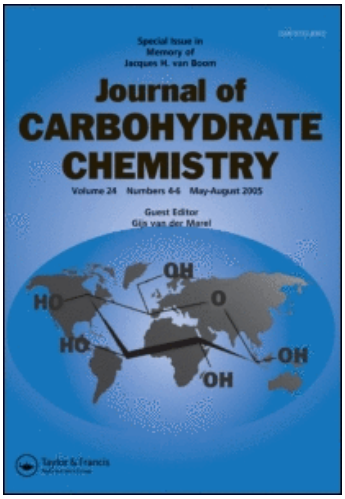

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Synthetic Studies on Sialoglycoconjugates 71: Synthesis of Sulfo- and Sialyl-Lewis × Epitope Analogs Containing the 1-Deoxy-*N*-acetylgulcosamine in Place of *N*-Acetylglucosamine Residue

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

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 71: SYNTHESIS OF SULFO- AND SIALYL-LEWIS X EPITOPE ANALOGS CONTAINING THE 1-DEOXY-*N*-ACETYLGLUCOSAMINE IN PLACE OF *N*-ACETYLGLUCOSAMINE RESIDUE

Hirokazu Maeda, Hideharu Ishida, Makoto Kiso and Akira Hasegawa*

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

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ABSTRACT

Sulfo and sialyl Le^x epitope analogs containing the 1-deoxy-*N*-acetylglucosamine in place of GlcNAc residue have been synthesized. Glycosylation of 2-acetamido-1,5-anhydro-3,6-di-*O*-benzyl-2-deoxy-D-glucitol (**10**) with 2,4,6-tri-*O*-benzoyl-3-*O*-levulinyl-α-D-galactopyranosyl trichloroacetimidate (**6**) prepared from 2-(trimethylsilyl)ethyl β-D-galactopyranoside (**1**) in five steps, or with the α-sialyl-(2→3)-galactose donor, afforded the desired β-glycosides **12** and **15**, respectively. Glycosylation of the acceptor **14** derived from **12** in two steps, or **16** derived from **15** by reductive removal of the benzyl group followed by selective *O*-benzoylation, with methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**17**), using dimethyl(methylthio)sulfonium triflate, gave the trisaccharide **18** and tetrasaccharide **23**. Compound **18** was converted *via* reductive removal of the benzyl groups, *O*-acetylation, selective removal of the levulinyl group, treatment with sulfur trioxide-pyridine complex, and *O*-deacylation, into the title sulfo Le^x analog **22**. Compound **23** was transformed by reductive removal of the benzyl groups, *O*-acetylation, *O*-deacylation and subsequent hydrolysis of the methyl ester, into the sLe^x epitope analog **25**.

INTRODUCTION

The selectins[1-4] [E-selectin (ELAM-1), L-selectin (LECAM-1) and P-selectin (PADGEM)] are a family of cell-adhesion receptors and recognize[5-9] the sialyl Le^x and sialyl Le^a determinants, which are found as the terminal carbohydrate structures of both cell membrane glycolipids and glycoproteins, and related oligosaccharides.[11,12] Binding of selectins to their carbohydrate ligands appears to be required for neutrophil extravasation, and plays a major role in lymphocyte recirculation and platelet adhesion. Based on the three-dimensional structure[9] of sLe^x and sLe^a, various types of sLe^x analogs[13-17] containing chemically modified sialic acid, fucose, galactose, and *N*-acetylglucosamine moieties have been synthesized in order to clarify the structural features of each component of the carbohydrate ligand required for selectin recognition.[18-19]

Recently, it has been demonstrated[19] that E- and L-selectin can bind to sulfo-Le^x-like structures isolated from an ovarian cyst adenoma, and using chemically synthesized sulfo Le^a and sulfo Le^x oligosaccharides, sulfo Le^a pentasaccharide has the most potent activity for E-selectin recognition. As a part of our continuing studies on structure-activity correlations in the sLe^x epitope, we describe the synthesis of sLe^x and sulfo Le^x epitope analogs containing the 1-deoxy-*N*-acetylglucosamine in place of *N*-acetylglucosamine moiety.

RESULTS AND DISCUSSION

For the synthesis of the desired sulfo and sialyl Le^x epitope analogs we employed 2,4,6-tri-*O*-benzoyl-3-levulinyl-α-D-galactopyranosyl trichloroacetimidate (**6**) as the glycosyl donor and 2-acetamido-1,5-anhydro-3,6-di-*O*-benzyl-2-deoxy-D-glucitol (**10**) as a suitably protected glycosyl acceptor. The acceptor **10** was coupled with **6** using boron trifluoride etherate,[20] or with the methyl thioglycoside derivative[21] (**11**) of α-sialyl-(2→3)-galactose as the donor using dimethyl(methylthio)sulfonium triflate[22] (DMTST), as promoter, to afford the corresponding di- and trisaccharides **12** and **15**. The di- and trisaccharide acceptors were then glycosylated with methyl 2,3,4-tri-*O*-

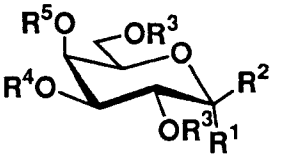
benzyl-1-thio-β-L-fucopyranoside[23] (**17**). By further processing according to our usual procedure[24] the resulting tri- and tetrasaccharide intermediates **18** and **23** could be converted into the end products **22** and **25**.

