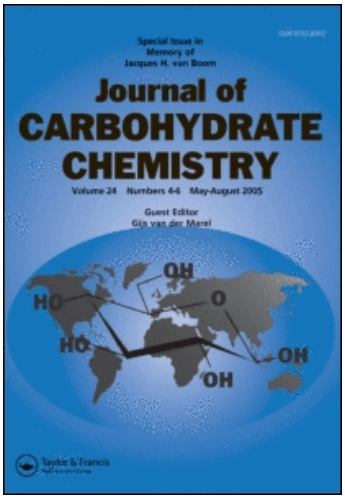

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 52: SYNTHESIS OF SIALYL LEWIS X ANALOGS CONTAINING AZIDOALKYL GROUPS AT THE REDUCING END

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ABSTRACT

Stereocontrolled synthesis of sialyl Le^x epitope analogs in which the terminal *N*-acetylglucosamine residue of sialyl Le^x determinant is replaced by a D-glucopyranose residue containing β-glycosidically linked azidoalkyl groups is described. Glycosylation of 2-(trimethylsilyl)ethyl *O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-2,6-di-*O*-benzoyl-β-D-glucopyranoside (**2**), prepared from 2-(trimethylsilyl)ethyl β-lactoside (**1**) by 3,4-*O*-isopropylidenation and selective-*O*-benzoylation, with methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**3**) gave the desired α-glycoside **4**, which was converted by *O*-deisopropylidenation into **7**, and *via* *O*-debenzoylation, selective 2,6,6'-tri-*O*-benzoylation and *O*-deisopropylidenation into **8**, respectively. *N*-Iodosuccinimide (NIS)-TfOH-promoted glycosylation of **7** or **8** with methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**9**) afforded the desired tetrasaccharides **10** and **11**.

Compound **11** was converted into the α-trichloroacetimidate **14** *via* reductive removal of the benzyl groups, *O*-acetylation, removal of the 2-(trimethylsilyl)ethyl group and treatment with trichloroacetonitrile. Coupling of **14** with 2-azidoethanol, 8-azidooctanol, and 2-[2-(2-azidoethoxy)ethoxy]ethanol, gave the desired β-glycosides **15-17**, respectively. *O*-Deacylation of **12**, **15-17** and subsequent hydrolysis of the methyl ester group yielded the title compounds.

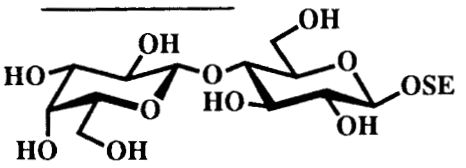
INTRODUCTION

Recently, it has been demonstrated[1-3] that the selectin family, such as E-selectin (endotherial leukocyte adhesion molecule-1, ELAM-1), P-selectin (granule membrane protein, GMP-140), and L-selectin (LECAM-1), recognizes the sialyl Le^x determinant, α-Neu5Ac-(2→3)-β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-β-GlcNAc, which is found as the terminal carbohydrate structure of both cell membrane glycolipids and glycoproteins.

Previously, we have reported the synthesis of sialyl Le^x ganglioside (a hexasaccharide[4] and pentasaccharide[5]), α-sialyl-(2→6)-Le^x ganglioside,[6] and the analogs,[7] and have examined their recognition activity by selectin family. The data[3,7b,8-11] showed that the fucose structure was required for full recognition, the side-chain structure of the sialic acid residue was not critical for the activity, and α-sialyl-(2→6)Le^x ganglioside was not recognized at all. Recently, it has been shown that the terminal *N*-acetylglucosamine residue of sialyl Le^x oligosaccharide could be replaced[12] by D-glucopyranose without decreasing the activity, indicating the more detailed structural requirement necessary for selectin recognition. In view of these facts, we describe herein the stereocontrolled synthesis of sialyl Le^x analogs in which the terminal *N*-acetylglucosamine is replaced by D-glucopyranose residues containing β-glycosidically linked azidoalkyl groups. Availability of these analogs is directed toward elucidation of cell-cell adhesion mechanism and application of the sialyl Le^x epitope structure to medicinal use.

