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An efficient synthesis of ganglioside GM_3: highly stereocontrolled glycosylations by use of auxiliaries*

Masaaki Numata, Mamoru Sugimoto
Central Research Institute, MECT Co., 1780, Kitano, Tokorozawa, Saitama 359 (Japan)
Yukishige Ito, and Tomoya Ogawa†
RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-01 (Japan)

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ABSTRACT

An efficiently stereocontrolled total synthesis of GM_3 α-D-Neu*p*5Ac-(2→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→1)-Cer was achieved by employing both methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-2-bromo-2,3,5-trideoxy-3-phenylthio-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate for the key sialylation step, and *O*-[methyl (5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-acetyl-2-*O*-pivaloyl-α-D-glucopyranosyl trichloroacetimidate and fluoride for the key coupling step with a ceramide derivative. These two steps were significantly altered and improved in comparison with our previous synthesis that had been executed without use of stereocontrolling auxiliaries. GM_3 was obtained in 4.5% overall yield in 19 steps starting from allyl *O*-(2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside.

INTRODUCTION

Ganglioside GM_3 (**1**) has been isolated, not only from neural tissues, but also from various other tissues and cells, and the compound has been chemically well characterized[2]. In 1985, the first synthesis[3] of GM_3 (**1**), as well as that of the β-epimer at C-2c (epi-GM_3), was described. Essentially the same strategy was successfully extended to the synthesis[4] of *N*-glycosyl GM_3 (**2**). Subsequently, both GM_3 (**1**) and epi-GM_3 have been demonstrated[5] to cause significant enhancement of neurite outgrowth in neuro-2A cells as well as in PC12 cells. Epitope specificity of a mouse monoclonal antibody M2590 raised against B16 melanoma cells was determined[6] through a t.l.c. enzyme–immunostaining study using both synthetic GM_3 (**1**) and the epimer. It was also reported that exogenously added GM_3 (**1**) could induce differentiation of human myeloid and monocytoid leukemic cell lines into a monocytic lineage[7]. These significant observations prompted our synthetic effort directed toward the development of a more efficient synthetic approach to GM_3.

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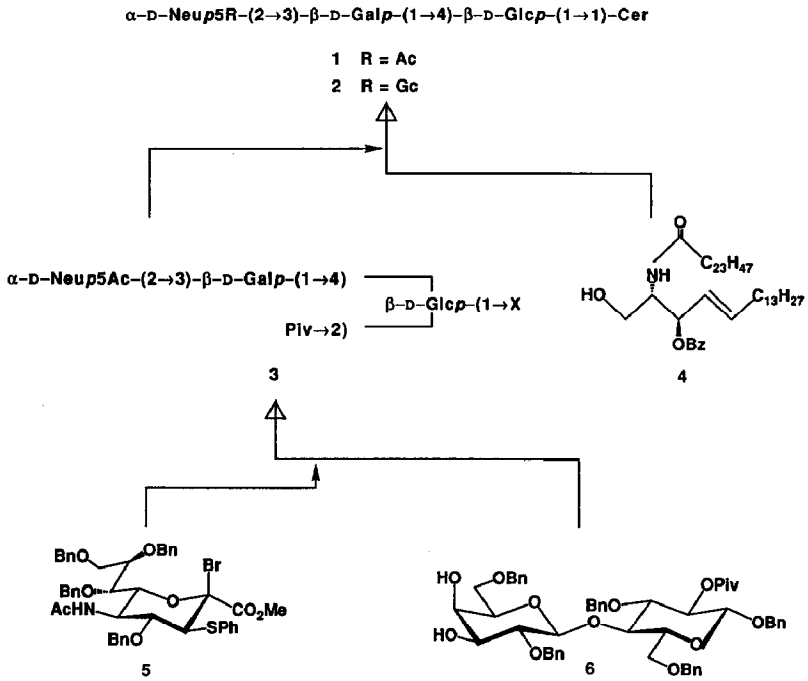
† To whom enquiries should be addressed.

RESULTS AND DISCUSSION

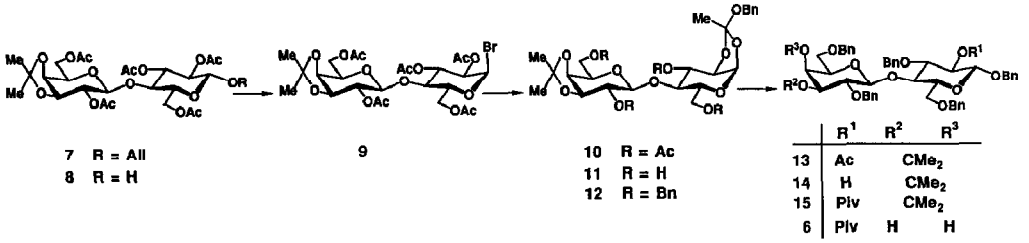
Glycosylation of a secondary alcohol with *N*-acetylneuraminic acid derivatives has been studied in several groups by use of anomeric halides[8], thioglycosides[9], and anomeric halides with C-3 auxiliaries such as C_3-Br[10], C_3-OH[11], C_3-SePh[12], and C_3-SPh[13,14]. In order to improve the inefficient steps in our previous total syntheses of gangliosides[3,4,15], the following new synthetic technologies were introduced in the synthetic plan of GM_3 as depicted in Scheme 1. First, a glycotriosyl donor **3**, armed with the pivaloyl auxiliary at O-2a[16], was designed to enhance the coupling efficiency between the glycosyl donor and the ceramide derivative **4**. The key intermediate **3**, in turn, may be obtainable from a coupling between a NeuAc donor **5** (ref. 13), armed with phenylthio auxiliary at C_3, and a properly protected lactose derivative **6**, which was prepared as described, in the following.



Scheme 1.

