Synthesis of Simple Sea Cucumber Ganglioside Analogs

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Two simple sea cucumber ganglioside analogs **8** (NeuAcα 2→6 Glcβ 1→1 docosanol) and **9** (NeuAcβ 2→6 Glcβ 1→1 docosanol), containing a long-chain alcohol as a mimic of ceramide, have been synthesized. Coupling of the methyl 2-thioglycoside derivative of *N*-acetylneuraminic acid **5** with docosyl glucoside derivative **3** afforded the protected ganglioside analogs **6** and **7**, which were deprotected to give the corresponding ganglioside analogs **8** and **9**, respectively. The ^{13}C-NMR data obtained for these anomers **8** and **9** should prove useful for the determination of anomeric configurations of sialic acid residues in gangliosides.

We have previously reported that the gangliosides obtained from echinoderms possess unique biological activities, such as supporting the survival of cultured neuronal cells of rat fetuses[1] and showing neuritogenesis toward the mouse neuroblastoma[2] and rat pheochromocytoma cell lines.[3] Therefore, structure-activity relationships of the gangliosides from echinoderms are of considerable interest. In view of the importance of synthesizing ganglioside analogs, a series of studies on the synthesis of analogs of the gangliosides obtained from echinoderms have been performed in our laboratory.[4] Continuing the preceding study,[4c] we have now carried out the synthesis of simple analogs of the unique ganglioside **HPG-8**,[3b] which was obtained from the sea cucumber *Holothuria pervicax* and possesses a NeuAc(*N*-dacetylneuraminic acid)α2→6Glcβ1→1Cer moiety (Scheme 1). In this paper, we report the synthesis of the simple ganglioside analogs **8** and **9**, which have a long-chain alcohol as a mimic of ceramide.

The glucoside **3** was synthesized from D-glucose as follows: Bromination (HBr, AcOH) of the reducing end of pentaacetyl D-glucose followed by glycosidation with 1-docosanol by the Konigs−Knorr method[5] gave **1** in 30% yield. **1** was then deacetylated (NaOMe, MeOH) to quantitatively afford **2**. The ^{1}H-NMR coupling constant (J = 7.9 Hz) of the anomeric proton (δ = 4.85, doublet) of **2** indicates a β configuration. Tritylation (TrCl, Py, DMAP) and benzoylation (BzCl) of **2** followed by detritylation (*p*-TsOH) yielded **3** (76%). The structure of **3** was confirmed by acetylation, which gave the corresponding monoacetate **4**. ^{1}H-NMR data showed that the Glc 6-H$_2$ (δ = 3.75−3.83) of **3** are deshielded and give rise to signals at δ = 4.27 and 4.34 in **4**, thus indicating the presence of a hydroxy group at C-6 of Glc in **3**.

Based on the Hasegawa method,[6] glycosylation of **3** with the NeuAc donor **5**, prepared from *N*-acetylneuraminic acid (NeuAc),[7] in EtCN/CH_2Cl_2 in the presence of *N*-iodosuccinimide (NIS), trifluoromethanesulfonic acid (TfOH), and 4 Å molecular sieves at −15°C gave the α- and β-sialosides **6** and **7** in 81% yield in a 62:38 ratio. The configurations of the sialic acid moieties in anomers **6** and **7** were determined from the $J_{H(7)-H(8)}$ coupling constants (J = 8.8 Hz in **6**, α-configuration)[8] and the chemical shift of 3-H$_{eq}$ (δ = 2.52 in **6**, α-configuration; δ = 2.44 in **7**, β-configuration).[9] Compounds **6** and **7** were deprotected (NaOMe, MeOH) to quantitatively afford the ganglioside analogs **8** and **9**, respectively (Scheme 2). The ^{13}C-NMR data (described in the Experimental Section) of these anomers **8** and **9** should prove useful for the determination of the anomeric configurations of sialic acid residues in gangliosides.

As for other synthetic work concerning gangliosides from echinoderms, as far as we are aware only a sea urchin ganglioside having a NeuGc(*N*-glycolylneuraminic acid)α 2→6 Glc moiety has been synthesized.[10] The assessment of the biological activities of the sea cucumber ganglioside analogs synthesized in the present work will be reported elsewhere

Experimental Section

General: Melting points: micro melting point apparatus (Yanaco MP-3), uncorrected values. − Optical rotations: Jasco DIP-370 digital polarimeter at 25°C. − ^{1}H NMR spectra: Jeol GX-270 spectrometer (270 MHz), Varian Unity-500 spectrometer (500 MHz), Varian Unity-600 spectrometer (600 MHz). − FAB mass spectra: Jeol SX102A (xenon atom beam); matrix HMPA/TEG (negative-ion mode) and *m*-nitrobenzyl alcohol (positive-ion mode). − Abbreviations used: Glc: glucose; NA: neuraminic acid; Doc: docosanol; ax: axial; eq: equatorial.

