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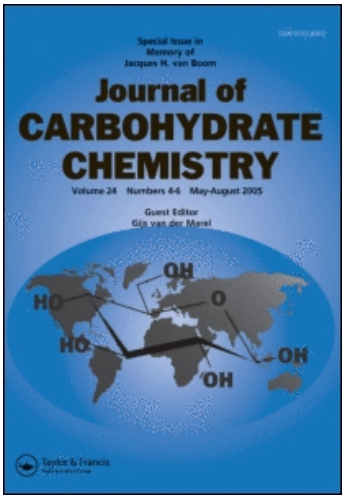

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Synthetic Studies on Sialoglycoconjugates 90: Total Synthesis of Sulfated Glucuronyl Paraglobosides

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 90: TOTAL SYNTHESIS OF SULFATED GLUCURONYL PARAGLOBOSIDES

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ABSTRACT

3-*O*-Sulfo glucuronyl paragloboside derivatives (pentasaccharides) have been synthesized. The important intermediate designed for a facile sulfation in the last step and effective, stereocontrolled glycosidation, methyl (4-*O*-acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-α-D-glucopyranosyl trichloroacetimidate)uronate (**8**) was prepared from methyl [2-(trimethylsilyl)ethyl β-D-glucopyranosid]uronate (**3**) *via* selective 4-*O*-acetylation, 2-*O*-benzoylation, 3-*O*-levulinoylation, removal of the 2-(trimethylsilyl)ethyl group and imidate formation. The glycosylation of **8** with 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**9**) using trimethylsilyl trifluoromethanesulfonate gave 2-(trimethylsilyl)ethyl *O*-(methyl 4-*O*-acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**10**), which was transformed *via* removal of the benzyl group, benzoylation, removal of the 2-(trimethylsilyl)ethyl group and imidate formation into the disaccharide donor **13**. On the other hand, 2-(trimethylsilyl)ethyl *O*-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1 → 3)-*O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**20**) as the acceptor was prepared from 2-(trimethylsilyl)ethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**14**) *via* *O*-acetylation, removal of the 2-(trimethylsilyl)ethyl group, imidate formation, coupling with 2-(trimethylsilyl)ethyl *O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**18**), removal of the *O*-acetyl and *N*-phthaloyl group followed by *N*-acetylation. Condensation of **13** with **20** using trimethylsilyl trifluoromethanesulfonate afforded the desired pentasaccharide **21**, which was transformed by removal of the benzyl group, *O*-acetylation, removal of

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the 2-(trimethylsilyl)ethyl group and imidate formation into the pentasaccharide donor **24**. Glycosylation of (2*S*, 3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (**25**) with **24** gave the desired β-glycoside **26**, which was transformed into the four target compounds, *via* reduction of the azido group, coupling with octadecanoic acid or tetracosanoic acid, selective removal of the levulinoyl group, *O*-sulfation, hydrolysis of the methyl ester group and *O*-deacylation.

INTRODUCTION

Many researchers have shown[1] that monoclonal antibodies of L2 and HNK-1 (anti-Leu-7), which are raised against a membrane antigen from T cell line HSB-2, react with a common epitope in the carbohydrate moiety of the neural cell adhesion molecules (N-CAM) and the myelin associated glycoprotein (MAG). Furthermore, unusual glycolipids from human peripheral nervous and embryonic fetal brain are recognized[2] by the L2 /HNK-1 antibodies. In 1986, these glycolipids were characterized[3] as 3-*O*-sulfo glucuronyl paragloboside and 3-*O*-sulfo glucuronyl neolactohexanosyl ceramide. The presence of the 3-*O*-sulfo glucuronyl moiety in the glycosphingolipids was essential for antibody binding. And interestingly, it has been reported that the HNK-1 reactive glycolipids react with L- and P-selectin, but not with E-selectin.[4] In view of these facts, it is of interest to synthesize these glycolipids to elucidate the structural requirements for recognition by selectin and HNK-1 antibody. We describe here a facile total synthesis of the 3-*O*-sulfo glucuronyl paraglobosides and the corresponding glucuronyl paraglobosides, in which fatty acid groups at the ceramide moiety consist of octadecanoyl and tetracosanoyl groups;

GlcAβ(1→3)Galβ(1→4)GlcNAcβ(1→3)Galβ(1→4)Glcβ-(1→1)Ceramide (C-18, **30**)

GlcAβ(1→3)Galβ(1→4)GlcNAcβ(1→3)Galβ(1→4)Glcβ-(1→1)Ceramide (C-24, **35**)

3-*O*-sulfo GlcAβ(1→3)Galβ(1→4)GlcNAcβ(1→3)Galβ(1→4)Glcβ-(1→1)Ceramide (C-18, **31**)

3-*O*-sulfo GlcAβ(1→3)Galβ(1→4)GlcNAcβ(1→3)Galβ(1→4)Glcβ-(1→1)Ceramide (C-24, **36**)

RESULTS AND DISCUSSION

The most essential factor for the total synthesis of the target molecules is to achieve an effective and regioselective sulfation and the stereoselective construction of

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the pentasaccharide unit. For these purposes, we designed methyl (4-*O*-acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-α-D-glucopyranosyl trichloroacetimidate)uronate (**8**) as the glucuronyl donor to be coupled with 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside[5] (**9**) to give the desired disaccharide, 2-(trimethylsilyl)ethyl *O*-(methyl 4-*O*-acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**10**). Coupling of *O*-(methyl 4-*O*-acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranosyl trichloroacetimidate (**13**) derived from **10**, with 2-(trimethylsilyl)ethyl *O*-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**20**), to be prepared by condensation of 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate (**17**) with 2-(trimethylsilyl)ethyl *O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[6] (**18**), will afford the corresponding pentasaccharide **21**. By further processing according to our procedures, the resulting pentasaccharide **21** could be converted into the end products *via* introduction of ceramides, sulfation and deprotection.

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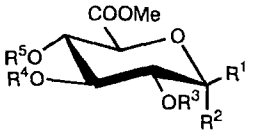
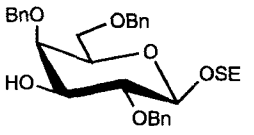
Compound **2** was prepared in 91% yield from the easily obtainable, crystalline methyl (2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate[7] (**1**) by coupling with 2-(trimethylsilyl)ethanol[8] under Koenigs-Knorr conditions in the presence of silver perchlorate and silver carbonate in dichloromethane at room temperature. Significant signals of the glucuronic acid unit in the ^{1}H NMR spectrum of the product were two one-proton doublets at δ 4.03 (d, $J_{4,5}$ = 9.7 Hz, H-5) and 4.56 (d, $J_{1,2}$ = 7.5 Hz, H-1), showing the newly formed β-glycosidic linkage. *O*-Deacetylation of **2** with sodium methoxide afforded **3** in 94% yield, which in turn was acetylated at the *O*-4 position to give **4** in 61% yield using acetyl chloride and triethylamine with the aid of dibutyltin oxide.[9] Dibutyltin oxide-mediated 2-*O*-benzoylation[9] of **4** with benzoic anhydride in toluene at 100 °C gave **5** in 60% yield. The ^{1}H NMR data for the glucuronic acid residue in **5** [δ 2.10 (s, AcO), 5.11 (dd, $J_{1,2}$ = 7.2 Hz, $J_{2,3}$ = 9.3 Hz, H-2), 5.22 (t, $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz, H-4) and 7.42-8.07 (Ph)] are characteristic of the structure assigned. Conversion of **5** into the 3-*O*-levulinoyl compound **6** (76%) was achieved