Treatment of 2-(trimethylsilyl)ethyl β-D-galactopyranoside[25] (**1**) with 2,2-dimethoxypropane in *N,N*-dimethylformamide (DMF) in the presence of *p*-toluenesulfonic acid monohydrate at 80 °C gave the 3,4-*O*-isopropylidene derivative, and this on *O*-benzoylation gave **2** in 77% yield. Hydrolysis of the isopropylidene group in **2** with aq 80% acetic acid gave the 2,6-di-*O*-benzoyl derivative **3**. Treatment of **3** with levulinic anhydride in pyridine for one h at -50 °C gave the 3-*O*-levulinyl derivative **4** in 87% yield, exclusively, and this on *O*-benzoylation and subsequent hydrolysis[25] of the 2-(trimethylsilyl)ethyl group with trifluoroacetic acid followed by treatment[20,26] with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), was converted into the glycosyl donor **6** in good yield. The ^{1}H NMR data of **6** [δ 6.86 ($J_{1,2}$ = 3.1 Hz, H-1), 8.62 (C = NH)] established the anomeric configuration of the imidate.

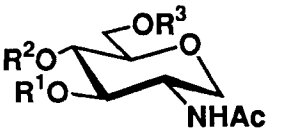
Treatment of 2-acetamido-1,2-anhydro-2-deoxy-D-glucitol[27] (**7**) with benzaldehyde dimethyl acetal in DMF in the presence of *p*-toluenesulfonic acid monohydrate gave the 4,6-*O*-benzylidene derivative **8** (97%). Treatment of **8** with benzyl bromide in DMF in the presence of sodium hydride for 3 h at room temperature gave the 3-*O*-benzyl derivative (71%) as crystals which, on reductive ring-opening[28] of the benzylidene group with sodium cyanoborohydride-hydrogen chloride in tetrahydrofuran, afforded the desired glycosyl acceptor **10** (91%) as crystals.

Glycosylation[20] of **10** with 1.5 equiv of **6** in dichloromethane for 3 h at room temperature in the presence of boron trifluoride etherate and 4Å molecular sieves gave the expected disaccharide derivative **12** (58%) which, on catalytic hydrogenolysis (10% Pd-C) in ethanol-acetic acid of the benzyl group and subsequent 6-*O*-benzoylation, gave the next glycosyl acceptor **14** in good yield.

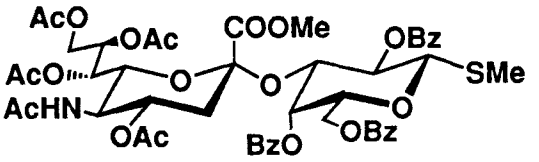
On the other hand, glycosylation[21] of **10** with 1.7 equiv of **11** in dichloromethane in the presence of DMTST and 4Å molecular sieves for 48 h at room temperature gave the trisaccharide **15** (92%) which, on reductive removal of the benzyl groups and subsequent 6-*O*-benzoylation as described for the preparation of **14**, gave another glycosyl acceptor **16** (76%).



	R^1	R^2	R^3	R^4	R^5
1	H	OSE	H	H	H
2	H	OSE	Bz	ipd	
3	H	OSE	Bz	H	H
4	H	OSE	Bz	Lev	H
5	H	OSE	Bz	Lev	Bz
6	$OC(=NH)CCl_3$	H	Bz	Lev	Bz



	R^1	R^2	R^3
7	H	H	H
8	H	benzylidene	
9	Bn	benzylidene	
10	Bn	H	Bn



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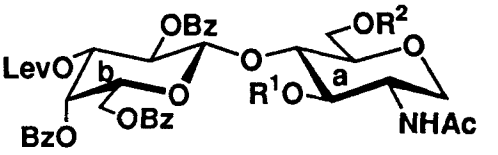
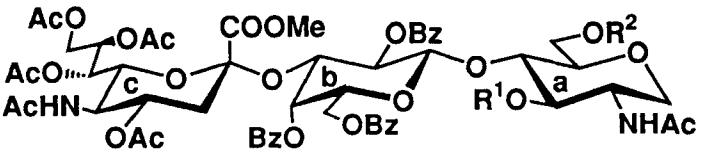
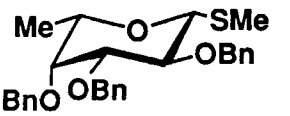


	R^1	R^2
12	Bn	Bn
13	H	H
14	H	Bz



	R^1	R^2
15	Bn	Bn
16	H	Bz



17

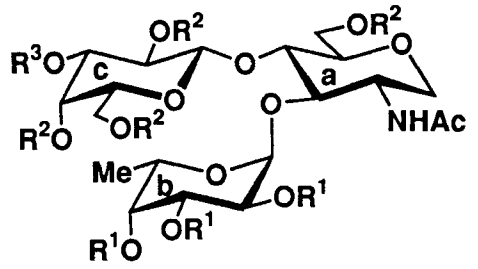
Glycosylation of **14** or **16** with methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**17**) in benzene in the presence of DMTST and 4Å molecular sieves afforded the corresponding α-glycosides **18** (76%) and **23** (88%), respectively. Hydrogenolysis of the benzyl group in **18** followed by acetylation gave **19** (81%). Significant signals in the ^{1}H NMR spectrum of **19** were at δ 4.78 (d, $J_{1,2}$ = 8.1 Hz, H-1c) and 5.43 (d, $J_{1,2}$ = 3.8 Hz, H-1b), which showed the anomeric configurations to be β and α respectively.

Treatment of **19** with hydrazine monoacetate in ethanol for 3 h at room temperature gave *O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-[(2,3,6-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2-acetamido-1,5-anhydro-6-*O*-benzoyl-D-glucitol (**20**) in 66% yield. When treated with sulfur trioxide pyridine complex in DMF for one h at room temperature, compound **20** gave the sulfated Le^x analog derivative **21** (93%), and this was transformed by removal of the protecting groups into *O*-(3-*O*-sulfo-β-D-galactopyranosyl)-(1→4)-*O*-[α-L-fucopyranosyl-(1→3)]-2-acetamido-1,5-anhydro-D-glucitol sodium salt (**22**) quantitatively.