Docosyl (2,3,4,6-Tetra-*O*-acetyl)-β-D-glucopyranoside (1): D-glucose pentaacetate (3.0 g, 7.69 mmol), obtained from D-glucose following the standard procedure (Ac_2O, Py), was added to a satd. solution of HBr in AcOH (12.0 mL) and the mixture was stirred for 30 min at room temperature. The reaction mixture was then diluted with ice water and extracted with EtOAc. The combined EtOAc extracts were washed with satd. aqueous $NaHCO_3$ solution and then con-

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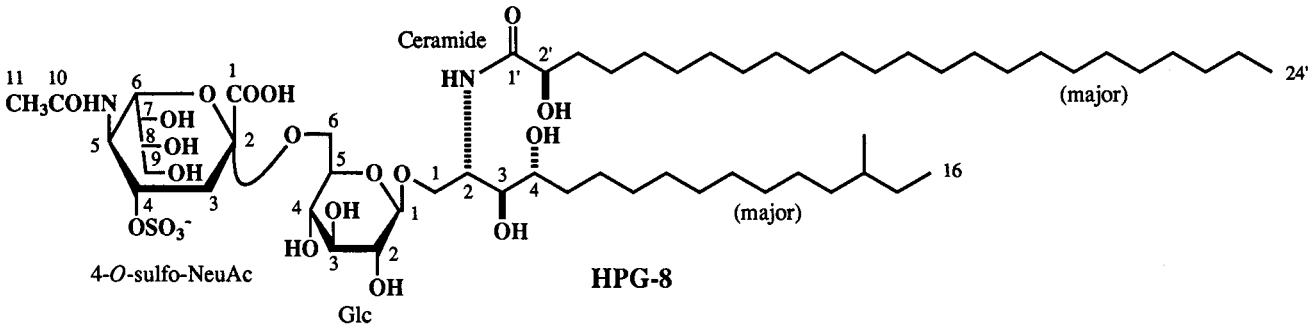
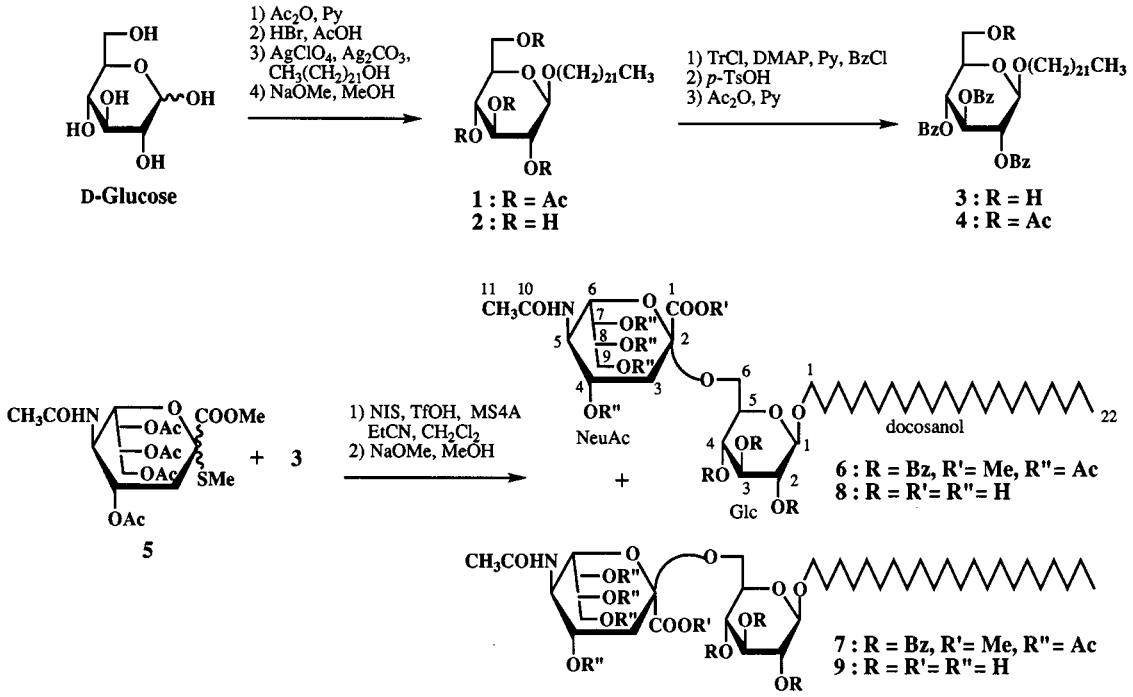