	R^1	R^2	R^3	R^4	R^5
1	H	Br	Ac	Ac	Ac
2	OSE	H	Ac	Ac	Ac
3	OSE	H	H	H	H
4	OSE	H	H	H	Ac
5	OSE	H	Bz	H	Ac
6	OSE	H	Bz	Lev	Ac
7	OH ,H		Bz	Lev	Ac
8	H	$OC(=NH)CCl_3$	Bz	Lev	Ac



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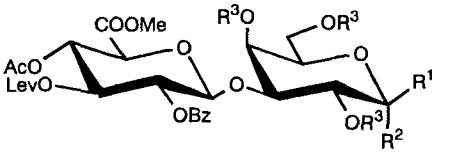
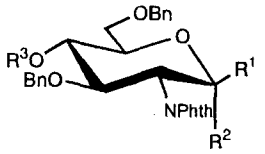
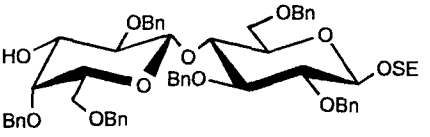


	R^1	R^2	R^3
10	OSE	H	Bn
11	OSE	H	Bz
12	OH ,H		Bz
13	H	$OC(=NH)CCl_3$	Bz



	R^1	R^2	R^3
14	OSE	H	H
15	OSE	H	Ac
16	OH ,H		Ac
17	$OC(=NH)CCl_3$	H	Ac



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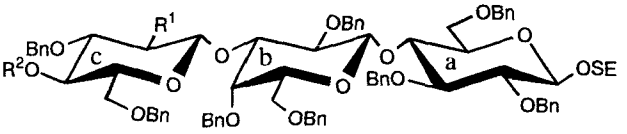

	R^1	R^2
19	NPhth	Ac
20	NHAc	H

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

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by treatment with levulinic anhydride and 4-dimethylaminopyridine in pyridine. Selective removal[10] of the 2-(trimethylsilyl)ethyl group in **6** with trifluoroacetic acid in dichloromethane for 2 h at room temperature gave **7** (quantitative). When treated with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 2 h at 0 °C, compound **7** gave the trichloroacetimidate[11] **8** as the α-anomer in 95% yield after column chromatography.

Glycosylation of 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galacto-pyranoside[5] (**9**) with **8** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the glycosyl promoter and powdered molecular sieves 4Å (MS-4Å) in dichloromethane afforded the desired β-glycosidic disaccharide **10** in 95% yield (based on **8**); significant signals in **10** in the ^{1}H NMR spectrum were two one-proton doublets at δ 3.98 (d, $J_{4,5}$ = 9.8 Hz, H-5') and 5.23 (d, $J_{1,2}$ = 7.7 Hz, H-1'), twenty aromatic protons at δ 7.19-7.90 (4Ph). Catalytic hydrogenolysis (10% Pd-C) of the benzyl group in **10** in ethyl acetate-methanol for 24 h at room temperature and subsequent *O*-benzoylation gave the per-*O*-acyl compound **11** in 82% yield. Compound **11** was transformed, as described for **7** and **8**, by removal of the 2-(trimethylsilyl)ethyl group and imidate formation into the disaccharide donor **13**. The ^{1}H NMR data for Gal unit in **13** [δ 6.73 (d, $J_{1,2}$ = 3.7 Hz, H-1), 8.47 (C=NH)] indicated the trichloroacetimidate to be α.

The acetylation of **14**[10] with acetic anhydride in pyridine gave **15** (quantitative), which was transformed, as described for **7** and **8**, by removal of the 2-(trimethylsilyl)ethyl group and imidate formation into the donor **17**. The ^{1}H NMR data for GlcNPhth unit in **17** [δ 6.43 (d, $J_{1,2}$ = 8.8 Hz, H-1), 8.59 (C=NH)] indicated the trichloroacetimidate to be β.

Glycosylation of **18** with **17** in the presence of TMSOTf as the glycosyl promoter and MS-4Å in dichloromethane afforded the desired β-glycosidic trisaccharide **19** in 93% yield (based on **17**); significant signals of **19** in the ^{1}H NMR spectrum were a one-proton doublet at δ 5.38 (d, $J_{1,2}$ = 8.4 Hz, H-1 for GlcN) and forty-four aromatic protons at δ 6.88-7.28 (8Ph and Phthaloyl-H). *O*-Deacetylation of **19** with sodium methoxide, followed by heating with hydrazine hydrate in aq 95% ethanol, and subsequent *N*-acetylation gave **20** in 84% yield after column chromatography.

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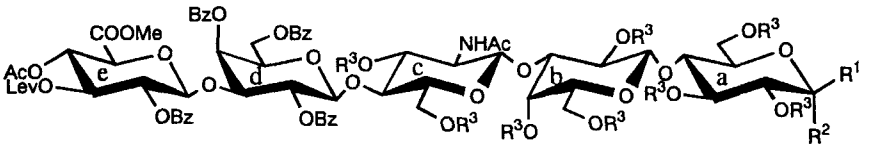
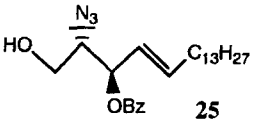


	R^1	R^2	R^3
21	OSE	H	Bn
22	OSE	H	Ac
23	OH ,H		Ac
24	H	$OC(=NH)CCl_3$	Ac



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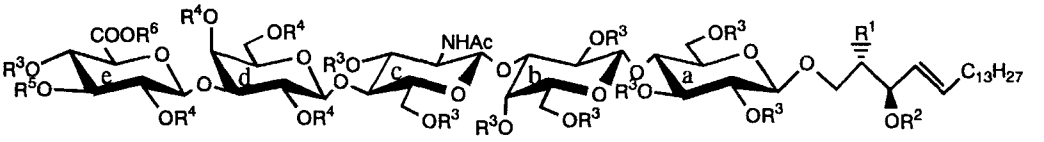

	R^1	R^2	R^3	R^4	R^5	R^6
26	N_3	Bz	Ac	Bz	Lev	Me
27	$NHCOC_{17}H_{35}$	Bz	Ac	Bz	Lev	Me
28	$NHCOC_{17}H_{35}$	Bz	Ac	Bz	H	Me
29	$NHCOC_{17}H_{35}$	Bz	Ac	Bz	SO_3Na	Me
30	$NHCOC_{17}H_{35}$	H	H	H	H	Na
31	$NHCOC_{17}H_{35}$	H	H	H	SO_3Na	Na
32	$NHCOC_{23}H_{47}$	Bz	Ac	Bz	Lev	Me
33	$NHCOC_{23}H_{47}$	Bz	Ac	Bz	H	Me
34	$NHCOC_{23}H_{47}$	Bz	Ac	Bz	SO_3Na	Me
35	$NHCOC_{23}H_{47}$	H	H	H	H	Na
36	$NHCOC_{23}H_{47}$	H	H	H	SO_3Na	Na