RESULTS AND DISCUSSION

Treatment of 2-(trimethylsilyl)ethyl *O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside[13] (**1**) with 2,2-dimethoxypropane (2.0 equiv to **1**) in *N*,*N*-dimethylformamide (DMF) containing *p*-toluenesulfonic acid monohydrate for 3 h at 80 °C, afforded the 3,4-*O*-isopropylidene derivative, which, on selective 2,6,2',6'-*O*-benzoylation with benzoyl chloride, gave the desired glycosyl acceptor **2** in 54% yield; significant signals in the ^1H NMR spectrum were a one-proton doublet of doublets at δ 5.36 ($J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 9.5 Hz, H-2 for Gal), a triplet at δ 5.52 due to H-2 of Glc, and twenty aromatic protons due to four phenyl groups at δ 7.31-8.26, indicating the structure assigned. Dimethyl(methylthio)sulfonium triflate[14] (DMTST)-promoted glycosylation of **2** with methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside[4b,15] (**3**) in benzene for 3 h at 0 °C gave the desired α-glycoside **4** in 90% yield. The ^1H NMR signal for the Fuc unit in **4** [δ 5.62 ($J_{1,2}$ = 4.1 Hz, H-1)] indicated the glycosidic configuration to be α. Hydrolytic removal of the isopropylidene group in **4** under mild, acidic conditions gave the glycosyl acceptor **7** in 90% yield. Alternatively, the other glycosyl acceptor **8**, in which the C-2, C-3 and C-4 hydroxyl groups of the galactose residue are not protected, designed to give a better yield for the next α-glycosylation using a sialic acid glycosyl donor, was prepared in good yield *via* *O*-debenzoylation of **4** and selective *O*-benzoylation followed by hydrolytic removal of the isopropylidene group; significant signals in the ^1H NMR spectrum were two one-proton doublets of doublets (δ 4.12, $J_{1,2}$ = 7.7 Hz, $J_{2,3}$ = 9.3 Hz, H-2 for Gal; δ 5.18, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 9.3 Hz, H-2 for Glc) and thirty aromatic protons due to six phenyl groups, indicating the structure assigned.



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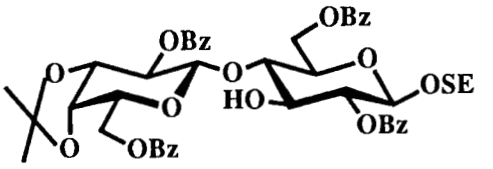

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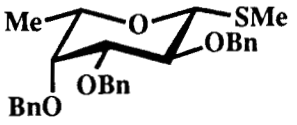
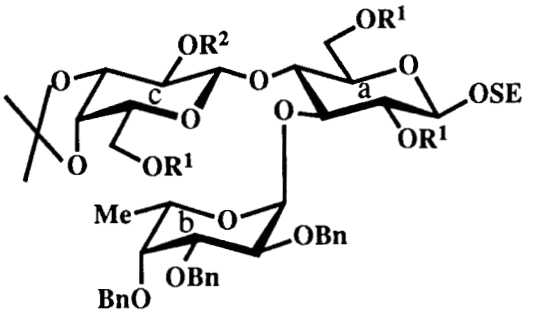
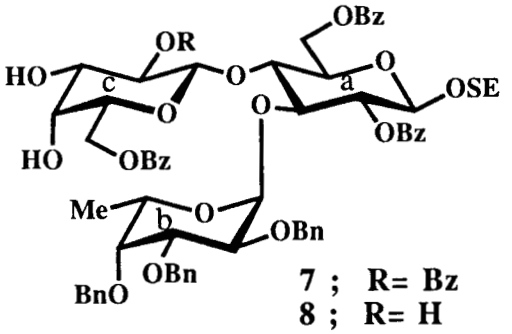


3

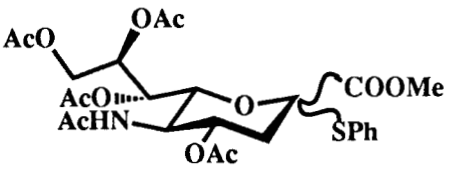
SE ; 2-(trimethylsilyl)ethyl
Bz ; benzoyl
Bn ; benzyl



	R^1	R^2
4	Bz	Bz
5	H	H
6	Bz	H



7 ; R= Bz
8 ; R= H



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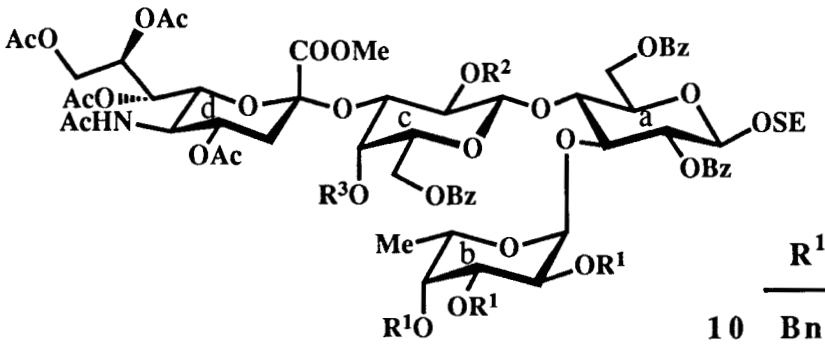
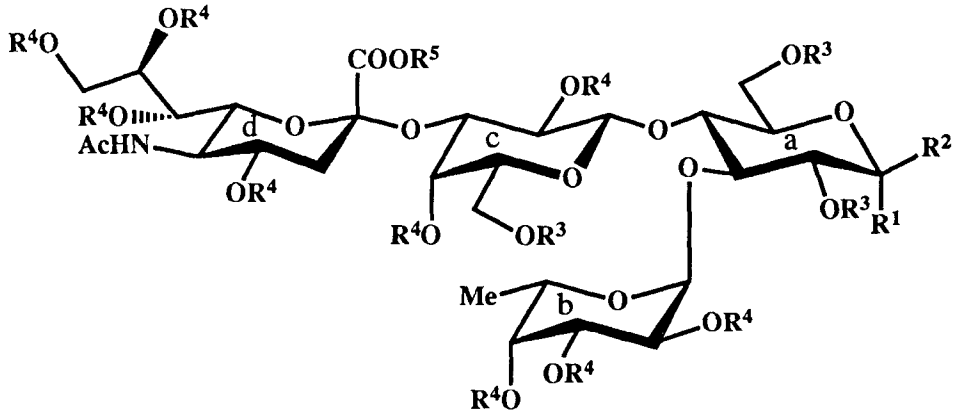
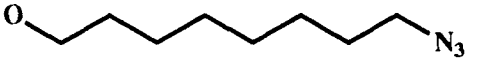


