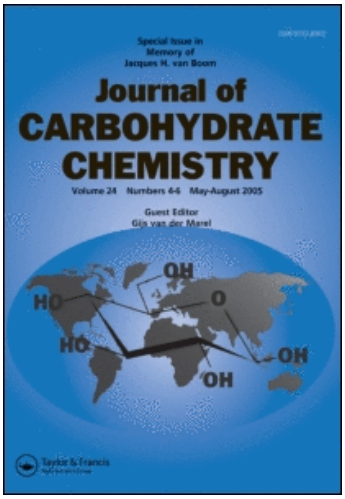

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AN EFFICIENT APPROACH TO THE SYNTHESIS OF LACTO-*N*-TRIOSYLCERAMIDE AND RELATED SUBSTANCES[1]

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ABSTRACT

Hexatriosyl fluorides **3** and **4** were prepared from the known trisaccharides **8** and **13**, respectively. These compounds were reacted with the sphingosine derivative **2** to afford coupled products **22** and **25** which, in turn, were converted into the protected glycosphingolipids **23** and **26** after reduction and acylation. Compound **2** was found to be a better substrate than the protected ceramide **1**, which had been used previously. Compound **23** was transformed into the lacto-*N*-triosylceramide **24**.

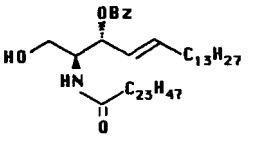
INTRODUCTION

Glycosphingolipids play important roles in cellular regulation such as cell growth, cell adhesion and cell recognition.[2] In addition, it has been shown that the change in their composition is related to differentiation and oncogenesis of cells.[2a,3] In spite of such potential biological importance, most glycosphingolipids exist as very minor cellular components and are quite difficult to obtain in a sufficient quantity to pursue detailed biological study. Hence, development of an efficient and widely applicable method for the synthesis of these molecules is of great importance. Toward this end, we have reported

several total syntheses of glycosphingolipids.[4] In all of these syntheses, the connection of the glycan chain with the ceramide, a hydrophobic part of the glycosphingolipids, was achieved at the final stage by use of monobenzoate **1** as a glycosyl acceptor. However, the efficiency of this crucial operation is quite dependent upon the structure of the glycan chain and the yield is modest at best. Considering the diversity of glycosphingolipids, a reliable solution for this problem is highly desirable.

RESULTS AND DISCUSSION

Glycan chains of most glycosphingolipids are linked to ceramide at the glucose residue having β-D-configuration. Glycosidic linkages of this type are most often constructed by utilizing the 1,2-trans directing nature of C-2 acetoxy group.[5] A major drawback of this method is the concomitant production of an orthoester, particularly for sizable substrates. The low yields we encountered previously can be rationalized as arising from the predominant formation of orthoesters which are presumed to be unstable under the reaction conditions or the aqueous work up. Recently we focused our attention on the azide **2**, introduced by Schmidt and Zimmermann[6] as a glycosyl acceptor in which the steric hindrance around the primary hydroxyl group is expected to be reduced considerably when compared to **1**. Because the



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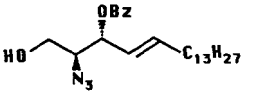

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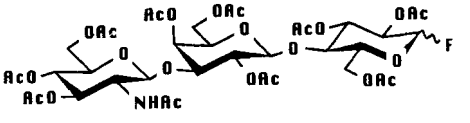

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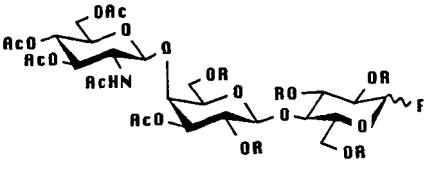
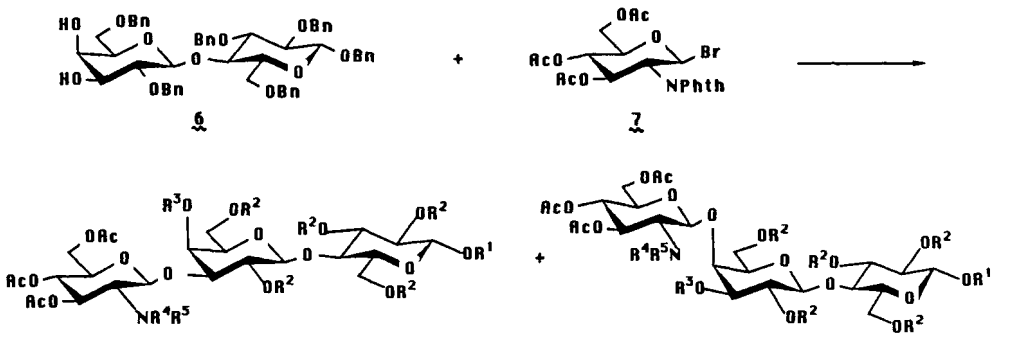


4 : R = Bz

5 : R = Ac

coupling of lactose with ceramide had been achieved in good yield without any difficulty,[4g] oligosaccharides with at least three sugar residues could be examined as model compounds. Trisaccharides **3** and **4** were chosen as glycosyl donors. We already had observed that trisaccharides with these sequences are particularly sluggish substrates and the reactions of **3**, **5** or the corresponding trichloroacetimidates with **1** did not give more than trace amounts of coupled products.[7]

Fluorides **3** and **4** were synthesized from trisaccharides **8** and **13**[4g,8] respectively, which in turn were derived from the lactose derivative **6**[9] and bromide **7**[10] (Scheme 1). Although the synthesis of **8** and **13** has been reported previously, the regioselectivity of the glycosylation reaction deserves comment. Thus, in nonpolar solvents such as 1,2-dichloroethane or toluene almost equal amounts of **8** and **13** were obtained while **8** was obtained as the major product when the reaction was performed in nitromethane (**8**:**13** = 3.1:1) at low temperature. Dephthaloylation of these compounds was performed under reductive conditions according to Ganem's procedure[11] which was originally reported for the deprotection of amino acid derivatives. After acetylation, acetamides **9** and **14** were obtained in high overall yields. Considering the high efficiency, relatively mild reaction conditions and



8 : $R^1 = R^2 = Bn$, $R^3 = H$, $R^4R^5 = Phth$
9 : $R^1 = R^2 = Bn$, $R^3 = R^4 = Ac$, $R^5 = H$
10 : $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = Ac$
11 : $R^1 = R^2 = R^3 = R^4 = Ac$, $R^5 = H$
12 : $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = Ac$

