(150 mg) was added. The suspension was stirred for 1 h and cooled to −20 °C. To the mixture, 2,6-lutidine (30 μL, 0.26 mmol), Cp_2HfCl_2 (250 mg, 0.65 mmol), and AgOTf (338 mg, 1.30 mmol) were added and stirring was continued for 2 h until TLC analysis (15:1, $CHCl_3/CH_3OH$) indicated the completion of the reaction. The reaction mixture was alkalized to pH ~ 8 with satd aq $NaHCO_3$ at 0 °C and filtered through Celite. The combined filtrate and washings were extracted with $CHCl_3$ and the organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (75:1, $CHCl_3/CH_3OH$) to give disaccharide **16** (76 mg, 40%) as an α/β-mixture (α:β = 1:1).

3.17. Phenyl 7-*O*-acetyl-5-amino-3,5-dideoxy-8,9-*O*-isopropylidene-2-thio-4-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-D-*glycero*-α-D-*galacto*-2-nonulopyranoside-1,5-lactam (17)

With fucosyl fluoride donor **14**: To a solution of compound **8** (110 mg, 0.29 mmol) and compound **14** (152 mg, 0.35 mmol) in CH_2Cl_2 (5.3 mL) was added 4 Å molecular sieves (150 mg). The suspension was stirred for 1 h and cooled to −40 °C. To the mixture were added 2,6-lutidine (40 μL, 0.35 mmol), Cp_2HfCl_2 (148 mg, 0.42 mmol), and AgOTf (100 mg, 0.42 mmol) and stirring was continued for 3 h. After the addition of 2,6-lutidine (40 μL, 0.35 mmol), Cp_2HfCl_2 (148 mg, 0.42 mmol), and AgOTf (100 mg, 0.42 mmol), stirring was continued for 3 h at −10 °C until TLC analysis (15:1, $CHCl_3/CH_3OH$) indicated the completion of the reaction. The reaction mixture was alkalized to pH ~ 8 with satd aq $NaHCO_3$ at 0 °C and filtered through Celite. The combined filtrate and washings were extracted with $CHCl_3$, and the organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (5:2, toluene/EtOAc) to give disaccharide as a α/β-mixture (α:β = 2:3), which was acetylated with Ac_2O and pyridine to afford **17α** (48 mg, 18%) and the corresponding β-isomer **17β** (71 mg, 27%).

With phenylthioglycoside donor **15**: To a solution of **8** (110 mg, 0.29 mmol) and **15** (184 mg, 0.35 mmol) in CH_2Cl_2 (5.3 mL), 4 Å molecular sieves (150 mg) was added. The suspension was stirred for 1 h and cooled to −40 °C. To the mixture, NIS (95 mg, 0.42 mmol) and TfOH (3.7 μL, 42 μmol) were added and stirring was continued for 5 min. The reaction mixture was alkalized to pH ~ 8 with satd aq $NaHCO_3$ at 0 °C and filtered through Celite. The combined filtrate and washings were extracted with EtOAc, and the organic layer was washed with satd aq $Na_2S_2O_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (75:1, $CHCl_3/CH_3OH$) to give the disaccharide as an α/β-mixture (α:β = 7:1), which was acetylated with Ac_2O and pyridine to afford **17α** (116 mg, 48%) and **17β** (16 mg, 7%); **17α**: $[\alpha]_D$ −13.3 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.57–7.26 (m, 20H, 4Ph), 5.99 (dd, 1H, $J_{6,7} = 7.4$ Hz, $J_{7,8} = 9.7$ Hz, H-7_{Neu}), 5.32 (t, 1H, $J_{4,5} = 2.3$ Hz, $J_{5,6} = 2.3$ Hz, H-5_{Neu}), 4.85 (s, 1H, $J_{1,2} = 4.0$ Hz, H-1_{Fuc}), 4.81–4.62 (m, 7H, H-6_{Neu}, 3PhCH_2), 4.64 (dd, 1H, $J_{2,3} = 7.4$ Hz, H-2_{Fuc}), 4.28 (dd, 1H, $J_{8,9} = 7.4$ Hz, H-9_{Neu}), 3.84–3.89 (m, 3H, H-4_{Neu}, H-8_{Neu}, and H-3_{Fuc}), 3.41 (dd, 1H, $J_{4,5} = 7.4$ Hz, $J_{5,6} = 6.3$ Hz, H-5_{Fuc}), 2.13 (s, 6H, Ac), 2.45 (dd, 1H, $J_{gem} = 14.9$ Hz, $J_{3eq,4} = 10.9$ Hz, H-$3eq_{Neu}$), 2.28 (dd, 1H, $J_{3ax,4} = 5.7$ Hz, H-$3ax_{Neu}$), 1.17 (d, 1H, H-6_{Fuc}), 1.28 and 1.16 (2s, 6H, 2Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 138.5, 138.5, 135.8, 129.0, 128.8, 128.7, 128.4, 128.4, 128.4, 128.2, 128.1, 127.6, 127.5, 127.5, 127.4, 108.9, 104.6, 85.9, 82.1, 78.9, 78.1, 76.3, 75.7, 75.5, 74.7, 73.6, 73.2, 71.6, 70.9, 64.0, 51.5, 38.5, 29.7, 26.1, 24.9, 21.1, 16.9; MALDI-TOFMS *m/z* calcd for $C_{47}H_{53}NO_{11}S$ $[M+Na]^+$: 862.32. Found 862.34. **17β**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.53–7.26 (m, 20H, 4Ph), 5.97 (dd, 1H, $J_{6,7} = 10.3$ Hz, H-7_{Neu}), 5.15 (m, 1H, H-5_{Neu}), 4.89 (dd, 1H, $J_{1,2} = 11.5$ Hz, H-1_{Fuc}), 4.54 (m, 8H, H-8_{Neu}, H-2_{Fuc} and 3PhCH_2), 3.91 (m, 3H, H-9_{Neu}, H-6_{Neu}, and H-4_{Fuc}), 3.81 (dd, 1H, H-9_{Neu}), 3.76 (m, 1H, H-4_{Neu}), 3.63 (m, 2H, H-5_{Fuc} and H-3_{Fuc}), 2.41 (dd, 1H, $J_{gem} = 14.9$ Hz, $J_{3eq,4} = 10.5$ Hz, H-$3eq_{Neu}$), 2.64 and 2.19 (2s, 6H, 2Ac), 2.13 (dd, 1H, $J_{3ax,4} = 5.7$ Hz, H-$3ax_{Neu}$), 1.25 and 1.07 (2s, 6H, 2Me), 0.70 (d, 1H, $J_{5,6} = 6.3$ Hz, H-6_{Fuc}); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 169.3, 167.5, 139.1, 138.7, 138.5, 136.2, 129.3, 128.9, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.5, 127.4, 127.4, 108.9, 101.6, 86.8, 79.4, 77.6, 76.2, 75.3, 74.7, 73.5, 73.4, 71.3, 67.9, 63.5, 49.5, 38.9, 26.5, 26.0, 25.0, 21.1, 16.3.

3.18. Methyl (phenyl 4,7-di-*O*-acetyl-3,5-dideoxy-9-*O*-benzyl-2-thio-8-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (21)

To a solution of compound **13** (102 mg, 0.16 mmol) and compound **14** (83 mg, 0.19 mmol) in CH_2Cl_2 (5.3 mL), 4 Å molecular sieves (240 mg) was added. The suspension was stirred for 1 h and cooled to −80 °C. To the mixture, Cp_2ZrCl_2 (85 mg, 0.22 mmol) and AgOTf (57 mg, 0.22 mmol) were added, and stirring was continued for 3 h till TLC analysis (4:1, toluene/EtOAc) indicated the completion of the reaction. The reaction mixture was filtered through Celite. The combined filtrate and washings were extracted with $CHCl_3$, and the organic layer was washed with satd aq $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated. The residue was purified with column chromatography on silica gel (4:1, *n*-Hex/EtOAc) to give **21α** (130 mg, 77%) and the corresponding β-isomer **21β** (8 mg, 5%).

21α; $[\alpha]_D$ −12.7 (*c* 1.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.56–7.22 (m, 25H, 5Ph), 6.50 (d, 1H, NH), 5.31 (dd, 1H, H-7), 5.18 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1_{Fuc}), 5.02–4.94 (m, 2H, H-4_{Neu} and PhCH_2), 4.82–4.46 (m, 7H, 4PhCH_2), 4.21–4.07 (m, 4H, H-6_{Neu}, H-3_{Fuc}, H-$9'_{Neu}$, and H-5_{Fuc}), 4.04–3.97 (m, 2H, H-2_{Fuc} and H-8_{Neu}), 3.81 (q, 1H, H-5_{Neu}), 3.68 (d, 1H, H-4_{Fuc}), 3.59–3.54 (m, 4H, H-9_{Neu} and Me), 2.78 (dd, 1H, H-3eq$_{Neu}$), 2.05–1.85 (m, 7H, H-3ax $_{Neu}$, 2Ac), 1.09 (d, 1H, $J_{5,6}$ = 6.6 Hz, H-6_{Fuc}); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 170.6, 169.7, 168.6, 139.3, 139.0, 138.3, 138.2, 137.1, 130.2, 129.0, 128.8, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 95.0, 86.9, 79.0, 78.1, 76.4, 75.2, 73.8, 73.5, 73.1, 73.0, 72.6, 69.8, 69.6, 67.1, 66.9, 53.0, 50.5, 38.1, 29.9, 21.0, 20.8, 17.1; MALDI-TOFMS *m/z* calcd for $C_{56}H_{60}F_3NO_{14}S$ $[M+Na]^+$: 1082.36. Found 1082.38.

3.19. Phenyl 4,7-di-*O*-acetyl-5-amino-9-*O*-benzyl-3,5-dideoxy-2-thio-8-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-D-*glycero*-α-D-*galacto*-2-nonulopyranoside-1,5-lactam (22)

With fucosyl fluoride donor **14**: To a solution of compound **12** (100 mg, 0.19 mmol) and compound **14** (100 mg, 0.23 mmol) in CH_2Cl_2 (5.3 mL), 4 Å molecular sieves (240 mg) was added. The suspension was stirred for 1 h and cooled to −80 °C. To the mixture, Cp_2ZrCl_2 (81 mg, 0.28 mmol) and AgOTf (71 mg, 0.28 mmol) were added, and stirring was continued for 44 h until TLC analysis (2:1, *n*-Hex/EtOAc) indicated the completion of the reaction. The reaction mixture was filtered through Celite. The combined filtrate and washings were extracted with $CHCl_3$, and the organic layer was washed with satd aq $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated. The residue was purified with column chromatography on silica gel (2:1, *n*-Hex/EtOAc) to give **22α** (115 mg, 65%) and the corresponding β-isomer **22β** (38 mg, 21%).

With phenylthioglycoside donor **15**: To a solution of compound **12** (100 mg, 0.19 mmol) and compound **15** (153 mg, 0.29 mmol) in toluene (2.0 mL) 4 Å molecular sieves (240 mg) was added. The suspension was stirred for 1 h and cooled to −20 °C. To the mixture, NIS (79 mg, 0.35 mmol) and TfOH (3.1 μL, 35 μmol) were added and stirring was continued for 2.5 h. The reaction mixture was alkalized to pH 8 with satd aq $NaHCO_3$ at 0 °C and filtered through Celite. The combined filtrate and washings were extracted with $CHCl_3$, and the organic layer was washed with satd $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified with column chromatography on silica gel (2:1, *n*-Hex/EtOAc) to afford **22α** (133 mg, 74%) and **22β** (31 mg, 17%). **22α**: $[\alpha]_D$ −30.6 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.24 (m, 25H, 5Ph), 6.74 (m, 1H, NH), 5.60 (dd, 1H, H-7_{Neu}), 5.05 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1_{Fuc}), 4.95 (d, 1H, PhCH_2), 4.86 (m, 1H, H-4_{Neu}), 4.78–4.38 (m, 7H, PhCH_2), 4.21 (dd, 1H, H-6_{Neu}), 4.01–3.96 (m, 2H, H-5_{Fuc} and H-2_{Fuc}), 3.87 (m, 1H, H-5_{Neu}), 3.81 (m, 1H, H-8_{Neu}), 3.73–3.70 (m, 3H, H-3_{Fuc}, H-4_{Fuc}, and H-9_{Neu}), 3.51 (dd, 1H, H-$9'_{Neu}$), 2.42 (dd, 1H, H-3ax$_{Neu}$), 1.96–1.89 (m, 7H, H-3eq$_{Neu}$ and 2Ac), 1.08 (d, 1H, H-6_{Fuc}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.7, 168.5, 138.6, 138.5, 138.3, 137.3, 136.1, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 127.7, 127.6, 127.3, 97.4, 85.7, 78.4, 78.1, 75.7, 75.3, 74.8, 73.6, 73.0, 72.8, 72.0, 68.9, 68.5, 67.1, 49.7, 37.8, 29.6, 21.0, 20.9, 16.7; MALDI-TOFMS *m/z* calcd for $C_{53}H_{57}NO_{12}S$ $[M+Na]^+$: 954.35. Found 954.35. **22β**: $[\alpha]_D$ +37.4 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.59–7.10 (m, 25H, 5Ph), 5.74 (m, 2H, NH and H-7_{Neu}), 4.82–4.73 (m, 5H, H-4_{Neu} and 2PhCH_2), 4.28 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1_{Fuc}), 4.26 (m, 1H, H-8_{Neu}), 3.89 (dd, 1H, H-6_{Neu}), 3.83–3.71 (m, 4H, H-9_{Neu}, H-$9'_{Neu}$, H-5_{Neu}, and H-2_{Fuc}), 3.55 (m, 1H, H-4_{Fuc}), 3.43–3.39 (m, 2H, H-3_{Fuc}, H-5_{Fuc}), 2.39 (near t, 1H, J_{gem} = 14.6 Hz, $J_{3eq,4}$ = 10.4 Hz, H-3eq$_{Neu}$), 2.07 and 157 (2s, 6H, 2Ac), 1.98 (dd, 1H, H-3ax$_{Neu}$), 1.12 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6_{Fuc}); ^{13}C NMR (100 MHz, $CDCl_3$); δ 170.5, 169.4, 168.7, 138.8, 138.2, 138.1, 137.7, 136.1, 128.9, 128.8, 128.8, 128.6, 128.4, 128.4, 128.4, 128.2, 128.2, 128.1, 128.0, 127.7, 127.6, 127.6, 127.5, 127.3, 105.6, 105.5, 85.7, 82.8, 79.1, 78.4, 78.2, 78.1, 78.0, 75.2, 74.7, 74.4, 73.5, 73.2, 73.2, 73.1, 72.7, 70.4, 69.3, 69.0, 49.6, 49.5, 49.5, 37.6, 29.6, 21.3, 21.3, 21.2, 20.4, 20.3, 16.8; MALDI-TOFMS *m/z* calcd for $C_{53}H_{57}NO_{12}S$ $[M+Na]^+$: 954.35. Found 954.33.

3.20. Phenyl 4,7-di-*O*-acetyl-9-*O*-benzyl-5-benzyloxycarbamoyl-3,5-dideoxy-2-thio-8-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-D-*glycero*-α-D-*galacto*-2-nonulopyranoside-1,5-lactam (23)

To a solution of compound **22** (207 mg, 0.22 mmol) in pyridine (2.2 mL), CbzOSu (166 mg, 0.68 mmol) was added under an argon atmosphere. The suspension was stirred for 18 h at rt (TLC; 3:1, PhMe/EtOAc). After the quenching by the addition of CH_3OH, the mixture was co-evaporated with toluene. The residue was dissolved in $CHCl_3$, washed with 2 M HCl, water, satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (15:1, toluene/EtOAc) to give **23** (217 mg, 92%): $[\alpha]_D$ +2.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.56–7.15 (m, 30H, 6Ph), 5.66 (dd, 1H, $J_{6,7}$ = 4.8 Hz, $J_{7,8}$ = 9.0 Hz, H-7_{Neu}), 5.25 and 5.21 (2d, 2H, J_{gem} = 12.4 Hz, PhCH_2), 5.08 (m, 1H, H-5_{Neu}), 5.01 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1_{Fuc}), 4.98 (m, 1H, $J_{3eq,4}$ = 10.4 Hz, $J_{3ax,4}$ = 5.8 Hz, H-4_{Neu}), 4.93–4.32 (m, 8H, PhCH_2), 4.30 (near dd, 1H, H-6_{Neu}), 3.94 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2_{Fuc}), 3.88 (m, 2H, H-8_{Neu} and

H-5_{Fuc}), 3.82 (dd, 1H, $J_{3,4}$ = 2.6 Hz, H-3_{Fuc}), 3.65 (m, 2H, H-4_{Fuc}, H-9_{Neu}), 3.45 (t, 1H, J_{gem} = 10.2 Hz, $J_{8,9'}$ = 10.2 Hz, H-9_{Neu}), 2.52 (dd, 1H, J_{gem} = 14.6 Hz, H-$3eq_{Neu}$), 2.12 (dd, 1H, H-$3ax_{Neu}$), 1.99 and 1.92 (2s, 6H, 2Ac), 0.99 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6_{Fuc}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 169.5, 164.9, 151.1, 138.9, 138.6, 138.5, 137.8, 137.3, 136.4, 134.6, 129.2, 129.1, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 125.2, 97.5, 86.8, 78.8, 76.6, 75.7, 75.3, 74.8, 73.4, 73.0, 72.7, 72.2, 69.4, 67.9, 67.3, 67.0, 52.3, 37.3, 29.6, 25.4, 21.0, 20.7, 16.6; MALDI-TOFMS *m/z* calcd for $C_{61}H_{63}NO_{14}S$ $[M+Na]^+$: 1088.39. Found 1088.37.

