

residue was purified by column chromatography on silica gel (hexane/EtOAc 4:1) to give **50** (82 mg, 90%).  $[\alpha]_D^{25} = +15.7^\circ$  ( $c = 0.8$ ,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.05\text{--}7.40$  (m, 10H; 2 Ph), 6.84 (d, 1H,  $J = 8.2$  Hz; NH), 5.88 (m, 1H), 5.60 (m, 2H), 5.43 (m, 1H), 4.29 (m, 1H), 3.68 (m, 2H), 2.70 (brs, 1H), 1.97 (m, 4H), 1.50 (m, 1H), 1.42 (m, 2H), 1.23 (m, 54H;  $-\text{CH}_2-$ ), 0.87 ppm (m, 9H;  $\text{CH}_3\text{CH}_2$ ,  $(\text{CH}_3)_2\text{CH}$ );  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.2$ , 166.2, 165.3, 137.4, 133.5, 133.3, 129.7, 129.6, 129.2, 128.6, 128.4, 124.3, 74.6, 74.4, 61.4, 53.5, 39.0, 32.3, 31.9, 29.9, 29.7, 29.4, 29.4, 29.3, 29.3, 28.7, 27.9, 27.4, 24.8, 22.7, 22.6, 14.1 ppm; HRMS:  $m/z$ : calcd for  $\text{C}_{35}\text{H}_{59}\text{NO}_6 + \text{Na}^+$ : 882.6588  $[\text{M} + \text{Na}]^+$ ; found: 882.6568.

**(Methyl 5-acetoxyacetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonate)-(2 $\rightarrow$ 4)-(methyl 5-acetamido-7,8,9-tri-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonate)-(2 $\rightarrow$ 6)-3,4-di-O-acetyl-2-O-benzoyl- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 1)-(2S,3R,4E)-3-O-benzoyl-2-[(R)-2-(benzoyloxy)tetraacosanoylamino]-15-methylhexadec-4-ene-1,3-diol (51)**: AW-300 4 Å molecular sieves (550 mg) were added to a solution of compounds **34** (62.5 mg, 42.4  $\mu\text{mol}$ ) and **50** (47.4 mg, 55.1  $\mu\text{mol}$ ) in  $\text{CH}_2\text{Cl}_2$  (500  $\mu\text{L}$ ). The suspension was stirred for 1.5 h at room temperature, then cooled to  $0^\circ\text{C}$ , whereupon TMSOTf (3.1  $\mu\text{L}$ , 17.0  $\mu\text{mol}$ ) was added. Stirring was continued for 30 min at  $0^\circ\text{C}$ . The mixture was then warmed to  $10^\circ\text{C}$  and stirred for 12 h as the progress of the reaction was monitored by TLC ( $\text{CHCl}_3/\text{MeOH}$  20:1). A further portion of TMSOTf (3.1  $\mu\text{L}$ , 17.0  $\mu\text{mol}$ ) was added and stirring was continued for 5 h at  $10^\circ\text{C}$ . The mixture was then warmed to room temperature and stirred for 1.5 h. After quenching with triethylamine, the mixture was filtered through Celite and concentrated. The residue was purified by column chromatography on silica gel ( $\text{CHCl}_3/\text{MeOH}$  70:1 $\rightarrow$ 60:1) to give **51** (44.9 mg, 49%).  $[\alpha]_D^{25} = +9.7^\circ$  ( $c = 0.9$ ,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.02\text{--}7.36$  (m, 15H; 3 Ph), 6.53 (d, 1H,  $J_{\text{NH}} = 8.9$  Hz; NH of sphingosine), 6.05 (d, 1H,  $J_{\text{NH},5} = 9.6$  Hz; NH-b), 5.74 (d, 1H,  $J_{\text{NH},5} = 10.3$  Hz; NH-c), 5.65 (m, 1H; H-5d), 5.60 (m, 1H; H-8b), 5.42 (m, 4H; H-7b, H-8c, H-3d, H-4d), 5.20 (m, 5H; H-2a, H-3a, H-4a, H-7c, H-2e), 4.80 (m, 1H; H-4c), 4.58 (d, 1H,  $J_{\text{gem}} = 15.2$  Hz;  $\text{AcOCH}_2\text{CO}$ ), 4.46 (m, 1H; H-2d), 4.42 (d, 1H,  $J_{1,2} = 8.2$  Hz; H-1a), 4.40 (dd, 1H,  $J_{\text{gem}} = 12.1$ ,  $J_{8,9} = 2.5$  Hz; H-9c), 4.32 (dd, 1H,  $J_{\text{gem}} = 12.4$ ,  $J_{8,9} = 2.8$  Hz; H-9b), 4.26 (d, 1H;  $\text{AcOCH}_2\text{CO}$ ), 4.06 (m, 4H; H-5b, H-9b, H-5c, H-1d), 3.90 (dd, 1H,  $J_{5,6} = 10.7$ ,  $J_{6,7} = 2.5$  Hz; H-6b), 3.83 (m, 9H; H-6a, H-6c, H-9c,  $\text{COOMe}$ ), 3.63 (m, 1H; H-4b), 3.53 (dd, 1H,  $J_{\text{gem}} = 9.6$ ,  $J_{1,2} = 6.2$  Hz; H-1'd), 3.44 (m, 1H; H-5a), 3.35 (app d, 1H; H-6'a), 2.61 (dd, 1H,  $J_{\text{gem}} = 12.8$ ,  $J_{3,4} = 4.5$  Hz; H-3c<sub>ax</sub>), 2.20–1.82 (m, 39H; H-3b<sub>eq</sub>, H-3c<sub>ax</sub>, H-6d, H-3e, 11 Ac), 1.77 (t, 1H,  $J_{\text{gem}} = J_{3,4} = 12.7$  Hz; H-3b<sub>ax</sub>), 1.51 (m, 1H; H-15d), 1.34–1.13 (m, 56H;  $-\text{CH}_2-$ ), 0.88 ppm (m, 9H;  $\text{CH}_3\text{CH}_2$ ,  $(\text{CH}_3)_2\text{CH}$ );  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta = 172.0$ , 171.2, 170.6, 170.4, 170.4, 170.3, 170.0, 169.9, 169.5, 169.5, 168.9, 167.7, 167.6, 167.0, 165.2, 165.1, 164.8, 137.2, 133.6, 133.3, 132.9, 130.1, 129.8, 129.7, 129.6, 129.2, 129.2, 128.7, 127.4, 128.3, 123.9, 100.4, 98.4, 98.0, 74.5, 74.3, 72.8, 72.5, 72.4, 72.3, 71.3, 71.3, 68.1, 68.0, 67.9, 67.7, 67.6, 67.2, 66.2, 64.0, 62.7, 62.7, 62.3, 53.2, 52.6, 50.6, 49.1, 48.8, 39.1, 38.8, 38.2, 32.2, 31.9, 29.9, 29.7, 29.6, 29.5, 29.4, 29.4, 29.3, 29.3, 28.8, 28.0, 27.4, 24.8, 23.3, 22.7, 22.7, 21.2, 21.2, 20.9, 20.9, 20.8, 20.7, 20.7, 20.6, 14.1 ppm; HRMS:  $m/z$ : calcd for  $\text{C}_{112}\text{H}_{161}\text{N}_3\text{O}_{39} + \text{Na}^+$ : 2195.0605  $[\text{M} + \text{Na}]^+$ ; found: 2195.0606.

**Ganglioside HLG-2 (1)**: A 2% solution of sodium methoxide in MeOH was added to a solution of compound **51** (9.9 mg, 4.55  $\mu\text{mol}$ ) in MeOH (0.6 mL)/THF (0.3 mL). The mixture was stirred for 4 h at room temperature, as the progress of the reaction was monitored by TLC ( $\text{CHCl}_3/\text{MeOH}/\text{water}$  4:3:1). Water (0.1 mL) was then added and stirring was continued for 116 h at room temperature. After neutralization with Dowex-50 ( $\text{H}^+$ ), the mixture was concentrated. The residue was purified by column chromatography on Sephadex LH-20 ( $\text{CHCl}_3/\text{MeOH}/\text{water}$  5:6:2) to give **1** (6.4 mg, quant.).  $[\alpha]_D^{25} = -44.1^\circ$  ( $c = 0.2$ ,  $\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}$  5:6:2);  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 5.72$  (m, 1H; H-5d), 5.45 (dd, 1H,  $J_{3,4} = 7.6$ ,  $J_{4,5} = 15.2$  Hz; H-4d), 4.39 (m, 1H; H-4c), 4.23 (d, 1H,  $J_{1,2} = 8.3$  Hz; H-1a), 3.19 (app t, 1H,  $J_{2,3} = 8.9$  Hz; H-2a), 2.90 (m, 2H; H-3b<sub>eq</sub>, H-3c<sub>eq</sub>), 2.11 (s, 3H; Ac), 2.03 (q, 2H; H-6d), 1.70 (m, 1H; H-15d), 1.56 (m, 4H; H-3b<sub>ax</sub>, H-3c<sub>ax</sub>, H-3e), 1.39–1.16 (m, 56H;  $-\text{CH}_2-$ ), 0.89 ppm (m, 9H;  $\text{CH}_3\text{CH}_2$ ,  $(\text{CH}_3)_2\text{CH}$ );  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 177.4$ , 177.3, 176.5, 174.9, 173.8, 135.0, 131.0, 104.8, 101.8, 99.9, 77.5, 76.4, 75.0, 74.5, 73.3, 73.1, 72.8, 72.6, 71.2, 70.9, 70.6, 70.2, 70.0, 69.1, 64.8, 64.6, 64.0,

62.6, 54.6, 54.0, 53.3, 48.3, 43.1, 40.4, 40.3, 35.9, 33.5, 33.1, 31.1, 30.9, 30.8, 30.6, 30.5, 30.3, 29.2, 28.6, 26.2, 23.7, 23.1, 22.8, 14.4 ppm; HRMS:  $m/z$ : calcd for  $\text{C}_{112}\text{H}_{161}\text{N}_3\text{O}_{39} - 2\text{H} + \text{Na}^+$ : 1432.8298  $[\text{M} - 2\text{H} + \text{Na}]^+$ ; found: 1432.8299.

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- [1] a) S. Hakomori, *Annu. Rev. Biochem.* **1981**, *50*, 733–764; b) S. Ando, *Neurochem. Int.* **1983**, *5*, 507–537; c) S. Hakomori, *J. Biol. Chem.* **1990**, *265*, 18713–18716; d) R. L. Schnaar, *Glycobiology* **1991**, *1*, 477–485; e) A. Varki, *Glycobiology* **1993**, *3*, 97–130.
- [2] A. Kameyama, H. Ishida, M. Kiso, A. Hasegawa, *J. Carbohydr. Chem.* **1991**, *10*, 729–738.
- [3] a) H.-K. Ishida, H. Ishida, M. Kiso, A. Hasegawa, *Carbohydr. Res.* **1994**, *260*, C1–C6; b) H.-K. Ishida, H. Ishida, M. Kiso, A. Hasegawa, *Tetrahedron: Asymmetry* **1994**, *5*, 2493–2512.
- [4] K. Hotta, H. Ishida, M. Kiso, A. Hasegawa, *J. Carbohydr. Chem.* **1995**, *14*, 491–506.
- [5] a) A. Hasegawa, M. Kiso, *Design and Synthesis of Cell Adhesion Carbohydrate Ligands/Inhibitor in Carbohydrates in Drug Design Vol. 4* (Eds.: Z. J. Witzczak, K. A. Nieforth), Marcel Dekker, New York, **1997**, pp. 137–155; b) H. Ishida, M. Kiso, *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 1108–1113.
- [6] M. Inagaki, R. Isobe, R. Higuchi, *Eur. J. Org. Chem.* **1999**, 771–774.
- [7] K. Yamada, R. Matsubara, M. Kaneko, T. Miyamoto, R. Higuchi, *Chem. Pharm. Bull.* **2001**, *49*, 447–452.
- [8] a) R. Higuchi, T. Natori, T. Komori, *Liebigs Ann. Chem.* **1990**, 51–55; b) T. Miyamoto, M. Inagaki, R. Isobe, Y. Tanaka, R. Higuchi, M. Iha, K. Teruya, *Liebigs Ann.* **1997**, 931–936; c) T. Miyamoto, A. Yamamoto, M. Wakabayashi, Y. Nagaregawa, M. Inagaki, R. Higuchi, M. Iha, K. Teruya, *Eur. J. Org. Chem.* **2000**, 2295–2301.
- [9] M. Kaneko, F. Kisa, K. Yamada, T. Miyamoto, R. Higuchi, *Eur. J. Org. Chem.* **1999**, 3171–3174; M. Kaneko, F. Kisa, K. Yamada, T. Miyamoto, R. Higuchi, *Eur. J. Org. Chem.* **2003**, 1004–1008.
- [10] a) S. Kawatake, M. Inagaki, R. Isobe, T. Miyamoto, R. Higuchi, *Liebigs Ann.* **1997**, 1797–1800; b) S. Kawatake, M. Inagaki, T. Miyamoto, R. Isobe, R. Higuchi, *Eur. J. Org. Chem.* **1999**, 765–769; c) S. Kawatake, M. Inagaki, R. Isobe, T. Miyamoto, R. Higuchi, *Chem. Pharm. Bull.* **2002**, *50*, 1386–1389.
- [11] M. Kaneko, K. Yamada, T. Miyamoto, M. Inagaki, R. Higuchi, *Chem. Pharm. Bull.* **2007**, *55*, 462–463.
- [12] H. Ando, Y. Koike, S. Koizumi, H. Ishida, M. Kiso, *Angew. Chem.* **2005**, *117*, 6917–6921; *Angew. Chem. Int. Ed.* **2005**, *44*, 6759–6763.
- [13] a) R. R. Schmidt, P. Zimmermann, *Angew. Chem.* **1986**, *98*, 722–723; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 725–726; b) T. Murase, H. Ishida, M. Kiso, A. Hasegawa, *Carbohydr. Res.* **1989**, *188*, 71–80; c) J. C. Castro-Palomino, G. Ritter, S. R. Fortunato, S. Reinhardt, L. J. Old, R. R. Schmidt, *Angew. Chem.* **1997**, *109*, 2081–2085; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1998–2001.
- [14] a) M. Sugimoto, T. Ogawa, *Glycoconjugate J.* **1985**, *2*, 5–9; b) M. Sugimoto, M. Numata, K. Koike, Y. Nakahara, T. Ogawa, *Carbohydr. Res.* **1986**, *156*, C1–C5; c) Y. Ito, M. Numata, M. Sugimoto, T. Ogawa, *J. Am. Chem. Soc.* **1989**, *111*, 8508–8510.
- [15] a) C.-T. Ren, C.-S. Chen, S.-H. Wu, *J. Org. Chem.* **2002**, *67*, 1376–1379; b) H. Ando, Y. Koike, H. Ishida, M. Kiso, *Tetrahedron Lett.* **2003**, *44*, 6883–6886; c) M. Adachi, H. Tanaka, T. Takahashi, *Synlett* **2004**, 609–614; d) H. Tanaka, M. Adachi, T. Takahashi, *Chem. Eur. J.* **2005**, *11*, 849–862; e) T. Fuse, H. Ando, A. Imamura, N. Sawada, H. Ishida, M. Kiso, T. Ando, S.-C. Li, Y.-T. Li, *Glycoconjugate J.* **2006**, *23*, 329–343; f) S. Hanashima, B. Castanger, D. Esposito, T. Nokami, P. H. Seeberger, *Org. Lett.* **2007**, *9*, 1777–1779.

- [16] a) S. Komba, C. Galustian, H. Ishida, T. Feizi, R. Kannagi, M. Kiso, *Angew. Chem.* **1999**, *111*, 1203–1206; *Angew. Chem. Int. Ed.* **1999**, *38*, 1131–1133; b) C. De Meo, A. V. Demchenko, G.-J. Boons, *J. Org. Chem.* **2001**, *66*, 5490–5497.
- [17] a) K. P. R. Kartha, A. Kameyama, M. Kiso, A. Hasegawa, *J. Carbohydr. Chem.* **1989**, *8*, 145–158; b) K. Hori, N. Sawada, H. Ando, H. Ishida, M. Kiso, *Eur. J. Org. Chem.* **2003**, 3752–3760.
- [18] T. Murakami, K. Furusawa, *Tetrahedron* **2002**, *58*, 9257–9263.
- [19] P. Garner, J. M. Park, *J. Org. Chem.* **1987**, *52*, 2361–2364.
- [20] K. Jansson, S. Ahlfors, T. Frejd, J. Kihlberg, G. Magnusson, *J. Org. Chem.* **1988**, *53*, 5629–5647.
- [21] C.-C. Wang, J.-C. Lee, S.-Y. Luo, H.-F. Fan, C.-L. Pai, W.-C. Yang, L.-D. Lu, S.-C. Hung, *Angew. Chem.* **2002**, *114*, 2466–2468; *Angew. Chem. Int. Ed.* **2002**, *41*, 2360–2362.
- [22] a) M. A. Nashed, L. Anderson, *Tetrahedron Lett.* **1976**, *17*, 3503–3506; b) S. David, A. Thieffry, A. Veyrières, *J. Chem. Soc. Perkin Trans. 1* **1981**, 1796–1801; c) J. Alais, A. Maranduba, A. Veyrières, *Tetrahedron Lett.* **1983**, *24*, 2383–2386.
- [23] S. Takano, M. Akiyama, S. Sato, K. Ogasawara, *Chem. Lett.* **1983**, 1593–1596.
- [24] a) G. H. Veeneman, S. H. van Leeuwen, J. H. van Boom, *Tetrahedron Lett.* **1990**, *31*, 1331–1334; b) P. Konradsson, U. E. Udodong, B. Fraser-Raid, *Tetrahedron Lett.* **1990**, *31*, 4313–4316; c) A. Hasegawa, T. Nagahama, H. Ohki, K. Hotta, H. Ishida, M. Kiso, *J. Carbohydr. Chem.* **1991**, *10*, 493–498.
- [25] a) J. Haverkamp, T. Spoormaker, L. Dorland, J. F. G. Vliegthart, R. Schauer, *J. Am. Chem. Soc.* **1979**, *101*, 4851–4853; b) H. Hori, T. Nakajima, Y. Nishida, H. Ohru, H. Meguro, *Tetrahedron Lett.* **1988**, 29, 6317–6320; c) S. Prytulla, J. Lauterwein, M. Klessinger, J. Thiem, *Carbohydr. Res.* **1991**, *215*, 345–349.
- [26] Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885–888.
- [27] A. F. Cook, *J. Org. Chem.* **1968**, *33*, 3589–3593.
- [28] a) R. R. Schmidt, J. Michel, *Angew. Chem.* **1980**, *92*, 763–764; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 731–732; b) R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213–236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212–235; c) K. K. Sadozai, T. Nukada, Y. Ito, Y. Nakahara, T. Ogawa, *Carbohydr. Res.* **1986**, *157*, 101–123; d) T. Ogawa, M. Sugimoto, T. Kitajima, K. K. Sadozai, T. Nukada, *Tetrahedron Lett.* **1986**, *27*, 5739–5742.
- [29] H. Takikawa, D. Nozawa, A. Kayo, S. Muto, K. Mori, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2467–2477.
- [30] S. Sugiyama, M. Honda, T. Komori, *Liebigs Ann. Chem.* **1990**, 1063–1068.
- [31] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
- [32] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.
- [33] a) G. A. Kraus, M. J. Taschner, *J. Org. Chem.* **1980**, *45*, 1175–1176; b) G. A. Kraus, B. Roth, *J. Org. Chem.* **1980**, *45*, 4825–4830; c) B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096.
- [34] a) P. Dave, H.-S. Byun, R. Engel, *Synth. Commun.* **1986**, *16*, 1343–1346; b) L. Schwink, P. Knochel, *Tetrahedron Lett.* **1994**, *35*, 9007–9010.

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## Synthetic study on $\alpha(2\rightarrow8)$ -linked oligosialic acid employing 1,5-lactamization as a key step

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### ABSTRACT

An attempt to synthesize  $\alpha(2\rightarrow8)$ -linked oligosialic acid utilizing a 1,5-lactamized sialyl acceptor is described. 1,5-Lactamization was experimentally proven to proceed only for  $\alpha$ -sialoside, which was integrated into the synthetic cycle of oligosialic acid as a chemical sorting step to collect the desired  $\alpha$ -sialoside and as a transformation step to produce a reactive sialyl acceptor for the next sialylation. Lactamized oligosialyl acceptors served as favorable coupling partners for sialylation, providing high stereoselectivities and high yields.

