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Synthesis of 3′- and 4′-deoxyfluorolactose and its $Me_3SiCH_2CH_2$ and ceramide † derivatives

Tomas Ekberg and Göran Magnusson *

Organic Chemistry 2, Chemical Center, The Lund Institute of Technology, University of Lund, P.O. BOX 124, S-221 00 Lund (Sweden)

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ABSTRACT

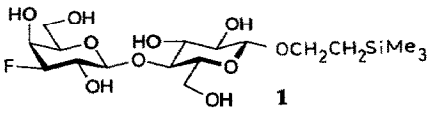
(2-Trimethylsilyl)ethyl ($Me_3SiCH_2CH_2$) 3′- and 4′-deoxyfluorolactosides (**1** and **3**) were synthesized by glycosylation of $Me_3SiCH_2CH_2$ 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside with 2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-β-D-galactopyranosyl bromide and 2,3,6-tri-*O*-benzyl-4-deoxy-4-fluoro-β-D-galactopyranosyl bromide. Anomeric deblocking of the fully acetyled $Me_3SiCH_2CH_2$ glycosides (**12** and **13**) gave the corresponding hemiacetals **14** and **15**. Removal of the acetyl groups gave 3′- and 4′-deoxyfluorolactose (**2** and **4**). The deoxyfluorolactosylceramides **5** and **6** were synthesized via boron trifluoride etherate- or silver triflate-activation of the trichloroacetimidates prepared from **14** and **15**. Silver triflate-mediated glycosylations showed lower reaction rates, and fewer byproducts were formed.

INTRODUCTION

Cell-surface glycoconjugates, such as glycolipids and glycoproteins, are important in cell adhesion and immunological responses to carbohydrate antigens[1,2]. Lactose is a common part of these glycoconjugates. A number of lectins and bacterial adhesins with lactose specificity have been identified recently[3,4]. Deoxy- and deoxyfluorolactosides[5,6], are potentially useful tools for investigating cell-adhesion phenomena where lactose-specific proteins are involved. The methyl 6- and 6′-monodeoxyfluoro-β-lactosides were recently reported[6]. We now report the synthesis of the 3′- and 4′-monodeoxyfluorolactose derivatives **1–6**.

Simple methyl pyranosides are readily available starting materials for the synthesis of oligosaccharides; however, methyl glycosides are not easily transformed into useful glycoconjugates. In contrast, $Me_3SiCH_2CH_2$ pyranosides permit conversion, typically in > 90% yield, into the corresponding 1-*O*-acyl-, hemiacetal, and 1-chloro-sugars, en route to glycoconjugates[7–9]. Normally, these transfor-

† Part 10 of the series 2-(Trimethylsilyl)ethyl ($Me_3SiCH_2CH_2$) Glycosides for part 9, see ref 17.
* Corresponding author.



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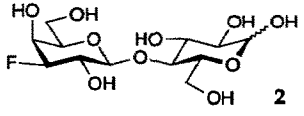

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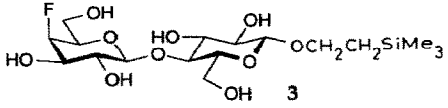

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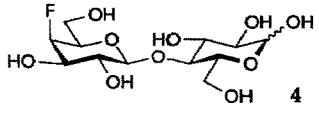

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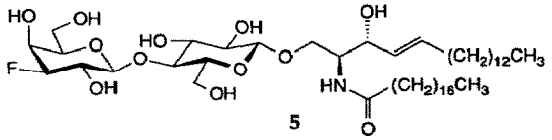

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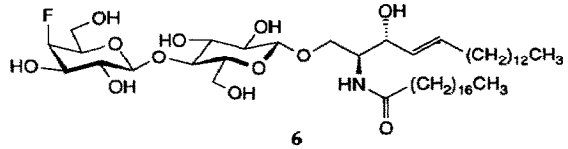

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mations are performed with oligosaccharides obtained late in multistep syntheses, and high yields are therefore important. Cleavage of methyl glycosides are in most cases better performed via acetolysis followed by deacetylation by reagents that are selective for 1-acetates[10], although the overall yield from such reaction sequences are normally lower than those obtained by direct $Me_3SiCH_2CH_2$ cleavage. The latter approach is exemplified here by the synthesis of the 2-deoxyfluorolactosyl-ceramides **5** and **6**.

SYNTHESIS

The 3- and 4-deoxyfluoro-galactose derivatives **7** and **8** were prepared as described[11] and transformed into 2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-α-D-galactopyranosyl bromide (**7a**) and 2,3,6-tri-*O*-benzyl-4-deoxy-4-fluoro-α-D-galactopyranosyl bromide (**8a**), respectively. Glycosylation of $Me_3SiCH_2CH_2$ 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[7] (**9**) with the galactosyl bromides **7a** and **8a** in the presence of silver triflate and silver silicate, gave the protected deoxyfluorolactosides **10** (75%) and **11** (65%). Hydrogenolytic debenzylation of **10**, followed by conventional acetylation, gave the acetylated deoxyfluoro lactoside **12** (98%).