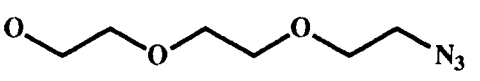
	R^1	R^2	R^3
10	Bn	Bz	H
11	Bn	H	H
12	Ac	Ac	Ac



	R1	R2	R3	R4	R5
13	H, OH		Bz	Ac	Me
14	$OC(=NH)CCl_3$, H		Bz	Ac	Me
15	H	X	Bz	Ac	Me
16	H	Y	Bz	Ac	Me
17	H	Z	Bz	Ac	Me
18	H	X	H	H	H
19	H	Y	H	H	H
20	H	Z	H	H	H
21	H	OSE	H	H	H

X = 

Y = 

Z = 

The glycosylation of **7** or **8** with methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate[16] (**9**) in the presence of *N*-iodosuccinimide (NIS)-trifluoromethanesulfonic acid (TfOH) as the glycosyl promoter[17] and powdered molecular sieves 3Å (MS-3Å) in CH_3CN overnight at -35 °C, afforded the corresponding desired α-glycosides **10** (41%) and **11** (58%), respectively. As expected, compound **8** having the three adjacent hydroxyl groups at C-2, -3, -4 of the galactose residue behaved as a suitable glycosyl acceptor for the selective α-glycosylation of Neu5Ac to the C-3, similar to what have been observed previously.[17c,18] The structure of the glycosides **10** and **11** were unambiguously proved by 270 MHz ^1H NMR spectroscopy. The observed chemical constants of Neu5Ac unit in the glycosides for H-3*eq* (δ 2.67, J_{gem} = 12.8 Hz, $J_{3eq,4}$ = 4.6 Hz, **10**; δ 2.54, J_{gem} = 12.6 Hz, $J_{3eq,4}$ = 4.3 Hz, **11**), H-4 (δ 4.95, **10**; δ 4.90, **11**), and H-7 (δ 5.43, $J_{6,7}$ = 2.0 Hz, $J_{7,8}$ = 9.3 Hz, **10**; δ 5.28, $J_{6,7}$ = 2.3 Hz, $J_{7,8}$ = 9.5 Hz, **11**) are characteristic of α-glycosidic linkages[18b,c] of Neu5Ac. Other ^1H NMR data are given in Experimental Section and are consistent with the structures assigned. Catalytic hydrogenolysis (10% Pd-C) of the benzyl groups of **11** in ethanol-acetic acid for 48 h at 40 °C and subsequent *O*-acetylation gave the per-*O*-acyl compound **12** in 89% yield, which, on *O*-deacylation with sodium methoxide in methanol and subsequent saponification of the methyl ester group, yielded the desired sialyl Le^x epitope analog **21** in quantitative yield. Treatment[4,13a] of **12** with trifluoroacetic acid in CH_2Cl_2 for 3 h at 0 °C gave the 1-hydroxy compound **13** in 95% yield. Compound **13** when treated with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 2 h at 0 °C gave the α-trichloroacetimidate **14** in 87% yield. The ^1H NMR data for Glc unit in **14** [δ 6.35 ($J_{1,2}$ = 3.8 Hz, H-1), 8.58 (C=NH)] indicated the imidate to be α.

The glycosylation of 2-azidoethanol, 8-azidooctanol, or 2-[2-(2-azidoethoxy)ethoxy]ethanol, with **14** thus obtained, in CH_2Cl_2 in the presence of boron trifluoride etherate[19] for 8 h at 0 °C afforded the expected β-glycosides **15-17** in high yields, respectively. The ^1H NMR data for the Glc unit of **15-17** [δ 4.78-4.84 ($J_{1,2}$ = 7.5~7.8 Hz, H-1)] indicated the glycosidic linkages to be β. Finally, *O*-deacylation of **15-17** with sodium methoxide in methanol, with subsequent saponification of the methyl ester group, yielded the corresponding, desired sialyl Le^x epitope analogs (**18-20**) in good yields, respectively.

EXPERIMENTAL

General Procedures. Specific rotations were determined with a Union PM-201 polarimeter at 25 °C, and IR spectra were recorded with a Jasco IRA-100 spec-

trophotometer. ^1H NMR spectra were recorded with a JEOL JNM-GX 270 spectrometer. Preparative chromatography was performed on silica gel (Wako Co., 200 mesh) with the solvent systems specified. Concentrations were conducted *in vacuo*.