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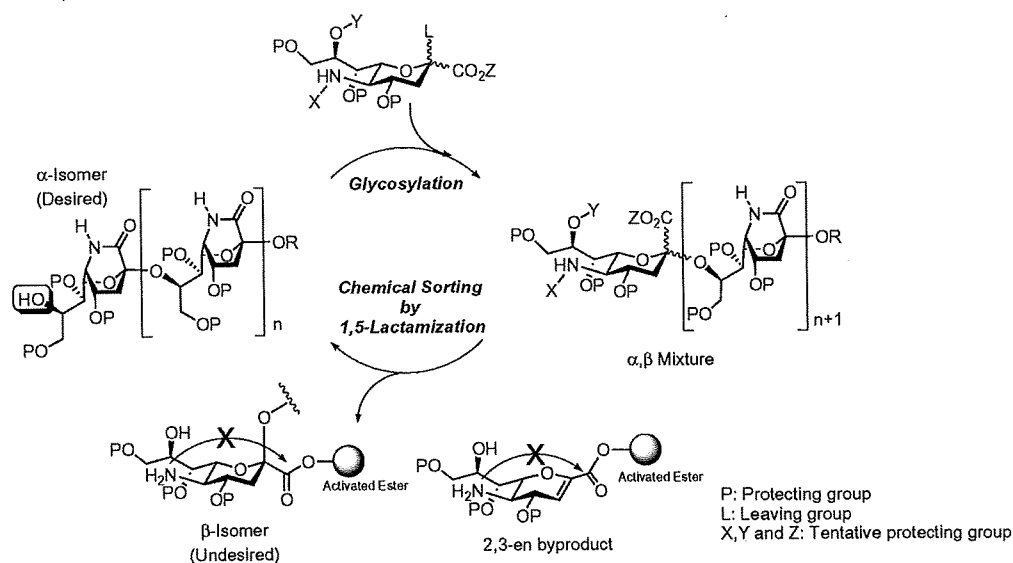
Sialic acids are expressed mostly on the glycan chains of glycoproteins and glycolipids, which play important roles in biological events such as cell adhesion, cell differentiation, viral infection, and neural network development.<sup>1</sup> In most cases, they occupy the distal end of glycan chains, being commonly linked to a galactose or *N*-acetylgalactosamine residue through an  $\alpha(2\rightarrow3)$  or  $\alpha(2\rightarrow6)$  linkage. In some cases, a sialic acid residue is further connected with another sialic acid at the C-4, C-8, or C-9 position, forming dimeric, oligomeric, or polymeric sialic acid. It is known that the expression of the  $\alpha(2\rightarrow8)$ -linked poly- and oligosialic acids in mammals is developmentally regulated, closely correlating to the stages of neural network formation,<sup>2</sup> and it was also demonstrated that  $\alpha(2\rightarrow8)$ -linked di- or trisialic acid-containing gangliosides showed neurite extension activity.<sup>3</sup>

Based on these impressive biological properties, the chemical synthesis of  $\alpha(2\rightarrow8)$ -linked oligosialic acid has been the subject of intensive investigation in carbohydrate chemistry. So far,  $\alpha(2\rightarrow8)$ -linked disialic acid has been successfully prepared using several approaches,<sup>4</sup> while tri- and tetrasialic acids have been synthesized only by Tanaka et al. whose approach involved utilizing a highly reactive 5-*N*,4-*O*-oxazolidino sialic acid donor and acceptor.<sup>5</sup> Herein, we report an attempt to synthesize  $\alpha(2\rightarrow8)$ -linked oligosialic acid based on a reactive 1,5-lactam sialyl acceptor.

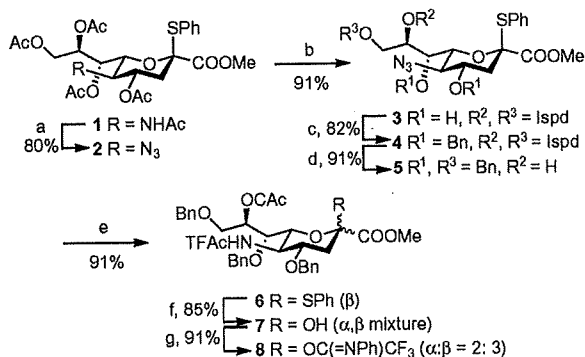
The critical issue in the formation of the  $\alpha(2\rightarrow8)$  linkage between sialic acids is the extremely low reactivity of the C-8 hydroxyl group, which is probably due to the hydrogen bonding with either the C-5 acetamido group or the C-1 methoxy carbonyl group.<sup>6</sup> Recently, we have demonstrated that the reactivity of the C-8 hydroxyl group could be dramatically enhanced by the formation of the 1,5-lactam of sialic acid, and this finding was successfully applied to the synthesis of the glycan moiety of a Hp-s6 ganglioside that possesses a 8-*O*-SO<sub>3</sub>H-Neu5Ac $\alpha(2\rightarrow8)$ Neu5Ac sequence.<sup>4f</sup> Based on these results, we developed a synthetic cycle to produce an  $\alpha(2\rightarrow8)$ -linked oligomer of sialic acid as a single anomer (Scheme 1). Simply, the synthesis comprises two reactions—sialylation and 1,5-lactamization. Since the 1,5-lactamization theoretically proceeds in the  $\alpha$ -configuration, the lactamization was expected to function as a chemical sorting step to collect the desired  $\alpha$ -glycoside exclusively as the lactamized sialyl acceptor for the next sialylation. Repetition of this cycle was expected to afford  $\beta$ -anomer-free  $\alpha(2\rightarrow8)$  oligosialic acids.

To carry out this cycle, we designed key sialyl units **6** and **8**, which bear a phenylthio<sup>7</sup> or trifluoroacetimidate group<sup>8</sup> at the anomeric position as a leaving group. A trifluoroacetyl group was used both to enhance the reactivity of the sialyl donor and to act as a tentative protecting group for the C-5 amino group.<sup>4e,9</sup> Benzyl groups were incorporated as persistent protecting groups during the chain extension, and the C-8 hydroxyl group was capped with a chloroacetyl group. The synthesis of sialyl donors **6** and **8** began

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with the complete deacetylation of *N*-Ac thioglycoside **1** with MsOH in MeOH, followed by a diazo transfer and *O*-acetylation to provide 5-azide derivative **2**<sup>10</sup> (80%, 3 steps) (Scheme 2). Compound **2** was then subjected to de-*O*-acetylation, 8,9-*O*-isopropylideneation, and 4,7-di-*O*-benzylation to give compound **4** (75%, 4 steps). Subsequent removal of the 8,9-*O*-isopropylidene acetal and selective 9-*O*-benzylation via a stannylene acetal intermediate afforded compound **5** (91%, 3 steps). Then, azido derivative **5** was converted into *N*-TFAc sialyl donor **6** through a reaction sequence including: (1) reduction of the azide group to an amino group with 1,3-propanedithiol and NEt<sub>3</sub> in MeOH<sup>11</sup>; (2) *N*-trifluoroacetylation; and (3) *O*-chloroacetylation (91%, 3 steps). Furthermore, the treatment of **6** with NBS in wet acetone afforded hemiketal **7** (85%), which, upon reaction with *N*-(phenyl)trifluoroacetimidoyl chloride

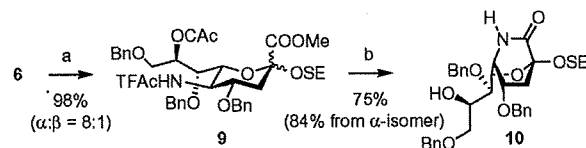


**Scheme 2.** Reagents and conditions: (a) (i) MsOH/MeOH, reflux; (ii) TfN<sub>3</sub>, DMAP/MeOH, rt; (iii) Ac<sub>2</sub>O, pyr, 0 °C → rt, 80% (3 steps); (b) (i) NaOMe/MeOH, rt; (ii) DMP, CSA/MeCN, rt, 91% (2 steps); (c) (i) BnBr, TBAI, NaH/DMF, rt; (ii) NaOMe/MeOH, rt, 82% (2 steps); (d) (i) 80% aq AcOH, 80 °C; (ii) DBTO/PhMe, 120 °C; (iii) BnBr, TBAI/PhMe, 120 °C, 91% (3 steps); (e) (i) 1,3-propanedithiol, Et<sub>3</sub>N/MeOH, reflux; (ii) TFAcOMe, NEt<sub>3</sub>, THF–MeOH (1:1), rt; (iii) CAcOH, DCC, DMAP/CH<sub>2</sub>Cl<sub>2</sub>, rt, 91% (3 steps); (f) NBS, wet acetone, rt, 85%; (g) CF<sub>3</sub>C(=NPh)Cl, K<sub>2</sub>CO<sub>3</sub>/acetone, rt, 91%. MsOH = methanesulfonic acid, TfN<sub>3</sub> = trifluoromethanesulfonyl azide, DMAP = 4-dimethylaminopyridine, DMP = 2,2-dimethoxypropane, CSA = (±)-10-camphorsulfonic acid, TBAI = tetra-*n*-butylammonium iodide, DBTO = di-*n*-butyltin oxide, TFAc = trifluoroacetyl, CAc = chloroacetyl, DCC = *N,N*-dicyclohexylcarbodiimide, Ispd = isopropylidene.

in the presence of K<sub>2</sub>CO<sub>3</sub> in acetone,<sup>8</sup> was converted into imidate donor **8** in 91% yield as a mixture of  $\alpha$ - and  $\beta$ -isomers ( $\alpha$ : $\beta$  = 2:3).

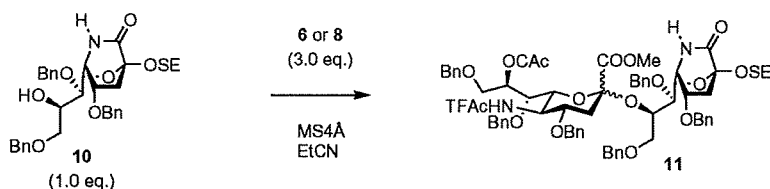
To assess the feasibility of the synthetic cycle, the sialyl unit **6** was subjected to glycosidation and subsequent 1,5-lactamization (Scheme 3). Then, sialyl donor **6** was reacted with 2-(trimethylsilyl)ethanol in the presence of NIS and TfOH<sup>12</sup> with the assistance of the nitrile solvent effect<sup>13</sup> at –40 °C to provide sialoside **9** as an anomeric mixture ( $\alpha$ : $\beta$  = 8:1) in 98% yield. Next, the resulting anomeric mixture was directly saponified and subsequently 1,5-lactamized by the treatment with HBTU and DIEA to afford acceptor **10** as a single isomer in 75% yield (84% as a conversion yield of the  $\alpha$ -isomer). In this reaction, the  $\beta$ -isomer was transformed into several unidentified highly polar compounds, which may include polymerized products,<sup>14</sup> thereby greatly facilitating the chromatographic separation of the lactamized  $\alpha$ -sialoside. In addition, from a mixture containing the corresponding 2,3-ene derivative, lactamized  $\alpha$ -sialoside **10** was easily collected by silica gel column chromatography. These results proved that 1,5-lactamization functions as a chemical sorting step for  $\alpha$ -sialoside.

Thus, with the lactamized acceptor **10** in hand, we then incorporated it into the cycle. First, we investigated the sialylation reaction of 1,5-lactamized acceptor **10** with donors **6** and **8** (Table 1). All reactions were carried out in EtCN as a stereocontrolling medium. The initial coupling of acceptor **10** with thioglycoside donor **6** using NIS–TfOH as the activator afforded the desired disaccharide **11** in 27% yield as an anomeric mixture ( $\alpha$ : $\beta$  = 16:1) (entry 1). The anomeric configuration of the major product in the mixture



**Scheme 3.** Reagents and conditions: (a) SEOH, NIS, TfOH, MS 3 Å/MeCN, –40 °C, 98% ( $\alpha$ : $\beta$  = 8:1); (b) (i) 1.0 M aq NaOH–THF–MeOH (1:2:2), rt; (ii) HBTU, DIEA/MeCN, rt; (iii) 1.0 M aq NaOH–THF–MeOH (1:2:2), rt, 75% (3 steps). SE = 2-(trimethylsilyl)ethyl, NIS = *N*-iodosuccinimide, TfOH = trifluoromethane sulfonic acid, HBTU = *O*-(benzotriazol-1-yl)-*N,N,N,N'*-tetramethyluronium hexafluorophosphate, DIEA = *N,N*-diisopropylethylamine.

Table 1



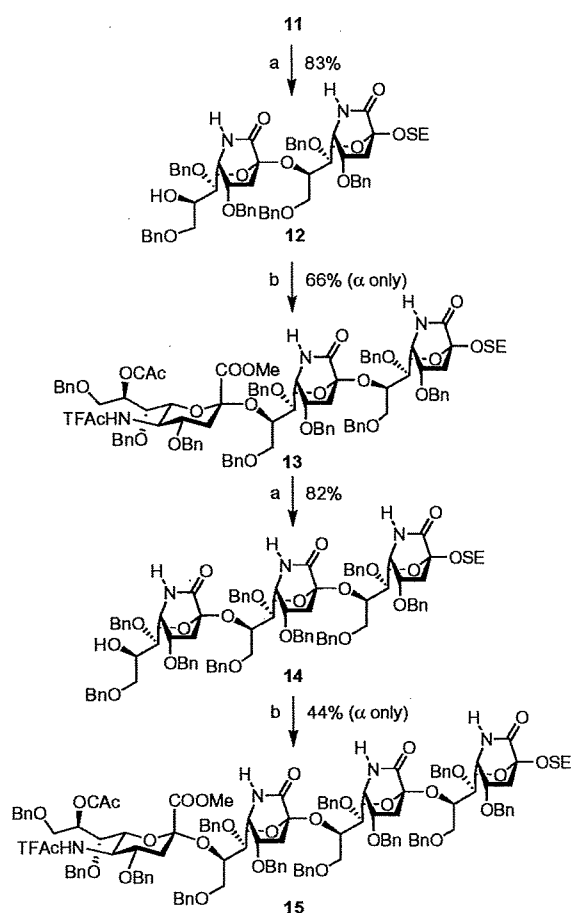
Entry	Donor	Promoter	Temp (°C)	Time (h)	Yield (%)	$\alpha$ : $\beta$ <sup>a</sup>
1	<b>6</b> ( $\beta$ )	NIS (4.5 equiv), TfOH (0.9 equiv)	-80 to 0	9	27	16:1
2	<b>6</b> ( $\beta$ )	PhSeBr (9.0 equiv), AgOTf (9.0 equiv) DTBMP (9.0 equiv)	-80 to -70	4	0	—
3	<b>6</b> ( $\beta$ )	Ph <sub>2</sub> SO (9.0 equiv), Tf <sub>2</sub> O (3.3 equiv) DTBMP (6.0 equiv)	-80 to rt	12	0	—
4	<b>8</b> ( $\alpha$ , $\beta$ )	TMSOTf (0.15 equiv)	-80	72	86	16:1

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of the  $\alpha$ / $\beta$  mixture.

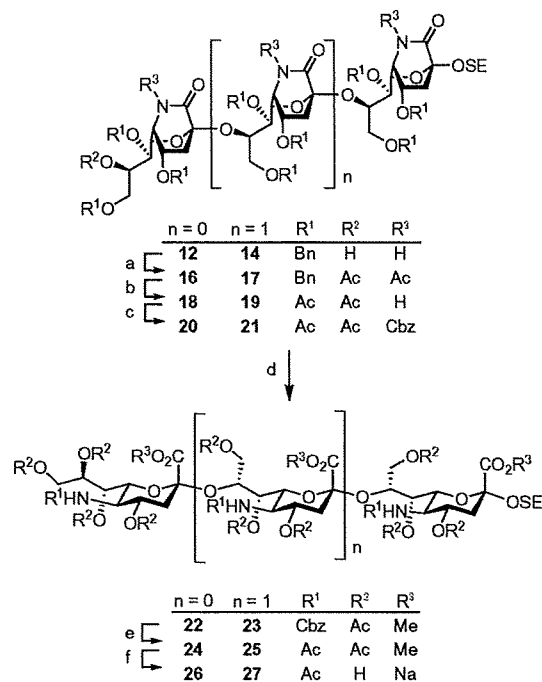
was determined to be  $\alpha$  from its <sup>3</sup>J<sub>C1,H3 $\alpha$</sub>  coupling constant (6.9 Hz)<sup>15</sup> while that of the minor product was less than 1.0 Hz, indicating it to be  $\beta$ .<sup>16</sup> When other activators<sup>17,18</sup> for thioglycoside **6** were used, none of the desired disaccharide **11** was produced (entries 2 and 3). It was found that these oxidative conditions were

not well suited for the sialylation of lactamized sialyl acceptor **10**. In entry 1, the corresponding *N*-hydroxy derivative of **10** was isolated as a byproduct, which was produced probably as a result of *N*-iodination within the lactam by NIS followed by hydrolysis during the aqueous work-up. As shown in entry 4, the coupling of **10** with the imidate donor **8** catalyzed by TMSOTf provided a high yield of **11** (86%) with excellent  $\alpha$ -selectivity ( $\alpha$ : $\beta$  = 16:1).

Next, the disaccharide **11** as an anomeric mixture was saponified and 1,5-lactamized to afford the acceptor **12** in pure form (Scheme 4). In the next cycle, to our delight, the coupling of **8** and **12** provided trisialic acid **13** as a single isomer



**Scheme 4.** Reagents and conditions: (a) (i) 1.0 M aq NaOH–THF–MeOH (1:2:2), rt; (ii) HBTU, DIEA/MeCN, rt; (iii) 1.0 M aq NaOH–THF–MeOH (1:2:2), rt, 83% (**12**, 3 steps), 82% (**14**, 3 steps); (b) **8**, TMSOTf/EtCN, -80 °C, 66% (**13**,  $\alpha$  only), 44% (**15**,  $\alpha$  only).



**Scheme 5.** Reagents and conditions: (a) (i) Ac<sub>2</sub>O, DMAP, pyr, rt, 89% (**16**), 94% (**17**), (ii) H<sub>2</sub>, Pd(OH)<sub>2</sub>–C/EtOAc–EtOH (1:1), 40 °C; (iii) Ac<sub>2</sub>O, DMAP, pyr, rt; (iv) hydrazine acetate/THF, rt, 84% (**18**, 3 steps), 85% (**19**, 3 steps); (b) CbzOSu, DMAP, pyr, rt, 61% (**20**), 56% (**21**); (c) (i) NEt<sub>3</sub>–MeCN–H<sub>2</sub>O (1:9:5), 40 °C; (ii) MeI, K<sub>2</sub>CO<sub>3</sub>/DMF, rt; (iii) Ac<sub>2</sub>O, DMAP, pyr, rt, 37% (**22**, 3 steps), 22% (**23**, 3 steps); (d) H<sub>2</sub>, Pd(OH)<sub>2</sub>–C/Ac<sub>2</sub>O–EtOAc (1:1), rt, 71% (**24**), 61% (**25**); (e) 1.0 M aq NaOH, 40 °C, 97% (**26**), 41% (**27**). CbzOSu = *N*-(benzyloxycarbonyloxy)succinimide.

( $^3J_{C1,H3ax} = 6.9$  Hz)<sup>15</sup> in 66% yield. Once again, **13** could be converted into 1,5-lactamized acceptor **14**, which was sialylated with **8** under the same reaction conditions to furnish the tetrasaccharide **15** again as a pure  $\alpha$ -isomer ( $^3J_{C1,H3ax} = 5.8$  Hz)<sup>15</sup> in 44% yield.

Finally, we attempted to convert the fully lactamized di- and trisaccharide **12** and **14** into their natural *N*-acetyl form (Scheme 5). According to our reported procedure,<sup>4f</sup> compounds **12** and **14** are predisposed for lactam opening. Thus, the following reaction sequences supplied the suitably protected **20** and **21** in 46% and 45% yields, respectively: acetylation, debenzoylation, acetylation, *N*-deacetylation, and *N*-benzyloxycarbonylation. Then, basic hydrolysis of **20** and **21** followed by methylation of the resulting carboxylic acids and acetylation afforded products **22** and **23**. Finally, debenzoylation and acetylation produced the *N*-Ac derivatives **24** and **25** in 71% and 61% yields, which were subjected to hydrolysis providing **26** and **27**.

In conclusion, the synthesis of  $\alpha(2\rightarrow8)$  trisialoside has been completed by a route incorporating 1,5-lactamization reactions. Since it was proven that the process of 1,5-lactamization is selective for  $\alpha$ -sialoside in a glycosylation mixture, this principle could be applied not only in sialoside synthesis in the liquid phase but also in syntheses in the solid phase. Applications of this methodology to the synthesis of gangliosides will be reported in the future.

#### Acknowledgments

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#### Supplementary data

Supplementary data ( $^1H$  and  $^{13}C$  NMR spectra of compounds **11**, **12**, **13**, **14**, **15**, **26**, and **27**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.057.