Deallylation of allyl glycoside[17] **7** with successive treatments with tris(triphenylphosphine)rhodium(I) chloride[18] and 1,4-diazabicyclo[2.2.2]octane (DABCO), and mercury(II) chloride and mercury(II) oxide[19] gave a hemiacetal **8** in 68% yield. Compound **8**, in turn, was treated with carbon tetrabromide and tris(dimethylamino) phosphine[20] in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) in 1,2-dichloroethane to afford a 67% yield of bromide **9**. In the absence of added TMSOTf, the transformation of hemiacetal **8** into bromide **9** became less efficient, most probably due to the formation of the 1,2-*O*-(1-bromoethylidene) derivative as a by-

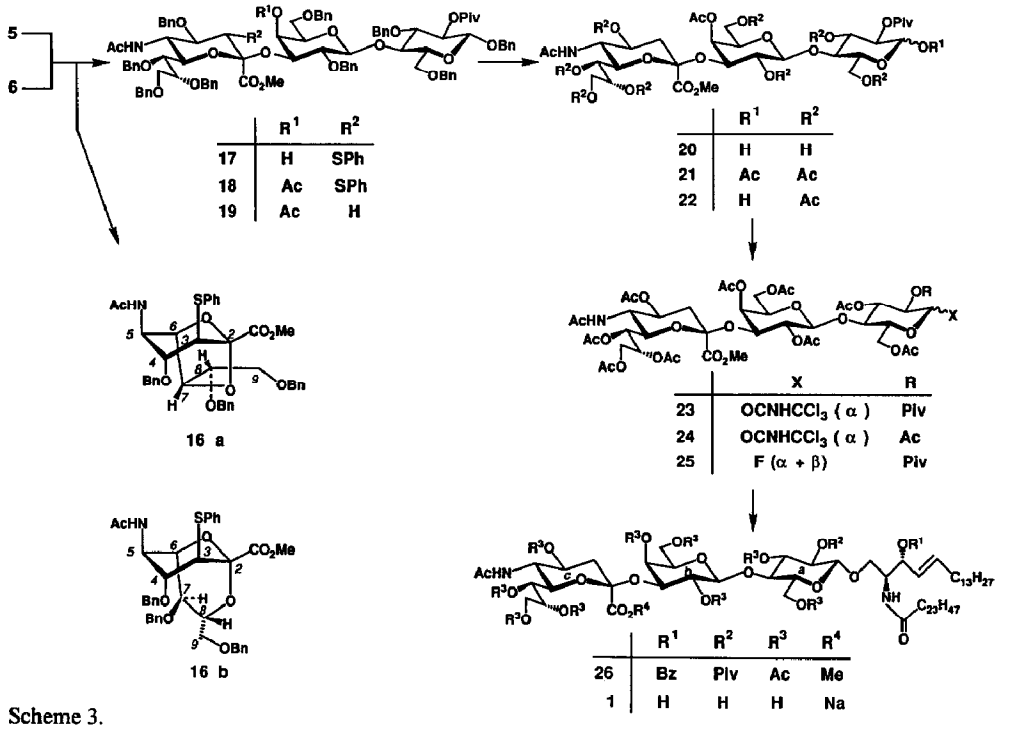
product. Moreover, about 50% of **8** was recovered after work-up of the reaction mixture. Treatment of the bromide **9** with tetrabutylammonium bromide in the presence of benzyl alcohol and triethylamine according to the procedure of Lemieux *et al.*[21] gave a 75% yield of orthoester **10**. A higher overall yield of 64% for **10** from **8** was attained by using crude bromide **9** without recourse to chromatography. Replacement of the acetyl groups of **10** with benzyl groups (**12**) and subsequent conversion of **12** into benzyl glycoside **13** were achieved in three steps in 52% overall yield *via* (*i*) deacylation with sodium methoxide in methanol, (*ii*) alkylation with benzyl bromide and sodium hydride, and (*iii*) TMSOTf[22] and powdered 4A molecular sieves. Further conversion of compound **13** into the desired diol **6** was readily performed in three steps in 83% overall yield *via* (*i*) sodium methoxide in methanol at 60°, (*ii*) pivaloyl chloride and 4-dimethylaminopyridine, and (*iii*) aq. trifluoroacetic acid. The structure of the diol **6** was readily deduced from the unambiguous synthetic sequence, as well as from reasonable ^{1}H- and ^{13}C-n.m.r. data for the synthetic intermediates.



Scheme 2.

Having prepared the key glycosyl acceptor **6**, a crucial coupling of the bromide **5** with 1.7 molar equivalents of **6** was performed in the presence of mercury(II) bromide and mercury(II) cyanide in carbon tetrachloride to give an 89% yield of glycotrioside **17**. The product showed remarkable α-D stereoselectivity in accordance with our previous experiments[13]. Unexpectedly, the 2,7-anhydro derivative **16a** was isolated in 10% yield as a by-product from the donor **5**. Compound **16a** was formed presumably *via* an intramolecular nucleophilic attack of the O-7 benzyl ether at the C-2 cationic center. An alternative attack by the O-8 benzyl ether should lead to the formation of the 2,8-anhydro derivative **16b**, which would suffer severe steric impediment between the O-4 and O-7 substituents. The structure of **16a** was firmly established by the ^{1}H-n.m.r. spectroscopic data. Particularly, a small coupling constant of 1.0 Hz between H-6 and H-7 indicated their steric arrangement with a dihedral angle of about 90° in harmony with the assigned structure for **16a**, but not with that for **16b**. The structure of **17** was assigned as follows. The configuration at C-2c in **17** was readily assigned from the ^{1}H-n.m.r. data which contained a deshielded doublet for H-3c at δ 3.367 with $J_{3,4}$ 9.2 Hz, in agreement with our previous observation[12]. The regiochemistry for the newly introduced interglycosidic linkage in **17** was determined as (2c→3b) by the ^{1}H-n.m.r. data of the acetate **18**, which revealed a deshielded doublet for H-4b at δ 5.401 with $J_{3,4}$ 3.3 Hz. Since acetonitrile has often been a solvent of choice[23] to obtain a thermodynamically less stable glycoside, the same coupling reaction was performed in acetonitrile instead of carbon tetrachloride. However, the reaction efficiency was hampered, and the desired product **17** was isolated only in 49% yield.

Reductive removal of phenylthio group in **18** was achieved by treatment with triphenyltin hydride in the presence of 2,2′-azobis(isobutyronitrile) in refluxing toluene to give an 87% yield of compound **19**, based on the consumed **18**. Conversion of compound **19** into a hemiacetal **22** was accomplished in three steps in 69% overall yield *via* (*i*) 10% palladium on carbon and hydrogen, (*ii*) acetic anhydride and 4-dimethylaminopyridine in pyridine, and (*iii*) hydrazine acetate in *N,N*-dimethylformamide[24]. Conversion of the hemiacetal **22** into a key glycosyl donor was achieved stereoselectively by treatment of **22** with trichloroacetonitrile[25] and 1,8-diazabicyclo[5.4.0]undec-7-ene to give in 85% yield trichloroacetimidate **23** having the α-D-configuration at C-1a. Treatment of compound **22** with diethylaminosulfur trifluoride[26], however, gave in 77% yield, a 3:1 mixture of β- and α-D fluoride **25**, another key glycosyl donor.



Scheme 3.