Deacetylation of **12** with methanolic sodium methoxide gave the unprotected deoxyfluorolactoside **1** (99%). Hydrogenolytic debenzylation of **11** gave the deoxyfluorolactoside **3** (98%), which was acetylated to give **13** (99%).

The $Me_3SiCH_2CH_2$ group of **1** and **3** was removed by treatment with trifluoroacetic acid in dichloromethane[7] to give the 3′- and 4′-deoxyfluorolactoses **2** (95%) and **4** (95%). Compounds **2** and **4** were also prepared by deacetylation of the hemiacetals **14** and **15**.

Removal of the $Me_3SiCH_2CH_2$ group in **12** and **13** was performed as above[7] to give the acetylated deoxyfluoro hemiacetals **14** (95%) and **15** (93%). Treatment of the hemiacetals **14** and **15** with trichloroacetonitrile and DBU[12] gave the corresponding α-trichloroacetimidates **16** and **17** in essentially quantitative yield after chromatography. $BF_3 \cdot Et_2O$-catalyzed glycosylation[12] of the azidosphingosine **22** (ref 13) by the donors **16** and **17** afforded the β-glycosides **18** (55%) and **19** (50%), respectively. The corresponding α-glycosides were also isolated in ~15% yield.

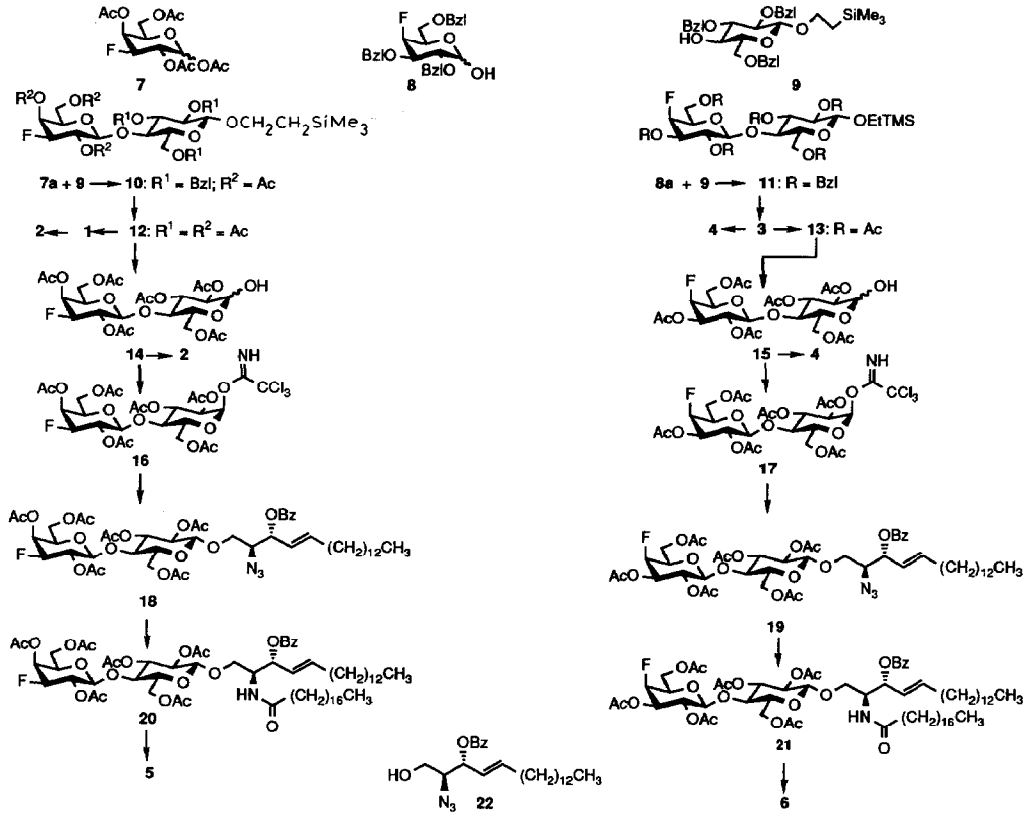
Recently, it was suggested[14] that silver triflate would be a more suitable agent for activatation of anomeric thrichloroacetimidates. A slight modification of this method permitted the glycosylation of **22** with trichloroacetimidates **16** and **17**, which gave **18** (65%) and **19** (60%). The corresponding α-glycosides were formed in ~5% yield, and the unreacted donors (**16** and **17**) could, to some extent, be recovered from the reaction mixtures.