#### References and notes

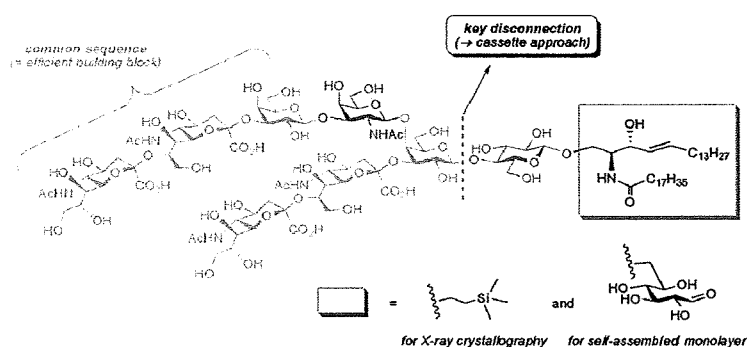
- (a) Angata, T.; Varki, A. *Chem. Rev.* **2002**, *102*, 439–470; (b) Varki, A. *Nature* **2007**, *446*, 1023–1029; (c) Murrey, H. E.; Hsieh-Wilson, L. C. *Chem. Rev.* **2008**, *108*, 1708–1731.
- (a) Daniloff, J. K.; Chuong, C.-M.; Levi, G.; Edelman, G. M. *J. Neurosci.* **1986**, *6*, 739–758; (b) Svennerholm, L.; Boström, K.; Fredman, P.; Månsson, J.-E.; Rosengren, B.; Rynmark, B.-M. *Biochim. Biophys. Acta* **1989**, *1005*, 109–117.
- Tsuji, S.; Arita, M.; Nagai, Y. *J. Biochem.* **1983**, *94*, 303–306.
- Indirect method: (a) Okamoto, K.; Kondo, T.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 5229–5232; (b) Ito, Y.; Numata, M.; Sugimoto, M.; Ogawa, T. *J. Am. Chem. Soc.* **1989**, *111*, 8508–8510; (c) Castro-Palomino, J. C.; Tsvetkov, Y. E.; Schmidt, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 5434–5440; (d) Hossain, N.; Magnusson, G. *Tetrahedron Lett.* **1999**, *40*, 2217–2220; Direct method: (e) De Meo, C.; Demchenko, A. V.; Boons, G.-J. *J. Org. Chem.* **2001**, *66*, 5490–5497; (f) Ando, H.; Koike, Y.; Koizumi, S.; Ishida, H.; Kiso, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6759–6763; (g) Tanaka, H.; Nishiura, Y.; Adachi, M.; Takahashi, T. *Heterocycles* **2006**, *67*, 107–112.
- Tanaka, H.; Nishiura, Y.; Takahashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 7124–7125.
- (a) Tsvetkov, Y. E.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *35*, 8583–8586; (b) Boons, G.-J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539–4566.
- Marra, A.; Sinaý, P. *Carbohydr. Res.* **1989**, *187*, 35–42.
- Cai, S.; Yu, B. *Org. Lett.* **2003**, *5*, 3827–3830.
- Komba, S.; Galustian, C.; Ishida, H.; Feizi, T.; Kannagi, R.; Kiso, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1131–1133.
- Matsuoka, K.; Oka, H.; Terunuma, D.; Kuzuhara, H. *Carbohydr. Lett.* **2001**, *4*, 123–130.
- Bayley, H.; Standring, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, *39*, 3633–3634.
- (a) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334; (b) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313–4316.
- (a) Schmidt, R. R.; Rücker, E. *Tetrahedron Lett.* **1980**, *21*, 1421–1424; (b) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379–1382; (c) Kanie, O.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1988**, *7*, 501–506; (d) Hasegawa, A.; Nagahama, T.; Ohki, H.; Hotta, K.; Ishida, H.; Kiso, M. *J. Carbohydr. Chem.* **1991**, *10*, 493–498.
- In the carbodiimide-mediated lactamization,  $\beta$ -sialoside was converted into the corresponding *N*-acylurea derivative.
- See the Supplementary data.
- (a) Hori, H.; Nakajima, T.; Nishida, Y.; Ohru, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317–6320; (b) Haverkamp, J.; Spoormaker, T.; Dorland, L.; Vliegthart, F. C.; Schauer, R. *J. Am. Chem. Soc.* **1979**, *101*, 4851–4853; (c) Prytulla, S.; Lauterwein, J.; Klessinger, M.; Thiem, J. *Carbohydr. Res.* **1991**, *215*, 345–349.
- Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 1061–1064.
- Crich, D.; Li, W. *Org. Lett.* **2006**, *8*, 959–962.

## Ganglioside GQ1b: Efficient Total Synthesis and the Expansion to Synthetic Derivatives To Elucidate Its Biological Roles

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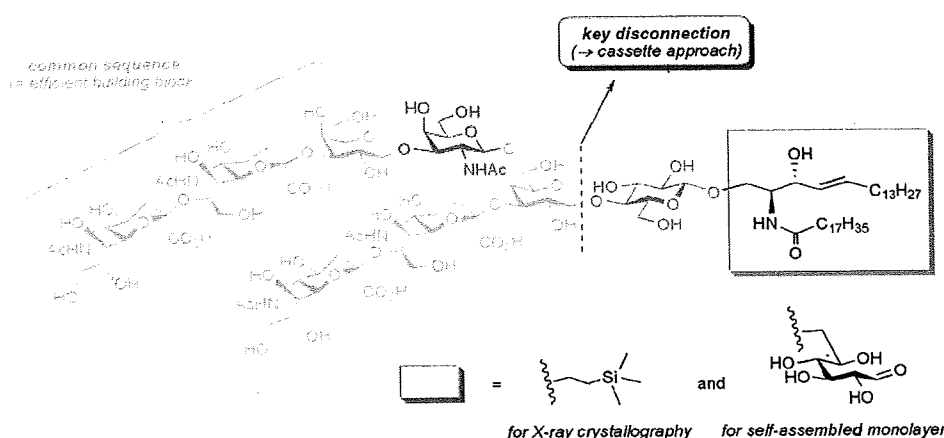
## Ganglioside GQ1b: Efficient Total Synthesis and the Expansion to Synthetic Derivatives To Elucidate Its Biological Roles<sup>†</sup>

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The convergent total synthesis of ganglioside GQ1b based on the “cassette approach” between the nonreducing end GQ1b-core heptasaccharide and glucosylceramide building blocks was accomplished in high overall yield. The use of a sialyl $\alpha$ (2 $\rightarrow$ 8)sialyl $\alpha$ (2 $\rightarrow$ 3)galactose sequence as the key building block enhanced the efficiency of the glycan assembly and led to preparative-scale synthesis readily applicable for large-scale preparation. In addition, a judicious choice of *p*-methoxybenzyl protecting groups on glucosylceramide provided a solution to the previous synthetic problems, including a decrease in the yield of the deprotection steps, and led to elevation of the total yield. Furthermore, unnatural-type GQ1b derivatives were synthesized systematically in good yields by capitalizing on a similar approach in order to elucidate their biological roles.

### Introduction

Gangliosides, sialylated glycosphingolipids, are the components of the membranes in the cells of all living organisms and are particularly abundant in the nervous system on the vertebrate cell plasma membrane.<sup>2</sup> For the past two decades, gangliosides have attracted wide attention in various scientific fields, because

they play various important roles in vital processes. Ganglioside GQ1b, which is classified as one of the b-series gangliosides, exists abundantly in the mammalian central nervous system and participates in many physiological events, such as neurite extension,<sup>3</sup> toxin binding,<sup>4</sup> modulation of protein phosphorylation,<sup>5</sup> cell adhesion and growth,<sup>6,7</sup> and apoptosis.<sup>8</sup> Despite its biological importance, advancement in the biological study of b-series gangliosides, including GQ1b, has been restricted due

<sup>†</sup> Synthetic studies on sialoglycoconjugates, part 147. For part 146, see ref 1.  
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(1) Yamaguchi, M.; Ishida, H.; Kiso, M. *Carbohydr. Res.* 2008, 343, 1849–1857.

(2) Wiegandt, H. In *Glycolipids*; Wiegandt, H., Ed.; Elsevier: New York, 1985; pp 199–260. (b) Lloyd, K. O.; Furukawa, K. *Glycoconjugate J.* 1998, 15, 627–636. (c) Sonnino, S.; Mauri, L.; Chigorno, V.; Prinetti, A. *Glycobiology* 2006, 17, 1R–13R.

(3) Tsuji, S.; Arita, M.; Nagai, Y. *J. Biochem.* 1983, 94, 303–306.

(4) Ångström, J.; Teneberg, S.; Karlsson, K.-L. *Proc. Natl. Acad. Sci. U.S.A.* 1994, 91, 11859–11863.



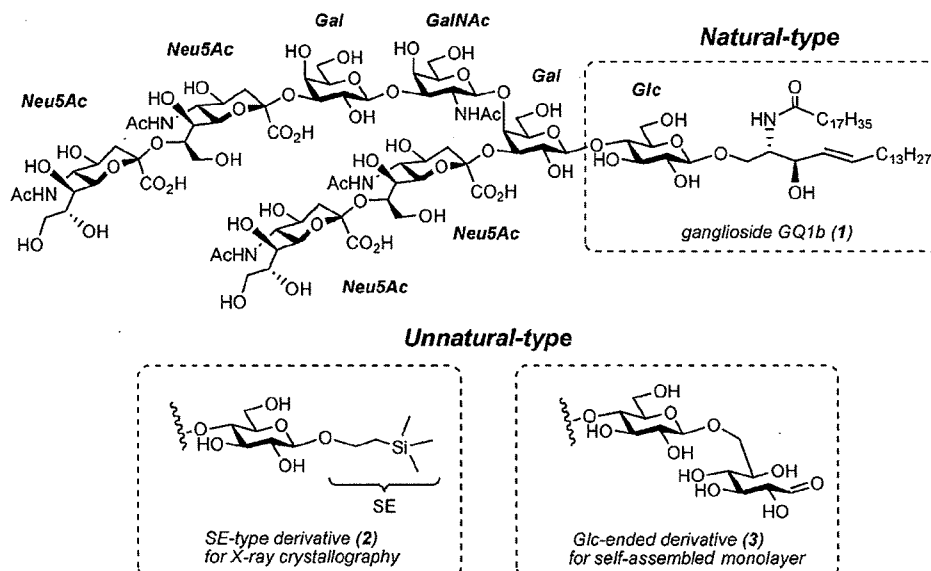


FIGURE 1. Structure of target compounds.

to a deficiency in the supply of pure gangliosides. In 1994, our group first achieved the total synthesis of ganglioside GQ1b, which led to the elucidation of the biological functions of GQ1b at the molecular level.<sup>9</sup> However, there were problems yet to be solved with regard to the overall yields and stereoselectivity of the coupling reactions, which prevented large quantity synthesis. Recently, it has become essential to develop large-scale synthesis of gangliosides, because of multifaceted research needs, e.g., microarray, molecular imaging, and X-ray crystallographic studies. Therefore, we envisioned renewal of the total synthetic method for natural ganglioside GQ1b (1) (Figure 1). Furthermore, we decided to develop access to versatile unnatural GQ1b derivatives to elucidate their biological roles. The following were designed as unnatural GQ1b derivatives (Figure 1): (i) *SE* [2-(trimethylsilyl)ethyl]-type derivative (2) demonstrated that SE-type GQ1b derivatives serve as good tools for X-ray crystallographic analysis with lectins such as Siglec-7,<sup>10</sup> botulinum neurotoxin,<sup>11</sup> and tetanus toxin,<sup>12</sup> because replacement of ceramide with an SE group may render it more amenable to crystallization (being more water-soluble, less flexible, and less likely to form micelles) and (ii) *Glc-ended derivative* (3) allowed accomplishment of the synthesis of GM1,

GM2, and GM3 bearing D-glucose at the reducing terminal and succeeded in the assembly of the sugar microarray.<sup>13</sup> The D-glucose residue in this derivative provided a reactive aldehyde functionality at the reducing end and served as a spacer between the targeted sugar chain and the scaffold for immobilization because of its appropriate hydrophilicity and flexibility.

Herein, we report the renewed efficient synthesis of natural ganglioside GQ1b and its unnatural derivatives.

## Results and Discussion

To achieve the efficient and systematic synthesis of the targeted compounds bearing different reducing terminals, sialyl $\alpha$ (2 $\rightarrow$ 8)sialyl $\alpha$ (2 $\rightarrow$ 3)galactose sequences were focused on as the common trisaccharide building blocks. Using this common sequence, a synthetic scheme for the targets was devised, as shown in Figure 2. This included four important glycosylation steps: (1) sialylation to produce the common trisaccharide; (2) galactosaminidation; (3) coupling of the trisaccharide donor and the tetrasaccharide acceptor, derived from the common trisaccharide; and (4) final glycosylation of the reducing terminal acceptors.

According to the above-mentioned scheme, disialylgalactose unit 6 was selected as the key compound and was prepared by glycosylation of the known galactose acceptor 5<sup>14</sup> with sialyl $\alpha$ (2 $\rightarrow$ 8)sialyl phenylthioglycoside donor 4.<sup>9</sup> We were eager to find out how stereo- and regioselectivity in sialylation increases, and therefore a series of sialylations under various conditions were conducted. The results are summarized in Table 1. First, the sialylation of 5 in the presence of dimethyl(methylthio)sulfonium triflate (DMTST)<sup>15</sup> as a promoter in acetonitrile at  $-35$  °C hardly gave 6 (entry 1). In entry 2, by using

(5) Tsuji, S.; Nakajima, T.; Sasaki, Y.; Nagai, Y. *J. Biochem.* **1985**, *97*, 969–972.

(6) (a) Kleinman, H. K.; Martin, G. R.; Fishman, P. H. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3367–3371. (b) Cheresch, D. A.; Pierschbacher, M. D.; Herzog, M. A.; Mujoo, K. *J. Cell Biol.* **1986**, *102*, 688–696.

(7) (a) Nakano, J.; Raj, B. K.; Asagami, C.; Lloyd, K. O. *J. Invest. Dermatol.* **1996**, *107*, 543–548. (b) Birkle, S.; Ren, S.; Slominski, A.; Zeng, G.; Gao, L.; Yu, R. K. *J. Neurochem.* **1999**, *72*, 954–961.

(8) De Maria, R.; Lenti, L.; Malisan, F.; d'Agostino, F.; Tomassini, B.; Zeuner, A.; Rippo, M. R.; Testi, R. *Science* **1997**, *277*, 1652–1655.

(9) (a) Ishida, H.-K.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1994**, *260*, C1–C6. (b) Ishida, H.-K.; Ishida, H.; Kiso, M.; Hasegawa, A.; *Tetrahedron: Asymmetry* **1994**, *5*, 2493–2512. (c) Nunomura, S.; Matsuzaki, Y.; Ito, Y.; Ogawa, T. *Pure Appl. Chem.* **1994**, *66*, 2123–2126.

(10) (a) Atrill, H.; Imamura, A.; Sharma, R. S.; Kiso, M.; Crocker, P. R.; van Aalten, D. M. F. *J. Biol. Chem.* **2006**, *281*, 32774–32783. (b) Atrill, H.; Takazawa, H.; Witt, S.; Kelm, S.; Isecke, R.; Brossmer, R.; Ando, T.; Ishida, H.; Kiso, M.; Crocker, P. R.; van Aalten, D. M. F. *Biochem. J.* **2006**, *397*, 271–278.

(11) Stenmark, P.; Dupuy, J.; Imamura, A.; Kiso, M.; Stevens, R. C. *PLoS Pathog.* **2008**, *4*, e1000129.

(12) Fotinou, C.; Emsley, P.; Black, I.; Ando, H.; Ishida, H.; Kiso, M.; Sinha, K. A.; Fairweather, N. F.; Isaacs, N. W. *J. Biol. Chem.* **2001**, *276*, 32274–32281.

(13) Imamura, A.; Yoshikawa, T.; Komori, T.; Ando, M.; Ando, H.; Wakao, M.; Suda, Y.; Ishida, H.; Kiso, M. *Glycoconjugate J.* **2008**, *25*, 269–278.

(14) Komba, S.; Ishida, H.; Kiso, M.; Hasegawa, A. *Glycoconjugate J.* **1996**, *13*, 241–254.

(15) (a) Ravenscroft, M.; Roberts, R. M. G.; Tillett, J. G. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1569–1572. (b) Fugedi, P.; Garegg, P. *J. Carbohydr. Res.* **1986**, *149*, C9–C12.

(16) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334.

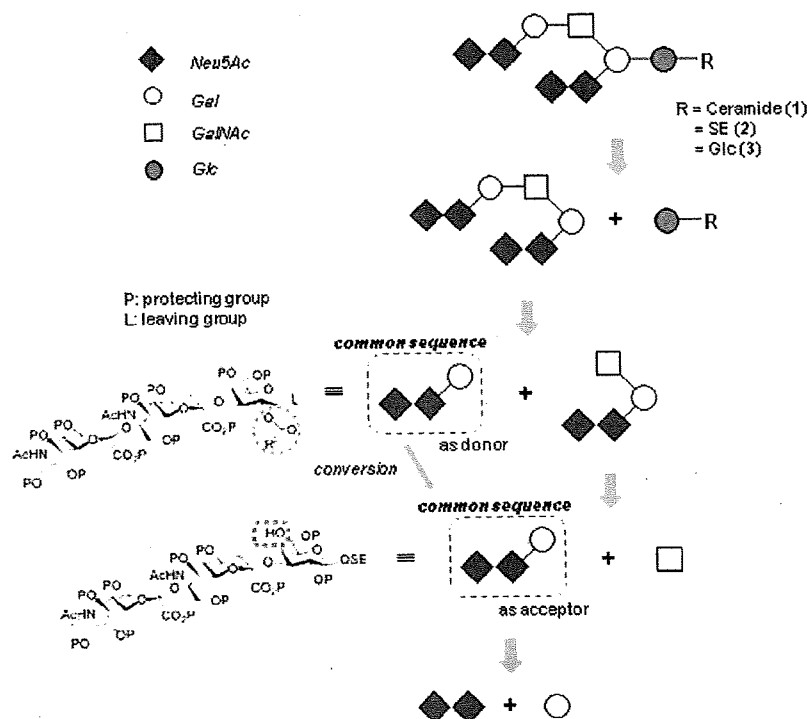


FIGURE 2. Outline of renewed synthetic approach for ganglioside GQ1b and its analogs.

TABLE 1. Preparation of the Key Building Block 6, Sialyl $\alpha$ (2 $\rightarrow$ 8)sialyl $\alpha$ (2 $\rightarrow$ 3)galactose Unit

entry	promoter	solvent	T (°C)	% yield of products <sup>a</sup>			
				(2 $\rightarrow$ 3) glycoside		(2 $\rightarrow$ 4) glycoside	2,3-ene of donor
				$\alpha$	$\beta$		
1	DMTST <sup>b</sup>	MeCN	-35	trace	trace	trace	trace
2	NIS-TfOH	MeCN	-35	33	17	10	22
3	NIS-BF <sub>3</sub> ·OEt <sub>2</sub>	MeCN	-35	21	19	11	23
4	NIS-TMSOTf	MeCN	-35	31	15	9	20
5	NIS-TfOH	EtCN	-50	44	14	8	16

<sup>a</sup> Isolated yield. <sup>b</sup> DMTST: dimethyl(methylthio)sulfonium triflate.

NIS-TfOH<sup>16</sup> as a promoter system with the assistance of the solvent effect of acetonitrile,<sup>17</sup> the desired  $\alpha$ -sialoside **6** was obtained in 33% yield with a scarcely better  $\alpha/\beta$ -ratio (2/1). However, adverse side reactions also occurred and resulted in a 2,3-ene derivative of the donor as a byproduct. In entry 3, the use of BF<sub>3</sub>·OEt<sub>2</sub> instead of TfOH led to a reduction in both the yield of **6** and its stereoselectivity. On the other hand, the use of NIS-TMSOTf (entry 4) as a promoter system gave results similar to NIS-TfOH. In entry 5, when the reaction was conducted in the presence of NIS-TfOH in propionitrile at -50 °C, the desired **6** was obtained in a rewarding 44% yield, and

stereoselectivity was improved with a slight reduction of the byproduct. The  $\alpha$ -configuration of the glycoside of **6** was assigned according to empirical rules<sup>18</sup> and was further confirmed by observation of a strong cross peak between H<sup>a</sup>-3ax and C<sup>a</sup>-1 in the HMBC spectrum<sup>19</sup> of **6**, because the  $\alpha$ -sialosides has a larger heteronuclear coupling constant (<sup>3</sup>J<sub>C-1,H-3ax</sub>) than  $\beta$ -sialoside (see the Supporting Information).

The difficulty of introducing a  $\beta$ -galactosaminyl glycoside at the C-4 position of galactose has been revealed in the literature<sup>20</sup> in relation to the assembly of a ganglio-series

(17) (a) Schmidt, R. R.; Rücker, E. *Tetrahedron Lett.* **1980**, *21*, 1421-1424. (b) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379-1382. (c) Murase, T.; Kameyama, A.; Kartha, K. P. R.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1989**, *8*, 265-283.

(18) (a) van der Vleugel, D. J. M.; van Heeswijk, W. A. R.; Vliegthart, J. F. G. *Carbohydr. Res.* **1982**, *102*, 121-130. (b) Paulsen, H.; Tietz, H. *Carbohydr. Res.* **1984**, *125*, 47-64.

(19) Xia, J.; Alderfer, J. L.; Piskorz, C. F.; Matta, K. L. *Chem.-Eur. J.* **2001**, *7*, 356-367.