Crucial glycosylations of the ceramide derivative **4** with the glycosyl donors **23** and **25** were examined as follows. First, boron trifluoride etherate promoted glycosylation with trichloroacetimidate **23** in chloroform did afford a 65% yield of the desired product **26**, ^{1}H-n.m.r. data for which showed two doublets for H-1a and H-1b at δ 4.421 and 4.160 with $J_{1,2}$ values of 8.1 Hz, which is in agreement with a configurational assignment for the newly introduced glycosidic linkage at C-1a. The observed coupling yield of 65% at this crucial step is roughly two times that of the 37% yield achieved[3] by the coupling that employed the same acceptor molecule **4** and trichloroacetimidate **24** carrying an acetyl, instead of a pivaloyl auxiliary at O-2a. Tin(II) triflate[12,27] promoted glycosylation of ceramide derivative **4** with glycosyl fluoride **25** in chloroform afforded a

46% yield of the desired **26**. This glycosylation suffered from incomplete conversion due to the low stereoselectivity (α:β = 1:3) in obtaining β-D fluoride **25**, since the α-D fluoride **25** was found not to be activated under the reaction conditions in spite of the higher activity of tin(II) triflate, in comparison with a mixture of tin(II) chloride and silver triflate[28] as promotors for glycosyl fluoride. Saponification of compound **26** was achieved in a conventional way to give an 85% yield of the target GM_3, which was showed to be identical with an authentic sample[3] by comparison of their ^{1}H-n.m.r. spectra. (See Fig. 1 for the ^{1}H-n.m.r. spectrum of the synthetic product.) The total synthesis was completed in 19 steps in 4.5% overall yield starting from allyl glycoside **7**, even though the yield of each reaction step was not optimized.

In summary, overall efficiency in the synthesis of GM_3 (**1**) was dramatically improved by use of a NeuAc donor **5** and the glycotriosyl donor **23** as the key intermediates, both of which were armed with specific neighboring auxiliaries.

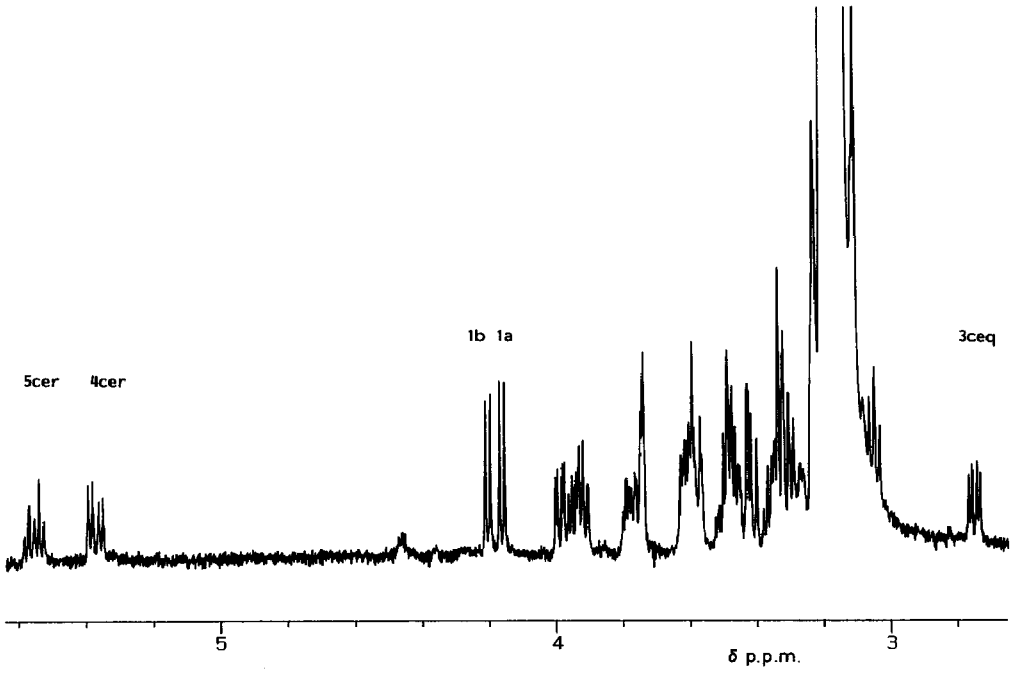


Fig. 1. 500-MHz ^{1}H-n.m.r. spectrum for a synthetic sample of compound **1** (Na salt) taken in 49:1 $(CD_3)_2SO$–D_2O at 65°.

EXPERIMENTAL

General. — Optical rotations were determined with a Perkin–Elmer Model 241MC polarimeter, for solutions in $CHCl_3$ at 25°, unless noted otherwise. Column chromatography was performed on Silica Gel-60 (Merck 70–230 mesh). Flash chromatography was performed on columns of Wakogel C-300 (200–300 mesh). T.l.c. and high-performance (h.p.) t.l.c. were performed on Silica Gel-60 F_{254} (Merck). Molecular

sieves (4A) were purchased from Nakarai Chemicals. N.m.r. spectra were recorded with either JEOL GX500 [^{1}H(500 MHz)] or FX90Q [^{13}C(22.50 MHz)] spectrometers. The values of δ_C and δ_H are expressed in p.p.m. downfield from the signal for internal Me_4Si, for solutions in $CDCl_3$, unless noted otherwise.

Conversion of **7** *into bromide* **9** via *hemiacetal* **8**. — To a solution of **7** (26 g, 41 mmol) in 7:3:1 EtOH–PhH–H_2O (1.1 L) were added $(Ph_3P)_3Rh(I)Cl$ (2.5 g, 2.7 mmol), and diazabicyclo[2.2.2]octane (DABCO, 780 mg, 8.6 mmol). The mixture was heated and stirred for 20 h under reflux, cooled, and filtered through Celite. The filtrate was then concentrated *in vacuo*. To a solution of the residue in 9:1 Me_2CO–H_2O (200 mL) was added $HgCl_2$ (3.9 g, 14.4 mmol) and HgO (780 mg, 3.6 mmol). The mixture was stirred for 1 h at 20° and filtered through Celite. The filtrate was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The organic layer was washed with aq. KI, aq. $Na_2S_2O_3$, H_2O, and aq. NaCl and dried ($MgSO_4$). The solvents were evaporated *in vacuo*, and the residue was chromatographed over SiO_2 using 80:20:1 $CHCl_3$–Me_2CO–Et_3N to give **8** (16.4 g, 68%): $[\alpha]_D$ +39.4° (*c* 1.0); n.m.r. data: δ_H 5.357 (d, 0.7 H, $J_{1,2}$ 3.7 Hz, H-1aα) and 4.740 (d, 0.3H, $J_{1,2}$ 7.7 Hz, H-1aβ); δ_C 110.8 (CMe_2), 100.5 (C-1bβ), 100.3 (C-1bα), 95.1 (C-1aβ), and 90.0 (C-1aα).