2-(Trimethylsilyl)ethyl *O*-(2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-2,6-di-*O*-benzoyl-β-D-glucopyranoside (2). To a solution of 2-(trimethylsilyl)ethyl β-lactoside[13] (**1**; 8,8 g, 20 mmol) in *N,N*-dimethylformamide (DMF, 50 mL) were added 2,2-dimethoxypropane (5.3 mL, 40 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg), and the mixture was stirred for 3 h at 80 °C and neutralized with Amberlite IR-410 (HO^-) resin. The resin was filtered off and washed with MeOH, and the combined filtrate and washings were concentrated. Column chromatography (50:1 CH_2Cl_2-MeOH) of the residue on silica gel (300 g) gave the 3',4'-*O*-isopropylidene derivative (6.1 g, 64%) as an amorphous mass, which was used for the next reaction. To a solution of the isopropylidene derivative (2.0 g, 4.1 mmol) in dry pyridine (6.7 mL) and CH_2Cl_2 (10 mL), cooled to -40 °C, was added dropwise, with stirring, a solution of benzoyl chloride (2.4 mL, 20.5 mmol) in CH_2Cl_2 (20 mL), and the stirring was continued for 6 h at -40 °C. Methanol (5 mL) was added to the mixture, concentrated and extracted with CH_2Cl_2. The extract was successively washed with 2M HCl and H_2O, dried (Na_2SO_4) and concentrated. Column chromatography (300:1 CH_2Cl_2-MeOH) of the residue on silica gel (50 g) gave **2** (2.0 g, 54%) as an amorphous mass: $[\alpha]_D$ +15.6° (*c* 0.4, $CHCl_3$); IR (KBr) 3600-3300 (OH), 1730 and 1250 (ester), and 840 (TMS, Me_2C), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.98 (m, 2H, $Me_3SiCH_2CH_2$),1.51, 1.79 (2s, 6H, Me_2C), 3.65, 4.02 (2m, 2H, $Me_3SiCH_2CH_2$), 4.14 (broad t, 1H, $J_{2,3} = J_{3,4} = 8.2$ Hz, H-3), 4.71 (d, 1H, $J_{1,2} = 8.1$ Hz, H-1'), 4.82 (d, 1H, $J_{1,2} = 8.2$ Hz, H-1), 5.36 (dd, 1H, $J_{2,3} = 9.5$ Hz, H-2'), 5.52 (broad t, 1H, H-2), and 7.31-8.26 (m, 20H, 4Ph).

Anal. Calcd for $C_{48}H_{54}O_{15}Si$ (899.0): C, 64.13; H, 6.05. Found: C, 63.86; H, 5.95.

2-(Trimethylsilyl)ethyl *O*-(2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranoside (4). To a solution of **2** (1.06 g, 1.2 mmol) and methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside[4b, 15] (**3**; 818 mg, 1.8 mmol) in dry benzene (5 mL) were added powdered molecular sieves 4Å (MS-4Å, 3 g), and the mixture was stirred for 5 h at room temperature, then cooled to 0 °C. Dimethyl(methylthio)sulfonium triflate[14] (DMTST; 1.5 g, 5.3 mmol) was added to the stirred mixture, and the stirring was continued for 3 h at 7 °C; the course of the reaction was monitored by TLC. Methanol (2 mL) and triethylamine (1 mL) were added to the mixture, concentrated, and extracted with CH_2Cl_2. The extract was washed with H_2O,

dried (Na_2SO_4) and concentrated. Column chromatography (400:1 CH_2Cl_2-MeOH) of the residue on silica gel (80 g) gave **4** (1.4 g, 90%) as an amorphous mass: $[\alpha]_D$ -25.0° (*c* 0.16, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (m, 2H, $Me_3SiCH_2CH_2$),1.46, 1.69 (2s, 6H, Me_2C), 1.52 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6b), 3.56, 4.32 (2m, 2H, $Me_3SiCH_2CH_2$), 4.95 (d, 1H, $J_{1,2}$ = 6.1 Hz, H-1a), 5.44 (broad t, 1H, $J_{1,2}$ = $J_{2,3}$ = 8.2 Hz, H-2c), 5.61 (broad t, 1H, $J_{1,2}$ = $J_{2,3}$ = 8.8 Hz, H-2a), 5.63 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1b), and 7.13-8.38 (m, 35H, 7Ph).

Anal. Calcd for $C_{75}H_{82}O_{19}Si$ (1315.6): C, 68.48; H, 6.28. Found: C, 68.46; H, 6.37.