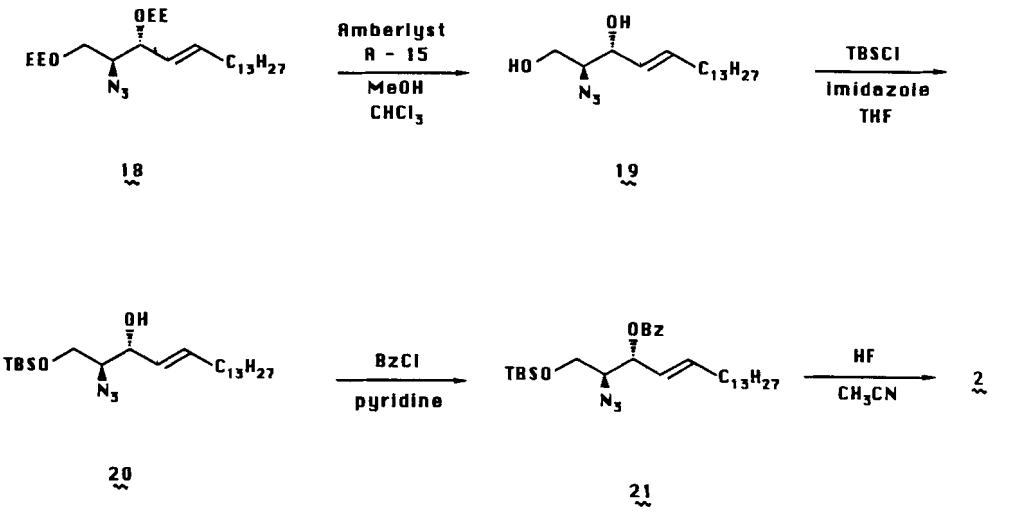
13 : $R^1 = R^2 = Bn$, $R^3 = H$, $R^4R^5 = Phth$
14 : $R^1 = R^2 = Bn$, $R^3 = R^4 = Ac$, $R^5 = H$
15 : $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = Ac$
16 : $R^1 = R^2 = Bz$, $R^3 = R^4 = Ac$, $R^5 = H$
17 : $R^1 = R^5 = H$, $R^2 = Bz$, $R^3 = R^4 = Ac$

Scheme 1

operational simplicity, this procedure should be an attractive alternative to the hydrazine method which has been employed conventionally. After removal of benzyl groups, polyols **10** and **15** were converted to the peracetate **11** and hexabenzoate **16**, respectively. These were treated with hydrazine acetate[12] to give hemiacetals **12** and **17**. Although the efficiency was not particularly high, the anomeric benzoyl group could also be removed selectively. Further treatment with DAST (diethylaminosulfur trifluoride)[13] gave fluorides **3** (α:β = 1:3) and **4** (α:β = 1:2.7).

The azide **2** was prepared from the known diethoxyethyl derivative **18**[14] via **19**, **20** and **21** in 64% overall yield as shown below (Scheme 2).

Reactions of fluorides **3** and **4** with **2** were performed in the presence of silver or trityl salts and tin(II) chloride[15] in 1,2-dichloroethane as a solvent and the results are summarized in Table **1**. In every case except entry 4, the coupled product **22** or **25** was obtained reproducibly. This is in contrast to the combinations examined before,[7] namely **1** with **3** or **5**. Although the effect of the counterion was negligible for peracetate **3**, silver triflate was much better than other silver salts when the pentabenzoate **4** was used as a glycosyl donor. The α-anomer of **4** was almost inert and was recovered

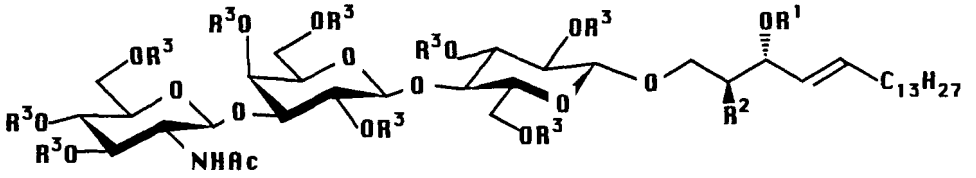


18 19 20 21

Scheme 2

unchanged. The azide group in **22** and **25** was reduced by Lindlar catalyst[16] and acylated under Mukaiyama's conditions[17] to give the fully protected hexatriosyl ceramides **23** and **26**. Deprotection of **23** afforded lacto-*N*-triosylceramide (LcOse3Cer) **24**.[18]

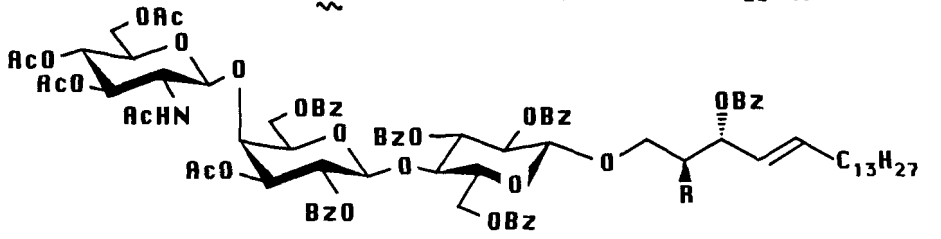
Although **3** and **4** are regioisomeric with respect to glycan chains, it may well be concluded that under appropriate reaction conditions a benzoyl group is more advantageous than an acetyl group for 1,2-trans glycoside synthesis using glycosyl donors derived from complex oligosaccharides. The optimum combination, i.e., the benzoyl protected β-fluoride 4β and silver triflate/tin(II) chloride was applied to the protected ceramide **1**. The reaction was performed in chloroform to give the coupled product **26** in a 44% yield.



22 : R^1 = Bz, R^2 = N_3, R^3 = Ac

23 : R^1 = Bz, R^2 = $NHCOC_{23}H_{47}$, R^3 = Ac

24 : R^1 = R^3 = H, R^2 = $NHCOC_{23}H_{47}$



25 : R = N_3

26 : R = $NHCOC_{23}H_{47}$

The results described above demonstrate that the connection between a glycan chain and ceramide can be achieved in better yield by proper modification of substrates and reaction conditions. Further refinement of the overall efficiency is under current investigation.

