for Gal), 5.26 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, H-3 for GlcN), 5.81 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1 for GlcN), 5.94 (dd, 1H, $J_{4,5}$ = 10.7 Hz, H-4 for GlcN), and 7.17-7.44 (m, 15H, 3Ph).

Anal. Calcd for $C_{52}H_{61}NO_{15}Si$ (968.1): C, 64.51; H, 6.35; N, 1.45. Found: C, 64.38; H, 6.40; N, 1.52.

2-(Trimethylsilyl)ethyl *O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (7). A solution of **6** (15.4 g, 16 mmol) in methanol (250 mL) was stirred with sodium methoxide (500 mg) for 2 h at room temperature. The mixture was treated with Amberlite IR-120 (H^+) resin and concentrated, and a solution of the residue in aqueous 95% ethanol (100 mL) was treated with hydrazine hydrate (3.5 mL) for 2 h under reflux. The precipitate was collected and washed with ethanol, and the combined filtrate and washings were concentrated. The residue was treated with acetic anhydride (7.5 mL) in methanol (100 mL) for 3 h at room temperature, pyridine (13 mL) was added, the mixture was concentrated, and a solution of the residue in dichloromethane (500 mL) was successively washed with 2 M hydrochloric acid, water, and M sodium carbonate, dried (Na_2SO_4) and concentrated. Column chromatography (4:1 ethyl acetate-hexane) of the residue on silica gel (300 g) afforded **7** (9.8 g, 82%) as crystals. Recrystallization from ethyl acetate-hexane gave needles: mp 94-96 °C, $[\alpha]_D$ -22.0° (*c* 0.9, $CHCl_3$); IR (KBr) 3600-3300 (OH, NH), 1650 and 1560 (amide), 860 and 840 (TMS), and 740 and 700 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.98 (m, 2H, $Me_3SiCH_2CH_2$), 1.56 (s, 3H, AcN), 5.87 (d, 1H, NH), and 7.20-7.40 (m, 15H, 3Ph).

Anal. Calcd for $C_{40}H_{55}NO_{11}Si$ (754.0): C, 63.72; H, 7.35; N, 1.86. Found: C, 53.81; H, 7.25; N, 1.85.

2-(Trimethylsilyl)ethyl *O*-(2-Acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (8). To a solution of **7** (9.7 g, 13 mmol) in DMF (80 mL) was added Drierite (2.5 g), and the mixture was stirred for 2 h at room temperature. Benzaldehyde dimethyl acetal (3.9 mL, 26 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg) were added, and the mixture was stirred for 48 h at room temperature, then neutralized with Amberlite IR-410 (HO^-) resin and concentrated. Column chromatography (1:1 ethyl acetate-hexane) of the residue on silica gel (300 g) afforded **8** (9.5 g, 88%) as an amorphous mass: $[\alpha]_D$ +22.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.99 (m, 2H, $Me_3SiCH_2CH_2$), 1.54 (s, 3H, AcN), 5.59 (s, 1H, PhC*H*), and 7.27-7.54 (m, 20H, 4Ph).

Anal. Calcd for $C_{47}H_{59}NO_{11}Si$ (842.1): C, 67.04; H, 7.06; N, 1.66. Found: C, 67.05; H, 7.17; N, 1.55.

2-(Trimethylsilyl)ethyl *O*-(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (10). To a solution of **8** (1.3 g, 1.54 mmol) and methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**9**[5b,13]; 860 mg, 1.85 mmol) in dry benzene (20 mL) were added powdered molecular sieves 4 Å (MS-4Å, 3.5 g), and the mixture was stirred for 8 h at room temperature then cooled to 7 °C. DMTST (2.1 g, 4.7

mmol) and MS-4Å (1.5 g) were added to the mixture, and the mixture was stirred for 10 h at 5~10 °C; the course of the reaction was monitored by TLC. The mixture was diluted with dichloromethane, the precipitate was collected and washed with dichloromethane, and the combined filtrate and washings were washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (1:3 ethyl acetate-hexane) of the residue on silica gel (150 g) gave **10** (1.88 g, 97%) as an amorphous mass: $[\alpha]_D$ -63.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6 for fucose), 0.97 (m, 2H, $Me_3SiCH_2CH_2$), 1.48 (s, 3H, AcN), 5.07 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1 for fucose), 5.21 (d, 1H, NH), 5.53 (s, 1H, PhC*H*), and 7.24-7.48 (m, 35H, 7Ph).

Anal. Calcd for $C_{74}H_{87}NO_{15}Si$ (1258.6): C, 70.62; H, 6.97; N, 1.11. Found: C, 70.51; H, 7.08; N, 1.11.