## SCHEME 1. Preparation of Novel GalNAc Glycosyl Donors

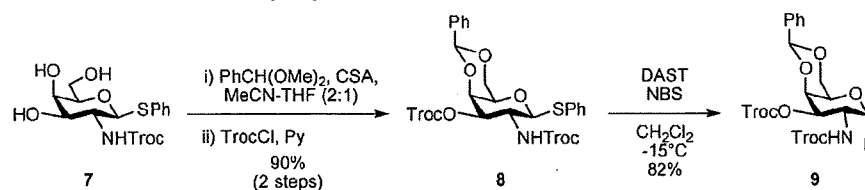
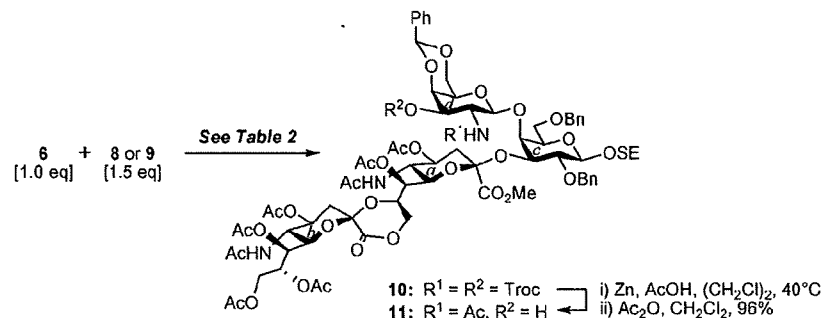


TABLE 2. Galactosaminidations of 6 and Subsequent Conversion into Tetrasaccharide Acceptor 11



entry	donor	promoter	solvent	T (°C)	% yield <sup>a</sup>
1	8	NIS-TfOH	CH <sub>2</sub> Cl <sub>2</sub>	0	58
2	8	NIS-TfOH	CH <sub>2</sub> Cl <sub>2</sub>	-35	50
3	9	SnCl <sub>2</sub> -AgClO <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	52
4	9	HNTf <sub>2</sub>	BTF- <sup>t</sup> BuCN <sup>b</sup>	rt	trace
5	9	Cp <sub>2</sub> ZrCl <sub>2</sub> -AgOTf	CH <sub>2</sub> Cl <sub>2</sub>	-20	85

<sup>a</sup> Isolated yield. <sup>b</sup> BTF: benzotrifluoride.

ganglioside skeleton, and the choice of the neighboring group of the anomeric center and the mode of protection for GalNAc has been examined in several ways.<sup>21</sup> In this study, two kinds of GalNAc donors **8** and **9**, which commonly carry a 2,2,2-trichloroethoxycarbonyl (Troc) group at C-2, were designed, as shown in Scheme 1. It is known that the Troc group should ensure  $\beta$ -selective glycosylation as well as increased reactivity as a glycosyl donor compared with the *N*-phthaloyl group.<sup>22</sup> Additionally, the advantage of the Troc group lies in the high degree of efficiency in installment and chemoselective deprotection.

Acetalization of the previously described phenylthio-galactosaminide **7**<sup>23</sup> with PhCH(OMe)<sub>2</sub> and ( $\pm$ )-10-camphorsulfonic acid (CSA) and subsequent protection of the remaining C-3-hydroxyl group by the Troc group afforded novel GalNAc thioglycoside donor **8** in 90% yield over two steps. Thiogly-

coside **8** was then efficiently converted into fluoride **9** as another GalNAc donor.<sup>24</sup> In the design of GalNAc donors, the Troc group was also exploited for the protection of the C-3 hydroxyl group to facilitate access to the tetrasaccharide acceptor for the next coupling reaction. The obtained GalNAc donors **8** and **9** were subjected to galactosaminidation with **6**. The results are summarized in Table 2.

In entries 1 and 2, the glycosidations of thioglycoside **8** with **6** were carried out in the presence of NIS-TfOH in CH<sub>2</sub>Cl<sub>2</sub>, affording the tetrasaccharide **10** in moderate yield along with several byproducts. Although the byproducts were inseparable, the mass spectrum of the mixture of byproducts indicated the presence of a molecule with the same molecular weight of **10**, probably  $\alpha$ -glycoside. This result is in accordance with the report<sup>25</sup> that the *galacto*-type donor bearing the benzylidene group at the C-4,6 positions gave  $\alpha$ -glycoside, which is unusual even in the presence of the neighboring participating acyl group at C-2. Next, in entries 3–5, the glycosidation of fluoride donor **9** in the presence of various promoters was attempted. When SnCl<sub>2</sub>-AgClO<sub>4</sub><sup>26</sup> was used (entry 3), the yield of **10** was not improved, and the stereoselectivity did not change appreciably. The use of HNTf<sub>2</sub><sup>27</sup> in the mixture solvent (BTF/<sup>t</sup>BuCN) hardly gave **10** (entry 4). On the other hand, when the reaction was conducted in the presence of Cp<sub>2</sub>ZrCl<sub>2</sub>-AgOTf<sup>28</sup> at -20 °C (entry 5), both yield and stereoselectivity were dramatically improved to afford **10** in 85% yield. Furthermore, it was found

(20) (a) Wessel, H. P.; Iversen, T.; Bundle, D. R. *Carbohydr. Res.* **1984**, *130*, 5–21. (b) Sugimoto, M.; Horisaki, T.; Ogawa, T. *Glycoconjugate J.* **1985**, *2*, 11–15. (c) Paulsen, H.; Paal, M. *Carbohydr. Res.* **1985**, *137*, 39–62. (d) Stauch, T.; Greilich, U.; Schmidt, R. R. *Liebigs Ann.* **1995**, 2101–2111.

(21) (a) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167–1195. (b) Matsuzaki, Y.; Nunomura, S.; Ito, Y.; Sugimoto, M.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1993**, *242*, C1–C6. (c) Greilich, U.; Brescello, R.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann.* **1996**, 663–672. (d) Castro-Palmino, J. C.; Ritter, G.; Fortunato, S. R.; Reinhardt, S.; Old, L. J.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **1997**, *36*, 1998–2001. (e) Castro-Palmino, J. C.; Schmidt, R. R. *Tetrahedron Lett.* **1995**, *36*, 6871–6874. (f) Debenham, J. S.; Madsen, R.; Robert, C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 3302–3303. (g) Jiao, H.; Hindsgaul, O. *Angew. Chem., Int. Ed.* **1999**, *38*, 346–348. (h) Bhattacharya, S. K.; Danishefsky, S. J. *J. Org. Chem.* **2000**, *65*, 144–151. (i) Liao, W.; Piskorz, C. F.; Locke, R. D.; Matta, K. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 793–795.

(22) (a) Dullenkopf, W.; Castro-Palmino, J. C.; Manzoni, L.; Schmidt, R. R. *Carbohydr. Res.* **1996**, *296*, 135–147. (b) Ellervik, U.; Magnusson, G. *Carbohydr. Res.* **1996**, *280*, 251–260.

(23) Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. *Org. Lett.* **2005**, *7*, 4415–4418.

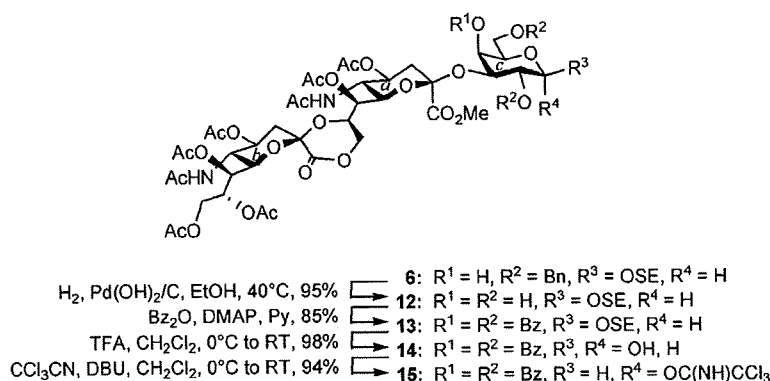
(24) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189–4192.

(25) (a) Yule, J. E.; Wong, T. C.; Ganghi, S. S.; Qiu, D.; Riopel, M. A.; Koganty, R. R. *Tetrahedron Lett.* **1995**, *36*, 6839–6842. (b) Bélot, F.; Jacquinet, J.-C. *Carbohydr. Res.* **2000**, *325*, 93–106. (c) Chen, L.; Kong, F. *Tetrahedron Lett.* **2003**, *44*, 3691–3695.

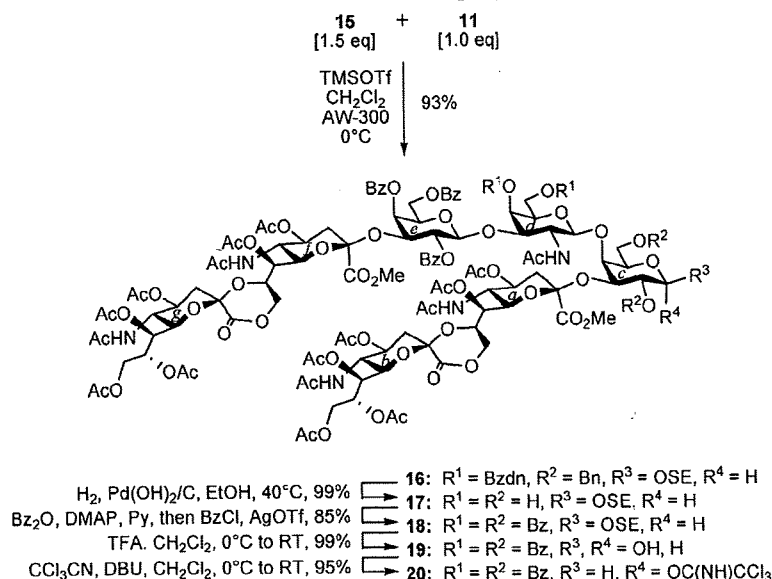
(26) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431–432.

(27) (a) Mukaiyama, T.; Maeshima, H.; Jona, H. *Chem. Lett.* **2001**, 426–427. (b) Jona, H.; Mandai, H.; Chavasiri, W.; Takeuchi, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291–309.

## SCHEME 2. Conversion of 6 into Donor Form 15



## SCHEME 3. Glycosylation of 11 with 15 and Conversion into GQ1b Epitope Donor 20



that these conditions were applicable in a large-scale synthesis. As expected, the obtained tetrasaccharide **10** could be efficiently converted into tetrasaccharide acceptor **11** through the removal of the Troc groups by treatment with preactivated zinc, followed by the selective acetylation of the liberated amine of the GalNAc residue at C-2.

Scheme 2 shows the facile conversion of the key common unit **6** into donor form **15**. Thus, hydrogenolysis of the benzyl groups afforded the triol **12** in excellent yield, and subsequent benzylation of the exposed three hydroxyl groups successfully proceeded to give **13** in 85% yield. In order to introduce a leaving group at the reducing end of **13**, the SE group was removed by exposure to trifluoroacetic acid.<sup>29</sup> The obtained hemiacetal **14** was then converted into  $\alpha$ -trichloroacetimidate **15** by treatment with  $\text{CCl}_3\text{CN}$  and DBU.<sup>30</sup>

Next, as shown in Scheme 3, the coupling reaction of **15** and **11** was conducted. The reaction was performed in the presence of TMSOTf in  $\text{CH}_2\text{Cl}_2$  at 0 °C. This block coupling

surprisingly afforded the desired GQ1b-core heptasaccharide **16** in excellent yield (93%). The reaction was also successful in large scale (~10 g). Undoubtedly, the branched tetrasaccharide acceptor **11** performed excellent couplings with other glycosyl donors. As shown in Scheme 4, the glycosylation of **11** with the known sialyl $\alpha(2\rightarrow3)$ galactose donor **21**<sup>31</sup> and galactose donor **22**<sup>32</sup> resulted in the delivery of other glycan structures of b-series gangliosides, **23** (GT1b-core hexasaccharide) and **24** (GD1b-core saccharide) in excellent 95% and 90% yields, respectively. These results demonstrated that **11** was the expedient common unit for the synthesis of the entire b-series gangliosides.

Referring back to Scheme 3, the cleavage of benzyl groups and the benzylidene group of **16** was executed by hydrogenolysis on  $\text{Pd}(\text{OH})_2$ , and the following benzylation of the resulting hydroxyl groups gave **18**. In this benzylation, the combination of  $\text{Bz}_2\text{O}$  and DMAP in pyridine could not completely protect

(28) (a) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567–3570. (b) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3571–3574. (c) Nicolaou, K. C.; Caulfield, T. J.; Kataoka, H.; Stylianides, N. A. *J. Am. Chem. Soc.* **1990**, *112*, 3693–3695.

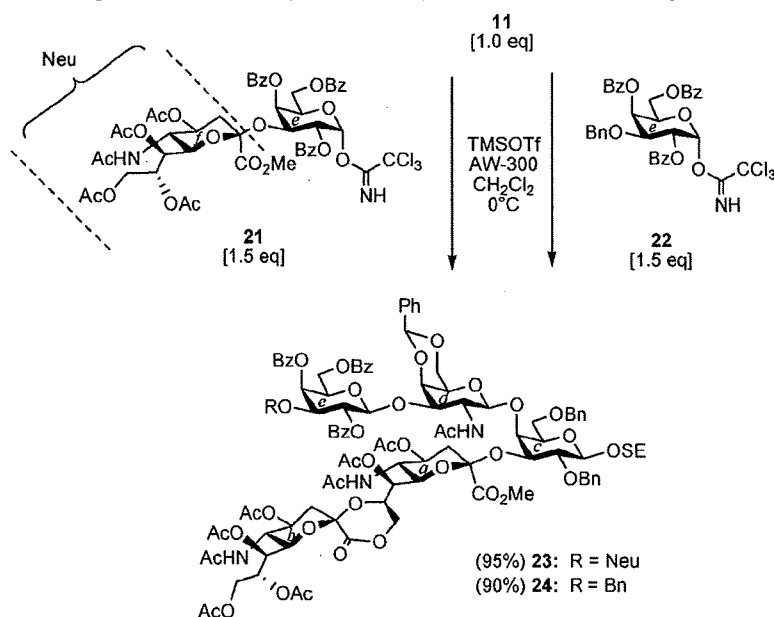
(29) Jansson, K.; Ahlfors, S.; Frejd, T.; Kihlberg, J.; Magnusson, G.; Dahmén, J.; Noori, G.; Stenvall, K. *J. Org. Chem.* **1988**, *53*, 5629–5647.

(30) (a) Grundler, G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1984**, 1826–1847. (b) Schmidt, R. R. *Angew. Chem., Int. Ed.* **1986**, *25*, 212–235. (c) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed.* **1980**, *19*, 731–732.

(31) Hasegawa, A.; Suzuki, N.; Ishida, H.; Kiso, M. *J. Carbohydr. Chem.* **1996**, *15*, 623–637. Physical data of compound **21** was described in the Supporting Information.

(32) Nikolaev, A. V.; Watt, G. M.; Ferguson, M. A. J.; Brimacombe, J. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 969–979.

SCHEME 4. Potential as an Acceptor of 11 for the Systematical Synthesis of B-Series Gangliosides



the hydroxyl groups. Therefore, to complete the reaction, BzCl and AgOTf were added, which generated more reactive BzOTf in situ, whereas the addition of BzCl and DMAP could not complete the reaction. The use of BzOTf from the beginning of the reaction gave a crude mixture of *O*- and *N*-benzoylated products. The reason underlying this phenomenon is yet unclear. Liberation of the anomeric hydroxyl group of 18 was achieved by treatment with TFA, and the resulting hemiacetal 19 was then converted into the  $\alpha$ -trichloroacetimidate 20, which was ready for the final glycosylation.

Hashimoto et al. reported the useful convergent synthesis of ganglioside GM3 using a glucosylceramide (GlcCer) building block equipped with benzyl groups at the C-3 and C-6 positions of the Glc residue.<sup>33</sup> However, the use of benzyl groups impaired the efficiency of the deprotection steps, since conventional hydrogenolysis of benzyl groups cannot be utilized due to the presence of the olefin functionality at the ceramide moiety. As a result, it has caused great loss of the samples at the final stage. Therefore, in this study, we envisioned the use of the *p*-methoxybenzyl (PMB) group as a surrogate of the benzyl group, since it can be removed by nonreductive conditions without affecting olefin functionality.

Starting from the known glucose derivative 25,<sup>34</sup> the GlcCer acceptor with PMB groups at the C-3 and C-6 positions (36) was prepared via eight steps (Scheme 5). Derivative 25 was subjected to selective *p*-methoxybenzylation by way of stannylation<sup>35</sup> with DBTO in toluene, followed by treatment of PMBCl with TBAB to afford the 3-PMB and 2-PMB derivatives in 61% and 35% yields, respectively. Benzoylation of 26 was achieved under standard conditions to give 28 in almost a quantitative yield. Reductive opening of the anisylidene ring of 28 by treatment with NaBH<sub>3</sub>CN and TFA in DMF<sup>36</sup>

afforded the 6-*O*-PMB derivative 29 (89%), along with a small amount (8%) of the 4-*O*-PMB derivative 30. Monochloroacetylation of 29 proceeded smoothly to provide 31 in 95% yield. Selective exposure of the anomeric hydroxyl group of 31 was executed by treatment of polymethylhydrosiloxane (PMHS), Pd(PPh<sub>3</sub>)<sub>4</sub>, and ZnCl<sub>2</sub> in THF,<sup>37</sup> which afforded the hemiacetal 32 in 85% yield. The obtained hemiacetal 32 was converted into the corresponding trichloroacetimidate 33 in 93% ( $\alpha/\beta = 40/53$ ) yield upon reaction with CCl<sub>3</sub>CN and DBU. The  $\alpha$ -imidate 33 $\alpha$  was then subjected to glycosidation with the known ceramide acceptor 34<sup>38</sup> in the presence of TMSOTf in CH<sub>2</sub>Cl<sub>2</sub> to afford 35 in 48% yield. The selective deprotection of the monochloroacetyl group was accomplished by treatment of DABCO in the mixed solvent of EtOH/1,2-dichloroethane<sup>39</sup> to furnish the novel GlcCer acceptor 36 in 96% yield.

The final couplings of GQ1b-core heptasaccharide donor 20 (1.0 equiv) with glucosyl acceptors 36, 37, 38, and 39 (1.5 equiv each) were conducted in the presence of TMSOTf (0.1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C, and the results are summarized in Table 3. In entry 1, the glycosylation of the novel GlcCer acceptor 36 with 20 afforded the desired fully protected ganglioside GQ1b 40 in an excellent 91% yield. On the other hand, a Hashimoto-type GlcCer acceptor 37 bearing the corresponding benzyl groups at the C-3 and C-6 positions afforded 41 in 73% yield (entry 2). These results indicated that the PMB groups at the C-3 and C-6 positions of the Glc residue enhanced the reactivity of the 4-hydroxyl group owing to its electron-donating property and elevated the coupling yield. Next, the previously described glucose derivative 38<sup>40</sup> was used as a coupling partner of 20 for the preparation of the SE-type GQ1b derivative (entry 3). As a result, the desired compound 42 was obtained in 63% yield.

(37) Chandrasekhar, S.; Reddy, Ch. R.; Rao, R. J. *Tetrahedron* 2001, 57, 3435–3438.

(38) (a) Kiso, M.; Nakamura, A.; Tomita, Y.; Hasegawa, A. *Carbohydr. Res.* 1986, 158, 101–111. (b) Kiso, M.; Nakamura, A.; Nakamura, J.; Tomita, Y.; Hasegawa, A. *J. Carbohydr. Chem.* 1986, 5, 335–340.

(39) Lefebvre, D. J.; Kamerling, J. P.; Vliegthart, J. F. G. *Org. Lett.* 2000, 2, 701–703.

(40) Fuse, T.; Ando, H.; Imamura, A.; Sawada, N.; Ishida, H.; Kiso, M.; Ando, T.; Li, S.-C.; Li, Y.-T. *Glycoconjugate J.* 2006, 23, 329–343.

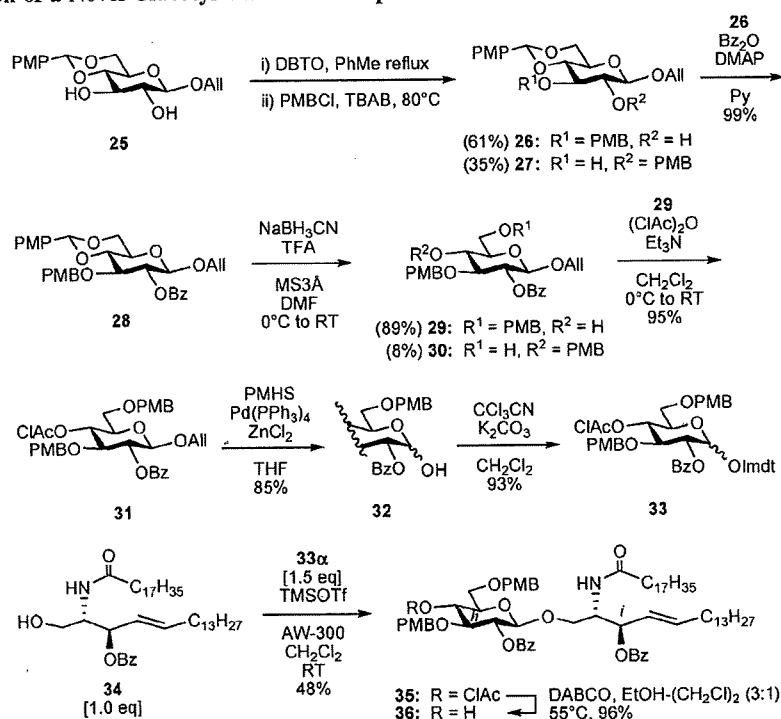
(33) Sakamoto, H.; Nakamura, S.; Tsuda, T.; Hashimoto, S. *Tetrahedron Lett.* 2000, 41, 7691–7695.

(34) Aspinall, G. O.; Gammon, D. W.; Sood, R. K.; Chatterjee, D.; Rivoire, B.; Brennan, P. J. *Carbohydr. Res.* 1992, 237, 57–77.

