JOC*Note*

Total Synthesis of an Immunosuppressive Glycolipid, (2*S*,3*S*,4*R*)-1-*O*-(α-D-Galactosyl)-2-tetracosanoylamino-1,3,4-nonanetriol

Kenji Murata,† Tetsuya Toba,† Kyoko Nakanishi,† Bitoku Takahashi,† Takashi Yamamura,‡ Sachiko Miyake,‡ and Hirokazu Annoura*,†

Daiichi Suntory Biomedical Research Co., Ltd., 1-1-1, Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka 618-8513, Japan, and Department of Immunology, National Institute of Neuroscience, National Center for Neuroscience and Psychiatry, Tokyo 187-8502, Japan

hirokazu_annoura@dsup.co.jp

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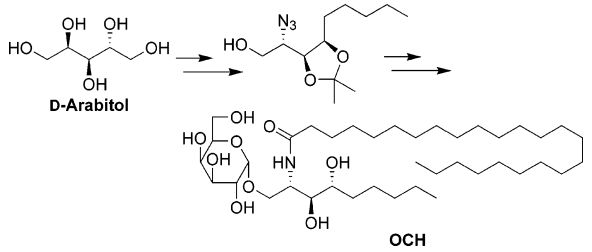
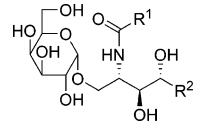


A practical and efficient total synthesis of (2*S*,3*S*,4*R*)-1-*O*-(α-D-galactosyl)-2-tetracosanoylamino-1,3,4-nonanetriol, OCH **1b**, a potential therapeutic candidate for Th1-mediated autoimmune diseases, is described. The synthesis incorporates direct alkylation onto epoxide **5** and stereospecific halide ion catalyzed α-glycosidation reaction. A key intermediate **10** was obtained in only eight steps and 37% overall yield from commercially available D-arabitol **2**, and the total synthesis of **1b** was accomplished in 12 steps and 19% overall yield. This method will enable the synthesis of a variety of phytosphingolipids, especially that with the shorter sphingosine side chain than **1a**, in a highly stereoselective manner.

Natural killer (NK) T cells are potent producers of immunoregulatory cytokines and specific for glycolipid antigens bound by a nonpolymorphic major histocompatibility complex (MHC) class I-like molecule, CD1d.[1] The glycolipids, an α-galactosylceramide named KRN7000 **1a**[2] and an altered analogue, OCH **1b**,[3] possessing a shorter C5 sphingosine side chain, have been identified as NKT cell ligands (Figure 1). Whereas **1a** has been shown to cause both interferon (IFN)-γ and interleukin (IL)-4 production, **1b** induces a predominant production of IL-4, a key Th2 cytokine controlling autoimmunity. Compound **1b** is significantly effective in animal models of Th1-mediated autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA), while **1a** showed only a minor effect.[3,4] It has recently been demonstrated that conversion of **1a** to its C-glycoside analogue leads to striking enhancement of activity on in vivo animal models of malaria and lung cancer.[5] Furthermore, similar substances including a tetraglycosylated glycolipid have recently been isolated from *Agelas Clathrodes*.[6] Consequently, considerable attention has been generated among synthetic chemists toward **1a**, **1b**, and their derivatives as new synthetic targets because of their distinctive biological and pharmacological properties as well as unique structural features. We present herein a practical and efficient total synthesis of immunosuppressive glycolipid **1b**.[7]



1a (R^1=*n*-$C_{25}H_{51}$; R^2=*n*-$C_{14}H_{29}$)
1b (R^1=*n*-$C_{23}H_{47}$; R^2=*n*-C_5H_{11})

FIGURE 1. Structure of KRN7000 **1a** and OCH **1b**.

The significant structural difference between **1a** and **1b** is the length of a sphingosine side chain R^2. Reported procedures[2,8] for the syntheses of **1a** and its sphingosine derivatives, which essentially utilize Wittig-type or aldol-type reaction for the installation of the sphingosine side chain, gave low overall yields for **1b** and its analogues with a chain length shorter than C5 for R^2 and proved to be impractical.[9] Our strategy for resolving this problem is based upon the direct alkylation on epoxide **5**, which

* To whom correspondence should be addressed. Phone: +81-75-962-8188. Fax: +81-75-962-6448.
† Daiichi Suntory Biomedical Research Co., Ltd.
‡ National Institute of Neuroscience, NCNP.