Scheme 1. Structure of HPG-8



Scheme 2

centrated. The resulting residue was redissolved in dry CH_2Cl_2 (20 mL) and this solution was stirred with 4 Å molecular sieves (2.4 g) for 3 h at room temperature. The solution was subsequently added to dry CH_2Cl_2 (45 mL) containing $AgClO_4$ (1.8 g, 8.7 mmol), Ag_2CO_3 (2.4 g, 8.7 mmol), 1-docosanol (5.0 g, 14.7 mmol), and 4 Å molecular sieves (3.6 g) and the mixture was stirred for 15 h at room temperature in the dark. The mixture was then filtered, and the filtrate was concentrated. The resulting residue was purified by chromatography on a silica gel column (eluent: *n*-hexane/EtOAc, 5:1) to afford **1** (1.54 g, 30% yield) as an amorphous powder; m.p. 85−86°C. − $[\alpha]_D = -14.3$ ($c = 1.0$ in $CHCl_3$). − Positive-ion FAB MS; *m/z*: 679 $[M + Na]^+$. − ^1H NMR ($CDCl_3$): δ = 5.20 (t, $J = 9.6$ Hz, 1 H, Glc 3-H), 5.08 (t, $J = 9.6$ Hz, 1 H, Glc 4-H), 4.98 (q, $J = 9.6$, 7.9 Hz, 1 H, Glc 2-H), 4.48 (d, $J = 7.9$ Hz, 1 H, Glc 1-H), 4.26 (q, $J = 11.2$, 4.6 Hz, 1 H, Glc 6-H), 4.13 (q, $J = 11.2$, 2.3 Hz, 1 H, Glc 6-H), 3.86 (sext, $J = 9.6$, 6.3, 6.3 Hz, 1 H, Doc 1-H), 3.68 (oct, $J = 9.6$, 4.6, 2.3 Hz, 1 H, Glc 5-H), 3.46 (sext, $J = 9.6$, 6.9, 6.9 Hz, 1 H, Doc 1-H), 2.08, 2.03, 2.02, 2.00 (each s, 12 H, 4 CH_3CO), 0.87 (t, $J = 6.6$ Hz, 3 H, CH_3). − $C_{36}H_{64}O_{10}$ (656.9): calcd. C 65.82, H 9.82; found C 66.04, H 9.71.

Docosyl β-D-Glucopyranoside (2): To a dry MeOH (30 mL)/CH_2Cl_2 (20 mL) solution of **1** (1.54 g, 2.34 mmol) was added 0.5 M NaOMe/MeOH (30 mL) and the resulting mixture was stirred for 30 min at room temperature. The solution was then neutralized with Dowex-50 (H^+ form) resin, filtered, and concentrated. The resulting residue was purified by chromatography on a silica gel column (eluent: $CHCl_3$/MeOH, 10:1) to give **2** (1.14 g, 100% yield) as an amorphous powder; m.p. 98−99°C. − $[\alpha]_D = -17.7$ ($c = 0.5$ in *n*PrOH). − Positive-ion FAB MS; *m/z*: 511 $[M + Na]^+$. − ^1H NMR (C_5D_5N): δ = 4.85 (d, $J = 7.9$ Hz, 1 H, Glc 1-H), 4.57 (q, $J = 11.9$, $J = 2.6$ Hz, 1 H, Glc 6-H), 4.39 (q, $J = 11.9$, 5.3 Hz, 1 H, Glc 6-H), 4.26−4.20 (m, 2 H, Glc 3-H, 4-H), 4.10 (sext, $J = 9.6$, 6.9, 6.9 Hz, 1 H, Doc 1-H), 4.04 (q, $J = 9.2$, 7.9 Hz, 1 H, Glc 2-H), 3.96 (oct, $J = 9.6$, 5.3, 2.3 Hz, 1 H, Glc 5-H), 3.66 (sext, $J = 9.6$, 6.9, 6.9 Hz, 1 H, Doc 1-H), 0.87 (t, $J = 6.6$ Hz, 3 H, CH_3). − $C_{28}H_{56}O_6$ (488.7): calcd. C 68.81, H 11.55; found C 68.21, H 11.53.