(35) Qin, H.; Grindley, B. J. *Carbohydr. Chem.* 1996, 15, 95–108.

(36) Johansson, R.; Samuelsson, B. J. *Chem. Soc., Perkin Trans. 1* 1984, 2371–2374.

## SCHEME 5. Preparation of a Novel Glucosyl Ceramide Acceptor 36



In entry 4, glycosylation of the previously described gentiobiose acceptor **39**<sup>13</sup> with **20** provided the nonasaccharide **43** in 80% yield. These results strongly suggested that our synthetic strategy is applicable to the assembly of both natural gangliosides and unnatural ganglioside derivatives.

Scheme 6 incorporated global deprotection steps toward target compounds. Selective removal of the PMB groups of **40** was performed in the presence of TFA in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C, and the reaction was completed within 1 h. After a facile workup and purification by silica gel column chromatography, the target compound **44** was obtained in almost a quantitative yield (97%). The outcome demonstrated that the use of the PMB group was effective for the synthesis of natural gangliosides. Importantly, this strategy can be applied to the syntheses of compounds with hydrogenolysis-sensitive functionalities, such as allyls, alkynes, azides, and so on. Furthermore, the sustainability of azide and alkyne groups enables their application to 1,3-dipolar cycloadditions. Finally, the conventional deacylation<sup>41</sup> and subsequent saponification gave natural ganglioside GQ1b **1** in 97% yield. It is noteworthy that the synthesis of the complex ganglioside GQ1b was first accomplished in the scale of ca. 80 mg per batch. Global deprotections of **42** and **43** were also executed by conventional methods to provide the targeted unnatural GQ1b derivatives **2** and **3** in good yields, respectively.

## Conclusion

In conclusion, we have accomplished the highly efficient and practical synthesis of complex ganglioside GQ1b and its unnatural derivatives by convergent synthetic routes, based on the key coupling reactions of a GQ1b-core heptasaccharide and derivatized-Glc building blocks. In particular, a judicious choice of a PMB group as a protecting group at the C-3 and C-6

positions of the GlcCer led to not only the elevation of coupling yields but also to facilitate global deprotection with almost quantitative yields. Furthermore, our approach can efficiently reach various unnatural ganglioside derivatives with azide or alkyne groups for 1,3-dipolar cycloaddition. We are currently undertaking the syntheses of various gangliosides using this approach, and the extension of synthesized ganglioside derivatives to the chemical biology field is in progress.

## Experimental Section

**Ganglioside GQ1b (1).** To a mixture of **44** (122 mg, 0.0316 mmol) in MeOH (6.2 mL) was added catalytic amounts of sodium methoxide (28% solution in MeOH). After stirring for 24 h at room temperature as the reaction was monitored by TLC (1-BuOH/MeOH/5% CaCl<sub>2</sub> (aq) = 2:1:1), the mixture was heated at 50 °C, and stirring was continued for 2 days at 50 °C. Then, H<sub>2</sub>O (0.3 mL) was added to the mixture. After stirring for 5 h at room temperature as the reaction was monitored by TLC (1-BuOH/MeOH/5% CaCl<sub>2</sub> (aq) = 2:1:1), the reaction was neutralized with IR-120 (H<sup>+</sup>) resin and filtered through cotton, and the resin was washed with mixed solvent (CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O = 5:5:1). The combined filtrate and washings were concentrated. The resulting residue was purified by gel filtration column chromatography on Sephadex LH-20 using CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O (5:5:1) as the eluent to give **1** (77 mg, 97%): [α]<sub>D</sub> = -6.3° (c 0.3, CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O = 5:5:1); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD/D<sub>2</sub>O = 5:5:1) δ 5.70 (m, 1 H, J<sub>4,5</sub> = 15.1 Hz, J<sub>5,6</sub> = 8.2 Hz, J<sub>5,6'</sub> = 6.8 Hz, H-5<sup>cer</sup>), 5.43 (dd, 1 H, J<sub>4,5</sub> = 15.1 Hz, J<sub>3,4</sub> = 7.5 Hz, H-4<sup>cer</sup>), 4.88 (d, 1 H, J<sub>1,2</sub> = 8.2 Hz, anomer H), 4.61 (d, 1 H, anomer H), 4.46 (d, 1 H, J<sub>1,2</sub> = 7.5 Hz, anomer H), 4.34 (d, 1 H, J<sub>1,2</sub> = 7.5 Hz, anomer H), 3.02, 2.80, 2.74, and 2.63 (4 br dd, 4 H, 4 H-3eq), 2.17 (t, 1 H, NHCOCH<sub>2</sub>), 2.06, 2.03, 2.03, and 2.02 (4 s, 17 H, 5 NAc, H-6<sup>cer</sup>, and 6<sup>cer</sup>), 1.84 (br t, 1 H, H-3ax), 1.69 (m, 3 H, 3 H-3ax), 1.57 (m, 1 H, NHCOCH<sub>2</sub>), 1.36 (m, 1 H, H-7<sup>cer</sup>), 1.27 (m, 51 H, H-7<sup>cer</sup>, 25 CH<sub>2</sub>), 0.89 (t, 6 H, 2 Me); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD/D<sub>2</sub>O = 5:5:1) δ 174.8, 174.0, 173.8, 173.7, 173.4, 173.3, 172.8, 172.6, 172.4, 172.3, 133.6, 128.8, 103.7, 102.7, 102.2, 101.9, 100.7, 100.1, 100.1, 99.0, 80.5, 78.5,

(41) Zemplén, G. *Ber. Dtsch. Chem. Ges.* 1927, 60, 1555–1564.

TABLE 3. Final Glycosylations

Entry	Acceptor	Product	% Yield <sup>a</sup>
$  \begin{array}{c}  \text{20} \\  [1.0 \text{ eq}]  \end{array}  +  \begin{array}{c}  \text{36, 37, 38, 39} \\  [1.5 \text{ eq}]  \end{array}  \xrightarrow[\text{0}^\circ\text{C}]{\text{TMSOTf}}  \begin{array}{c}  \text{AW-300} \\  \text{CH}_2\text{Cl}_2  \end{array}  \begin{array}{c}  \text{Fully protected GQ1b} \\  \text{and unnatural GQ1b derivatives}  \end{array}  $			
1			91
2			73
3			63
4			80

<sup>a</sup> Isolated yield.

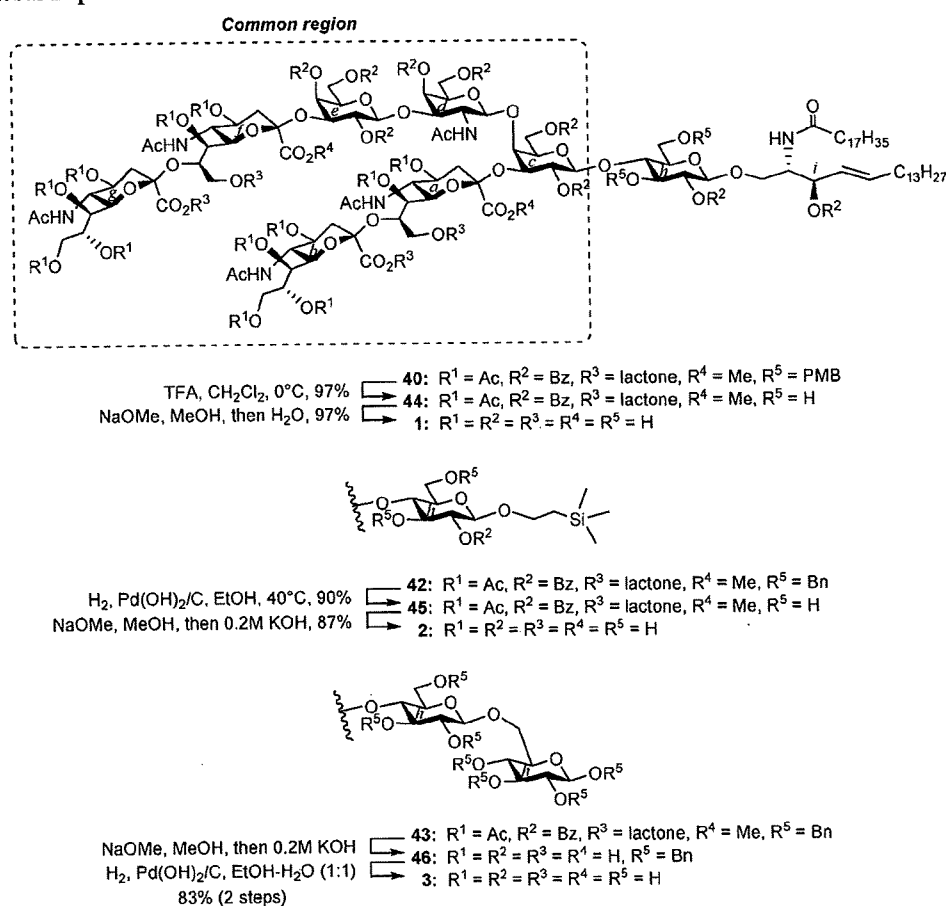
74.3, 73.9, 73.8, 73.8, 73.5, 73.4, 73.3, 73.2, 73.0, 72.8, 72.5, 72.4, 70.9, 70.8, 69.1, 69.0, 68.9, 68.9, 68.3, 68.1, 68.0, 67.9, 67.3, 67.3, 67.0, 66.6, 66.2, 66.1, 65.5, 65.5, 64.9, 62.6, 62.5, 61.2, 61.1, 61.0, 60.9, 60.7, 60.6, 60.5, 59.7, 59.6, 59.3, 59.3, 52.7, 52.4, 52.1, 51.9, 51.7, 50.9, 40.3, 37.9, 35.5, 31.5, 31.0, 31.0, 28.8, 28.8, 28.7, 28.7, 28.6, 28.6, 28.4, 28.4, 25.2, 22.2, 21.7, 21.4, 21.3, 21.2, 21.0, 12.7; HRMS (ESI) *m/z* found  $[M - 2H^+]^{2-}$  1208.5783,  $C_{106}H_{182}N_6O_{55}$  calcd for  $[M - 2H^+]^{2-}$  1208.5736.

**2-(Trimethylsilyl)ethyl (5-Acetamido-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonic acid)-(2 $\rightarrow$ 8)-(5-acetamido-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonic acid)-(2 $\rightarrow$ 3)- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 3)-2-acetamido-2-deoxy- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-[(5-acetamido-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonic acid)-(2 $\rightarrow$ 8)-(5-acetamido-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonic acid)-(2 $\rightarrow$ 3)]- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-glucopyranoside (2).** To a mixture of 45 (40 mg, 0.0121 mmol) in MeOH (1.0 mL) was added catalytic amounts of sodium methoxide (28% solution in MeOH). After stirring for 17 h at room temperature as the reaction was monitored by TLC (1-BuOH/MeOH/5%  $CaCl_2$  (aq) = 2:1:1), the mixture was heated at 50  $^\circ C$ , and the stirring was continued for 17 h at 50  $^\circ C$ . Then, 0.2 M KOH (0.5 mL) was added to the mixture. After stirring for 30 h at 75  $^\circ C$  as the reaction was monitored by TLC (1-BuOH/MeOH/5%  $CaCl_2$  (aq) = 2:1:1), the reaction was neutralized with IR-120 ( $H^+$ ) resin and filtered through cotton, and the resin was washed with MeOH and  $H_2O$ . The

combined filtrate and washings were concentrated. The resulting residue was purified by gel filtration column chromatography on Sephadex LH-20 using  $H_2O$  as the eluent to give 2 (20 mg, 87%):  $[\alpha]_D = -5.0^\circ$  (c 0.7,  $H_2O$ );  $^1H$  NMR (500 MHz,  $D_2O/(CD_3)_2CO = 10:1$ )  $\delta$  4.73 (d, 1 H, H-1h), 4.59 (d, 1 H,  $J_{1,2} = 7.4$  Hz, H-1e), 4.49 (d, 1 H,  $J_{1,2} = 8.6$  Hz, H-1c), 4.47 (d, 1 H,  $J_{1,2} = 8.0$  Hz, H-1d), 3.41 (t, 1 H,  $J_{1,2} = J_{2,3} = 8.6$  Hz, H-2c), 3.25 (near t, 1 H,  $J_{1,2} = 8.0$  Hz,  $J_{2,3} = 9.1$  Hz, H-2d), 2.77–2.63 (m, 4 H, H-3eq-a, 3eq-b, 3eq-f, and 3eq-g), 2.05, 2.04, and 2.01 (3 s, 15 H, 5 NAc), 1.76–1.69 (m, 4 H, H-3ax-a, 3ax-b, 3ax-f, and 3ax-g), 1.07–0.91 (m, 2 H,  $OCH_2CH_2SiMe_3$ ), 0.00 (s, 9 H,  $OCH_2CH_2SiMe_3$ );  $^{13}C$  NMR (125 MHz,  $D_2O/(CD_3)_2CO = 10:1$ )  $\delta$  175.2, 175.1, 175.0, 173.9, 173.6, 173.6, 173.5, 104.5, 103.1, 102.8, 101.7, 100.8, 100.6, 100.5, 100.5, 80.2, 78.8, 78.6, 75.6, 75.5, 75.1, 74.9, 74.7, 74.6, 74.5, 74.3, 74.0, 73.1, 72.9, 72.0, 69.8, 69.8, 69.7, 69.5, 68.8, 68.7, 68.5, 68.3, 68.3, 67.9, 67.6, 62.9, 61.9, 61.8, 61.3, 61.2, 60.9, 60.3, 52.6, 52.5, 52.1, 51.4, 40.9, 40.8, 39.9, 39.8, 22.9, 22.6, 22.6, 22.3, 17.8, -2.1; HRMS (ESI) *m/z* found  $[M - 4H^+]^{4-}$  491.9194,  $C_{75}H_{125}N_5O_{53}Si$  calcd for  $[M - 4H^+]^{4-}$  491.9192.

**(5-Acetamido-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonic acid)-(2 $\rightarrow$ 8)-(5-acetamido-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonic acid)-(2 $\rightarrow$ 3)- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 3)-2-acetamido-2-deoxy- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-[(5-acetamido-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonic acid)-(2 $\rightarrow$ 8)-(5-acetamido-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonic acid)-(2 $\rightarrow$ 3)]- $\beta$ -D-galacto-**

## SCHEME 6. Global Deprotections



**pyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 6)-D-glucopyranose (3).** To a mixture of **43** (46 mg, 0.0118 mmol) in MeOH (0.8 mL) was added catalytic amounts of sodium methoxide (28% solution in MeOH). After stirring for 12 h at room temperature as the reaction was monitored by TLC (1-BuOH/MeOH/5% CaCl<sub>2</sub> (aq) = 2:1:1), the mixture was heated at 50 °C, and the stirring was continued for 24 h at 50 °C. Then 0.2 M KOH (0.2 mL) was added to the mixture. After stirring for 3 h at room temperature as the reaction was monitored by TLC (1-BuOH/MeOH/5% CaCl<sub>2</sub> (aq) = 2:1:1), the reaction was neutralized with IR-120 (H<sup>+</sup>) resin and filtered through cotton, and the resin was washed with H<sub>2</sub>O. The combined filtrate and washings were concentrated. The resulting residue was purified by gel filtration column chromatography on Sephadex LH-20 using H<sub>2</sub>O as the eluent. Then, to a solution of the obtained white solid **46** in EtOH/H<sub>2</sub>O (1.0 mL/1.0 mL) was added palladium hydroxide [20 wt % Pd (dry basis) on carbon, wet] (90 mg) at room temperature. After stirring for 14 h at room temperature under a H<sub>2</sub> atmosphere as the reaction was monitored by TLC (1-BuOH/MeOH/5% CaCl<sub>2</sub> (aq) = 1:1:1), the mixture was filtered through a membrane filter and washed with H<sub>2</sub>O. The combined filtrate and washings were concentrated. The resulting residue was purified by gel filtration column chromatography on Sephadex LH-20 using H<sub>2</sub>O as the eluent to give **3** (20 mg, 83%):  $[\alpha]_D^{25} = -3.7^\circ$  (c 0.4, H<sub>2</sub>O); <sup>1</sup>H NMR (600 MHz, D<sub>2</sub>O)  $\delta$  5.20 (d, 1 H,  $J_{1,2} = 3.4$  Hz, H-1 of Glc unit), 4.71 (m, anomer H), 4.63 (d, 1 H,  $J_{1,2} = 8.2$  Hz, H-1 of Glc unit), 4.58 (m, anomer H), 4.52 (d, 1 H,  $J_{1,2} = 8.2$  Hz, anomer H), 4.50 (d, 1 H,  $J_{1,2} = 7.5$  Hz, anomer H), 4.47 (d, 1 H,  $J_{1,2} = 8.2$  Hz, anomer H), 3.51 (dd, 1 H,  $J_{1,2} = 3.4$  Hz,  $J_{2,3} = 10.3$  Hz, H-2 of Glc unit), 3.44 (t, 1 H,  $J_{2,3} = J_{3,4} = 8.9$  Hz, H-3 of Glc unit), 3.40–3.30 (m, 3 H, 3 H-2), 3.22 (near t, 1 H,  $J_{1,2} = 8.2$  Hz,  $J_{2,3} = 8.9$  Hz, H-2), 2.76–2.62 (m, 4 H, H-3eq-a, 3eq-b, 3eq-f,

and 3eq-g), 2.04, 2.03, 2.02, and 2.00 (4 s, 15 H, 5 NAc), 1.78–1.69 (m, 4 H, H-3ax-a, 3ax-b, 3ax-f, and 3ax-g); <sup>13</sup>C NMR (150 MHz, D<sub>2</sub>O/(CD<sub>3</sub>)<sub>2</sub>CO = 10:1)  $\delta$  165.9, 164.8–163.9, 95.3, 93.8, 93.6, 93.5, 92.0–90.9, 87.0, 83.1, 71.0, 69.2, 69.1, 66.7, 66.4, 65.9, 65.8, 65.8, 65.6, 65.3, 65.2, 65.1, 65.1, 64.8, 63.7, 62.7, 62.4, 61.4, 60.6, 60.5, 60.4, 60.2, 59.8, 59.8, 59.6, 59.4, 59.3, 59.2, 59.0, 58.6, 58.6, 53.6, 52.5, 52.4, 52.0, 52.0, 51.6, 51.0, 43.3, 43.2, 42.8, 42.1, 31.6, 31.5, 30.7, 30.2, 13.6, 13.4, 13.3, 13.1; HRMS (ESI)  $m/z$  found  $[M - 4H]^+$  507.4145, C<sub>76</sub>H<sub>123</sub>N<sub>5</sub>O<sub>58</sub> calcd for  $[M - 4H]^+$  507.4143.