Table 1. Results of coupling reactions.

entry	fluoride	acceptor	promoter	product	yield (%)
1	3	2	$AgClO_4$	22	27
2	3	2	AgOTf	22	30
3	3	2	$AgBF_4$	22	24
4	3	2	Ag Silicate	--	--
5	3	2	TrOTf[19]	22	19
6	4a)	2	$AgClO_4$	25	25c)
7	4b)	2	AgOTf	25	75
8	4b)	2	$AgBF_4$	25	36
9	4a)	2	TrOTf	25	16c)
10	4b)	1	AgOTf	26	44

a) A mixture of α- and β-anomers was used.
b) Pure β-anomer was used.
c) Yields were based on consumed **4**.

EXPERIMENTAL

General Procedures. Optical rotations were determined with a Perkin-Elmer Model 241 MC polarimeter, for solutions in $CHCl_3$ at 20-22 °C, unless noted otherwise. Column chromatography was performed using Wako gel C-300 (200-300 mesh). Analytical TLC was performed on Silica Gel $60F_{254}$ (Merck, Darmstadt). Preparative TLC was performed by using 20 cm x 20 cm plates coated with 0.5 mm thickness of silica gel containing PF_{254} indicator (Merck, Darmstadt). ^1H NMR spectra were measured on either a JNM-GX400 or a JNM-FX90Q instrument, in solutions of $CDCl_3$, unless noted otherwise. The values of δ are expressed in ppm downfield from the signal for internal Me_4Si. All reactions except hydrogenation were performed under atmospheres of dry nitrogen or argon. 1,2-Dichloroethane, pyridine and DMF were distilled from CaH_2. Toluene and THF were distilled from sodium benzophenone ketyl. 1,2-Dimethoxyethane was distilled from $LiAlH_4$. Chloroform was passed through a column of alumina and distilled from

P_2O_5. Imidazole was recrystallized from benzene. All other solvents and reagents were used as received.

Benzyl O-(3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-O-(2,6-di-O-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (8) and **Benzyl O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-O-(2,6-di-O-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (13).** (A) To a mixture of 2,4,6-collidine (0.60 mL, 4.5 mmol), compounds **6** (2.00 g, 2.26 mmol) and **7** (1.80 g, 3.61 mmol) and powdered molecular sieves (4A) (10 g) in nitromethane (50 mL) was added a solution of $AgOSO_2CF_3$ (1.17 g, 4.55 mmol) in nitromethane at -23 °C. After stirring for 3 h at -23 °C, the mixture was filtered through Celite and the filtrate was diluted with ether (150 mL). The solution was washed with water (100 mL) and the aqueous layer was extracted with ether (100 mL). The combined organic layers were washed successively with aq $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 3:2 n-hexane-ethyl acetate afforded **8** (2.11 g, 72%) and **13** (0.682 g, 23%).[4g,8] (B) To a mixture of $AgOSO_2CF_3$ (45 mg, 0.12 mmol), 2,4,6-collidine (20 μl, 0.15 mmol) and powdered molecular sieves (4A) (250 mg) in toluene (1 mL) was added a solution of compounds **6** (68.1 mg, 0.0771 mmol) and **7** (50.2 mg, 0.102 mmol) in toluene (3 mL) at -40 °C. The mixture was stirred at -40 to 10 °C for 18 h. Work-up and chromatographic separation afforded **8** (37.6 mg, 38%) and **13** (48.7 mg, 49%).

Benzyl O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-O-(4-O-acetyl-2,6-di-O-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (9). To a solution of compound **8** (426 mg, 0.328 mmol) in 5:1 2-propanol-H_2O (12 mL) was added $NaBH_4$ (250 mg, 6.61 mmol) and the mixture was stirred for 20 h at room temperature. Acetic acid (5 mL) was added to the mixture carefully. The mixture was stirred at 100 °C for 3 h. After evaporation *in vacuo*, the residue was coevaporated *in vacuo* with methanol (50 mL x 3) and toluene (50 mL), successively. To a suspension of the residue in methylene chloride (20 mL) were added pyridine (0.5 mL), 4-dimethylaminopyridine (5 mg) and acetic anhydride (0.5 mL) and the mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with ethyl acetate (50

mL), washed with water (30 mL) and brine (30 mL) successively, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 2:1 ethyl acetate-n-hexane afforded **9** (325 mg, 79%); $[\alpha]_D$ -3.1° (c 1.2); Rf 0.37 in 2:1 ethyl acetate-n-hexane; ^1H NMR (400 MHz) δ 5.412 (d, 1 H, $J_{3b,4b}$=3.2 Hz, H-4b), 4.727 (d, 1 H, $J_{1c,2c}$=8.3 Hz, H-1c), 4.486 (d, 1 H, J=7.6 Hz, H-1a or H-1b), 4.451 (d, 1 H, J=7.8 Hz, H-1b or H-1a), 2.065 (s, 3 H, Ac), 2.038 (s, 3 H, Ac), 2.018 (s, 3 H, Ac), 1.971 (s, 3 H, Ac) and 1.510 (s, 3 H, Ac).

Anal. Calc. for $C_{70}H_{79}NO_{20}$: C, 67.03; H, 6.35; N, 1.12. Found: C, 67.07; H, 6.45; N, 1.18.

Benzyl O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (14). Compound **13** (842 mg, 0.647 mmol) was treated as described for the preparation of compound **9** to give **14** (763 mg, 94%); $[\alpha]_D$ +12.1° (c 1.2); Rf 0.38 in 2:1 ethyl acetate-n-hexane; ^1H NMR (400 MHz) δ 4.935 (d, 1 H, $J_{1c,2c}$=8.2 Hz, H-1c), 4.866 (dd, 1 H, $J_{2b,3b}$=10.4 Hz, $J_{3b,4b}$=2.8 Hz, H-3b), 4.118 (d, 1 H, H-4b), 2.106 (s, 3 H, Ac), 2.050 (s, 3 H, Ac), 2.013 (s, 3 H, Ac), 1.998 (s, 3 H, Ac) and 1.792 (s, 3 H, Ac).

Anal. Calc. for $C_{70}H_{79}NO_{20}$: C, 67.03; H, 6.35; N, 1.12. Found; C, 66.56; H, 6.33; N, 1.12.