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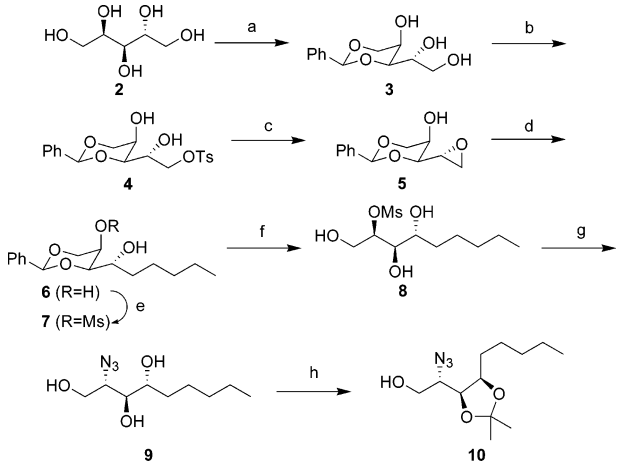
SCHEME 1[a]

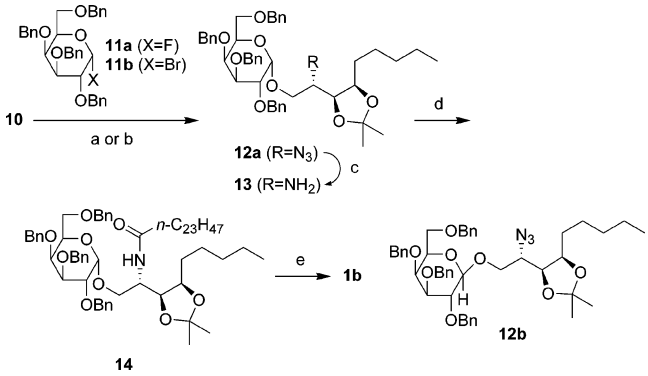


[a] Reagents and conditions: (a) PhCHO, dry HCl, rt, 91%; (b) *p*-TsCl, Et_3N, cat. Bu_2SnO, CH_2Cl_2, rt, quant; (c) *t*-BuOK, THF, rt, 91%; (d) *n*-Bu_2CuLi, THF, −40 °C, 98%; (e) MsCl, pyridine, −40 °C, 93%; (f) H_2, cat. $Pd(OH)_2$, EtOH, rt, quant; (g) NaN_3, DMF, 95 °C, 66%; (h) (i) cat. *p*-TsOH, 2,2-dimethoxypropane, rt; (ii) MeOH, rt, 75%.

has adequate stereocenters for the desired sphingosine side chain.[10]

Upon treatment of compound **3**,[11] which was readily prepared from D-arabitol **2** and benzaldehyde in 91% yield, with *p*-toluenesulfonyl chloride (*p*-TsCl) and triethylamine in the presence of a catalytic amount of dibutyltin oxide (Bu_2SnO),[12] regiospecific tosylation proceeded at the primary alcohol moiety to give **4** quantitatively (Scheme 1). The use of Bu_2SnO not only reduced the cost of this transformation but also greatly simplified the purification process since the yield was decreased to less than 30% when the reaction was carried out in the absence of Bu_2SnO. Treatment of **4** with *t*-BuOK produced the requisite epoxide **5** in 91% yield. Direct *n*-butylation onto **5** using organocopper lithium reagent in THF at −40 to −20 °C afforded 1,3-*O*-benzylidene-1,2,3,4-nonanetetrol **6** in 98% yield as the single product. Regioselective mesylation of the axial-OH in **6** with 1 equiv of methanesulfonyl chloride (MsCl) in pyridine at −40 °C to room temperature afforded **7** in 93% yield.

SCHEME 2[a]



[a] Reagents and conditions: (a) **11a**, $BF_3{\cdot}Et_2O$, MS4Å, $CHCl_3$, −50 °C, 57% for **12a**, 25% for **12b**; (b) **11b**, *n*-Bu_4NBr, MS4Å, DMF−toluene (1:2.5), rt, 68% for **12a**; (c) H_2, Lindlar catalyst, EtOH, rt, quant; (d) *n*-$C_{23}H_{47}COOH$, EDCI, HOBt, *i*-Pr_2NEt, DMF−CH_2Cl_2 (1:3.5), 40 °C, 89%; (e) (i) HCl-dioxane, rt; (ii) H_2, cat. $Pd(OH)_2$, MeOH−$CHCl_3$ (3:1), rt, 84%

Deprotection of the benzylidene acetal in **7** by hydrogenation at atmospheric pressure in the presence of palladium hydroxide [$Pd(OH)_2$] in EtOH and subsequent azidation of **8** with sodium azide in DMF afforded **9** in 66% overall yield. Protection of the vicinal diols in **9** with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in 2,2-dimethoxypropane at room temperature and quenching with MeOH afforded 3,4-isopropylidene acetal **10** in 75% yield.