The azido groups in **18** and **19** were reduced by hydrogen sulfide[15], and the primary amino groups were subsequently acylated by octadecanoic acid[16] to give **20** and **21** in >90% overall yield. Finally, deacylation of **20** and **21** using methanolic sodium methoxide afforded the deoxyfluorolactosylceramides **5** and **6**.

EXPERIMENTAL

General methods.—All transformations except hydrogenolyses were performed under Ar. 2,4,6-Tri-*O*-acetyl-3-deoxy-3-fluoro-α-D-galactopyranosyl bromide (**7a**) was prepared as previously described[11a]. 2,3,6-Tri-*O*-benzyl-4-deoxy-4-fluoro-α-D-galactopyranosyl bromide (**8a**) was prepared by treatment of the hemiacetal **8** (ref 11b) with oxalyl bromide and DMF[11c]. ^1H NMR spectra were recorded with a Varian XL-300 spectrometer. ^{19}F NMR spectra were recorded with external CF_3CO_2H as standard. Chemical shifts (δ, ppm) are relative to internal $CFCl_3$. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. TLC was performed on Kieselgel 60 F_{254} (Merck) with detection by UV light and/or by charring with H_2SO_4. Column chromatography was performed on Kieselgel 60 (Grace, 35–70 μm). Powdered molecular sieves were activated by heating with a flame until no more water condensed on the inside of the flask. Chloroform and CH_2Cl_2 were dried by passage through alumina (Merck, neutral, activity grade 1) immediately before use.

2-(Trimethylsilyl)ethyl 4-O-(3-deoxy-3-fluoro-β-D-galactopyranosyl)-β-D-glucopyranoside (**1**).—Compound **12** (70.0 mg, 0.1 mmol) was dissolved in dry MeOH (1 mL) and a catalytic amount of NaOMe was added. The solution was stirred at room temperature. TLC (9:1 EtOAc–MeOH and 200:150:3 $CHCl_3$–MeOH–H_2O) showed that **12** was completely consumed after 12 h. The solution was



Scheme 1.

neutralized by addition of silica, filtered (Celite), and concentrated. The residue was dissolved in water and freeze-dried to give **1** (44 mg, 99%); $[\alpha]_D^{25}$ −17° (*c* 1, H_2O); ^1H NMR (D_2O): δ 5.00 (d, 1 H, *J* 7.7 Hz, H-1′), 4.80 (ddd, 1 H, *J* 49.8, 10.0, 3.2 Hz, H-3′), 4.39 (d, 1 H, *J* 7.8 Hz, H-1), 4.00 (ddd, 1 H, *J* 10.0, 7.8, 3.3 Hz, H-2′), 1.00 (ddt, 2 H, CCH_2Si); 0.00 [s, 9 H, $Si(CH_3)_3$]; ^{19}F NMR data (D_2O): δ 220 (dd, *J* 49.5, 3 Hz, F-3′).

*4-O-(3-Deoxy-3-fluoro-β-*D*-galactopyranosyl)-*D*-glucopyranose* (**2**).—(*a*) Compound **1** (44 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and CF_3CO_2H (1 mL) was added. The mixture was stirred for 30 min at room temperature, 1:2 propyl acetate–toluene (9 mL) was added and the solution was concentrated. A second portion of toluene was added and evaporated. Column chromatography of the residue (SiO_2, 100:50:1 $CHCl_3$–MeOH–H_2O) gave **2** (33 mg, 95%).

(*b*) Compound **14** (60 mg, 0.1 mmol) was dissolved in dry MeOH (1 mL) and a catalytic amount of NaOMe was added. The solution was stirred overnight at room temperature, neutralized (SiO_2), and concentrated. Column chromatography (SiO_2, 100:50:1 $CHCl_3$–MeOH–H_2O) of the residue gave **2** (31 mg, 89%, slightly

contaminated with a faster-moving impurity according to TLC, but pure according to NMR); $[\alpha]_D^{25}$ +45° (2 h at 25°C, *c* 2, H_2O); ^1H NMR (D_2O): δ 5.10 (d, 1 H, *J* 7.8 Hz, H-1′), 4.90 (ddd, 1 H, *J* 49.8, 10.0, 3.2 Hz, H-3′), 5.60, 4.45 (2d, 1 H, *J* 3.3, 7.8 Hz, H-1α, H-1β), 4.20 (ddd, 1 H, *J* 10.0, 7.8, 3.3 Hz, H-2′); ^{19}F NMR data (D_2O): δ 220 (dd, *J* 49.5, 3 Hz, F-3′).

