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Total synthesis of VIM-2 ganglioside isolated from human chronic myelogenous leukemia cells [1]

Taro Ehara [a], Akihiko Kameyama [a], Yutaka Yamada [a], Hideharu Ishida [b], Makoto Kiso [b], Akira Hasegawa [b,*]

[a] *The Nisshin Oil Mills, Ltd, 3, 1-chome, Chiwaka-cho, Kanagawa-ku, Yokohama 221, Japan*

[b] *Department of Applied Bioorganic Chemistry, Gifu University, Yanagido, Gifu 501-11, Japan*

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Abstract

A total synthesis of the tumor associated glycolipid antigen, VIM-2, is described [2]. Phenyl 2,3,4-tri-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**7**), a key intermediate prepared by condensation of phenyl 6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**6**) and 2,3,4-tri-*O*-benzoyl-6-*O*-benzyl-α-D-galactopyranosyl bromide (**5**), was glycosylated with methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**8**) to give the trisaccharide donor **9**, which, on coupling with 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**10**), afforded the pentasaccharide **11**. The regioselective glycosylation of **12** (derived by *O*-debenzoylation of **11**) with **7** gave the heptasaccharide **13**, which was converted by treatment with hydrazine monohydrate and subsequent *N*-acetylation into the hexasaccharide acceptor **14**. The stereo- and regio-selective glycosylation of **14** with methyl (phenyl 5-acetamido-4,7,8,9-*O*-benzoyl-3,5-dideoxy-2-thio-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate (**16**) gave the desired octasaccharide **18**. Hydrogenolytic removal of the benzyl groups in **18** and successive *O*-acetylation, removal of the 2-(trimethylsilyl)ethyl group, and treatment with trichloroacetonitrile gave the α-trichloroacetimidate **21**, which was then coupled with (2*S*,3*R*,4*E*)-2-azido-3-*O*-(*tert*-butyldiphenylsilyl)-4-octadecene-1,3-diol (**22**) to give **23**. Compound **23** was transformed, via selective reduction of the azido group, *N*-introduction of octadecanoic acid, *O*-desilylation, *O*-deacylation, and saponification of the methyl ester group, into the title VIM-2 ganglioside **26**.

Keywords: Synthesis, ganglioside; Synthesis, VIM-2; Antigen, tumor-associated; Glycolipid

* Corresponding author.

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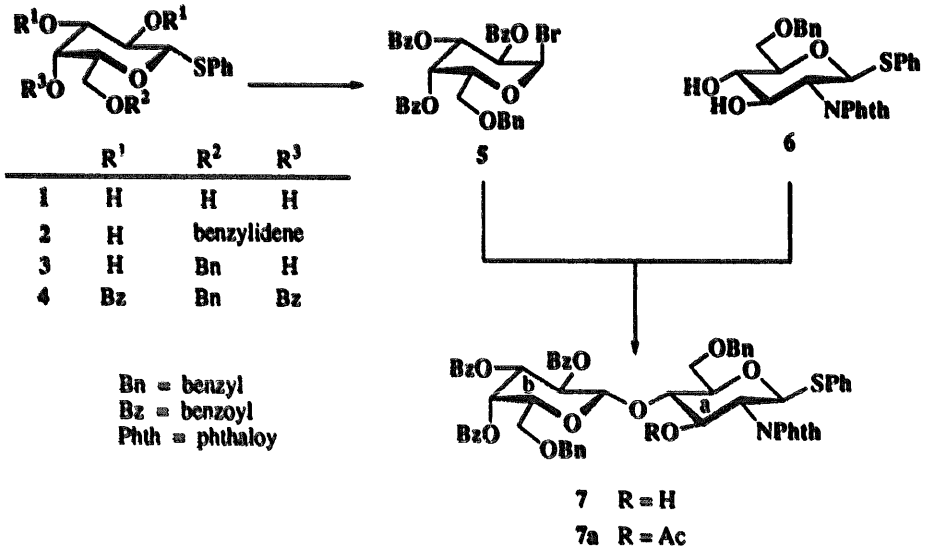
1. Introduction

Sialylated and fucosylated lactosaminyl structures such as sialyl Lewis^x (sLe^x), sialyl dimeric Le^x, and its internally monofucosylated derivative VIM-2, are regarded as the differential and tumor-associated carbohydrate antigens [2,3], and recently have been proposed [4,5] as the ligands for E- and P-selectin, cell-adhesion receptors that are implicated in the leukocyte traffic and extravasation to sites of inflammation, platelet adhesion, and probably tumor metastasis [6]. As only a limited number of these carbohydrate structures are available from natural sources, the systematic synthesis of these compounds is therefore currently the best way to supply sufficient amounts of gangliosides for extensive biological research work. Along this line, we have succeeded in the first total synthesis of sLe^x [7] and sialyl dimeric Le^x gangliosides [8].

As a part of our ongoing project aimed at the systematic synthesis and elucidation of the functions of neolacto-series gangliosides [9], we describe herein the total synthesis of VIM-2 ganglioside, which has been isolated from human chronic myelogenous leukemia cell [10] and seems to be related to the level of cellular differentiation [11].

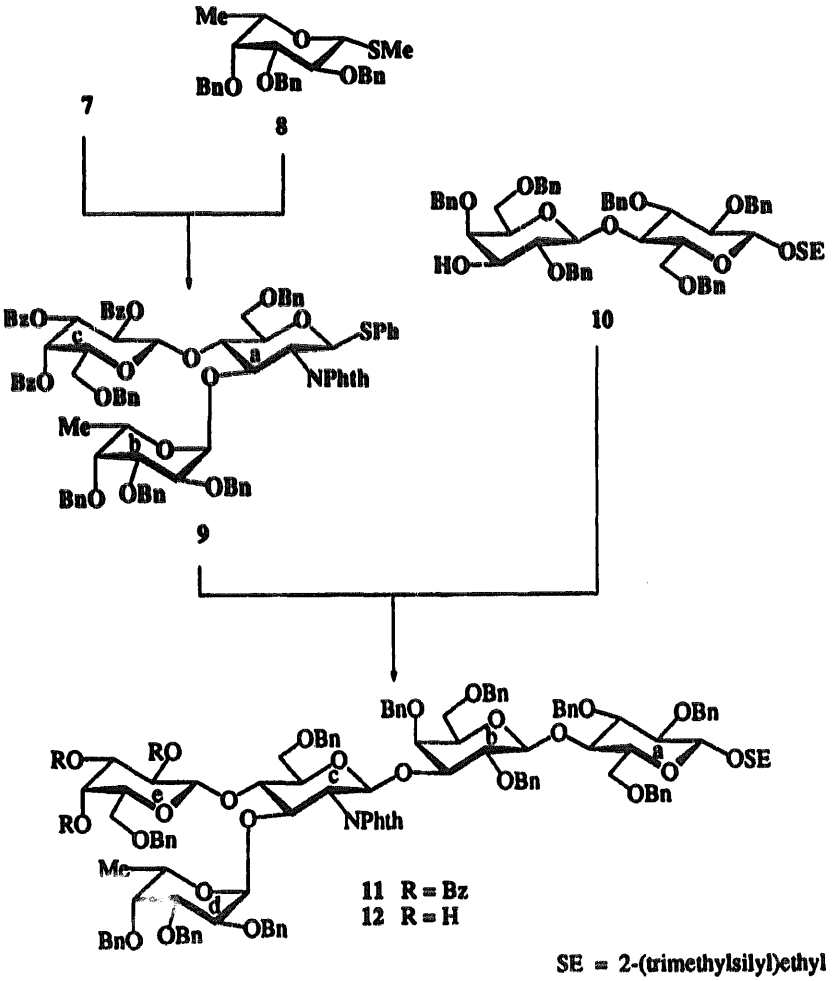
2. Results and discussion

For the synthesis of neolacto-series ganglioside, VIM-2, we selected four intermediates, among them phenyl 2,3,4-tri-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**7**), methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside [12] (**8**), 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside [13] (**10**), and methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-benzoyl-3,5-dideoxy-2-thio-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate (**16**).