As the key intermediate **10**, a glycosyl acceptor, was available, we next examined α-selective glycosidation reaction employing a variety of Lewis acids. After extensive experimentation, we found that glycosidation catalyzed by $BF_3{\cdot}Et_2O$ or *n*-Bu_4NBr with molecular sieves 4Å (MS4Å) worked well, but $AgClO_4$ reported for the synthesis[2] of **1a** gave only the undesired β-glycosylated product. Thus, treatment of **10** with benzyl protected galactosyl fluoride **11a** (1.8 equiv) in the presence of $BF_3{\cdot}Et_2O$ and MS4Å in $CHCl_3$ at −50 °C afforded α-galactosylceramide **12a** in 57% yield along with its β-isomer **12b** in 25% yield (Scheme 2). The stereochemistry of galactoside linkage was unambiguously determined by their NMR spectra[13] as well as conversion of **12a** into **1b** (vide infra). Surprisingly, when benzyl protected galactosyl bromide **11b**[14a] (1.8 equiv) and *n*-Bu_4NBr[14b] (3 equiv) with MS4Å were employed in toluene−DMF (2.5:1) at room temperature, **12a** was exclusively obtained in 68% yield. The corresponding β-galactosylated isomer **12b** could not be detected on TLC and NMR spectra. Upon using other ammonium bromides such as *n*-Hex_4NBr and Et_4NBr, the isolated yield of **12a** was decreased.

(9) According to the procedure reported in ref 2a, periodate oxidation of readily available tri-*O*-benzyl-D-galactose followed by Wittig-type reaction with a 5-fold molar excess of butylidene(triphenyl)phosphorane gave the desired (2*R*,3*S*,4*R*)-1,3,4-tri-*O*-benzyl-5-nonane-1,2,3,4-tetraol in less than 20% yield and consequently gave **1b** in low overall yield; see ref 3b. Also, when the more practical method for **1a** reported by Wong et al.[2e] was pursued for **1b**, similar Wittig reaction employing 3,4-di-*O*-benzyl-2-deoxy-6-*O*-triisopropylsilyl-D-galactopyranoside and propylidene(triphenyl)phosphorane resulted in complex mixtures containing an unavoidable byproduct in which the 3-benzyloxy group of galactopyranoside was eliminated. Therefore, our method is more efficient and practical for the synthesis of **1b** than those previously reported; however, this might not be the case for the synthesis of **1a**.

(10) During the preparation of this manuscript, Savage et al. have reported an alternative and efficient route for **1b**, although it requires the separation step of a 2:1 mixture of diastereomeric diols: Goff, R. D.; Gao, Y.; Mattner, J.; Zhou, D.; Yin, N.; Cantu, C., III; Teyton, L.; Bendelac, A.; Savage, P. B. *J. Am. Chem. Soc.* **2004**, *126*, 13602.

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(13) In the ^{13}C NMR (100 MHz, $CDCl_3$), the signal attributable to the anomeric carbon of **12a** appeared at δ 99.3, whereas that of **12b** was at δ 104.1. For ^{13}C NMR of glycosides: Pretsch, E.; Buhlmann, P.; Affolter, C. In *Structure Determination of Organic Compounds,* 3rd ed.; Springer-Verlag: 2000; pp 152−153. Also, in the ^1H NMR (400 MHz, $CDCl_3/CD_3OD$ 3:1) of **1b** derived from **12a**, the signal assignable to the hydrogen on the anomeric position was at δ 4.71 (d, 1H, $J = 3.8$ Hz), showing α-glycosidation product.