Docosyl (2,3,4-Tri-*O*-benzoyl)-β-D-glucopyranoside (3): Compound **2** (0.2 g, 0.41 mmol), triphenylmethyl chloride (TrCl; 1.13 g, 4.10 mmol), and dimethylaminopyridine (DMAP; 50.0 mg, 0.41 mmol) were added to dry pyridine (8.0 mL) and the mixture

was stirred for 2 h at 65°C. To this mixture, 350 μL (3.06 mmol) of benzoyl chloride (BzCl) was added and stirring was continued for 4 h at room temperature. The reaction mixture was then diluted with EtOAc and successively washed with 2 N HCl, H_2O, and satd. aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated. The resulting residue was dissolved in $CHCl_3$ (2.0 mL)/MeOH (2.0 mL) and then *p*-toluenesulfonic acid (*p*-TsOH; 10 mg, 53 μmol) was added. The resulting mixture was stirred for 3.5 h at room temperature, then diluted with satd. aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate was concentrated. The residue was purified by column chromatography on a silica gel column (eluent: *n*-hexane/EtOAc, 5:1) to give **3** (240.1 mg, 76% yield) as an amorphous powder; m.p. 83−84°C. − $[\alpha]_D$ = −9.0 (*c* = 1.0 in $CHCl_3$). − Positive-ion FAB MS; *m/z*: 823 $[M + Na]^+$. − ^1H NMR ($CDCl_3$): δ = 7.97−7.26 (m, 15 H, aromatic H), 5.93 (t, *J* = 9.9 Hz, 1 H, Glc 3-H), 5.50 (t, *J* = 9.9 Hz, 1 H, Glc 4-H), 5.50 (q, *J* = 9.9, 7.9 Hz, 1 H, Glc 2-H), 4.82 (d, *J* = 7.9 Hz, 1 H, Glc 1-H), 3.94 (sext, *J* = 9.6, 6.3, *J* = 6.3 Hz, 1 H, Doc 1-H), 3.83−3.75 (m, 3 H, Glc 5-H, 6-H_2), 3.54 (sext, *J* = 9.6, 6.6, 6.6 Hz, 1 H, Doc 1-H), 3.51 (m, 1 H, Glc 6-H), 3.33 (m, 1 H, Glc 6-H), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3). − $C_{49}H_{68}O_9$ (801.0): calcd. C 73.47, H 8.56; found C 73.34, H 8.56.

Docosyl (2,3,4-Tri-*O*-benzoyl-6-*O*-acetyl)-β-D-glucopyranoside (4): Compound **3** (40.0 mg, 49.9 μmol) was stirred in pyridine (1.0 mL) and acetic anhydride (Ac_2O, 1.0 mL) for 1.5 h at room temperature. The reaction mixture was then diluted with EtOAc, successively washed with 2 N HCl, H_2O, and satd. aqueous $NaHCO_3$ solution, and the organic layer was dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue obtained was purified by column chromatography on a silica gel column (eluent: *n*-hexane/EtOAc, 5:1) to afford **4** (43.0 mg, 100% yield) as an amorphous powder. − Positive-ion FAB MS; *m/z*: 865 $[M + Na]^+$. − ^1H NMR ($CDCl_3$): δ = 7.97−7.28 (m, 15 H, aromatic H), 5.87 (t, *J* = 9.9 Hz, 1 H, Glc 3-H), 5.59 (t, *J* = 9.9 Hz, 1 H, Glc 4-H), 5.50 (q, *J* = 9.9, 7.9 Hz, 1 H, Glc 2-H), 4.80 (d, *J* = 7.9 Hz, 1 H, Glc 1-H), 4.34 (q, *J* = 12.2, 5.0 Hz, 1 H, Glc 6-H), 4.27 (q, *J* = 12.2, 3.3 Hz, 1 H, Glc 6-H), 4.01 (oct, *J* = 9.9, 5.0, 3.3 Hz, 1 H, Glc 5-H), 3.93 (sext, *J* = 9.6, 6.3, 6.3 Hz, 1 H, Doc 1-H), 3.53 (sext, *J* = 9.6, 6.6, 6.6 Hz, 1 H, Doc 1-H), 2.04 (s, 3 H, CH_3CO), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3).