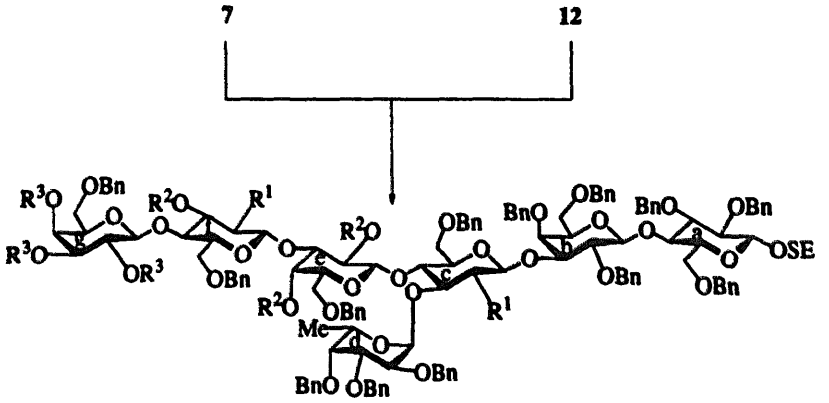
Scheme 1.

The lactosamine unit **7** was prepared by condensation of 2,3,4-tri-*O*-benzoyl-6-*O*-benzyl-α-D-galactopyranosyl bromide (**5**) with the diol derivative **6** [14] of *N*-phthaloyl-D-glucosamine (Scheme 1). An immediate precursor **4** for the galactosyl donor **5** was readily prepared in three steps from compound **1** in 60% overall yield, via **2** [15] and **3**. This sequence resulted from successive treatments with (*i*) benzaldehyde dimethylacetal and 4-toluenesulfonic acid in *N*,*N*-dimethylformamide; (*ii*) sodium cyanoborohydride and hydrogen chloride [16] in tetrahydrofuran; and (*iii*) benzoyl chloride in pyridine. Conversion of compound **4** into the α-bromide **5** (79%) was achieved by treatment [17] with bromine in dichloromethane. The glycosylation of the diol **6** with the galactosyl bromide **5** in toluene for 16 h at −40 °C in the presence of silver trifluoromethanesulfonate [18] afforded the desired β-glycoside **7** (75%). The structure of **7** was confirmed as follows. Acetylation of **7** with acetic anhydride in pyridine gave the acetate **7a** in quantitative yield. The ^{1}H NMR spectrum of **7a** showed the presence of H-3 of the glucosamine unit at δ 5.78, indicating the position of the new glycosidic linkage in **7** to be at OH-4 of the acceptor.

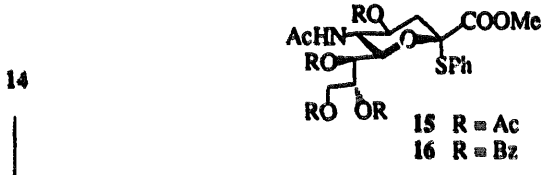


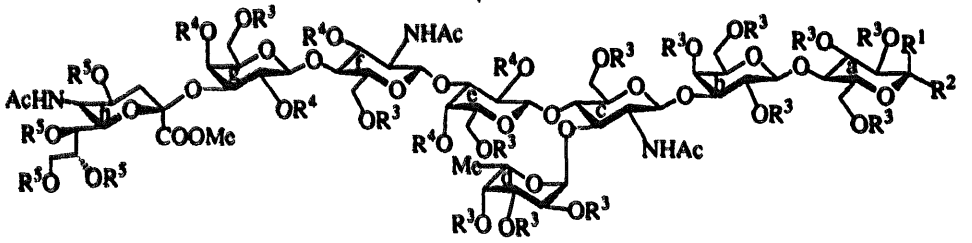
Scheme 2.

The glycosylation of **7** with **8** in toluene for 16 h at −15 °C in the presence of *N*-iodosuccinimide (NIS)–trifluoromethanesulfonic acid (TfOH) [19,20] gave the desired α-glycoside **9** in 93% yield (Scheme 2). Significant signals of the fucose unit in the ^{1}H



	R^1	R^2	R^3
13	NPhth	H	Bz
13a	NPhth	Ac	Bz
14	NHAc	H	H





	R^1	R^2	R^3	R^4	R^5
17	H	OSE	Bn	H	Ac
17a	H	OSE	Bn	Ac	Ac
18	H	OSE	Bn	H	Bz
18a	H	OSE	Bn	Ac	Bz
19	H	OSE	Ac	Ac	Bz
20	H,OH		Ac	Ac	Bz
21	$OC(=NH)CCl_3$	H	Ac	Ac	Bz

Scheme 3.

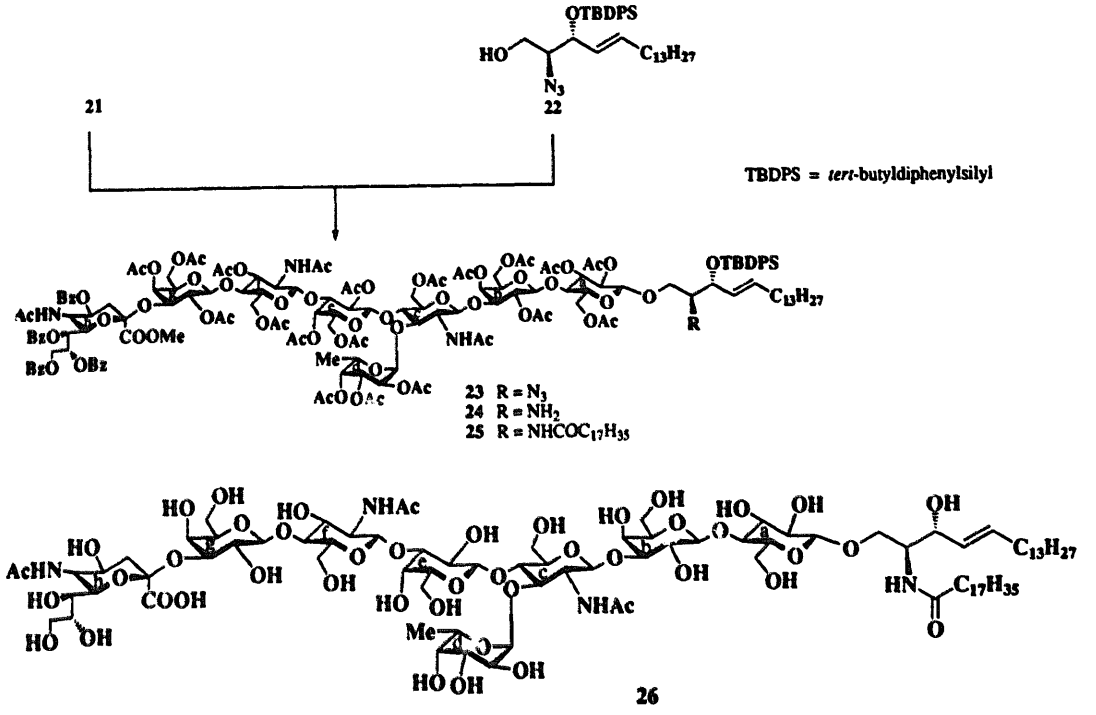
NMR spectrum of **9** were a three-proton doublet at δ 1.30 ($J_{5,6}$ 6.5 Hz, H-6b), and a one-proton doublet at δ 5.07 ($J_{1,2}$ 2.8 Hz, H-1b), indicating the structure assigned.

The coupling [14] of trisaccharide **9** with **10** was performed in the presence of NIS–TfOH in dichloromethane for 1 h at −60 °C, giving the desired pentasaccharide derivative **11** in 86% yield. Significant signal of the glucosamine unit in the ^{1}H NMR spectrum of **11** was at δ 5.31 (d, $J_{1,2}$ 8.3 Hz, H-1c), indicating the newly formed glycosidic linkage to be β. *O*-Debenzoylation of **11** with sodium methoxide gave the triol **12** in 98% yield.

The regioselective condensation [14,21] of the triol **12** and **7** in the presence of NIS–TfOH as the glycosyl promoter in dichloromethane for 5 h at −60 °C afforded the hexasaccharide **13** in 83% yield (Scheme 3), which had the expected stereochemistry. The ^{1}H NMR spectrum of **13** contained signals appropriate to the structure assigned, including a doublet at δ 5.40 ($J_{1,2}$ 8.5 Hz, H-1f) due to the newly formed β-glycosidic linkage. The regiochemistry for the newly introduced interglycosidic linkage in **13** was determined as (1f → 3e) by 2D ^{1}H NMR data of the acetate **13a**, which revealed three deshielded signals for H-2e, H-4e and H-3f at δ 4.72, 5.48 and 5.80, respectively. Treatment of compound **13** with hydrazine monohydrate, followed by *N*-acetylation, afforded, in 93% yield, the designed heptasaccharide acceptor **14** containg six free hydroxyl groups.