3.21. Methyl [phenyl 4,7-di-*O*-acetyl-9-*O*-benzyl-5-benzyloxycarbamoyl-3,5-dideoxy-2-thio-8-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (24)

To compound **23** (23 mg, 21.5 μmol), a 10% Et_3N solution was added in CH_3CN/THF (3:1) (1.0 mL) and water (0.5 mL). The mixture was stirred for 50 h at 40 °C as monitored by TLC (15:1:0.1, $CHCl_3$/CH_3OH/AcOH). The mixture was diluted with EtOAc, washed with 2 M HCl and brine, dried (Na_2SO_4), evaporated, and dried in vacuo for 6 h. The crude material was dissolved in DMF (1.5 mL) under an argon atmosphere, cooled to 0 °C and CH_3I (44 μL, 0.71 mmol) and K_2CO_3 (146 mg, 1.06 mmol) were added to the solution. The mixture was stirred for 20 min at rt (TLC; 30:1, $CHCl_3$/CH_3OH), neutralized with IR-120 (H^+) and filtered through Celite. The combined filtrate and washings were concentrated and co-evaporated with toluene to remove DMF. The resulting syrup was purified by column chromatography on silica gel (150:1, $CHCl_3$/CH_3OH) to give **25** (89 mg, 92%); $[\alpha]_D$ −4.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.18 (m, 30H, 6Ph), 5.39 (dd, 1H, $J_{6,7}$ = 3.7 Hz, H-7_{Neu}), 5.18 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1_{Fuc}), 5.08–4.72 (6d, 6H, PhCH_2), 4.80 (td, 1H, $J_{3ax,4}$ = 11.9 Hz, $J_{3eq,4}$ = 5.1 Hz, $J_{4,5}$ = 11.2 Hz, H-4_{Neu}), 4.66 and 4.60 (2d, 2H, PhCH_2), 4.51 (d, 1H, NH), 4.50 (2d, 2H, PhCH_2), 4.22 (m, 2H, H-5_{Fuc} and H-8_{Neu}), 4.08 (dd, 1H, $J_{2,3}$ = 7.3 Hz, H-3_{Fuc}), 3.99 (dd, 1H, H-2_{Fuc}), 3.95 (m, 2H, H-9_{Neu} and H-6_{Neu}), 3.64 (m, 1H, H-4_{Fuc}), 3.59 (m, 4H, H-$9'_{Neu}$ and Me), 3.51 (near q, 1H, H-5_{Neu}), 2.73 (dd, 1H, J_{gem} = 12.4 Hz, H-$3eq_{Neu}$), 2.07 and 1.79 (2s, 6H, 2Ac), 1.83 (near t, 1H, H-$3ax_{Neu}$), 1.03 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6_{Fuc}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.31, 170.08, 168.38, 155.65, 139.18, 138.80, 138.75, 138.41, 136.67, 136.45, 129.82, 129.22, 128.94, 128.81, 128.74, 128.69, 128.36, 128.34, 128.23, 128.11, 128.08, 128.07, 127.96, 127.67, 127.60, 127.42, 127.39, 127.32, 127.26, 127.21, 127.16, 97.48, 87.13, 78.92, 77.80, 77.31, 76.59, 76.24, 75.98, 75.28, 74.72, 73.32, 72.91, 71.98, 70.62, 69.53, 69.09, 66.78, 66.74, 52.81, 51.71, 51.64, 37.92, 20.91, 20.56, 16.68; MALDI-TOFMS *m/z* calcd for $C_{62}H_{67}NO_{15}S$ $[M+Na]^+$: 1120.41. Found: 1120.42.

Acknowledgments

This work was financially supported by CREST of JST (M.K.), MEXT of Japan (Grant-in-Aid for Scientific Research to H.A., No. 16780083 and H.I., No. 16580086), and the Mitsubishi Chemical Corporation Fund (H.A.). We thank Ms. Kiyoko Ito for technical assistance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.03.017.

References

1. (a) Schauer, R. *Glycoconjugate J.* **2000**, *17*, 485–499; (b) Varki, A. In *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harber Laboratory Press: New York, 1999; pp 195–209.
2. (a) Otsubo, N.; Yamaguchi, M.; Ishida, H.; Kiso, M. *J. Carbohydr. Chem.* **2001**, *20*, 329–334; (b) Yamaguchi, M.; Ishida, H.; Kanamori, A.; Kannagi, R.; Kiso, M. *Carbohydr. Res.* **2003**, *338*, 2793–2812.
3. (a) Komba, S.; Galustian, C.; Ishida, H.; Feizi, T.; Kannagi, R.; Kiso, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1131–1133; (b) Komba, S.; Yamaguchi, M.; Ishida, H.; Kiso, M. *Biol. Chem.* **2001**, *382*, 233–240.
4. Ando, H.; Koike, Y.; Koizumi, S.; Ishida, H.; Kiso, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6759–6763.
5. Yamada, K.; Harada, Y.; Nagaregawa, Y.; Miyamoto, T.; Isobe, R.; Higuchi, R. *Eur. J. Org. Chem.* **1998**, 2519–2525.
6. Yamada, K.; Harada, Y.; Miyamoto, T.; Isobe, R.; Higuchi, R. *Chem. Pharm. Bull.* **2000**, *48*, 157–159.
7. Cao, S.; Meunier, S. J.; Andersson, F. O.; Letellier, M.; Roy, R. *Tetrahedron: Asymmetry* **1994**, *5*, 2303–2312.
8. Ek, M.; Garegg, P. J.; Hultberg, H.; Oscarson, S. *J. Carbohydr. Chem.* **1983**, *2*, 305–311.
9. Nicolaou, K. C.; Caulfield, T. J.; Kataoka, H.; Stylianides, N. A. *J. Am. Chem. Soc.* **1990**, *112*, 3693–3695.
10. Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073–12074.
11. Suzuki, K.; Maeta, H.; Matsumoto, T. *Tetrahedron Lett.* **1989**, *30*, 4853–4856.
12. Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334.
13. De MeO, C.; Demchenko, A. V.; Boons, G. J. *J. Org. Chem.* **2001**, *66*, 5490–5497.
14. Ikami, T.; Ishida, H.; Kiso, M. In *Methods in Enzymology*; Merrill, A. H., Jr., Hannun, Y. A., Eds.; Academic Press: San Diego, 2000; Vol. 311, pp 547–568.
15. Slomiany, B. L.; Kojima, K.; Banas-Gruszka, Z.; Murty, V. L. N.; Galicki, N. I.; Slomiany, A. *Eur. J. Biochem.* **1981**, *119*, 647–650.

A Novel Synthetic Route to α-Galactosyl Ceramides and iGb3 Using DTBS-Directed α-Selective Galactosylation

Akiyoshi Kimura,[a] Akihiro Imamura,*[a,b] Hiromune Ando,[c] Hideharu Ishida,[a,b] Makoto Kiso*[a,b]

[a] Department of Applied Bioorganic Chemistry, Faculty of Applied Biological Sciences, Gifu University, 1-1 Yanagido, Gifu-shi, Gifu 501-1193, Japan

[b] CREST, Japan Science and Technology Corporation (JST), 1-1 Yanagido, Gifu-shi, Gifu 501-1193, Japan

[c] Division of Instrumental Analysis, Life Science Research Center, Gifu University, 1-1 Yanagido, Gifu-shi, Gifu 501-1193, Japan
Fax +81(58)2932918; E-mail: imamu@cc.gifu-u.ac.jp; E-mail: kiso@cc.gifu-u.ac.jp

Received 27 June 2006

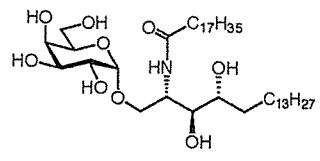
Abstract: A novel synthetic route to α-galactosyl ceramides and isoglobotrihexosylceramide (iGb3), which can activate NKT cells, was developed by exploiting a di-*tert*-butylsilylene-directed α-selective galactosylation procedure.

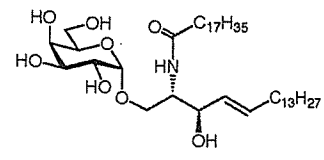
Key words: glycolipids, glycosylations, glycosides, galactosylceramides, iGb3

α-Galactosyl ceramides [Galα(1→1)Cer] (α-GalCers) were first isolated from the marine sponge *Agelas mauritianus* in 1993,[1] and since then several biological functions of α-GalCers have been studied.[2] α-GalCer, which is obtained from CD1d, is recognized by a T cell antigen receptor on a NKT cell, thereby resulting in the stimulation of NKT cells, which are essential not only for defense against pathogens, but also for the initiation of adaptive immune responses and in regulating autoimmune responses. Recently Zhou et al. have suggested[3] that isoglobotrihexosylceramide [Galα(1→3)Galβ(1→4)Glcβ(1→1)Cer] (iGb3) acts as an endogenous ligand for NKT cells, which may be involved in controlling NKT cell responses to infections, malignancy and in autoimmunity. Therefore α-GalCers and iGb3 have become a new attractive option for the treatment of microbial infection, cancer, and autoimmune diseases.

The complex isolation procedure of the glycolipids from natural sources led us to investigate a synthetic approach. Herein, we report an effective method for the synthesis of α-GalCers (KRN7000; **1**, and the 4,5-dehydro analogue of KRN7000; **2**) and iGb3 (**3**) based on di-*tert*-butylsilylene (DTBS)-directed α-galactosylation (Figure 1).

So far, several methods for the syntheses of α-GalCer[4] and iGb3[5] have been reported; per-*O*-benzylated galactosyl donors with leaving groups such as fluoride, chloride, aryl sulfenyl, and trichloroacetimidate have been used for the formation of α-galactosyl linkages. However, α-selectivity and yield of glycosylation strictly depends on the structure of the glycosyl acceptor. In particular, galactosylation of the ceramide part is far from highly stereoselective or high-yielding.





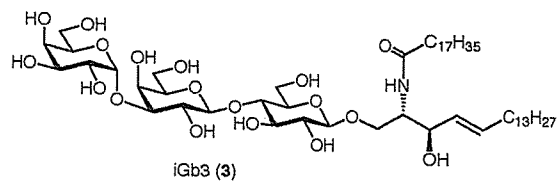
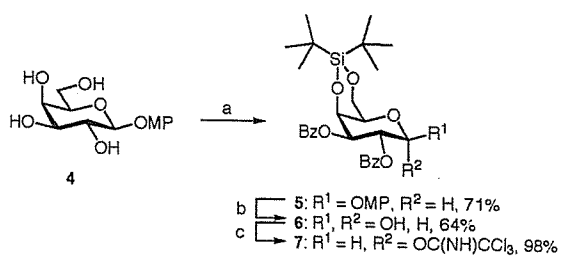


Figure 1 Structure of α-GalCers **1** and **2** and iGb3 **3**

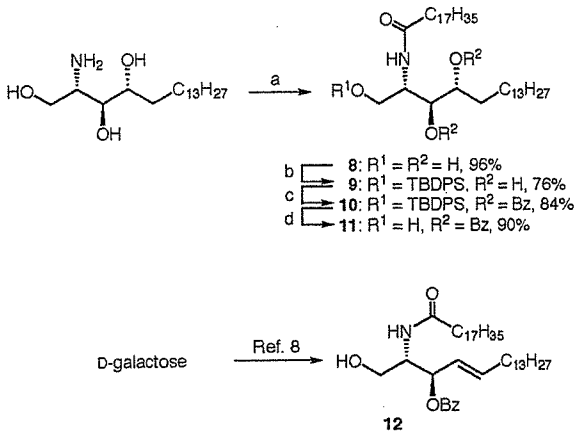


Scheme 1 Preparation of DTBS-Gal donor. *Reagents and conditions*: a) $DTBS(OTf)_2$, Py then Bz_2O; b) CAN, $MeCN–H_2O$–toluene; c) CCl_3CN, DBU, CH_2Cl_2.

We have recently demonstrated[6] that a DTBS group at the O-4,6 position of a *galacto*-type sugar directed the highly α-selective glycosylation in spite of the presence of a participatory group at C2 such as benzoyl and Troc groups. We envisaged that the DTBS-directed galactosylation can be utilized for the preparation of the α-galactosyl linkage in compounds **1**, **2**, and **3**.

SYNLETT 2006, No. 15, pp 2379–2382
Advanced online publication: 08.09.2006
DOI: 10.1055/s-2006-949649; Art ID: U07906ST

As shown in Scheme 1, we readily prepared the common galactosyl donor **7** having a DTBS group mounted on the C-4,6 hydroxyl groups. *p*-Methoxyphenyl galactopyranoside **4**[7] was treated with $DTBS(OTf)_2$ in pyridine at room temperature, and successive addition of benzoic anhydride gave **5** in 71% yield. Oxidative cleavage of the anomeric methoxyphenyl group by CAN gave the hemiacetal **6** in 64% yield. Finally, the hemiacetal **6** was converted into the α-trichloroacetimidate donor **7** by treatment with trichloroacetonitrile and DBU in dichloromethane in excellent yield.

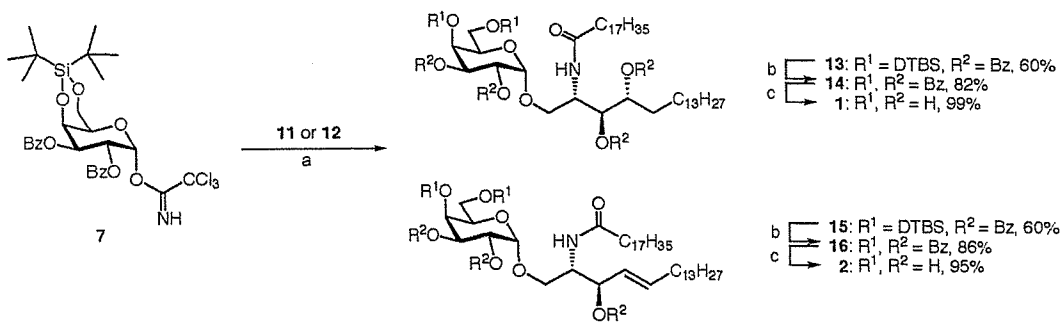


Scheme 2 Preparation of two lipid parts. *Reagents and conditions*: a) stearic acid, EDCI, CH_2Cl_2; b) TBDPSCl, DMAP, CH_2Cl_2–Et_3N (1:1), 50 °C; c) BzCl, DMAP, Py; d) TBAF, THF.

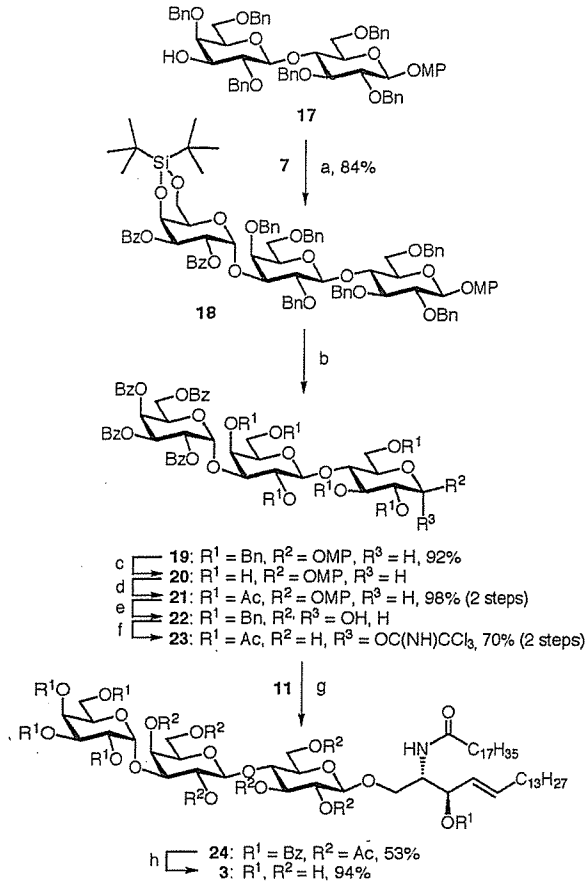
Next, the two lipid parts **11** and **12** were prepared as depicted in Scheme 2. The commercially available phytosphingosine was reacted with stearic acid in the presence of EDCI to furnish the ceramide derivative **8**. The primary hydroxyl group of **8** was then tentatively silylated with TBDPSCl to give silyl ether **9** in 76% yield. The remaining hydroxyl groups of **9** were benzoylated then desilylated with TBAF to produce ceramide acceptor **11** (76%, over 2 steps). The alternative ceramide acceptor **12** was synthesized from D-galactose according to the reported procedure.[8]

Having the DTBS-galactosyl donor **7** in hand, we then conducted DTBS-directed α-galactosylation of ceramide acceptors **11** and **12**. In both the cases, the glycosylation was performed in the presence of TMSOTf at 0 °C to afford α-GalCer sequences **13** and **15**, exclusively, in 60% yield as single isomers. The α-configurations of **13** and **15** were ascertained by ^1H NMR spectroscopy.[9] Recently, Wang's group performed direct α-galactosylation of the ceramide part with a perbenzylated trichloroacetimidate donor, thereby producing the KRN7000 skeleton in 59% yield.[4d] Thus, DTBS-protected galactosyl donor **7** can be applicable to the synthesis of α-GalCers. Removal of the 4,6-*O*-DTBS group within **13** and **15** by tributylamine hydrofluoride (TBAHF)[10] and sequential benzoylation yielded per-*O*-benzoylated α-GalCers **14** and **16** in 82% and 86% yields, respectively. In this step, the use of TBAF as an alternative desilylating reagent did not provide a clear reaction, and the tentative masking of the resulting free hydroxyls was critical to obtain a single product by preventing the migration of the adjacent benzoyl group to the resulted free hydroxyl groups. Finally, debenzoylation of **14** and **16** with NaOMe in MeOH provided KRN7000 (**1**) and the analogue (**2**) in 99% and 95% yields, respectively.

As depicted in Scheme 4, we next investigated the synthesis of iGb3 (**3**), again using DTBS-directed α-galactosylation. The known lactoside acceptor **17**[11] was glycosylated with the common DTBS-protected galactosyl donor **7**. As expected, the desired α-glycoside **18** was obtained again as a single isomer in 84% yield. Then, the trisaccharide **18** was transformed into the trichloroacetimidate form **23** for the next coupling. Removal of the DTBS group from **18** with TBAHF, and successive benzoylation of the hydroxyl groups provided compound **19** in 92% yield. Hydrogenolysis of the benzyl groups was performed under a hydrogen atmosphere in the presence of $Pd(OH)_2/C$ and sequential acetylation gave per-*O*-acylated compound **21** in quantitative yield. Removal of the *p*-methoxyphenyl group of **21** was achieved by CAN in water to afford hemiacetal **22**, which was successively converted into trichloroacetimidate donor **23** in good yield. Glycosylation of the lipid acceptor **11** with trichloroacetimidate do-



Scheme 3 Synthesis of α-galactosyl ceramides. *Reagents and conditions*: a) TMSOTf, AW-300, CH_2Cl_2, 0 °C; b) TBAHF then Bz_2O, DMAP, Py; c) NaOMe, MeOH.



Scheme 4 Synthesis of iGb3. *Reagents and conditions*: a) **7**, TMSOTf, AW-300, CH_2Cl_2, 0 °C; b) TBAHF then Bz_2O, DMAP, Py; c) H_2, $Pd(OH)_2$/C, 1,4-dioxane, 40 °C; d) Ac_2O, Py; e) CAN, MeCN–H_2O–toluene; f) CCl_3CN, DBU, CH_2Cl_2; g) **11**, TMSOTf, AW-300, CH_2Cl_2, 0 °C; h) NaOMe, MeOH–THF, 40 °C.

nor **23** was achieved in the presence of TMSOTf, to give a 53% yield of completely protected isoglobotrihexosylceramide **24**. The corresponding α-isomer of **24** was not isolated from the reaction mixture. The stereochemistry of the glycosylation product was assigned as the β-configuration from the ^1H NMR spectrum [4.43 ppm (d, $J_{1,2}$ = 8.0 Hz, H-1)]. Finally, deacylation of compound **24** with NaOMe in MeOH–THF afforded the target iGb3 (**3**).

In conclusion, we have succeeded in the stereoselective synthesis of α-GalCers and iGb3 using DTBS-directed α-galactosylation as a key reaction. In our previous paper, we confirmed that 4,6-benzylidene-2-acyl donor was β-selectively glycosidated.[6a] Taking advantage of the compatibility of DTBS-directed α-glycosylation with C-2 acyl groups, the DTBS-protected galactose derivative can act as a donor for the β-galactosylation by exchange of DTBS groups with a benzylidene group. In this context, our galactosylation method is strategically versatile for the delivery of a wide spectrum of galactosyl–glyco sequences.