2-(Trimethylsilyl)ethyl *O*-(3,4-*O*-Isopropylidene-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-D-glucopyranoside (5). To a solution of **4** (2.27 g, 1.73 mmol) in MeOH (20 mL) and CH_2Cl_2 (3 mL) was added sodium methoxide (100 mg) and the mixture was kept at 60 °C; the course of the reaction was monitored by TLC. After completion of the reaction, the mixture was neutralized by Amberlite IR-120 (H^+) resin. The solution was concentrated. Column chromatography (30:1 CH_2Cl_2-MeOH) of the residue on silica gel afforded **5** (1.34 g, 86%) as an amorphous mass: $[\alpha]_D$ -71.5° (*c* 0.2, MeOH); ^1H NMR (CD_3OD) δ 0.98 (m, 2H, $Me_3SiCH_2CH_2$),1.04, (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.27, 1.33 (2s, 6H, Me_2C), 3.44 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 9.0 Hz, H-2c), 4.27 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1a), 5.67 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1b), and 7.21-7.93 (m, 15H, 3Ph).

Anal. Calcd for $C_{47}H_{66}O_{15}Si$ (899.1): C, 62.79; H, 7.40. Found: C, 62.65; H, 7.57.

2-(Trimethylsilyl)ethyl *O*-(6-*O*-Benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-[*O*-(2, 3, 6-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranoside (6). To a solution of **5** (621 mg, 0.69 mmol) in pyridine (1 mL) and CH_2Cl_2 (10 mL), cooled to -40 °C, was added a solution of benzoyl chloride (0.48 mL, 4.1 mmol), and the mixture was stirred for 6 h at -40 °C and then worked-up, as described for **2**, to give **6** (620 mg, 74%) as an amorphous mass: $[\alpha]_D$ -41.5° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.98 (m, 2H, $Me_3SiCH_2CH_2$),1.35 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.60, 1.64 (2s, 6H, Me_2C), 3.74 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.4 Hz, H-2c), 5.29 (dd, 1H, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 7.3 Hz, H-2a), 5.38 (d, 1H, $J_{1,2}$ = 3.1 Hz, H-1b), and 7.24-8.21 (m, 30H, 6Ph).

Anal. Calcd for $C_{68}H_{78}O_{18}Si$ (1211.4): C, 67.42; H, 6.49. Found: C, 67.39; H, 6.29.

2-(Trimethylsilyl)ethyl *O*-(2,6-Di-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[*O*-(2, 3, 4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-ben-

zoyl-β-D-glucopyranoside (7). A solution of **4** (240 mg, 0.18 mmol) in aqueous 80% AcOH was heated overnight at 50 °C and concentrated. Column chromatography (200:1 CH_2Cl_2-MeOH) of the residue on silica gel gave **7** (209 mg, 90%) as an amorphous mass: $[\alpha]_D$ -37.5° (*c* 0.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.98 (m, 2H, $Me_3SiCH_2CH_2$), 1.47 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6b), 5.45 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 8.2 Hz, H-2c), 5.57 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1b), 5.63 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 8.4 Hz, H-2a), and 7.13-8.38 (m, 35H, 7Ph).

Anal. Calcd for $C_{72}H_{78}O_{19}Si$ (1275.5): C, 67.80; H, 6.16. Found: C, 67.54; H, 6.32.

2-(Trimethylsilyl)ethyl *O*-(6-*O*-Benzoyl-β-D-galactopyranosyl)-[*O*-(2, 3, 4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-2, 6-di-*O*-benzoyl-β-D-glucopyranoside (8). A solution of **6** (400 mg, 0.33 mmol) in aqueous 80% AcOH (40 mL) was stirred overnight at room temperature and concentrated. Column chromatography (80:1 CH_2Cl_2-MeOH) of the residue on silica gel (40 g) gave **8** (351 mg, 91%) as an amorphous mass: $[\alpha]_D$ -51.5° (*c* 0.2, $CHCl_3$); IR (KBr) 3450 (OH), 1730 and 1230 (ester), and 860 and 840 (TMS), and 750 and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.98 (m, 2H, $Me_3SiCH_2CH_2$), 1.27 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 3.67 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, H-3a), 3.68 (dd, 1H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 4.5 Hz, H-3c), 3.96 (t, 1H, $J_{4,5}$ = 9.5 Hz, H-4a), 4.11 (dd, 1H, $J_{1,2}$ = 2.9 Hz, $J_{2,3}$ = 12.5 Hz, H-2b), 4.12 (dd, 1H, $J_{1,2}$ = 7.7 Hz, H-2c), 4.27 (d, 1H, H-1c), 4.59 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1a), 5.18 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2a), 5.34 (d, 1H, H-1b), and 7.16-8.08 (m, 30H, 6Ph).

Anal. Calcd for $C_{65}H_{74}O_{18}Si$ (1171.4): C, 66.65; H, 6.37. Found: C, 66.40; H, 6.33.