The stereo- and regio-selective sialylation of **14** with the phenyl β-thioglycoside of the acetate derivative [22] **15** or the benzoate derivative **16** of sialic acid has been attempted. The benzoate derivative **16** was prepared in two steps in 59% overall yield from the acetate derivative **15** by sodium methoxide treatment and subsequent benzoylation. The glycosylation of **14** with the acetate derivative **15** or the benzoate derivative **16** by use of NIS–TfOH [23] in acetonitrile at −43 °C afforded the corresponding octasaccharides **17** and **18** in 39 and 72% yields, respectively, showing that the benzoate derivative **16** is a more efficient glycosyl donor than the acetate **15**. The structures of **17** and **18** were confirmed by ^{1}H NMR data of the corresponding acetates **17a** and **18a**, respectively. On acetylation of the remaining hydroxyls of **17**, five protons were significantly deshielded to δ 4.92 (H-2g), 5.04 (H-4g), 5.00 (H-3f), 4.88 (H-2e) and 5.48 (H-4e), indicating that the Neu5Ac residue in **17** was introduced at C-3g of the galactose residue. The stereochemistry of the anomeric configuration of Neu5Ac in **17** was assigned as α, based on the chemical shifts of H-3h*e*, H-4h and H-7h that were observed at δ 2.59 (dd, J_{gem} 12.5, $J_{3e,4}$ 4.5 Hz, H-3e), 4.93 (H-4) and 5.37 (dd, $J_{6,7}$ 2.4, $J_{7,8}$ 8.7 Hz, H-7), respectively. Similarly, the regio- and stereo-chemistry of the glycosidic linkage of Neu5Ac in **18** were determined from the ^{1}H NMR data of **18a** in which the five deshielded signals were each observed at δ 5.05 (H-2g), 5.12 (H-4g), 5.00 (H-3f), 4.88 (H-2e) and 5.49 (H-4e), as expected for (2h → 3g)-linkage, and the characteristic signals for the α-glycoside of Neu5Ac were observed at δ 2.78 (dd, J_{gem} 12.6, $J_{3e,4}$ 4.5 Hz, H-3h*e*), 5.21 (H-4h) and 5.91 (dd, $J_{6,7}$ 2.8, $J_{7,8}$ 7.4 Hz, H-7h), respectively.

Catalytic hydrogenolysis (10% Pd–C) of the benzyl groups in **18** in methanol–ethanol–acetic acid and subsequent *O*-acetylation gave the per-*O*-acyl compound **19** in 63% yield. Further, selective removal of the 2-(trimetylsilyl)ethyl group in **19** was performed by treatment [13] with trifluoroacetic acid in dichloromethane for 2 h at room



Scheme 4.

temperature to give the 1-hydroxy compound **20** in good yield. Treatment [24] of **20** with trichloroacetonitrile in dichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 3 h at 0 °C gave the α-trichloroacetimidate **21** in 89% yield.

The final glycosylation [25] of (2*S*,3*R*,4*E*)-2-azido-3-*O*-(*tert*-butyldiphenylsilyl)-4-octadecene-1,3-diol [26] (**22**) with **21** in dichloromethane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) for 3.5 h at 0 °C afforded the expected β-glycoside **23** in 47% yield. The observed chemical shifts and coupling constants due to the newly coupled 2-azidosphingosine unit were a one-proton doublet at δ 4.34 ($J_{1,2}$ 7.7 Hz, H-1a) and three-proton triplet at δ 0.88 ($MeCH_2$), indicating the structure assigned. Selective reduction [27] of the azido group in **23** with triphenylphosphine in benzene–water gave the amine **24**, which on condensation [28] with octadecanoic acid by use of 2-chloro-1,3-dimethylimidazolium chloride (DMC) in benzene, afforded the fully protected VIM-2 (**25**) in 80% yield.

Finally, **25** was converted into the target compound **26** as follows: desilylation [29] of **25** by treatment with tetrabutylammonium fluoride in acetonitrile, and *O*-deacylation with sodium methoxide in methanol, with subsequent saponification of the methyl ester group, yielded the desired VIM-2 ganglioside **26** in 87% yield after chromatography on a column of silica gel and Sephadex LH-20 (Scheme 4).

In conclusion, the synthesis of VIM-2 ganglioside was efficiently accomplished by employing thioglycosides **7**, **8**, **9** and **16** as the glycosyl donors in the presence of NIS-TfOH as an effective thiophilic promoter. The key intermediate **7** was extremely useful for constructing the repeating lactosamine structure. The regio- and α-stereo-

selective sialylation of the heptasaccharide **14** was successfully achieved by use of the per-*O*-benzoyl thioglycoside donor **16** in acetonitrile under kinetically controlled conditions.

3. Experimental

General methods.—Optical rotations were determined with a Jasco DIP-370 digital polarimeter at 20 °C, and IR spectra were recorded with a Jasco IR-700 spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz with a General Electric QE-plus spectrometer. Preparative chromatography was performed on silica gel (Wako Chemical Co., 300 mesh) with the solvent systems specified. Concentrations were conducted in vacuo.

*Phenyl 6-O-benzyl-1-thio-β-*D*-galactopyranoside* (**3**).—To a solution of phenyl 1-thio-β-D-galactopyranoside (**1**; 8.0 g, 29.4 mmol) in *N*,*N*-dimethylformamide (50 mL) was added Drierite (25 g), and the mixture was stirred for 1 h at room temperature. Benzaldehyde dimethylacetal (11 mL, 71.3 mmol) and 4-toluenesulfonic acid (30 mg) were added, and the mixture was stirred for 16 h at room temperature. The course of the reaction was monitored by TLC. The reaction mixture was neutralized with $NaHCO_3$, the solids were collected and washed with CH_2Cl_2, and the combined filtrate and washings was concentrated to a syrup that was extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4) and concentrated. To a solution of the residue **2** in dry tetrahydrofuran (200 mL) was added 3A molecular sieves (MS-3A, 14 g), and the mixture was stirred for 2 h at room temperature. Sodium cyanoborohydride (28 g, 446 mmol) was gradually added under a nitrogen atmosphere, and the mixture was stirred for 1.5 h at room temperature. Hydrogen chloride in Et_2O was added to the reaction mixture at room temperature until the evolution of gas ceased. TLC indicated that the reaction was complete after 5 min. The mixture was neutralized with $NaHCO_3$, filtered and concentrated. The residue was dissolved in CH_2Cl_2 (150 mL), and the solution was washed with M NaCl, dried (Na_2SO_4) and concentrated to a syrup that was chromatographed on a column of silica gel (350 g) with 20:1 CH_2Cl_2–MeOH to give **3** (6.35 g, 60%) as an amorphous mass: $[\alpha]_D$ −46.4° (*c* 1.16, $CHCl_3$). The structure of **3** was deduced by the ^{1}H NMR spectrum of its benzoylated derivative **4**. Anal. Calcd for $C_{19}H_{22}O_5S$ (362.5): C, 62.96; H, 6.12. Found: C, 62.85; H, 5.92.

*Phenyl 2,3,4-tri-O-benzoyl-6-O-benzyl-1-thio-β-*D*-galactopyranoside* (**4**).—To a solution of **3** (2.18 g, 6.0 mmol) in pyridine (20 mL) was added benzoyl chloride (3.5 mL, 30 mmol) at 0 °C, and the mixture was stirred for 8 h at room temperature. Methanol (5 mL) was added, and the solution was concentrated to a syrup that was extracted with CH_2Cl_2. The extract was successively washed with 2 M HCl and water, dried (Na_2SO_4) and concentrated. Column chromatography (1:3 EtOAc–hexane) of the residue on silica gel (210 g) gave **4** (3.42 g, 84%) as a syrup: $[\alpha]_D$ +115.5° (*c* 1.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.63 (dd, 1 H, J_{gem} 9.8, $J_{5,6}$ 6.3 Hz, H-6), 3.74 (dd, 1 H, $J_{5,6'}$ 6.3 Hz, H-6'), 4.21 (m, 1 H, H-5), 4.45, 4.54 (2 d, 2 H, J_{gem} 11.8 Hz, CH_2Ph), 4.99 (d, 1 H, $J_{1,2}$ 9.8 Hz, H-1), 5.55 (dd, 1 H, $J_{2,3}$ 9.9, $J_{3,4}$ 3.2 Hz, H-3), 5.71 (t, 1 H, H-2), 5.95 (d, 1 H,

H-4), 7.20–7.99 (m, 25 H, 5 Ph). Anal. Calcd for $C_{40}H_{34}O_8S$ (674.8): C, 71.20; H, 5.08. Found: C, 71.13; H, 5.07.