2-(Trimethylsilyl)ethyl *O*-(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-*O*-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (11). To a solution of **10** (1.8 g, 1.43 mmol) in dry tetrahydrofuran (20 mL) were added MS-3Å (3 g), and the mixture was stirred for 1 h at room temperature, and sodium cyanoborohydride (1.3 g) was gradually added. After the reagent had dissolved, hydrogen chloride in ether was added dropwise at room temperature until the evolution of gas ceased. TLC indicated that the reaction was complete after 5 min. The mixture was neutralized with triethylamine and filtered, the residue was washed with methanol and the combined filtrate and washings were concentrated then extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (1:2 ethyl acetate-hexane) of the residue on silica gel (100 g) afforded **11** (1.38 g, 77%) as an amorphous mass: $[\alpha]_D$ -32.0° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.99 (m, 2H, $Me_3SiCH_2CH_2$), 1.16 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6 for fucose), 1.41 (s, 3H, AcN), and 7.24-7.43 (m, 35H, 7Ph).

Anal. Calcd for $C_{74}H_{89}NO_{15}Si$ (1260.6): C, 70.51; H, 7.12; N, 1.11. Found: C, 70.41; H, 7.28; N, 1.12.

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)-(1-4)-*O*-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)] -*O*-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (13). To a solution of **11** (79 mg, 0.079 mmol) and **12**[6] (200 mg, 0.16 mmol) in dry dichloromethane (0.8 mL) was added MS-4Å (460 mg), and the mixture was stirred for 5 h at room temperature and cooled to 0 °C. DMTST (61 mg, 0.235 mmol) was added to the mixture, and the mixture was stirred for 16 h at 6 °C, filtered, washed with dichloromethane. The combined filtrate and washings were washed with water, dried (Na_2SO_4) and concentrated. Column

chromatography (4:1 ethyl acetate-hexane) of the residue on silica gel (20 g) gave **13** (98.5 mg, 57%) as an amorphous mass: $[\alpha]_D$ -25.7° (*c* 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.98 (m, 2H, $Me_3SiCH_2CH_2$), 1.15 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6e), 1.58, 1.61 (2s, 6H, 2AcN), 1.80, 1.93, 1.98, 2.15 (4s, 12H, 4AcO), 2.44 (dd, 1H, Jgem = 12.8 Hz, $J_{3eq,4}$ = 4.7 Hz, H-3d-*eq*), 3.79 (s, 3H, MeO), 5.26 (dd, 1H, $J_{6,7}$ = 2.9 Hz, $J_{7,8}$ = 9.5 Hz, H-7d), 5.34 (d, 1H, $J_{3,4}$ = 3.3 Hz, H-4c), 5.46 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 10.1 Hz, H-2c), 5.69 (m, 1H, H-8d), and 7.14-8.22 (m, 50H, 10Ph).

Anal. Calcd for $C_{121}H_{138}N_2O_{35}Si$ (2208.5): C, 65.81; H, 6.30; N, 1.27. Found: C, 65.73; H, 6.45; N, 1.28.

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→4)-*O*-[(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-*O*-(2-acetamido-6-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (14). A solution of **13** (180 mg, 0.082 mmol) in ethanol (24 mL) and formic acid (5 mL) was hydrogenolyzed in the presence of 10% Pd-C (180 mg) for 48 h at 45 °C, then filtered and concentrated. The residue was acetylated with acetic anhydride (0.2 mL)-pyridine (0.8 mL) for 16 h at room temperature. The product was purified by chromatography on a column of silica gel (15 g) with 2:1 ethyl acetate-hexane afforded **14** (100 mg, 66%) as an amorphous mass: $[\alpha]_D$ -23.5° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.91 (m, 2H, $Me_3SiCH_2CH_2$), 1.21 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6e), 1.57, 1.78 (2s, 6H, 2AcN), 1.83-2.12 (11s, 33H, 11AcO), 2.42 (dd, 1H, Jgem = 12.8 Hz, $J_{3eq,4}$ = 4.7 Hz, H-3d-*eq*), 3.81 (s, 3H, MeO), 5.24 (dd, 1H, $J_{6,7}$ = 3.3 Hz, $J_{7,8}$ = 10.5 Hz, H-7d), 5.65 (m, 1H, H-8e), and 7.45-8.12 (m, 15H, 3Ph).

Anal. Calcd for $C_{86}H_{110}N_2O_{42}Si$ (1871.9): C, 55.18; H, 5.92; N, 1.50. Found: C, 55.03; H, 5.98; N, 1.49.