2-(Trimethylsilyl)ethyl 4-O-(4-deoxy-4-fluoro-β-D-galactopyranosyl)-β-D-glucopyranoside (**3**).—Compound **11** (102.0 mg, 0.10 mmol) was dissolved in AcOH (10 mL) and hydrogenolyzed (H_2, 1 atm, 50 mg Pd–C, 10%; room temperature) during 12 h. The mixture was filtered (Celite) and concentrated. Column chromatography of the residue (9:1 EtOAc–MeOH) gave **3** (43.6 mg, 98%); $[\alpha]_D^{25}$ −15° (*c* 1, H_2O); ^1H NMR (D_2O): δ 4.90 (dd, 1 H, *J* 51.1, 3.2 Hz, H-4′), 4.85 (d, 1 H, *J* 7.7 Hz, H-1′), 4.42 (d, 1 H, *J* 7.9 Hz, H-1), 3.80 (ddd, 1 H, *J* 29.1, 10.0, 3.2 Hz, H-3′), 0.95 (ddt, 2 H, CCH_2Si), 0.00 [s, 9 H, $Si(CH_3)_3$]; ^{19}F NMR data (D_2O): δ 220 (dt, *J* 51.1 and 30.1 Hz, F-4′).

4-O-(4-Deoxy-4-fluoro-β-D-galactopyranosyl)-D-glucopyranose (**4**).—(*a*) Compound **3** (44 mg, 0.10 mmol) was treated with CF_3CO_2H as described for the preparation of **2**. Column chromatography (SiO_2, 100:50:1 $CHCl_3$–MeOH–H_2O) gave **4** (33 mg, 95%).

(*b*) Compound **15** (60 mg, 0.1 mmol) was treated with methanolic NaOMe as described for **2**. Column chromatography gave **4** (32 mg, 92%); $[\alpha]_D^{25}$ +47° (2 h at 25°C, *c* 2, H_2O); ^1H NMR (D_2O): δ 5.00 (dd, 1 H, *J* 51.1, 3.4 Hz, H-4′), 4.85 (d, 1 H, *J* 7.7 Hz, H-1′), 5.51, 4.42 (2d, 1 H, *J* 3.1, 7.8 Hz, H-1α, H-1β); ^{19}F NMR (D_2O): δ 220 (dt, *J* 51.1 and 29.8 Hz, F-4′).

4-O-(3-Deoxy-3-fluoro-β-D-galactopyranosyl)-β-D-glucopyranosyl-(1 → 1)-(2S, 3R,4E)-2-N-octadecanoylsphingenine (**5**).—Compound **20** (12.5 mg, 0.01 mmol) was dissolved in MeOH (1 mL) and NaOMe (5 mg, 0.1 mmol) was added. The mixture was stirred for 12 h at room temperature, silica was added and the stirring was continued for 1 h. Filtration of the mixture (Celite), evaporation of the solvent, and column chromatography (9:1 EtOAc–MeOH) of the amorphous residue gave **5** (8.4 mg, 94%); $[\alpha]_D^{25}$ −5° (*c* 1, $CDCl_3$); ^1H NMR (CD_3OD): δ (lactose unit) 4.98 (d, 1 H, *J* 7.9 Hz, H-1′), 4.81 (ddd, 1 H, *J* 50.1, 9.9, 3.3 Hz, H-3′), 4.41 (d, 1 H, *J* 7.9 Hz, H-1); 4.00 (ddd, 1 H, *J* 10.0, 7.9, 3.5 Hz, H-2′), (ceramide unit) 5.71 (dt, 1 H, *J* 15.4, 7.6 Hz, C=CHCH_2), 5.48 (dd, 1 H *J* 15.4, 7.5 Hz, CH=C), 2.05 (m, 2 H, C=CHCH_2), 1.96 (m, 2 H, CH_2CO), 1.41–1.15 (m, 54 H, 27 CH_2), 0.87 (bt, 6 H, *J* 6.5 Hz, 2 CH_3). Anal. Calcd for $C_{48}H_{90}FO_{12}N$: C, 64.6; H 10.2. Found: C, 64.7; H, 10.3.

4-O-(4-Deoxy-4-fluoro-β-D-galactopyranosyl)-β-D-glucopyranosyl-(1 → 1)-(2S, 3R,4E)-2-N-octadecanoylsphingenine (**6**).—Treatment of compound **21** (12.6 mg, 0.01 mmol) as described for **5**, gave **6** (8.5 mg, 96%); $[\alpha]_D^{25}$ −8° (*c* 1, $CDCl_3$); ^1H NMR (CD_3OD): δ (lactose unit) 4.89 (dd, 1 H, *J* 50.8, 3.4 Hz, H-4′), 4.87 (d, 1 H, *J* 8.0 Hz, H-1′), 4.40 (d, 1 H, *J* 7.9 Hz, H-1), 3.78 (ddd, 1 H, *J* 29.7, 10.0, 3.3 Hz, H-3′), (ceramide unit) 5.70 (dt, 1 H, *J* 15.4, 7.6 Hz, C=CHCH_2), 5.48 (dd, 1 H, *J* 15.4, 7.6 Hz, CH=C), 2.05 (m, 2 H, C=CHCH_2), 1.95 (m, 2 H, CH_2CO), 1.41–1.15

(m, 54 H, 27 CH_2), 0.88 (bt, 6 H, *J* 6.5 Hz, 2 CH_3). Anal. Calcd for $C_{48}H_{90}FO_{12}N$: C, 64.6; H 10.2. Found: C, 64.6; H, 10.3.