2,3,4-Tri-O-benzoyl-6-O-benzyl-α-D-galactopyranosyl bromide (**5**).—To a solution of **4** (4.25 g, 6.6 mmol) in CH_2Cl_2 (30 mL), cooled to −20 °C, was added bromine (370 μL, 7.2 mmol), and the solution was stirred for 30 min. To the reaction mixture was added tetraethylammonium bromide (686 mg, 3.27 mmol), and the stirring was continued for 2 h at −20 °C. The mixture was washed thoroughly with M $Na_2S_2O_3$ and M $NaHCO_3$, dried (Na_2SO_4), and concentrated. Column chromatography (1:3 EtOAc–hexane) of the residue on silica gel (350 g) gave **5** (3.22 g, 79%) as an amorphous mass: $[\alpha]_D$ +226.7° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.43, 4.54 (2 d, 2 H, J_{gem} 11.9 Hz, CH_2Ph), 4.75 (m, 1 H, H-5), 5.60 (dd, 1 H, $J_{2,3}$ 10.4, $J_{1,2}$ 3.9 Hz, H-2), 6.00 (dd, 1 H, $J_{3,4}$ 3.3 Hz, H-3), 6.06 (d, 1 H, H-4), 6.95 (d, 1 H, H-1), 7.18–8.04 (m, 20 H, 4 Ph). Anal. Calcd for $C_{34}H_{29}BrO_8$ (645.5): C, 63.26; H, 4.53. Found: C, 63.01; H, 4.41.

Phenyl 2,3,4-tri-O-benzoyl-6-O-benzyl-β-D-galactopyranosyl-(1 → 4)-6-O-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**7**).—To a solution of phenyl 6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**6**; 477 mg, 0.97 mmol) and **5** (752 mg, 1.16 mmol) in dry toluene (10 mL) was added 4A molecular sieves (MS-4A, 3 g), and the mixture was stirred for 8 h at room temperature, then cooled to −40 °C. To the cooled mixture was added silver trifluoromethanesulfonate (329 mg, 1.28 mmol) under a nitrogen atmosphere, and the mixture was stirred for 16 h at −40 °C in the dark. The progress of the reaction was monitored by TLC. Methanol (1 mL) and triethylamine (1 mL) were added, and the mixture was stirred for 30 min. The precipitate was filtered off through Celite and washed with CH_2Cl_2. The filtrate and washings were combined, and the solution was washed with M $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column of silica gel (210 g) with 9:1 CH_2Cl_2–hexane to give **7** as crystals. Recrystallization from EtOAc–hexane gave **7** as needles (773 mg, 75%): mp 197.8–199.8 °C; $[\alpha]_D$ +80.6° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.49 (d, 1 H, $J_{3,OH}$ 2.8 Hz, HO-3a), 4.59 (m, 1 H, H-3a), 4.86 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1b), 5.50 (dd, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 3.4 Hz, H-3b), 5.56 (d, 1 H, $J_{1,2}$ 10.5 Hz, H-1a), 5.76 (dd, 1 H, H-2b), 5.85 (br d, 1 H, H-4b), 7.10–8.00 (m, 34 H, 6 Ph and NPhth). Anal. Calcd for $C_{61}H_{53}NO_{14}S$ (1056.2): C, 69.37; H, 5.06; N, 1.33. Found: C, 69.11; H, 4.87; N, 1.32.

Phenyl 2,3,4-tri-O-benzoyl-6-O-benzyl-β-D-galactopyranosyl-(1 → 4)-3-O-acetyl-6-O-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**7a**).—Compound **7** (100 mg) was acetylated with Ac_2O (1 mL) in pyridine (2 mL) to give **7a** (111 mg, quant) as an amorphous mass: $[\alpha]_D$ +66.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.79 (s, 3 H, AcO), 3.94 (m, 1 H, H-5b), 4.11 (t, 1 H, H-4a), 4.31 (t, 1 H, H-2a), 4.84 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1b), 5.39 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 3.3 Hz, H-3b), 5.60 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 10.4 Hz, H-2b), 6.65 (d, 1 H, $J_{1,2}$ 10.6 Hz, H-1a), 5.78 (dd, 1 H, $J_{2,3}$ 10.2, $J_{3,4}$ 9.0 Hz, H-3a), 5.89 (br d, 1 H, H-4b), 7.15–7.98 (m, 34 H, 6 Ph and Phth). Anal. Calcd for $C_{63}H_{55}NO_{15}S$ (1098.2): C, 68.90; H, 5.05; N, 1.28. Found: C, 68.62; H, 4.83; N, 1.12.

Phenyl 2,3,4-tri-O-benzoyl-6-O-benzyl-β-D-galactopyranosyl-(1 → 4)-[2,3,4-tri-O-benzyl-α-L-fucopyranosyl-(1 → 3)]-6-O-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**9**).—To a solution of **7** (100 mg, 94.7 μmol) and methyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**8**; 100 mg, 190 μmol) in dry toluene (2 mL) was added

MS-4A (700 mg), and the mixture was stirred for 3 h at room temperature. *N*-Iodosuccinimide (NIS; 43 mg, 191 μmol) was added, and the mixture was stirred for 1 h, then cooled to −15 °C. To the cooled mixture was added trifluoromethanesulfonic acid (TfOH; 17 μL, 19 μmol), and the stirring was continued for 16 h at −15 °C, the course of the reaction being monitored by TLC. Methanol (0.5 mL) and triethylamine (0.2 mL) were added, and the mixture was stirred for 1 h. The precipitate was filtered with aid of Celite and washed with CH_2Cl_2. The filtrate and washings were combined, and the solution was successively washed with M $Na_2S_2O_3$, M $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated. Column chromatography (2:5 EtOAc–hexane) of the residue on silica gel (50 g) gave **9** (129 mg, 93%) as an amorphous mass: $[\alpha]_D$ +8.2° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.30 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6b), 4.47 (t, 1 H, $J_{1,2} = J_{2,3} = 10.5$ Hz, H-2a), 4.78 (dd, 1 H, $J_{3,4}$ 9.0 Hz, H-3a), 5.05 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1c), 5.07 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1b), 5.40 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 3.6 Hz, H-3c), 5.45 (d, 1 H, $J_{1,2}$ 10.6 Hz, H-1a), 5.66 (dd, 1 H, $J_{1,2}$ 8.2, $J_{2,3}$ 10.3 Hz, H-2c), 5.87 (br d, 1 H, $J_{3,4}$ 3.6 Hz, H-4c), 7.10–7.98 (m, 49 H, 9 Ph and NPhth). Anal. Calcd for $C_{88}H_{81}NO_{18}S$ (1472.7): C, 71.77; H, 5.54; N, 0.95. Found: C, 71.59; H, 5.37; N, 0.90.

*2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-*O*-[2,3,4-tri-*O*-benzyl-α-*L*-fucopyranosyl-(1 → 3)]-(6-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl)-(1 → 3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**11**).—To a solution of 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**10**; 48 mg, 48.8 μmol) and **9** (48 mg, 32.6 μmol) in dry CH_2Cl_2 (2 mL) was added MS-4A (1.0 g), and the mixture was stirred for 3 h at room temperature. NIS (23 mg, 102 μmol) was added, then the mixture was cooled to −60 °C. To the cooled mixture was added TfOH (1.4 μL, 15.8 μmol), and the stirring was continued for 1 h at −60 °C. The course of the reaction was monitored by TLC. Methanol (0.5 mL) and triethylamine (0.3 mL) were added to the mixture, and this was stirred for 1 h. The precipitate was filtered through Celite and washed with CH_2Cl_2. The combined filtrate and washings was successively washed with M $Na_2S_2O_3$, M $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. Column chromatography (2:7 EtOAc–hexane) of the residue on silica gel (50 g) gave **11** (66 mg, 86%) as an amorphous mass: $[\alpha]_D$ −18.6° (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 0.99 (m, 2 H, $Me_3SiCH_2CH_2O$), 1.37 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6d), 5.02 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1d), 5.10 (d, 1 H, $J_{1,2}$ 8.7 Hz, H-1d), 5.31 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1c), 5.44 (dd, 1 H, $J_{3,4}$ 3.5, $J_{2,3}$ 10.4 Hz, H-3e), 5.71 (dd, 1 H, H-2e), 5.93 (d, 1 H, H-4e), 6.83–7.98 (m, 74 H, 14 Ph and NPhth). Anal. Calcd for $C_{141}H_{145}NO_{29}Si$ (2345.8): C, 72.20; H, 6.23; N, 0.60. Found: C, 72.01; H, 6.07; N, 0.55.