O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-O-(2,4,6-tri-O-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-D-glucopyranosyl acetate (11). A mixture of compound **9** (325 mg, 0.259 mmol), formic acid (2 mL) and 10% Pd-C (200 mg) in methanol (20 mL) was stirred for 3 h at 50 °C and then filtered through Celite. The filtrate was evaporated *in vacuo* to afford crude **10** which was dissolved in methanol (10 mL). To the solution was added potassium carbonate (200 mg, 1.45 mmol) and the mixture was stirred for 2 h at room temperature. The resulting mixture was acidified by acetic acid (1 mL) and evaporated *in vacuo*. To the residue were added pyridine (5 mL), acetic anhydride (2 mL) and 4-dimethylaminopyridine (10 mg). The mixture was stirred for 3 h at room temperature and then evaporated *in vacuo*. The residue was diluted with ethyl acetate (5 mL), washed with water (30 mL) and brine (30 mL) successively, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 4:1 methylene chloride-acetone afforded **11** as an 1:1 mixture of α and β anomers (237 mg,

95%); Rf 0.63 in 2:1 methylene chloride-acetone; ^{1}H NMR (400 MHz) δ 6.256 (d, 0.5 H, $J_{1a,2a}$=3.7 Hz, H-1aα) and 5.664 (d, 0.5 H, $J_{1a,2a}$=8.2 Hz, H-1aβ).

Anal. Calc. for $C_{40}H_{55}NO_{26}$: C, 49.74; H, 5.74; N, 1.45. Found: C, 49.78; H, 5.80; N, 1.45.

O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzoyl-D-glucopyranosyl benzoate (16). A mixture of compound **14** (574 mg, 0.465 mmol) and 10% Pd-C (600 mg) in methanol (10 mL) was stirred under hydrogen for 4 h at 45 °C. The mixture was filtered through Celite and the filtrate was evaporated *in vacuo* to afford crude **15** which was dissolved in pyridine (10 mL). To the solution were added benzoyl chloride (0.5 mL, 4.3 mmol) and 4-dimethylaminopyridine (60 mg, 0.49 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and at room temperature for 4.5 h. To the mixture were added ethyl acetate (50 mL) and aq $NaHCO_3$ (30 mL) and the mixture was stirred vigorously for 10 min at room temperature. Layers of the mixture were separated and the organic layer was washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 1:1 toluene-ethyl acetate afforded **16** as an 1:1 mixture of α and β anomers (511 mg, 82%); Rf 0.35 and 0.31 in 3:2 ethyl acetate-toluene; ^{1}H NMR (400 MHz) δ 6.709 (d, 0.5 H, $J_{1a,2a}$=3.7 Hz, H-1aα), 6.101 (d, 0.5 H, $J_{1a,2a}$=8.1 Hz, H-1aβ), 5.748 (dd, 0.5 H, $J_{2a,3a}$=9.5 Hz, H-2aβ), 5.565 (dd, 0.5 H, $J_{2a,3a}$=10.3 Hz, H-2aα), 5.118 and 5.111 (d, 1 H, $J_{1c,2c}$=8.1 Hz, H-1c), 4.748 and 4.681 (d, 1 H, $J_{1b,2b}$=8.1 and 7.8 Hz, H-1b), 4.017 (d, 1 H, $J_{3b,4b}$=2.4 Hz, H-4b).

Anal. Calc. for $C_{70}H_{67}NO_{26}$•H_2O; C, 61.99; H, 5.12; N, 1.03. Found: C, 62.18; H, 5.09; N, 1.01.

O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-O-(2,4,6-tri-O-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-D-glucopyranose (12). To a solution of compound **11** (370 mg, 0.383 mmol) in DMF (5 mL) was added hydrazine acetate (53 mg, 0.57 mmol) and the mixture was stirred for 10 min at 50 °C. The mixture was diluted with ethyl acetate (30 mL) and washed with water (30 mL). The aqueous layer was extracted with ethyl acetate (20 mL x 2) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 3:1 methylene

chloride-acetone afforded **12** (295 mg, 83%); Rf 0.36 in 2:1 methylene chloride-acetone; ^{1}H NMR (90 MHz) δ 1.8-2.2 (m, 30 H, 10 Ac).

Anal. Calc. for $C_{38}H_{53}NO_{25}$: C, 49.37; H, 5.84; N, 1.52. Found: C, 49.22; H, 5.79; N, 1.53.

O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzoyl-D-glucopyranose (17). A mixture of compound **16** (462 mg, 0.345 mmol) and hydrazine acetate (48 mg, 0.52 mmol) in DMF (10 mL) was stirred for 30 min at 50 °C. The mixture was diluted with ethyl acetate (100 mL) and washed with water. The aqueous layer was extracted with ethyl acetate (50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 4:1 carbon tetrachloride-acetone afforded recovered **16** (150 mg, 32%) and **17** (197 mg, 46%, 68% based on consumed **16**) as a 4:1 mixture of α and β anomers; Rf 0.26 in 2:1 carbon tetrachloride-acetone; ^{1}H NMR (400 MHz) δ 5.609 (d, 0.8 H, $J_{1a,2a}$=3.4 Hz, H-1aα), 5.467 (dd, 1 H, $J_{1b,2b}$=7.8 Hz, $J_{2b,3b}$=10.3 H, H-2b), 5.227 (d, 0.8 H, $J_{2a,3a}$=10.3 Hz, H-2aα), 5.127 (d, 1 H, $J_{1c,2c}$=8.3 Hz, H-1c), 4.980 (dd, 1 H, $J_{3b,4b}$=2.6 Hz, H-3b), 4.732 (d, 0.8 H, H-1bα), 4.703 (d, 0.2 H, H-1bβ) and 4.014 (d, 1 H, H-4b).

Anal. Calc. for $C_{63}H_{63}NO_{25}$•H_2O: C, 60.42; H, 5.23; N, 1.12. Found: C, 60.66; H, 5.20; N, 1.15.