*2-(Trimethylsilyl)ethyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**10**).—Compound **9** (ref 7, 681 mg, 1.2 mmol), silver trifluoromethanesulfonate (308 mg, 1.2 mmol), and *N,N,N′,N′*-tetramethylurea (180 μL, 1.5 mmol), were dissolved in dry CH_2Cl_2 (10 mL) and 3A molecular sieves (0.7 g) were added. The mixture was stirred at room temperature for 30 min and then cooled to −20°C. Freshly prepared 2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-α-D-galactopyranosyl bromide (**7a**)[11a] (370 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added dropwise during 15 min. The mixture was stirred overnight at room temperature. The mixture was filtered (Celite) and concentrated. Flash chromatography of the residue (1:3 EtOAc–heptane) gave **10** (630 mg, 75%); $[\alpha]_D^{25}$ −8° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): 5.50 (dd, 1 H, *J* 4.4, 3.2 Hz, H-4′), 5.30 (ddd, 1 H, *J* 10.4, 8.1, 3.1 Hz, H-2′), 5.10 (d, 1 H, *J* 8.1 Hz, H-1′), 4.90 (ddd, 1 H, *J* 50.0, 10.4, 3.2 Hz, H-3′), 4.95–4.60 (m, 6 H, C*H*Ph), 4.37 (d, 1 H, *J* 7.7 Hz, H-1), 2.12, 2.01, 1.97 (3 s, 3 H each, OAc), 1.03 (m, 2 H, CCH_2Si), 0.03 [s, 9 H, $Si(CH_3)_3$]. Anal. Calcd for $C_{44}H_{57}FO_{13}Si$: C, 62.8; H 6.8. Found: C, 62.8; H, 6.8.

*2-(Trimethylsily)ethyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-4-deoxy-4-fluoro-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**11**).—2,3,6-Tri-*O*-benzyl-4-deoxy-4-fluoro-α-D-galactopyranosyl bromide (**8a**) (prepared as described[11c] from 250 mg, 0.54 mmol of **8**, ref 11b) and **9** (ref 7, 363 mg, 0.64 mmol) were dissolved in CH_2Cl_2 (2.5 mL, distilled from CaH_2). Activated 3A molecular sieves (350 mg) were added and the system was stirred under Ar at room temperature for 1 h. Silver silicate (350 mg) was added, the mixture was protected from light, and the stirring was continued at room temperature for 5 h. The mixture was filtered and concentrated and the residue was chromatographed (SiO_2, 2:1 EtOAc–heptane) to give **11** (352 mg, 65% based on **8**); $[\alpha]_D^{25}$ +8° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.90 (dd, 1 H, *J* 51.0, 3.3 Hz, H-4′), 4.84 (d, 1 H, *J* 7.8 Hz, H-1′), 4.42 (d, 1 H, *J* 7.9 Hz, H-1), 3.70 (ddd, 1 H, *J* 29.2, 9.8, 3.4 Hz, H-3′), 1.01 (ddt, 2 H, CCH_2Si), 0.00 [s, 9 H, $Si(CH_3)_3$]. Anal. Calcd for $C_{59}H_{69}FO_{10}Si$: C, 71.9; H, 7.1. Found: C, 72.0; H, 7.1.

*2-(Trimethylsilyl)ethyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**12**).—Compound **10** (500 mg, 0.59 mmol) was dissolved in AcOH (30 mL) and hydrogenolyzed (H_2, 1 atm, 150 mg Pd–C, 10%; room temperature) during 12 h. The mixture was filtered (Celite) and concentrated. The residue was dissolved in 2:7 Ac_2O–pyridine (10 mL), and stirred overnight at room temperature. Concentration of the solution and column chromatography of the residue (1:2 EtOAc–heptane) gave **12** (403 mg, 98%); $[\alpha]_D^{25}$ −10° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): 5.70 (dd, 1 H, *J* 4.0, 3.3 Hz, H-4′), 5.30 (ddd, 1 H, *J* 10.4, 8.1, 3.1 Hz, H-2′), 5.18 (dd, 1 H, *J* 9.5, 9.1 Hz, H-3), 4.90 (ddd, 1 H, *J* 50.0, 10.4, 3.2 Hz, H-3′), 5.10 (d, 1 H, *J* 8.1 Hz, H-1′), 4.89 (dd, 1 H, *J* 9.7, 7.8 Hz, H-2), 4.50 (m, H-6 or 6′), 4.03–4.20 (m, 3 H, H-6,6′), 4.37 (d, 1 H, *J* 7.7 Hz, H-1), 2.20–2.00 (5 s, 18 H, OAc), 1.01 (m, 2 H, CCH_2Si), 0.00 [s, 9 H, $Si(CH_3)_3$]. Anal. Calcd for $C_{29}H_{45}FO_{16}Si$: C, 50.0; H 6.5. Found: C, 49.9; H, 6.5.