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, 6-di-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranoside (10). To a solution of **7** (120 mg, 94 μmol) and **9** (115 mg, 197 μmol) in dry CH_3CN (2.5 mL) were added molecular sieves 3Å (MS-3Å, 1.5 g) and the mixture was stirred for 5 h at room temperature and cooled to -40 °C. *N*-Iodosuccinimide (120 mg, 0.54 mmol) and TfOH (12 μL, 0.14 μmol) were added to the reaction mixture under N_2 atmosphere and it was stirred overnight at -35 °C, neutralized with triethylamine, concentrated, and then extracted with CH_2Cl_2. The extract was successively washed with M $Na_2S_2O_3$ and water, dried (Na_2SO_4) and concentrated. Column chromatography (50:1 toluene-MeOH) of the residue on silica gel (40 g) gave **10** (67 mg, 41%) as an amorphous mass: $[\alpha]_D$ -14.0° (*c* 0.9, $CHCl_3$); IR (KBr) 3370 (OH, NH), 1740 and 1220 (ester), 1660 and

1540 (amide), 860 and 840 (TMS), and 720 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.98 (m, 2H, $Me_3SiCH_2CH_2$), 1.56 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6b), 1.71, 1.97, 2.02, 2.14, 2.21 (5s, 15H, AcN, 4AcO), 2.67 (dd, 1H, J_{gem} = 12.8 Hz, $J_{3eq,4}$ = 4.6 Hz, H-3d*eq*), 4.95 (m, 1H, H-4d), 5.43 (dd, 1H, $J_{6,7}$ = 2.0 Hz, $J_{7,8}$ = 9.3 Hz, H-7d), 5.55 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1b), 5.72 (m, 1H, H-8d), and 7.13-8.36 (m, 35H, 7Ph).

Anal. Calcd for $C_{92}H_{105}NO_{31}Si$ (1748.9): C, 63.18; H, 6.05; N, 0.80. Found: C, 63.27; H, 5.92; N, 0.79.

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*-(6-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[*O*-(2, 3, 4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranoside (11). To a solution of **8** (500 mg, 0.42 mmol) and **9** (420 mg, 0.72 mmol) in dry CH_3CN (5 mL) were added MS-3Å (3 g) and the mixture was stirred for 5 h at room temperature, and cooled to -40 °C. NIS (562 mg, 2.5 mmol) and TfOH (64 μL, 0.72 mmol) were added, with stirring, to the mixture at -35 °C under N_2 atmosphere. A similar work-up as described for **10** gave **11** (405 mg, 58.2%) as an amorphous mass: $[\alpha]_D$ -8.8° (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (m, 2H, $Me_3SiCH_2CH_2$), 1.39 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6b), 1.55, 1.82, 1.90, 2.00, 2.09 (5s, 15H, AcN, 4AcO), 2.54 (dd, 1H, J_{gem} = 12.6 Hz, $J_{3eq,4}$ = 4.3 Hz, H-3d*eq*), 4.29 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1c), 4.90 (m, 1H, H-4d), 5.10 (near t, 1H, $J_{2,3}$ = 10.0 Hz, H-2a), 5.28 (dd, 1H, $J_{6,7}$ = 2.3 Hz, $J_{7,8}$ = 9.5 Hz, H-7d), 5.43 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1b), 5.56 (m, 1H, H-8d), and 7.30-8.23 (m, 30H, 6Ph).

Anal. Calcd for $C_{85}H_{101}NO_{30}Si$ (1644.8): C, 62.07; H, 6.19 N, 0.85. Found: C, 61.89; H, 5.91; N, 0.87.

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-di-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2, 6-di-*O*-benzoyl-β-D-glucopyranoside (12). A solution of **11** (390 mg, 0.237 mmol) in EtOH (120 mL) and AcOH (20 mL) was hydrogenolyzed in the presence of 10% Pd-C (700 mg) for 2 days at 40 °C, then filtered and concentrated. The residue was acetylated with Ac_2O (5 mL) in pyridine (10 mL) in the presence of 4-dimethylaminopyridine (10 mg) overnight at room temperature. The product was purified by column chromatography (100:1 CH_2Cl_2-MeOH) on silica gel (50 g), to give **12** (340 mg, 89%) as an amorphous mass: $[\alpha]_D$ -6.0° (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (m, 2H, $Me_3SiCH_2CH_2$), 1.40 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.50, 1.74, 1.83, 1.99, 2.01, 2.03, 2.11 (2), 2.24, 2.29 (9s, 30H, AcN, 9AcO), 2.60 (dd, 1H, J_{gem} = 12.3 Hz, $J_{3eq,4}$ = 4.2 Hz, H-3d*eq*), 3.84 (s,

3H, MeO), 4.32 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1c), 4.78 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1a), 5.17 (dd, 1H, $J_{6,7}$ = 3.3 Hz, $J_{7,8}$ = 7.2 Hz, H-7d), 5.44 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1b), 5.55 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4c), and 7.22-8.28 (m, 15H, 3Ph).

Anal. Calcd for $C_{74}H_{107}NO_{35}Si$ (1598.7): C, 55.60; H, 6.75 N, 0.88. Found: C, 55.61; H, 6.86; N, 0.77.