Nonulopyranoside Methyl Ester 5: See ref.[7]

Synthesis of α- and β-Sialosides 6 and 7: A mixture of **3** (30.0 mg, 37.5 μmol), **5** (55.0 mg, 93.6 μmol), and powdered 4 Å molecular sieves (78 mg) in dry EtCN (0.2 mL) and dry CH_2Cl_2 (0.1 mL) was stirred for 3 h at room temperature and then cooled to −15°C. To the stirred, cooled mixture were added *N*-iodosuccinimide (NIS; 32.0 mg, 140.0 μmol) and trifluoromethanesulfonic acid (TfOH, 5 L) and stirring was continued for a further 30 min at −15°C. The mixture was then filtered through Celite, the solids were washed with CH_2Cl_2, and the combined filtrate and washings were successively washed with 5% aqueous $Na_2S_2O_3$ and satd. aqueous $NaHCO_3$. The organic phase was dried with Na_2SO_4, filtered, and the filtrate was concentrated. The residue was separated by column chromatography on a silica gel column (eluent: $CHCl_3$/acetone, 15:1) to afford **6** (23.9 mg, 50% yield) and **7** (14.8 mg, 31% yield), both as amorphous powders.

α-Sialoside 6: M.p. 72°C. − $[\alpha]_D$ = −7.9 (*c* = 1.0 in $CHCl_3$). − Positive-ion FAB MS: *m/z*: 1296 $[M + Na]^+$. − ^1H NMR ($CDCl_3$): δ = 7.95−7.26 (m, 15 H, aromatic H), 5.78 (t, *J* = 9.6 Hz, 1 H, Glc 3-H), 5.68 (t, *J* = 9.6 Hz, 1 H, Glc 4-H), 5.43 (q, *J* = 9.6, 7.8 Hz, 1 H, Glc 2-H), 5.23 (m, 1 H, NA 7-H), 5.22 (oct, *J* = 8.8, 4.8, 2.5 Hz, 1 H, NA 8-H), 5.04 (d, *J* = 9.8 Hz, 1 H, NH), 4.81 (m, 1 H, NA 4-H), 4.74 (d, *J* = 7.8 Hz, 1 H, Glc 1-H), 4.12 (q, *J* = 12.4, 2.1 Hz, 1 H, NA 9-H), 3.99 (q, *J* = 11.4, 3.7 Hz, 1 H, Glc 6-H), 3.97−3.89 (m, 4 H, Doc 1-H, Glc 5-H, NA 5-H, NA 6-H), 3.83 (q, *J* = 12.4, 4.6 Hz, 1 H, NA 9-H), 3.76 (s, 3 H, $CO-OCH_3$), 3.69 (q, *J* = 11.4, 2.6 Hz, 1 H, Glc 6-H), 3.50 (sext, *J* = 9.6, 6.9, 6.9 Hz, 1 H, Doc 1-H), 2.52 (q, *J* = 12.8, 4.6 Hz, 1 H, NA 3-H_{eq}), 2.09, 2.02, 2.01, 2.00, 1.84 (each s, 15 H, 5 CH_3CO), 1.82 (m, 1 H, NA 3-H_{ax}), 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3). − $C_{69}H_{95}NO_{21}$ (1274.5): calcd. C 65.03, H 7.51, N 1.10; found C 64.70, H 7.53, N 1.14.

β-Sialoside 7: M.p. 57−58°C. − $[\alpha]_D$ = −5.6 (*c* = 1.0 in $CHCl_3$). − Positive-ion FAB MS: *m/z*: 1296 $[M + Na]^+$. − ^1H NMR ($CDCl_3$): δ = 7.96−7.26 (m, 15 H, aromatic H), 5.85 (t, *J* = 9.6 Hz, 1 H, Glc 3-H), 5.71 (d, *J* = 10.1 Hz, 1 H, NH), 5.69 (t, *J* = 9.6 Hz, 1 H, Glc 4-H), 5.46 (q, *J* = 9.6, 7.8 Hz, 1 H, Glc 2-H), 5.37 (m, 1 H, NA 7-H), 5.18 (m, 2 H, NA 4-H and 8-H), 4.85 (q, *J* = 12.4, 2.5 Hz, 1 H, NA 9-H), 4.79 (d, *J* = 7.8 Hz, 1 H, Glc 1-H), 4.15−4.10 (m, 2 H, NA 5-H and 6-H), 4.07 (q, *J* = 12.4, 8.2 Hz, 1 H, NA 9-H), 4.00−3.94 (m, 2 H, Doc 1-H, Glc 5-H), 3.89 (q, *J* = 10.6, 2.7 Hz, 1 H, Glc 6-H), 3.68 (q, *J* = 10.6, 3.4 Hz, 1 H, Glc 6-H), 3.54 (s, 3 H, $COOCH_3$), 3.52 (m, 1 H, Doc 1-H), 2.44 (q, *J* = 13.0, 4.8 Hz, 1 H, NA 3-H_{eq}), 2.13, 2.05, 2.03, 1.98, 1.88 (each s, 15 H, 5 CH_3CO), 1.84 (m, 1 H, NA 3-H_{ax}), 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3). − $C_{69}H_{95}NO_{21}\cdot H_2O$ (1310.5): calcd. C 63.24, H 7.61, N 1.07; found C 63.44, H 7.41, N 1.13.