The biological activity of the 4,5-dehydro analogue of KRN7000 **2** will be discussed elsewhere.

Acknowledgment

This work was financially supported by the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan (Grant-in-Aid for Scientific Research to M. K., No. 17101007) and CREST of JST (Japan Science and Technology Corporation).

References and Notes

(1) Natori, N.; Koezuka, Y.; Higa, T. *Tetrahedron Lett.* **1993**, *34*, 5591.

(2) (a) Kinjo, Y.; Wu, D.; Kim, G.; Xing, G.-W.; Poles, M. A.; Ho, D. D.; Tsuji, M.; Kawahara, K.; Wong, C.-H.; Kronenberg, M. *Nature (London)* **2005**, *434*, 520. (b) Kawano, T.; Cui, J.; Koezuka, Y.; Toura, I.; Kaneko, Y.; Motoki, K.; Ueno, H.; Nakagawa, R.; Sato, H.; Kondo, E.; Koseki, H.; Taniguchi, M. *Science (Washington, D. C.)* **1997**, *278*, 1626.

(3) Zhou, D.; Mattner, J.; Cantu, C. III; Schrantz, N.; Yin, N.; Gao, Y.; Sagiv, Y.; Hudspeth, K.; Wu, Y.-P.; Yamashita, T.; Teneberg, S.; Wang, D.; Proia, R. L.; Levery, S. B.; Savage, P. B.; Teyton, L.; Bendelac, A. *Science (Washington, D. C.)* **2004**, *306*, 1786.

(4) (a) Takikawa, H.; Muto, S.-E.; Mori, K. *Tetrahedron* **1998**, *54*, 3141. (b) Figueroa-Perez, S.; Schmidt, R. R. *Carbohydr. Res.* **2000**, *328*, 95. (c) Du, W.; Gervay-Hague, J. *Org. Lett.* **2005**, *7*, 2063. (d) Xia, C.; Yao, Q.; Schümann, J.; Rossy, E.; Chen, W.; Zhu, L.; Zhang, W.; Libero, G. D.; Wang, P. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2195. (e) Fan, G.-T.; Pan, Y.-S.; Lu, K.-C.; Cheng, Y.-P.; Lin, W.-C.; Lin, S.; Lin, C.-H.; Wong, C.-H.; Fang, J.-M.; Lin, C.-C. *Tetrahedron* **2005**, *61*, 1855. (f) Ndonye, R. M.; Izmirian, D. P.; Dunn, M. F.; Yu, K. O. A.; Porcelli, S. A.; Khurana, A.; Kronenberg, M.; Richardson, S. K.; Howell, A. R. *J. Org. Chem.* **2005**, *70*, 10260.

(5) (a) Koike, K.; Sugimoto, M.; Sato, S.; Ito, Y.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1987**, *163*, 189. (b) Yao, Q.; Song, J.; Xia, C.; Zhang, W.; Wang, P. G. *Org. Lett.* **2006**, *8*, 911.

(6) (a) Imamura, A.; Ando, H.; Korogi, S.; Tanabe, G.; Muraoka, O.; Ishida, H.; Kiso, M. *Tetrahedron Lett.* **2003**, *44*, 6725. (b) Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. *Org. Lett.* **2005**, *7*, 4415.

(7) Ohlsson, J.; Magnusson, G. *Carbohydr. Res.* **2000**, *329*, 49.

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

(9) Compound **13**: ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, 6 H, 2 × CH_3), 0.96 and 1.11 (2 s, 18 H, 2 *t*-Bu), 1.24 (m, 52 H, CH_2), 1.65 (q, 2 H, $NHCOCH_2CH_2$), 1.86 (m, 2 H, H-5^{Cer}, H-$5'^{Cer}$), 2.20 (t, 2 H, $NHCOCH_2CH_2$), 3.70 (dd, 1 H, H-1^{Cer}), 3.79 (dd, 1 H, H-$1'^{Cer}$), 3.95 (s, 1 H, H-5^{Gal}), 4.25 (s, 2 H, H-6^{Gal}, H-$6'^{Gal}$), 4.60 (m, 1 H, $J_{2,3}$ = 3.4 Hz, H-2^{Cer}), 4.85 (d, 1 H, $J_{3,4}$ = 3.2 Hz, H-4^{Gal}), 5.21 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1^{Gal}), 5.32 (m, 1 H, $J_{3,4}$ = 4.6 Hz, H-4^{Cer}), 5.49 (dd, 1 H, $J_{2,3}$ = 10.7 Hz, $J_{3,4}$ = 3.2 Hz, H-3^{Gal}), 5.55 (dd, 1 H, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 4.6 Hz, H-3^{Cer}), 5.71 (dd, 1 H, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 10.7 Hz, H-2^{Gal}), 6.38 (d, 1 H, NH), 7.61 (m, 20 H, 4 × Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 20.7, 22.7, 23.3, 25.6, 25.7, 27.1, 27.2, 27.5, 28.8, 29.4, 29.5, 29.6, 29.6, 29.7, 29.7, 31.9, 36.9, 48.8, 66.9, 67.7, 68.5, 69.0, 70.8, 71.1, 72.9, 73.8, 98.5, 128.2, 128.3, 128.4, 128.6, 129.4, 129.5, 129.7, 129.7, 129.8, 130.0, 133.0, 133.3, 165.1, 166.0, 166.2, 166.3, 173.0. Compound **15**: ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, 6 H, 2 × CH_3), 0.96 and 1.11 (2 s, 18 H, 2 × *t*-Bu), 1.24 (m, 50 H, CH_2), 1.57 (t, 2 H, $NHCOCH_2CH_2$), 1.98 (q,

2 H, H-6^{Cer}, H-6$'^{Cer}$), 2.10 (m, 2 H, NHCOCH_2CH$_2$), 3.70 (dd, 1 H, J_{gem} = 10.7 Hz, $J_{1,2}$ = 4.6 Hz, H-1$'^{Cer}$), 3.84 (dd, 1 H, J_{gem} = 10.7 Hz, H-1^{Cer}), 4.19 (dd, 1 H, J_{gem} = 12.6 Hz, H-6$'^{Gal}$), 3.92 (s, 1 H, H-5^{Gal}), 4.28 (dd, 1 H, J_{gem} = 12.6 Hz, H-6^{Gal}), 4.50 (m, 1 H, $J_{1,2}$ = 4.6 Hz, H-2^{Cer}), 4.88 (d, 1 H, H-4^{Gal}), 5.28 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1^{Gal}), 5.49 (m, 2 H, H-3^{Cer}, H-4^{Cer}), 5.56 (dd, 1 H, H-3^{Gal}), 5.74 (m, 2 H, H-5^{Cer}, NH), 5.76 (dd, 1 H, $J_{1,2}$ = 3.7 Hz, H-2^{Gal}), 7.66 (m, 15 H, 3 × Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 20.7, 22.7, 23.3, 25.8, 27.2, 27.5, 28.9, 29.2, 29.3, 29.4, 29.4, 29.5, 29.5, 29.6, 29.6, 29.7, 29.7, 31.9, 32.3, 36.9, 51.2, 66.8, 67.4, 67.7, 68.5, 70.9, 71.1, 74.4, 97.9, 124.6, 128.2, 128.3, 128.3, 128.4, 129.0, 129.4, 129.6, 129.7, 129.7, 129.8, 129.9, 133.0, 133.1, 133.2, 137.5, 165.2, 166.0, 166.2, 172.7.

(10) Furusawa, K. *Chem. Lett.* **1989**, 509.
(11) Borbás, A.; Csávás, M.; Szilágyi, L.; Májer, G.; Lipták, A. *J. Carbohydr. Chem.* **2004**, *23*, 133.

CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200600832

Extended Applications of Di-*tert*-butylsilylene-Directed α-Predominant Galactosylation Compatible with C2-Participating Groups toward the Assembly of Various Glycosides

Akihiro Imamura,[b] Akiyoshi Kimura,[b] Hiromune Ando,*[a] Hideharu Ishida,[b] and Makoto Kiso*[b]

Abstract: The high versatility of di-*tert*-butylsilylene(DTBS)-directed α-predominant galactosylation have been extended to the construction of difficult glycan sequences. First, to investigate the compatibility of the α-predominant reaction with various glycosylation systems a variety of 4,6-*O*-DTBS-tethered galactosaminyl or galactosyl donors were synthesized efficiently, which have C2-participating groups with a wide variety of leaving groups such as alkylsulfenyl, halide, trichloroacetimidate groups. The results of the detailed examination of the glycosylation reaction using the glycosyl donors showed the wide scope of the 4,6-DTBS-directed α-galactosylation. In the next step, the stereoselective construction of α-GalN-Ser/Thr sequences was examined by employing the DTBS-directed glycosylation. As a result, various types of serine and threonine derivatives were glycosylated α-selectively, producing α-GalN-Ser/Thr sequences in high yields. Moreover, the DTBS-directed galactosylation was successfully applied for the synthesis of α-tetrasaccharyl-Ser segment of glycophorin A.

Keywords: carbohydrates · glycosylation · neighboring-group effect · oligosaccharides

Introduction

α-Gal-type linkages are ubiquitously found in natural oligosaccharides such as globoseries and isogloboseries glycolipids (Galα(1→4)Gal sequence) and mucin-type glycoproteins (GalNHAcα(1→)Ser/Thr core sequences). These oligosaccharides are involved in a variety of important biological processes[1] such as recognition of toxin receptors, the innate immune response, malignant alteration. These biological profiles are spurring efforts toward the synthesis of α-galactosyl glycan sequences.[2]

α-Gal-type linkages can be established using the anomeric effect, often with the aid of the etheral solvent effect.[2c] To minimize β-isomer formation, C2 hydroxyl or amino group protection is limited to the nonparticipating mode. Therefore, despite the elaborate procedure, the synthesis of 2-azido-galactosyl donors became a part of the standard protocol to generate α-galactosaminyl linkages.[2a] However, the anomeric selectivity and yield of conventional glycosylation varies greatly depending on the structures of the coupling partners; therefore difficult separation procedures are occasionally required. In particular, this drawback causes the drastic decrease in the overall yield of the α-galactosaminyl glycan synthesis. In this context, Schmidt and co-worker have described the nitroglycal-based approach toward the synthesis of various mucin-type O-glycans to circumvent the arduous preparation of the 2-azido-galactosyl donor.[3] Very recently, Boons and co-workers have developed a novel general method toward 1,2-*cis* glycosides synthesized by the neighboring-group participation of the (1*S*)-phenyl-2-(phenylsulfanyl)ethyl group at the C2-hydroxyl position.[4]

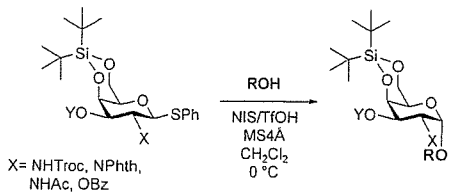
Previously, we reported that the phenylthio glycoside of 4,6-di-*tert*-butylsilylene(DTBS)-protected galactose performs

[a] Dr. H. Ando
Division of Instrumental Analysis
Life Science Research Center, Gifu University
1-1 Yanagido, Gifu-shi, Gifu 501-1193 (Japan)
Fax: (+81) 58-293-2617
E-mail: hando@cc.gifu-u.ac.jp

[b] Dr. A. Imamura, A. Kimura, Prof. H. Ishida, Prof. M. Kiso
Department of Applied Bioorganic Chemistry
Faculty of Applied Biological Sciences, Gifu University and CREST
Japan Science and Technology Corporation (JST)
1-1 Yanagido, Gifu-shi, Gifu 501-1193 (Japan)
Fax: (+81) 58-293-2916
E-mail: kiso@cc.gifu-u.ac.jp

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

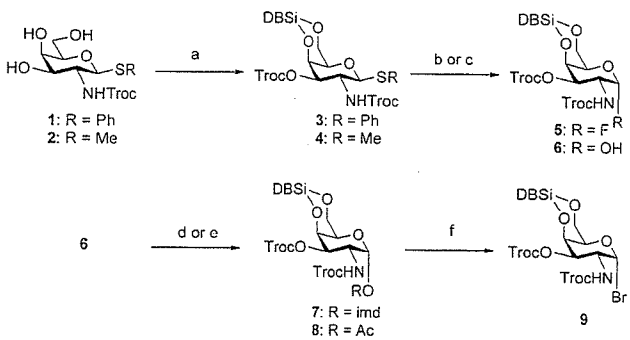
α-selective glycosidation despite the presence of participating groups at the C2 position (Scheme 1).[5] In this study, we demonstrate that the new glycosylation method is a comprehensive and powerful method for the synthesis of α-galactosyl and galactosaminyl glycans.



Scheme 1. Di-*tert*-butylsilylene-directed α-galactosylation. Troc = 2,2,2-trichloroethoxycarbonyl, Phth = phthaloyl, Bz = benzoyl, NIS = *N*-iodosuccinimide, TfOH = trifluoromethanesulfonic acid, and MS = molecular sieves.

Results and Discussion

Among the compatible protecting groups of the C2-amino group, 2,2,2-trichloroethoxycarbonyl (Troc) was selected because of its easy introduction and chemoselective cleavage. For C2 hydroxyl protection, a conventional benzoyl group was used. The installation of the DTBS group on the 4,6-hydroxyl groups of the galactosides proceeded almost quantitatively. As exemplified in Scheme 2, the thioglycosides of



Scheme 2. a) i) DTBS(OTf)$_2$/pyr, RT, 3 min; ii) subsequent addition of TrocCl, 30 min, 93% (**3**) and 54% (**4**); b) **3**, DAST, NBS/CH_2Cl_2, −15 °C, 5 h, 88%; c) **3**, NBS/aq. acetone, RT, 30 min, 83%; d) **6**, CCl_3CN, DBU, CH_2Cl_2, 0 °C, 30 min, 70%; e) **6**, Ac_2O, pyr, RT, 1 h, 94%; f) **8**, 25% HBr in AcOH, CH_2Cl_2, RT, 2 h, 86%. DB = di-*tert*-butyl, DTBS(OTf)$_2$ = di-*tert*-butylsilyl bis(trifluoromethanesulfonate), DAST = (diethylamino)sulfur trifluoride, NBS = *N*-bromosuccinimide, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

N-Troc-protected galactosamine **1** and **2**, which were easily prepared from galactosamine hydrochloride **1**,[5b] successively reacted with DTBS(OTf)$_2$[6] and 2,2,2-trichloroethyl chloroformate (TrocCl) in pyridine to produce 4,6-DTBS-protected **3** and **4** in almost quantitative yield, respectively. Further, the phenylsulfenyl group of **3** could be successfully replaced with fluoride by action of *N*-bromosuccinimide (NBS) and (diethylamino)sulfur trifluoride (DAST), yielding **5** in 88% yield. The anomeric arrangement of **5** was exclusively α, as indicated by the ^{1}H NMR spectrum (δ 5.76; d, $J_{1,F}$ = 52.9 Hz), probably a result of the DTBS effect during the fluorination. For the synthesis of other glycosyl donors, compound **3** was subsequently hemiacetalized by NBS in aqueous acetone to produce **6**. Then, the C1 hydroxyl in **6** was transformed into trichloroacetimidate to form **7**,[7] or acetylated to yield acetoxy derivative **8**, which, upon the treatment with 25% HBr solution in acetic acid, afforded galactosaminyl bromide **9** with again predominant α-stereochemistry. Other types of glycosyl donors, namely, **10**–**12**[8] and **13**[5b] were also prepared in high yields. These compounds were used with various coupling partners, namely, compounds **14**–**22** (Figures 1 and 2).

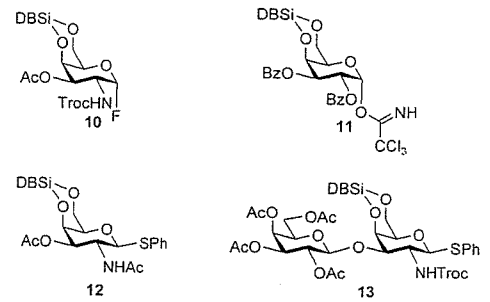


Figure 1. DTBS-bridged galactosyl donors used in this study. Bz = benzoyl.

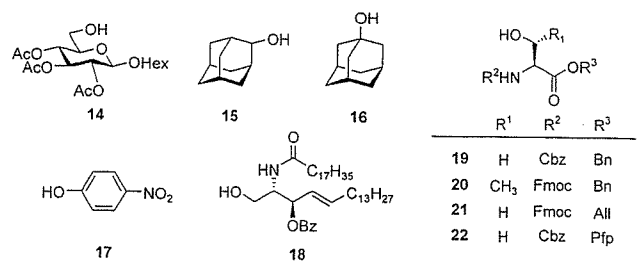
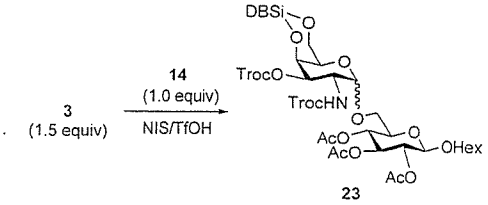


Figure 2. Various glycosyl acceptors used in this study. Hex = *n*-hexyl, Cbz = benzyloxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl, All = allyl, Pfp = pentafluorophenyl.

As summarized in Table 1, we have explored the versatility of the DTBS-directed α-galactosylation with a special focus on α-galactosaminyl bond formation. First, the silylene-bridged glycosyl donor **3** reacted with glucosyl acceptor **14** in various solvents affected by NIS/TfOH[9] (entries 1–5). As a result, the α-selectivity of this DTBS-directed coupling was found to be independent of solvent effects; thus, in all cases the α-anomer **23** was stereoselectively produced in 84% to 100% *de*. Notably even the glycosidation in CH_3CN[10] exclusively yielded the α-glycoside (23%, 100% *de*).

Next, in Table 2, various leaving groups such as the methylsulfenyl,[9,11] fluoride,[12,13] and trichloroacetimidate[14] groups were examined. The glycosyl donors **3**–**7** were treated with 2-adamantanol (**15**). All stereochemical outcomes in entries 1–7 were predominantly α with sufficiently high

Table 1. Glycosidation of galactosyl donor **3** with glucosyl acceptor **14** under various condition.