To a solution of **8** (110 mg, 0.19 mmol) and CBr_4 (250 mg, 1.5 mmol) in CH_2Cl_2 (2 mL), was added $(Me_2N)_3P$ (242 mg, 1.5 mmol) at −20°. After stirring 10 min, TMSOTf (3 μL, 35 μmol) was added, and the mixture was stirred for 16 h at 25°, at the end of which time, it was diluted with EtOAc. The solution was washed with cold aq. $NaHCO_3$, cold aq. HCl, cold aq. $NaHCO_3$, H_2O, and aq. NaCl, and dried ($MgSO_4$). The solvents were evaporated *in vacuo*, and the residue was chromatographed over SiO_2 using 50:50:1 EtOAc–toluene–Et_3N to give the recovered **8** (11 mg) and *O*-(2,6-di-*O*-benzyl-3,4-di-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl bromide (**9**, 73 mg, 60%): $[\alpha]_D$ +48.6° (*c* 1.3); R_F 0.45 (1:1 EtOAc–toluene); n.m.r. data: δ_H 6.541 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1a), 5.571 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.5 Hz, H-3a), 4.877 (dd, 1 H, $J_{1,2}$ 7.3 and $J_{2,3}$ 6.3 Hz, H-2b), 4.772 (dd, 1 H, $J_{2,3}$ 9.9 Hz, H-2a), 4.437 (d, 1 H, H-1b), 2.123, 2.121, 2.097, 2.097, and 2.080 (5 s, 15 H, 4 Ac), and 1.548 and 1.322 (2 s, 6 H, $C(CH_3)_2$); δ_C 111.0 (CMe_2), 100.0 (C-1b), 86.7 (C-1a), and 27.4 and 26.2 (CMe_2).

O-*(2,6-Di-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-3,6-di-*O*-acetyl-1,2-*O*-(1-benzyloxyethylidene)-α-D-glucopyranose* (**10**). — *Procedure A*. To a solution of **9** (175 mg, 0.27 mmol) and Bu_4NBr (38 mg, 0.12 mmol) in CH_2Cl_2 (15 mL) were added Et_3N (41 mg, 0.41 mmol) and $PhCH_2OH$ (117 mg, 1.1 mmol) under Ar. The mixture was stirred for 16 h at 60°, and the solvent was then evaporated *in vacuo*. The residue was chromatographed on SiO_2 using 60:30:1 hexane–EtOAc–Et_3N to give **10** (139 mg, 75%): $[\alpha]_D$ −48.0° (*c* 0.7); R_F 0.46 (1:1 toluene–EtOAc); n.m.r. data: δ_H 7.4–7.2 (m, 5 H, C_6H_5), 5.628 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1a), 5.584 (dd, 1 H, $J_{2,3}$, $J_{3,4}$ 1.46 and 1.47 Hz, H-3a), 4.962 (dd, $J_{1,2}$ 8.1 and $J_{2,3}$ 4.6 Hz, H-2b), 4.507 (d, 1 H, H-1b), 2.110, 2.098, 2.095 and 2.072 (4 s, 12 H, 4 Ac), 1.792 (s, 3 H, C-Me), and 1.575 and 1.340 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{34}H_{45}O_{16}$: C, 55.06; H, 6.12. Found: C, 55.02; H, 6.27.

Procedure B. To a solution of **8** (110 mg, 0.19 mmol) and CBr_4 (250 mg, 1.5 mmol) in $(CH_2Cl)_2$ (2 mL) were added $(Me_2N)_3P$ (242 mg, 1.5 mmol) and TMSOTf (3 μL, 35

μmol) at −20° under Ar. The mixture was stirred for 15 h at 20°, and the solvent was then evaporated *in vacuo*. To a solution of the residue and Bu_4NBr (30 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (16 mg, 0.16 mmol) and $PhCH_2OH$ (45 mg, 0.40 mmol). After stirring for 16 h at 60°, the volatiles were evaporated *in vacuo*. The residue was chromatographed over SiO_2 using 60:30:1 hexane–EtOAc–Et_3N to give **10** (81 mg, 64% overall).

Conversion of orthoester **10** *into* **12**. — A solution of **10** (3.37 g, 4.94 mmol) in 0.1M NaOMe in MeOH (55 mL) was stirred for 5 h at 20° and then evaporated *in vacuo* to give crude **11** (4.05 g), R_F 0.40 (8:1 $CHCl_3$–MeOH).

To a solution of crude **11** in DMF (60 mL) was added portionwise NaH (60% oil dispersion, 1.0 g, 25 mmol) at 0° under Ar. After stirring for 1 h, $PhCH_2Br$ (4.3 g, 25 mmol) was added dropwise at 0°. The mixture was stirred for 16 h at 20°, and excess $PhCH_2Br$ was decomposed by adding MeOH (3 mL). After stirring for 1 h, the volatiles were evaporated *in vacuo*. The residue was extracted with EtOAc, and the combined organic layers were washed with H_2O and aq. NaCl and dried ($MgSO_4$). The solvents were evaporated *in vacuo*, and the residue was chromatographed over SiO_2 using 100:10:1 toluene–EtOAc–Et_3N to give *O*-(2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-3,6-di-*O*-benzyl-1,2-*O*-(1-benzyloxyethylidene)-α-D-glucopyranose **12** (4.44 g, 86% overall): $[\alpha]_D$ +16.6° (*c* 0.6); R_F 0.52 (5:1 toluene–EtOAc): n.m.r. data: δ_H 7.4–7.1 (m, 25 H, $5C_6H_5$), 5.681 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1a), 4.247 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1b), 1.747 (s, 3 H, C*Me*), and 1.336 and 1.313 (2 s, 6 H, C*Me*$_2$); δ_C 109.9 (*C*Me$_2$), 104.4 (C-1b), 97.6 (C-1a), 27.9 and 26.4 (C*Me*$_2$), and 21.0 (C*Me*).