**2-(Trimethylsilyl)ethyl [Methyl 5-acetamido-8-O-(5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonate]-(2 $\rightarrow$ 3)-2,6-di-O-benzyl- $\beta$ -D-galactopyranoside (6).** To a mixture of **4** (200 mg, 210  $\mu$ mol) and **5** (196 mg, 420  $\mu$ mol) in propionitrile (4.0 mL) were added 3 Å molecular sieves (400 mg) at room temperature. After stirring for 1 h, NIS (96 mg, 420  $\mu$ mol) was added to the mixture. After cooling to -50 °C, TfOH (11  $\mu$ L, 130  $\mu$ mol) was added to the mixture. After stirring for 96 h at -50 °C as the reaction was monitored by TLC (EtOAc/MeOH = 10:1), reagents (NIS, 2  $\times$  96 mg, 192 mg in total; TfOH, 2  $\times$  11  $\mu$ L, 22  $\mu$ L in total) were added to the mixture after 120 and 144 h. The mixture was stirred for a total of 168 h at the same temperature. Then, the reaction was quenched by triethylamine and filtered through a Celite pad, and the pad was washed with CHCl<sub>3</sub>. The combined filtrate and washings were evaporated. The residue was extracted with CHCl<sub>3</sub> and washed with saturated Na<sub>2</sub>CO<sub>3</sub> (aq), saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (aq), and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by flash column chromatography twice (first with CHCl<sub>3</sub>/MeOH = 50:1 and second with EtOAc) to give **6** (120



mg, 44%) and its  $\beta$ -isomer **6 $\beta$**  (39 mg, 14%). **6 $\alpha$** :  $[\alpha]_D = -28.1^\circ$  (c 3.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.35–7.24 (m, 10 H, 2 Ph), 5.69 (d, 1 H, NH-a), 5.67 (d, 1 H, NH-b), 5.38 (dt, 1 H, H-4b), 5.35 (dd, 1 H, H-7b), 5.15 (dt, 1 H, H-8b), 5.09 (dd, 1 H, H-7a), 5.07 (dt, 1 H, H-4a), 4.90 and 4.62 (2 d, 2 H,  $J_{\text{gem}} = 11.2$  Hz, PhCH<sub>2</sub>), 4.56 (2 d, 2 H,  $J_{\text{gem}} = 11.6$  Hz, PhCH<sub>2</sub>), 4.40 (d, 1 H,  $J_{1,2} = 8.0$  Hz, H-1c), 4.37 (dd, 1 H, H-9'a), 4.29–4.19 (m, 3 H, H-9a, 9'b, and 8a), 4.18 (q, 1 H, H-5b), 4.07–3.95 (m, 6 H, H-9b, 5a, 3c, 6a, 6b, and OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 3.87 (br s, 1 H, H-4c), 3.82 (s, 3 H, CO<sub>2</sub>Me), 3.81 (dd, 1 H, H-6'c), 3.73 (dd, 1 H, H-6c), 3.61 (m, 2 H, H-5c and OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 3.54 (t, 1 H,  $J_{1,2} = 8.0$  Hz,  $J_{2,3} = 9.1$  Hz, H-2c), 2.80 (s, 1 H, OH), 2.46 (dt, 2 H, H-3eq-a and H-3eq-b), 2.14–1.88 (8 s and 2 t, 26 H, H-3ax-a, H-3ax-b, and 8 Ac), 1.03 (t, 2 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 0.02 (s, 9 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.8, 170.7, 170.6, 170.5, 170.2, 169.8, 169.7, 168.1, 165.4, 138.6, 138.1, 128.4, 128.1, 128.0, 127.7, 127.6, 127.5, 103.3, 99.4, 96.1, 75.8, 74.9, 73.6, 73.0, 72.8, 72.1, 70.7, 69.4, 69.2, 69.1, 68.9, 67.8, 67.4, 67.1, 67.1, 66.6, 61.8, 53.1, 49.3, 49.0, 38.3, 35.8, 35.8, 23.1, 20.8, 20.8, 20.7, 20.6, 18.5; HRMS (ESI)  $m/z$  found  $[M + Na]^+$  1313.4779, C<sub>60</sub>H<sub>82</sub>N<sub>2</sub>O<sub>27</sub>Si calcd for  $[M + Na]^+$  1313.4771. **6 $\beta$** :  $[\alpha]_D = -31.9^\circ$  (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.50–7.27 (m, 10 H, 2 Ph), 5.46 (dt, 1 H,  $J_{3\text{eq},4} = 5.4$  Hz,  $J_{4,5} = 10.2$  Hz, H-4b), 5.38 (d, 1 H, NH-b), 5.35 (dd, 1 H, H-7b), 5.17–5.09 (m, 3 H, H-4a, 7a, and 8b), 5.06 and 4.62 (2 d, 2 H,  $J_{\text{gem}} = 10.9$  Hz, PhCH<sub>2</sub>), 4.58–4.52 (m, 4 H, H-9'a, PhCH<sub>2</sub>, and H-9a), 4.45 (d, 1 H,  $J_{1,2} = 7.5$  Hz, H-1c), 4.34–4.28 (m, 3 H, H-6a, 8a, and 9b), 4.17 (q, 1 H,  $J_{4,5} = 10.2$  Hz, H-5b), 4.05–3.99 (m, 3 H, H-5a, 9b, and OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 3.83 (br s, 1 H, H-4c), 3.81–3.75 (m, 3 H, H-6b, 3c, and 6'c), 3.73 (s, 3 H, CO<sub>2</sub>Me), 3.71 (dd, 1 H,  $J_{5,6} = 9.6$  Hz, H-6c), 3.61 (m, 2 H,  $J_{5,6} = 9.6$  Hz, H-5c, and OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 3.64 (t, 1 H,  $J_{1,2} = 7.5$  Hz, H-2c), 3.62–3.58 (m, 2 H, H-5c and OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 3.30 (s, 1 H, OH), 2.56 (dd, 1 H,  $J_{\text{gem}} = 13.7$  Hz,  $J_{3\text{eq},4} = 4.3$  Hz, H-3eq-a), 2.46 (dd, 1 H,  $J_{\text{gem}} = 13.5$  Hz,  $J_{3\text{eq},4} = 5.4$  Hz, H-3eq-b), 2.12, 2.08, 2.04, 2.03, 2.02, and 2.00 (6 s, 18 H, 6 Ac), 2.02 (m, 1 H,  $J_{\text{gem}} = 13.7$  Hz, H-3ax-a), 1.91 (t, 1 H,  $J_{\text{gem}} = 13.5$  Hz, H-3ax-b), 1.89 and 1.73 (2 s, 6 H, 2 NAc), 1.02 (t, 2 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 0.01 (s, 9 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.0, 170.9, 170.6, 170.5, 170.3, 169.9, 169.8, 169.6, 168.2, 164.7, 138.9, 137.8, 128.5, 128.4, 128.3, 128.1, 128.1, 127.8, 127.7, 103.3, 99.3, 96.6, 77.9, 77.7, 74.9, 73.6, 72.7, 72.3, 72.2, 70.8, 69.8, 69.0, 68.7, 68.6, 68.2, 67.6, 67.5, 66.6, 61.6, 53.2, 49.0, 48.4, 37.9, 34.7, 30.3, 23.2, 23.1, 21.0, 20.9, 20.8, 20.7, 20.6, 18.5; HRMS (ESI)  $m/z$  found  $[M + Na]^+$  1313.4773, C<sub>60</sub>H<sub>82</sub>N<sub>2</sub>O<sub>27</sub>Si calcd for  $[M + Na]^+$  1313.4771.

**2-(Trimethylsilyl)ethyl 2-Acetamido-4,6-O-benzylidene-2-deoxy- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-[methyl 5-acetamido-8-O-(5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylono-1',9-lactone]-2,6-di-O-benzyl- $\beta$ -D-galactopyranoside (11).** To a solution of **10** (6.30 g, 3.33 mmol) in (CH<sub>2</sub>Cl<sub>2</sub>)<sub>2</sub> (30 mL) were added activated Zn powder (25.2 g) and acetic acid (60 mL) at room temperature. After stirring for 1 h at 40 °C as the reaction was monitored by TLC (CHCl<sub>3</sub>/MeOH = 10:1), the mixture was filtered through a Celite pad and washed with CHCl<sub>3</sub>. The combined filtrate and washings were diluted with CHCl<sub>3</sub> and washed with saturated NaHCO<sub>3</sub> (aq), H<sub>2</sub>O, and brine. After drying over Na<sub>2</sub>SO<sub>4</sub> and being concentrated, the resulting residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Acetic anhydride (471  $\mu$ L, 5.00 mmol) was then added to the mixture at room temperature. After stirring for 30 min as the reaction was monitored by TLC (CHCl<sub>3</sub>/MeOH = 10:1), the reaction mixture was concentrated. The residue was purified by flash column chromatography using CHCl<sub>3</sub>/MeOH (28:1 to 20:1) as the eluent to give **11** (5.04 g, 96%):  $[\alpha]_D = -23.6^\circ$  (c 0.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.53–7.23 (m, 15 H, 3 Ph), 6.86 (d, 1 H, NH-d), 5.59 (s, 1 H, PhCH<), 5.56 (d, 1 H, NH-b), 5.46 (near d, 1 H, NH-a), 5.40 (dt, 1 H,  $J_{4,5} = 10.4$  Hz, H-4b), 5.33 (dd, 1 H,  $J_{6,7} = 2.1$  Hz, H-7b), 5.12 (m, 2 H, H-8b and 4a), 4.98 and 4.51 (2

d, 2 H,  $J_{\text{gem}} = 11.2$  Hz, PhCH<sub>2</sub>), 4.96 (d, 1 H, H-4d), 4.92 (dd, 1 H, H-7a), 4.77 (d, 1 H,  $J_{1,2} = 8.3$  Hz, H-1d), 4.60 and 4.52 (2 d, 2 H,  $J_{\text{gem}} = 11.7$  Hz, PhCH<sub>2</sub>), 4.44 (d, 1 H,  $J_{1,2} = 7.5$  Hz, H-1c), 4.43 (dd, 1 H,  $J_{\text{gem}} = 12.4$  Hz, H-9a), 4.26 (dd, 1 H, H-9'b), 4.19 (q, 1 H,  $J_{4,5} = J_{5,6} = J_{5,\text{NH}} = 10.4$  Hz, H-5b), 4.17 (m, 2 H, H-2d and 4c), 4.15–3.98 (m, 14 H, H-6a, 5a, 6d, 6'd, 5d, 3c, 9b, 6'c, 8a, and OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 3.89 (s, 3 H, COOMe), 3.82 (dd, 1 H,  $J_{\text{gem}} = 12.4$  Hz, H-9'a), 3.74 (dd, 1 H,  $J_{5,6} = 10.4$  Hz,  $J_{6,7} = 2.1$  Hz, H-6b), 3.70 (s, 3 H, COOMe), 3.66 (dd, 1 H, H-6c), 3.62–3.54 (m, 3 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>, H-3d, and 5c), 3.51 (near t, 1 H,  $J_{1,2} = 7.5$  Hz, H-2c), 3.02 (s, 1 H, OH), 2.32 (m, 3 H, H-3eq-b, 3eq-a, and 3ax-a), 2.12–1.89 (8 s, 24 H, 8 Ac), 1.81 (near t, 1 H, H-3ax-b), 1.04 (m, 2 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 0.02 (s, 9 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>); HRMS (ESI)  $m/z$  found  $[M + Na]^+$  1604.5873, C<sub>73</sub>H<sub>99</sub>N<sub>3</sub>O<sub>32</sub>Si calcd for  $[M + Na]^+$  1604.5878.

**[Methyl 5-Acetamido-8-O-(5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylono-1',9-lactone]-2,6-di-O-benzyl- $\beta$ -D-galactopyranoside (15).** To a solution of **13** (2.50 g, 1.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was added trifluoroacetic acid (4.0 mL) at 0 °C. After stirring for 5 h at room temperature as the reaction was monitored by TLC (CHCl<sub>3</sub>/MeOH = 10:1), the reaction mixture was coevaporated with toluene. The residue was purified by flash column chromatography using CHCl<sub>3</sub>/MeOH (30:1) as the eluent to give the hemiacetal **14** (2.29 g, 98%): HRMS (ESI)  $m/z$  found  $[M + Na]^+$  1345.3912, C<sub>62</sub>H<sub>70</sub>N<sub>2</sub>O<sub>30</sub> calcd for  $[M + Na]^+$  1345.3911.

To a solution of **14** (827 mg, 624  $\mu$ mol) in CH<sub>2</sub>Cl<sub>2</sub> (6.2 mL) were added trichloroacetonitrile (1.25 mL, 12.5 mmol) and DBU (112  $\mu$ L, 750  $\mu$ mol) at 0 °C. After stirring for 2 h at room temperature as the reaction was monitored by TLC (CHCl<sub>3</sub>/MeOH = 10:1), the reaction mixture was concentrated. The resulting residue was purified by flash column chromatography using CHCl<sub>3</sub>/MeOH (30:1) as the eluent to give **15** (862 mg, 94%):  $[\alpha]_D = +21.4^\circ$  (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.59 (s, 1 H, C=NH), 8.10–7.40 (m, 15 H, 3 Ph), 6.83 (d, 1 H,  $J_{1,2} = 3.6$  Hz, H-1c), 5.94 (d, 1 H,  $J_{3,4} = 3.6$  Hz,  $J_{4,5} = 1.2$  Hz, H-4c), 5.68 (dd, 1 H,  $J_{1,2} = 3.6$  Hz,  $J_{2,3} = 10.4$  Hz, H-2c), 5.56 (dt, 1 H,  $J_{3\text{eq},4} = 5.3$  Hz,  $J_{3\text{ax},4} = 11.4$  Hz,  $J_{4,5} = 10.4$  Hz, H-4b), 5.44 (d, 1 H, NH-a), 5.35 (dd, 1 H,  $J_{6,7} = 2.1$  Hz, H-7b), 5.27 (d, 1 H,  $J_{5,\text{NH}} = 10.4$  Hz, NH-b), 5.19 (m, 2 H, H-4a and 8b), 4.98 (dd, 1 H,  $J_{6,7} = 1.7$  Hz,  $J_{7,8} = 9.2$  Hz, H-7a), 4.93 (dd, 1 H,  $J_{2,3} = 10.4$  Hz,  $J_{3,4} = 3.6$  Hz, H-3c), 4.74 (near dt, 1 H,  $J_{4,5} = 1.2$  Hz, H-5c), 4.65 (dt, 1 H,  $J_{7,8} = 9.2$  Hz,  $J_{8,9} = 2.6$  Hz, H-8a), 4.48–4.40 (m, 3 H, H-6c, 9a, and 6c), 4.28 (dd, 1 H,  $J_{\text{gem}} = 12.6$  Hz, H-9'b), 4.17 (q, 1 H,  $J_{4,5} = J_{5,\text{NH}} = 10.4$  Hz, H-5b), 4.15 (q, 1 H, H-5a), 4.04 (dd, 1 H,  $J_{8,9} = 2.6$  Hz, H-9'a), 4.02 (dd, 1 H,  $J_{\text{gem}} = 12.6$  Hz, H-9b), 3.96 (dd, 1 H,  $J_{6,7} = 1.7$  Hz, H-6a), 3.91 (dd, 1 H,  $J_{6,7} = 2.1$  Hz, H-6b), 3.36 (s, 3 H, COOMe), 2.56 (dd, 1 H,  $J_{\text{gem}} = 13.1$  Hz,  $J_{3\text{eq},4} = 5.3$  Hz, H-3eq-b), 2.24 (dd, 1 H, H-3eq-a), 2.12–1.89 (8 s and t, 25 H, 8 Ac and H-3ax-a), 1.70 (t, 1 H,  $J_{\text{gem}} = 13.1$  Hz,  $J_{3\text{ax},4} = 11.4$  Hz, H-3ax-b); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 170.5, 170.4, 170.0, 169.8, 169.8, 167.4, 166.0, 165.6, 165.2, 164.4, 160.2, 133.5, 133.3, 133.2, 129.9, 129.7, 129.5, 129.3, 129.3, 128.9, 128.5, 128.4, 98.9, 97.0, 93.9, 90.8, 77.1, 72.5, 71.9, 70.6, 69.8, 69.5, 69.5, 69.2, 68.8, 68.4, 68.3, 67.9, 67.7, 66.7, 62.9, 62.0, 52.5, 49.1, 38.2, 36.1, 23.1, 23.0, 20.7, 20.7, 20.7, 20.7, 20.6, 20.4; HRMS (ESI)  $m/z$  found  $[M + Na]^+$  1488.3004, C<sub>64</sub>H<sub>70</sub>Cl<sub>3</sub>N<sub>3</sub>O<sub>30</sub> calcd for  $[M + Na]^+$  1488.3007.

**2-(Trimethylsilyl)ethyl [Methyl 5-acetamido-8-O-(5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylono-1',9-lactone]-2,6-di-O-benzyl- $\beta$ -D-galactopyranoside (15).** To a solution of **13** (2.50 g, 1.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was added trifluoroacetic acid (4.0 mL) at 0 °C. After stirring for 5 h at room temperature as the reaction was monitored by TLC (CHCl<sub>3</sub>/MeOH = 10:1), the reaction mixture was coevaporated with toluene. The residue was purified by flash column chromatography using CHCl<sub>3</sub>/MeOH (30:1) as the eluent to give the hemiacetal **14** (2.29 g, 98%): HRMS (ESI)  $m/z$  found  $[M + Na]^+$  1345.3912, C<sub>62</sub>H<sub>70</sub>N<sub>2</sub>O<sub>30</sub> calcd for  $[M + Na]^+$  1345.3911.

ulopyranosylonate]-(2→3))-2,6-di-*O*-benzyl-β-*D*-galactopyranoside (16). To a mixture of 15 (2.71 g, 1.84 mmol) and 11 (1.93 g, 1.22 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added 4 Å molecular sieves (AW-300) (4.6 g) at room temperature. After stirring for 1 h and then cooling to 0 °C, TMSOTf (6.7 μL, 36.8 μmol) was added to the mixture. After stirring for 22 h at 0 °C as the reaction was monitored by TLC (CHCl<sub>3</sub>/MeOH/EtOAc = 15:1:1), the reaction was quenched by saturated NaHCO<sub>3</sub> (aq) and filtered through a Celite pad, and the pad was washed with CHCl<sub>3</sub>. The combined filtrate and washings were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The resulting residue was purified by flash column chromatography using CHCl<sub>3</sub>/MeOH/EtOAc (20:1:1) to CHCl<sub>3</sub>/MeOH (9:1) as the eluent to give 16 (3.29 g, 93%): [α]<sub>D</sub> = -11.5° (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.09–7.18 (m, 30 H, 6 Ph), 5.74 (d, 1 H, H-4e), 5.54 (dt, 1 H, *J*<sub>3eq,4</sub> = 5.2 Hz, *J*<sub>4,5</sub> = 10.5 Hz, H-4g), 5.48 (t, 1 H, *J*<sub>1,2</sub> = 7.7 Hz, H-2e), 5.43 (m, 3 H, H-4b, NH-f, and PhCH), 5.34 (m, 6 H, H-7b, 7g, and 4 NH), 5.17 (m, 3 H, H-4f, 8b, and 8g), 5.14 (d, 1 H, *J*<sub>1,2</sub> = 8.0 Hz, H-1d), 5.03 (dd, 1 H, H-7a), 4.97 (br d, 1 H, *J*<sub>1,2</sub> = 7.7 Hz, H-1e), 4.95 (dd, 1 H, *J*<sub>7,8</sub> = 9.6 Hz, H-7f), 4.88 (m, 2 H, H-4a and 3d), 4.80 and 4.52 (2 d, 2 H, *J*<sub>gem</sub> = 11.4 Hz, PhCH<sub>2</sub>), 4.65 (dt, 1 H, *J*<sub>7,8</sub> = 9.6 Hz, H-8f), 4.57 (dd, 1 H, H-6e), 4.52 and 4.46 (2 d, 2 H, *J*<sub>gem</sub> = 11.6 Hz, PhCH<sub>2</sub>), 4.42 (m, 3 H, H-9'a, 6'e, and 3e), 4.38–4.19 (m, 8 H, H-8a, 9'f, 1c, 4d, 9'g, 9'b, 5b, and 5e), 4.11 (2 q, 2 H, H-5g, and 5f), 4.08–3.80 (m, 18 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>, H-5a, 9a, 9b, 9g, 6a, 6'd, 4c, 9f, 3c, 6g, 6f, 6b, 6'c, 5d, and COOMe-a), 3.71 (d, 1 H, H-6d), 3.55 (m, 2 H, H-6c and OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 3.44 (t, 1 H, H-5c), 3.34 (near q, 1 H, *J*<sub>1,2</sub> = 8.0 Hz, H-2d), 3.33 (near t, 1 H, H-2c), 3.17 (s, 3 H, COOMe-f), 2.54 (dt, 2 H, H-3eq-a and 3eq-b), 2.44 (dd, 1 H, *J*<sub>3eq,4</sub> = 5.2 Hz, *J*<sub>gem</sub> = 13.5 Hz, H-3eq-g), 2.13–1.88 (m, 55 H, 17 Ac, H-3ax-a, 3ax-b, 3ax-f, and 3eq-f), 1.59 (t, 1 H, *J*<sub>gem</sub> = 13.5 Hz, H-3ax-g), 1.01 (near t, 2 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 0.00 (s, 9 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.8, 170.8, 170.7, 170.6, 170.5, 170.5, 170.5, 170.4, 170.4, 170.3, 170.3, 169.9, 169.8, 169.8, 169.8, 169.7, 169.6, 167.7, 167.3, 166.0, 164.7, 164.4, 164.2, 138.7, 138.5, 138.4, 133.4, 133.2, 133.0, 130.2, 129.9, 129.6, 129.5, 128.7, 128.6, 128.4, 128.4, 128.1, 128.0, 128.0, 127.9, 127.6, 127.5, 127.3, 126.4, 126.2, 103.4, 102.3, 100.7, 99.4, 99.1, 98.1, 97.1, 96.7, 77.8, 77.2, 75.9, 75.5, 74.6, 73.3, 72.9, 72.6, 72.5, 72.4, 72.1, 71.8, 71.5, 71.0, 70.6, 70.1, 69.6, 69.5, 69.3, 68.9, 68.7, 68.6, 68.5, 67.8, 67.7, 67.4, 66.7, 66.6, 66.0, 62.7, 62.0, 61.8, 54.3, 52.3, 49.1, 49.0, 48.9, 38.2, 35.9, 35.7, 30.0, 29.6, 23.1, 22.8, 20.9, 20.7, 20.7, 20.6, 20.6, 20.6, 20.5, 20.5, 18.5, 14.1, -1.5; HRMS (ESI) *m/z* found [M + 2Na]<sup>2+</sup> 1465.9833, C<sub>137</sub>H<sub>167</sub>N<sub>5</sub>O<sub>61</sub>Si calcd for [M + 2Na]<sup>2+</sup> 1465.9838.

[Methyl 5-Acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylonate]-(2→3))-2,4,6-tri-*O*-benzoyl-β-*D*-galactopyranosyl-(1→3))-2-acetamido-4,6-di-*O*-benzoyl-2-deoxy-β-*D*-galactopyranosyl-(1→4))-[methyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosylonate]-(2→3))-2,6-di-*O*-benzoyl-α-*D*-galactopyranosyl Trichloroacetimidate (20). To a solution of 18 (795 mg, 261 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.9 mL) was added trifluoroacetic acid (1.3 mL) at 0 °C. After stirring for 3 h at room temperature as the reaction was monitored by TLC (PhMe/MeOH = 5:1), the reaction mixture was coevaporated with toluene. The resulting residue was purified by flash column chromatography using CHCl<sub>3</sub>/MeOH (17.5:1 → 15:1 → 10:1) as the eluent to give 19 (765 mg, 99%): HRMS (ESI) *m/z* found [M + 2Na]<sup>+</sup> 1489.9383, C<sub>139</sub>H<sub>155</sub>N<sub>5</sub>O<sub>65</sub> calcd for [M + 2Na]<sup>+</sup> 1489.9380.