O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-O-(2,4,6-tri-O-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-D-glucopyranosyl fluoride (3). To the solution of compound **12** (125 mg, 0.135 mmol) in 1,2-dimethoxyethane (3 mL) was added diethylaminosulfur trifluoride (80 μl, 0.66 mmol) at -15 °C and the mixture was stirred for 1 h at -15 to 0 °C. The mixture was poured into a stirred mixture of ethyl acetate (30 mL) and ice-water (30 mL). Layers were separated and the aqueous layer was extracted wtih ethyl acetate (30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 3:1 methylene chloride-acetone afforded recovered **12** (30.7 mg, 25%) and **3** (87.4 mg, 70%, 93% based on consumed **12**) as a 1:3 mixture of α and β anomers; Rf 0.26 in 3:1 methylene chloride-acetone; ^{1}H NMR (400 MHz) δ 5.640 (dd, 0.25 H, $J_{1a,F}$= 54.0 Hz, $J_{1a,2a}$=3.5 Hz, H-1aα), 5.364 (dd, 0.75 H,

$J_{1a,F}$=52.5 Hz, $J_{1a,2a}$=5.6 Hz, H-1aβ), 5.342 (d, 1 H, $J_{3b,4b}$=2.6 Hz, H-4b), 4.526 (dd, 1 H, $J_{2b,3b}$=9.8 Hz, H-3b), 4.411 (d, 1 H, $J_{1b,2b}$=8.1 Hz, H-1b), 3.943 (dd, 1 H, J=9.3 and 8.8 Hz, H-4a).

Anal. Calc. for $C_{38}H_{52}FNO_{24}$: C, 49.30; H, 5.66; N, 1.51. Found: C, 48.90; H, 5.63; N, 1.55.

O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzoyl-D-glucopyranosyl fluoride (4). To a solution of compound **17** (185 mg, 0.150 mmol) in THF (2 mL) was added diethylaminosulfur trifluoride (100 μl, 0.82 mmol) at 0 °C and the mixture was stirred for 1 h at 0 °C. After work-up as described for the preparation of compound **3**, chromatography on silica gel in 3:1 carbon tetrachloride-acetone afforded recovered **17** (72.1 mg, 39%) and **4** (92.0 mg, 50%, 82% based on consumed **17**). 65.0 Mg of **4** was further purified by preparative TLC in 3:1 carbon tetrachloride-acetone to afford 17.2 mg of **4α** and 45.7 mg of **4β** (**4α**:**4β**= 1:2.7).

Compound **4α**: $[\alpha]_D$ +51.3° (c 0.8); Rf 0.37 in 2:1 carbon tetrachloride-acetone; ^1H NMR (400 MHz) δ 5.883 (dd, 1 H, $J_{1a,F}$=52.5 Hz, $J_{1a,2a}$=3.4 Hz, H-1a), 5.468 (dd, 1 H, $J_{1b,2b}$=7.8 Hz, $J_{2b,3b}$=10.5 Hz, H-2b), 5.307 (ddd, 1 H, $J_{2a,F}$=24.0 Hz, $J_{2a,3a}$=9.7 Hz, H-2a), 5.121 (d, 1 H, $J_{1c,2c}$= 8.1 Hz, H-1c), 4.975 (dd, 1 H, $J_{3b,4b}$=2.6 Hz, H-3b), 4.710 (d, 1 H, H-1b), 4.018 (d, 1 H, H-4b), 2.443 (ddd, 1 H, J=10.5, 8.1 and 6.8 Hz, H-2c), 2.080 (s, 3 H, Ac), 2.005 (s, 3 H, Ac), 1.984 (s, 3 H, Ac), 1.981 (s, 3 H, Ac) and 1.976 (s, 3 H, Ac).

Anal. Calc. for $C_{63}H_{62}FNO_{25}$•0.5 H_2O; C, 60.77; H, 5.10; N, 1.13. Found: C, 60.78; H, 5.09; N, 1.17.

Compound **4β**: $[\alpha]_D$ +32.2° (c 1.0); Rf 0.33 in 2:1 carbon tetrachloride-acetone; ^1H NMR (400 MHz) δ 5.563 (dd, 1 H, $J_{1a,F}$=52.0 Hz, $J_{1a,2a}$=5.1 Hz, H-1a), 5.124 (d, 1 H, $J_{1c,2c}$=8.1 Hz, H-1c), 4.980 (dd, 1 H, $J_{2b,3b}$=10.4 Hz, $J_{3b,4b}$=2.6 Hz, H-3b), 4.730 (d, 1 H, $J_{1b,2b}$=8.1 Hz, H-1b), 4.025 (d, 1 H, H-4b), 2.587 (ddd, 1 H, J=9.0, 8.1 and 6.8 Hz, H-2c), 2.070 (s, 3 H, Ac), 2.006 (s, 3 H, Ac), 1.986 (s, 6 H, 2Ac) and 1.977 (s, 3 H, Ac).

Anal. Calc. for $C_{63}H_{62}FNO_{24}$•0.5 H_2O: C, 60.77; H, 5.10; N, 1.13. Found: C, 60.74; H, 5.16; N, 1.15.

2-Azido-1,3-dihydroxy-4-E-D-*erythro*-octadec-4-ene (19). A mixture of compound **18** (203 mg, 0.433 mmol) and Amberlyst 15 resin in 1:1 chloroform-methanol (3 mL) was stirred for 3 h at room

temperature. The mixture was filtered and the filtrate was evaporated *in vacuo*. Chromatography of the residue on silica gel in 2:1 n-hexane-ethyl acetate afforded **19** (104 mg, 74%); $[\alpha]_D$ -34.1° (c 1.1); Rf 0.22 in 3:1 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 5.821 (dt, 1 H, $J_{4,5}$=15.4 Hz, $J_{5,6}$=$J_{5,6'}$=6.7 Hz, H-5), 5.537 (dd, 1 H, $J_{3,4}$=7.3 Hz, H-4), 4.251 (dd, 1 H, $J_{2,3}$=5.2 Hz, H-3), 3.80 (m, 2 H, H-1,1'), 3.509 (m, 1 H, H-2), 2.071 (m, 2 H, H-6,6') and 0.881 (t, 3 H, J_{CH_3,CH_2}=6.9 Hz, CH_3CH_2-).

Anal. Calc for $C_{18}H_{35}N_3O_2$: C, 66.42; H, 10.84; N, 12.91. Found: C, 66.51; H, 11.00; N, 12.29.