Rearrangement of **12** *into benzyl glycoside* **13**. — To a mixture of **12** (530 mg, 0.60 mmol) and 4A molecular sieves (0.8 g) in CH_2Cl_2 (5 mL) was added TMSOTf (81 mg, 0.36 mmol), at 0° under Ar. After stirring for 90 min at 0°, the mixture was filtered through Celite. The filtrate was washed with aq. $NaHCO_3$ and aq. NaCl and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the residue was chromatographed over SiO_2 using 90:10:1 toluene–EtOAc–Et_3N to give benzyl *O*-(2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-2-*O*-acetyl-3,6-di-*O*-benzyl-β-D-glucopyranoside (**13**) (302 mg, 60%): $[\alpha]_D$ +1.8° (*c* 3.4); R_F 0.37 (6:1 toluene–EtOAc); n.m.r. data: δ_H 7.4–7.1 (m, 25 H, $5C_6H_5$), 5.053 (dd, 1 H, $J_{1,2}$ 8.1 and $J_{2,3}$ 9.2 Hz, H-2a), 4.415 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1b), 4.407 (d, 1 H, H-1a), 1.935 (s, 3 H, Ac), and 1.398 and 1.338 (2 s, 6 H, C*Me*$_2$); δ_C 109.9 (*C*Me$_2$), 102.2 (C-1b), 99.8 (C-1a), 28.0 and 26.5 (C*Me*$_2$), and 20.9 (CO*C*H$_3$).

Benzyl O-*(2,6-di*-O-*benzyl-3,4*-O-*isopropylidene-β*-D-*galactopyranosyl)-(1→4)-3,6-di*-O-*benzyl-2*-O-*pivaloyl-β*-D-*glucopyranoside* (**15**). — A solution of **13** (300 mg, 0.34 mmol) in 0.05M NaOMe in MeOH (10 mL) was stirred for 15 h at 60° and then treated with Amberlite IRC-50 resin [H^+]. The resin was filtered, and, after evaporation of the solvent *in vacuo*, the residue was chromatographed over SiO_2 using 100:10:1 toluene–EtOAc–Et_3N to give **14** (283 mg, 99%): $[\alpha]_D$ −1.1° (*c* 0.8); R_F 0.23 (6:1 toluene–EtOAc); n.m.r. data: δ_H 4.410 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1a), 4.372 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1b), and 1.394 and 1.344 (2 s, 6 H, C*Me*$_2$); δ_C 109.9 (*C*Me$_2$), 102.0 (C-1a), 101.6 (C-1b), and 28.0 and 26.5 (C*Me*$_2$).

A mixture of **14** (3.86 g, 4.6 mmol), *t*-BuCOCl (660 mg, 5.5 mmol) and DMAP (200 mg) in pyridine (160 mL) was stirred for 15 h at 80°, and then the volatiles were evaporated *in vacuo*. The residue was dissolved in EtOAc, and the organic solution was washed with H_2O and aq. NaCl and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the residue was chromatographed over SiO_2 using 80:10:1 toluene–EtOAc–Et_3N to give **15** (3.87 g, 91%): $[\alpha]_D$ −51.9° (*c* 2.6); R_F 0.44 (6:1 toluene–EtOAc); n.m.r. data: δ_H 7.4–7.1 (m, 25 H, 5C$_6$*H*$_5$), 5.128 (dd, 1 H, $J_{1,2}$ 8.1 and $J_{2,3}$ 9.5 Hz, H-2a), 4.463 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1b), 4.405 (d, 1 H, H-1a), 1.397 and 1.334 (2 s, 6 H, C*Me*$_2$), and 1.136 (s, 9 H, *t*-Bu); δ_C 176.7 (C=O), 109.8 (*C*Me$_2$), 102.1 (C-1a), 99.9 (C-1b), 38.8 (*C*Me$_3$), 28.0 and 26.4 (C*Me*$_2$), and 27.2 (C*Me*$_3$). An analytical sample was obtained after concentration to dryness of a solution of **15** in $CHCl_3$.

Anal. Calc. for $C_{55}H_{64}O_{12}\cdot 0.17\,CHCl_3$: C, 70.72; H, 6.90. Found: C, 70.83; H, 6.45.

Benzyl O-*(2,6-di-*O*-benzyl-β-*D*-galactopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-*D*-glucopyranoside* (**6**). — A solution of **15** (95 mg, 0.10 mmol) in 20:1 CH_2Cl_2–90% aq. CF_3COOH (5 mL) was stirred for 2.5 h at 20°, then neutralized with aq. $NaHCO_3$ and diluted with EtOAc. The organic layer was washed with H_2O and aq. NaCl and dried ($MgSO_4$). The solvents were evaporated *in vacuo*, and the residue was chromatographed over SiO_2 using 2:1 toluene–EtOAc to give **6** (84 mg, 92%): $[\alpha]_D$ −3.7° (*c* 0.4); R_F 0.19 (4:1 toluene–EtOAc); n.m.r. data: δ_H 7.5–7.1 (m, 25 H, 5C$_6$*H*$_5$), 5.144 (dd, 1 H, $J_{1,2}$ 7.7 and $J_{2,3}$ 9.5 Hz, H-2a), 4.476 (d, 1 H, H-1a), and 1.124 (s, 9 H, *t*-Bu); δ_C 102.8 (C-1a), 99.8 (C-1b), 38.8 (*C*Me$_3$), and 27.2 (C*Me*$_3$).

Anal. Calc. for $C_{52}H_{60}O_{12}$: C, 71.21; H, 6.90. Found: C, 71.35; H, 6.93.

Benzyl O-*[methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylthio-*D*-erythro-α-*L*-gluco-2-nonulopyranosyl)onate]-(2→3)-*O*-*(2,6-di-*O*-benzyl-β-*D*-galactopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-*D*-glucopyranoside* (**17**). — To a mixture of 4A molecular sieves (0.6 g), $Hg(CN)_2$ (105 mg, 0.42 mmol) and $HgBr_2$ (48 mg, 0.13 mmol) in CCl_4 (1 mL) was added a solution of **6** (389 mg, 0.44 mmol) in CCl_4 (2 mL) under Ar. After stirring for 1 h at 20°, a solution of **5** (222 mg, 0.26 mmol) in CCl_4 (1 mL) was added dropwise at 0°. The mixture was stirred for 20 h at 20°, then diluted with $CHCl_3$ and filtered through Celite. The filtrate was washed with aq. KI, H_2O and aq. NaCl and dried ($MgSO_4$). The solvents were evaporated *in vacuo*, and the residue was chromatographed over SiO_2 using 4:1 toluene–EtOAc to give **16a** (19 mg, 10%) and **17** (380 mg, 89%): $[\alpha]_D$ +9.0° (*c* 0.4); R_F 0.46 (3:1 toluene–EtOAc); n.m.r. data: δ_H 5.069 (dd, 1 H, $J_{1,2}$ 8.1 and $J_{2,3}$ 9.2 Hz, H-2a), 4.397 (d, 1 H, H-1a), 4.345 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4c), 4.120 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1b), 3.617 (s, 3 H, O*Me*), 3.367 (d, 1 H, $J_{3,4}$ 9.2 Hz, H-3c), 1.654 (s, 3 H, NAc), and 1.113 (s, 9 H, *t*-Bu); δ_C 102.5 (C-1a), 101.2 (C-1b), 99.6 C-2c), 38.7 (*C*Me$_3$), 27.2 (C*Me*$_3$), and 23.7 (NAc).