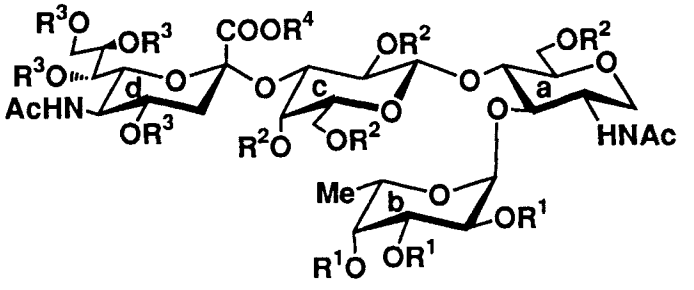
Hydrogenolysis of the benzyl groups in **23** and subsequent acetylation gave the protected sLe^x analog **24** in 85% yield. Significant signals in the ^{1}H NMR spectrum of **24** were at δ 5.35 (d, $J_{1,2}$ = 3.8 Hz, H-1b) and 5.48 (dd, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 10.1 Hz, H-2c), indicating the expected anomeric configurations. Finally, *O*-deacylation of **24** with sodium methoxide in methanol and hydrolysis of the methyl ester group yielded the desired sLe^x epitope analog **25** in almost quantitative yield after chromatography on a column of Sephadex LH-20.

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. ^{1}H NMR spectra were recorded with a JEOL JNM-GX 270 spectrometer. Mass spectra were recorded using an electroscopy mass spectrometer (Perkin-Elmer Sciex Instrument, Thornhill, Canada) fitted with an atmospheric pressure ionization source. Preparative chromatography was performed on silica gel



	R^1	R^2	R^3
18	Bn	Bz	Lev
19	Ac	Bz	Lev
20	Ac	Bz	H
21	Ac	Bz	$SO_3 \cdot Pyr$
22	H	H	SO_3Na



	R^1	R^2	R^3	R^4
23	Bn	Bz	Ac	Me
24	Ac	Bz	Ac	Me
25	H	H	H	H

SE = 2-(trimethylsilyl)ethyl

Bz = benzoyl

Bn = benzyl

Lev = $CH_3COCH_2CH_2CO$—

ipd = isopropylidene

(Wako Chemical Co., 200 mesh) with the solvent systems specified. Concentrations were conducted *in vacuo*.

2-(Trimethylsilyl)ethyl 2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (2). To a solution of 2-(trimethylsilyl)ethyl β-D-galactopyranoside[25] (**1**, 2.7 g, 9.4 mmol) in *N,N*-dimethylformamide (DMF, 10 mL) were added 2,2-dimethoxypropane (2.3 mL) and *p*-toluenesulfonic acid monohydrate (50 mg) and the mixture was stirred for 2 h at 80 °C; the course of the reaction was

monitored by TLC. After completion of the reaction, the solution was neutralized with Na_2CO_3 and filtered. The solution was concentrated to a syrup, which was treated with benzoyl chloride (2.1 mL) in pyridine (4 mL) for 30 min at room temperature. MeOH (1 mL) was added to the mixture and concentrated to a syrup, which was extracted with CH_2Cl_2. The extract was successively washed with 2 M HCl, M Na_2CO_3 and water, dried (Na_2SO_4), and concentrated. Column chromatography (1:10 EtOAc-hexane) of the residue on silica gel (150 g) gave **2** (3.8 g, 77%) as crystals. Recrystallization from EtOAc-hexane gave needles: mp 123 °C; $[\alpha]_D$ +19.0° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 (m, 2H, $Me_3SiCH_2CH_2$), 1.47, 1.75 (2s, 6H, Me_2C), 3.66, 4.06 (2m, 2H, $Me_3SiCH_2CH_2$), 4.31 (m, 1H, H-5), 4.48 (dd, 1H, $J_{2,3}$ = 7.2 Hz, $J_{3,4}$ = 4.5 Hz, H-3), 4.65 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 4.78 (m, 2H, H-6, 6'), 5.36 (dd, 1H, H-2), and 7.37-8.19 (m, 10H, 2Ph).

Anal. Calcd for $C_{23}H_{36}O_8Si$ (528.7): C, 52.25; H, 6.86. Found: C, 52.30; H, 6.85.

2-(Trimethylsilyl)ethyl 2,6-Di-*O*-benzoyl-β-D-galactopyranoside (3). A solution of **2** (3.8 g, 6.4 mmol) in aq 80% AcOH (50 mL) was heated for 4 h at 60 °C then concentrated. Column chromatography (100:1 CH_2Cl_2-MeOH) of the residue on silica gel (150 g) gave **3** (3.1 g, quantitative) as crystals. Recrystallization from EtOAc-hexane gave needles: mp 124 °C; $[\alpha]_D$ -15.0° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 (m, 2H, $Me_3SiCH_2CH_2$), 3.68, 4.04 (2m, 2H, $Me_3SiCH_2CH_2$), 4.04 (m, 2H, H-5, H-6), 4.12 (d, 1H, $J_{3,4}$ = 4.0 Hz, H-4), 4.69 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.70 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-3), 4.76 (dd, 1H, J_{gem} = 11.3 Hz, $J_{5,6'}$ = 6.2 Hz, H-6'), 5.33 (dd, 1H, H-2), and 7.35-8.16 (m, 10H, 2Ph).