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The glycosylation of **20** with the disaccharide imidate **13** in the presence of 0.15 equiv of TMSOTf and MS-4Å overnight at room temperature afforded the pentasaccharide **21** in 94% yield (based on **13**). Catalytic hydrogenolysis (10% Pd-C) of the benzyl groups in **21** in ethyl acetate-methanol for 30 h at room temperature and subsequent *O*-acetylation gave the per-*O*-acyl compound **22** in quantitative yield. Compound **22** was transformed, as described for **7** and **8**, by removal of the 2-(trimethylsilyl)ethyl group and imidate formation into the disaccharide donor **24**. The ^{1}H NMR data for Glc unit in **24** [δ 6.46 (d, $J_{1,2}$ = 3.8 Hz, H-1), 8.64 (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[12,13] (**25**) with **24** thus obtained, in dichloromethane in the presence of boron trifluoride etherate for 7 h at 0 °C afforded the expected β-glycoside **26** in 72% yield. Selective reduction[14,15] of the azido group in **26** with hydrogen sulfide in aq pyridine for 2.5 days at 10 °C gave the amine, which, on condensation with octadecanoic acid and tetracosanoic acid, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) in dichloromethane afforded **27** (78%) and **32** (71%), respectively. Selective removal of the levulinoyl group in **27** and **32** with hydrazine-monoacetate gave **28** and **33** in good yields. Treatment of **28** and **33** in *N,N*-dimethylformamide (DMF) with excess of sulfur trioxide trimethylamine complex for 20 h at 40 °C afforded the sulfated **29** (97%) and **34** (96%), respectively. Finally, saponification of the methyl ester group in **28**, **29**, **33** and **34** with lithium hydroxide monohydrate in tetrahydrofuran and water, followed by *O*-deacylation with sodium methoxide in methanol-tetrahydrofuran at 10 °C, yielded the desired glycolipids **30**, **31**, **35** and **36**. Four target glycosphingolipids (**30**, **31**, **35** and **36**), thus obtained, were purified by column chromatography on Sephadex LH-20, and the structures were confirmed by FAB-MS spectroscopy.

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

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spectrophotometer. ^1H NMR spectra were recorded with a JEOL JNM-GX 270 spectrometer. FAB-MS spectra were determined with a JEOL JMS-SX 102A mass spectrometer/JMA-DA 7000 data system. Each sample was mixed with triethanolamine matrix on a target. The ion accelerating voltage was 8.0 KV, and the primary beam for the bombardment was 6.0 KeV of xenon. Preparative chromatography was performed on silica gel (Wako Chemical Co., 200 mesh) with the solvent systems specified. Concentrations were conducted in vacuo.

Methyl [2-(Trimethylsilyl)ethyl 2,3,4-Tri-*O*-acetyl-β-D-glucopyranosid]uronate (2). To a solution of 2-(trimethylsilyl)ethanol (24.0 g, 203.3 mmol) in CH_2Cl_2 (70 mL) were added silver carbonate (32.0 g, 116.0 mmol), silver perchlorate (25.5 g, 123.0 mmol) and powdered molecular sieves 4Å (MS-4Å; 30 g), and the mixture was stirred for 10 h at room temperature in the dark (mixture A). Methyl (2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate (**1**; 40.0 g, 100.1 mmol) was added to the mixture A at 10 °C. After vigorous stirring for 6 h in the dark, the precipitate was collected and washed with CH_2Cl_2, and the combined filtrate and washings concentrated. Column chromatography (1:2 ethyl acetate-hexane) of the residue on silica gel (1200 g) gave **2** (39.8 g, 91%). Recrystallization from ethyl acetate-hexane gave needles: mp 85.5-87.5 °C; $[\alpha]_D$ -32.4° (*c* 0.5, $CHCl_3$); IR (KBr) 1760 and 1220 (ester), and 860 and 840 cm^{-1} (TMS); ^1H NMR ($CDCl_3$) δ 0.93 (m, 2H, $Me_3SiCH_2CH_2O$), 2.01-2.03 (3s, 9H, 3AcO), 3.55 (m, 1H, $Me_3SiCH_2CH_2O$), 3.75 (s, 3H, MeO), 4.03 (d, 1H, $J_{4,5}$ = 9.7 Hz, H-5), 4.56 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), and 4.99 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2).

Anal. Calcd for $C_{18}H_{30}O_{10}Si$ (434.5): C, 49.76; H, 6.96. Found: C, 49.47; H, 6.68.

Methyl [2-(Trimethylsilyl)ethyl β-D-Glucopyranosid]uronate (3). To a solution of **2** (39.8 g, 91.6 mmol) in MeOH (200 mL) was added NaOMe (1.0 g), and the mixture was stirred for 2 h at room temperature and treated with Amberlite IR-120 (H^+) resin then concentrated. Column chromatography (3:1 ethyl acetate-hexane) of the residue on silica gel (500 g) gave **3** (26.5 g, 94%), isolated as a syrup: $[\alpha]_D$ -48.4° (*c* 0.6, $CHCl_3$); IR (film) 3500-3350 (OH), 1740 and 1220 (ester), and 860 and 840 cm^{-1} (TMS).

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Anal. Calcd for $C_{12}H_{24}O_7Si$ (308.4): C, 46.73; H, 7.84. Found: C, 46.50; H, 7.63.

Methyl [2-(Trimethylsilyl)ethyl 4-*O*-Acetyl-β-D-glucopyranosid]uronate (4). A suspension of **3** (26.5 g, 85.9 mmol) and di-*n*-butyltin oxide (32.1 g, 129.0 mmol) in MeOH (720 mL) was heated, with stirring, for 5 h at 60 °C, concentrated, then diluted with tetrahydrofuran (THF; 300 mL). To the solution was added triethylamine (11.3 g, 111.7 mmol), and after heating at 45 °C, acetyl chloride (7.4 g, 94.3 mmol) was carefully added and the mixture was stirred for 5 h at 45 °C. After addition of MeOH (10 mL), the solution was concentrated. Column chromatography (2:1 ethyl acetate-hexane) of the residue on silica gel (1000 g) gave **4** (18.2 g, 61%). Compound **4** was recrystallized from ethyl acetate-hexane to give needles: mp 132.5-134.0 °C; $[\alpha]_D$ -63.0° (*c* 0.8, $CHCl_3$); IR (KBr) 3490 (OH), 1760 and 1230 (ester), and 860 and 840 cm^{-1} (TMS); ^1H NMR ($CDCl_3$) δ 1.02 (m, 2H, $Me_3SiCH_2CH_2O$), 2.10 (s, 3H, AcO), 3.73 (t, 1H, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3), 3.74 (s, 3H, MeO), 3.94 (d, 1H, H-5), 4.34 (d, 1H, $J_{1,2} = 7.7$ Hz, H-1), and 5.03 (t, 1H, $J_{4,5} = 9.3$ Hz, H-4).