To a solution of 19 (200 mg, 68.1 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.68 mL) were added trichloroacetonitrile (136 μL, 1.36 mmol) and DBU (12 μL, 81.7 μmol) at 0 °C. After stirring for 2 h at room temperature as the reaction was monitored by TLC (PhMe/MeOH = 5:1), the reaction mixture was evaporated. The resulting residue was purified by flash column chromatography using CHCl<sub>3</sub>/MeOH

(20:1 to 13:1) as the eluent to give 20 (199 mg, 95%): [α]<sub>D</sub> = +4.8° (c 0.9, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.46 (s, 1 H, C=NH), 8.12–7.25 (m, 35 H, 7 Ph), 6.55 (d, 1 H, *J*<sub>1,2</sub> = 3.4 Hz, H-1c), 5.95 (br d, 1 H, H-4d), 5.89 (br d, 2 H, 2 NH), 5.70 (d, 1 H, H-4e), 5.63 (dd, 1 H, *J*<sub>1,2</sub> = 3.4 Hz, *J*<sub>2,3</sub> = 10.4 Hz, H-2c), 5.58 (d, 1 H, NH-b), 5.55 (dt, 1 H, H-4g), 5.46 (2 d, 2 H, 2 NH), 5.36–5.31 (m, 4 H, H-4b, 2e, 7g, and 7b), 5.29 (d, 1 H, *J*<sub>1,2</sub> = 8.5 Hz, H-1d), 5.24 (m, 1 H, H-8b), 5.16 (m, 1 H, H-8g), 5.10 (near q, 1 H, H-4f), 5.04 (br d, 1 H, H-1e), 5.20 (m, 2 H, H-4a and 7a), 4.93 (br dd, 1 H, H-3d), 4.86 (dd, 1 H, H-7f), 4.80 (dd, 1 H, *J*<sub>2,3</sub> = 10.4 Hz, H-3c), 4.63–4.58 (m, 3 H, H-8f, 6'e, and 6'd), 4.45–4.33 (m, 5 H, H-5d, 6'c, 3e, 6c, and 6d), 4.30–4.16 (m, 10 H, H-8a, 9g, 9b, 9f, 4c, 6b, 5b, 9'a, 9a, and 5e), 4.11 (q, 1 H, H-5g), 4.06–3.98 (m, 6 H, H-5f, 9b, 9g, 6b, 5c, and 5a), 3.91 (2 dd, 2 H, H-6a and 6g), 3.86 (dd, 1 H, H-6f), 3.82 (s, 3 H, COOMe-a), 3.75 (m, 2 H, H-2d and 9'f), 3.24 (s, 3 H, COOMe-f), 2.57–2.49 (m, 3 H, H-3eq-a, 3eq-b, and 3eq-g), 2.10–1.81 (m, 53 H, 17 Ac, H-3eq-f, and 3ax-f), 1.63 (t, 1 H, H-3ax-g); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 174.5, 171.2, 170.6, 170.6, 170.4, 170.2, 170.2, 169.8, 169.7, 169.6, 167.7, 167.1, 166.5, 166.0, 165.9, 165.5, 165.3, 164.8, 164.2, 160.0, 133.4, 133.2, 133.1, 133.0, 132.8, 132.8, 130.0, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 129.4, 129.3, 129.0, 128.4, 128.3, 128.2, 101.3, 99.8, 99.0, 98.9, 96.8, 95.4, 95.1, 94.1, 90.8, 76.2, 75.0, 73.3, 72.5, 71.9, 71.5, 71.3, 71.1, 71.0, 70.6, 70.1, 69.8, 69.6, 69.3, 69.2, 69.1, 68.8, 68.6, 68.1, 67.5, 67.1, 66.8, 66.7, 66.4, 64.2, 62.3, 62.1, 62.1, 61.9, 54.3, 53.0, 52.3, 49.0, 48.9, 48.7, 38.8, 38.2, 36.9, 36.1, 35.4, 29.5, 22.9, 22.8, 22.8, 22.6, 22.5, 20.7, 20.6, 20.6, 20.5, 20.4, 20.3, 20.2, 13.9; HRMS (ESI) *m/z* found [M + 2Na]<sup>2+</sup> 1561.3934, C<sub>141</sub>H<sub>155</sub>Cl<sub>3</sub>N<sub>6</sub>O<sub>65</sub> calcd for [M + 2Na]<sup>2+</sup> 1561.3934.

**2-*O*-Benzoyl-4-*O*-chloroacetyl-3,6-di-*O*-*p*-methoxybenzyl-*D*-glucopyranosyl Trichloroacetimidate (33).** To a solution of 31 (500 mg, 0.779 mmol) in degassed THF (7.8 mL) were added polymethylhydrosiloxane (PMHS) (140 μL, 2.33 mmol), tetrakis(triphenylphosphine)palladium (179 mg, 0.155 mmol), and ZnCl<sub>2</sub> (106 mg, 0.779 mmol) at room temperature. After stirring for 32 h at room temperature, the completion of the reaction was confirmed by TLC (EtOAc/PhMe = 1:4). Then, H<sub>2</sub>O was added to the mixture and filtered through a Celite pad, and the pad was washed with EtOAc. The combined filtrate and washings were washed with saturated NaHCO<sub>3</sub> (aq), and brine. After drying over Na<sub>2</sub>SO<sub>4</sub> and being concentrated, the resulting residue was purified by flash column chromatography using EtOAc/PhMe (1:5) as the eluent to give the hemiacetal 32 (400 mg, 85%, α/β = 7/1): <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.05–7.42 (m, 5 H, Ph), 7.21–6.75 (4 d, 8 H, Ar), 5.55 (br t, 1 H, *J*<sub>1,2</sub> = *J*<sub>1,OH</sub> = 3.4 Hz, H-1α), 5.19 (t, 1 H, *J*<sub>3,4</sub> = 8.9 Hz, H-4β), 5.15 (t, 1 H, *J*<sub>1,2</sub> = *J*<sub>2,3</sub> = 8.9 Hz, H-2β), 5.09 (t, 1 H, *J*<sub>3,4</sub> = *J*<sub>4,5</sub> = 9.6 Hz, H-4α), 5.08 (dd, 1 H, *J*<sub>1,2</sub> = 3.4 Hz, *J*<sub>2,3</sub> = 9.6 Hz, H-2α), 4.73 (t, 1 H, *J*<sub>1,2</sub> = *J*<sub>1,OH</sub> = 8.9 Hz, H-1β), 4.67 and 4.52 (2 d, 2 H, *J*<sub>gem</sub> = 11.6 Hz, ArCH<sub>2</sub>O), 4.44 and 4.39 (2 d, 2 H, *J*<sub>gem</sub> = 11.7 Hz, ArCH<sub>2</sub>O), 4.18 (m, 2 H, *J*<sub>2,3</sub> = *J*<sub>3,4</sub> = 9.6 Hz, H-3α and 5α), 3.92 (d, 1 H, *J*<sub>1,OH</sub> = 8.9 Hz, OH-β), 3.87 (t, 1 H, *J*<sub>2,3</sub> = *J*<sub>3,4</sub> = 8.9 Hz, H-3β), 3.78 and 3.74 (2 s, 6 H, 2 MeO), 3.69 and 3.61 (2 d, 2 H, *J*<sub>gem</sub> = 14.4 Hz, ClCH<sub>2</sub>), 3.58 (d, 1 H, *J*<sub>1,OH</sub> = 3.4 Hz, OH-α), 3.47 (dd, 1 H, *J*<sub>gem</sub> = 10.3 Hz, *J*<sub>5,6</sub> = 5.5 Hz, H-6α), 3.43 (dd, 1 H, *J*<sub>gem</sub> = 10.3 Hz, *J*<sub>5,6'</sub> = 3.4 Hz, H-6'α); HRMS (ESI) *m/z* found [M + Na]<sup>+</sup> 623.1658, C<sub>31</sub>H<sub>33</sub>ClO<sub>10</sub> calcd for [M + Na]<sup>+</sup> 623.1659.

To a solution of 32 (352 mg, 0.585 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.8 mL) were added trichloroacetonitrile (1.2 mL, 11.7 mmol) and K<sub>2</sub>CO<sub>3</sub> (243 mg, 1.76 mmol) at room temperature. After stirring for 3 h at room temperature as the reaction was monitored by TLC (EtOAc/hexane = 1:2), the reaction mixture was filtered through cotton, washed with CH<sub>2</sub>Cl<sub>2</sub>, and then evaporated. The resulting residue was purified by flash column chromatography using EtOAc/hexane (1:5 to 1:4) as the eluent to give 33: [α]<sub>D</sub> = +77.1° (c 0.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.54 (s, 1 H, C=NH), 7.98–7.41 (m, 5 H, Ph), 7.23–6.75 (4 d, 8 H, Ar), 6.63 (d, 1 H, *J*<sub>1,2</sub> = 3.5 Hz, H-1), 5.38 (dd, 1 H, *J*<sub>1,2</sub> = 3.5 Hz, *J*<sub>2,3</sub> = 9.5 Hz, H-2), 5.35 (t, 1

H,  $J_{3,4} = J_{4,5} = 10.0$  Hz, H-4), 4.65 and 4.54 (2 d, 2 H,  $J_{\text{gem}} = 11.5$  Hz, ArCH<sub>2</sub>O), 4.46 and 4.37 (2 d, 2 H,  $J_{\text{gem}} = 11.5$  Hz, ArCH<sub>2</sub>O), 4.23 (near t, 1 H,  $J_{2,3} = 9.5$  Hz,  $J_{3,4} = 10.0$  Hz, H-3), 4.11 (m, 1 H,  $J_{4,5} = 10.0$  Hz,  $J_{5,6} = J_{5,6'} = 4.0$  Hz, H-5), 3.80 and 3.75 (2 s, 6 H, 2 MeO), 3.71 and 3.66 (2 d, 2 H,  $J_{\text{gem}} = 15.0$  Hz, ClCH<sub>2</sub>), 3.57 (dd, 1 H,  $J_{\text{gem}} = 11.0$  Hz,  $J_{5,6} = 4.0$  Hz, H-6), 3.52 (dd, 1 H,  $J_{\text{gem}} = 11.0$  Hz,  $J_{5,6'} = 4.0$  Hz, H-6'), <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  165.8, 165.1, 160.3, 159.3, 133.4, 129.7, 129.7, 129.7, 129.4, 129.0, 128.4, 113.7, 93.5, 75.8, 74.3, 73.2, 72.3, 71.7, 71.1, 68.2, 55.2, 55.2, 40.5; HRMS (ESI)  $m/z$  found [M + Na]<sup>+</sup> 766.0750, C<sub>33</sub>H<sub>33</sub>Cl<sub>4</sub>NO<sub>10</sub> calcd for [M + Na]<sup>+</sup> 766.0756. **33 $\beta$** : [ $\alpha$ ]<sub>D</sub> = +43.5° (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.63 (s, 1 H, C=NH), 7.98–7.40 (m, 5 H, Ph), 7.24–6.69 (4 d, 8 H, Ar), 5.96 (d, 1 H,  $J_{1,2} = 7.8$  Hz, H-1), 5.58 (near t, 1 H,  $J_{1,2} = 7.8$  Hz,  $J_{2,3} = 8.6$  Hz, H-2), 5.33 (t, 1 H,  $J_{3,4} = J_{4,5} = 9.1$  Hz, H-4), 4.58 and 4.50 (2 d, 2 H,  $J_{\text{gem}} = 11.4$  Hz, ArCH<sub>2</sub>O), 4.45 and 4.40 (2 d, 2 H,  $J_{\text{gem}} = 11.2$  Hz, ArCH<sub>2</sub>O), 3.93 (near t, 1 H,  $J_{2,3} = 8.6$  Hz,  $J_{3,4} = 9.1$  Hz, H-3), 3.85 (m, 1 H,  $J_{4,5} = 9.1$  Hz, H-5), 3.79 and 3.71 (2 s, 6 H, 2 MeO), 3.74–3.59 (m, 4 H, ClCH<sub>2</sub>, H-6, and 6'); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  165.9, 164.5, 161.2, 159.3, 159.2, 133.3, 129.7, 129.6, 129.5, 129.4, 129.3, 128.4, 113.7, 113.6, 95.8, 90.2, 78.5, 73.7, 73.4, 73.2, 72.2, 71.8, 68.8, 55.2, 55.1, 40.5; HRMS (ESI)  $m/z$  found [M + Na]<sup>+</sup> 766.0750, C<sub>33</sub>H<sub>33</sub>Cl<sub>4</sub>NO<sub>10</sub> calcd for [M + Na]<sup>+</sup> 766.0756.

**2-O-Benzoyl-4-O-chloroacetyl-3,6-di-O-p-methoxybenzyl- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 1)-(2S,3R,4E)-3-O-benzoyl-2-octadecanamide-4-octadecene-1,3-diol (35).** To a mixture of **33 $\alpha$**  (176 mg, 0.236 mmol) and **34** (105 mg, 0.157 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.9 mL) was added 4 Å molecular sieves (AW-300) (300 mg) at room temperature. After stirring for 2 h, TMSOTf (2.1  $\mu$ L, 11.8  $\mu$ mol) was added to the mixture. After stirring for 3 h at room temperature as the reaction was monitored by TLC (EtOAc/PhMe = 1:5), the reaction was quenched by saturated NaHCO<sub>3</sub> (aq) and filtered through a Celite pad, and the pad was washed with CHCl<sub>3</sub>. The combined filtrate and washings were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The resulting residue was purified by flash column chromatography using EtOAc/PhMe (1:10) as the eluent to give **35** (95 mg, 48%): [ $\alpha$ ]<sub>D</sub> = +10.7° (c 1.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.03–7.39 (m, 10 H, 2 Ph), 7.16–6.68 (4 d, 8 H, Ar), 5.83 (m, 1 H,  $J_{4,5} = 15.1$  Hz,  $J_{5,6} = 7.3$  Hz,  $J_{5,6'} = 6.8$  Hz, H-5i), 5.71 (d, 1 H,  $J_{2,\text{NH}} = 9.1$  Hz, NH), 5.51 (t, 1 H,  $J_{2,3} = J_{3,4} = 6.8$  Hz, H-3i), 5.44 (dd, 1 H,  $J_{3,4} = 6.8$  Hz,  $J_{4,5} = 15.1$  Hz, H-4i), 5.25 (near t, 1 H,  $J_{1,2} = 8.2$  Hz,  $J_{2,3} = 9.6$  Hz, H-2h), 5.15 (t, 1 H,  $J_{3,4} = J_{4,5} = 9.6$  Hz, H-4h), 4.53 and 4.46 (2 d, 2 H,  $J_{\text{gem}} = 11.4$  Hz, ArCH<sub>2</sub>O), 4.50 (d, 1 H,  $J_{1,2} = 8.2$  Hz, H-1h), 4.40 (m, 1 H,  $J_{1,2} = 2.7$  Hz,  $J_{2,3} = 6.8$  Hz, H-2i), 4.28 and 4.22 (2 d, 2 H,  $J_{\text{gem}} = 11.0$  Hz, ArCH<sub>2</sub>O), 4.10 (dd, 1 H,  $J_{\text{gem}} = 9.6$  Hz,  $J_{1,2} = 2.7$  Hz, H-1i), 3.82 (t, 1 H,  $J_{2,3} = J_{3,4} = 9.6$  Hz, H-3h), 3.78 and 3.70 (2 s, 6 H, 2 MeO), 3.65 (m, 2 H, ClCH<sub>2</sub>), 3.58 (m, 2 H, H-5h and H-1'i), 3.45 (dd, 1 H,  $J_{\text{gem}} = 10.0$  Hz,  $J_{5,6} = 5.0$  Hz, H-6h), 3.38 (dd, 1 H,  $J_{\text{gem}} = 10.0$  Hz,  $J_{5,6'} = 4.6$  Hz, H-6'h), 1.98 (br dd, 2 H,  $J_{\text{gem}} = 14.1$  Hz,  $J_{5,6} = 7.3$  Hz,  $J_{5,6'} = 6.8$  Hz, H-6i and 6'i), 1.74 and 1.37 (2 m, 2 H, NHC(=O)CH<sub>2</sub>), 1.26 (m, 52 H, 26 CH<sub>2</sub>), 0.87 (t, 6 H, 2 Me); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.5, 165.9, 165.0, 164.9, 159.2, 159.1, 137.2, 133.3, 132.8, 130.2, 129.6, 129.5, 129.5, 129.3, 128.4, 128.2, 124.7, 113.7, 113.6, 100.6, 78.8, 74.3, 73.6, 73.5, 73.2, 72.9, 72.6, 69.3, 67.1, 55.1, 55.0, 50.3, 40.5, 36.3, 32.2, 31.8, 29.6, 29.4, 29.4, 29.3, 29.2, 29.1, 28.8, 25.4, 22.6, 14.0; HRMS (ESI)  $m/z$  found [M + Na]<sup>+</sup> 1274.7255, C<sub>74</sub>H<sub>106</sub>ClNO<sub>13</sub> calcd for [M + Na]<sup>+</sup> 1274.7250.

**2-O-Benzoyl-3,6-di-O-p-methoxybenzyl- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 1)-(2S,3R,4E)-3-O-benzoyl-2-octadecanamide-4-octadecene-1,3-diol (36).** To a solution of **35** (95 mg, 0.0758 mmol) in EtOH/CH<sub>2</sub>Cl<sub>2</sub> (3.6 mL/1.2 mL) was added DABCO (127 mg, 1.13 mmol) at room temperature. After stirring for 5 h at 55 °C as the reaction was monitored by TLC (EtOAc/PhMe = 1:3), the mixture was diluted with EtOAc. The organic layer was washed with 2 M HCl, saturated NaHCO<sub>3</sub> (aq), and brine. After drying over Na<sub>2</sub>SO<sub>4</sub> and being concentrated, the resulting residue was purified by flash

column chromatography using EtOAc/PhMe (1:5) as the eluent to give **36** (85 mg, 96%): [ $\alpha$ ]<sub>D</sub> = +5.4° (c 1.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.01–7.37 (m, 10 H, 2 Ph), 7.18–6.66 (4 d, 8 H, Ar), 5.81 (m, 1 H,  $J_{4,5} = 15.1$  Hz,  $J_{5,6} = 7.8$  Hz,  $J_{5,6'} = 6.8$  Hz, H-5i), 5.70 (d, 1 H,  $J_{2,\text{NH}} = 9.1$  Hz, NH), 5.48 (t, 1 H,  $J_{2,3} = J_{3,4} = 7.3$  Hz, H-3i), 5.42 (dd, 1 H,  $J_{3,4} = 7.3$  Hz,  $J_{4,5} = 15.1$  Hz, H-4i), 5.16 (near t, 1 H,  $J_{1,2} = 7.8$  Hz,  $J_{2,3} = 9.2$  Hz, H-2h), 4.64 (t, 2 H,  $J_{\text{gem}} = 11.4$  Hz, 2 ArCH<sub>2</sub>O), 4.45 (d, 1 H,  $J_{1,2} = 7.8$  Hz, H-1h), 4.40 and 4.33 (2 d, 2 H,  $J_{\text{gem}} = 11.4$  Hz, 2 ArCH<sub>2</sub>O), 4.38 (m, 1 H, H-2i), 4.08 (dd, 1 H,  $J_{\text{gem}} = 9.6$  Hz,  $J_{1,2} = 2.3$  Hz, H-1i), 3.78 and 3.74 (2 s, 6 H, 2 MeO), 3.74 (dt, 1 H,  $J_{3,4} = J_{4,5} = 9.2$  Hz,  $J_{4,\text{OH}} = 1.8$  Hz, H-4h), 3.63 (t, 1 H,  $J_{2,3} = J_{3,4} = 9.2$  Hz, H-3h), 3.57 (m, 3 H, H-6h, 6'h, and H-1'i), 3.45 (m, 1 H,  $J_{4,5} = 9.2$  Hz, H-5h), 2.93 (d, 1 H,  $J_{4,\text{OH}} = 1.8$  Hz, OH), 1.97 (near dd, 2 H,  $J_{\text{gem}} = 13.2$  Hz,  $J_{5,6} = 7.8$  Hz,  $J_{5,6'} = 6.8$  Hz, H-6i and 6'i), 1.72 (t, 1 H, NHC(=O)CH<sub>2</sub>), 1.37 (m, 1 H, NHC(=O)CH<sub>2</sub>), 1.26 (m, 52 H, 26 CH<sub>2</sub>), 0.87 (t, 6 H, 2 Me); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.5, 165.2, 165.0, 159.2, 159.1, 137.1, 133.2, 132.7, 130.3, 130.0, 129.6, 129.5, 129.3, 128.4, 128.2, 124.7, 113.7, 113.6, 100.8, 81.1, 74.3, 73.9, 73.8, 73.5, 73.3, 72.6, 70.1, 67.0, 55.1, 55.0, 50.3, 36.3, 32.2, 31.8, 29.6, 29.6, 29.4, 29.4, 29.3, 29.2, 29.1, 28.8, 25.4, 22.6, 14.0; HRMS (ESI)  $m/z$  found [M + Na]<sup>+</sup> 1198.7533, C<sub>72</sub>H<sub>105</sub>NO<sub>12</sub> calcd for [M + Na]<sup>+</sup> 1198.7534.