Anal. Calcd for $C_{25}H_{32}O_8Si$ (488.6): C, 61.45; H, 6.60. Found: C, 61.43; H, 6.67.

2-(Trimethylsilyl)ethyl 2,6-Di-*O*-benzoyl-3-*O*-levulinyl-β-D-galactopyranoside (4). To a solution of **3** (1.0 g, 2 mmol) in pyridine (10 mL), cooled to -50 °C, were added levulinic anhydride (780 mg, 4 mmol), and the mixture was stirred for 10 min at -50 °C. After completion of the reaction, MeOH (0.5 mL) was added and the mixture was concentrated then extracted with CH_2Cl_2. The extract was washed with 2M HCl and water, dried (Na_2SO_4) and concentrated. Column chromatography (200:1 CH_2Cl_2-MeOH) of the residue on silica gel (70 g) gave **4**

(1.04 g, 87%) as an amorphous mass: $[\alpha]_D$ +4.2° (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.0 (m, 2H, $Me_3SiCH_2CH_2$), 2.52-2.82 (m, 4H, $MeCOCH_2CH_2$), 4.36 (br d, 1H, $J_{3,4}$ = 3.3 Hz, H-4), 4.75 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 5.18 (dd, 1H, $J_{2,3}$ = 10.3 Hz, H-3), 5.68 (dd, 1H, H-2), and 7.34-8.18 (m, 10H, 2Ph).

Anal. Calcd for $C_{30}H_{38}O_{10}Si$ (586.7): C, 61.41; H, 6.53. Found: C, 61.38; H, 6.45.

2-(Trimethylsilyl)ethyl 2,4,6-Tri-*O*-benzoyl-3-*O*-levulinyl-β-D-galactopyranoside (5). To a solution of **4** (2.27 g, 3.85 mmol) in pyridine (1 mL) and CH_2Cl_2 (10 mL), cooled to 0 °C, was added benzoyl chloride (0.7 mL, 4.8 mmol) and the mixture was stirred overnight at room temperature. Processing as described for **4** gave **5** (2.44 g, 89%) as an amorphous mass: $[\alpha]_D$ +23.3° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.0 (m, 2H, $Me_3SiCH_2CH_2$), 2.38-2.78 (m, 4H, $MeCOCH_2CH_2$), 3.70, 4.11 (2m, 2H, $Me_3SiCH_2CH_2$), 4.30 (m, 1H, H-5), 4.46 (dd, 1H, J_{gem} = 11.1 Hz, $J_{5,6}$ = 6.9 Hz, $J_{5,6'}$ = 6.4 Hz, H-6'), 4.71 (dd, 1H, H-6), 4.82 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 5.43 (dd, 1H, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 5.67 (dd, 1H, H-2), 5.90 (d, 1H, H-4), and 7.33-8.25 (m, 15H, 3Ph).

Anal. Calcd for $C_{37}H_{42}O_{11}Si$ (690.8): C, 64.33; H, 6.13. Found: C, 64.53; H, 6.03.

2,4,6-Tri-*O*-benzoyl-3-*O*-levulinyl-α-D-galactopyranosyl Trichloroacetimidate (6). A solution of **5** (2.27 g, 3.2 mmol) in CH_2Cl_2 (5 mL) and CF_3CO_2H (5 mL) was stirred overnight at room temperature then concentrated. Column chromatography (1:2 EtOAc-hexane) of the residue on silica gel (100 g) gave the 1-hydroxy compound (2.05 g, quantitative). Drierite (250 mg) was added to a solution of the 1-hydyoxy compound (500 mg, 0.85 mmol) in CH_2Cl_2 (1 mL), which was then cooled to -5 °C. Cl_3CCN (0.26 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.07 mL) were then added and the mixture was stirred for one h at room temperature and then concentrated. Column chromatography (1:4 EtOAc-hexane) of the residue on silica gel (50 g) gave **6** (520 mg, 83%) as an amorphous mass: $[\alpha]_D$ +84.5° (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.33-2.73 (m, 4H, $MeCOCH_2CH_2$), 4.04 (dd, 1H, J_{gem} = 11.4 Hz, $J_{5,6}$ = 6.6 Hz, $J_{5,6'}$ = 5.9 Hz, H-6'), 4.57 (dd, 1H, H-6), 4.77 (m, 1H, H-5), 5.76 (dd, 1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$

= 3.3 Hz, H-3), 5.82 (dd, 1H, $J_{1,2}$= 3.1 Hz, H-2), 6.00 (br d, 1H, H-4), 6.86 (d, 1H, H-1), 7.26-8.15 (m, 15H, 3Ph), and 8.62 (s, 1H, C = NH).

Anal. Calcd for $C_{34}H_{30}Cl_3NO_{11}$ (735.0): C, 55.56; H, 4.11; N, 1.91. Found: C, 55.38; H, 4.10; N, 1.65.