Anal. Calcd for $C_{14}H_{26}O_8Si$ (350.4): C, 47.98; H, 7.48. Found: C, 47.76; H, 7.28.

Methyl [2-(Trimethylsilyl)ethyl 4-*O*-Acetyl-2-*O*-benzoyl-β-D-glucopyranosid]uronate (5). A suspension of **4** (18.0 g, 51.4 mmol) and di-*n*-butyltin oxide (18.0 g, 72.3 mmol) in toluene (150 mL) was stirred for 1 h at 100 °C with azeotropic removal of water. To the solution was added benzoic anhydride (34.0 g, 150.3 mmol) in toluene (34 mL) and the reaction mixture was stirred for 10 min at 100 °C then concentrated. Column chromatography (1:1 ethyl acetate-hexane) of the residue on silica gel (700 g) gave **5** (14.0 g, 60%). Compound **5** was recrystallized from ethyl acetate-hexane to give needles: mp 119.0-121.0 °C; $[\alpha]_D$ -33.9° (*c* 0.9, $CHCl_3$); IR (KBr) 3480 (OH), 1750, 1730, 1270, and 1250 (ester), 860 and 840 (TMS), and 770 and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.91 (m, 2H, $Me_3SiCH_2CH_2O$), 2.10 (s, 3H, AcO), 3.58 (m, 1H, Me3CH2CH_2O), 3.78 (s, 3H, MeO), 4.05 (d, 1H, H-5), 4.70 (d, 1H, $J_{1,2} = 7.2$ Hz, H-1), 5.11 (dd, 1H, $J_{2,3} = 9.3$Hz, H-2), 5.22 (t, 1H, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), and 7.42-8.07 (m, 5H, Ph).

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Anal. Calcd for $C_{21}H_{30}O_9Si$ (454.6): C, 55.49; H, 6.65. Found: C, 55.27; H, 6.56.

Methyl [2-(Trimethylsilyl)ethyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosid]uronate (6). To a solution of levulinic anhydride (24.0 g, 112.0 mmol) in pyridine (70 mL) were added **5** (10.0 g, 22.0 mmol) and 4-dimethylaminopyridine (1.3 g, 106.4 mmol). The mixture was stirred overnight at room temperature and concentrated. Column chromatography (3:2 ethyl acetate-hexane) of the residue on silica gel (500 g) afforded **6** (9.2 g, 76%) as needles: mp 89.5-91.0 °C; $[\alpha]_D$ +11.8° (*c* 1.0, $CHCl_3$); IR (KBr) 1750, 1720, 1270, and 1240 (ester), 860 and 840 (TMS), and 770 and 720 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.88 (m, 2H, $Me_3SiCH_2CH_2O$), 2.04 and 2.08 (2s, 6H, AcO and $CH_3COCH_2CH_2CO$), 3.56 (m, 1H, $Me_3CH_2CH_2O$), 3.78 (s, 3H, MeO), 4.01 (m, 1H, $Me_3SiCH_2CH_2O$), 4.11 (d, 1H, $J_{4,5}$ = 9.6 Hz, H-5), 4.70 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 5.26 (dd, 1H, H-2), 5.30 (t, 1H, H-4), 5.46 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.6 Hz, H-3), and 7.42-8.07 (m, 5H, Ph).

Anal. Calcd for $C_{26}H_{36}O_{11}Si$ (552.6): C, 56.51; H, 6.57. Found: C, 56.29; H, 6.36.

Methyl (4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-D-glucopyranos)uronate (7). To a solution of **6** (9.0 g, 16.3 mmol) in CH_2Cl_2 (50 mL) was added trifluoroacetic acid (20 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature then concentrated. Column chromatography (2:1 ethyl acetate-hexane) of the residue on silica gel (200 g) gave **7** (7.3 g, quantitative) as an amorphous mass: $[\alpha]_D$ +113.1° (*c* 1.2, $CHCl_3$); IR (film) 3440 (OH), and 1750, 1720, 1260, and 1230 (ester).

Anal. Calcd for $C_{21}H_{24}O_{11}$ (452.4): C, 55.75; H, 5.35. Found: C, 55.62; H, 5.08.

Methyl (4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-α-D-glucopyranosyl trichloroacetimidate)uronate (8). To a solution of **7** (5.0 g, 11.1 mmol) in CH_2Cl_2 (50 mL) and trichloroacetonitrile (11 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.30 g) at 0 °C, and the mixture was stirred for 2 h at 0 °C. The solution was directly chromatographed on a column of silica gel (300 g) with 1:1 ethyl acetate-hexane to afford **8** (6.2 g, 95%) as an amorphous mass: $[\alpha]_D$

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+103.9° (*c* 0.7, $CHCl_3$); IR (KBr) 3320 (NH) 1760, 1730, 1270, and 1220 (ester), and 760 and 720 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 2.07 and 2.14 (2s, 6H, AcO and $CH_3COCH_2CH_2CO$), 2.56 (m, 4H, $CH_3COCH_2CH_2CO$), 3.70 (s, 3H, MeO), 4.55 (d, 1H, $J_{4,5}$ = 10.2 Hz, H-5), 5.87 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 10.2 Hz, H-3), 6.78 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 7.39-7.99 (m, 5H, Ph), and 8.64 (s, 1H, C=NH).

Anal. Calcd for $C_{23}H_{24}Cl_3NO_{11}$ (596.8): C, 46.29; H, 4.05; N 2.35. Found: C, 46.04; H, 4.05; N 2.12.

2-(Trimethylsilyl)ethyl *O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (10). To a solution of **8** (2.3 g, 3.85 mmol) in CH_2Cl_2 (10 mL) were added 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**9**; 3.5 g, 6.35 mmol) and MS-4Å (3 g), and the mixture was stirred for 5 h at room temperature (mixture A). A solution of trimethylsilyl trifluoromethanesulfonate (TMSOTf; 0.85 g, 3.82 mmol) in CH_2Cl_2 (1 mL) was stirred with MS-4Å (1 g) for 1 h at room temperature and the mixture was added to the mixture A at 0 °C. After stirring for 1 h, the reaction mixture was neutralized with triethylamine and filtered, the residue was washed with CH_2Cl_2 then the combined filtrate and washings concentrated. Column chromatography (1:2 ethyl acetate-hexane) of the residue on silica gel (100 g) afforded **10** (3.6 g, 95%) as crystals: mp 144.0-146.0 °C; $[\alpha]_D$ -0.6° (*c* 0.7, $CHCl_3$); IR (KBr) 1760, 1720, 1270, and 1230 (ester), 860 and 840 (TMS), and 770, 740 and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.92 (m, 2H, $Me_3SiCH_2CH_2O$), 2.03 and 2.09 (2s, 6H, AcO and $CH_3COCH_2CH_2CO$), 2.46 (m, 4H, $CH_3COCH_2CH_2CO$), 3.72 (s, 3H, MeO), 3.85 (dd, 1H, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 3.0 Hz, H-3 for Gal), 3.94 (d, 1H, H-4 for Gal), 3.98 (d, 1H, $J_{4,5}$ = 9.8 Hz, H-5 for GlcA), 4.28 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1 for Gal), 5.23 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1 for GlcA), 5.31 (t, 1H, $J_{3,4}$ = 9.8 Hz, H-4 for GlcA), and 7.19-7.90 (m, 20H, 4Ph).