Entry	Solvent	T [°C]	t [h]	Yield (α/β)[a] [%]
1[b]	CH_2Cl_2	0	0.5	96:3
2	*n*-hexane	RT	8.0	58:3
3	PhMe	0	0.5	91:7
4	CH_3NO_2	0	0.5	93:6
5	CH_3CN	0—40	22	23:0

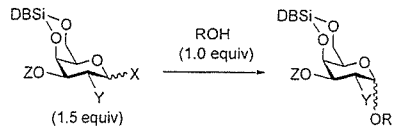
[a] Isolated yield. [b] ref. [5a]. Hex = *n*-hexyl

yields ranging from 68 to 91%. The results reveal the broad compatibility of DTBS-directed coupling with various leaving groups and promoters. Moreover, the results of entries 4–7 where α-fluoride or α-imidate donors were used ruled out the possibility that the α-anomeric selectivity of the DTBS-directed reaction is attributed to the stereoconversion of the β-glycosyl donor via S_N2-like mechanism. Interestingly, in contrast to these results, when insoluble silver silicate[15] was selected as a promoter for the glycosyl bromide donor **9**, the glycosylation predominantly produced the corresponding β-anomeric outcome **25** at 77% yield (entry 8). For entry 9, the smallest alkyl alcohol, that is, methanol was α-selectively glycosylated with **3**. In addition, tertiary alcohol **16** and aryl alcohol **17**[16] functioned as α-predominant coupling partners, thus producing the corresponding galactosides **27** and **28** in high yields (entries 10 and 11). At the final stage of this study, we attempted to directly α-galactosylate the hindered 1-hydroxyl of the ceramide fragment **18** with the 2,3-benzoylated galactosyl donor **11**. This reaction resulted in the successful synthesis of biologically-important α-Gal-Cer frame **29** in a relatively high yield (entry 12).[17]

In accordance with the above-mentioned results, the DTBS galactosyl donors have also been successfully used in the efficient synthesis of α-galactosaminyl Ser/Thr sequences (Table 3). Thus, various types of Ser derivatives, namely, **19**, **21**, and **22** as well as Thr derivative **20** were α-selectively galactosylated by the GalNTroc donors **3** and **7** in high yields (entries 1–3). The 2-acetamido-galactosyl donor **12** also served as an α-selective glycosylation unit to produce an α-GalNAc-Ser linkage in a moderate yield (entry 4). In entry 5, we found that the glycosidation of the Gal-GalN-Troc disaccharide donor **13** with Ser derivative **22** yielded the T-antigen structure **34** in 88% yield.

Moreover, the DTBS-containing trisaccharide **35**[8] was applied to the coupling of the Fmoc-Ser derivative **36** (Scheme 3). Fortunately, this coupling also confirmed our expectations by producing a Neu5Acα(2→3)Galβ(1→3)GalNα(1→)Ser sequence **37** as a single α-isomer in high yield. Further, to establish an α-sialyl branch on the C6 of

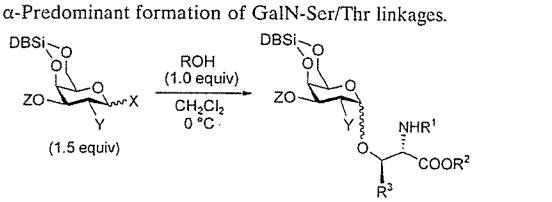
Table 2. Examination of various leaving groups in DTBS-directed galactosylation.



Entry	Donor	ROH	Promoter	T [°C]	t [h]	Product	Yield (α/β)[a] [%]
1	**3**	**15**	NIS/TfOH	0	0.5	**24**	91:7
2	**3**	**15**	DMTST[b]	0	21	**24**	83:15
3	**4**	**15**	NIS/TfOH	0	0.5	**24**	87:11
4	**5**	**15**	$SnCl_2$/$AgClO_4$[c]	0	1.5	**24**	82:0
5	**5**	**15**	Cp_2HfCl_2/AgOTf[d]	−20	0.5	**24**	71:0
6	**7**	**15**	TMSOTf	0	0.5	**24**	91:8
7	**7**	**15**	$BF_3{\cdot}OEt_2$	0	0.5	**24**	68:9
8	**9**	**15**	Ag-silicate[e]	−20	2.0	**25**	6:77
9	**3**	MeOH	NIS/TfOH	0	4.0	**26**	90:9
10	**3**	**16**	NIS/TfOH	0	0.5	**27**	90:5
11	**10**	**17**	BF_3OEt_2/Et_3N[f]	0	3.0	**28**	95:0
12	**11**	**18**	TMSOTf	0	48	**29**	60:0

[a] Isolated yield. [b] See ref. [11]. [c] See ref. [12]. [d] See ref. [13]. [e] See ref. [15]. [f] See ref. [16]. DMTST = dimethyl(methylthio)sulfonium trifluoromethanesulfonate.

Table 3. α-Predominant formation of GalN-Ser/Thr linkages.

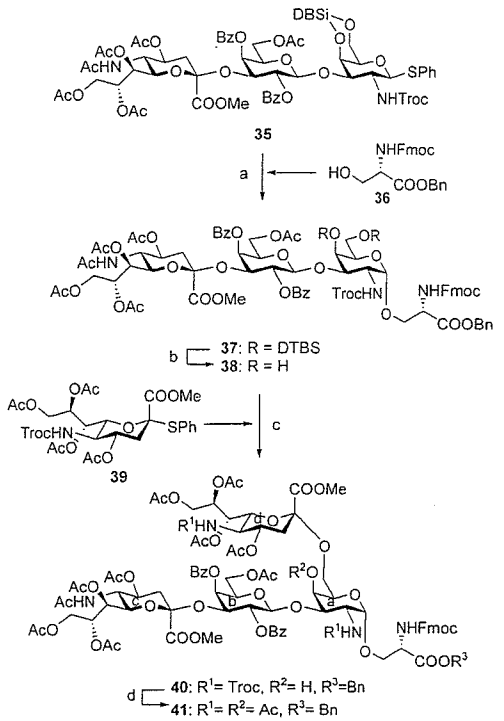


Entry	Donor	ROH	Promoter	t [h]	Product	Yield (α/β)[a] [%]
1	**3**	**19**	NIS/TfOH	0.5	**30**	95:2
2	**3**	**20**	NIS/TfOH	0.5	**31**	93:0
3	**7**	**21**	TMSOTf	0.5	**32**	97:0
4	**12**	**19**	NIS/TfOH	0.5	**33**	65:0
5	**13**	**22**	NIS/TfOH	1.0	**34**	88:0

[a] Isolated yield.

the GalN residue, the 4,6-DTBS group was cleaved by the action of the fluoride anion released from *n*-tributylammonium hydrogenfluoride (TBAHF)[18] without affecting the Fmoc moiety. The resulting 4,6-diol glycan **38** was then sialylated with the previously obtained *N*-Troc sialyl donor **39**[19] to afford the tetrasaccharide **40** in 88% yield. Finally, the Troc groups within **40** were chemoselectively replaced by acetyl groups to produce glycophorin A glycan frame **41**.[20]

In summary, we have described the broad application of the DTBS-directed glycosylation for use in the synthesis of various α-galactosyl glycosides. As exemplified by the high α-selectivity and high-yielding synthesis of biologically significant α-Gal-Cer and glycophorin A glycan frames, this approach will greatly improve the efficiency of the general strategy toward the synthesis of α-galactosyl glycan structures.



Scheme 3. a) NIS/TfOH, MS 4 Å, CH_2Cl_2, 0 °C, 8 h, 88% (only α); b) TBAHF, THF, H_2O, RT, 5 h, 86%; c) NIS/TfOH, MS 3 Å, CH_3CN, CH_2Cl_2, −35 °C, 31 h, 94% (α/β 73:21); d) i) Zn, AcOH, 40 °C, 3 h, 68%; ii) Ac_2O, pyr, RT, 11 h, 68%. MS = molecular sieves, TBAHF = tri-*n*-butylammonium hydrogenfluoride.

Experimental Section

General procedures: ^1H and ^{13}C NMR spectra were taken by Varian INOVA 400 and 500. Chemical shifts are expressed in ppm (δ) relative to the signal of either $CHCl_3$ or Me_4Si, adjusted to δ 7.26 or 0.00 ppm, respectively. MALDI-TOF MS spectra were recorded in positive ion mode on a Bruker Autoflex with the use of α-cyano-4-hydroxycinnamic acid (CHCA) as a matrix. Molecular sieves were purchased from Wako Chemicals Inc. and dried at 300 °C for 2 h in muffle furnace prior to use. Drierite was powdered and dried at 300 °C for 6 h in muffle furnace prior to use. Solvents as reaction media were dried over molecular sieves and used without purification. TLC analysis was performed on Merck TLC (silica gel $60F_{254}$ on glass plate). Silica gel (80 mesh and 300 mesh) manufactured by Fuji Silysia Co. was used for flash column chromatography. Quantity of silica gel was usually estimated as 100 to 150-fold weight of sample to be charged. Solvent systems in chromatography were specified in v/v. Evaporation and condensation were carried out in vacuo.

Phenyl 2-deoxy-4,6-*O*-di-*tert*-butylsilylene-1-thio-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-β-D-galactopyranoside (3): Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (2.20 mL, 6.15 mmol) was added at 0 °C under argon atmosphere to a solution of compound **1** (2.50 g, 5.59 mmol) in pyridine (110 mL), and the mixture was stirred for 3 min at ambient temperature. After the complete consumption of the starting material was confirmed on TLC analysis ($CHCl_3$/MeOH 10:1), 2,2,2-trichloroethyl chloroformate (1.15 mL, 8.39 mmol) was added and stirred for 30 min (TLC monitoring: EtOAc/hexane 1:3). The reaction mixture was coevaporated with toluene and extracted with $CHCl_3$. The organic phase was washed with 2 M HCl, H_2O, satd. aq. Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane 1:6) to give **3** (3.05 g, 93%). $[\alpha]_D = +27.7°$ (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 8.05 (d, 1H, $J_{2,NH}$ = 9.3 Hz, NH), 7.40–7.24 (m, 5H, Ph), 5.50 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1), 5.03, 4.90 (2d, 2H, J_{gem} = 12.3 Hz, OCH_2CCl_3), 4.85 (q, 2H, J_{gem} = 12.3 Hz, OCH_2CCl_3), 4.82 (dd, 1H, $J_{2,3}$ = 10.5, $J_{3,4}$ = 2.9 Hz, H-3), 4.74 (d, 1H, H-4), 4.24 (dd, 1H, J_{gem} = 12.5 Hz, H-6), 4.10 (q, 1H, H-2), 4.07 (dd, 1H, H-6'), 3.83 (s, 1H, H-5), 1.04, 0.96 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 152.7, 134.7, 129.1, 129.1, 126.6, 96.1, 94.8, 86.0, 78.2, 76.0, 73.3, 68.9, 66.6, 66.3, 49.4, 27.4, 27.2, 22.7, 20.2; MALDI MS: *m/z*: calcd for $C_{26}H_{35}Cl_6NO_8SSiNa$: 781.98; found: 781.95 $[M+Na]^+$.

Methyl 2-deoxy-4,6-*O*-di-*tert*-butylsilylene-1-thio-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-β-D-galactopyranoside (4): Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (1.32 mL, 3.62 mmol) was added at 0 °C under argon atmosphere to a solution of compound **2** (1.16 g, 3.02 mmol) in pyridine (15 mL), and the mixture was stirred for 3 min at ambient temperature. After the complete consumption of the starting material was confirmed on TLC analysis ($CHCl_3$/MeOH 10:1), 2,2,2-trichloroethyl chloroformate (1.25 mL, 9.06 mmol) was added and stirred for 30 min (TLC: EtOAc/hexane 1:3). The reaction mixture was coevaporated with toluene and extracted with $CHCl_3$. The organic phase was washed with 2 M HCl, H_2O, satd. aq. Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane 1:5) to give **4** (1.13 g, 54%). $[\alpha]_D = +33.3°$ (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.93 (d, 1H, NH), 4.97, 4.82 (2d, 2H, OCH_2CCl_3), 4.75 (dd, 1H, $J_{2,3}$ = 10.3, $J_{3,4}$ = 2.9 Hz, H-3), 4.72 (d, 1H, H-4), 4.53 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 4.25 (dd, 1H, J_{gem} = 12.5 Hz, H-6), 4.07 (dd, 1H, H-6'), 4.01 (q, 1H, H-2), 3.71 (s, 1H, H-5), 2.12 (s, 3H, Me), 1.02, 0.95 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 154.3, 152.8, 96.1, 94.8, 84.4, 79.2, 78.4, 76.1, 74.0, 73.3, 68.9, 66.6, 49.3, 27.4, 27.3, 23.0, 20.2, 12.5; MALDI MS: *m/z*: calcd for $C_{21}H_{33}Cl_6NO_8SSiNa$: 719.97; found: 720.04 $[M+Na]^+$.

2-Deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranosyl fluoride (5): (Diethylamino)sulfur trifluoride (260 μL, 1.97 mmol) and *N*-bromosuccinimide (303 mg, 1.7 mmol) at −15 °C under argon were added to a solution of compound **3** (1.00 g, 1.31 mmol) in CH_2Cl_2 (13 mL) and the mixture was stirred for 5 h (TLC: EtOAc/hexane 1:3). The reaction mixture was diluted with $CHCl_3$ and satd. aq. $NaHCO_3$ was added with ice. The mixture was stirred for 5 min vigorously. The organic layer was washed with water and dried over Na_2SO_4. After concentration, the resulted residue was subjected to column chromatography on silica gel (EtOAc/hexane 1:8) to give **5** (778 mg, 88%). $[\alpha]_D = +86.0°$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.38 (d, 1H, NH), 5.76 (d, 1H, $J_{1,F}$ = 52.9 Hz, H-1), 5.08, 4.94 (2d, 2H, OCH_2CCl_3), 4.90 (dd, 1H, H-3), 4.85 (m, 2H, OCH_2CCl_3), 4.82 (d, 1H, H-4), 4.30 (m, 2H, H-2, H-6), 4.09 (s, 1H, H-5), 1.01, 0.97 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 154.7, 152.6, 107.7, 105.5, 95.9, 94.8, 76.0, 73.8, 73.7, 68.7, 68.7, 68.5, 65.9, 48.5, 48.3, 27.2, 27.0, 22.7, 20.3; MALDI MS: *m/z*: calcd for $C_{20}H_{30}Cl_6FNO_8SSiNa$: 691.97; found: 691.95 $[M+Na]^+$.

2-Deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranose (6): *N*-Bromosuccinimide (2.33 g, 13.1 mmol) was added at ambient temperature to a solution of compound **3** (2.00 g, 2.62 mmol) in acetone (44 mL)/water (9 mL), and the stirring was continued for 30 min until TLC analysis (EtOAc/hexane 1:3) indicated the completion of the reaction. The reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane 1:5) to give **6** (1.45 g, 83%). ^1H NMR (500 MHz, $CDCl_3$): mixture of rotamers **6a** and **6b** (**a**/**b** 3:1); **6a**: δ = 5.42 (d, 1H, $J_{1,2}$ = 2.9 Hz, H-1), 5.03 (d, 1H, NH), 4.86 (dd, 1H, $J_{2,3}$ = 11.0, $J_{3,4}$ = 2.6 Hz, H-3), 4.84, 4.70 (2d, 2H, OCH_2CCl_3), 4.77 (d, 1H, H-4), 4.58 (td, 1H, H-2), 4.23 (m, 2H, H-6, H-6'), 4.01 (s, 1H, H-5), 2.92 (s, 1H, OH), 1.08, 1.03 (2s, 18H, 2 *t*Bu); **6b**: δ 5.41 (d, 1H, $J_{1,2}$ = 2.9 Hz, H-1), 5.29 (d, 1H, NH), 4.95 (dd, 1H, $J_{2,3}$ = 11.0, $J_{3,4}$ = 2.6 Hz, H-3), 4.84, 4.70 (2d, 2H, OCH_2CCl_3), 4.77 (dd, 1H, H-4), 4.58 (td, 1H, H-2), 4.32 (d, 1H, H-6), 4.17 (d, 1H, H-6'), 4.01 (s, 1H, H-5), 2.86 (s, 1H, OH), 1.08, 1.03 (2s, 18H, 2 *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.4, 154.0, 95.4, 94.4, 92.6, 75.8, 74.7, 70.2, 67.3, 67.0, 49.7, 49.2, 27.6, 27.5, 27.4, 23.4, 20.8; MALDI MS: *m/z*: calcd for $C_{20}H_{31}Cl_6NO_9SiNa$: 689.97; found: 689.97 $[M+Na]^+$.

2-Deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranosyl trichloroacetimidate (7): Trichloroacetonitrile (1.0 mL, 10.4 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (93.7 μL, 0.63 mmol) were added at 0°C to a solution of compound **6** (350 mg, 0.52 mmol) in CH_2Cl_2 (5.2 mL), and the mixture was stirred for 30 min at ambient temperature (TLC: EtOAc/hexane 1:3). The reaction mixture was evaporated. The residue was purified with column chromatography on silica gel (EtOAc/hexane 1:2) to give **7** (293 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): mixture of rotamers **7a** and **7b** (**a**/**b** 4:1); **7a**: δ = 8.75 (s, 1H, C=NH), 6.25 (d, 1H, $J_{1,2}$=3.5 Hz, H-1), 5.14 (d, 1H, NH), 4.99 (dd, 1H, $J_{2,3}$=11.5, $J_{3,4}$=3.0 Hz, H-3), 4.80 (m, 5H, H-2, 2 OCH_2CCl_3), 4.75 (d, 1H, H-4), 4.26 (m, 2H, H-6, H-6'), 3.96 (s, 1H, H-5), 1.10, 1.04 (2s, 18H, 2 *t*Bu); **7b**: δ = 8.79 (s, 1H, C=NH), 6.50 (d, 1H, $J_{1,2}$=2.9 Hz, H-1), 4.93 (d, 1H, NH), 4.99 (dd, 1H, $J_{2,3}$=11.5, $J_{3,4}$=3.0 Hz, H-3), 4.80 (m, 5H, H-2, 2 OCH_2CCl_3), 4.75 (d, 1H, H-4), 4.26 (m, 2H, H-6, H-6'), 3.96 (s, 1H, H-5), 1.10, 1.04 (2s, 18H, 2 *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.4, 154.1, 154.0, 96.1, 95.2, 94.1, 90.9, 75.2, 74.6, 69.8, 69.5, 66.5, 49.3, 48.9, 31.6, 27.5, 27.2, 23.3, 21.0, 20.7; MALDI MS: *m/z*: calcd for $C_{22}H_{31}Cl_9N_2O_9SiK$: 848.86; found: 848.96 $[M+K]^+$.

Acetyl 2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranoside (8): Acetic anhydride (1.5 mL) was added at 0°C to a solution of compound **6** (1.00 g, 1.49 mmol) in pyridine (1.5 mL), and the stirring was continued for 1 h at ambient temperature (TLC: EtOAc/hexane 1:3). The reaction mixture was coevaporated with toluene and extracted with EtOAc. The organic phase was washed with 2M HCl, H_2O, satd. aq. Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane 1:5) to give **8** (1.01 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): mixture of rotamers **8a** and **8b** (**a**/**b** 3:1); **8a**: δ = 6.31 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 5.05 (d, 1H, NH), 4.94 (dd, 1H, $J_{2,3}$=11.4, $J_{3,4}$=2.9 Hz, H-3), 4.78 (m, 6H, H-2, H-4, 2 OCH_2CCl_3), 4.23 (2d, 2H, H-6, H-6'), 3.83 (s, 1H, H-5), 2.17 (s, 3H, Ac), 1.09, 1.03 (2s, 18H, 2 *t*Bu); **8b**: δ 6.35 (d, 1H, $J_{1,2}$=3.3 Hz, H-1), 5.02 (d, 1H, NH), 4.88 (dd, 1H, $J_{2,3}$=7.0, $J_{3,4}$=2.9 Hz, H-3), 4.78 (m, 6H, H-2, H-4, 2 OCH_2CCl_3), 4.23 (m, 2H, H-6, H-6'), 3.83 (s, 1H, H-5), 2.16 (s, 3H, Ac), 1.09, 1.03 (2s, 18H, 2 *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0, 154.1, 96.3, 94.8, 94.2, 91.7, 75.3, 74.7, 70.1, 69.3, 66.6, 48.6, 48.2, 27.5, 23.3, 21.0, 20.8; MALDI MS: *m/z*: calcd for $C_{22}H_{33}Cl_6NO_{10}SiNa$: 731.99; found: 731.95 $[M+Na]^+$.