2-Azido-1-(t-butyldimethylsilyloxy)-3-hydroxy-4-E-D-*erythro*-octadec-4-ene (20). To a solution of compound **19** (334 mg, 1.03 mmol) and imidazole (210 mg, 3.08 mmol) in THF (5 mL) was added t-butyldimethylsilyl chloride (230 mg, 1.53 mmol) at 0°C. After standing at 0 to 4 °C for 18 h, the mixture was diluted with ether (50 mL) and washed with water (30 mL). The aqueous layer was extracted with ether (50 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 10:1 n-hexane-ethyl acetate afforded **20** (442 mg, 98%); $[\alpha]_D$ -1.5° (c 1.0); Rf 0.61 in 4:1 n-hexane-ethyl acetate; ^1H NMR (90 MHz) δ 5.80 (dt, 1 H, $J_{4,5}$=15.4 Hz, $J_{5,6}$=$J_{5,6'}$=6.4 Hz, H-5), 5.47 (dd, 1 H, $J_{3,4}$=6.5 Hz, H-4), 4.21 (m, 1 H, H-3), 3.80 (m, 2 H, H-1,1'), 3.42 (m, 1 H, H-2), 2.32 (d, 1 H, J=5.1 Hz, OH), 2.07 (m, 2 H, H-6,6'), 0.91 [s, 9 H, $(CH_3)_3C$-] and 0.10 [s, 6 H, $(CH_3)_2Si(O-)$-].

Anal. Calc. for $C_{24}H_{49}N_3O_2Si$: C, 65.55; H, 11.23; N, 9.56. Found: C, 65.60; H, 11.19; N, 9.30.

2-Azido-3-(benzoyloxy)-1-(t-butyldimethylsilyloxy)-4-E-D-*erythro*-octadec-4-ene (21). To a solution of compound **20** (416 mg, 0.946 mmol) and 4-dimethylaminopyridine (12 mg, 0.098 mmol) in pyridine (5 mL) was added benzoyl chloride (0.17 mL, 1.4 mmol) at 0 °C and the mixture was stirred for 3 h at room temperature. To the mixture were added ether (50 mL) and aq $NaHCO_3$ (20 mL). After stirring at room temperature for 10 min, layers of the mixture were separated and the organic layer was washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 20:1 n-hexane-ethyl acetate afforded **21** (476 mg, 93%); $[\alpha]_D$ -24.9° (c 1.0); Rf 0.73 in 5:1 n-hexane-ethyl acetate; ^1H NMR (90 MHz) δ 5.4-6.1 (m, 3 H, H-3,4,5), 3.6-3.9 (m, 3 H, H-1,1',2), 2.01 (m, 2 H, H-6), 0.91 [s, 9 H, $(CH_3)_3C$-], and 0.07 [s, 6 H, $(CH_3)_2Si(O-)$-].

Anal. Calc. for $C_{31}H_{53}N_3O_3Si$: C, 68.46; H, 9.82; N, 7.73. Found: C, 68.43; H, 9.84; N, 7.63.

2-Azido-3-(benzoyloxy)-1-hydroxy-4-E-D-*erythro*-octadec-4-ene (2). To a solution of compound **21** (455 mg, 0.837 mmol) in acetonitrile (4 mL) was added a 2% solution of hydrofluoric acid (47%) in acetonitrile (4 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The mixture was diluted with ether (50 mL) and washed with water (30 mL). The aqueous layer was extracted with ether (30 mL) and the combined organic layers were washed successively with aq $NaHCO_3$ (30 mL) and brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 6:1 n-hexane-ethyl acetate afforded **2** (340 mg, 95%); $[\alpha]_D$ -48.2° (c 1.0); Rf 0.27 in 6:1 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 5.95 (m, 1 H, H-5), 5.63 (m, 1 H, H-3), 5.604 (dd, 1 H, $J_{3,4}$=8.1 Hz, $J_{4,5}$=14.9 Hz, H-4), 3.81 (m, 1 H, H-2), 3.760 (dd, 1 H, $J_{1,1'}$=11.5 Hz, $J_{1,2}$=3.7 Hz, H-1), 3.629 (dd, 1 H, $J_{1',2}$=7.1 Hz, H-1'), 2.083 (m, 2 H, H-6,6'), 2.05 (bs, 1 H, OH) and 0.879 (t, 3 H, J_{CH_3,CH_2}=6.8 Hz, CH_3CH_2-).

Anal. Calc. for $C_{25}H_{39}N_3O_3$: C, 69.90; H, 9.15; N, 9.78. Found: C, 69.84; H, 9.20; N, 9.51.

2-Azido-3-(benzoyloxy)-4-E-D-*erythro*-octadec-4-ene-1-yl O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-gluco-pyranosyl)-(1→3)-O-(2,4,6-tri-O-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-β-D-glucopyranoside (22).
(A): To a suspension of $AgClO_4$ (16 mg, 77 μmol), $SnCl_2$ (16 mg, 84 μmol) and powdered molecular sieves (4A) (100 mg) in 1,2-dichloro-ethane (0.5 mL) was added a solution of compounds **3** (34.0 mg, 36.7 μmol) and **2** (17.7 mg, 41.2 μmol) in 1,2-dichloroethane (1.5 mL) at -15 °C and the mixture was stirred at -15 to 0 °C for 3.5 h. The mixture was diluted with ethyl acetate (30 mL) and filtered through Celite. The filtrate was washed successively with aq $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica gel in 2:1 toluene-acetone afforded **22** (13.3 mg, 27%); $[\alpha]_D$ +1.2° (c 0.54); Rf 0.32 in 2:1 toluene-acetone; ^1H NMR (400 MHz) δ 5.917 (dt, 1 H, $J_{4,5}$=14.9 Hz, $J_{5,6}$=$J_{5,6'}$=6.8 Hz, H-5), 5.597 (dd, 1 H, $J_{2,3}$=4.0 Hz, $J_{3,4}$=8.2 Hz, H-3), 5.534 (dd, 1 H, H-4), 5.472 (d, 1 H, $J_{2c,NH}$=8.8 Hz, N*H*Ac), 5.330 (d, 1 H, $J_{3b,4b}$=3.2 Hz, H-4b), 5.015 (d, 1 H, $J_{1c,2c}$=8.3 Hz, H-1c), 4.930 (dd, 1 H, $J_{1b,2b}$=7.8 Hz, $J_{2b,3b}$=9.5 Hz, H-2b), 4.505 (d, 1 H, H-1b), 4.350 (d, 1 H, $J_{1a,2a}$=8.1 Hz, H-1a), 2.117 (s, 3 H, Ac), 2.110 (s, 3 H,

Ac), 2.104 (s, 3 H, Ac), 2.075 (s, 6 H, 2 Ac), 2.049 (s, 3 H, Ac), 2.026 (s, 3 H, Ac), 2.021 (s, 3 H, Ac), 2.012 (s, 3 H, Ac) and 1.908 (s, 3 H, Ac).