2-Acetamido-1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-glucitol (8). To a solution of 7[27] (4.97 g, 24.2 mmol) in DMF (50 mL) was added Drierite (5 g) and the mixture was stirred for 3 h at room temperature. Benzaldehyde dimethyl acetal (7.3 mL) and *p*-toluenesulfonic acid monohydrate (50 mg) were added to the mixture which was stirred overnight at room temperature and then neutralized with $NaHCO_3$. The precipitate was filtered off and the solution was concentrated. Column chromatography (50:1 CH_2Cl_2-MeOH) of the residue on silica gel (400 g) gave **8** (6.9 g, 97%) as crystals. Recrystallization from ether-hexane gave needles: mp 196 °C; $[\alpha]_D$ -41.7° (*c* 1.1, MeOH); ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H, AcN), 3.23 (t, 1H, $J_{gem} = J_{1ax,2}$ = 9.3 Hz, H-1*ax*), 3.38 (m, 1H, H-5), 3.53 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 3.69 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.3 Hz, H-3), 3.73 (t, 1H, $J_{gem} = J_{5,6ax}$ = 10.4 Hz, H-6*ax*), 3.93 (dd, 1H, $J_{1eq,2}$ = 5.5 Hz, H-1*eq*), 4.00 (m, 1H, H-2), 4.28 (dd, 1H, J_{gem} = 10.4 Hz, $J_{5,6eq}$ = 4.9 Hz, H-6*eq*), 4.60 (d, 1H, N*H*), 5.58 (s, 1H, C*H*-Ph), and 7.34-7.55 (m, 5H, Ph).

Anal. Calcd for $C_{15}H_{19}NO_5$ (293.3): C, 61.42; H, 6.53; N, 4.78. Found: C, 61.30; H, 6.41; N, 4.79.

2-Acetamido-1,5-anhydro-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-glucitol (9). To a solution of **8** (3.5 g, 11.9 mmol) in DMF (40 mL) was added a suspension of sodium hydride in oil (430 mg, 60% of sodium hydride by weight). The mixture was stirred for one h at 0 °C, benzyl bromide (2.13 g) was added dropwise, and stirring was continued for 3 h at room temperature. Methanol (1 mL) was added and the mixture was concentrated then extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and concentrated. Recrystallization from ether-hexane gave **9** (3.25 g, 71%) as needles: mp 269 °C; $[\alpha]_D$ -43.2° (*c* 1.1, 1:1 $CHCl_3$-MeOH); ^1H NMR ($CDCl_3$) δ 1.88 (s, 3H, AcN), 3.21 (t, 1H, $J_{gem} = J_{1ax,2}$ = 12.7 Hz, H-1*ax*), 3.38 (m, 1H, H-5), 3.93 (dd, 1H, $J_{1eq,2}$ = 5.3 Hz, H-1*eq*), 4.31 (dd, 1H, $J_{5,6eq}$ = 4.8 Hz, J_{gem} = 10.4 Hz, H-6*eq*), 5.60 (s, 1H, C*H*-Ph), and 7.27-7.56 (m, 10H, 2Ph).

Anal. Calcd for $C_{22}H_{25}NO_5$ (383.4): C, 68.91; H, 6.57; N, 3.65. Found: C, 68.73; H, 6.61; N, 3.58.

2-Acetamido-1,5-anhydro-3,6-di-*O*-benzyl-2-deoxy-D-glucitol (10). To a solution of **9** (3.6 g, 9.4 mmol) in dry THF (36 mL) were added powdered MS-3Å (7.2 g), and the mixture was stirred for one h at room temperature, and sodium cyanoborohydride (8.8 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. The mixture was diluted with CH_2Cl_2 (100 mL), and this was washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (1:1 EtOAc-hexane) of the residue on silica gel (150 g) gave **10** (3.3 g, 91%) as crystals. Recrystallization from ether-hexane gave needles: mp 152 °C; $[\alpha]_D$ +18.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.86 (s, 3H, AcN), 6.18 (br s, 1H, OH), 7.25-7.56 (m, 10H, 2Ph).

Anal. Calcd for $C_{22}H_{27}NO_5$ (385.4): C, 68.55; H, 7.06; N, 3.63. Found: C, 68.51; H, 7.20; N, 3.50.

***O*-(2,4,6-Tri-*O*-benzoyl-3-*O*-levulinyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-1,5-anhydro-3,6-di-*O*-benzyl-2-deoxy-D-glucitol (12).** To a solution of **6** (1.2 g, 1.63 mmol) and **10** (420 mg, 1.1 mmol) in CH_2Cl_2 (6 mL) were added MS-4Å (AW-300, 2 g), and the mixture was stirred overnight at room temperature, then cooled to 0 °C. Boron trifluoride etherate (20 μL) was added and this was stirred for 3 h at room temperature. After completion of the reaction, the mixture was neutralized with Et_3N and filtered. The precipitate was washed with CH_2Cl_2. The combined filtrate and washings were successively washed with M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (100:1 CH_2Cl_2-MeOH) of the residue on silica gel (100 g) gave **12** (595 mg, 58%) as an amorphous mass: $[\alpha]_D$ +11.1° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.88, 1.91 (2s, 6H, Ac, AcN), 2.38, 2.55 (2m, 4H, $MeCOCH_2CH_2$), 3.07 (t, 1H, $J_{gem} = J_{1ax,2}$ = 8.1 Hz, H-1a*ax*), 4.75 (4d, 4H, $2CH_2Ph$), 5.25 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 3.4 Hz, H-3b), 5.56 (dd, 1H, $J_{1,2}$ = 8.2 Hz, H-2b), 5.75 (d, 1H, H-4b), and 7.23-8.13 (m, 25H, 5Ph).

Anal. Calcd for $C_{54}H_{55}NO_{15}$ (958.0): C, 67.70; H, 5.79; N, 1.46. Found: C, 67.53; H, 5.88; N, 1.50.