2-Deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranosyl bromide (9): 25% HBr solution in acetic acid (182 μL, 0.56 mmol) was added at 0°C to a solution of compound **8** (200 mg, 0.28 mmol) in CH_2Cl_2 (1.4 mL), and the mixture was stirred for 2 h at ambient temperature (TLC: EtOAc/hexane 1:3). The reaction mixture was extracted with $CHCl_3$. The organic phase was washed with satd. aq. Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated. The residue was purified chromatography on silica gel (EtOAc/hexane 1:20) to give **9** (177 mg, 86%). $[\alpha]_D$ = +131.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.70 (d, 1H, $J_{1,2}$= 3.4 Hz, H-1), 5.12 (d, 1H, NH), 4.99 (dd, 1H, $J_{2,3}$=10.9, $J_{3,4}$=2.3 Hz, H-3), 4.79 (m, 5H, H-4, 2 OCH_2CCl_3), 4.67 (td, 1H, $J_{2,NH}$=9.7 Hz, H-2), 4.07 (s, 1H, H-5), 1.07, 1.04 (2s, 18H, 2 *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.0, 153.9, 95.1, 94.8, 94.1, 75.8, 74.8, 72.3, 69.2, 66.2, 50.7, 29.7, 27.4, 27.1, 23.3, 21.0, 20.8.

2-Adamantyl 2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranoside (24): *With glycosyl donor 3*: Molecular sieves 4 Å (140 mg) was added under argon atmosphere to a solution of **3** (120 mg, 157 μmol) and **15** (16 mg, 105 μmol) in CH_2Cl_2 (2.6 mL). The mixture was stirred at room temperature for 2 h. To the mixture was added dimethyl(methylthio)sulfonium triflate (DMTST, 48%) (338 mg, 629 μmol) at 0°C, and the stirring was continued for 21 h at 0°C. The reaction was monitored by TLC ($PhCH_3$/EtOAc 50:1). The precipitate was filtered off and washed with $CHCl_3$. The filtrate and washings were combined, and the solution was successively washed with satd. aq. Na_2CO_3 and brine, dried and concentrated. Purification by column chromatography ($PhCH_3$/EtOAc 130:1) gave **24** (70 mg, 83%) and its β-isomer (13 mg, 15%).

With glycosyl donor 5: Molecular sieves 4 Å (170 mg) under argon atmosphere was added to a solution of **5** (150 mg, 223 μmol) and **15** (22 mg, 144 μmol) in CH_2Cl_2 (3.7 mL). The mixture was stirred at room temperature for 1 h. To the mixture were added $SnCl_2$ (42 mg, 223 μmol) and $AgClO_4$ (55 mg, 267 μmol) at 0°C, and the stirring was continued for 16 h at 0°C. The precipitate was filtered off and washed with $CHCl_3$. The filtrate and washings were combined, and the solution was successively washed with satd. aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Purification by column chromatography ($PhCH_3$/EtOAc 130:1) gave **22** (93 mg, 78%) and its β-isomer (12 mg, 10%).

With glycosyl donor 7: Molecular sieves 4 Å (AW300) (170 mg) was added under argon atmosphere to a solution of **7** (150 mg, 184 μmol) and **15** (19 mg, 124 μmol) in CH_2Cl_2 (3.1 mL). To the mixture was added trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.67 μL, 3.68 μmol) at 0°C, and the stirring was continued for 1 h at 0°C. A similar work-up and purification as mentioned above gave **24** (91 mg, 91%) and its β-isomer (8 mg, 8%). $[\alpha]_D$ = +95.0° (*c* 1.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.15 (d, 1H, NH), 5.11 (dd, 1H, $J_{2,3}$=11.2, $J_{3,4}$=2.7 Hz, H-3), 5.10 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 4.85, 4.75 (2d, 2H, J_{gem}=11.4 Hz, OCH_2CCl_3), 4.77, 4.70 (2d, 2H, J_{gem}=11.9 Hz, OCH_2CCl_3), 4.75 (d, 1H, $J_{3,4}$=2.7 Hz, H-4), 4.57 (td, 1H, $J_{1,2}$=3.6, $J_{2,3}$=11.2 Hz, H-2^{GalN}), 4.28, 4.16 (2dd, 2H, J_{gem}=12.8 Hz, H-6, 6'), 3.83 (s, 1H, H-5), 3.80 (t, 1H, H-2^{adamantane}), 2.07–1.54 (m, 14H, adamantane), 1.08, 1.02 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 154.1, 95.9, 80.1, 79.8, 76.9, 76.8, 76.5, 76.3, 75.2, 74.6, 70.1, 70.0, 67.5, 67.0, 49.3, 37.3, 36.7, 36.3, 33.6, 32.0, 31.8, 30.8, 27.6, 27.4, 27.3, 27.1, 23.4, 20.8; MALDI MS: *m/z*: calcd for $C_{30}H_{45}Cl_6NO_9SiNa$: 824.08; found: 824.16 $[M+Na]^+$.

2-Adamantyl 2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-β-D-galactopyranoside (25): Molecular sieves 4 Å (180 mg) under argon atmosphere was added to a solution of **9** (21 mg, 137 μmol) and Ag-silicate (180 mg) in CH_2Cl_2 (2.1 mL). The suspension was stirred for 1 h at room temperature. To the suspension was added the solution of **15** (150 mg, 205 μmol) in CH_2Cl_2 (1.3 mL) at −20°C dropwise, and the stirring was continued for 1 h at −20°C. The reaction was monitored by TLC (EtOAc/hexane 1:4). The reaction mixture was diluted with $CHCl_3$ and filtered through Celite. The filtrate and washings were combined and concentrated. Purification by column chromatography ($PhCH_3$/EtOAc 130:1) gave **25** (85 mg, 77%) and **24** (7 mg, 6%). $[\alpha]_D$ = +22.0° (*c* 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, [D$_6$]DMSO) δ = 7.80 (d, 1H, NH), 5.04, 4.93 (2d, 2H, J_{gem}=12.5 Hz, OCH_2CCl_3), 4.77 (q, 2H, J_{gem}=12.5 Hz, OCH_2CCl_3), 4.72 (dd, 1H, $J_{3,4}$= 3.4 Hz, H-3), 4.64 (d, 1H, H-4), 4.61 (d, 1H, $J_{1,2}$=8.0 Hz, H-1), 4.22, 4.04 (2dd, 2H, J_{gem}=11.2 Hz, H-6, 6'), 3.94 (pseudo q, 1H, $J_{1,2}$=8.0 Hz, H-2), 3.74 (brt, 1H, adamantane), 3.62 (s, 1H, H-5), 2.00–1.22 (m, 14H, adamantane), 1.02, 0.95 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 154.3, 152.9, 98.9, 96.1, 94.9, 79.8, 79.1, 77.6, 75.9, 73.6, 73.3, 69.4, 68.9, 66.6, 55.5, 50.9, 36.9, 35.9, 35.6, 32.9, 30.9, 30.8, 30.6, 29.0, 27.4, 27.1, 26.7, 26.5, 22.7, 20.4; MALDI MS: *m/z*: calcd for $C_{30}H_{45}Cl_6NO_9SiNa$: 824.08; found: 824.24 $[M+Na]^+$.

Methyl 2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranoside (26): Molecular sieves 3 Å (500 mg) was added to a solution of compound **3** (100 mg, 131 μmol) and MeOH (10.6 μL, 262 μmol) in CH_2Cl_2 (1.3 mL). The suspension was stirred for 1 h and cooled to 0°C. To the mixture were added *N*-iodosuccinimide (NIS) (59 mg, 262 μmol) and trifluoromethanesulfonic acid (TfOH) (2.3 μL, 26.2 μmol), and the stirring was continued for 4 h. The termination of reaction was confirmed by TLC (EtOAc/hexane 1:3). The reaction mixture was filtered through Celite. The combined filtrate and washings were extracted with $CHCl_3$, and the organic layer was washed with satd. aq. Na_2CO_3, satd. aq. $Na_2S_2O_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified with column chromatography on silica gel (EtOAc/hexane 1:30) to give **26** (72 mg, 90%) and the corresponding β-isomer (16 mg, 9%). $[\alpha]_D$ = + 85.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.22 (d, 1H, NH), 4.80 (m, 4H, H-1, H-3, OCH_2CCl_3), 4.58 (td, 1H, $J_{1,2}$=3.7, $J_{2,3}$=$J_{2,NH}$= 10.6 Hz, H-2), 4.24 (2d, 2H, H-6, H-6'), 3.73 (s, 1H, H-5), 3.41 (s, 3H, OMe), 1.09, 1.03 (2s, 18H, 2 *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.0, 154.7, 99.8, 96.2, 95.1, 75.4, 70.8, 68.0, 67.7, 56.4, 50.3, 49.8, 28.3,

28.1, 24.1, 21.5; MALDI MS: *m/z*: calcd for $C_{21}H_{33}Cl_6NO_9Si$: 703.99; found: 704.00 $[M+Na]^+$; β-isomer: $[\alpha]_D=+26.5°$ (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.87 (d, 1H, NH), 4.97–4.81 (4d, 4H, 2 OCH_2CCl_3), 4.72 (dd, 1H, H-3), 4.65 (d, 1H, H-4), 4.41 (d, $J_{1,2}=8.0$ Hz, H-1), 4.17 (2d, 2H, H-6, H-6'), 3.89 (q, 1H, $J_{2,3}=J_{2,NH}=10.8$ Hz, H-2), 3.66 (s, 1H, H-5), 3.37 (s, 3H, OMe), 1.01, 0.95 (2s, 18H, 2 *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.0, 153.6, 100.8, 94.3, 70.8, 69.4, 67.0, 57.0, 52.3, 29.7, 27.4, 27.4, 23.3, 20.7; MALDI MS: *m/z*: calcd for $C_{21}H_{33}Cl_6NO_9SiNa$: 703.99; found: 703.93 $[M+Na]^+$.

1-Adamantyl 2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranoside (27): Molecular sieves 4 Å (170 mg) was added to a solution of compound **3** (150 mg, 196 μmol) and compound **16** (20 mg, 131 μmol) in CH_2Cl_2 (3.3 mL). The suspension was stirred for 1 h and cooled to 0 °C. To the mixture were added NIS (88 mg, 392 μmol) and TfOH (3.4 μL, 13.1 μmol), and the stirring was continued for 30 min. A similar work-up and purification by silica gel column chromatography (EtOAc/hexane 1:30) as described for **26** gave **27** (95 mg, 90%) and the corresponding β-isomer (10 mg, 5%). $[\alpha]_D=+85.5°$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.33 (d, 1H, $J_{1,2}=3.4$ Hz, H-1), 5.07 (d, 1H, $J_{2,NH}=9.7$ Hz, NH), 4.85, 4.72 (2d, 2H, $J_{gem}=12.1$ Hz, OCH_2CCl_3), 4.83 (dd, 1H, $J_{2,3}=11.4$, $J_{3,4}=3.2$ Hz, H-3), 4.77, 4.70 (2d, 2H, $J_{gem}=12.0$ Hz, OCH_2CCl_3), 4.75 (d, 1H, H-4), 4.50 (td, 1H, $J_{1,2}=3.4$, $J_{2,3}=11.4$, $J_{2,NH}=9.7$ Hz, H-2), 4.28, 4.11 (2d, 2H, $J_{gem}=12.8$ Hz, H-6, H-6'), 3.92 (s, 1H, H-5), 2.16–1.56 (m, 15H, adamantane), 1.08, 1.02 (2s, 18H, 2 *t*Bu); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 156.0, 155.8, 97.3, 96.2, 93.0, 92.8, 76.3, 71.9, 68.9, 68.8, 62.2, 51.3, 51.0, 44.2, 37.9, 32.4, 29.4, 29.1, 25.1, 22.9, 22.5, 16.0; MALDI MS: *m/z*: calcd for $C_{30}H_{45}Cl_6NO_9SiNa$: 824.08; found: 824.08 $[M+Na]^+$; β-isomer: $[\alpha]_D=+23.5°$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 7.69 (d, 1H, NH), 5.15, 4.92 (2d, 2H, $J_{gem}=11.9$ Hz, OCH_2CCl_3), 4.85, 4.80 (2d, 2H, $J_{gem}=12.3$ Hz, OCH_2CCl_3), 4.77 (d, 1H, $J_{1,2}=8.0$ Hz, H-1), 4.75 (dd, 1H, $J_{3,4}=3.4$ Hz, H-3), 4.63 (d, 1H, H-4), 4.23, 4.00 (2d, 2H, $J_{gem}=11.4$ Hz, H-6, H-6'), 3.78 (pseudo q, 1H, H-2), 3.60 (s, 1H, H-5), 2.05–1.50 (m, 15H, adamantane), 1.02, 0.94 (2s, 18H, 2 *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.1, 152.8, 96.3, 94.8, 93.7, 79.1, 77.6, 75.9, 73.9, 73.2, 69.3, 68.7, 66.9, 51.0, 41.1, 38.0, 29.9, 27.4, 27.1, 22.7, 20.3; MALDI MS: *m/z*: calcd for $C_{30}H_{45}Cl_6NO_9SiNa$: 824.09; found: 824.08 $[M+Na]^+$.

***p*-Nitrophenyl 3-*O*-acetyl-2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-α-D-galactopyranoside (28)**: Molecular sieves 4 Å (700 mg) was added under argon atmosphere to a solution of compound **10** (583 mg, 1.08 mmol) and **17** (100 mg, 721 μmol) in CH_2Cl_2 (18 mL). The suspension was stirred for 1 h and cooled to 0 °C. To the mixture were added triethylamine (75 μL, 541 μmol) and $BF_3{\cdot}Et_2O$ complex (340 μL, 2.70 mmol) and stirring was continued for 3 h at 0 °C. The termination of reaction was confirmed by TLC (EtOAc/hexane 1:3). To the reaction mixture, satd. aq. $NaHCO_3$ was added. The mixture was extracted with $CHCl_3$. The organic phase was washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The residue was purified with column chromatography on silica gel (EtOAc/$PhCH_3$ 1:50) to give **28** (450 mg, 95%). $[\alpha]_D=+180.0°$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21, 7.20 (2d, 4H, Ar), 5.80 (d, 1H, $J_{1,2}=3.2$ Hz, H-1), 5.35 (d, 1H, $J_{2,NH}=9.8$ Hz, NH), 5.22 (dd, 1H, $J_{2,3}=10.9$, $J_{3,4}=2.5$ Hz, H-3), 4.84, 4.63 (2d, 2H, $J_{gem}=12.0$ Hz, OCH_2CCl_3), 4.73 (td, 1H, H-2), 4.69 (d, 1H, H-4), 4.22, 4.09 (2dd, 2H, $J_{gem}=12.8$ Hz, H-6, 6'), 3.79 (s, 1H, H-5), 2.15 (s, 3H, Ac), 1.12, 1.04 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 160.8, 154.3, 142.9, 125.8, 116.3, 96.8, 95.2, 74.5, 70.3, 70.0, 68.6, 66.5, 48.9, 27.4, 27.1, 23.2, 20.8, 20.7; MALDI MS: *m/z*: calcd for $C_{25}H_{35}Cl_3N_2O_{10}SiNa$: 679.10; found: 679.48 $[M+Na]^+$.

2,3-Di-*O*-benzoyl-4,6-*O*-di-*tert*-butylsilylene-α-D-galactopyranosyl-(1→1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol (29): Molecular sieves 4 Å AW-300 (200 mg) was added to a solution of compound **11** (240 mg, 357 μmol) and compound **18** (80 mg, 119 μmol) in CH_2Cl_2 (3.0 mL). The suspension was stirred for 1 h and cooled to 0 °C. To the mixture was added TMSOTf (1.2 μL, 7.16 μmol) and the stirring was continued for 48 h. The termination of reaction was confirmed by TLC (EtOAc/hexane 1:5). The reaction mixture was filtered through Celite. The combined filtrate and washings were extracted with $CHCl_3$, and the organic layer was washed with satd. aq. Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated. The residue was purified with column chromatography on silica gel (EtOAc/$PhCH_3$ 1:100) to give **29** (83 mg, 59%). $[\alpha]_D=+96.5°$ (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 8.02–7.33 (m, 15H, 3 Ph), 5.78 (d, 1H, NH), 5.76 (dd, 1H, $J_{1,2}=3.7$, $J_{2,3}=10.4$ Hz, H-2^{GalN}), 5.74 (m, 1H, $J_{5,6}=6.8$ Hz, H-5^{Cer}), 5.56 (dd, 1H, $J_{3,4}=3.1$ Hz, H-3^{GalN}), 5.49 (m, 2H, H-3^{Cer}, H-4^{Cer}), 5.28 (d, 1H, H-1^{GalN}), 4.88 (d, 1H, H-4^{GalN}), 4.50 (m, 1H, $J_{1,2}=4.6$ Hz, H-2^{Cer}), 4.28, 4.19 (2dd, 2H, $J_{gem}=12.6$ Hz, H-6^{GalN}, H-6'^{GalN}), 3.92 (s, 1H, H-5^{GalN}), 3.84 (dd, 1H, $J_{gem}=10.7$ Hz, H-1'^{Cer}), 3.70 (dd, 1H, $J_{gem}=10.7$ Hz, H-1^{Cer}), 2.10 (m, 2H, NHCOCH_2CH_2), 1.98 (q, 2H, $J_{5,6}=6.8$ Hz, H-6^{Cer}, H-6'^{Cer}), 1.57 (m, 2H, NHCOCH_2CH_2), 1.24 (m, 52H, CH_2), 1.11, 0.96 (2s, 18H, 2 *t*Bu), 0.88 (t, 6H, 2 CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 166.2, 166.0, 165.2, 137.5, 133.2, 133.1, 133.0, 129.9, 129.8, 129.7, 129.7, 129.6, 129.4, 129.0, 128.4, 128.3, 128.3, 128.2, 124.6, 97.9, 74.4, 71.1, 70.9, 68.5, 67.7, 67.4, 66.8, 51.2, 36.9, 32.3, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.2, 28.9, 27.5, 27.2, 25.8, 23.3, 22.7, 20.7, 14.1; MALDI MS: *m/z*: calcd for $C_{71}H_{109}NO_{11}SiNa$: 1202.77; found: 1202.96 $[M+Na]^+$.