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Selective reduction of the azido group of **12a** was achieved by hydrogenation with Lindlar catalyst in EtOH at room temperature to give amine **13** quantitatively. Compound **13** was acylated with *n*-tetracosanoic acid in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt) and *N,N*-diisopropylethylamine (*i*-Pr_2NEt) at 40 °C in DMF−CH_2Cl_2 (1:3.5) to afford amide **14** in 89% yield. Finally, deprotection of the isopropylidene acetal of **14** under acidic conditions and subsequent removal of the benzyl groups by hydrogenation with $Pd(OH)_2$ in MeOH−$CHCl_3$ (3:1) at room temperature furnished **1b** in 84% yield. The synthetic sample displayed satisfactory ^1H and ^{13}C NMR spectra, FABMS, and elemental analysis [mp 142−145 °C (recrystalized from EtOH/H_2O), $[\alpha]^{30}_D$ +53.9 (*c* 0.5, pyridine)].

In conclusion, we have developed an efficient and practical protocol for the synthesis of **1b** involving 12 steps starting from commercially available D-arabitol **2** in 19% overall yield. The key intermediate **10** as a glycosyl acceptor was obtained in only eight steps and 37% overall yield. Our method, amenable for large-scale synthesis, can provide a dozen grams of **1b** and enables the synthesis of a variety of phytosphingolipids related to **1a** and **1b**, especially those with the shorter sphingosine side chain or substituents other than aliphatic alkyl groups, in a highly stereoselective manner. The synthesis and structure−activity relationships of this series of compounds will be reported elsewhere in due course.[7]

Experimental Section

1,3-*O*-Benzylidene-D-arabitol (3). According to the reported procedures,[11] dry HCl was slowly bubbled into a mixture of D-arabitol **2** (98.8 g, 649 mmol) and benzaldehyde (78.8 mL, 775 mmol) for 15 min at room temperature. The mixture was allowed to stand at room temperature for 18 h. The resulting solid crystalline mass was broken up and placed in an evacuated desiccator containing KOH and H_2SO_4 for 24 h. The mass was triturated with Et_2O, neutralized with sat. $NaHCO_3$ aq., and filtered and washed with H_2O until the pH of the filtrate was neutral. The product was washed with Et_2O and recrystallized from 2-PrOH containing 0.5% v/v NH_4OH to give **3** (142.2 g, 91% yield) as colorless crystals; mp 130−131 °C; ^1H NMR (CD_3OD) δ 7.51−7.30 (m, 5H), 5.58 (s, 1H), 4.18 (d, 1H, J = 12 Hz), 4.11 (d, 1H, J = 12 Hz), 3.87−3.28 (m, 5H); HRMS calcd for $C_{12}H_{17}O_5$ $[M + H]^+$ 241.1076, found 241.1086.

1,3-*O*-Benzylidene-5-*O*-toluenesulfonyl-D-arabitol (4). To a suspension of **3** (34.0 g, 141 mmol) in CH_2Cl_2 (1200 mL) were added *p*-toluenesulfonyl chloride (27.0 g, 141 mmol), triethylamine (19.7 mL, 141 mmol) and dibutyltinoxide (702 mg, 2.82 mmol) at 0 °C. After being stirred for 21 h at room temperature, the mixture was concentrated in vacuo. The obtained residue was purified by column chromatography (CH_2Cl_2/MeOH 20:1) to give **4** (55.3 g, quant) as a white solid: ^1H NMR (DMSO-d_6) δ 7.73 (d, 2H, J = 8.2 Hz), 7.37−7.24 (m, 7H), 5.43 (s, 1H), 5.34 (d, 1H, J = 6.1 Hz), 4.77 (d, 1H, J = 6.5 Hz), 4.11 (dd, 1H, J = 9.8, 1.9 Hz), 4.04−3.85 (m, 4H), 3.71 (d, 1H, J = 9.2 Hz), 3.59 (d, 1H, J = 5.7 Hz), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.1, 137.3, 132.5, 129.9, 129.1, 128.2, 128.0, 125.8, 101.0, 77.9, 72.4, 70.9, 67.6, 62.7, 21.6; MS-ESI (*m/z*) 395 $[M + H]^+$; HRMS−FAB (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{23}O_7S$, 395.1164, found 395.1189.

4,5-Anhydro-1,3-*O*-benzylidene-D-arabitol (5). To a solution of **4** (51.1 g, 130 mmol) in dry THF (800 mL) was added potassium *tert*-butoxide (18.1 g, 161 mmol) at 0 °C. The reaction mixture was stirred for 38 h at room temperature and then quenched with water. After being extracted with ethyl acetate, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 1:1) to give **5** (26.2 g, 91%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.52−7.34 (m, 5H), 5.57 (s, 1H), 4.25 (dd, 1H, J = 12, 1.8 Hz), 4.08 (dd, 1H, J = 12, 1.2 Hz), 3.78−3.75 (m, 2H), 3.35−3.31 (m, 1H), 2.93−2.84 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 137.4, 129.3, 128.4, 126.0, 101.4, 79.7, 72.3, 64.4, 50.8, 45.9; MS-ESI (*m/z*) 223 $[M + H]^+$; HRMS−FAB (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{15}O_4$, 223.0971, found 223.0895.