***O*-(2,4,6-Tri-*O*-benzoyl-3-*O*-levulinyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-1,5-anhydro-2-deoxy-glucitol (13).** A solution of **12** (593 mg, 0.63 mmol) in EtOH (30 mL) and AcOH (7 mL) was hydrogenolyzed in the presence of 10% Pd-C (600 mg) overnight at 40 °C, then filtered, and concentrated. Column chromatography (80:1 CH_2Cl_2-MeOH) of the residue on silica gel (60 g) gave **13** (433 mg, 90%) as an amorphous mass: $[\alpha]_D$ +63.5° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.88, 1.91 (2s, 6H, Ac, AcN), 2.38, 2.55 (2m, 4H, MeCOC*H*2C*H*2), 3.07 (t, 1H, $J_{gem} = J_{1ax,2} = 8.1$ Hz, H-1a*ax*), 5.25 (dd, 1H, $J_{2,3} = 10.6$ Hz, $J_{3,4} = 3.4$ Hz, H-3b), 5.56 (dd, 1H, $J_{1,2} = 8.2$ Hz, $J_{2,3} = 10.2$ Hz, H-2b), 5.67 (d, 1H, $J_{2,NH} = 7.1$ Hz, N*H*), 5.75 (d, 1H, H-4b), and 7.23-8.13 (m, 15H, 3Ph).

Anal. Calcd for $C_{40}H_{43}NO_{15}$ (777.8): C, 61.76; H, 5.57; N, 1.80. Found: C, 61.77; H, 5.43; N, 1.62.

***O*-(2,4,6-Tri-*O*-benzoyl-3-*O*-levulinyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-1,5-anhydro-6-*O*-benzoyl-2-deoxy-D-glucitol (14).** To a solution of **13** (62 mg, 0.08 mmol) in pyridine (1 mL) and CH_2Cl_2 (1 mL), cooled to -40 °C, was added benzoyl chloride (0.11 mL), and the mixture was stirred for one h at -40 °C. MeOH (0.1 mL) was added, and the mixture was concentrated then extracted with CH_2Cl_2. The extract was washed with 2 M HCl, M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (1:2 EtOAc-hexane) of the residue on silica gel (20 g) gave **14** (67 mg, 95%) as an amorphous mass: $[\alpha]_D$ +84.5° (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.87, 1.91 (2s, 6H, Ac, AcN), 2.34, 2.48 (2m, 4H, MeCOC*H*2C*H*2), 3.08 (t, 1H, $J_{gem} = J_{1ax,2} = 10.7$ Hz, H-1a*ax*), 4.95 (d, 1H, $J_{1,2} = 8.2$ Hz, H-1b), 5.38 (dd, 1H, $J_{2,3} = 10.5$ Hz, $J_{3,4} = 3.2$ Hz, H-3b), 5.72 (dd, 1H, H-2b), 5.75 (d, 1H, $J_{2,NH} = 7.1$ Hz, N*H*), 5.83 (d, 1H, H-4b), and 7.15-8.14 (m, 20H, 4Ph).

Anal. Calcd for $C_{47}H_{47}NO_{16}$ (881.9): C, 64.01; H, 5.37; N, 1.59. Found: C, 64.23; H, 5.40; N, 1.56.

***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)-2-acetamido-1,5-anhydro-3,6-di-*O*-benzyl-2-deoxy-D-glucitol (15).** To a solution of **11**[21] (220 mg, 0.22 mmol)

and **10** (52 mg, 0.13 mmol) in CH_2Cl_2 (1.5 mL) were added MS-4Å (250 mg) and the mixture was stirred overnight at room temperature then cooled to 0 °C. Dimethyl(methylthio)sulfonium triflate (DMTST, 260 mg) and MS-4Å (260 mg) were added to the mixture, and this was stirred for 2 days at room temperature. Reaction progress was monitored by TLC. The precipitate was collected and washed with CH_2Cl_2, and the combined filtrate and washings were washed with M $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. Column chromatography (3:1 EtOAc-hexane) of the residue on silica gel (30 g) gave **15** (165 mg, 92%) as an amorphous mass: $[\alpha]_D$ +24.3° (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.61-2.15 (6s, 18H, 4AcO, 2AcN), 2.46 (dd, 1H, J_{gem} = 12.5 Hz, $J_{3eq,4}$ = 4.5 Hz, H-3c*eq*), 3.76 (s, 3H, MeO), 4.50 (4d, 4H, 2CH_2Ph), 4.83 (m, 1H, $J_{3ax,4} = J_{4,5}$ = 11.2 Hz, H-4c), 5.04 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1b), 5.40 (d, 1H, H-4b), 5.50 (dd, 1H, $J_{2,3}$ = 10.1 Hz, H-2b), 5.68 (m, 1H, H-8c), and 7.21-8.20 (m, 25H, 5Ph).

Anal. Calcd for $C_{69}H_{75}N_2O_{24}$ (1333.4): C, 62.15; H, 5.67; N, 2.10. Found: C, 62.03; H, 5.77; N, 1.95.

***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)-2-acetamido-1,5-anhydro-6-*O*-benzoyl-2-deoxy-D-glucitol (16).** A solution of **15** (462 mg, 0.35 mmol) in EtOH (40 mL) and AcOH (7 mL) was stirred with 10% Pd-C (300 mg) overnight at 45 °C under hydrogen. The catalyst was collected and washed with MeOH, the combined filtrate and washings was concentrated. To a solution of the residue in pyridine (0.5 mL) and CH_2Cl_2 (1.5 mL), cooled to -50 °C, was added a solution of benzoyl chloride (0.38 mL) in CH_2Cl_2 (4 mL), and the mixture was stirred for 3 h at -50~-20 °C; the course of the reaction was monitored by TLC. A workup as described for **14** gave **16** (146 mg, 84%) as an amorphous mass: $[\alpha]_D$ +51.0° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.48-2.11 (6s, 18H, 4AcO, 2AcN), 2.43 (dd, 1H, J_{gem} = 12.6 Hz, $J_{3eq,4}$ = 4.5 Hz, H-3c*eq*), 3.02 (t, 1H, $J_{gem} = J_{1ax,2}$ = 10.8 Hz, H-1a*ax*), 4.78 (m, 1H, H-4c), 5.09 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1b), 5.23 (dd, 1H, $J_{6,7}$ = 2.6 Hz, $J_{7,8}$ = 9.4 Hz, H-7c), 5.33 (d, 1H, $J_{3,4}$ = 3.3 Hz, H-4b), 5.50 (dd, 1H, H-2b), and 7.15-8.13 (m, 20H, 4Ph).