*2-(Trimethylsilyl)ethyl 6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-[2,3,4-tri-*O*-benzyl-α-*L*-fucopyranosyl-(1 → 3)]-6-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**12**).—To a solution of **11** (1.88 g, 0.8 mmol) in MeOH (40 mL) and CH_2Cl_2 (20 mL) was added NaOMe (43 mg), and the mixture was stirred for 4 h at room temperature and treated with Amberlite IR-120 B (H^+) resin to remove the base. The solution was concentrated to a syrup that was chromatographed on a column of silica gel (130 g) with 65:1 CH_2Cl_2–MeOH to give **12** (1.60 g, 98%) as an amorphous mass: $[\alpha]_D$ −18.6° (*c* 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.99 (m, 2 H,

$Me_3SiCH_2CH_2O$), 1.05 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6d), 5.42 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1c), 7.15–7.65 (m, 59 H, 11 Ph and NPhth). Anal. Calcd for $C_{120}H_{133}NO_{26}Si$ (2033.5): C, 70.88; H, 6.59; N, 0.69. Found: C, 70.83; H, 6.49; N, 0.52.

*2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-6-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl-(1 → 3)-6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-[2,3,4-tri-*O*-benzyl-α-*L*-fucopyranosyl-(1 → 3)]-6-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**13**).—To a solution of **7** (100 mg, 95 μmol) and **12** (288 mg, 142 μmol) in dry CH_2Cl_2 (8 mL) was added MS-4A (4 g), and the mixture was stirred for 5 h at room temperature. NIS (65 mg, 283 μmol) was added, then the mixture was cooled to −60 °C. To the cooled mixture was added TfOH (4 μL, 45.2 μmol), and the stirring was continued for 1.5 h at −60 °C. Methanol (1 mL) and triethylamine (1 mL) were added to the mixture, and the precipitate was filtered with aid of Celite and washed with CH_2Cl_2. The combined filtrate and washings was successively washed with M $Na_2S_2O_3$, M $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated to a syrup that was chromatographed on a column of silica gel (50 g) with 2:3 EtOAc–hexane, to give **13** (223 mg, 83%) as an amorphous mass: $[\alpha]_D$ +8.2° (*c* 1.0, $CHCl_3$); *ν* 3476 (OH), 2922 and 2868 (methyl, methylene), 1777, 1716, 1390 and 1361 (imide), 1716, 1281 and 1261 (ester), 858 and 838 (TMS), 738, 719 and 700 cm^{-1} (Ph, Phth); ^1H NMR ($CDCl_3$): δ 0.79 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6d), 0.98 (m, 2 H, $Me_3SiCH_2CH_2O$), 4.51 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1d), 4.89 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1g), 5.29 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1c), 5.40 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1f), 5.54 (dd, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 3.4 Hz, H-3g), 5.80 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 10.5 Hz, H-2g), 5.88 (br d, $J_{3,4}$ 3.4 Hz, H-4g), 6.87–8.04 (m, 88 H, 16 Ph and 2 Phth). Anal. Calcd for $C_{175}H_{180}N_2O_{40}Si$ (2979.4): C, 70.55; H, 6.09; N, 0.94. Found: C, 70.28; H, 6.07; N, 0.93.

*2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl-(1 → 3)-2,4-di-*O*-acetyl-6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-[2,3,4-tri-*O*-benzyl-α-*L*-fucopyranosyl-(1 → 3)]-6-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**13a**).—To a solution of **13** (130 mg, 43.6 μmol) in pyridine (3 mL) was added Ac_2O (2 mL) and 4-dimethylaminopyridine (DMAP, 5 mg), and the mixture was stirred for 18 h at 45 °C. After completion of the reaction, MeOH (1 mL) was added, and the mixture was stirred for 1 h at room temperature, concentrated, and dissolved in CH_2Cl_2. The solution was washed with 2 M HCl, M $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. Column chromatography (1:2 EtOAc–hexane) of the residue on silica gel (50 g) gave **13a** (116 mg, 86%) as an amorphous mass: $[\alpha]_D$ +0.3° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.94 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6d), 0.98 (m, 2 H, $Me_3SiCH_2CH_2O$), 1.72, 1.82 and 1.89 (3 s, 9 H, AcO), 3.51 (H-3e), 4.72 (H-2e), 4.93 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1g), 5.08 (d, 1 H, J_{gem} 10.4 Hz, $PhCH_2$), 5.23 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1f), 5.28 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1c), 5.46 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 3.4 Hz, H-3g), 5.48 (br d, 1 H, H-4e), 5.80 (dd, 1 H, $J_{2,3}$ 10.9, $J_{3,4}$ 9.1 Hz, H-3f), 5.93 (br d, $J_{3,4}$ 3.2 Hz, H-4g), 6.84–8.02 (m, 88 H, 16 Ph and 2 Phth). Anal. Calcd for $C_{181}H_{186}N_2O_{43}Si$ (3105.5): C, 70.00; H, 6.04; N, 0.90. Found: C, 69.97; H, 5.80; N, 0.82.

*2-(Trimethylsilyl)ethyl 6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2-acetamido-6-*O*-*

*benzyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-6-O-benzyl-β-*D*-galactopyranosyl-(1 → 4)-[2,3,4-tri-O-benzyl-α-*L*-fucopyranosyl-(1 → 3)]-(2-acetamido-6-O-benzyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-O-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-β-*D*-glucopyranoside* (**14**).—A solution of **13** (1.05 g, 0.35 mmol) in EtOH (38 mL) and water (2 mL) was treated with hydrazine monohydrate (755 μL), heated for 4 h under reflux, and then concentrated. The residue was treated with Ac_2O (15 mL)–MeOH (40 mL) for 18 h at 40 °C, and concentrated. The residue was chromatographed on a column of silica gel (130 g) with 200:15:1 CH_2Cl_2–MeOH–20% aq NH_3 and Sephadex LH-20 (100 g) with 1:1 $CHCl_3$–MeOH to give **14** (815 mg, 93%) as an amorphous mass: $[\alpha]_D$ −28.1° (*c* 1.0, $CHCl_3$); *ν* 3414 (NH, OH), 2920 and 2868 (methyl, methylene), 1660 and 1537 (amide), 859 and 838 (TMS), 738 and 699 cm^{-1} (Ph); ^1H NMR ($CDCl_3$): δ 0.99 (m, 2 H, $Me_3SiCH_2CH_2O$), 1.07 (s, 3 H, AcN), 1.14 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6d), 1.81 (s, 3 H, AcN), 7.08–7.34 (m, 45 H, 9 Ph). Anal. Calcd for $C_{142}H_{168}N_2O_{35}Si$ (2491.0): C, 68.47; H, 6.80; N, 1.12. Found: C, 68.34; H, 6.54; N, 0.93.

*Methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-benzoyl-3,5-dideoxy-2-thio-*D*-*glycero*-β-*D*-galacto-2-nonulopyranosid)onate* (**16**).—To a solution of methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-*D*-*glycero*-β-*D*-*galacto*-2-nonulopyranosid)onate [22] (**15**; 150 mg, 257 μmol) in dry MeOH (1.5 mL) was added NaOMe (5 mg), and the mixture was stirred for 2 h at room temperature and treated with Amberlite IR-120 B (H^+) resin to remove the base. The solution was concentrated, and the residue was dissolved in dry pyridine (2 mL). To the stirred solution was added benzoyl chloride (166 μL, 1.42 mmol) at 0 °C, and the mixture was gradually warmed to room temperature and stirred for 20 h. Then MeOH (1 mL) was added at 0 °C and the solution was concentrated. A solution of the residue in CH_2Cl_2 (20 mL) was washed with 2 M HCl, water and M $NaHCO_3$, dried (Na_2SO_4) and concentrated. Column chromatography (1:2 EtOAc–hexane) of the residue on silica gel (50 g) gave **16** (126 mg, 59%) as an amorphous mass: $[\alpha]_D$ −56.8° (*c* 1.0, $CHCl_3$); *ν* 3370 (NH), 1724 and 1266 (ester), 1690 and 1534 (amide), 713 cm^{-1} (Ph); ^1H NMR ($CDCl_3$): δ 1.79 (s, 3 H, AcN), 2.33 (dd, 1 H, J_{gem} 13.6, $J_{3a,4}$ 11.7 Hz, H-3*a*), 2.96 (dd, 1 H, J_{gem} 13.8, $J_{3e,4}$ 4.7 Hz, H-3*e*), 3.64 (s, 3 H, MeO), 4.38 (q, 1 H, H-5), 4.52 (dd, 1 H, J_{gem} 12.2, $J_{8,9}$ 8.9 Hz, H-9), 4.97 (dd, J_{gem} 12.2, $J_{8,9'}$ 2.1 Hz, H-9'), 5.03 (dd, 1 H, H-8), 6.04 (m, 1 H, H-7), 7.05–8.09 (m, 25 H, 5 Ph). Anal. Calcd for $C_{46}H_{41}NO_{12}S$ (831.9): C, 66.42; H, 4.97; N, 1.68. Found: C, 66.12; H, 4.69; N, 1.56.

*2-(Trimethylsilyl)ethyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylonate)-(2 → 3)-6-O-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2-acetamido-6-O-benzyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-6-O-benzyl-β-*D*-galactopyranosyl-(1 → 4)-[2,3,4-tri-O-benzyl-α-*L*-fucopyranosyl-(1 → 3)]-2-acetamido-6-O-benzyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-O-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-β-*D*-glucopyranoside* (**17**).—To a solution of **14** (30 mg, 12.0 μmol) and **15** (14 mg, 24.0 μmol) in dry CH_3CN (0.8 mL) was added MS-3A (250 mg), and the mixture was stirred for 5 h at room temperature. Then NIS (17 mg, 74.0 μmol) was added at −43 °C, and the mixture was stirred for 1 h at −43 °C, at the end of which time TfOH (2.7 μL, 30.5 μmol) was added. The mixture was then stirred for another 40 h at −43 °C. Sodium thiosulfate (100 mg) was added to the mixture with

stirring for 1 h. The precipitate was filtered with aid of Celite and washed thoroughly with EtOAc. The filtrate and washings were combined, and the solution was successively washed with M $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. Column chromatography (18:1 CH_2Cl_2–MeOH) of the residue on silica gel (50 g) gave **17** (14 mg, 39%) as an amorphous mass: $[\alpha]_D$ −18.3° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.00 (m, 2 H, $Me_3SiCH_2CH_2O$), 1.10 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6d), 1.24–2.09 (7 s, 21 H, 3 AcN and 4 AcO), 2.68 (dd, 1 H, J_{gem} 13.0, $J_{3e,4}$ 4.1 Hz, H-3h*e*), 3.74 (H-2g), 3.78 (s, 3 H, MeO), 4.06 (H-3g), 4.48 (H-1g), 4.93 (H-4h), 5.29 (m, 1 H, H-7h), 5.36 (m, 1 H, H-8h), 7.11–7.40 (m, 65 H, 13 Ph). Anal. Calcd for $C_{162}H_{195}N_3O_{47}Si$ (2964.4): C, 65.64; H, 6.63; N, 1.42. Found: C, 65.48; H, 6.35; N, 1.27.

*2-(Trimethylsilyl)ethyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylonate)-(2 → 3)-2,4-di-*O*-acetyl-6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-2,4-di-*O*-acetyl-6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-[2,3,4-tri-*O*-benzyl-α-*L*-fucopyranosyl-(1 → 3)]-2-acetamido-6-*O*-benzyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**17a**).—Compound **17** (14 mg, 4.7 μmol) was acetylated, as described for **13a**, and the product was purified by chromatography on a column of silica gel (26 g) with 25:1 CH_2Cl_2–MeOH to give **17a** (12 mg, 80%) as an amorphous mass: $[\alpha]_D$ −26.2° (*c* 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.01 (m, 2 H, $Me_3SiCH_2CH_2O$), 1.09 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6d), 1.25–2.13 (12 s, 36 H, 3 AcN and 9 AcO), 2.59 (dd, 1 H, J_{gem} 12.5, $J_{3e,4}$ 4.5 Hz, H-3h*e*), 3.56 (H-3e), 3.85 (s, 3 H, MeO), 4.54 (H-3g), 4.88 (H-2e), 4.92 (H-2g), 4.93 (H-4h), 5.04 (br d, 1 H, $J_{3,4}$ 3.5 Hz, H-4g), 5.37 (dd, 1 H, $J_{6,7}$ 2.4, $J_{7,8}$ 8.7 Hz, H-7h), 5.48 (br d, $J_{3,4}$ 3.6 Hz, H-4e), 5.54 (m, 1 H, H-8h), 7.00–7.40 (m, 65 H, 13 Ph). Anal. Calcd for $C_{172}H_{208}N_3O_{52}Si$ (3174.6): C, 65.08; H, 6.51; N, 1.32. Found: C, 64.90; H, 6.24; N, 1.26.

*2-(Trimethylsilyl)ethyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-benzoyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylonate)-(2 → 3)-6-O-benzyl-β-D-galactopyranosyl-(1 → 4)-2-acetamido-6-O-benzyl-2-deoxy-β-D-glucopyranosyl-(1 → 3)-6-O-benzyl-β-D-galactopyranosyl-(1 → 4)-[2,3,4-tri-O-benzyl-α-L-fucopyranosyl-(1 → 3)]-2-acetamido-6-O-benzyl-2-deoxy-β-D-glucopyranosyl-(1 → 3)-2,4,6-tri-O-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside* (**18**).—To a solution of **14** (30 mg, 12 μmol) and **16** (20 mg, 24 μmol) in dry CH_3CN (0.8 mL) was added MS-3A (250 mg), and the mixture was stirred for 5 h at room temperature. NIS (17 mg, 74.0 μmol) was added, and the mixture was stirred for 1 h at −43 °C. TfOH (2.7 μL, 30.5 μmol) was added, and stirring was continued for 42 h at −43 °C. Processing as described for **17** gave **18** (28 mg, 72%) as an amorphous mass: $[\alpha]_D$ +27.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.00 (m, 2 H, $Me_3SiCH_2CH_2O$), 1.10 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6d), 1.25, 1.84 and 1.85 (3 s, 9 H, 3 AcN), 2.22 (H-3h*a*), 2.85 (dd, 1 H, J_{gem} 13.0, $J_{3e,4}$ 4.5 Hz, H-3h*e*), 3.53 (s, 3 H, MeO), 3.85 (H-2g), 4.27 (H-3g), 4.58 (H-1g), 5.38 (m, 1 H, H-4h), 5.85 (H-7h), 5.90 (H-8h), 6.99–8.15 (m, 85 H, 17 Ph). Anal. Calcd for $C_{182}H_{203}N_3O_{47}Si$ (3212.7): C, 68.04; H, 6.37; N, 1.31. Found: C, 68.02; H, 6.29; N, 1.18.

*2-(Trimethylsilyl)ethyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-benzoyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylonate)-(2 → 3)-2,4-di-*O*-acetyl-6-*O*-benzyl-β-*D*-

*galactopyranosyl-(1 → 4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-*D*-glucopyranosyl)-(1 → 3)-2,4-di-*O*-acetyl-6-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-[2,3,4-tri-*O*-benzyl-α-*L*-fucopyranosyl-(1 → 3)]-2-acetamido-6-*O*-benzyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**18a**).—Compound **18** (100 mg, 31.1 μmol) was acetylated, as described for **17a**, and the product was purified by chromatography on a column of silica gel (50 g) with 30:1 CH_2Cl_2–MeOH to give **18a** (98 mg, 92%) as an amorphous mass: $[\alpha]_D$ +5.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.00 (m, 2 H, $Me_3SiCH_2CH_2O$), 1.09 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6d), 1.25–2.18 (8 s, 24 H, 5 AcO and 3 AcN), 2.78 (dd, 1 H, J_{gem} 12.6, $J_{3e,4}$ 4.5 Hz, H-3h*e*), 3.61 (s, 3 H, MeO), 4.77 (dd, 1 H, $J_{2,3}$ 10.3, $J_{3,4}$ 3.2 Hz, H-3g), 4.80 (dd, 1 H, $J_{8,9}$ 8.6 Hz, H-9h), 5.05 (dd, 1 H, $J_{1,2}$ 8.5, $J_{2,3}$ 10.3 Hz, H-2g), 5.12 (d, 1 H, $J_{3,4}$ 3.2 Hz, H-4g), 5.49 (d, $J_{3,4}$ 3.4 Hz, H-4e), 5.91 (dd, $J_{6,7}$ 2.8, $J_{7,8}$ 7.4 Hz, H-7h), 6.10 (m, 1 H, H-8h), 7.05–8.02 (m, 85 H, 17 Ph). Anal. Calcd for $C_{192}H_{213}N_3O_{52}Si$ (3422.9): C, 67.37; H, 6.27; N, 1.23. Found: C, 67.36; H, 6.13; N, 1.20.