(2*R*,3*S*,4*R*)-1,3-*O*-Benzylidene-1,2,3,4-nonanetetrol (6). To a suspension of cupper iodide (I) (42.9 g, 225 mmol) in dry THF (560 mL) was added dropwise a solution of *n*-butyllithium (341 mL, 900 mmol, 2.64 M in hexane) at −40 °C under a nitrogen atmosphere. The reaction mixture was stirred for 30 min at −30 °C and then a solution of epoxide **5** (50.0 g, 225 mmol) in dry THF (400 mL) was added dropwise at −40 °C. After being stirred for 3 h at −20 °C, sat. $NaHCO_3$ aq. was added and the product was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give **6** (61.7 g, 98%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.52−7.50 (m, 2H), 7.42−7.38 (m, 3H), 5.60 (s, 1H), 4.28 (dd, 1H, J = 12, 1.8 Hz), 4.05 (1H, dd, J = 12, 1.3 Hz), 3.95−3.88 (m, 2H), 3.71 (dd, 1H, J = 6.6, 1.3 Hz), 3.25 (d, 1H, J = 8.7 Hz), 2.34 (d, 1H, J = 4.5 Hz), 1.73−1.53 (m, 2H), 1.40−1.30 (m, 6H), 0.90 (t, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 129.1, 128.3, 126.0, 105.0, 101.2, 81.3, 72.6, 71.2, 63.8, 32.8, 31.8, 25.2, 22.6, 14.0; MS−FAB (*m/z*) 281 $[M + H]^+$; HRMS−FAB (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{25}O_4$, 281.1753, found 281.1658.

(2*R*,3*S*,4*R*)-1,3-*O*-Benzylidene-2-*O*-methanesulfonyl-1,2,3,4-nonanetetrol (7). To a solution of **6** (3.90 g, 13.9 mmol) in dry pyridine (142 mL) was added methansulfonyl chloride (1.05 mL) at −40 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 5 h and then gradually warmed to room temperature over 16 h. Azeotropic removal of pyridine by using toluene twice gave a residue that was subjected to column chromatography (*n*-hexane/EtOAc 3:2) to give **7** (4.65 g, 93%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.51−7.48 (m, 2H), 7.42−7.35 (m, 3H), 5.59 (s, 1H), 4.99 (d, 1H, J = 1.4 Hz), 4.53 (dd, 1H, J = 13, 1.6 Hz), 4.18 (dd, 1H, J = 13, 1.1 Hz), 3.84−3.75 (m, 2H), 3.19 (s, 3H), 1.60−1.27 (m, 8H), 0.90 (t, 3H, J = 6.8 Hz); ^{13}C NMR (CDCl3) δ 129.3, 128.4, 126.1, 101.1, 80.9, 70.4, 70.0, 68.7, 38.7, 33.0, 32.0, 25.1, 22.8, 14.2; MS−FAB (*m/z*) 359 $[M + H]^+$; HRMS−FAB (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{27}O_6S$, 359.1528, found 359.1448.

(2*R*,3*S*,4*R*)-2-*O*-Methanesulfonyl-1,2,3,4-nonanetetrol (8). To a solution of **7** (87.0 mg, 242 μmol) in EtOH (5.0 mL) was added palladium hydroxide ($Pd(OH)_2$) (45 mg). After hydrogenation of the mixture for 16 h at atmospheric pressure, the catalyst was filtered off and the filtrate was concentrated in vacuo to give **8** (65.7 mg, quant) as a white solid: ^1H NMR ($CDCl_3$) δ 5.03−5.00 (m, 1H), 4.02−4.00 (m, 2H), 3.62−3.60 (m, 2H), 3.19 (s, 3H), 1.76−1.72 (m, 1H), 1.56−1.28 (m, 7H), 0.90 (t, 3H, J = 6.7 Hz); ^{13}C NMR (CD_3OD) δ 83.8, 74.1, 71.3, 62.6, 38.6, 34.6, 33.2, 26.1, 23.8, 14.4; MS-ESI (*m/z*) 293 $[M + Na]^+$; HRMS−FAB (*m/z*) $[M - OH]^+$ calcd for $C_{10}H_{21}O_5S$, 253.1110, found 253.1069.