Anal. Calcd for $C_{53}H_{64}O_{16}Si$ (985.2): C, 64.62; H, 6.55. Found: C, 64.33; H, 6.33.

2-(Trimethylsilyl)ethyl *O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-2,4,6-tri-*O*-benzoyl-β-D-

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galactopyranoside (11). A solution of **10** (9.5 g, 9.64 mmol) in MeOH (100 mL) and ethyl acetate (50 mL) was hydrogenated in the presence of 10% Pd-C (3.0 g) for 24 h at room temperature, and the reaction mixture was filtered and then concentrated. The residue was benzoylated with benzoyl chloride (5.1 g, 36.3 mmol)-pyridine (30 mL) overnight at room temperature and the product was purified by chromatography on a column of silica gel (500 g) with 1:1 ethyl acetate-hexane to give **11** (8.1 g, 82%) as crystals: mp 118.5-120.5 °C; $[\alpha]_D$ +36.2° (*c* 0.4, $CHCl_3$); IR (KBr) 1730 and 1270 (ester), 860 and 840 (TMS), and 770 and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.79 (m, 2H, $Me_3SiCH_2CH_2O$), 1.97 and 2.02 (2s, 6H, AcO and $CH_3COCH_2CH_2CO$), 2.31 (m, 4H, $CH_3COCH_2CH_2CO$), 3.68 (s, 3H, MeO), 4.02 (d, 1H, $J_{4,5}$ = 9.8 Hz, H-5 for GlcA), 4.28 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$=3.4 Hz, H-3 for Gal), 4.61 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1 for Gal), 4.88 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1 for GlcA), 5.06 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2 for GlcA), 5.56 (dd, 1H, H-2 for Gal), 5.85 (d, 1H, H-4 for Gal), and 7.17-8.11 (m, 20H, 4Ph).

Anal. Calcd for $C_{53}H_{58}O_{19}Si$ (1027.1): C, 61.98; H, 5.69. Found: C, 61.93; H, 5.45.

***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-2,4,6-tri-*O*-benzoyl-D-galactopyranose (12).** To a solution of **11** (5.1 g, 4.97 mmol) in CH_2Cl_2 (60 mL) was added trifluoroacetic acid (10 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature then concentrated. Column chromatography (1:1 ethyl acetate-hexane) of the residue on silica gel (200 g) afforded **12** (4.6 g, quantitative) as an amorphous mass: $[\alpha]_D$ +72.0° (*c* 0.5, $CHCl_3$); IR (film) 3480 (OH), 1730 and 1270 (ester), and 710 and 690 cm^{-1} (Ph).

Anal. Calcd for $C_{48}H_{46}O_{19}$ (926.9): C, 62.20; H, 5.00. Found: C, 61.95; H, 4.76.

***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranosyl Trichloroacetimidate (13).** To a solution of **12** (2.5 g, 3.13 mmol) in CH_2Cl_2 (30 mL) and trichloroacetonitrile (5 mL) was added DBU (50 mg) at 0 °C, and the mixture was stirred for 2 h at 0 °C. The solution was directly chromatographed on a column of

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silica gel (100 g) with 2:3 ethyl acetate-hexane to give **13** (2.7 g, 93%) as an amorphous mass: $[\alpha]_D$ +79.0° (*c* 0.9, $CHCl_3$); IR (KBr) 3340 (NH), 1730 and 1270 (ester), and 760, 710 and 690 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.98 and 2.05 (2s, 6H, AcO and $CH_3COCH_2CH_2CO$), 2.32 (m, 4H, $CH_3COCH_2CH_2CO$), 3.75 (s, 3H, MeO), 4.15 (d, 1H, $J_{4,5}$ = 9.2 Hz, H-5 for GlcA), 5.03 (d, 1H, $J_{1,2}$ = 7.0 Hz, H-1 for GlcA), 5.71 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2 for Gal), 6.02 (d, 1H, $J_{3,4}$ = 3.1 Hz, H-4 for Gal), 6.73 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1 for GlcA), 7.09-8.10 (m, 20H, 4Ph), and 8.47 (s, 1H, C=NH).

Anal. Calcd for $C_{50}H_{46}Cl_3NO_{19}$ (1071.3): C, 56.06; H, 4.33; N, 1.31 Found: C, 55.99; H, 4.09, N, 1.31.

2-(Trimethylsilyl)ethyl 4-*O*-Acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (15). To a solution of 2-(trimethylsilyl)ethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**14**; 8.0 g, 13.6 mmol) in pyridine (40 mL) was added acetic anhydride (10 mL) at 0 °C, and the mixture was stirred for 5 h at room temperature then concentrated. Column chromatography (1:2 ethyl acetate-hexane) of the residue on silica gel (200 g) gave **15** (8.6 g, quantitative) as crystals: mp 87.5-89.5 °C; $[\alpha]_D$ +54.2° (*c* 0.7, $CHCl_3$); IR (KBr) 1750 and 1230 (ester), 860 and 840 (TMS), and 740, 720 and 700 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.77 (m, 2H, $Me_3SiCH_2CH_2O$), 1.95 (s, 3H, AcO), 4.24 (dd, 1H, $J_{1,2}$ = 8.3 Hz, $J_{2,3}$ = 10.8 Hz, H-2), 4.42 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 5.14 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.17 (d, 1H, H-1), and 6.87-7.68 (m, 14H, 2Ph, Phthaloyl-H).

Anal. Calcd for $C_{35}H_{41}NO_8Si$ (631.8): C, 66.54; H, 6.54; N, 2.22. Found: C, 66.38; H, 6.45; N, 1.93.

4-*O*-Acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-D-glucopyranose (16). To a solution of **15** (8.5 g, 13.5 mmol) in CH_2Cl_2 (80 mL) was added trifluoroacetic acid (15 mL) at 0 °C, the reaction mixture was stirred for 2 h at room temperature and then concentrated. Column chromatography (1:1 ethyl acetate-hexane) of the residue on silica gel (200 g) afforded **16** (7.1 g, quantitative) as a syrup: $[\alpha]_D$ +64.9° (*c* 0.5, $CHCl_3$); IR (film) 3470 (OH), 1750 and 1230 (ester), and 740, 720 and 700 cm^{-1} (Ph).

Anal. Calcd for $C_{30}H_{29}NO_8$ (531.6): C, 67.79; H, 5.50; N, 2.64. Found: C, 67.50; H, 5.33; N, 2.45.