***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→4)-*O*-[(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-*O*-(2-acetamido-6-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-D-galactopyranose (15).** To a solution of **14** (150 mg, 0.08 mmol) in dichloromethane 10.8 mL) was added trifluoroacetic acid (1.6 mL) at 0 °C, and the mixture was stirred for 30 min at 0 °C and concentrated. Column chromatography (3:1 ethyl acetate-hexane) of the residue on silica gel (20 g) gave **15** (140 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -5.2° (*c* 1.2, $CHCl_3$); IR (KBr) 3600-3300 (OH, NH), 1740 and 1230 (ester), 1670 and 1550 (amide), and 760 and 720 (Ph).

Anal. Calcd for $C_{81}H_{98}N_2O_{42}$ (1771.7): C, 54.91; H, 5.58; N, 1.58. Found: C, 55.03; H, 5.71; N, 1.59.

***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→4)-*O*-[(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-*O*-(2-acetamido-6-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (16).** To a solution of **15** (60 mg, 0.034 mmol) in dichloromethane (0.7 mL) and trichloroacetonitrile (0.1 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 5.2 mg) at -5 °C, and the mixture was stirred for 3 h at 0 °C, then concentrated. Column chromatography (30:1 dichloromethane-methanol) of the residue on silica gel (20 g) gave **16** (55 mg, 85%) as an amorphous mass: $[\alpha]_D$ +6.0° (*c* 1.1, $CHCl_3$); IR (KBr) 3350 (NH), 1750 and 1230 (ester), 1680 and 1540 (amide), and 750 and 720 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.21 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6e), 1.56, 1.77 (2s, 6H, 2AcN), 1.81-2.11 (11s, 33H, 11AcO), 2.41 (dd, 1H, Jgem = 12.7 Hz, $J_{3eq,4}$ = 4.5 Hz, H-3d-*eq*), 3.81 (s, 3H, MeO), 5.63 (m, 1H, H-8d), 6.49 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1a), 7.45-8.17 (m, 15H, 3Ph), and 8.65 (s, 1H, C=NH).

Anal. Calcd for $C_{83}H_{98}N_3O_{42}Cl_3$ (1916.1): C, 52.03; H, 5.16; N, 2.19. Found: C, 52.01; H, 5.25; N, 2.25.

2-(Trimethylsilyl)ethyl *O*-(5-Acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→3)-*O*-(β-D-galactopyranosyl)-(1→4)-*O*-[(α-L-fucopyranosyl)-(1→3)]-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-β-D-galactopyranoside (17). To a solution of **14** (93 mg, 0.05 mmol) in methanol (5 mL) was added sodium methoxide (30 mg), and the mixture was stirred for 24 h at 40 °C, and water (0.2 mL) was added. The solution was stirred for 10 h at room temperature, then treated with Amberlite IR-120 (H^+) resin, and filtered. The resin was washed with methanol, and the combined filtrate and washings were concentrated. Column chromatography (1:1 water-methanol) of the residue on Sephadex LH-20 (30 g) gave **17** (53 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -40.5° (*c* 0.4, MeOH); ^1H NMR (CD_3OD) δ 0.99 (m, 2H, $Me_3SiCH_2CH_2$), 1.13 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6e), 1.95, 1.98 (2s, 6H, 2AcN), 2.85 (dd, 1H, H-3d-*eq*), 4.21 (d, 1H, $J_{1,2}$ = 7.1 Hz, H-1 for Gal), 4.48 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1 for Gal), 4.66 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1b), and 5.03 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1e).

Anal. Calcd for $C_{42}H_{75}N_2O_{28}Si$ (1084.1): C, 46.53; H, 6.97; N, 2.58. Found: C, 46.47; H, 7.18; N, 2.61.

***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→4)-*O*-[(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-*O*-(2-acetamido-6-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,3,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (19).** To a