(2*S*,3*S*,4*R*)-2-Azido-1,3,4-nonanetriol (9). To a solution of **8** (36.9 mg, 136 μmol) in dry DMF (1.0 mL) was added NaN_3 (17.7 mg, 272 μmol) under a nitrogen atmosphere. The mixture was stirred for 3 h at 95 °C and then quenched with water. After being extracted with ethyl acetate, the organic layer was washed with brine twice, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (CH_2Cl_2/MeOH 15:1) to give **9** (19.5 mg, 66%) as a white solid: ^1H NMR ($CDCl_3$) δ 4.05−3.98 (m, 1H), 3.91−3.74 (m, 3H), 3.71−3.66 (m, 1H), 2.67 (brs 1H), 2.52 (d, 1H, J = 4.4 Hz), 2.20 (brs, 1H), 1.61−1.52 (m, 2H), 1.40−1.31 (m, 6H), 0.91 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 74.8, 72.7, 63.3, 61.9, 32.0, 31.9, 25.6, 22.7, 14.2; MS−FAB (*m/z*) 218 $[M + H]^+$; HRMS−FAB (*m/z*) $[M + H]^+$ calcd for $C_9H_{20}N_3O_3$, 218.1505, found 218.1469.

(2*S*,3*S*,4*R*)-2-Azido-3,4-*O*-isopropylidene-1,3,4-nonanetriol (10). To a solution of **9** (4.00 g, 18.4 mmol) in dimethoxypropane (73 mL) was added a catalytic amount of *p*-toluenesulfonic acid monohydrate (175 mg, 92 μmol) at 0 °C. Stirring was continued for 2 h at room temperature. The mixture was

quenched with MeOH and then stirred for 1 h at room temperature. Removal of the solvent gave a residue, which was purified by column chromatography (*n*-hexane/EtOAc 4:1) to give **10** (3.61 g, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.21−4.16 (m, 1H), 4.02−3.95 (m, 2H), 3.90−3.84 (m, 1H), 3.50−3.45 (m, 1H), 2.11 (t, 1H, J = 5.6 Hz), 1.63−1.54 (m, 2H), 1.43 (s, 3H), 1.40−1.34 (m, 9H), 0.91(t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 108.6, 77.8, 76.6, 63.9, 61.2, 31.8, 29.4, 28.0, 26.2, 25.6, 22.6, 14.0; MS-ESI (*m/z*) 280 $[M + Na]^+$; HRMS−FAB (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{24}N_3O_3$, 258.1818, found 258.1737.

(2*S*,3*S*,4*R*)-2-Azido-3,4-*O*-isopropylidene-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactosyl)-1,3,4-nonanetriol (12a). To a suspension of **10** (100 mg, 389 μmol), **11b** (428 mg, 710 μmol), and molecular sieves 4Å (powder, 340 mg) in dry toluene (3.4 mL) and dry DMF (1.4 mL) was added tetra-*n*-butylammonium bromide (*n*-Bu_4NBr) (377 mg, 1.17 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 5 days at room temperature. The mixture was quenched with MeOH (0.1 mL) and stirred for 1 h at room temperature. After being passed through Celite, the filtrate was washed with sat. $NaHCO_3$ aq. and brine and then dried over anhydrous $MgSO_4$. Removal of the solvent gave a residue, which was purified by column chromatography (*n*-hexane/EtOAc 7:1) to give **12a** (206 mg, 68%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.40−7.26 (m, 20H), 4.97−4.93 (m, 2H), 4.87−4.79 (m, 2H), 4.74−4.70 (m, 2H), 4.57 (d, 1H, J = 12 Hz), 4.49 (d, 1H, J = 12 Hz), 4.41 (d, 1H, J = 12 Hz), 4.10−3.94 (m, 7H), 3.75−3.70 (m, 1H), 3.56−3.44 (m, 3H), 1.62−1.49 (m, 2H), 1.40−1.26 (m, 12H), 0.91 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 139.3, 139.1, 138.5, 128.8, 128.8, 128.7, 128.7, 128.7, 128.2, 128.1, 128.1, 128.0, 127.9, 108.6, 99.3, 79.1, 78.2, 77.0, 75.8, 75.7, 75.2, 73.9, 73.8, 73.3, 70.3, 70.0, 69.6, 60.3, 32.3, 29.7, 28.6, 26.7, 26.2, 23.0, 14.5; MS-ESI (*m/z*) 803 $[M + Na]^+$; HRMS−FAB (*m/z*) $[M - N_2]^+$ calcd for $C_{46}H_{57}NO_8$, 751.4084, found 751.4134.