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4-*O*-Acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl Trichloroacetimidate (17). To a solution of **16** (6.9 g, 13.0 mmol) in CH_2Cl_2 (70 mL) and trichloroacetonitrile (12 mL) was added DBU (0.2 g) at 0 °C, and the mixture was stirred for 1 h at 0 °C. The solution was directly chromatographed on a column of silica gel (200 g) with 1:1 ethyl acetate-hexane to afford **17** (7.9 g, 90%) as an amorphous mass: IR (film) 1770 and 1270 (ester), 1720 (C=N), and 740, 720 and 700 cm^{-1}(Ph); ^1H NMR ($CDCl_3$) δ 1.95 (s, 3H, AcO), 4.12 (dd, 1H, H-3), 5.25 (m, 1H, H-4), 6.43 (d, 1H, $J_{1,2}$ = 8.8 Hz, H-1), and 6.87-7.68 (m, 14H, 2Ph, Phthaloyl-H).

Anal. Calcd for $C_{32}H_{29}Cl_3N_2O_8$ (676.0): C, 56.86; H, 4.32; N, 4.14. Found: C, 56.86; H, 4.26; N, 3.97.

2-(Trimethylsilyl)ethyl *O*-(4-*O*-Acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside. (19) To a solution of **17** (5.0 g, 7.40 mmol) in CH_2Cl_2 (20 mL) were added 2-(trimethylsilyl)ethyl *O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**18**; 14.5 g, 14.7 mmol) and MS-4Å (5.0 g), and the mixture was stirred for 5 h at room temperature (mixture A). A solution of TMSOTf (0.5 g, 2.2 mmol) in CH_2Cl_2 was stirred with MS-4Å (0.6 g) for 1 h at room temperature and then added to the mixture A at 0 °C. After stirring for 1 h at 10 °C, the reaction mixture was neutralized with triethylamine and filtered, the residue was washed with CH_2Cl_2 and the combined filtrate and washings were then concentrated. Column chromatography (1:2 ethyl acetate-hexane) of the residue on silica gel (500 g) gave **10** (10.3 g, 93%) as a syrup: $[\alpha]_D$ +7.4° (*c* 0.8, $CHCl_3$); IR (film) 1770 and 1270 (ester), 1720 (imide), and 740, 720 and 700 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.97 (m, 2H, $Me_3SiCH_2CH_2O$), 1.96 (s, 3H, AcO), 5.12 (dd, 1H, H-4c), 5.38 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1c), and 6.88-7.28 (m, 44H, 8Ph, Phthaloyl-H).

Anal. Calcd for $C_{89}H_{97}NO_{18}Si$ (1496.8): C, 71.42; H, 6.53; N, 0.94. Found: C, 71.33; H, 6.44; N, 0.92.

2-(Trimethylsilyl)ethyl *O*-(2-Acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-

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(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (20). To a solution of **19** (10.0 g, 6.7 mmol) in MeOH (150 mL) was added NaOMe (300 mg) the mixture was stirred for 3 h at room temperature, treated with Amberlite IR-120 (H^+) resin and concentrated. A solution of the residue in aq 95% ethanol (80 mL) was then heated with hydrazine monohydrate (5 mL) for 4 h under reflux. The precipitate was collected and washed with EtOH, and the combined filtrate and washings concentrated. The residue was treated with acetic anhydride (5 mL) in MeOH (80 mL) for 1 h at room temperature, pyridine (10 mL) was added, and the mixture was concentrated and extracted with CH_2Cl_2 (300 mL). The extract was successively washed with 2M HCl, water, and M Na_2CO_3, dried (Na_2SO_4) and concentrated. Column chromatography (2:3 ethyl acetate-hexane) of the residue on silica gel (400 g) gave **20** (7.7 g, 84%) as a syrup: $[\alpha]_D$ -6.8° (*c* 1.2, $CHCl_3$); IR (film) 3410 (OH and NH), 1640 and 1540 (amide), 860 and 840 (TMS), and 740 and 700 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.02 (m, 2H, $Me_3SiCH_2CH_2O$), 1.47 (s, 3H, AcN), and 7.12-7.33 (m, 40H, 8Ph).

Anal. Calcd for $C_{81}H_{95}NO_{16}Si$ (1366.7): C, 71.18; H, 7.01; N, 1,02. Found: C, 71.16; H, 6.75; N, 0.99.

2-(Trimethylsilyl)ethyl *O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (21). To a solution of **13** (2.4 g, 2.24 mmol) in CH_2Cl_2 (12 mL) were added **20** (6.0 g, 4.40 mmol) and MS-4Å (2.5 g), and the mixture was stirred for 5 h at room temperature (mixture A). A solution of TMSOTf (75 mg, 0.34 mmol) in CH_2Cl_2 (1 mL) was stirred with MS-4Å (0.5 g) for 1 h at room temperature, and the mixture was added to the mixture A at room temperature and stirred overnight at room temperature. The mixture was neutralized with triethylamine and the precipitate was collected and washed with CH_2Cl_2. The combined filtrate and washings was concentrated. Column chromatography (1:1 ethyl acetate-hexane) of the residue on silica gel (300 g) gave **21** (4.8 g, 94%): $[\alpha]_D$ +3.2° (*c* 0.4, $CHCl_3$); IR (film) 3400 (NH), 1730 and 1270 (ester), 1680 and 1590 (amide), and 740, 710 and 700 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ

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1.01 (m, 2H, $Me_3SiCH_2CH_2O$), 1.67 (s, 3H, AcN), 1.97 and 2.04 (2s, 6H, AcO and $CH_3COCH_2CH_2CO$), 2.32 (m, 4H, $CH_3COCH_2CH_2CO$), 3.70 (s, 3H, MeO), and 7.01-8.06 (m, 60H, 12Ph).

Anal. Calcd for $C_{129}H_{139}NO_{34}Si$ (2275.6): C, 68.09; H, 6.16; N, 0.62. Found: C, 67.93; H, 5.99; N, 0.60.

2-(Trimethylsilyl)ethyl *O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (22). A solution of **21** (4.5 g, 2.0 mmol) in MeOH (50 mL) and ethyl acetate (20 mL) was hydrogenated in the presence of 10% Pd-C (2.0 g) for 30 h at room temperature, then filtered and concentrated. The residue was acetylated with acetic anhydride (20 mL)-pyridine (40 mL) for 20 h at room temperature. The product was purified by chromatography on a column of silica gel (350 g) with 4:1 ethyl acetate-hexane to give **22** (3.7 g, quantitative) as needles: $[\alpha]_D$ +12.5° (*c* 0.5, $CHCl_3$); IR (film) 3390 (NH), and 1750 and 1230 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ 0.88 (m, 2H, $Me_3SiCH_2CH_2O$), 1.77 (s, 3H, AcN), 1.84-2.09 (10s, 30H, 9AcO and $CH_3COCH_2CH_2CO$), 2.33 (m, 4H, $CH_3COCH_2CH_2CO$), 3.71 (s, 3H, MeO), 4.27, 4.45, 4.51 and 4.64 (4d, 4H, $J_{1,2}$ = 7.9 Hz, H-1a-d), 4.82 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1e), 5.50 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2b or d), 5.86 (dd, 1H, $J_{3,4}$ = 3.2 Hz, H-4b or d), and 7.15-8.10 (m, 20H, 4Ph).