Anal. Calc. for $C_{98}H_{107}NO_{20}S$: C, 71.30; H, 6.53; N, 0.85. Found: C, 71.05; H, 6.50; N, 0.85.

Compound **16** had $[\alpha]_D$ −7.5° (*c* 0.7), R_F 0.35 (3:1 toluene–EtOAc); n.m.r. data: δ_H 6.380 (d, 1 H, $J_{5,NH}$ 8.8 Hz, NH), 4.698 (bs, 1 H, H-6), 4.684 (dd, 1 H, $J_{6,7}$ 1.0, $J_{7,8}$ 8.2 Hz, H-7), 4.291 (tdd, 1 H, $J_{4,5}$ 1.5, $J_{5,6} = J_{5,3}$ = 1.0 Hz, H-5), 3.872 (td, 1 H, $J_{3,4} = J_{4,6}$ = 1.0 Hz, $J_{4,5}$ 1.5 Hz, H-4), 3.744 (s, 3 H, OMe), 3.722 (dd, 1 H, $J_{8,9}$ 2.6, $J_{9,9'}$ 11.0 Hz, H-9), 3.621

(bs, 1 H, H-3), 3.559 (dd, 1 H, $J_{8,9'}$ 4.5, H-9'), 3.519 (ddd, 1 H, H-8), and 2.030 (s, 3 H, NAc); δ_C 169.1 and 165.8 (2C=O), 104.8 (C-2), 52.8 (OMe), 51.8 (C-3), and 48.1 (C-5).

Anal. Calc. for $C_{39}H_{40}NO_8S$: C, 68.50; H, 6.04; N, 2.05. Found: C, 68.47; H, 6.07; N, 1.61.

Benzyl O-*[methyl(5-acetamido-4,7,8,9-tetra*-O-*benzyl-3,5-dideoxy-3-phenylthio-*D-*erythro-α-*L-gluco-*2-nonulopyranosyl)onate]-(2→3)*-O-*(4*-O-*acetyl-2,6-di*-O-*benzyl-β-*D-*galactopyranosyl)-(1→4)-3,6-di*-O-*benzyl-2*-O-*pivaloyl-β-*D-*glucopyranoside* (**18**). — A mixture of **17** (2.38 g, 1.44 mmol) and DMAP (36 mg, 0.29 mmol) in Ac_2O (10 mL) and pyridine (10 mL) was stirred for 17 h at 20° and then evaporated *in vacuo*. The residue was chromatographed over SiO_2 using 4:1 toluene–EtOAc to give **18** (2.34 g, 96%): $[\alpha]_D$ −3.6° (*c* 0.8); R_F (h.p.t.l.c.) 0.37 (4:1 toluene–EtOAc); n.m.r. data: δ_H 5.401 (d, 1 H, $J_{3,4}$ 3.3 Hz, H-4b), 5.068 (dd, 1 H, $J_{1,2}$ 8.1 and $J_{2,3}$ 9.2 Hz, H-2a), 4.368 (d, 1 H, H-1a), 4.272 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1b), 3.709 (s, 3 H, O*Me*), 3.334 (d, 1 H, $J_{3,4}$ 10.6 Hz, H-3c), 1.884 (s, 3 H, OAc), 1.596 (s, 3 H, NAc), 1.121 (s, 9 H, *t*-Bu); δ_C 102.6 (C-1a), 99.9 (C-1b), 99.6 (C-2c), 38.7 (CMe_3), 27.2 (CMe_3), 23.6 (NAc), and 20.8 (OAc).

Anal. Calc. for $C_{100}H_{109}NO_{21}S$: C, 70.94; H, 6.49; N, 0.83. Found: C, 70.53; H, 6.46; N, 0.85.

Benzyl O-*[methyl(5-acetamido-4,7,8,9-tetra*-O-*benzyl-3,5-dideoxy-*D-*glycero-α-*D-galacto-*2-nonulopyranosyl)onate]-(2→3)*-O-*(4*-O-*acetyl-2,6-di*-O-*benzyl-β-*D-*galactopyranosyl)-(1→4)-3,6-di*-O-*benzyl-2*-O-*pivaloyl-β-*D-*glucopyranoside* (**19**). — To a solution of **18** (1.217 g, 0.72 mmol) in dry toluene (40 mL) were added Ph_3SnH (757 mg, 2.16 mmol) and AIBN (24 mg, 0.14 mmol) under N_2. After heating under reflux for 2 h, Ph_3SnH (757 mg, 2.16 mmol) and AIBN (24 mg, 0.14 mmol) were again added, and the mixture was heated under reflux for an additional 2 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed over SiO_2 using 3:1 toluene–EtOAc to give **19** (754 mg, 67%) and recovered **18** (291 mg, 23.9%).

Compound **19** had $[\alpha]_D$ −6.1° (*c* 1.1); R_F 0.29 (3:1 toluene–EtOAc); n.m.r. data: δ_H 5.368 (d, 1 H, $J_{3,4}$ 3.3 Hz, H-4b), 5.117 (dd, 1 H, $J_{1,2}$ 7.7 and $J_{2,3}$ 9.5 Hz, H-2a), 4.439 (d, 1 H, H-1a), 4.138 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1b), 2.368 (dd, 1 H, $J_{3,4}$ 4.4 and $J_{3,3}$ 13.6 Hz, H-3ceq), 2.015 and 1.938 (2 s, 6 H, 2 Ac), and 1.126 (s, 9 H, *t*-Bu).

Anal. Calc. for $C_{94}H_{105}NO_{21}$: C, 71.24; H, 6.68; N, 0.88. Found: C, 71.44; H, 6.74; N, 1.04.