***N*-Benzyloxycarbonyl-*O*-[2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranosyl]-L-serine benzyl ester (30)**: Molecular sieves 4 Å (400 mg) was added to a solution of compound **3** (277 mg, 364 μmol) and **19** (100 mg, 303 μmol) in CH_2Cl_2 (6.6 mL). The suspension was stirred for 1 h and cooled to 0 °C. To the mixture were added NIS (163 mg, 728 μmol) and TfOH (6.4 μL, 72.8 μmol) and stirring was continued for 0.5 h. The termination of reaction was confirmed by TLC (EtOAc/hexane 1:2). A similar work-up as described for **26** and purification by silica gel column chromatography (EtOAc/hexane 1:5) gave **30** (283 mg, 95%) and the corresponding β-isomer (7 mg, 2%). $[\alpha]_D=+68.2°$ (*c* 2.9, $CHCl_3$); ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.86 (d, 1H, NH^{Ser}), 7.71 (d, 1H, $J_{2,NH}=9.0$ Hz, NH^{GalN}), 7.38–7.31 (m, 10H, 2 Ph), 5.12 (2 d, 2H, $J_{gem}=12.4$ Hz, OCH_2), 5.10, 5.05 (2 d, 2H, $J_{gem}=12.2$ Hz, OCH_2), 5.04, 4.92 (2 d, 2H, OCH_2), 4.91, 4.65 (2 d, 2H, $J_{gem}=12.2$ Hz, OCH_2), 4.87 (dd, 1H, $J_{2,3}=11.2$, $J_{3,4}=2.4$ Hz, H-3), 4.83 (d, 1H, $J_{1,2}=3.1$ Hz, H-1), 4.65 (d, 1H, $J_{3,4}=2.4$ Hz, H-4), 4.49 (m, 1H, CH^{Ser}), 4.26 (td, 1H, H-2), 4.11, 3.97 (2 dd, 2H, $J_{gem}=12.2$ Hz, H-6, 6'), 3.82 (m, 2H, CH_2^{Ser}), 3.78 (s, 1H, H-5), 1.00, 0.95 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.9, 156.1, 154.4, 152.8, 136.6, 135.6, 128.4, 128.3, 128.1, 127.9, 127.8, 127.3, 98.2, 95.9, 94.8, 79.1, 75.9, 74.9, 73.6, 69.3, 67.3, 66.6, 66.3, 65.8, 54.2, 48.5, 27.2, 27.1, 22.7, 20.3, 0.0; MALDI MS: *m/z*: calcd for $C_{38}H_{48}Cl_6N_2O_{13}SiNa$: 1001.09; found: 1001.08 $[M+Na]^+$; β-isomer: $[\alpha]_D=-28.3°$ (*c* 0.3, $CHCl_3$); ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.87 (d, 1H, $J_{2,NH}=9.0$ Hz, NH^{GalN}), 7.39–7.30 (m, 10H, 2 Ph), 7.20 (d, 1H, NH^{Ser}), 5.11 (q, 2H, $J_{gem}=12.6$ Hz, OCH_2), 5.07, 5.02 (2 d, 2H, $J_{gem}=12.6$ Hz, OCH_2), 5.02, 4.92 (2 d, 2H, $J_{gem}=12.4$ Hz, OCH_2), 4.80, 4.65 (2 d, 2H, $J_{gem}=12.4$ Hz, OCH_2), 4.74 (dd, 1H, $J_{2,3}=10.9$, $J_{3,4}=2.9$ Hz, H-3), 4.64 (d, 1H, H-4), 4.56 (d, 1H, $J_{1,2}=8.3$ Hz, H-1), 4.38 (m, 1H, CH^{Ser}), 4.24, 4.06 (2 dd, 2H, $J_{gem}=10.4$ Hz, H-6, 6'), 4.04, 3.82 (2 dd, 2H, $J_{gem}=10.4$ Hz, CH_2^{Ser}), 3.89 (q, 1H, H-2), 3.64 (s, 1H, H-5), 0.96, 0.94 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 156.0, 153.9, 153.5, 136.1, 135.2, 128.6, 128.5, 128.4, 128.3, 128.1, 99.8, 96.2, 94.2, 92.7, 77.2, 74.3, 70.8, 69.3, 67.5, 67.1, 66.7, 54.2, 52.0, 29.6, 27.4, 27.3, 23.2, 20.6, 0.0; MALDI MS: *m/z*: calcd for $C_{38}H_{48}Cl_6N_2O_{13}SiNa$: 1001.09; found: 1001.09 $[M+Na]^+$.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-[2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranosyl]-L-threonine benzyl ester (31)**: $[\alpha]_D=+72.0°$ (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.57 (d, 1H, NH), 7.52 (m, 14H, NH^{Thr}, Ph), 5.08 (q, 2H, OCH_2CCl_3), 4.98 (q, 2H, PhCH_2), 4.84 (dd, 1H, H-3), 4.81 (q, 2H, OCH_2CCl_3), 4.80 (d, 1H, $J_{1,2}=3.7$ Hz, H-1), 4.69 (d, 1H, H-4), 4.52 (dd, 2H, CH_2 of Fmoc), 4.36 (dd, 1H, CH^{Thr}), 4.26 (m, 3H, CH of Fmoc, CH_2^{Thr}), 4.25 (m, 1H, $J_{1,2}=3.7$ Hz, H-2), 4.11 (2 d, 2H, H-6, H-6'), 3.83 (s, 1H, H-5), 1.01, 0.98 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 170.7, 170.5, 157.5, 155.2, 153.6, 144.5, 144.3, 141.5, 141.4, 136.3, 129.6, 129.1, 129.0, 128.9, 128.8, 128.3, 128.2, 127.8, 126.0, 125.6, 120.9, 120.8, 96.7, 95.5, 79.9, 76.7, 75.9, 74.6, 74.4, 70.2, 67.4, 67.2, 66.9, 66.2, 59.3, 47.5, 28.0, 27.9, 27.8, 23.5, 21.7, 21.0, 19.3; MALDI MS: *m/z*: calcd for $C_{46}H_{54}Cl_6N_2O_{13}SiNa$: 1103.14; found: 1103.04 $[M+Na]^+$.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-[2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-galactopyranosyl]-L-serine allyl ester (32)**: Molecular sieves 4 Å (AW-300) (200 mg) was added to a solution of compound **7** (154 mg, 189 μmol) and **21** (46 mg, 126 μmol) in CH_2Cl_2 (3.1 mL). The suspension was stirred for 1 h. To the mixture were added TMSOTf (0.68 μL, 3.78 μmol) and stirring was continued for 0.5 h. The termination of reaction was confirmed by TLC (EtOAc/hexane 1:3). A similar work-up and purification as described for **29** gave **32** (125 mg, 97%). $[\alpha]_D = +81.1°$ (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$); mixture of rotamers **32a** and **32b** (**a**/**b** 2.3:1), **32a**: δ = 7.77–7.26 (m, 8H, Ph), 5.93 (m, 2H, CH_2CH=CH_2, NH^{Ser}), 5.37, 5.31 (2 d, 2H, CH_2CH=CH_2), 5.22 (d, 1H, $J_{2,NH}$ = 10.0 Hz, NH^{GalN}), 4.94 (d, 1H, $J_{1,2}$ = 2.6 Hz, H-1), 4.83, 4.71 (2 d, 2H, J_{gem} = 11.9 Hz, OCH_2CCl_3), 4.82 (m, 1H, H-3), 4.80, 4.59 (2 d, 2H, J_{gem} = 11.9 Hz, OCH_2CCl_3), 4.73 (d, 1H, $J_{3,4}$ = 2.1 Hz, H-4), 4.70 (d, 2H, CH_2CH=CH_2), 4.65 (s, 1H, CH^{Ser}), 4.57 (td, 1H, $J_{1,2}$ = 2.6, $J_{2,NH}$ = 10.0 Hz, H-2), 4.47–4.35 (2 m, 2H, J_{gem} = 10.4, J = 7.0 Hz, CH_2 of Fmoc), 4.22 (t, 1H, J = 7.0 Hz, CH of Fmoc), 4.18–4.09 (m, 2H, H-6, 6′), 3.99 (brs, 2H, CH_2^{Ser}), 3.74 (s, 1H, H-5), 1.07, 1.00 (2s, 18H, 2 *t*Bu); **32b**: δ = 7.77–7.26 (m, 8H, Ph), 6.01 (d, 1H, NH^{Ser}), 5.93 (m, 1H, CH_2CH=CH_2), 5.37, 5.31 (2 d, 2H, CH_2CH=CH_2), 5.13 (d, 1H, $J_{2,NH}$ = 10.0 Hz, NH^{GalN}), 4.98 (d, 1H, $J_{1,2}$ = 2.6 Hz, H-1), 4.83, 4.71 (2 d, 2H, J_{gem} = 11.9 Hz, OCH_2CCl_3), 4.82 (m, 1H, H-3), 4.80, 4.59 (2 d, 2H, J_{gem} = 11.9 Hz, OCH_2CCl_3), 4.73 (d, 1H, $J_{3,4}$ = 2.1 Hz, H-4), 4.70 (d, 2H, CH_2CH=CH_2), 4.65 (s, 1H, CH^{Ser}), 4.57 (td, 1H, $J_{1,2}$ = 2.6, $J_{2,NH}$ = 10.0 Hz, H-2), 4.47–4.35 (2 m, 2H, CH_2 of Fmoc), 4.22 (t, 1H, CH of Fmoc), 4.18–4.09 (m, 2H, H-6, 6′), 3.99 (brs, 2H, CH_2^{Ser}), 3.74 (s, 1H, H-5), 1.03, 1.00 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 155.7, 154.1, 153.7, 143.6, 143.5, 141.2, 131.0, 127.7, 127.0, 127.0, 124.99, 124.9, 120.0, 119.8, 99.1, 95.3, 94.2, 77.2, 76.8, 75.7, 74.9, 74.5, 69.7, 69.6, 67.7, 67.3, 66.6, 66.5, 54.3, 49.3, 48.8, 46.9, 27.4, 27.2, 23.2, 20.6, 0.0; MALDI MS: *m*/*z*: calcd for $C_{41}H_{50}Cl_6N_2O_{13}SiNa$: 1039.11; found: 1039.20 $[M+Na]^+$.

***N*-Benzyloxycarbonyl-*O*-(2-acetamido-3-*O*-acetyl-2-deoxy-4,6-*O*-di-*tert*-butylsilylene-α-D-galactopyranosyl)-L-serine benzyl ester (33)**: Molecular sieves 4 Å (120 mg) was added to a solution of compound **12** (90 mg, 182 μmol) and **19** (30 mg, 91.0 μmol) in CH_2Cl_2 (2.7 mL). The suspension was stirred for 1 h and cooled to 0°C. To the mixture were added NIS (82 mg, 364 μmol) and TfOH (3.2 μL, 36.4 μmol) and stirring was continued for 3 h. The termination of reaction was confirmed by TLC (EtOAc/hexane 2:1). A similar work-up and purification with silica gel column chromatography as described for **26** gave **33** (42 mg, 65%). $[\alpha]_D$ = +103.3° (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $[D_6]$DMSO): δ = 7.81 (d, 1H, NH^{Ser}), 7.65 (d, 1H, $J_{2,NH}$ = 8.7 Hz, NH^{GalN}), 7.38–7.30 (m, 10H, 2 Ph), 5.10 (s, 2H, $PhCH_2$), 5.08, 5.05 (2 d, 2H, J_{gem} = 12.6 Hz, $PhCH_2$), 4.84 (dd, 1H, $J_{2,3}$ = 11.4, $J_{3,4}$ = 2.6 Hz, H-3), 4.75 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.52 (d, 1H, $J_{3,4}$ = 2.6 Hz, H-4), 4.44 (m, 1H, CH^{Ser}), 4.41 (td, 1H, $J_{1,2}$ = 3.6, $J_{2,3}$ = 11.4, $J_{2,NH}$ = 8.7 Hz, H-2), 4.08, 3.92 (2 dd, 2H, J_{gem} = 11.7 Hz, H-6, 6′), 3.80 (td, 2H, J_{gem} = 11.2 Hz, CH_2^{Ser}), 3.76 (s, 1H, H-5), 2.01, 1.77 (2s, 6H, 2 Ac), 1.00, 0.96 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 170.2, 169.9, 169.4, 156.1, 136.7, 135.5, 128.4, 128.3, 128.1, 127.9, 127.9, 127.9, 98.4, 70.2, 69.6, 67.3, 66.5, 66.4, 66.3, 65.7, 54.3, 45.8, 27.3, 27.1, 26.9, 22.7, 22.5, 20.7, 20.2, 1.1; MALDI MS: *m*/*z*: calcd for $C_{38}H_{48}Cl_6N_2O_{13}SiNa$: 737.18; found: 737.30 $[M+Na]^+$.

***N*-Benzyloxycarbonyl-*O*-{2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-α-D-galactopyranosyl}-L-serine pentafluorophenyl ester (34)**: Molecular sieves 4 Å (80 mg) was added to a solution of compound **13** (54 mg, 59.2 μmol) and **22** (20 mg, 49.3 μmol) in CH_2Cl_2 (1.0 mL). The suspension was stirred for 1 h and cooled to 0°C. To the mixture were added NIS (26 mg, 118 μmol) and TfOH (1.0 μL, 11.8 μmol) and the stirring was continued for 1 h. The termination of reaction was confirmed by TLC (EtOAc/hexane 2:3). A similar work-up and purification by silica gel column chromatography (EtOAc/hexane 1:30) as described for **26** gave **34** (52 mg, 88%). $[\alpha]_D$ = +61.3° (*c* 0.46, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): mixture of rotamers **34a** and **34b** (**a**/**b** 1.4:1); **34a**: δ = 7.36–7.26 (m, 5H, Ph), 5.88 (d, 1H, NH^{Ser}), 5.36 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-4^{Gal}), 5.24 (t, 1H, $J_{1,2}$ = 7.5, $J_{2,3}$ = 10.2 Hz, H-2^{Gal}), 5.16 (brs, 2H, $PhCH_2$), 5.11 (d, 1H, H-1^{GalN}), 5.06 (d, 1H, $J_{2,NH}$ = 7.8 Hz, NH^{GalN}), 4.98 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3^{Gal}), 4.93 (m, 1H, CH^{Ser}), 4.78 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1^{Gal}), 4.76, 4.59 (2 d, 2H, J_{gem} = 12.2 Hz, OCH_2CCl_3), 4.63 (d, 1H, $J_{3,4}$ = 2.1 Hz, H-4^{GalN}), 4.42 (td, 1H, $J_{2,3}$ = 11.3, H-2^{GalN}), 4.22–4.07 (m, 6H, H-6^{GalN}, 6′^{GalN}, 6^{Gal}, 6′^{Gal}, CH_2^{Ser}), 3.90 (t, 1H, H-5^{Gal}), 3.75 (dd, 1H, H-3^{GalN}), 3.63 (s, 1H, H-5^{GalN}), 2.13, 2.04, 2.00, 1.97 (4s, 12H, 4 Ac), 1.06, 1.05 (2s, 18H, 2 *t*Bu); **34b**: δ = 7.36–7.26 (m, 5H, Ph), 5.84 (d, 1H, NH^{Ser}), 5.37 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-4^{Gal}), 5.25 (t, 1H, $J_{1,2}$ = 7.8, $J_{2,3}$ = 10.2 Hz, H-2^{Gal}), 5.17 (brs, 2H, $PhCH_2$), 4.98 (d, 1H, $J_{1,2}$ = 3.1 Hz, H-1^{GalN}), 4.97 (dd, 1H, H-3^{Gal}), 4.94, 4.49 (2 d, 2H, J_{gem} = 11.9 Hz, OCH_2CCl_3), 4.92 (m, 1H, CH^{Ser}), 4.71 (brs, 1H, H-4^{GalN}), 4.66 (d, 1H, $J_{2,NH}$ = 9.5 Hz, NH^{GalN}), 4.64 (d, 1H, H-1^{Gal}), 4.50 (td, 1H, $J_{2,3}$ = 11.7 Hz, H-2^{GalN}), 4.22–4.07 (m, 6H, H-6^{GalN}, 6′^{GalN}, 6^{Gal}, 6′^{Gal}, CH_2^{Ser}), 3.90 (t, 1H, H-5^{Gal}), 3.61 (s, 1H, H-5^{GalN}), 3.55 (dd, 1H, H-3^{GalN}), 2.13, 2.05, 2.00, 1.97 (4s, 12H, 4 Ac), 1.05, 1.03 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 170.1, 170.1, 169.6, 169.2, 166.7, 155.5, 154.1, 153.9, 142.1, 139.1, 136.7, 135.6, 128.6, 128.5, 128.2, 103.0, 101.5, 99.9, 99.1, 95.2, 79.1, 77.2, 76.4, 74.7, 74.6, 72.2, 71.1, 70.9, 70.8, 70.6, 69.5, 69.0, 68.8, 68.5, 67.6, 66.7, 61.4, 61.2, 54.3, 49.8, 49.6, 31.5, 29.6, 27.4, 27.2, 23.3, 22.6, 20.6, 20.5, 20.5, 14.1, 0.0; MALDI MS: *m*/*z*: calcd for $C_{48}H_{58}Cl_3F_5N_2O_{20}SiNa$: 1233.22; found: 1233.24 $[M+Na]^+$.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-[(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-(6-*O*-acetyl-2,4-di-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-2-deoxy-4,6-*O*-di-*tert*-butylsilylene-2-(2,2,2-trichloroethoxycarbamoyl)-α-D-galactopyranosyl]-L-serine benzyl ester (37)**: Molecular sieves 4 Å (320 mg) was added to a solution of compound **35** (270 mg, 183 μmol) and **36** (51 mg, 122 μmol) in CH_2Cl_2 (3 mL). The suspension was stirred for 1 h and cooled to 0°C. To the mixture were added NIS (82 mg, 366 μmol) and TfOH (3.2 μL, 36.6 μmol) and stirring was continued for 8 h. The termination of reaction was confirmed by TLC ($PhCH_3$/acetone/MeOH 10:6:1). A similar work-up and purification with silica gel column chromatography ($PhCH_3$/acetone/MeOH 90:6:1) as described for **26** gave **37** (190 mg, 88%). $[\alpha]_D$ = +72.0° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $[D_6]$DMSO) δ = 7.87 (d, 1H, NH^{Ser}), 7.66 (d, 1H, NH^{Neu}), 7.61 (m, 23H, Ph), 7.17 (d, 1H, NH^{GalN}), 5.44 (m, 1H, H-8^{Neu}), 5.35 (d, 1H, H-4^{Gal}), 5.30 (q, 1H, H-2^{Gal}), 5.18 (dd, 1H, H-7^{Neu}), 5.12 (d, 1H, H-1^{Gal}), 5.10 (s, 2H, $PhCH_2$), 4.83 (dd, 1H, H-3^{Gal}), 4.74 (s, 1H, H-4^{GalN}), 4.71 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1^{GalN}), 4.63 (m, 1H, H-4^{Neu}), 4.53 (d, 1H, J_{gem} = 12.2 Hz, OCH_2CCl_3), 4.41 (m, 3H, CH^{Ser}, CH_2 of Fmoc), 4.25 (t, 1H, J_{gem} = 12.7 Hz, H-9^{Neu}), 4.16 (t, 1H, H-6^{Gal}), 4.07 (td, 1H, H-2^{GalN}), 4.03 (dd, 1H, H-9^{Neu}), 4.02 (m, 5H, H-3^{GalN}, H-6^{GalN}, H-5^{Gal}, H-6′^{Gal}, CH of Fmoc), 3.74 (m, 5H, H-3^{GalN}, H-6^{GalN}, H-6^{Neu}, CH_2^{Ser}), 3.73 (s, 3H, COOMe), 2.96 (d, 1H, J_{gem} = 12.2 Hz, OCH_2CCl_3), 2.19 (dd, 1H, H-3_{eq}^{Neu}), 1.88 (6s, 18H, 6 Ac), 1.22 (m, 1H, H-3_{ax}^{Neu}), 1.01, 0.92 (2s, 18H, 2 *t*Bu); ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 170.4, 170.2, 170.2, 170.1, 170.0, 169.5, 169.2, 167.8, 165.0, 164.7, 156.3, 154.1, 153.0, 143.9, 141.0, 140.5, 137.5, 137.3, 135.8, 134.0, 133.5, 129.8, 129.7, 129.4, 129.1, 129.1, 129.0, 129.0, 128.8, 128.6, 128.4, 128.3, 128.0, 127.8, 127.3, 126.7, 125.5, 125.2, 125.0, 120.3, 105.1, 102.0, 100.9, 98.9, 98.0, 97.0, 96.9, 96.7, 95.9, 94.1, 86.3, 77.4, 75.4, 73.0, 72.6, 71.8, 71.2, 70.6, 70.1, 69.4, 68.7, 67.7, 67.5, 66.9, 66.4, 66.2, 65.9, 63.5, 62.0, 61.7, 59.6, 54.5, 53.6, 53.3, 52.0, 49.6, 47.6, 46.8, 39.0, 37.8, 37.3, 36.0, 27.4, 23.0, 22.9, 22.8, 22.7, 21.4, 21.2, 20.8, 20.6, 20.5, 20.4; MALDI MS: *m*/*z*: calcd for $C_{84}H_{98}Cl_3N_3O_{31}SiNa$: 1800.49; found: 1800.32 $[M+Na]^+$.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-[(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-(6-*O*-acetyl-2,4-di-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-2-deoxy-2-(2,2,2-trichloroethoxycarbamoyl)-α-D-galactopyranosyl]-L-serine benzyl ester (38)**: A 1M solution of *n*-tributylammonium hydrogenfluoride·1.25 H_2O (0.80 mL, 0.80 mmol) was added to a flask containing compound **37** (160 mg, 89.9 μmol), and the mixture was stirred at ambient temperature for 5 h. The termination of reaction was confirmed by TLC ($CHCl_3$/MeOH 10:1). The reaction mixture was extracted with EtOAc, and the organic layer was washed with 2M HCl, H_2O, satd. aq. Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated. The residue was purified with column chromatography on silica gel ($CHCl_3$/MeOH 70:1) to give **38** (126 mg, 86%). $[\alpha]_D$ = +65.5° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (m, 23H, Ph), 6.31 (d, 1H, NH^{Ser}), 5.68 (m, 1H, H-8^{Neu}), 5.43 (t, 1H, H-2^{Gal}), 5.23 (d, 1H, H-4^{Gal}), 5.21 (dd, 1H, H-7^{Neu}), 5.14 (q, 2H, $PhCH_2$), 5.00 (d, 1H, NH^{Neu}), 4.95 (d, 1H, H-1^{Gal}), 4.88 (m, 2H, H-3^{Gal}, OCH_2CCl_3), 4.78 (d, 1H, $J_{1,2}$ = 2.9 Hz, H-1^{GalN}), 4.77 (m, 1H, $J_{3,4}$ =