2-(Trimethylsilyl)ethyl 2,3,6-tri-O-acetyl-4-O-(2,3,6-tri-O-acetyl-4-deoxy-4-fluoro-β-D-galactopyranosyl)-β-D-glucopyranoside (**13**).—Compound **3** (20 mg, 0.045 mmol) was dissolved in 2:1 Ac_2O–pyridine (1 mL). The solution was stirred overnight at room temperature and then concentrated. Column chromatography of the residue (1:2 EtOAc–heptane) gave **13** (31 mg, 99%); $[\alpha]_D^{25}$ −8° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.79 (dd, 1 H, *J* 51.0, 3.1 Hz, H-4′), 5.30 (ddd, 1 H, *J* 30.0, 10.4, 3.3 Hz, H-3′), 5.25 (dd, 1 H, *J* 9.4, 9.1 Hz, H-3), 5.21 (dd, 1 H, *J* 10.3, 7.4 Hz, H-2′), 4.61 (d, 1 H, *J* 7.9 Hz, H-1′), 4.52 (m, 2 H, H-1,6), 4.12 (dd, 1 H, *J* 12.1, 5.1 Hz, H-6), 3.80–4.00 (m, 3 H, CHCSi, H-4,5′), 3.66 (m, 1 H, H-5), 3.50 (dt, 1 H, CHCSi), 3.45 (2 H, H-6′), 2.13–1.94 (4 s, 18 H, OAc), 1.02 (m, 2 H, CCH_2Si), 0.01 [s, 9 H, $Si(CH_3)_3$]. Anal. Calcd for $C_{29}H_{45}FO_{16}Si$: C, 50.0; H 6.5. Found: C, 50.0; H, 6.5.

2,3,6-Tri-O-acetyl-4-O-(2,4,6-tetra-O-acetyl-3-deoxy-3-fluoro-β-D-galactopyranosyl)-D-glucopyranose (**14**).–Compound **12** (69.7 mg, 0.10 mmol) was treated with CF_3CO_2H as described for the preparation of **2**. Column chromatography of the residue (1:1 EtOAc–heptane) gave **14** (57 mg, 95%) as an α/β mixture; ^1H NMR ($CDCl_3$): 5.60, 4.50 (2d, 1 H, *J* 3.0 and 7.7 Hz, H-1α, H-1β), 4.90 (ddd, 1 H, *J* 50.0, 10.4, 3.2 Hz, H-3′), 5.00 (d, 1 H, *J* 8.0 Hz, H-1′), 2.20–2.00 (m, 18 H, OAc). Anal. Calcd for $C_{24}H_{33}FO_{16}$: C, 48.3; H 5.6. Found: C, 48.3; H, 5.5.

2,3,6-Tri-O-acetyl-4-O-(2,3,6-tetra-O-acetyl-4-deoxy-4-fluoro-β-D-galactopyranosyl)-D-glucopyranose (**15**).—Compound **13** (69.7 mg, 0.10 mmol) was treated with CF_3CO_2H as described for the preparation of **2**. Column chromatography (1:1 EtOAc–heptane) gave **15** (55 mg, 93%) as an α/β mixture; ^1H NMR ($CDCl_3$): δ 5.10 (dd, 1 H, *J* 51.0, 3.4 Hz, H-4′), 4.90 (d, 1 H, *J* 7.7, H-1′), 5.56, 4.42 (2d, 1 H, *J* 3.4 and 7.9 Hz, H-1α, H-1β), 2.10–1.90 (m, 18 H, OAc). Anal. Calcd for $C_{24}H_{33}FO_{16}$: C, 48.3; H 5.6. Found: C, 48.1; H, 5.6.

2,3,6-Tri-O-acetyl-4-O-(2,4,6-tetra-O-acetyl-3-deoxy-3-fluoro-β-D-galactopyranosyl)-β-D-glucopyranosyl-(1 → 1)-(2S,3R,4E)-2-azido-3-O-benzoyl-4-octadecen-1,3-diol (**18**).—To a solution of compound **14** (238 mg, 0.4 mmol) in CH_2Cl_2 (4 mL) was added trichloroacetonitrile (201 μL, 2.0 mmol) and DBU (8 μL, 0.05 mmol) at 0°C. The mixture was allowed to attain room temperature. The reaction was shown to be complete after 6 h (TLC), where upon the mixture was concentrated. The residue was chromatographed (SiO_2, 1:1 EtOAc–heptane) and the α-trichloroacetimidate **16** [^1H NMR ($CDCl_3$): δ 8.50 (s, 1 H, CNH), 6.70 (d, 1 H, *J* 3.4 Hz, H-1)] was divided in two portions of equal size and treated as follows.