Anal. Calcd for $C_{62}H_{67}N_2O_{25}$ (1257.2): C, 59.23; H, 5.37; N, 2.23. Found: C, 59.41; H, 5.44; N, 2.25.

***O*-(2,4,6-Tri-*O*-benzoyl-3-*O*-levulinyl-β-D-galactopyranosyl)-(1→4)-*O*-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-2-acetamido-1,5-anhydro-6-*O*-benzoyl-2-deoxy-D-glucitol (18).** To a solution of **14** (68 mg, 0.078 mmol) and methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside[23] (**17**, 43 mg, 0.092 mmol) in benzene (0.5 mL) were added MS-4Å (400 mg), and the mixture was stirred for 4 h at room temperature then cooled to 0 °C. DMTST (80 mg) was added to the mixture, and this was stirred overnight at 5 °C. The precipitate was collected and washed with CH_2Cl_2. The combined filtrate and washings were concentrated to a syrup which was chromatographed on a column of silica gel (20 g) with 100:1 CH_2Cl_2-MeOH to give **18** (77 mg, 76%) as an amorphous mass: $[\alpha]_D$ -16.0° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6b), 1.89 (s, 3H, AcN), 2.04 (s, 3H, Ac), 2.04-2.55 (m, 4H, MeCOC*H*$_2$C*H*$_2$), 3.08 (t, 1H, H-1a*ax*), 4.95 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1c), 5.42 (dd, 1H, H-3c), 5.57 (dd, 1H, $J_{2,3}$ = 10.5 Hz, H-2c), 5.83 (d, 1H, H-4c), and 7.23-8.17 (m, 35H, 7Ph).

Anal. Calcd for $C_{74}H_{75}NO_{20}$ (1298.4): C, 68.45; H, 5.82; N, 1.08. Found: C, 68.31; H, 5.85; N, 1.03.

***O*-(2,4,6-Tri-*O*-benzoyl-3-*O*-levulinyl-β-D-galactopyranosyl)-(1→4)-*O*-[(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2-acetamido-1,5-anhydro-6-*O*-benzoyl-2-deoxy-D-glucitol (19).** A solution of **18** (75 mg, 0.058 mmol) in EtOH (4 mL) and AcOH (1 mL) was stirred with 10% Pd-C (75 mg) for 12 h at 40 °C under hydrogen. The catalyst was collected and the solution was concentrated, the residue was treated with Ac_2O (0.5 mL) and pyridine (1 mL) overnight at room temperature. The mixture was concentrated then extracted with CH_2Cl_2, and the extract was washed with 2 M HCl and M Na_2CO_3, dried (Na_2SO_4) and concentrated. Column chromatography (100:1 CH_2Cl_2-MeOH) of the residue on silica gel (10 g) gave **19** (54 mg, 81%) as an amorphous mass: $[\alpha]_D$ -14.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.91-2.16 (5s, 15H, 3AcO, Ac, AcN), 3.17 (t, 1H, H-1a*ax*), 4.78 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1c), 5.15 (dd, 1H, $J_{2,3}$ = 8.3 Hz, $J_{3,4}$ = 3.3 Hz, H-3c), 5.43 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1b), 5.53 (t, 1H, H-2c), 5.77 (d, 1H, H-4c), and 7.27-8.11 (m, 20H, 4Ph).

Anal. Calcd for $C_{59}H_{63}NO_{23}$ (1154.2): C, 61.39; H, 5.50; N, 1.21. Found: C, 61.48; H, 5.68; N, 1.12.

***O*-(2,4,6-Tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-[(2,3,6-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2-acetamido-1,5-anhydro-6-*O*-benzoyl-D-glucitol (20).** To a solution of **19** (54 mg, 0.047 mmol) in EtOH (1 mL) was added hydrazine monoacetate (5.2 mg), and the mixture was stirred for 3 h at room temperature then concentrated. Column chromatography (80:1 CH_2Cl_2-MeOH) of the residue on silica gel (10 g) gave **20** (33 mg, 66%) as an amorphous mass: $[\alpha]_D$ -31.1° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.87-2.10 (4s, 12H, 3AcO, AcN), 3.07 (t, 1H, H-1a*ax*), 4.13 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.3 Hz, H-3c), 5.13 (dd, 1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 3.9 Hz, H-3b), 5.63 (d, 1H, H-4c), 6.16 (d, 1H, $J_{NH,2}$ = 9.3 Hz, N*H*), and 7.27-8.02 (m, 20H, 4Ph).

Anal. Calcd for $C_{54}H_{57}NO_{21}$ (1056.0): C, 61.41; H, 5.44; N, 1.33. Found: C, 61.35; H, 5.64; N, 1.31.