***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-di-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-benzoyl-D-glucopyranose (13).** To a solution of **12** (191 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL) and the mixture was stirred for 3 h at 0 °C, then concentrated. Column chromatography (60:1 CH_2Cl_2-MeOH) of the residue on silica gel (40 g) afforded **13** (171 mg, 95%) as an amorphous mass: $[\alpha]_D$ +10.0° (*c* 1.7, $CHCl_3$); IR (KBr) 3380 (OH, NH), 1740 and 1230 (ester), 1640 and 1540 (amide), and 750 and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.34 (d, 1H, $J_{5,6}$ = 6.6 Hz, H-6b), 1.42-2.35 (30H, AcN, 9AcO), 2.51 (dd, 1H, J_{gem} = 12.6 Hz, $J_{3eq,4}$ = 4.8 Hz, H-3d*eq*), 3.75 (s, 3H, MeO), 4.90 (dt, 1H, H-4d), 5.17 (dd, 1H, $J_{6,7}$ = 2.2 Hz, $J_{7,8}$ = 7.8 Hz, H-7d), 5.26 (d, 1H, $J_{1,2}$ = 2.5 Hz, H-1b), 5.47 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4c), 5.57 (m, 1H, H-8d), and 7.12-8.18 (m, 15H, 3Ph).

Anal. Calcd for $C_{69}H_{95}NO_{35}$ (1498.5): C, 55.31; H, 6.39 N, 0.93. Found: C, 55.13; H, 6.65; N, 0.97.

***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-di-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2,4-di-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (14).** A solution of **13** (70 mg, 47 μmol) and trichloroacetonitrile (0.14 mL) in CH_2Cl_2 (1 mL) was cooled to 0 °C, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 10 mg) was added. The mixture was stirred for 2 h at 0 °C and chromatographed on a column of silica gel (15 g) with 60:1 CH_2Cl_2-MeOH, to give **14** (67 mg, 87%) as an amorphous mass: $[\alpha]_D$ +13.0° (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.36 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6b), 1.44, 1.68, 1.75, 1.93, 1.94 (2), 2.01 (2), 2.17, 2.21 (8s, 30H, AcN, 9AcO), 2.54 (dd, 1H, H-3d*eq*), 3.76 (s, 3H, MeO), 4.82 (m, 1H, H-4d), 5.45 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4c), 5.47 (d, 1H, $J_{1,2}$ = 2.8 Hz, H-1b), 6.35 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1a), 7.15-8.17 (m, 15H, 3Ph), and 8.58 (s, 1H, C=NH).

Anal. Calcd for $C_{71}H_{97}N_2O_{35}Cl_3$(1644.9): C, 51.84; H, 5.94, N, 1.73. Found: C, 51.75; H, 5.77; N, 1.53.

2-Azidoethyl *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-

di-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranoside (15). To a solution of **14** (67 mg, 41 μmol) and 2-azidoethanol (8.6 mg, 90 μmol) in dry CH_2Cl_2 (0.5 mL) were added MS-4Å (AW-300, 200 mg) and the mixture was stirred for 5 h at room temperature, then cooled to 0 °C. Boron trifluoride etherate (3 μL) was added and the mixture was stirred for 8 h at 0 °C and then filtered. Dichloromethane (50 mL) was added, and the solution was successively washed with M Na_2CO_3 and H_2O, dried (Na_2SO_4), then concentrated. Column chromatography (60:1 CH_2Cl_2-MeOH) of the residue on silica gel (20 g) gave **15** (58 mg, 91%) as an amorphous mass: $[\alpha]_D$ -4.5° (*c* 1.2, $CHCl_3$); IR (KBr) 3350 (NH), 2100 (N_3), 1740 and 1230 (ester), 1670 and 1540 (amide), and 750 and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.33 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.42, 1.66, 1.75, 1.92, 1.94, 1.96, 2.03, 2.06, 2.17, 2.22 (10s, 30H, AcN, 9AcO), 3.77 (s, 3H, MeO), 4.32 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1c), 4.79 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1a), 5.35 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1b), 5.47 (d, 1H, $J_{3,4}$ = 2.8 Hz, H-4c), and 7.27-8.20 (m, 15H, 3Ph).

Anal. Calcd for $C_{71}H_{98}N_4O_{35}$(1567.6): C, 54.40; H, 6.30, N, 3.57. Found: C, 54.66; H, 6.32; N, 3.65.

8-Azidooctyl *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-di-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranoside (16). Coupling of **14** (52 mg, 32 μmol) and 8-azidooctanol (8 mg, 47 μmol), as described for **15**, gave **16** (43 mg, 78%) as an amorphous mass: $[\alpha]_D$ -8.0° (*c* 0.8, $CHCl_3$); IR (KBr) 3350 (NH), 2940 (CH2), 2100 (N_3), 1750 and 1230 (ester), 1660 and 1540 (amide), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.34 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6b), 1.43-2.20 (10s, 30H, AcN, 9AcO), 2.52 (dd, 1H, J_{gem} = 12.8 Hz, $J_{3eq,4}$ = 4.9 Hz, H-3d*eq*), 3.76 (s, 3H, MeO), 4.37 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1c), 4.84 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1a), 5.46 (d, 1H, $J_{1,2}$ = 2.6 Hz, H-1b), and 7.18-8.23 (m, 15H, 3Ph).

Anal. Calcd for $C_{77}H_{110}N_4O_{35}$(1651.7): C, 55.99; H, 6.71, N, 3.39. Found: C, 56.14; H, 6.75; N, 3.38.