(*a*) To a solution of **16** (147 mg) and **22** (129 mg, 0.3 mmol) in CH_2Cl_2 (2 mL, containing 4A molecular sieves) at 0°C was added $BF_3 \cdot Et_2O$ (27 μL, 0.22 mmol). The mixture was kept for 3 h at 0°C. The mixture was diluted with CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. Column chromatography (SiO_2, 3:1 → 1:1 EtOAc–heptane) gave **18** (111 mg, 55%).

(*b*) Compound **16** (147 mg), **22** (129 mg, 0.3 mmol), and silver triflate (57 mg, 0.22 mmol) in a dark, round-bottomed flask was dried on a vacuum pump overnight. The flask was filled with Ar and CH_2Cl_2 (2 mL) was added at room temperature. The reaction was allowed to proceed for 18 h, then the mixture was

treated as for (*a*) to give **18** (131 mg, 65%); $[\alpha]_D^{25}$ −7° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: (lactose unit) 5.69 (dd, 1 H, *J* 4.0, 3.3 Hz, H-4′), 5.32 (ddd, 1 H, *J* 10.3, 8.0, 3.2 Hz, H-2′), 5.20 (dd, 1 H, *J* 9.9, 9.2 Hz, H-3); 4.87 (ddd, 1 H, *J* 50.0, 10.3, 3.2 Hz, H-3′), 5.07 (d, 1 H, *J* 7.9 Hz, H-1′); 4.89 (dd, 1 H, *J* 9.8, 7.8, Hz, H-2), 4.50 (m, H-6 or 6′), 4.05–4.18 (m, 3 H, H-6,6′), 4.35 (d, 1 H, *J* 7.8 Hz, H-1), 2.18–2.00 (5 s, 18 H, OAc); (azidosphingosine unit) 5.80 (dt, 1 H, *J* 15.3, 7.6 Hz, H-5), 5.60 (dd, 1 H, *J* 7.8, 4.8 Hz, H-3); 5.41 (dd, 1 H, *J* 15.3, 7.6 Hz, H-4), 3.90 (m, CHN_3) 2.04 (bd, 2 H, *J* 7.5 Hz, H-6), 1.35–1.15 (m, 22 H, CH_2), 0.85 (t, 3 H, *J* 6.5 Hz, CH_3). Anal. Calcd for $C_{49}H_{70}FN_3O_{18}$: C, 58.4; H 7.0. Found: C, 58.3; H, 6.9.

*2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-β-*D*-galactopyranosyl)-β-*D*-glucopyranosyl-(1 → 1)-(2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecen-1,3-diol* (**19**).–Compound **15** (214 mg, 0.36 mmol) was treated as for **14** to give the α-trichloroacetimidate **17** [^1H NMR ($CDCl_3$): δ 8.60 (s, 1 H, CNH); 6.60 (d, 1 H, *J* 3.4 Hz, H-1)], and then **19** (91 mg, 50% yield according to procedure *a*, and 109 mg, 60% yield according to procedure *b*); $[\alpha]_D^{25}$ −5° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (lactose unit) 5.79 (dd, 1 H, *J* 51.0, 3.3 Hz, H-4′), 5.31 (ddd, 1 H, *J* 30.1, 10.4, 3.3 Hz, H-3′), 5.26 (dd, 1 H, *J* 9.4, 9.0 Hz, H-3), 5.20 (dd, 1 H, *J* 10.3, 7.7 Hz, H-2′), 4.62 (d, 1 H, *J* 7.8 Hz, H-1′), 4.49 (m, 2 H, H-1,6), 4.13 (dd, 1 H, *J* 12.0, 5.2 Hz, H-6), 3.79–3.97 (m, 3 H, H-4,5′), 3.64 (m, 1 H, H-5), 3.42 (2 H, H-6′), 2.08–1.95 (5 s, 18 H, OAc), (azidosphingosine unit) 5.79 (dt, 1 H, *J* 15.4, 7.6 Hz, H-5), 5.61 (dd, 1 H, *J* 7.8, 4.8 Hz, H-3), 5.41 (dd, 1 H, *J* 15.3, 7.6 Hz, H-4), 3.90 (m, CHN_3), 2.01 (m, 2 H, H-6), 1.35–1.15 (m, 22 H, 11 CH_2), 0.87 (t, 3 H, *J* 6.5 Hz, CH_3). Anal. Calcd for $C_{49}H_{70}FN_3O_{18}$: C, 58.4; H 7.0. Found: C, 58.5; H, 7.0.