Anal. Calcd for $C_{89}H_{107}NO_{42}Si$ (1890.9): C, 56.53; H, 5.70; N, 0.74. Found: C, 56.44; H, 5.53; N, 0.57.

***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranose (23).** To a solution of **22** (3.3 g, 1.74 mmol) in CH_2Cl_2 (25 mL) was added trifluoroacetic acid (8 mL) at 0 °C, and the mixture was stirred for 1.5 h at room temperature then concentrated. Column chromatography (ethyl acetate) of the residue on silica gel (200 g) gave **23** (3.0 g, 96%) as a syrup :

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$[\alpha]_D$ +31.6° (*c* 0.4, $CHCl_3$); IR (film) 3380 (OH and NH), and 1750 and 1230 cm^{-1} (ester).

Anal. Calcd for $C_{84}H_{95}NO_{42}$ (1790.7): C, 56.34; H, 5.35; N, 0.78. Found: C, 56.16; H, 5.21; N, 0.48.

***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl Trichloroacetimidate (24).** To a solution of **23** (1.5 g, 0.85 mmol) in CH_2Cl_2 (30 mL) and trichloroacetonitrile (3 mL) was added DBU (25 mg) at -10 °C, and the mixture was stirred for 4 h at 0 °C. The solution was directly chromatographed on a column of silica gel (300 g) with 4:1 ethyl acetate-hexane to give **24** (1.5 g, 94%) as an amorphous mass: $[\alpha]_D$ +41.3° (*c* 1.7, $CHCl_3$); IR (film) 3350 (NH), 1750 and 1220 (ester), 1680 and 1540 (amide), and 760 and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.76 (s, 3H, AcN), 1.84-2.09 (10s, 30H, 9AcO and $CH_3COCH_2CH_2CO$), 2.32 (m, 4H, $CH_3COCH_2CH_2CO$), 3.70 (s, 3H, MeO), 4.01 (d, 1H, $J_{4,5}$ = 9.8 Hz, H-5e), 4.31, 4.52 and 4.65 (3d, 3H, $J_{1,2}$ = 7.9 Hz, H-1b-d), 4.82 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1e), 5.03 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2a), 6.46 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1a), 7.15-8.10 (m, 20H, 4Ph), and 8.64 (s, 1H, C=NH).

Anal. Calcd for $C_{86}H_{95}Cl_3N_2O_{42}$ (1935.0): C, 53.38; H, 4.95; N, 1.45. Found: C, 53.32; H, 4.69; N, 1.27.

***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (26).** To a solution of **24** (1.0 g, 0.52 mmol) and (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (**25**; 0.47 g, 1.09 mmol) in CH_2Cl_2 (10 mL) were added powdered molecular sieves 4Å (AW-300, 1.5 g), the mixture was stirred for 5 h at room temperature and then cooled to 0 °C. Boron trifluoride etherate (0.25 g) was added, and the mixture was stirred for 7 h at 0 °C and

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filtered. The insoluble material was washed with CH_2Cl_2, and the combined filtrate and washings were washed with M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (40:1 CH_2Cl_2-MeOH) of the residue on silica gel (100 g) gave amorphous **26** (0.82 g, 72%): $[\alpha]_D$ +6.0° (*c* 0.8, $CHCl_3$); IR (film) 3380 (NH), 2930 and 2860 (Me, CH_2), 2110 (azide), and 1750 and 1230 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J_{Me,CH_2} = 6.6 Hz, *Me*CH_2), 1.23 (s, 22H, 11CH_2), 1.70 (s, 3H, AcN), 1.84-2.07 (10s, 30H, 9AcO and *CH*$_3$COCH$_2$CH$_2$CO), 2.32 (m, 4H, CH$_3$COC*H*$_2$C*H*$_2$CO), 3.65 (s, 3H, MeO), 4.27, 4.48, 4.51 and 4.64 (4d, 4H, $J_{1,2}$ = 7.5-7.9 Hz, H-1a-d), 4.82 (d, 1H, $J_{1,2}$ = 7.1 Hz, H-1e), 5.83 (dt, 1H, H-5 of sphingosine), 7.15-8.09 (m, 25H, 5Ph).

Anal. Calcd for $C_{109}H_{132}N_4O_{44}$ (2202.2): C, 59.45; H, 6.04; N, 2.54. Found: C, 59.36; H, 5.98; N, 2.43.

***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol (27).** Hydrogen sulfide was bubbled through a stirred solution of **26** (700 mg, 0.32 mmol) in aq 80% pyridine (50 mL) for 60 h at 10 °C. The mixture was concentrated, and the residue was stirred with octadecanoic acid (270 mg, 0.95 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC; 240 mg, 1.25 mmol) in CH_2Cl_2 (5 mL) overnight 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 CH_2Cl_2-MeOH) of the residue on silica gel (100 g) gave amorphous **27** (606 mg, 78%): $[\alpha]_D$ +14.2° (*c* 1.0, $CHCl_3$); IR (film) 3380 (NH), 2930 and 2860 (Me, CH_2), 1750 and 1230 (ester), and 1680 and 1540 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, *2Me*CH_2), 1.25 (s, 52H, 26CH_2), 1.73 (s, 3H, AcN), 1.84-2.08 (10s, 30H, 9AcO and *CH*$_3$COCH$_2$CH$_2$CO), 2.32 (m, 4H, CH$_3$COC*H*$_2$C*H*$_2$CO), 3.65 (s, 3H, MeO), 5.85 (dt, 1H, H-5 of sphingosine), and 7.15-8.09 (m, 25H, 5Ph).

Anal. Calcd for $C_{127}H_{168}N_2O_{45}$ (2442.7): C, 62.45; H, 6.93; N, 1.15. Found: C, 62.35; H, 6.91; N, 1.11.

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***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol (28).** A mixture of **27** (300 mg, 0.12 mmol) and hydrazine monoacetate (55 mg, 0.60 mmol) in EtOH (10 mL) was stirred for 1 h at room temperature. Dichloromethane (50 mL) was added, and the mixture was washed with M $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. Column chromatography (25:1 CH_2Cl_2-MeOH) of the residue on silica gel (50 g) afforded amorphous **28** (282 mg, 98%): $[\alpha]_D$ +6.1° (*c* 1.5, $CHCl_3$); IR (film) 3380 (OH and NH), 2930 and 2850 (Me, CH_2), 1750 and 1230 (ester), and 1680 and 1540 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, *Me*CH_2), 1.25 (s, 52H, 26CH_2), 1.61 (s, 3H, AcN), 1.85-2.08 (9s, 27H, 9AcO), 3.65 (s, 3H, MeO), 5.86 (dt, 1H, H-5 of sphingosine), and 7.18-8.08 (m, 25H, 5Ph).

Anal. Calcd for $C_{122}H_{162}N_2O_{43}$ (2344.6): C, 62.50; H, 6.96; N, 1.19. Found: C, 62.23; H, 6.83; N, 0.93.