O-*[Methyl(5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5-dideoxy-*D-glycero-α-D-galacto-*2-nonulopyranosyl)onate]-(2→3)*-O-*(2,4,6-tri*-O-*acetyl-β-*D-*galactopyranosyl)-(1→4)-3,6-di*-O-*acetyl-2*-O-*pivaloyl-*D-*glucopyranosyl acetate* (**21**). — A mixture of **19** (26 mg, 16 μmol) and 10% Pd–C (30 mg) was stirred for 17 h at 20° under H_2. After filtration through Celite, the filtrate was concentrated *in vacuo* to give crude **20** (12 mg, 95%): R_F 0.59 (2:1:1 BuOH–EtOH–H_2O); n.m.r. data: δ_H (CD_3OD) 5.221 (d, 0.5 H, $J_{1,2}$ 4.4 Hz, H-1a*α*), 5.213 (d, 1 H, $J_{3,4}$ 3.7 Hz, H-4b), 4.703 (t, 0.5 H, $J_{1,2} = J_{2,3}$ = 8.1 Hz, H-2a*β*), 4.654 (d, 0.5 H, $J_{1,2}$ 8.1 Hz, H-1a*β*), 4.603 (dd, 0.5 H, $J_{1,2}$ 3.7 and $J_{2,3}$ 10.3 Hz, H-2a*α*), 4.508 (d, 0.5 H, $J_{1,2}$ 8.1 Hz, H-1b), 4.505 (d, 0.5 H, $J_{1,2}$ 7.7 Hz, H-1b), 3.810 (s, 3 H, O*Me*), 2.606 (dd, 1 H, $J_{3,4}$ 4.4 and $J_{3,3}$ 13.2 Hz, H-3ceq), 2.058 (s, 1.5 H, Ac), 2.047 (s, 1.5 H, Ac), 1.994 (s, 3 H, Ac), 1.855 and 1.846 (2 t, 1 H, H-3cax), and 1.219 and 1.221 (2 s, 9 H, *t*-Bu).

A mixture of crude **20** (12 mg) and DMAP (6 mg) in 1:1 Ac_2O–pyridine (2 mL) was stirred for 20 h at 20°, and the volatiles were then evaporated *in vacuo*. The residue was chromatographed over SiO_2 using 97:3 $CHCl_3$–MeOH to give **21** (16 mg, 85%): $[\alpha]_D$ +15.5° (*c* 0.9); R_F 0.29 (97:3 $CHCl_3$–MeOH); n.m.r. data: δ_H 6.295 (d, 0.5 H, $J_{1,2}$ 3.7 Hz, H-1aα), 5.717 (d, 0.5 H, $J_{1,2}$ 8.4 Hz, H-1aβ), 4.650 (d, 0.5 H, $J_{1,2}$ 7.7 Hz, H-1b), 4.643 (d, 0.5 H, $J_{1,2}$ 8.1 Hz, H-1b), 2.578 (m, 1 H, H-3ceq), 1.135 and 1.124 (2 s, 9 H, *t*-Bu).

Anal. Calc. for $C_{49}H_{69}NO_{30}\cdot 0.25\ CHCl_3$: C, 50.05; H, 5.91; N, 1.19. Found: C, 50.21; H, 5.93; N, 1.21.

O-*[Methyl(5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5-dideoxy*-D-glycero-α-D-galacto-*2-nonulopyranosyl)onate]-(2→3)*-O-*(2,4,6-tri*-O-*acetyl-β*-D-*galactopyranosyl)-(1→4)-3,6-di*-O-*acetyl-2*-O-*pivaloyl*-D-*glucopyranose* (**22**). — A mixture of **21** (127 mg, 0.11 mmol) and $NH_2NH_2\cdot AcOH$ (13.5 mg, 0.15 mmol) in DMF (1 mL) was stirred for 5 min at 50–60° and then diluted with EtOAc. The organic layer was washed with H_2O and aq. NaCl and dried ($MgSO_4$). The volatiles were evaporated *in vacuo*, and the residue was chromatographed over SiO_2 using 97:3 $CHCl_3$–MeOH to give **22** (104 mg, 85%): $[\alpha]_D$ +22.6° (*c* 1.2); R_F 0.21 (97:3 $CHCl_3$–MeOH); n.m.r. data: δ_H 3.856 (s, 3 H, OMe), 2.577 (dd, 1 H, $J_{3,4}$ 4.0 and $J_{3,3}$ 12.1 Hz, H-3ceq), 1.680 and 1.674 (2 t, 2 × 0.5 H, $J_{3,4}$ 12.4 Hz, H-3ax), and 1.181 and 1.179 (2 s, 2 × 4.5 H, *t*-Bu).

Anal. Calc. for $C_{47}H_{67}NO_{29}\cdot 0.125\ CHCl_3$: C, 50.31; H, 6.01; N, 1.25. Found: C, 50.23; H, 5.99; N, 1.20.

Conversion of **22** *into trichloroacetimidate* **23**. — A solution of **22** (23 mg, 21 μmol), CCl_3CN (11 μL, 0.11 mmol), and DBU (4.1 μL, 27 μmol) in $(ClCH_2)_2$ (0.5 mL) was stirred for 2 h at 20° under Ar. The reaction mixture was directly chromatographed over SiO_2 using EtOAc to give *O*-[methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-3,6-di-*O*-acetyl-2-*O*-pivaloyl-α-D-glucopyranosyl trichloroacetimidate **23** (22 mg, 85%): $[\alpha]_D$ +32.6° (*c* 1.5); R_F (h.p.t.l.c.) 0.33 (EtOAc); n.m.r. data: δ_H 8.640 (s, 1 H, C=N*H*), 6.515 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1a), 5.600 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.9 Hz, H-3a), 5.504 (m, 1 H, H-8c), 5.412 (dd, 1 H, *J* 2.6 and 9.2 Hz, H-7c), 5.059 (dd, 1 H, $J_{2,3}$ 10.3 Hz, H-2a), 4.965 (dd, 1 H, $J_{1,2}$ 8.1 and $J_{2,3}$ 10.3 Hz, H-2b), 4.897 (dt, 1 H, $J_{3,4}$ 4.8 and 11.2, $J_{4,5}$ 11.2 Hz, H-4c), 4.897 (d, 1 H, $J_{3,4}$ 3.7 Hz, H-4b), 4.680 (d, 1 H, H-1b), 3.847 (s, 3 H, O*Me*), 2.582 (dd, 1 H, $J_{3,4}$ 4.8 and $J_{3,3}$ 12.8 Hz, H-3ceq), 2.249, 2.159, 2.093, 2.081, 2.079, 2.069, 2.063, 2.023, 2.006 and 1.855 (10 s, 30 H, 10Ac), 1.683 (t, 1 H, H-3cax), and 1.132 (s, 9 H, *t*-Bu).