*2,3,6-Tri-*O*-acetyl-4-*O*-(2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro-β-*D*-galactopyranosyl)-β-*D*-glucopyranosyl-(1 → 1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-*N*-octadecanoylsphingenine* (**20**).—Hydrogen sulfide was bubbled through a solution of **18** (50 mg, 0.05 mmol) in 10:1 pyridine–Et_3N (10 mL)[15] for 2 h. The flask was sealed and the solution was stirred for 24 h. Argon was bubbled through the solution to remove H_2S. The solvent was removed and the residue (which was used in the subsequent step without further purification) was dissolved in CH_2Cl_2 (5 mL). Octadecanoic acid (28 mg, 0.1 mmol) and 1-ethyl-3-(3-dimethylaminoisopropyl)carbodiimide hydrochloride (EDC, 29 mg, 0.15 mmol) was added[16] and the mixture was stirred at room temperature for 18 h, then CH_2Cl_2 (15 mL) was added, the solution was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (SiO_2, 70:1 CH_2Cl_2–MeOH) to give **20** (59 mg, 95%) ^1H NMR ($CDCl_3$) δ: (lactose unit) 5.80 (dd, 1 H, *J* 51.0, 3.2 Hz, H-4′), 5.30 (ddd, 1 H, *J* 30.0, 10.4, 3.3 Hz, H-3′), 5.27 (dd, 1 H, *J* 9.4, 9.0 Hz, H-3), 5.19 (dd, 1 H, *J* 10.3, 7.6 Hz, H-2′), 4.62 (d, 1 H, *J* 7.8 Hz, H-1′), 4.49 (m, 2 H, H-1,6), 4.13 (dd, 1 H, *J* 12.0, 5.2 Hz, H-6), 3.79–3.99 (m, 3 H, H-4,5′), 3.64 (m, 1 H, H-5), 3.42 (2 H, H-6′), 2.10–1.95 (4 s, 18 H, OAc), (ceramide unit) 5.68 (dt, 1 H, *J* 15.3, 7.6 Hz, C=C*H*CH_2), 5.58 (dd, 1 H, *J* 7.8, 4.8 Hz, CHOBz), 5.48 (dd, 1 H, *J* 15.3, 7.6 Hz, CH=C), 2.01 (m, 4 H, H-6, CH_2CO), 1.40–1.15 (m, 54 H, CH_2), 0.86 (bt, 6 H, *J* 6.5 Hz, CH_3). Anal. Calcd for $C_{67}H_{106}FNO_{19}$: C, 64.5; H 8.6. Found: C, 64.4; H, 8.6.

2,3,6-Tri-O-acetyl-4-O-(2,3,6-tri-O-acetyl-4-deoxy-4-fluoro-β-D-galactopyranosyl)-β-D-glucopyranosyl-(1 → 1)-(2S,3R,4E)-3-O-benzoyl-2-N-octadecanoylsphingenine **(21).**—Compound **19** (50 mg, 0.05 mmol) was reduced with H_2S and treated with octadecanoic acid–EDC as for **18** to give **21** (58 mg, 91%); $[\alpha]_D^{25}$ −7° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: (lactose unit) 5.79 (dd, 1 H, *J* 51.0, 3.1 Hz, H-4′), 5.30 (ddd, 1 H, *J* 30.0, 10.4, 3.3 Hz, H-3′), 5.25 (dd, 1 H, *J* 9.4, 9.1 Hz, H-3), 5.21 (dd, 1 H, *J* 10.3, 7.4 Hz, H-2′), 4.61 (d, 1 H, *J* 7.9 Hz, H-1′), 4.52 (m, 2 H, H-1,6), 4.12 (dd, 1 H, *J* 12.1, 5.1 Hz, H-6), 3.80–4.00 (m, 3 H, H-4,5′), 3.66 (m, 1 H, H-5), 3.45 (2 H, H-6′), 2.13–1.94 (4 s, 18 H, OAc), (ceramide unit) 5.67 (dt, 1 H, *J* 15.3, 7.6 Hz, C=C*H*CH_2), 5.58 (dd, 1 H, *J* 7.7, 4.8 Hz, CHOBz), 5.48 (dd, 1 H, *J* 15.4, 7.6 Hz, CH=C), 2.01 (m, 4 H, C=CHCH_2, CH_2CO), 1.41–1.15 (m, 54 H, 27 CH_2), 0.86 (bt, 6 H, *J* 6.5 Hz, CH_3). Anal. Calcd for $C_{67}H_{106}FNO_{19}$: C, 64.5; H 8.6. Found: C, 64.4; H, 8.5.

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