2-[2-(2-Azidoethoxy)ethoxy)ethyl *O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3, 5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl-onate)-(2 → 3)-*O*-(2, 4-di-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranoside (17). Coupling of **14** (95.5mg, 58 μmol) and 2-[2-(2-azidoethoxy)ethoxy]ethanol (15 mg, 87 μmol), as described for **15**, gave **17** (76 mg,

79%) as an amorphous mass: $[\alpha]_D$ -4.3° (*c* 1.5, $CHCl_3$); IR (KBr) 3350 (NH), 2120 (N_3), 1750 and 1220 (ester), 1660 and 1540 (amide), and 760 and 720 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.32 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.34, 1.42, 1.64, 1.75, 1.92, 1.94, 1.95, 2.04, 2.16, 2.21 (10s, 30H, AcN, 9AcO), 2.52 (dd, 1H, J_{gem} = 12.8 Hz, $J_{3eq,4}$ = 4.9 Hz, H-3d*eq*), 3.76 (s, 3H, MeO), 4.33 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1c), 4.78 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1a), 5.35 (dd, 1H, $J_{6,7}$ = 2.0 Hz, $J_{7,8}$ = 9.5 Hz, H-7d), 5.47 (d, 1H, $J_{1,2}$ = 2.5 Hz, H-1b), and 7.28-8.20 (m, 15H, 3Ph).

Anal. Calcd for $C_{75}H_{106}N_4O_{37}$(1655.7): C, 54.41; H, 6.45, N, 3.39. Found: C, 54.43; H, 6.39; N, 3.33.

2-Azidoethyl *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)]-β-D-glucopyranoside (18). To a solution of **15** (58 mg, 37 μmol) in MeOH (5 mL) was added NaOMe (20 mg) and the mixture was stirred overnight at 40 °C; the course of the reaction was monitored by TLC. Water (3 mL) was added to the mixture, and this was stirred overnight at room temperature, 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 (MeOH) of the residue on Sephadex LH-20 (40 g) gave **18** (33 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -39.0° (*c* 0.9, MeOH); ^1H NMR (CD_3OD) δ 1.27 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6b), 2.11 (s, 3H, AcN), 2.55 (broad dd, 1H, H-3d*eq*), 4.44 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1c), 4.58 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1a), and 5.56 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1b).

Anal. Calcd for $C_{31}H_{52}N_4O_{23}$(848.8): C, 43.87; H, 6.18, N, 6.60. Found: C, 44.06; H, 6.35; N, 6.54.

8-Azidooctyl *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)]-β-D-glucopyranoside (19). Deacylation and saponification of **16** (42.5 mg, 24.7 μmol), as described for **18**, yielded compound **19** (25 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -33.7° (*c* 0.9, MeOH); ^1H NMR (CD_3OD) δ 1.07 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6b), 1.18-1.69 (m, 12H, $6CH_2$), 1.91 (s, 3H, AcN), 2.37, 3.18 (m, 4H, CH_2), 2.78 (broad dd, 1H, H-3d*eq*), 4.17 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1c), 4.38 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1a), and 5.36 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1b).

Anal. Calcd for $C_{37}H_{64}N_4O_{23}$(932.9): C, 47.64; H, 6.92, N, 6.01. Found: C, 47.52; H, 7.12; N, 5.81.

2-[2-(2-Azidoethoxy)ethoxy]ethyl *O*-(5-Acetamido-3, 5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→3)-*O*-(β-D-galac-

topyranosyl)-(1→4)-[*O*-(α-L-fucopyranosyl)-(1→3)]-β-D-glucopyranoside (20). Deacylation and saponification of **17** (76 mg, 46 μmol), as described for **18**, afforded compound **20** (45 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -34.0° (*c* 1.5, MeOH); ^{1}H NMR (CD_3OD) δ 1.07 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.92 (s, 3H, AcN), 2.78 (broad dd, 1H, H-3d*eq*), 3.40-3.90 (m, 12H, $6CH_2$), 4.24 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1c), 4.38 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1a), and 5.37 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1b).

Anal. Calcd for $C_{35}H_{60}N_4O_{25}$(936.9): C, 44.87; H, 6.46, N, 5.98. Found: C, 44.69; H, 6.71; N, 5.83.

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)]-β-D-glucopyranoside (21). Deacylation and saponification of **12** (71.5 mg, 44.4 μmol), as described for **18**, gave compound **21** (39 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -19.1° (*c* 1.3, MeOH); ^{1}H NMR (CD_3OD) δ 0.98 (m, 2H, $MeSiCH_2CH_2$), 1.13 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6b), 1.99 (s, 3H, AcN), 2.83 (broad dd, 1H, H-3d*eq*), 4.26 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1c), 4.45 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1a), and 5.45 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1b).

Anal. Calcd for $C_{34}H_{61}NO_{23}Si$(879.9): C, 47.64; H, 6.99, N, 1.59. Found: C, 47.52; H, 7.15; N, 1.47.

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