(2*S*,3*S*,4*R*)-2-Azido-3,4-*O*-isopropylidene-1-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactosyl)-1,3,4-nonanetriol (12b). To a suspension of **10** (100 mg, 389 μmol), **11a** (285 mg, 524 μmol), and molecular sieves 4Å (powder, 400 mg) in dry $CHCl_3$ (5 mL) was added BF_3·Et_2O (47 μL, 368 μmol) in dry $CHCl_3$ (2 mL) at −50 °C under a nitrogen atmosphere. After stirring was continued for 14 h at the same temperature, the workup in the same manner for the reaction of **10** and **11b** provided **12a** (173 mg, 57%) along with **12b** (76 mg, 25%) as a colorless oil. **Data for 12b**: ^{1}H NMR ($CDCl_3$) δ 7.38−7.23 (m, 20H), 4.96−4.90 (m, 2H), 4.83−4.61 (m, 4H), 4.46−4.39 (m, 3H), 4.12−4.04 (m, 2H), 3.92−3.77 (m, 4H), 3.62−3.51 (m, 5H), 1.64−1.23 (m, 14H), 0.91 (t, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 138.9, 138.6, 138.5, 137.9, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.6, 127.6, 108.3, 104.1, 82.2, 79.7, 77.8, 75.8, 75.3, 74.6, 73.6, 73.6, 73.5, 73.1, 70.6, 68.7, 60.5, 31.9, 29.4, 28.2, 26.1, 25.7, 22.6, 14.1; MS-ESI (*m/z*) 803 $[M + Na]^+$; HRMS−FAB (*m/z*) $[M - N_2]^+$ calcd for $C_{46}H_{57}NO_8$, 751.4084, found 751.4005.

(2*S*,3*S*,4*R*)-2-Amino-3,4-*O*-isopropylidene-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactosyl)-1,3,4-nonanetriol (13). To a solution of **12a** (2.58 g, 3.31 mmol) in EtOH (260 mL) was added palladium on calcium carbonate poisoned with lead (Lindlar catalyst) (2.60 g). After hydrogenation was carried out for 16 h at atmospheric pressure, the catalyst was filtered off and the filtrate was concentrated in vacuo to give **13** (2.46 g, quant) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.40−7.25 (m, 20H), 4.96−4.92 (m, 2H), 4.84−4.64 (m, 4H), 4.58 (d, 1H, J = 11 Hz), 4.50 (d, 1H, J = 12 Hz), 4.41 (d, 1H, J = 12 Hz), 4.13−3.86 (m, 6H), 3.58−3.51 (m, 2H), 3.42−3.37 (m, 1H), 3.07−3.01 (m, 1H), 1.65−1.20 (m, 14H), 0.90 (t, 3H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.7, 138.6, 138.0, 128.4, 128.4, 128.2, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4, 107.9, 99.0, 79.1, 79.0, 77.9, 74.9, 74.8, 73.5, 73.3, 73.0, 72.4, 69.5, 69.0, 50.7, 31.9, 29.8, 28.3, 26.0, 25.9, 22.6, 14.1; MS-ESI (*m/z*) 754 $[M + H]^+$; HRMS−FAB (*m/z*) $[M + H]^+$ calcd for $C_{46}H_{60}NO_8$, 754.4319, found 754.4194.