4.4 Hz, H-4^{Neu}), 4.66 (d, 1H, NH^{GalN}), 4.59 (d, 1H, CH^{Ser}), 4.41 (m, 3H, H-9^{Neu}, CH_2 of Fmoc), 4.22 (m, 3H, H-2^{GalN}, H-6^{Gal}, CH of Fmoc), 4.11 (m, 4H, H-4^{Gal}, H-5^{Gal}, H-6′^{Gal}, CH_2^{Ser}), 4.04 (d, 1H, H-4^{GalN}), 3.88 (m, 3H, COOMe), 3.86 (m, 5H, H-6^{GalN}, H-5^{Neu}, H-9′^{Neu}, CH_2^{Ser}, OCH_2CCl_3), 3.74 (dd, 1H, H-3^{GalN}), 3.69 (m, 2H, H-5^{GalN}, H-6′^{GalN}), 3.65 (dd, 1H, H-6^{Neu}), 2.96 (s, 1H, OH-4^{GalN}), 2.46 (dd, 1H, $J_{3,4}$=4.4, J_{gem}=12.7 Hz, H-3$_{eq}^{Neu}$), 2.37 (s, 1H, OH), 1.88 (6s, 18H, 6 Ac), 1.62 (t, 1H, H-3$_{ax}^{Neu}$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2, 170.8, 170.5, 170.2, 170.1, 170.0, 168.2, 166.0, 165.2, 156.0, 154.1, 143.7, 141.3, 135.1, 133.6, 133.4, 130.2, 130.1, 129.0, 128.8, 128.7, 128.6, 128.5, 127.8, 127.1, 125.1, 120.5, 101.0, 99.8, 96.8, 95.7, 93.0, 88.7, 78.8, 74.0, 72.0, 71.7, 71.2, 71.1, 70.6, 70.0, 69.2, 68.3, 68.0, 67.6, 67.2, 67.1, 66.8, 62.9, 62.7, 62.5, 54.7, 53.4, 50.0, 48.8, 47.1, 37.4, 37.1, 34.4, 33.1, 32.8, 31.9, 30.3, 30.1, 29.7, 29.4, 27.1, 23.1, 22.7, 21.6, 21.0, 20.7, 20.6, 20.4, 19.7, 14.2, 14.1; MALDI MS: *m/z*: calcd for $C_{76}H_{82}Cl_3N_5O_{31}$: 1660.39; found: 1660.25 $[M+Na]^+$.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-[(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate-(2→3)-6-*O*-acetyl-2,4-di-*O*-benzoyl-β-D-galactopyranosyl-(1→3)]-(methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-(2,2,2-trichloroethoxycarbamoyl)-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate-(2→6)]-2-deoxy-2-(2,2,2-trichloroethoxycarbamoyl)-α-D-galactopyranosyl]-L-serine benzyl ester (40)**: Molecular sieves 3 Å (170 mg) was added to a solution of compound **39** (71 mg, 98.8 μmol) and **38** (108 mg, 65.9 μmol) in CH_3CN/CH_2Cl_2 (1.5/0.2 mL). The suspension was stirred for 1 h and cooled to −35 °C. To the mixture were added NIS (45 mg, 198 μmol) and TfOH (2.0 μL, 19.8 μmol) and stirring was continued for 31 h. The termination of reaction was confirmed by TLC ($CHCl_3$/MeOH/$PhCH_3$ 10:1:1). The reaction mixture was filtered through Celite. The combined filtrate and washings were extracted with $CHCl_3$, and the organic layer was washed with satd. aq. Na_2CO_3, satd. aq. $Na_2S_2O_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/$PhCH_3$ 70:1:7) to give **40α** (108 mg, 73%) and **40β** (32 mg, 21%). **40α**: $[\alpha]_D$=+43.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (m, 23H, Ph), 6.11 (d, 1H, NH^{Ser}), 5.65 (m, 1H, H-8c), 5.42 (t, 1H, H-2b), 5.37 (m, 2H, H-7d, H-8d), 5.26 (d, 1H, H-4b), 5.20 (m, 1H, H-7c), 5.12 (q, 2H, PhCH_2), 5.00 (d, 1H, NHc), 4.97 (m, 3H, H-4d, NHd, OCH_2CCl_3), 4.96 (d, 1H, H-1b), 4.89 (d, 1H, OCH_2CCl_3), 4.84 (d, 1H, H-3b), 4.78 (m, 2H, H-1a, H-4c), 4.66 (m, 1H, NHa), 4.25 (t, 1H, CH^{Ser}), 4.45 (d, 1H, OCH_2CCl_3), 4.40 (d, 1H, H-9c), 4.30 (m, 5H, H-2a, H-6b, H-9d, CH_2 of Fmoc), 4.15 (m, 5H, H-5b, H-6′b, H-6d, H-9′d, CH of Fmoc), 4.04 (s, 1H, H-4a), 3.99 (m, 1H, H-6a), 3.94 (s, 1H, CH_2^{Ser}), 3.90 (m, 5H, H-3a, CH_2^{Ser}, COOMe), 3.82 (m, 3H, H-6′, H-5c, H-9′c), 3.73 (d, 1H, OCH_2CCl_3), 3.71 (s, 3H, COOMe), 3.65 (m, 2H, H-6c, H-5d), 3.58 (t, 1H, H-5a), 2.77 (s, 1H, OH-4a), 2.64 (dd, 1H, J_{gem}=12.5 Hz, H-3$_{eq}$d), 2.46 (dd, 1H, J_{gem}=12.5 Hz,H-3$_{eq}$c), 2.07 (10s, 30H, 10 Ac), 1.59 (t, 2H, J_{gem}=12.5 Hz, H-3$_{ax}$c, H-3$_{ax}$d); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 171.0, 170.8, 170.7, 170.7, 170.4, 170.3, 170.3, 170.2, 170.1, 169.8, 168.2, 168.1, 167.8, 165.9, 165.2, 155.9, 154.0, 143.7, 143.6, 141.2, 137.8, 135.0, 133.5, 133.4, 130.0, 129.0, 129.0, 128.8, 128.7, 128.6, 128.2, 128.1, 127.7, 127.1, 125.3, 125.2, 125.0, 120.0, 100.8, 99.1, 98.6, 96.7, 95.6, 95.4, 78.4, 74.4, 73.9, 72.1, 72.0, 71.1, 70.7, 69.2, 68.8, 68.7, 68.4, 68.2, 67.5, 67.3, 67.0, 66.8, 63.7, 62.7, 62.1, 54.4, 53.3, 52.8, 51.5, 50.0, 48.7, 47.0, 37.5, 37.3, 37.1, 32.7, 31.9, 30.0, 29.7, 29.3, 27.0, 23.1, 22.7, 21.5, 21.4, 20.9, 20.8, 20.7, 20.7, 20.5, 20.4, 19.7, 14.1; MALDI MS: *m/z*: calcd for $C_{97}H_{108}Cl_6N_4O_{44}Na$: 2265.44; found: 2265.48 $[M+Na]^+$; **40β**: $[\alpha]_D$=+44.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (m, 23H, Ph), 6.41 (d, 1H, NHa), 6.27 (d, 1H, NHd), 5.62 (m, 1H, H-8c), 5.50 (m, 2H, H-4d, H-7d), 5.44 (t, 1H, H-2b), 5.35 (m, 1H, H-8d), 5.29 (d, 1H, H-4b), 5.18 (m, 3H, H-7c, PhCH_2), 4.99 (d, 1H, H-1b), 4.96 (d, 1H, NHc), 4.86 (m, 2H, H-3b, OCH_2CCl_3), 4.83 (d, 1H, $J_{1,2}$=2.7 Hz, H-1a), 4.73 (m, 4H, NHa, H-4c, H-9d, CH^{Ser}), 4.36 (m, 3H, H-9d, CH_2 and CH of Fmoc), 4.32 (td, 1H, $J_{1,2}$=2.7 Hz, H-2a), 4.24 (s, 3H, H-4a, H-6b, H-6′b), 4.14 (m, 4H, H-6d, H-9′d, OCH_2CCl_3), 4.06 (t, 1H, H-5b), 4.02 (dd, 1H, CH_2^{Ser}), 3.95 (d, 1H, OCH_2CCl_3), 3.91 (dd, 1H, H-9′c), 3.87 (s, 3H, COOMe), 3.79 (m, 5H, H-3a, H-6a, H-6′a, H-5c, CH_2^{Ser}), 3.71 (s, 3H, COOMe), 3.65 (m, 2H, H-5a, H-6c), 2.93 (s, 1H, OH), 2.59 (dd, 1H, H-3$_{eq}$d), 2.46 (dd, 1H, H-3$_{eq}$c), 1.96 (10s, 30H, 10 Ac), 1.78 (t, 1H, H-3$_{ax}$d), 1.65 (t, 1H, H-3$_{ax}$c); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.9, 170.8, 170.7, 170.2, 170.1, 170.0, 169.9, 168.2, 166.8, 166.0, 165.3, 156.1, 154.5, 154.0, 143.7, 141.3, 141.2, 137.8, 133.5, 133.4, 130.1, 130.0, 129.0, 128.7, 128.7, 128.6, 128.5, 128.2, 128.2, 127.9, 127.8, 127.7, 127.1, 127.1, 125.4, 125.3, 125.3, 125.2, 125.2, 120.3, 119.9, 100.8, 98.7, 98.2, 96.7, 95.6, 95.5, 78.0, 77.2, 74.2, 74.0, 72.1, 71.6, 71.4, 71.2, 71.0, 70.9, 69.1, 68.8, 68.4, 67.8, 67.6, 67.5, 66.7, 62.5, 61.9, 54.2, 53.3, 52.7, 51.0, 50.0, 48.8, 46.9, 37.5, 37.3, 37.1, 31.9, 30.0, 29.7, 29.3, 27.1, 23.1, 22.7, 21.5, 20.9, 20.8, 20.8, 20.7, 20.6, 20.5, 14.1; MALDI MS: *m/z*: calcd for $C_{97}H_{112}N_4O_{43}Na$: 2043.66; found: 2043.67 $[M+Na]^+$.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-[(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-(6-*O*-acetyl-2,4-di-*O*-benzoyl-β-D-galactopyranosyl]-(1→3)-[(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)]-4-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbamoyl)-α-D-galactopyranosyl]-L-serine benzyl ester (41)**: Zinc powder (280 mg) was added to a solution of compound **40α** (28 mg, 12.5 μmol) in AcOH (0.2 mL). The suspension was stirred for 3 h at 40 °C. The termination of reaction was confirmed by TLC ($CHCl_3$/MeOH/$PhCH_3$ 10:1:1). The reaction mixture was filtered through Celite. The combined filtrate and washings were extracted with $CHCl_3$, and the organic layer was washed with satd. aq. Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated. To the residue in pyridine (0.4 mL) was added acetic anhydride (47 μL) at 0 °C under argon atmosphere, and the mixture was stirred for 11 h at ambient temperature. The reaction mixture was coevaporated with toluene and extracted with $CHCl_3$. The organic phase was washed with 2 M HCl, H_2O, satd. aq. Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH/$PhCH_3$ 35:1:3.5) to give **41** (17 mg, 68%). $[\alpha]_D$=+44.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (m, 23H, Ph), 6.11 (d, 1H, NH^{Ser}), 5.69 (m, 1H, H-8c), 5.45 (d, 1H, NHa), 5.40 (s, 1H, H-4a), 5.34 (t, 1H, $J_{1,2}$=7.8 Hz, H-2b), 5.32 (m, 2H, H-7d, H-8d), 5.22 (d, 1H, $J_{3,4}$=3.2 Hz, H-4b), 5.21, 5.02 (2 d, 2H, PhCH_2), 5.15 (dd, 1H, H-7c), 5.11 (d, 1H, NHc), 4.96 (d, 1H, NHc), 4.91 (d, 1H, $J_{1,2}$=7.8 Hz, H-1b), 4.87 (d, 1H, $J_{1,2}$=2.9 Hz, H-1a), 4.84 (m, 1H, H-4d), 4.77 (dd, 1H, H-4c), 4.75 (dd, 1H, $J_{3,4}$=3.2 Hz, H-3b), 4.57 (m, 1H, CH^{Ser}), 4.41 (m, 5H, $J_{1,2}$=2.9 Hz, H-2a, H-6b, H-6′b, H-9d, CH of Fmoc), 4.26 (m, 2H, H-5b, H-9d), 4.07 (m, 6H, H-3a, H-5d, H-6d, H-9′d, CH_2 of Fmoc), 3.92 (m, 5H, H-5a, CH_2^{Ser}, CO(O)CH_3), 3.79 (m, 7H, H-6a, H-5c, H-9′c, CH_2^{Ser}, CO(O)CH_3), 3.61 (dd, 1H, H-6c), 3.37 (dd, 1H, H-6′a), 2.55 (dd, 1H, H-3$_{eq}$d), 2.47 (dd, 1H, H-3$_{eq}$c), 1.99 (13s, 39H, Ac), 1.97 (t, 1H, H-3$_{ax}$d), 1.63 (t, 1H, H-3$_{ax}$c); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 170.9, 170.8, 170.6, 170.3, 170.2, 170.1, 170.0, 169.9, 169.6, 168.2, 167.8, 165.7, 164.8, 156.1, 143.8, 143.7, 141.3, 134.9, 133.4, 133.3, 130.3, 130.2, 130.1, 129.4, 128.9, 128.8, 128.5, 128.4, 127.8, 127.1, 125.1, 120.0, 117.1, 116.9, 116.6, 100.8, 99.9, 98.6, 96.8, 75.0, 72.6, 71.9, 71.3, 71.2, 71.0, 69.3, 69.1, 68.9, 68.5, 68.2, 67.4, 67.2, 67.1, 64.2, 63.0, 62.2, 61.8, 54.6, 53.3, 52.8, 49.3, 48.9, 48.7, 47.1, 37.5, 37.2, 37.1, 32.8, 31.9, 30.4, 30.0, 29.7, 29.4, 27.5, 27.1, 23.2, 23.1, 22.7, 22.2, 21.5, 21.1, 21.0, 20.8, 20.7, 20.6, 20.3, 14.1; MALDI MS: *m/z*: calcd for $C_{97}H_{112}N_4O_{43}Na$: 2043.66; found: 2043.67 $[M+Na]^+$.

Acknowledgements

This work was financially supported in part by MEXT of Japan (Grant-in-Aid for Scientific Research to H.A., no. 16780083, H.I., no. 16580086, and M.K., no. 1701007), and Mitsubishi Chemical Corporation Fund (H.A.). We thank Ms. Kiyoko Ito for technical assistance.

[1] A. Varki, *Glycobiology* **1993**, *3*, 97–130.