**[Methyl 5-acetamido-8-O-(5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonate]-(2 $\rightarrow$ 3)-2,4,6-tri-O-benzoyl- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 3)-2-acetamido-4,6-di-O-benzoyl-2-deoxy- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-{[methyl 5-acetamido-8-O-(5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-O-acetyl-3,5-dideoxy-D-glycero- $\alpha$ -D-galacto-2-nonulopyranosylonate]-(2 $\rightarrow$ 3)-2,6-di-O-benzoyl- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-2-O-benzoyl-3,6-di-O-p-methoxybenzyl- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 1)-(2S,3R,4E)-3-O-benzoyl-2-octadecanamide-4-octadecene-1,3-diol (40).** To a mixture of **20** (146 mg, 0.0474 mmol) and **36** (85 mg, 0.0722 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.2 mL) was added 4 Å molecular sieves (AW-300) (200 mg) at room temperature. After stirring for 2 h and then cooling to 0 °C, TMSOTf (1.0  $\mu$ L, 5.52  $\mu$ mol) was added to the mixture. After stirring for 1 h at 0 °C as the reaction was monitored by TLC (PhMe/MeOH = 4:1), the reaction was quenched by saturated NaHCO<sub>3</sub> (aq) and filtered through a Celite pad, and the pad was washed with CHCl<sub>3</sub>. The combined filtrate and washings were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The resulting residue was purified by flash column chromatography using PhMe/MeOH (8:1 to 7:1) as the eluent to give **40** (177 mg, 91%): [ $\alpha$ ]<sub>D</sub> = +3.2° (c 0.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  8.08–7.28 (m, 45 H, 9 Ph), 7.07–6.56 (4 d, 8 H, Ar), 5.97 (near s, 1 H, H-4d), 5.76 (m, 1 H,  $J_{4,5} = 14.4$  Hz,  $J_{5,6} = 7.5$  Hz,  $J_{5,6'} = 6.9$  Hz, H-5i), 5.69 (d, 1 H,  $J_{3,4} = 4.1$  Hz, H-4e), 5.66 (d, 1 H,  $J_{2,\text{NH}} = 8.9$  Hz, NH-i), 5.55 (dt, 2 H,  $J_{3,\text{eq},4} = 4.0$  Hz,  $J_{4,5} = 10.9$  Hz, H-4g and NH-d), 5.49 (br d, 1 H, NH-b), 5.45 (t, 1 H, H-3i), 5.39 (dd, 2 H, H-4i and NH-f), 5.35–5.26 (m, 5 H, H-7g, 7b, 4b, 2c, and 2e), 5.22 (d, 1 H,  $J_{1,2} = 8.9$  Hz, H-1d), 5.15 (m, 4 H, H-8b, 8g, 2h, and NH-a), 5.08 (m, 1 H, H-4f), 4.98 (br dd, 1 H, H-7a), 4.95 (m, 1 H, H-4a), 4.84 (br dd, 1 H, H-7f), 4.82 (d, 1 H,  $J_{1,2} = 9.6$  Hz, H-1c), 4.80 (m, 2 H, H-3d and ArCH<sub>2</sub>O), 4.63 (m, 3 H, H-6c, 8f, and ArCH<sub>2</sub>O), 4.55 (d, 1 H,  $J_{\text{gem}} = 10.9$  Hz, ArCH<sub>2</sub>O), 4.40 (br d, 2 H,  $J_{1,2} = 7.5$  Hz, H-1e and 3e), 4.34 (d, 1 H,  $J_{1,2} = 8.2$  Hz, H-1h), 4.32 (m, 1 H, H-2i), 4.28–3.96 (m, 24 H, H-9'b, 9'g, 9'f, 9'a, 4c, 5b, 3c, 6'c, 5g, 6b, 8a, 9a, 9b, 9g, 5a, 4h, 5e, 6e, 6'e, 5d, 6'd, 6d, 1i, and ArCH<sub>2</sub>O), 3.89 (dd, 1 H, H-6g), 3.84 (dd, 2 H, H-6a and 6f), 3.80 (t, 1 H,  $J_{2,3} = J_{3,4} = 8.9$  Hz, H-3h), 3.77 (s, 3 H, COOMe-a), 3.71 (s, 3 H, MeO), 3.70 (m, 2 H, H-2d and 9f), 3.62 (near t, 1 H, H-5c), 3.43 (m, 6 H, H-6'h, 6h, 1'i, and MeO), 3.33 (m, 1 H, H-5h), 3.23 (s, 3 H, COOMe-f), 2.57 (dd, 1 H,  $J_{\text{gem}} = 13.0$  Hz,  $J_{3,\text{eq},4} = 4.1$  Hz, H-3eq-b), 2.50 (dd, 1 H,  $J_{\text{gem}} = 12.2$  Hz,  $J_{3,\text{eq},4} = 4.0$  Hz, H-3eq-g), 2.33 (br dd, 1 H, H-3eq-a), 2.10–1.76 (m, 57 H, 17 Ac, H-3eq-f, 3ax-f, 3ax-a, 3ax-b, 6i, and

6'i), 1.67 (t, 1 H, NHCOCH<sub>2</sub>), 1.63 (t, 1 H,  $J_{gem} = J_{3ax,4} = 12.2$  Hz, H-3ax-g), 1.34 (m, 1 H, NHCOCH<sub>2</sub>), 1.26 (m, 52 H, 26 CH<sub>2</sub>), 0.87 (2 t, 6 H, 2 Me); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 172.4, 170.8, 170.6, 170.5, 170.4, 170.3, 170.3, 170.1, 170.1, 169.7, 169.6, 169.5, 167.3, 167.1, 166.3, 165.9, 165.8, 165.6, 165.4, 165.2, 165.0, 164.9, 164.7, 164.1, 164.0, 158.9, 158.7, 136.9, 133.1, 133.0, 132.9, 132.6, 130.1, 130.1, 130.0, 129.8, 129.6, 129.5, 129.4, 129.4, 129.3, 128.9, 128.8, 128.4, 128.3, 128.1, 124.6, 113.4, 113.3, 101.3, 100.8, 100.3, 99.6, 99.4, 98.9, 96.8, 95.7, 80.1, 77.2, 76.4, 75.1, 74.3, 73.9, 73.8, 73.4, 73.1, 72.8, 72.5, 72.1, 71.8, 71.5, 71.3, 71.2, 71.1, 70.8, 70.7, 70.3, 69.8, 69.4, 69.3, 69.2, 68.7, 68.5, 68.2, 67.8, 67.1, 66.8, 66.6, 63.3, 62.0, 61.7, 55.0, 54.6, 53.0, 52.2, 50.2, 48.9, 48.7, 38.8, 38.2, 36.9, 36.2, 35.4, 32.5, 32.1, 31.7, 29.8, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.8, 25.3, 22.9, 22.8, 22.6, 22.5, 20.6, 20.6, 20.5, 20.4, 20.2, 20.1, 14.0; HRMS (ESI) *m/z* found [M + 2Na]<sup>2+</sup> 2068.8101, C<sub>211</sub>H<sub>258</sub>N<sub>6</sub>O<sub>76</sub> calcd for [M + 2Na]<sup>2+</sup> 2068.8146.

[Methyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero- $\alpha$ -*D*-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-*D*-glycero- $\alpha$ -*D*-galacto-2-nonulopyranosylate]-(2 $\rightarrow$ 3)-2,4,6-tri-*O*-benzoyl- $\beta$ -*D*-galactopyranosyl-(1 $\rightarrow$ 3)-2-acetamido-4,6-di-*O*-benzoyl-2-deoxy- $\beta$ -*D*-galactopyranosyl-(1 $\rightarrow$ 4)-{[methyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero- $\alpha$ -*D*-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-*D*-glycero- $\alpha$ -*D*-galacto-2-nonulopyranosylate]-(2 $\rightarrow$ 3)-2,6-di-*O*-benzoyl- $\beta$ -*D*-galactopyranosyl-(1 $\rightarrow$ 4)-2-*O*-benzoyl-3,6-di-*O*-benzyl- $\beta$ -*D*-glucopyranosyl-(1 $\rightarrow$ 1)-(2*S*,3*R*,4*E*)-3-*O*-benzyl-2-octadecanamide-4-octadecene-1,3-diol (41)}. To a mixture of 20 (148 mg, 0.0480 mmol) and 37 (79 mg, 0.0720 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was added 4 Å molecular sieves (AW-300) (180 mg) at room temperature. After stirring for 2 h and then cooling to 0 °C, TMSOTf (1.0 μL, 5.52 μmol) was added to the mixture. After stirring for 2 h at 0 °C as the reaction was monitored by TLC (PhMe/MeOH = 4:1), additional TMSOTf (1.0 μL, 5.52 μmol) was added to the mixture. After the stirring was continued for 24 h, the reaction was quenched by saturated NaHCO<sub>3</sub> (aq) and filtered through a Celite pad, and the pad was washed with CHCl<sub>3</sub>. The combined filtrate and washings were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The resulting residue was purified by flash column chromatography (PhMe/MeOH = 9:1 to 8:1) to give 41 (140 mg, 73%): [α]<sub>D</sub> = -2.5° (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.01–6.89 (m, 55 H, 11 Ph), 5.97 (near s, 1 H, H-4d), 5.69 (d, 1 H,  $J_{3,4} = 2.7$  Hz, H-4e), 5.54 (m, 4 H, H-4g, 5i, and 2 NH), 5.36 (m, 5 H, H-4b, 7b, and 3 NH), 5.32 (dd, 1 H,  $J_{6,7} = 2.0$  Hz,  $J_{7,8} = 8.2$  Hz, H-7g), 5.19 (m, 7 H, H-8b, 2e, 2c, 1d, 2h, 8g, and 4i), 5.08 (m, 1 H, H-4f), 5.01 (near d, 1 H,  $J_{7,8} = 8.9$  Hz, H-7a), 4.98 (m, 1 H, H-4a), 4.89 (d, 1 H,  $J_{gem} = 10.9$  Hz, PhCH<sub>2</sub>), 4.83 (near dd, 1 H,  $J_{7,8} = 9.6$  Hz, H-7f), 4.62 (m, 5 H, H-3d, 8f, 6c, 6'c, and PhCH<sub>2</sub>), 4.60 (d, 1 H,  $J_{1,2} = 7.5$  Hz, H-1c), 4.49 and 4.28 (2 d, 2 H,  $J_{gem} = 11.6$  Hz, PhCH<sub>2</sub>), 4.49 and 4.17 (2 d, 2 H,  $J_{gem} = 11.6$  Hz, PhCH<sub>2</sub>), 4.44 (m, 2 H, H-1e and 3e), 4.35 (d, 1 H,  $J_{1,2} = 7.5$  Hz, H-1h), 4.31–4.20 (m, 8 H, H-9'g, 9'b, 9'f, 9f, 5b, 9'a, 1'i, and 8a), 4.13–3.97 (m, 10 H, H-6b, 5a, 5g, 4h, 4c, 3c, 5f, 2i, 9b, and 9g), 3.89 (dd, 1 H,  $J_{5,6} = 10.3$  Hz,  $J_{6,7} = 2.0$  Hz, H-6g), 3.84 (m, 2 H, H-6a and 6f), 3.78 (m, 5 H, H-3h, 2d, and COOMe-a), 3.71 (m, 2 H, H-3i and 9a), 3.61 (br t, 1 H, H-5c), 3.53 (br dd, 1 H,  $J_{gem} = 10.9$  Hz, H-6'h), 3.46 (br d, 1 H,  $J_{gem} = 10.9$  Hz, H-6h), 3.35 (br dd, 1 H, H-1i), 3.26 (m, 1 H, H-5h), 3.23 (s, 3 H, COOMe-f), 2.57 (br dd, 1 H, H-3eq-b), 2.48 (dd, 1 H, H-3eq-g), 2.22 (m, 1 H, H-3eq-a), 2.11–1.82 (13 s and m, 57 H, 17 Ac, H-3eq-f, 3ax-f, 3ax-a, 3ax-b, 6i, and 6'i), 1.61 (m, 3 H, H-3ax-g, NHCOCH<sub>2</sub>), 1.26 (m, 52 H, 26 CH<sub>2</sub>), 0.87 (t, 6 H, 2 Me); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.3, 170.8, 170.7, 170.6, 170.6, 170.5, 170.4, 170.4, 170.2, 169.8, 169.8, 169.7, 167.5, 167.3, 166.2, 166.0, 165.8, 165.4, 165.2, 164.6, 164.2, 164.1, 138.5, 138.2, 138.0, 137.0, 133.4, 133.3, 133.1, 133.1, 133.0, 132.8, 130.3, 130.0, 129.9, 129.8, 129.8, 129.7, 129.6, 129.6, 129.5, 129.5, 129.3, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.6, 127.5, 127.4, 127.3, 127.2, 101.3, 100.2, 100.2, 99.9, 99.6, 99.0, 97.1, 96.1, 80.3, 79.0,

75.6, 74.8, 74.2, 74.0, 73.6, 73.3, 73.1, 72.5, 72.1, 72.0, 71.6, 71.4, 71.0, 70.9, 70.4, 70.1, 69.9, 69.5, 69.4, 69.4, 69.0, 68.7, 68.6, 68.5, 67.9, 67.7, 67.2, 67.0, 66.7, 63.7, 62.1, 62.0, 61.8, 54.0, 53.2, 52.4, 51.2, 49.1, 48.9, 48.8, 38.8, 38.3, 36.4, 35.4, 32.2, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.2, 25.4, 23.1, 23.1, 23.0, 22.6, 20.8, 20.7, 20.6, 20.3, 14.1; HRMS (ESI) *m/z* found [M + 2Na]<sup>2+</sup> 2031.8146, C<sub>209</sub>H<sub>256</sub>N<sub>6</sub>O<sub>73</sub> calcd for [M + 2Na]<sup>2+</sup> 2031.8149.

2-(Trimethylsilyl)ethyl [Methyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero- $\alpha$ -*D*-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-*D*-glycero- $\alpha$ -*D*-galacto-2-nonulopyranosylate]-(2 $\rightarrow$ 3)-2,4,6-tri-*O*-benzoyl- $\beta$ -*D*-galactopyranosyl-(1 $\rightarrow$ 3)-2-acetamido-4,6-di-*O*-benzoyl-2-deoxy- $\beta$ -*D*-galactopyranosyl-(1 $\rightarrow$ 4)-{[methyl 5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero- $\alpha$ -*D*-galacto-2-nonulopyranosylono-1',9-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-*D*-glycero- $\alpha$ -*D*-galacto-2-nonulopyranosylate]-(2 $\rightarrow$ 3)-2,6-di-*O*-benzoyl- $\beta$ -*D*-galactopyranosyl-(1 $\rightarrow$ 4)-2-*O*-benzoyl-3,6-di-*O*-benzyl- $\beta$ -*D*-glucopyranoside (42)}. To a mixture of 20 (189 mg, 0.0613 mmol) and 38 (52 mg, 0.0919 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added 4 Å molecular sieves (AW-300) (250 mg) at room temperature. After stirring for 2 h and then cooling to 0 °C, TMSOTf (1.1 μL, 6.13 μmol) was added to the mixture. After stirring for 2 h at 0 °C as the reaction was monitored by TLC (PhMe/MeOH = 4:1), the reaction was quenched by saturated NaHCO<sub>3</sub> (aq) and filtered through a Celite pad, and the pad was washed with CHCl<sub>3</sub>. The combined filtrate and washings were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by flash column chromatography using PhMe/MeOH (6:1) as the eluent to give 42 (135 mg, 63%): [α]<sub>D</sub> = -0.6° (c 1.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.13–6.89 (m, 50 H, 10 Ph), 5.95 (br s, 1 H, H-4d), 5.85 (br d, 1 H, NH-d), 5.70 (d, 1 H,  $J_{3,4} = 3.4$  Hz, H-4e), 5.63 (d, 1 H,  $J_{5,NH} = 9.0$  Hz, NH-b), 5.54 (dt, 1 H,  $J_{3eq,4} = 5.3$  Hz,  $J_{3ax,4} = 12.2$  Hz,  $J_{4,5} = 10.2$  Hz, H-4g), 5.45 (d, 1 H,  $J_{5,NH} = 8.7$  Hz, NH-g), 5.43 (d, 1 H,  $J_{5,NH} = 8.5$  Hz, NH-a), 5.34 (m, 1 H, H-4b), 5.32 (dd, 3 H,  $J_{6,7} = 2.1$  Hz,  $J_{7,8} = 9.0$  Hz,  $J_{1,2} = 7.8$  Hz, H-7b, 7g, and 2e), 5.27 (d, 1 H, NH-f), 5.24 (t, 1 H,  $J_{1,2} = 7.8$  Hz,  $J_{2,3} = 9.5$  Hz, H-2c), 5.21 (d, 1 H,  $J_{1,2} = 8.5$  Hz, H-1d), 5.17 (m, 3 H,  $J_{1,2} = 7.8$  Hz,  $J_{7,8} = 9.0$  Hz, H-2h, 8b, and 8g), 5.08 (m, 1 H, H-4f), 5.01 (dd, 1 H,  $J_{6,7} = 1.7$  Hz,  $J_{7,8} = 11.2$  Hz, H-7a), 4.96 (br dt, 1 H, H-4a), 4.86 and 4.62 (2 d, 2 H,  $J_{gem} = 10.9$  Hz, PhCH<sub>2</sub>), 4.84 (dd, 1 H,  $J_{6,7} = 2.9$  Hz,  $J_{7,8} = 9.2$  Hz, H-7f), 4.75 (br dd, 1 H, H-3d), 4.67 (d, 1 H,  $J_{1,2} = 7.8$  Hz, H-1c), 4.63 (m, 1 H,  $J_{7,8} = 9.2$  Hz, H-8f), 4.55 (br d, 1 H, H-6c), 4.50 and 4.28 (2 d, 2 H,  $J_{gem} = 12.2$  Hz, PhCH<sub>2</sub>), 4.42 (d, 3 H,  $J_{1,2} = 7.8$  Hz, H-1e, 3e, and 1h), 4.33–4.19 (m, 10 H, H-9'b, 9'g, 9'a, 9'f, 8a, 6e, 6'c, 6'd, 6d, and 5b), 4.11 (q, 1 H,  $J_{4,5} = 10.2$  Hz,  $J_{5,6} = 10.4$  Hz,  $J_{5,NH} = 8.7$  Hz, H-5g), 4.06–3.97 (m, 12 H, H-5f, 6b, 5a, 3c, 9a, 9b, 4c, 4h, 6'c, 9b, 5e, and 5d), 3.92 (dd, 1 H,  $J_{5,6} = 10.4$  Hz,  $J_{6,7} = 2.1$  Hz, H-6g), 3.87 (m, 1 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 3.85–3.72 (m, 8 H, H-6a, 6f, 3h, 9f, 2d, and COOMe-a), 3.56 (m, 2 H,  $J_{gem} = 10.7$  Hz, H-6'h and 5c), 3.50 (dd, 1 H,  $J_{gem} = 10.7$  Hz, H-6h), 3.41 (m, 1 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), 3.35 (m, 1 H, H-5h), 3.22 (s, 3 H, COOMe-f), 2.58 (br dd, 1 H, H-3eq-b), 2.50 (dd, 1 H,  $J_{3eq,4} = 5.3$  Hz,  $J_{gem} = 12.2$  Hz, H-3eq-g), 2.27 (br dd, 1 H, H-3eq-a), 2.11–1.80 (m, 55 H, 17 Ac, H-3ax-b, 3ax-a, 3eq-f, and 3ax-f), 1.63 (t, 1 H,  $J_{3ax,4} = J_{gem} = 12.2$  Hz, H-3ax-g), 0.81 (m, 2 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>), -0.12 (s, 9 H, OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.9, 170.6, 170.5, 170.5, 170.5, 170.4, 170.3, 170.2, 170.2, 169.8, 169.7, 169.7, 169.6, 167.4, 167.2, 166.1, 165.9, 165.9, 165.7, 165.4, 164.9, 164.6, 164.1, 138.2, 138.2, 133.2, 133.1, 132.9, 132.8, 132.7, 130.2, 130.1, 129.9, 129.9, 129.7, 129.6, 129.6, 129.5, 129.5, 129.4, 128.9, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 127.9, 127.8, 127.7, 127.4, 127.1, 101.2, 100.4, 100.1, 99.8, 99.5, 99.0, 97.1, 96.0, 80.8, 77.2, 76.4, 76.2, 74.7, 74.0, 73.8, 73.2, 73.1, 72.5, 72.1, 72.0, 71.6, 71.3, 70.9, 70.4, 69.8, 69.5, 69.3, 69.2, 69.0, 68.7, 68.5, 68.4, 68.0, 67.2, 67.1, 67.0, 66.9, 66.7, 63.5, 62.1, 62.0, 61.8, 54.3, 53.1, 52.3, 49.1, 48.9, 38.7, 38.2, 35.5, 35.4, 29.6, 23.0, 23.0, 22.9, 22.7, 20.7, 20.7, 20.6, 20.6, 20.6, 20.5, 20.3, 20.2, 17.8, -1.5; HRMS (ESI) *m/z* found [M + 2Na]<sup>2+</sup> 1763.0599, C<sub>171</sub>H<sub>193</sub>N<sub>5</sub>O<sub>71</sub>Si calcd for [M + 2Na]<sup>2+</sup> 1763.0599.