Anal. Calc. for $C_{63}H_{90}N_{40}O_{27}$: C, 56.66; H, 6.79; N, 4.20. Found: C, 56.55; H, 6.81; N, 4.03.

(B): To a suspension of $AgOSO_2CF_3$ (14 mg, 54 μmol), $SnCl_2$ (10 mg, 53 μmol) and powdered molecular sieves (4A) (100 mg) in 1,2-dichloroethane (0.5 mL) was added a solution of compounds **3** (24.2 mg, 26.1 μmol) and **2** (11.8 mg, 27.5 μmol) in 1,2-dichloroethane (1.5 mL) at -15 °C and the mixture was stirred at -15 °C to room temperature for 18 h. Work-up and chromatographic separation afforded **22** (10.3 mg, 30%).

(C): To a suspension of $AgBF_4$ (12 mg, 62 μmol), $SnCl_2$ (12 mg, 63 μmol) and powdered molecular sieves (4A) (100 mg) in 1,2-dichloroethane (0.5 mL) was added a solution of compounds **3** (23.6 mg, 25.5 μmol) and **2** (13.3 mg, 31.0 μmol) in 1,2-dichloroethane (1.5 mL) at -15 °C and the mixture was stirred at -15 °C to room temperature for 18 h. Work-up and chromatographic separation afforded **22** (8.0 mg, 24%).

(D): To a suspension of $SnCl_2$ (9 mg, 50 μmol) and powdered molecular sieves (4A) (100 mg) in 1,2-dichloroethane (0.5 mL) were added successively $TrOSO_2CF_3$ (170 μl from 0.26 M solution in 1,2-dichloroethane, 44 μmol) and a solution of compounds **3** (16.7 mg, 18 μmol) and **2** (14.2 mg, 33 μmol) in 1,2-dichloroethane (1 mL) at -15 °C. The mixture was stirred at -15 °C to room temperature for 18 h. Work-up and chromatographic separation afforded **22** (4.6 mg, 19%).

2-Azido-3-(benzoyloxy)-4-E-D-*erythro*-octadec-4-ene-1-yl O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucoyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzoyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside (25).

(A): To a suspension of $AgOSO_2CF_3$ (12 mg, 47 μmol), $SnCl_2$ (9 mg, 50 μmol) and powdered molecular sieves (4A) (100 mg) in 1,2-dichloroethane (0.5 mL) was added a solution of compounds **4** (25.7 mg, 20.7 μmol; α:β=1:2.7) and **2** (10.2 mg, 23.7 μmol) in 1,2-dichloroethane (1 mL) at -15 °C. The mixture was stirred at -15 °C to room temperature for 3 h. After work-up as described for the preparation of compound **22**, chromatography on silica gel in 3:1 carbon tetrachloride-acetone afforded recovered **4α** (6.5 mg, 25%) and **25** (16.3 mg, 48%, 64% based on consumed **4**); $[\alpha]_D$ +11.8° (c 1.2); Rf 0.41 in 2:1 carbon tetrachloride-acetone; ^1H NMR (400 MHz) δ 5.675 (dt, 1 H, $J_{4,5}$=15.5 Hz, $J_{5,6}$=$J_{5,6'}$=6.5 Hz, H-5), 5.395 (dd, 1 H, $J_{3,4}$=7.8 Hz, H-4), 5.105 (d, 1 H, $J_{1c,2c}$=8.1 Hz, H-

1c), 4.953 (dd, 1 H, $J_{2b,3b}$=10.4 Hz, $J_{3b,4b}$=2.6 Hz, H-3b), 4.690 (d, 1 H, J=7.6 Hz, H-1a or H-1b), 4.656 (d, 1 H, J=7.8 Hz, H-1b or H-1a), 4.247 (t, 1 H, $J_{3a,4a}$=$J_{4a,5a}$=9.5 Hz, H-4a), 4.004 (d, 1 H, H-4b), 2.069 (s, 3 H, Ac), 1.996 (s, 3 H, Ac), 1.979 (s, 3 H, Ac), 1.974 (s, 3 H, Ac), and 1.971 (s, 3 H, Ac).

Anal. Calc. for $C_{88}H_{100}N_4O_{27}$: C, 64.22; H, 6.12; N, 3.40. Found: C, 63.83; H, 6.16; N, 3.29.

The same reaction was performed by using anomerically pure **4β** (21.5 mg, 17.4 μmol) with **2** (16.5 mg, 38.4 μmol), to afford **25** (21.5 mg, 75%).

(B): To a suspension of $AgClO_4$ (7 mg, 30 μmol), $SnCl_2$ (7 mg, 40 μmol) and powdered molecular sieves (4A) (400 mg) in 1,2-dichloroethane was added a solution of compounds **4** (19.5 mg, 15.7 μmol; α:β=1:2.7) and **2** (9.9 mg, 23 μmol) in 1,2-dichloroethane (0.6 mL) at -15 °C. The mixture was stirred at -15 °C to room temperature for 18 h. Work-up and chromatographic separation afforded recovered **4α** (5.3 mg, 27%) and **25** (4.6 mg, 18%, 25% based on consumed **4**).

(C): To a suspension of $AgBF_4$ (10 mg, 51 μmol), $SnCl_2$ (10 mg, 53 μmol) and powdered molecular sieves (4A) (100 mg) in 1,2-dichloroethane (0.5 mL) was added a solution of compounds **4β** (24.5 mg, 19.8 μmol) and **2** (10.2 mg, 23.7 μmol) in 1,2-dichloroethane (1 mL) at -15 °C. The mixture was stirred at -15 °C to room temperature for 18 h. Work-up and chromatographic separation afforded **25** (11.6 mg, 36%).