***O*-(Methyl 4-*O*-Acetyl-3-*O*-sulfo-2-*O*-benzoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol Sodium Salt (29).** A solution of **28** (280 mg, 0.12 mmol) and sulfur trioxide trimethylamine complex (250 mg, 1.8 mmol) in DMF (3 mL) was stirred at 40 °C for 20 h then cooled to room temperature. Methanol (0.5 mL) and CH_2Cl_2 (0.5 mL) were added, and the solution was applied to a column of Sephadex LH-20 with 1:1 CH_2Cl_2-MeOH. Glycolipid-containing fractions were concentrated. Column chromatography (MeOH) of the residue on Dowex-50×2 (Na^+) resin gave amorphous **29** (283 mg, 97%): $[\alpha]_D$ +11.8° (*c* 0.6, $CHCl_3$); IR (film) 3380 (NH), 2930 and 2860 (Me, CH_2), 1750 and 1230 (ester), and 1670 and 1540 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 0.89 (t, 6H, *Me*CH_2), 1.26 (s, 52H, 26CH_2), 1.60 (s, 3H,

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AcN), 1.81-2.05 (9s, 27H, 9AcO), 3.65 (s, 3H, MeO), 5.87 (dt, 1H, H-5 of sphingosine), and 7.09-8.09 (m, 25H, 5Ph).

***O*-β-D-Glucopyranosyluronic acid-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-*O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-(1→1)-(2*S*,3*R*,4*E*)-2-octadecanamido-4-octadecene-1,3-diol Sodium Salt (30).** To a solution of **28** (140 mg, 59.7 μmol) in THF (5 mL) was added lithium hydroxide monohydrate (13 mg, 0.31 mmol) in water (1 mL), and the mixture was stirred for 3 h at 5 °C and concentrated at 30 °C. Tetrahydrofuran (7mL), MeOH (7 mL) and NaOMe (10 mg) were added to the mixture and this was stirred overnight at 10 °C, and chromatographed on a column of Sephadex LH-20 with 6:4:1 $CHCl_3$-MeOH-H_2O to give **30** (52 mg, 61%): FAB-MS (negative ion mode); *m/z* 1429.91 $(M-Na)^-$, $C_{68}H_{121}N_2O_{29}^-$ requires 1429.8055.

***O*-3-*O*-Sulfo-β-D-glucopyranosyluronic Acid-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-*O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-(1→1)-(2*S*,3*R*,4*E*)-2-octadecanamido-4-octadecene-1,3-diol Disodium Salt (31).** Deacylation and saponification of **29** (140 mg, 57.2 μmol), as described for **30**, yielded **31** (67.6 mg, 77%): FAB-MS (negative ion mode); *m/z* 1531.91 $(M-Na)^-$, 1553.89 $(M-H)^-$, $C_{68}H_{120}N_2O_{32}SNa^-$ requires 1531.7443 and $C_{68}H_{119}N_2O_{32}SNa_2^-$ requires 1553.7262.

***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-tetracosanamido-4-octadecene-1,3-diol (32).** Selective reduction of the azido group in **26** (700 mg, 0.32 mmol) and subsequent coupling with tetracosanoic acid (370 mg, 1.0 mmol), as described for **27**, afforded amorphous **32** (570 mg, 71%): $[\alpha]_D$ +13.8° (*c* 1.2, $CHCl_3$); IR (film) 3380 (NH), 2930 and 2850 (Me, CH_2), 1750 and 1230 (ester), and 1680 and 1540 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H,

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2MeCH_2), 1.25 (s, 64H, $32CH_2$), 1.68 (s, 3H, AcN), 1.84-2.08 (10s, 30H, 9AcO and $CH_3COCH_2CH_2CO$), 2.28 (m, 4H, $CH_3COCH_2CH_2CO$), 3.65 (s, 3H, MeO), 5.85 (dt, 1H, H-5 of sphingosine), and 7.14-8.09 (m, 25H, 5Ph).

Anal. Calcd for $C_{133}H_{180}N_2O_{45}$ (2526.9): C, 63.22; H, 7.18; N, 1.11. Found: C, 63.12; H, 7.05; N, 1.06.

***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-tetracosanamido-4-octadecene-1,3-diol (33).** Selective removal of the levulinoyl group in **32** (300 mg, 0.12 mmol), as described for **28**, afforded amorphous **33** (285 mg, quantitative): $[\alpha]_D$ +6.2° (*c* 0.8, $CHCl_3$); IR (film) 3390 (OH and NH), 2930 and 2850 (Me, CH_2), 1750 and 1230 (ester), and 1680 and 1540 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, 2*Me*CH_2), 1.26 (s, 64H, $32CH_2$), 1.60 (s, 3H, AcN), 1.85-2.02 (9s, 27H, 9AcO), 3.65 (s, 3H, MeO), 5.86 (dt, 1H, H-5 of sphingosine), and 7.18-8.08 (m, 25H, 5Ph).

Anal. Calcd for $C_{128}H_{174}N_2O_{43}$ (2428.8): C, 63.30; H, 7.22; N, 1.15. Found: C, 63.18; H, 6.99; N, 1.05.

***O*-(Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-sulfo-β-D-glucopyranosyluronate)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-*O*-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-tetracosanamido-4-octadecene-1,3-diol Sodium Salt (34).** Sulfation of **33** (270 mg, 0.11 mmol), as described for **29**, yielded amorphous **34** (270 mg, 96%): $[\alpha]_D$ +3.3° (*c* 0.7, $CHCl_3$); IR (film) 3390 (NH), 2930 and 2850 (Me, CH_2), 1750 and 1230 (ester), and 1680 and 1540 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, 2*Me*CH_2), 1.26 (s, 64H, $32CH_2$), 1.60 (s, 3H, AcN), 1.83-2.06 (9s, 27H, 9AcO), 3.67 (s, 3H, MeO), 5.85 (dt, 1H, H-5 of sphingosine), and 7.18-8.08 (m, 25H, 5Ph).

***O*-β-D-Glucopyranosyluronic Acid-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-*O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→3)-*O*-β-D-galact-**

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opyranosyl-(1→4)-*O*-β-D-glucopyranosyl-(1→1)-(2*S*,3*R*,4*E*)-2-tetracosanamido-4-octadecene-1,3-diol Sodium Salt (35). Deacylation and saponification of **33** (150 mg, 61.8 μmol), as described for **30**, yielded **35** (48.7 mg, 52%): FAB-MS (negative ion mode); *m/z* 1513.97 $(M-Na)^-$, $C_{74}H_{133}N_2O_{29}^-$ requires 1513.8994.

***O*-3-*O*-Sulfo-β-D-glucopyranosyluronic Acid-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-*O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-(1→1)-(2*S*,3*R*,4*E*)-2-tetracosanamido-4-octadecene-1,3-diol Disodium Salt (36).** Deacylation and saponification of **34** (130 mg, 51.4 μmol), as described for **30**, yielded **36** (56.3 mg, 65%): FAB-MS (negative ion mode); *m/z* 1615.85 $(M-Na)^-$, 1637.66 $(M-H)^-$, $C_{74}H_{132}N_2O_{32}SNa^-$ requires 1615.8382 and $C_{74}H_{131}N_2O_{32}SNa_2^-$ requires 1637.8201.

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