*2-(Trimethylsilyl)ethyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-benzoyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylonate)-(2 → 3)-2,4,6-tri-*O*-acetyl-β-*D*-galactopyranosyl-(1 → 4)-2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-*O*-acetyl-β-*D*-galactopyranosyl-(1 → 4)-[2,3,4-tri-*O*-acetyl-α-*L*-fucopyranosyl-(1 → 3)]-2-acetamido-6-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-*O*-acetyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-acetyl-β-*D*-glucopyranoside* (**19**).—A solution of **18** (915 mg, 285 μmol) in a mixture of MeOH (90 mL), EtOH (90 mL) and CH_3CO_2H (20 mL) was hydrogenated in the presence of 10% Pd–C (1 g) for 10 h at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was acetylated with Ac_2O (30 mL)–pyridine (50 mL) and DMAP (10 mg) for 18 h at 40 °C. The product was purified by chromatography on a column of silica gel (130 g) with 20:1:14 CH_2Cl_2–MeOH–EtOAc to give **19** (502 mg, 63%) as an amorphous mass: $[\alpha]_D$ +8.2° (*c* 1.0, $CHCl_3$); ν 3374 (NH), 2956 and 2875 (methyl, methylene), 1748 and 1228 (ester), 1689 and 1532 (amide), 858 and 840 (TMS), 715 cm^{-1} (Ph); ^{1}H NMR ($CDCl_3$): δ 0.92 (m, 2 H, $Me_3SiCH_2CH_2O$), 1.16 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6d), 1.77–2.28 (21 s, 63 H, 18 AcO and 3 AcN), 2.79 (dd, 1 H, J_{gem} 12.6, $J_{3e,4}$ 4.7 Hz, H-3h*e*), 3.07 (m, 1 H, H-2e), 3.62 (s, 3 H, MeO), 4.27 (H-3g), 4.34 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1b), 4.46 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1e), 4.47 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1a), 4.60 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1f), 5.37 (d, 1 H, $J_{2,NH}$ 5.9 Hz, NH-2f), 5.96 (dd, 1 H, $J_{6,7}$ 2.7, $J_{7,8}$ 7.5 Hz, H-7h), 6.10 (m, 1 H, H-8h), 7.33–8.11 (m, 20 H, 4 Ph). Anal. Calcd for $C_{127}H_{161}N_3O_{65}Si$ (2797.7): C, 54.52; H, 5.80; N, 1.50. Found: C, 54.45; H, 5.80; N, 1.45.

*Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzoyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylonate-(2 → 3)-2,4,6-tri-*O*-acetyl-β-*D*-galactopyranosyl-(1 → 4)-2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-*O*-acetyl-β-*D*-galactopyranosyl-(1 → 4)-[2,3,4-tri-*O*-acetyl-α-*L*-fucopyranosyl-(1 → 3)]-2-acetamido-6-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 3)-2,4,6-tri-*O*-acetyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-acetyl-*D*-glucopyranose* (**20**).—To a solution of **19** (470 mg, 168 μmol) in dry CH_2Cl_2 (2.5 mL) was gradually added CF_3CO_2H (5 mL) at 0 °C, and the mixture was stirred 2 h at room temperature. Ethyl acetate (20 mL) was added to the

mixture, and it was concentrated to a syrup that was chromatographed on a column of silica gel (130 g) with 15:1 CH_2Cl_2–MeOH to give **20** (443 mg, 99%) as an amorphous mass; ν 3380 (NH, OH), 2970 (methyl, methylene), 1747 and 1228 (ester), 1689 and 1537 (amide), 716 cm^{-1} (Ph). Anal. Calcd for $C_{122}H_{149}N_3O_{65}$ (2697.5): C, 54.32; H, 5.57; N, 1.56. Found: C, 54.14; H, 5.35; N, 1.47.

Methyl 5-acetamido-4,7,8,9-tetra-O-*benzoyl-3,5-dideoxy*-D-glycero-α-D-galacto-*2-nonulopyranosylonate-(2 → 3)-2,4,6-tri*-O-*acetyl*-β-D-*galactopyranosyl-(1 → 4)-2-acetamido-3,6-di*-O-*acetyl-2-deoxy*-β-D-*glucopyranosyl-(1 → 3)-2,4,6-tri*-O-*acetyl*-β-D-*galactopyranosyl-(1 → 4)-[2,3,4-tri*-O-*acetyl*-α-L-*fucopyranosyl-(1 → 3)]-2-acetamido-6-O-acetyl-2-deoxy*-β-D-*glucopyranosyl-(1 → 3)-2,4,6-tri*-O-*acetyl*-β-D-*galactopyranosyl-(1 → 4)-2,3,6-tri*-O-*acetyl*-α-D-*glucopyranosyl trichloroacetimidate* (**21**).—A solution of **20** (441 mg, 165 μmol) and trichloroacetonitrile (0.5 mL) in CH_2Cl_2 (4 mL) was cooled to −5 °C, and to this solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 25 μL). The mixture was stirred for 3 h at 0 °C, then concentrated. Column chromatography of the residue on silica gel (130 g) with 35:2 CH_2Cl_2–MeOH afforded **21** (413 mg, 89%) as an amorphous mass: $[\alpha]_D$ +1.1° (*c* 1.0, $CHCl_3$); ν 3370 (NH), 2976 (methyl, methylene), 2120 (isonitrile), 1749 and 1227 (ester), 1680 and 1533 (amide), 716 cm^{-1} (Ph); ^{1}H NMR ($CDCl_3$): δ 1.16 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6d), 1.77–2.28 (21 s, 63 H, 18 AcO and 3 AcN), 2.79 (dd, 1 H, J_{gem} 12.4, $J_{3e,4}$ 4.7 Hz, H-3h*e*), 3.07 (m, 1 H, H-2c), 3.63 (s, 3 H, MeO), 4.37 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1b), 4.46 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1e), 4.61 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1f), 5.05 (dd, 1 H, $J_{1,2}$ 3.8, $J_{2,3}$ 10.1 Hz, H-2a), 5.16 (dd, 1 H, J_{gem} 10.7, $J_{8,9}$ 3.3 Hz, H-9h), 5.40 (br d, 1 H, $J_{3,4}$ 3.3 Hz, H-4e), 5.53 (t, 1 H, $J_{2,3} = J_{3,4} = 9.7$ Hz, H-3a), 5.96 (dd, 1 H, $J_{6,7}$ 2.8, $J_{7,8}$ 7.6 Hz, H-7h), 6.10 (m, 1 H, H-8h), 6.44 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1a), 7.27–8.06 (m, 20 H, 5 Ph), 8.65 (s, 1 H, C=NH). Anal. Calcd for $C_{124}H_{149}Cl_3N_4O_{65}$ (2841.9): C, 52.41; H, 5.28; N, 1.97. Found: C, 52.13; H, 5.06; N, 1.85.