(2*S*,3*S*,4*R*)-3,4-*O*-Isopropylidene-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactosyl)-2-tetracosanoylamino-1,3,4-nonanetriol (14). To a suspension of *n*-tetracosanoic acid (1.22 g, 3.31 mmol) in DMF (90 mL) and CH_2Cl_2 (210 mL) were added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI) (761 mg, 3.97 mmol) and 1-hydroxybenzotriazol (HOBt) (536 mg, 3.97 mmol) at 0 °C. After the mixture was stirred for 30 min at room temperature, **13** (2.46 g, 3.26 mmol) and *i*-Pr_2NEt (1.38 mL, 7.97 mmol) in CH_2Cl_2 (120 mL) were added and stirred for 16 h at 30 °C. The mixture was diluted with EtOAc/Et_2O (4:1) and sat. $NaHCO_3$ aq., and then the organic layer was separated and washed with 1 M HCl aq. and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent gave a residue, which was purified by column chromatography (*n*-hexane/EtOAc 3:1) to give **14** (3.25 g, 89%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.41−7.24 (m, 20H), 6.28 (d, 1H, J = 8.4 Hz), 4.95−4.90 (m, 2H), 4.83−4.73 (m, 2H), 4.75 (d, 1H, J = 12 Hz), 4.66 (d, 1H, J = 11 Hz), 4.58 (d, 1H, J = 12 Hz), 4.49 (d, 1H, J = 12 Hz), 4.38 (d, 1H, J = 12 Hz), 4.13−4.03 (m, 4H), 3.98 (t, 1H, J = 6.2 Hz), 3.93−3.90 (m, 3H), 3.63−3.53 (m, 2H), 3.39 (dd, 1H, J = 9.4, 5.7 Hz), 2.08−1.95 (m, 2H), 1.55−1.25 (m, 50H), 1.40 (s, 3H), 1.32 (s, 3H), 0.90−0.84 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 138.7, 138.4, 137.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 107.8, 99.9, 79.0, 77.8, 76.8, 75.5, 74.8, 74.7, 73.6, 73.5, 73.0, 70.8, 69.9, 69.6, 48.7, 36.8, 31.9, 31.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 28.9, 28.2, 26.2, 26.0, 25.7, 22.7, 22.6, 14.1, 14.1; MS−FAB 1105 $[M + H]^+$; HRMS−FAB (*m/z*) $[M + H]^+$ calcd for $C_{70}H_{106}NO_9$, 1104.7868, found 1104.7589.

(2*S*,3*S*,4*R*)-1-*O*-(α-D-Galactosyl)-2-tetracosanoylamino-1,3,4-nonanetriol (1b). To a solution of **14** (89 mg, 81 μmol) in MeOH (1.0 mL) and CH_2Cl_2 (5.0 mL) was added 4 M HCl aq. in dioxane (100 μL) at 0 °C. After the mixture was stirred for 2 h at room temperature, evaporation of the solvent gave a residue, which was purified by column chromatography (CH_2Cl_2/MeOH 30:1) to give the product by which the acetal group was deprotected. To a solution of the obtained diol in MeOH (3.0 mL) and $CHCl_3$ (1.0 mL) was added $Pd(OH)_2$ (25 mg). After hydrogenation was carried out for 3 h at atmospheric pressure, the catalyst was filtered off and the filtrate was evaporated to give **1b** (46 mg, 84%) as colorless crystals, mp 142−145 °C (recrystallized from EtOH/H_2O 10:1); $[\alpha]^{30}_D$ +53.9 (*c* 0.5, pyridine); ^{1}H NMR ($CDCl_3$/CD_3OD 3:1) δ 4.71 (d, 1H, J = 3.8 Hz), 4.01−3.98 (m, 1H), 3.74−3.65 (m, 2H), 3.62−3.45 (m, 6H), 3.35−3.31 (m, 2H), 2.00 (t, 2H, J = 7.6 Hz), 1.51−1.01 (m, 50H), 0.71−0.67 (m, 6H); ^{13}C NMR (pyridine-d_5) δ 173.8, 102.1, 77.3, 73.6, 73.0, 72.2, 71.6, 70.9, 69.2, 63.2, 52.0, 37.4, 34.9, 33.0, 32.7, 30.6, 30.6, 30.5, 30.4, 30.4, 30.3, 30.2, 27.0, 26.7, 23.6, 23.5, 14.8; MS−FAB (*m/z*) 704 $[M + H]^+$; HRMS−FAB (*m/z*) $[M + H]^+$ calcd for $C_{39}H_{78}NO_9$, 704.5677, found 704.5687. Anal. Calcd for $C_{39}H_{77}NO_9$·H_2O: C, 64.87; H, 11.03; N, 1.94. Found: C, 64.71; H, 10.88; N, 1.94.

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Note Added after ASAP Publication. As the result of a production error, the formatting of the compound names in the Experimental Section was inconsistent in the version published ASAP February 16, 2005. These have been corrected, and the solvent was changed in the synthesis of **12b**. The corrected version was published February 18, 2005.

Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra of **1b**, **3**−**10**, **12a**, **12b**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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