solution of **16** (117 mg, 0.06 mmol) and (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (**18**[17]; 78 mg, 0.18 mmol) in dichloromethane (1.2 mL) was added MS-4Å (AW-300, 1.2 g) and the mixture was stirred for 5 h at room temperature, then cooled to 0°C. Boron trifluoride etherate (32 μL) was added, and the mixture was stirred for 8 h at 0 °C and then filtered. The insoluble material was washed with dichloromethane, and the combined filtrate and washings were washed with M sodium hydrogen carbonate and water, dried (Na_2SO_4) and concentrated. Column chromatography (40:1 dichloromethane-methanol) of the residue on silica gel (20 g) gave **19** (94 mg, 71%) as an amorphous mass: $[\alpha]_D$ -18.0° (*c* 0.6, $CHCl_3$); IR (KBr) 3370 (NH), 2940 and 2860 (methyl, methylene), 2100 (N_3), 1740 and 1230 (ester), 1690 and 1540 (amide), and 750 and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, $J_{Me,CH2}$ = 6.7 Hz, *Me*CH_2), 1.24 (s, 22H, 11CH_2), 1.56, 1.77 (2s, 6H, 2AcN), 1.82-2.11 (11s, 33H, 11AcO), 2.41 (dd, 1H, Jgem = 12.8 Hz, $J_{3eq,4}$ = 4.6 Hz, H-3d-*eq*), 3.81 (s, 3H, MeO), 5.28 (dd, 1H, $J_{6,7}$ = 2.9 Hz, $J_{7,8}$ = 10.9 Hz, H-7d), 5.64 (m, 1H, H-8d), 5.91 (m, 1H, H-5 for sphingosine), and 7.41-8.17 (m, 20H, 4Ph).

Anal. Calcd for $C_{106}H_{135}N_5O_{44}$ (2183.2): C, 58.32; H, 6.23; N, 3.21. Found: C, 58.22; H, 6.31; N, 3.18.

***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→4)-*O*-[(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-*O*-(2-acetamido-6-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol (20).** Hydrogen sulfide was bubbled through a stirred solution of **19** (30 mg, 0.0137 mmol) in aqueous 83% pyridine (3 mL) for 3 days at 0 °C. The mixture was concentrated, and the residue was stirred with octadecanoic acid (8 mg, 0.028 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (8 mg, 0.042 mmol) in dry dichloromethane (0.7 mL) for 24 h at room temperature. Dichloromethane (50 mL) was added, and the mixture was washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (40:1 dichloromethane-methanol) of the residue on silica gel (20 g) gave **20** (26.5 mg, 80%) as an amorphous mass: $[\alpha]_D$ -9.7° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, 2*Me*CH_2), 1.26 (s, 52H, 26CH_2) 1.57, 1.78 (2s, 6H, 2AcN), 1.83-2.11 (11s, 33H, 11AcO), 2.41 (dd, 1H, Jgem = 13.0 Hz, $J_{3eq,4}$ = 4.4 Hz, H-3d-*eq*), 3.43 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 3.7 Hz, H-3a), 3.81 (s, 3H, MeO), 5.06 (d, 1H, $J_{1,2}$ = 3.1 Hz, H-1e), 5.28 (dd, 1H, $J_{6,7}$ = 2.6 Hz, $J_{7,8}$ = 9.9 Hz, H-7d), 5.65 (m, 1H, H-8d), 5.85 (dt, 1H, H-5 for sphingosine), and 7.40-8.17 (m, 20H, 4Ph).

Anal. Calcd for $C_{124}H_{171}N_3O_{45}$ (2423.7): C, 61.45; H, 7.11; N, 1.73. Found: C, 61.37; H, 7.29; N, 1.71.

***O*-(5-Acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→3)-*O*-(β-D-galactopyranosyl)-(1→4)-*O*-[(α-L-fucopyranosyl)-(1→3)]-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(β-D-galactopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-2-octadecanamido-4-octadecene-1,3-diol (21).** Deacylation and saponification of **20** (36 mg, 0.015 mmol), as described for **17**, yielded **21** (22 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -18.5° (*c* 0.69, 5:4:0.7 $CHCl_3$-MeOH-H_2O); ^1H NMR [49:1 $(CD_3)_2SO$-D_2O] δ 0.92 (t, 6H, 2*Me*CH_2), 1.05 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6e), 1.30 (s, 52H, 26CH_2), 1.88, 1.97 (2s, 6H, 2AcN), 2.09 (t, 2H, COC*H*$_2$$CH_2$), 2.84 (dd, 1H, H-3d-*eq*), 4.36 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1 for Gal), 4.76 (d, 1H, $J_{1,2}$ = 6.0 Hz, H-1b), 4.92 (d, 1H, $J_{1,2}$ = 3.1 Hz, H-1e), 5.40 (dd, 1H, $J_{3,4}$ = 6.8 Hz, $J_{4,5}$ = 15.2 Hz, H-4 for sphingosine), and 5.60 (dt, 1H, $J_{5,6}$ = $J_{5,6'}$ = 7.5 Hz, H-5 for sphingosine).

Anal. Calcd for $C_{73}H_{131}N_3O_{30}$ (1530.8): C, 57.27; H, 8.63; N, 2.74. Found: C, 57.08; H, 8.90; N, 2.69.

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