Conversion of **22** *into fluoride* **25**. — To a stirred solution of **22** (22 mg, 20 μmol) in $(CH_2Cl)_2$ (0.5 mL), maintained under Ar and cooled with a dry ice–CCl_4 bath, was added DAST (26 μL, 0.20 mmol). After stirring for 2 h at 20°, the mixture was diluted with EtOAc. The organic solution was washed with aq. $NaHCO_3$ and aq. NaCl and dried ($MgSO_4$). The solvents were evaporated *in vacuo*, and the residue was chromatographed over SiO_2 using EtOAc to give *O*-[methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-3,6-di-*O*-acetyl-2-*O*-pivaloyl-α and β-D-glucopyranosyl fluoride **25** (17 mg, 77% α:β = 1:3): R_F (h.p.t.l.c.) 0.38 (EtOAc); n.m.r. data:

δ_H 5.606 (dd, 0.25 H, $J_{1,2}$ 3.0 and $J_{1,F}$ 53.8 Hz, H-1aα), 4.705 (d, 0.75 H, $J_{1,2}$ 8.1 Hz, H-1bβ), 4.649 (d, 0.25 H, $J_{1,2}$ 8.1 Hz, H-1bα), 3.846 (s, 3 H, OMe), 2.581 (dd, 1 H, $J_{3,4}$ 4.8 and $J_{3,3}$ 12.8 Hz, H-3ceq), and 1.195 and 1.188 (2 s, ratio 3:1, 9 H, *t*-Bu); δ_C 106.2 ($^1J_{C,H}$ 172 and $^1J_{C,F}$ 218 Hz, C-1aβ), 103.8 ($^1J_{C,H}$ 186 and $^1J_{C,F}$ 229 Hz, C-1aα), 101.3 ($^1J_{C,H}$ 164 Hz, C-1bβ), 101.0 ($^1J_{C,H}$ 164 Hz, C-1bα), 96.9 (C-2cβ), and 96.8 (C-2cα).

O-*[Methyl (5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5-dideoxy*-D-glycero-α-D-galacto-*2-nonulopyranosyl)onate]-(2→3)*-O-*(2,4,6-tri*-O-*acetyl-β-*D-*galactopyranosyl)-(1→4)*-O-*(3,6-di*-O-*acetyl-2*-O-*pivaloyl-β-*D-*glucopyranosyl)-(1→1)-(2*S,*3*R,*4*E*)-*3*-O-*benzoyl-2*-N-*tetracosanoylsphingenine* (**26**). — *Procedure A.* To a stirred mixture of **23** (22 mg, 18 μmol), **4** (20 mg, 26 μmol), and powdered 4A molecular sieves (200 mg) in $CHCl_3$ (0.5 mL, freshly purified by passing through an active alumina column) was added $BF_3{\cdot}OEt_2$ (3 μL, 23 μmol) at −5° under Ar. The mixture was stirred for 3 h at −5°, then for 12 h at 20°, diluted with $CHCl_3$, and filtered through Celite. The filtrate was neutralized with Et_3N, and the solvent was evaporated *in vacuo*. The residue was chromatographed over SiO_2 using 49:1 $CHCl_3$–MeOH to give **26** (21 mg, 65%): $[\alpha]_D$ +3.9° (*c* 1.4); R_F (h.p.t.l.c.) 0.41 (97:3 $CHCl_3$–MeOH); n.m.r. data: δ_H 7.995 (d, 2 H, *J* 7.0 Hz, C_6H_5CO), 7.550 (t, 1 H, *J* 7.0 Hz, C_6H_5CO), 7.430 (t, 2 H, *J* 7.0 Hz, C_6H_5CO), 5.864 (dt, 1 H, $J_{4,5}$ 15.0 and $J_{5,6}$ 8.1 Hz, H-5cer), 5.753 (d, 1 H, *J* 9.2 Hz, NH), 5.457 (dd, 1 H, $J_{3,4}$ 7.7 Hz, H-4cer), 4.610 and 4.421 (2 d, 2 H, $J_{1,2}$ 8.1 Hz, H-1ab), 3.839 (s, 3 H, OMe), 2.568 (dd, 1 H, $J_{3,4}$ 4.8 and $J_{3,3}$ 12.8 Hz, H-3ceq), 2.203, 2.159, 2.078, 2.078, 2.073, 2.004, 2.004, 1.902, 1.854, and 1.691 (8 s, 30 H, 10Ac), 1.667 (t, 1 H, H-3cax), 1.144 (s, 9 H, *t*-Bu), and 0.878 (t, 6 H, 2 CH_2CH_3).

Anal. Calc. for $C_{96}H_{152}N_2O_{32}{\cdot}0.17\ CHCl_3$: C, 61.90; H, 8.22; N, 1.50. Found: C, 61.93; H, 8.20; N, 1.47.

Procedure B. To a stirred mixture of **25** (16 mg, 14 μmol), **4** (15 mg, 20 μmol), and powdered 4A molecular sieves (200 mg) in $CHCl_3$ (0.5 mL) maintained under Ar was added $Sn(OTf)_2$ (8.4 mg, 20 μmol). The mixture was stirred for 12 h at 20° and then for 2 h at 50°. T.l.c. examination of the reaction mixture using 97:3 $CHCl_3$–MeOH showed that about 20% of fluoride **25** (probably the α-anomer) remained unreacted. After dilution with $CHCl_3$, the mixture was neutralized with Et_3N and filtered through Celite. The filtrate was concentrated *in vacuo*, and the residue was chromatographed over SiO_2 using 49:1 $CHCl_3$–MeOH to give **26** (12 mg, 46%).

Deprotection of **26** *into* GM_3 (**1**). — To a solution of **26** (19 mg, 10 μmol) in 1:1 THF–MeOH (1 mL) was added M NaOMe in MeOH (60 μL). The mixture was stirred for 3 h at 20°, and H_2O (0.5 mL) was added. The mixture was stirred for an additional 12 h at 20°, and the solvents were evaporated *in vacuo*. The residue was purified by Sephadex LH-20 in 300:150:23 $CHCl_3$–MeOH–H_2O (1.5 mL) to give **1** (11 mg, 85%): $[\alpha]_D$ +4.1° (*c* 0.2, 1:1 $CHCl_3$–MeOH); R_F 0.24 (2:1:1 BuOH–EtOH–H_2O); n.m.r. data: δ_H (49:1 $(CD_3)_2SO$–D_2O, 65°) 5.552 (dt, 1 H, $J_{4,5}$ and $J_{5,6}$ 6.6 Hz, H-5cer), 5.373 (dd, 1 H, $J_{3,4}$ 6.8 Hz, H-4cer), 4.204 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1b), 4.136 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1a), 2.754 (dd, 1 H, $J_{3,4}$ 4.9 and $J_{3,3}$ 11.9 Hz, H-3ceq), 1.370 (t, 1 H, $J_{3,4}$ 11.5 Hz, H-3cax), 1.882 (s, 3 H, NAc), 1.241 (s, 64 H, 32CH_2), and 0.854 (t, 6 H, *J* 6.8 Hz, 2CH_2CH_3).

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