O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-O-(2,4,6-tri-O-acetyl-β-D-galactopyranosyl)-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→1)-(2S,3R,4E)-3-O-benzoyl-2-N-tetracosanoylsphingenine (23). A mixture of compound **22** (12.0 mg, 8.98 μmol) and Lindlar catalyst (8 mg) in 1:1 ethyl acetate-ethanol (1 mL) was stirred under hydrogen for 18 h at room temperature. The mixture was diluted with ethyl acetate (20 mL) and filtered through Celite. The filtrate was evaporated *in vacuo* and the residue was dissolved in 1,2-dichloroethane (1 mL). The solution was added to a suspension of lignoceric acid (7 mg, 20 μmol) and 2-chloro-1-methylpyridinium iodide (5 mg, 20 μmol) in 1,2-dichloroethane (0.2 mL) containing tributylamine (9 μl, 40 μmol). The mixture was stirred for 1.5 h at room temperature. Resulting yellow suspension was diluted with ethyl acetate (30 mL) and washed with water (20 mL). The aqueous layer was extracted with ethyl acetate (20

mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was separated by preparative TLC in 3:2 carbon tetrachloride-acetone to afford **23** (9.2 mg, 62%); $[\alpha]_D$ +15.3° (c 0.5); Rf 0.43 in 3:2 carbon tetrachloride-acetone; ^1H NMR (400 MHz) δ 5.868 (dt, 1 H, $J_{4,5}$=15.0 Hz, $J_{5,6}$=$J_{5,6'}$=7.0 Hz, H-5), 5.734 (d, 1 H, $J_{2c,NH}$=9.3 Hz, NH), 5.326 (d, 1 H, $J_{3b,4b}$=2.9 Hz, H-4b), 5.003 (d, 1 H, $J_{1c,2c}$=8.1 Hz, H-1c), 4.892 (dd, 1 H, $J_{1b,2b}$=7.8 Hz, $J_{2b,3b}$=9.5 Hz, H-2b), 4.432 (d, 1 H, J=7.8 Hz, H-1a or H-1b), 4.311 (d, 1 H, J=7.8 Hz, H-1b or H-1a), 3.278 (ddd, 1 H, $J_{2c,3c}$=10.3 Hz, H-2c), 2.112 (s, 9 H, 3Ac), 2.053 (s, 3 H, Ac), 2.020 (s, 9 H, 3 Ac), 2.011 (s, 3 H, Ac), 1.946 (s, 3 H, Ac) and 1.904 (s, 3 H, Ac).

Anal. Calc. for $C_{87}H_{138}N_2O_{28}\cdot H_2O$: C, 62.27; H, 8.41; N, 1.67. Found: C, 62.03; H, 8.26; N, 1.68.

O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-O-β-D-galactopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→1)-2-N-tetracosanoyl-(2S,3R,4E)-sphingenine (24). To a solution of compound **23** (6.4 mg, 3.9 μmol) in chloroform (0.5 mL) was added 0.1N methanolic sodium methoxide (1 mL) and the mixture was stirred at room temperature overnight. Resulting mixture was neutralized with Amberlyst 15 resin and evaporated *in vacuo*. Purification of the residue by chromatography on Sephadex LH-20 in 60:40:4.6 chloroform-methanol-water afforded **24** (3.8 mg, 83%); $[\alpha]_D$ -15° (c 0.1, pyridine); Rf 0.67 in 2:1:1 n-butanol-ethanol-water; ^1H NMR (400 MHz, DMSO-d_6-D_2O, 40 °C) δ 5.544 (dt, 1 H, $J_{4,5}$=15.0 Hz, $J_{5,6}$=$J_{5,6'}$=7.0 Hz, H-5), 5.357 (dd, 1 H, $J_{3,4}$=7.0 Hz, H-4), 4.629 (d, 1 H, $J_{1c,2c}$=7.9 Hz, H-1c), 4.297 (d, 1 H, $J_{1b,2b}$=6.7 Hz, H-1b), 4.169 (d, 1 H, $J_{1a,2a}$=7.6 Hz, H-1a), 2.028 (t, 2 H, J_{CH_2,CH_2}=7.3 Hz, $COCH_2CH_2$) and 1.833 (s, 3 H, Ac).

O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzoyl-β-D-galactopyranosyl)-(1→4)-O-(2,3,6-tri-O-benzoyl-β-D-glucopyranosyl)-(1→1)-(2S,3R,4E)-3-O-benzoyl-2-N-tetracosanoylsphingenine (26).

(A): Compound **25** (26.7 mg, 16.2 μmol) was treated as described for the preparation of compound **23**. Separation by preparative TLC in 4:1 carbon tetrachloride-acetone afforded **26** (19.4 mg, 61%); $[\alpha]_D$ +20.2° (c 0.6); Rf 0.52 in 2:1 carbon tetrachloride-acetone; ^1H NMR (400 MHz) δ 5.778 (dt, 1 H, $J_{4,5}$=15.0 Hz, $J_{5,6}$=$J_{5,6'}$=6.8 Hz, H-5), 5.596 (d, 1 H, $J_{2c,NH}$=9.3 Hz, NH), 5.472 (t, 1 H, $J_{2,3}$=$J_{3,4}$=7.3 Hz, H-3), 5.096 (d, 1 H,

$J_{1c,2c}$=8.1 Hz, H-1c), 4.935 (dd, 1 H, $J_{2b,3b}$=10.5 Hz, $J_{3b,4b}$=2.6 Hz, H-3b), 4.613 (d, 1 H, J=7.8 Hz, H-1a or H-1b), 4.597 (d, 1 H, J=7.8 Hz, H-1b or H-1a), 4.191 (t, 1 H, $J_{3a,4a}$=$J_{4a,5a}$=9.6 Hz, H-4a), 3.996 (d, 1 H, H-4b), 2.066 (s, 3 H, Ac), 1.994 (s, 3 H, Ac), 1.975 (s, 3 H, Ac) and 1.966 (s, 6 H, 2 Ac).

Anal. Calc. for $C_{112}H_{148}N_2O_{28}\cdot H_2O$: C, 67.65; H, 7.67; N, 1.41. Found: C, 67.73; H, 7.52; N, 1.32.

(B): To a suspension of $AgOSO_2CF_3$ (11 mg, 43 μmol), $SnCl_2$ (9 mg, 50 μmol) and molecular sieves (4A) (80 mg) in chloroform (0.5 mL) was added a solution of compounds **4**β (26.5 mg, 21.4 μmol) and **1** (20.0 mg, 26.5 μmol) in chloroform (1 mL) at -15 °C. After stirring at -15 °C to room temperature for 18 h, the mixture was diluted with dichloromethane (10 mL) and filtered through Celite. The filtrate was diluted with ethyl acetate (30 mL), washed successively with aq $NaHCO_3$ (20 mL) and brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was separated by preparative TLC in 5:2 carbon tetrachloride-acetone to afford **26** (18.7 mg, 44%).

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