Ganglioside Analog 8: To a solution of **6** (86.9 mg, 68.2 μmol) in MeOH (2.7 mL), 0.5 M NaOMe/MeOH (2.7 mL) was added and the mixture was stirred for 20 min at room temperature. Then, H_2O (2 mL) was added and stirring was continued for a further 1 h. The solution was subsequently treated with Dowex-50 (H^+ form) resin to remove the base, and then concentrated in vacuo. Column chromatography of the residue on Sephadex LH-20 (eluent: $CHCl_3$/MeOH/H_2O, 5:5:1) gave **8** as an amorphous powder (53.0 mg, 100% yield), m.p. 154−155°C. − $[\alpha]_D$ = −23.4 (*c* = 1.0 in C_5H_5N). − Negative-ion FAB MS; *m/z*: 778 $[M - H]^-$. − ^1H NMR (C_5D_5N): δ = 4.69 (d, *J* = 7.0 Hz, 1 H, Glc 1-H), 4.65−3.80 (br. m, 11 H, sugar protons), 1.98 (s, 3 H, CH_3CO), 0.84 (t, *J* = 6.6 Hz, 3 H, CH_3). − ^{13}C NMR (C_5D_5N): δ = 104.6 (d, Glc C-1), 75.0 (d, Glc C-2), 77.9 (d, Glc C-3), 71.8 (d, Glc C-4), 76.3 (d, Glc C-5), 69.9 (t, Glc C-6), 173.5 (s, NA C-1), 101.0 (s, NA C-2), 42.6 (t, NA C-3), 68.9 (d, NA C-4), 54.4 (d, NA C-5), 75.0 (d, NA C-6), 69.9 (d, NA C-7), 72.7 (d, NA C-8), 64.9 (t, NA C-9), 173.5 (s, NA C-10), 22.9 (q, NA C-11), 63.8 (t, docosanol C-1), 14.2 (q, docosanol C-22). − $C_{39}H_{73}NO_{14}$ (780.0): calcd. C 60.05, H 9.43, N 1.80; found C 59.42, H 9.18, N 1.71.

Ganglioside Analog 9: The preparation was carried out in the same manner as described for **6**. Compound **7** (43.6 mg, 34.2 μmol) was deprotected to give **9** as an amorphous powder (26.0 mg, 98% yield); m.p. 197−198°C. − $[\alpha]_D$ = −12.0 (*c* = 1.0 in C_5H_5N). − Negative-ion FAB MS; *m/z*: 778 $[M - H]^-$. − ^1H NMR (C_5D_5N): δ = 4.63 (d, *J* = 7.6 Hz, 1 H, Glc 1-H), 4.60−3.80 (br. m, 8 H, sugar protons), 1.98 (s, 3 H, CH_3CO), 0.85 (t, *J* = 6.6 Hz, 3 H, CH_3). − ^{13}C NMR (C_5D_5N): δ = 105.0 (d, Glc C-1), 75.3 (d, Glc C-2), 78.2 (d, Glc C-3), 71.2 (d, Glc C-4), 77.0 (d, Glc C-5), 70.1 (t, Glc C-6), 173.0 (s, NA C-1), 103.5 (s, NA C-2), 42.4 (t, NA C-3), 67.5 (d, NA C-4), 54.4 (d, NA C-5), 75.3 (d, NA C-6), 71.2 (d, NA C-7), 73.0 (d, NA C-8), 65.8 (t, NA C-9), 173.0 (s, NA C-10), 22.8 (q, NA C-11), 64.4 (t, docosanol C-1), 14.2 (q, docosanol C-22). − $C_{39}H_{73}NO_{14}\cdot 2H_2O$ (816.0): calcd. C 57.40, H 9.51, N 1.72; found C 57.38, H 9.00, N 1.83.

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