Methyl 5-acetamido-4,7,8,9-tetra-O-*benzoyl-3,5-dideoxy*-D-glycero-α-D-galacto-*2-nonulopyranosylonate-(2 → 3)-2,4,6-tri*-O-*acetyl*-β-D-*galactopyranosyl-(1 → 4)-2-acetamido-3,6-di*-O-*acetyl-2-deoxy*-β-D-*glucopyranosyl-(1 → 3)-2,4,6-tri*-O-*acetyl*-β-D-*galactopyranosyl-(1 → 4)-[2,3,4-tri*-O-*acetyl*-α-L-*fucopyranosyl-(1 → 3)]-2-acetamido-6-O-acetyl-2-deoxy*-β-D-*glucopyranosyl-(1 → 3)-2,4,6-tri*-O-*acetyl*-β-D-*galactopyranosyl-(1 → 4)-2,3,6-tri*-O-*acetyl*-β-D-*glucopyranosyl-(1 → 1)-(2S,3R,4E)-2-azido-3*-O-(*tert-butyldiphenylsilyl)-4-octadecene-1,3-diol* (**23**).—To a solution of **21** (50 mg, 17.8 μmol) and (2*S*,3*R*,4*E*)-2-azido-3-*O*-(*tert*-butyldiphenylsilyl)-4-octadecene-1,3-diol (**22**; 25 mg, 44.4 μmol) in dry CH_2Cl_2 (0.8 mL) was added MS-4A (AW-300; 500 mg), and the mixture was stirred for 1 h at room temperature, then cooled to 0 °C. To the cooled mixture was added trimethylsilyl trifluoromethanesulfonate (10 μL, 51.7 μmol), and the mixture was stirred for 3.5 h at 0 °C, the course of the reaction being monitored by TLC. Triethylamine (0.1 mL) was added to the reaction mixture, and the precipitate was filtered with aid of Celite and washed with CH_2Cl_2. The combined filtrate and washings was washed with water, dried (Na_2SO_4) and concentrated. Chromatography (35:2 CH_2Cl_2–MeOH) of the residue on silica gel (50 g) gave **23** (27 mg, 47%) as an amorphous mass: $[\alpha]_D$ −55.1° (*c* 1.0, $CHCl_3$); ν 3380 (NH), 2926 and 2856 (methyl, methylene), 2100 (azide), 1749 and 1227 (ester), 1692 and 1532 (amide), 713 cm^{-1} (Ph); ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3 H, *Me*CH_2), 1.05 (s, 9 H, *Me*$_3$C), 1.16 (d, 3 H,

$J_{5,6}$ 6.5 Hz, H-6d), 1.26 (s, 22 H, 11 CH_2), 1.77–2.28 (21 s, 63 H, 18 AcO and 3 AcN), 2.79 (dd, 1 H, J_{gem} 12.5, $J_{3e,4}$ 4.7 Hz, H-3h*e*), 3.06 (m, 1 H, H-2c), 3.63 (s, 3 H, MeO), 4.33 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1b), 4.34 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1a), 4.46 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1e), 4.60 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1f), 5.96 (dd, 1 H, $J_{6,7}$ 2.6, $J_{7,8}$ 7.6 Hz, H-7h), 6.10 (m, 1 H, H-8h), 7.31–8.08 (m, 30 H, 6 Ph). Anal. Calcd for $C_{156}H_{200}N_6O_{66}Si$ (3243.4): C, 57.77; H, 6.22; N, 2.59. Found: C, 57.66; H, 6.11; N, 2.56.

Methyl 5-acetamido-4,7,8,9-tetra-O-*benzoyl-3,5-dideoxy*-D-glycero-α-D-galacto-*2-nonulopyranosylonate-(2 → 3)-2,4,6-tri*-O-*acetyl*-β-D-*galactopyranosyl-(1 → 4)-2-acetamido-3,6-di*-O-*acetyl-2-deoxy*-β-D-*glucopyranosyl-(1 → 3)-2,4,6-tri*-O-*acetyl*-β-D-*galactopyranosyl-(1 → 4)-[2,3,4-tri*-O-*acetyl*-α-L-*fucopyranosyl-(1 → 3)]-2-acetamido-6*-O-*acetyl-2-deoxy*-β-D-*glucopyranosyl-(1 → 3)-2,4,6-tri*-O-*acetyl*-β-D-*galactopyranosyl-(1 → 4)-2,3,6-tri*-O-*acetyl*-β-D-*glucopyranosyl-(1 → 1)-(2S,3R,4E)-3*-O-(tert-*butyldiphenylsilyl)-2-octadecanamido-4-octadecene-1,3-diol* (**25**).—To a solution of **23** (177 mg, 55 μmol) in benzene (5 mL) and water (0.2 mL) was added triphenylphosphine (30 mg, 114 μmol), and the mixture was heated, with stirring, for 20 h at 50 °C. The course of the reaction was monitored by TLC. The mixture was concentrated, and the residue **24** was stirred with octadecanoic acid (45 mg, 158 μmol), 2-chloro-1,3-dimethylimidazolium chloride (DMC; 20 mg, 118 μmol) and triethylamine (24 μL, 173 μmol) in dry benzene (4 mL) for 20 h at room temperature. Methanol (2 mL) was added, and the mixture was treated with Amberlite IR-410 (OH^-) resin to remove the acid. The solution was concentrated to a syrup that was chromatographed on a column of silica gel (50 g) with 35:2 CH_2Cl_2–MeOH to give **25** (154 mg, 80%) as an amorphous mass: $[\alpha]_D$ +2.9° (*c* 1.0, $CHCl_3$); *ν* 3384 (NH), 2924 and 2854 (methyl, methylene), 1750 and 1226 (ester), 1690 and 1527 (amide), 713 cm^{-1} (Ph); ^1H NMR ($CDCl_3$): δ 0.88 (t, 6 H, 2 *Me*CH_2), 1.00 (s, 9 H, *Me*$_3$C), 1.16 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6d), 1.25 (s, 52 H, 26 CH_2), 1.80–2.28 (21 s, 63 H, 18 AcO and 3 AcN), 2.79 (dd, 1 H, J_{gem} 12.6, $J_{3e,4}$ 4.7 Hz, H-3h*e*), 3.07 (m, 1 H, H-2c), 3.63 (s, 3 H, MeO), 4.32 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1b), 4.41 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1a), 4.46 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1e), 4.61 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1f), 5.40 (br d, 1 H, $J_{3,4}$ 3.8 Hz, H-4e), 5.96 (dd, 1 H, $J_{6,7}$ 2.6, $J_{7,8}$ 7.6 Hz, H-7h), 6.10 (m, 1 H, H-8h), 7.30–8.10 (m, 30 H, 6 Ph). Anal. Calcd for $C_{174}H_{236}N_4O_{67}Si$ (3483.9): C, 59.99; H, 6.83; N, 1.61. Found: C, 59.84 H, 6.75; N, 1.33.

VIM-2 ganglioside (**26**).—To a solution of **25** (154 mg, 44.3 μmol) in CH_3CN (3 mL) was added 1.0 M tetrabutylammonium fluoride (0.8 mL) at 0 °C, and the mixture was stirred for 18 h at room temperature and concentrated. The residue was treated with NaOMe (55 mg) in MeOH (4 mL) for 3 h at room temperature, then water (0.5 mL) was added. The solution was stirred for 18 h at room temperature, neutralized with Amberlite IR-120 B (H^+) resin, and filtered. The resin was washed with 5:4:1 $CHCl_3$–MeOH–H_2O, and the combined filtrate and washings was concentrated. The residue was chromatographed on a column of silica gel (50 g) with 25:20:4 $CHCl_3$–MeOH–H_2O, then on a column of Sephadex LH-20 (40 g) with 5:4:1 $CHCl_3$–MeOH–H_2O, to give **26** (79 mg, 87%) as an amorphous mass: $[\alpha]_D$ −17.4° (*c* 1.25, 5:4:1 $CHCl_3$–MeOH–H_2O); ^1H NMR [49:1 $(CD_3)_2SO$–D_2O]: δ 0.85 (t, 6 H, 2 *Me*CH_2), 1.01 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6d), 1.24 (s, 52 H, 26 CH_2), 1.82, 1.89 (3 s, 9 H, 3 AcN), 2.04 (t, 2 H, CO*C*H_2CH_2), 2.76 (dd, 1 H, J_{gem} 12.0, $J_{3e,4}$ 4.2 Hz, H-3h*e*), 3.12 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1a), 4.22 (d,

1 H, $J_{1,2}$ 7.8 Hz, H-1g), 4.28 (br d, 1 H, H-1b), 4.34 (br d, 1 H, H-1e), 4.59 (m, 1 H, H-5d), 4.70 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1f), 4.74 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1c), 4.88 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1d), 5.37 (dd, 1 H, $J_{3,4}$ 7.2, $J_{4,5}$ 15.5 Hz, H-4, sphingosine unit), 5.55 (br dt, 1 H, H-5, sphingosine unit). Anal. Calcd for $C_{93}H_{164}N_4O_{45}$ (2058.32): C, 54.27; H, 8.03; N, 2.72. Found: C, 54.06; H, 7.76; N, 2.66.

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