***O*-(2,4,6-Tri-*O*-benzoyl-3-sulfo-β-D-galactopyranosyl)-(1→4)-*O*-[(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)]-2-acetamido-1,5-anhydro-6-*O*-benzoyl-D-glucitol pyridine salt (21).** To a solution of **20** (33 mg, 0.031 mmol) in DMF (0.3 mL) was added sulfur trioxide pyridine complex (25 mg), and the mixture was stirred for one h. Methanol (0.1 mL) was added to the mixture and concentrated at 25 °C. Column chromatography (15:1 CH_2Cl_2-MeOH) of the residue on silica gel (10 g) gave **21** (35 mg, 93%) as an amorphous mass: $[\alpha]_D$ -5.5° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.01 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6b), 1.88-2.08 (4s, 12H, 3AcO, AcN), and 7.10-8.10 (m, 25H, 4Ph, C_5H_5N).

Anal. Calcd for $C_{59}H_{62}N_2O_{24}S$ (1215.2): C, 58.31; H, 5.14; N, 2.31. Found: C, 58.58; H, 5.35; N, 2.20.

***O*-(3-*O*-Sulfo-β-D-galactopyranosyl)-(1→4)-*O*-[α-L-fucopyranosyl-(1→3)]-2-acetamido-1,5-anhydro-D-glucitol sodium salt (22).** To a solution of **21** (50 mg, 0.041 mmol) in MeOH (1 mL) was added NaOMe (5 mg) and the mixture was stirred overnight at room temperature then concentrated at 30 °C. Column chromatography (4:1 MeOH-H_2O) of the residue on Sephadex LH-20 (30 g) gave **22** (25.5 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -24.0° (*c* 0.6, 1:1 MeOH-H_2O); ^1H NMR (D_2O) δ 1.20 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6b), 2.25 (s, 3H, AcN), 3.33 (t, 1H, J_{gem} = $J_{1ax,2}$ = 11.2 Hz, H-1a*ax*), and 4.58 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-

1c). The mass spectrum of **22** (negative ion mode) showed the base peak at *m/z* 592.5 $(M-H)^-$.

***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)]-2-acetamido-1,5-anhydro-6-*O*-benzoyl-2-deoxy-D-glucitol (23).** To a solution of **16** (102 mg, 0.081 mmol) and **17** (80 mg, 0.172 mmol) in benzene (1.5 mL) were added MS-4Å (180 mg) and the mixture was stirred overnight at room temperature then cooled to 0 °C. DMTST (130 mg, 0.486 mmol) was added to the mixture, and this was stirred for 12 h at 15 °C. After completion of the reaction, MeOH (1 mL) was added and the mixture was neutralized with Et_3N, and the precipitate was collected and washed with CH_2Cl_2. A workup as described for **15** gave **23** (120 mg, 88%) as an amorphous mass: $[\alpha]_D$ +3.3° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.52-2.15 (6s, 18H, 4AcO, 2AcN), 2.40 (dd, 1H, J_{gem} = 12.5 Hz, $J_{3eq,4}$ = 4.5 Hz, H-3d*eq*), 3.78 (s, 3H, MeO), 4.77 (m, 1H, H-4d), 5.13 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1b), 5.28 (d, 1H, $J_{6,7}$ = 2.8 Hz, $J_{7,8}$ = 10.0 Hz, H-7d), 5.38 (d, 1H, H-4c), 5.48 (dd, 1H, $J_{2,3}$ = 10.1 Hz, H-2c), 5.68 (m, 1H, H-8d), and 7.21-8.20 (m, 35H, 7Ph).

Anal. Calcd for $C_{89}H_{95}N_2O_{29}$ (1673.8): C, 63.86; H, 5.72; N, 1.67. Found: C, 63.71; H, 5.55; N, 1.78.

***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)]-2-acetamido-1,5-anhydro-6-*O*-benzoyl-2-deoxy-D-glucitol (24).** A solution of **23** (158 mg, 0.095 mmol) in EtOH (20 mL) and AcOH (5 mL) was stirred with 10% Pd-C (160 mg) overnight at room temperature under hydrogen, then filtered and concentrated. The residue was treated with Ac_2O (1 mL) and pyridine (2 mL) overnight at room temperature and concentrated. Column chromatography (50:1 CH_2Cl_2-MeOH) of the product on silica gel (30 g) gave **24** (120 mg, 85%) as an amorphous mass: $[\alpha]_D$ +0.5° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6b), 1.49-2.06 (9s, 27H, 7AcO, 2AcN), 2.40 (dd, 1H, J_{gem} = 12.5 Hz,

$J_{3eq,4}$ = 4.5 Hz, H-3d*eq*), 3.78 (s, 3H, MeO), 4.77 (m, 1H, H-4d), 5.35 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1b), 5.48 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 10.1 Hz, H-2c), 5.65 (m, 1H, H-8d), and 7.26-8.15 (m, 20H, 4Ph).

Anal. Calcd for $C_{74}H_{83}N_2O_{32}$ (1529.5): C, 58.11; H, 5.47; N, 1.83. Found: C, 58.24; H, 5.61; N, 1.59.

***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)]-2-acetamido-1,5-anhydro-2-deoxy-D-glucitol (25).** To a solution of **24** (80 mg, 0.054 mmol) in MeOH (2 mL) was added NaOMe (6 mg), and the mixture was stirred overnight at room temperature. Water (1 mL) was added to the mixture, and this was stirred for 5 h 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 (30 g) gave **25** (42 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -25.0° (*c* 0.7, MeOH); ^1H NMR (Me_2SO-*d*6) δ 1.12 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6b), 1.89,1.98 (2s, 6H, 2AcN), 3.19 (t, 1H, H-1a*ax*), 4.42 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1c), and 5.02 (d, 1H, $J_{1,2}$ = 2.8 Hz, H-1b).

Anal. Calcd for $C_{31}H_{52}N_2O_{22}$ (804.8): C, 46.26; H, 6.51; N, 3.48. Found: C, 46.15; H, 6.80; N, 3.34.

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