[2] Recent reviews: a) H. Herzner, T. Reipen, M. Schultz, H. Kuntz, *Chem. Rev.* **2000**, *100*, 4495–4537; b) K. C. Nicolaou, H. J. Mitchell, *Angew. Chem.* **2001**, *113*, 1624–1672; *Angew. Chem. Int. Ed.* **2001**, *40*, 1576–1624; c) A. V. Demchenko, *Synlett* **2003**, 1225–1240; recent papers on α-galactosyl or galacatosamyl glycan synthesis: d) H. Tanaka, H. Sakamoto, A. Sano, S. Nakamura, M. Nakajima, S. Hashimoto, *Chem. Commun.* **1999**, 1259–1260; e) D. K. Baeschlin,

A. R. Chaperon, L. G. Green, M. G. Hahn, S. J. Ince, S. V. Ley, *Chem. Eur. J.* **2000**, *6*, 172–186; f) H. Dohi, Y. Nishida, H. Tanaka, K. Kobayashi, *Synlett* **2001**, 1446–1448; g) F. Burkhart, Z. Zhang, S. Wacowich-Sgarbi, C. H. Wong, *Angew. Chem.* **2001**, *113*, 1314–1317; *Angew. Chem. Int. Ed.* **2001**, *40*, 1274–1277; h) Y. P. Cheng, H. T. Chen, C. C. Lin, *Tetrahedron Lett.* **2002**, *43*, 7721–7723; i) 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; j) Y. Nishida, Y. Shingu, H. Dohi, K. Kobayashi, *Org. Lett.* **2003**, *5*, 2377–2380; k) L. Chen, F. Kong, *Tetrahedron Lett.* **2003**, *44*, 3691–3695; l) Y. Wang, X. Huang, L. H. Zhang, X. S. Ye, *Org. Lett.* **2004**, *6*, 4415–4417; m) N. Shao, Z. Guo, *Org. Lett.* **2005**, *7*, 3589–3592; n) T. Buskas, S. Ingale, G. J. Boons, *Angew. Chem.* **2005**, *117*, 6139–6142; *Angew. Chem. Int. Ed.* **2005**, *44*, 5985–5988; o) H. Hojo, Y. Matsumoto, Y. Nakahara, E. Ito, Y. Suzuki, M. Suzuki, A. Suzuki, Y. Nakahara, *J. Am. Chem. Soc.* **2005**, *127*, 13720–13725.

[3] G. A. Winterfeld, R. R. Schmidt, *Angew. Chem.* **2001**, *113*, 2718–2721; *Angew. Chem. Int. Ed.* **2001**, *40*, 2654–2657.

[4] J. H. Kim, H. Yang, J. Park, G. J. Boons, *J. Am. Chem. Soc.* **2005**, *127*, 12090–12097.

[5] a) A. Imamura, H. Ando, S. Korogi, G. Tanabe, O. Muraoka, H. Ishida, M. Kiso, *Tetrahedron Lett.* **2003**, *44*, 6725–6728; b) A. Imamura, H. Ando, H. Ishida, M. Kiso, *Org. Lett.* **2005**, *7*, 4415–4418.

[6] a) E. J. Corey, P. B. Hopkins, *Tetrahedron Lett.* **1982**, *23*, 4871–4874; b) K. Furusawa, K. Ueno, T. Katsura, *Chem. Lett.* **1990**, 97–100.

[7] M. Numata, M. Sugimoto, K. Koike, T. Ogawa, *Carbohydr. Res.* **1987**, *163*, 209–225.

[8] For the synthesis, see Supporting Information.

[9] 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-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313–4316.

[10] S. Hashimoto, M. Hayashi, R. Noyori, *Tetrahedron Lett.* **1985**, *26*, 1379–1382.

[11] F. Dasgupta, P. J. Garegg, *Carbohydr. Res.* **1990**, *202*, 225–238.

[12] T. Mukaiyama, Y. Murai, S. Shoda, *Chem. Lett.* **1981**, 431–432.

[13] K. Suzuki, H. Maeta, T. Suzuki, T. Matsumoto, *Tetrahedron Lett.* **1989**, *30*, 6879–6882.

[14] R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212–235.

[15] C. A. A. van Boeckel, T. Beetz, S. F. van Aelst, *Tetrahedron*, **1984**, *40*, 4097–4107.

[16] M. Yamaguchi, A. Horiguchi, A. Fukuda, T. Minami, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1079–1082.

[17] Recent papers on α-Gal-Cer synthesis: a) G. T. Fan, Y. S. Pan, K. C. Lu, Y. P. Cheng, W. C. Lin, S. Lin, C. H. Lin, C. H. Wong, J. M. Fang, C. C. Lin, *Tetrahedron* **2005**, *61*, 1855–1862; b) W. Du, J. Gervay-Hague, *Org. Lett.* **2005**, *7*, 2063–2065.

[18] K. Furusawa, *Chem. Lett.* **1989**, 509–510.

[19] H. Ando, Y. Koike, H. Ishida, M. Kiso, *Tetrahedron Lett.* **2003**, *44*, 6883–6886.

[20] First report on the synthesis of glycophorin A: Y. Nakahara, H. Iijima, T. Ogawa, *Tetrahedron Lett.* **1994**, *35*, 3321.

Received: June 14, 2006
Published online: August 22, 2006

総合論文

シアル酸分子多様性を網羅する糖鎖合成法の開拓－シアロ糖鎖多機能性の分子理解を目指して－

安藤 弘宗
石田 秀治
木曾 眞*

Study on the Method for Oligosaccharide Synthesis Covering the Structural Diversity of Sialic Acid -Aiming at the Understanding of the Polymorphous Functions at the Molecular Level-

Hiromune Ando, Hideharu Ishida, and Makoto Kiso*

For the purpose of the scrutiny of multi-functions of oligosaccharides at the molecular level, the practical method for the chemical construction is essential. In 1989, we have established the practical method for α-selective sialylation that utilizes nitrile solvent effect to fashion thermodynamically-disfavored equatorial glycoside. Due to the powerful method, we have succeeded in many first syntheses of sialyl oligosaccharide complexes such as sialyl Lewis X, GQ 1 b.

Recently, we have developed highly reactive *N*-Troc-protected sialyl donor and 1, 5-lactamized sialyl acceptor. *N*-Troc sialyl donor enabled us to perform high-yielding sialylation, and obtained sialoside could be pivotally derived into various homologues containing Neu 5 Gc, $NeuNH_2$ and 8-*O*-sulfo-Neu 5 Ac. Further, the synergic coupling with 1, 5-lactamized acceptor produced α(2-4)- and α(2-8)-linked disialic acid sequences in high yields, thereby resulting in the first synthesis of glycan portions of gangliosides HLG-2 and Hp-s 6.

Key words: sialic acid, oligosialic acid, polysialic acid, oligosaccharide, ganglioside, glycosylation, Troc, lactam

はじめに

近年，にわかに糖鎖の生物学的機能研究が注目されるようになった。生体内に発現する糖鎖の機能を網羅的に解析する研究領域はグライコミクスと呼ばれているが，とくに，このグライコミクスは，ポストゲノム科学の一翼を担う領域として一層の発展が期待されている。糖鎖は，単糖を構成単位とし，それらがグリコシド結合を介して連結した，文字どおり，「鎖」のような分子である。この糖鎖が動植物の細胞表面に存在する場合は，脂質，タンパク質と結合した複合体(複合糖質)を形成している。糖鎖は，厳密な特異性を持つ糖転移酵素をはじめ種々の酵素群の働きによって生合成されているが，タンパク質のように核酸の塩基配列から一義的に一次構造が決定されるわけではない。また，単糖には可能な結合部位(水酸基)がいくつか存在し，かつ結合様式にはα, βの2種が存在するため，同一の単糖配列には，膨大な異性体が存在しうる。そのため，糖鎖の高次構造を含めた分子構造に基づいた機能理解には，構造が明確でかつ純度の高い糖鎖を十分量確保することが必須である。しかし，生体から研究試料としての糖鎖を十分量確保するのは至難であり，天然由来の異成分の混入など，純度も問題となる。さらに，糖鎖は，タンパク質のように遺伝子工学的な分子増幅が現在不可能である。従って，純粋かつ大量の糖鎖および複合糖質を擁する分子資源の創出には，有機化学的手法による糖鎖合成が有力な手段の1つとなる。

我々の研究室では，糖鎖の有機化学から分子生物学への展開という視座に立ち，実用性の高い糖鎖合成法の開発を命題にして，長年研究に携わってきた。とくに，化学的，生物学的に興味深いシアル酸含有糖鎖およびその複合体の合成に注力してきた。本稿では，これまでの研究経緯を概観し，多様なシアル酸修飾体を有する糖鎖の合成に関する，最近の研究成果について報告する。

1. シアル酸グリコシド化反応

シアル酸は，図1に示すような3-deoxy-non-2-ulosonic acid誘導体の一群を指す。天然に，約40以上の類縁体が知られているが，図に示した3種がシアル酸ファミリーの主要な分子である。ヒトでは，*N*-アセチル体が発現しているため，化学合成の標的分子として，もっぱら*N*-アセチルシアル酸を含む糖鎖が設定されてきた。シアル酸は，ほとんどの場合，糖鎖の非還元末端に結合しており，かつグリコシドはエクアトリアル配向

* 岐阜大学応用生物科学部食品生命科学課程
(501-1193 岐阜市柳戸 1-1)
* Department of Applied Bioorganic Chemistry, Faculty of Applied Biological Sciences, Gifu University (1-1 Yanagido, Gifu 501-1193, Japan)

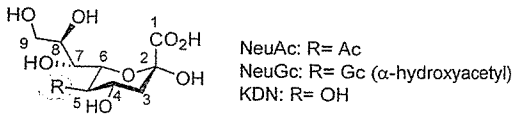
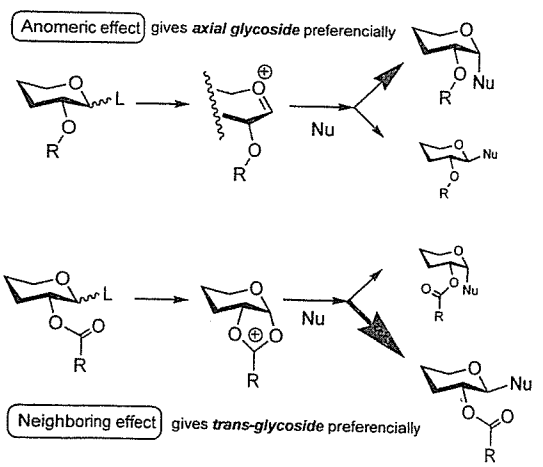


Fig. 1 Typical sialic acids.

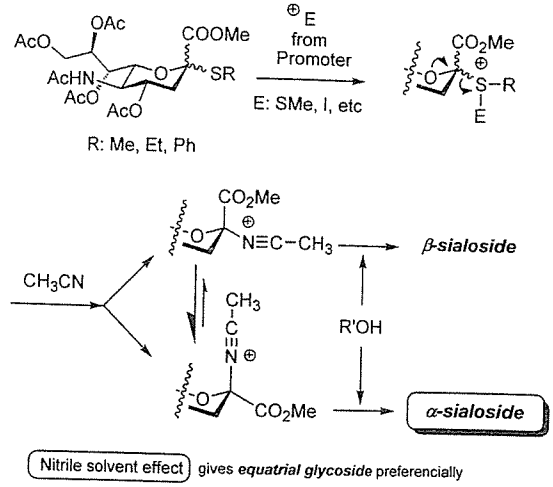
のα-グリコシドに限定されている。

通常，アノマー位に脱離基を有する求電子剤(糖供与体)と遊離の水酸基を有する求核剤(糖受容体)によるグリコシル化反応では，アノマー効果によりアキシアル位のグリコシドが優先的に生ずるため，エクアトリアル位のグリコシド形成には，隣接基効果を発現する置換基を隣接位の水酸基に導入する方法がとられる(スキーム1)。しかし，これはエクアトリアル位のグリコシド結合に対して，隣接する水酸基がトランス配置の糖(いわゆるグルコ型の糖)においてのみ有効であり，シス配置の糖(いわゆるマンノ型)や隣接炭素上に水酸基を有しないデオキシ型の糖に対して利用できない。そのため，マンノ型とデオキシ型のエクアトリアルグリコシドは，合成が非常に困難な結合様式である。シアル酸の場合は，デオキシ糖である上に，アノマー炭素上のカルボキシル基の電子求引性と立体障害により，アノマー炭素の求電子剤としての反応性を低下させ，さらに副反応としての2,3-エン体の生成が促進される。また，6位炭素から伸張しているグリセロール側鎖もグリコシル化の際に立体障害を及ぼしているとの見解もあり，このような負の相乗効果により，他のデオキシ糖よりもはるかに構築難易度が上である。



Scheme 1 General scheme of glycosylation.

上述の問題を克服するひとつの方法として，我々の研究室が発表したシアル酸のグリコシル化(シアリル化)をスキーム2に示した[1]。この手法は，脱離基の活性化により生じたオキソカルベニウムイオンに対するアセトニトリルの溶媒効果により，α選択性を発現するもので，広範な糖受容体との反応に有効であり，また，鍵化合物となるチオグリコシド供与体は，無保護シアル酸から3



Scheme 2 Nitrile solvent-assisted α-selective sialylation.

段階で収率よく調製できる。そのため，大量合成にも適しており，生物学的研究に十分量の糖鎖を合成することが可能である。

我々は，このα選択的シアリル化を鍵反応として，シアリルルイスX[2]を始め，様々な天然型糖脂質の全合成に成功を収めることができた[3]。これらは，種々の類縁体糖鎖と合わせて，生物学的研究の糖鎖プローブとして利用され，セレクチンを主としたレクチンの認識特異性の解明，生体内での真のレクチンリガンドの同定などの成果を学際的な共同研究により挙げている[4]。そして，近年ではこれらの成果を受け，生物学的な重要性がうたわれながらも，複雑な構造ゆえに機能解明が進んでいないシアロ糖鎖の合成研究を重点的に推し進めている。

2. 高度にシアロ化された糖鎖の合成

生体に存在する糖鎖には，多数のシアル酸残基を含むものが存在している。糖脂質の一系列であるガングリオ系ガングリオシドは，複数のシアル酸残基を有する代表的なもので，これらは，シアル酸二量体，三量体を糖鎖の末端構造として有している。他に，神経細胞接着分子(N-CAM)やナトリウムチャネルには，重合度8−200のポリシアル酸構造が確認されている。また，最近では，糖脂質のみならず糖タンパク質上にもオリゴシアル酸(重合度2−7)構造が存在することが報告され，普遍的な糖鎖部分構造として認識されるようになった[5]。これらの高度にシアロ化された糖鎖には，細菌毒素およびウィルス受容体，細胞接着因子，レクチンリガンドとしての機能があり，細菌・ウィルス感染，脳形成，細胞性免疫など，動的な生命現象に深く関わっていると示唆されているが，それらに対する分子的な裏づけは未だ明確ではない。

そこで，我々は，当時注目を集めていたGQ1bガングリオシドの全合成に挑戦した(図2)。

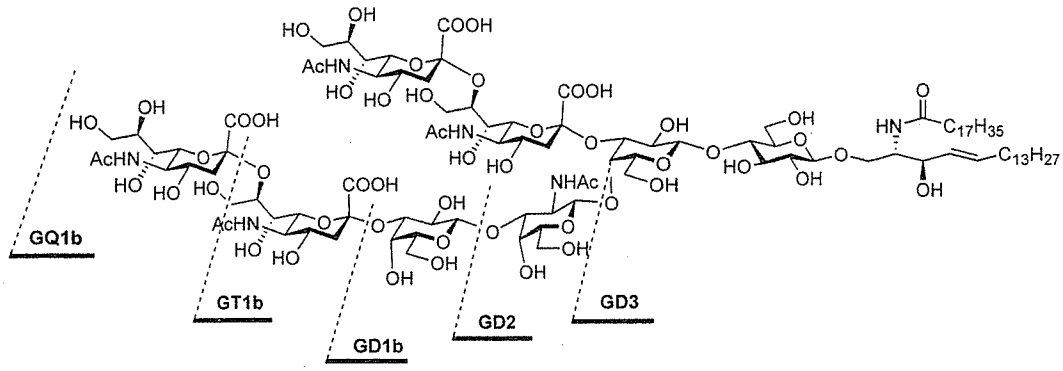
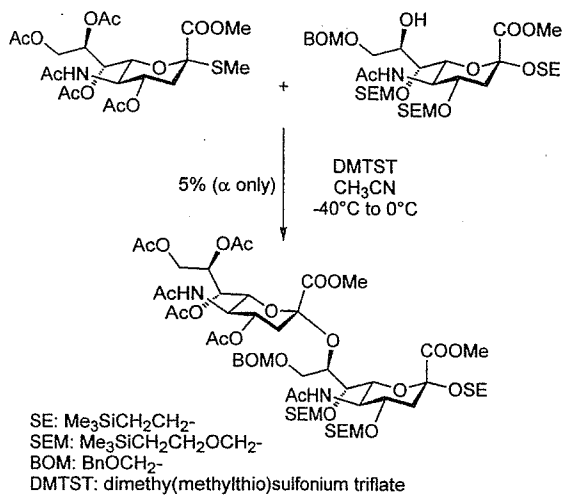


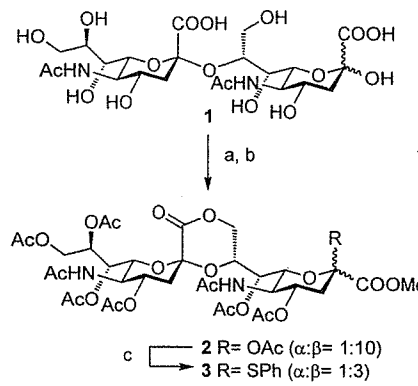
Fig. 2　Structure of b-series gangliosides.

ここでは，いかにしてシアル酸二量体構造を糖鎖中に構築してゆくかが大きな課題となった。上述の我々のシアリル化反応では，極度に反応性の低いシアル酸８位水酸基に収率よくシアル酸を導入することは，極めて困難であった(スキーム３)[6]。



Scheme 3　C８ hydroxyl is unreactive toward sialylation.

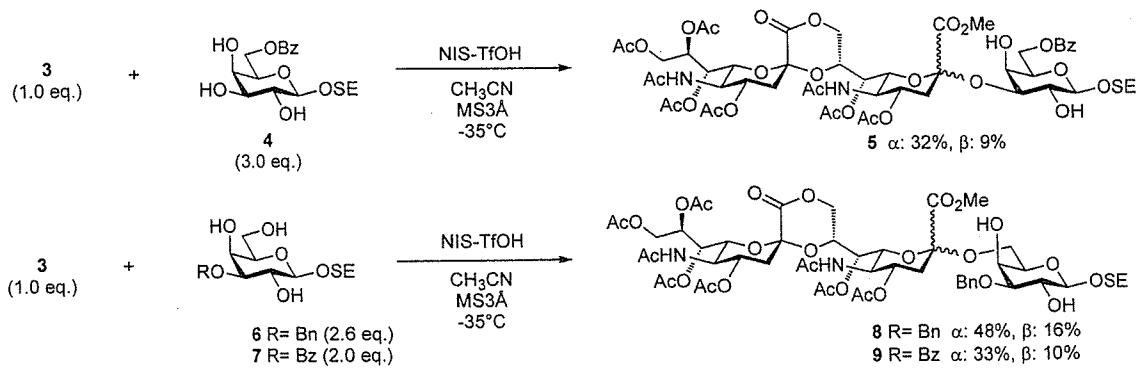
この問題を解決するために，我々は天然から入手可能なシアル酸二量体を出発原料として利用することを着想した。すなわち，まず，大腸菌細胞壁由来のシアル酸ポリマーであるコロミン酸を限定加水分解して，シアル酸二量体１を調製し，それをメチルエステル化およびラクトン化させた後，水酸基をアセチル化して中間体２とした。続いて，ルイス酸存在下でチオフェノールを作用させ，チオグリコシド供与体３を３段階75％の収率で調製した(スキーム４)。



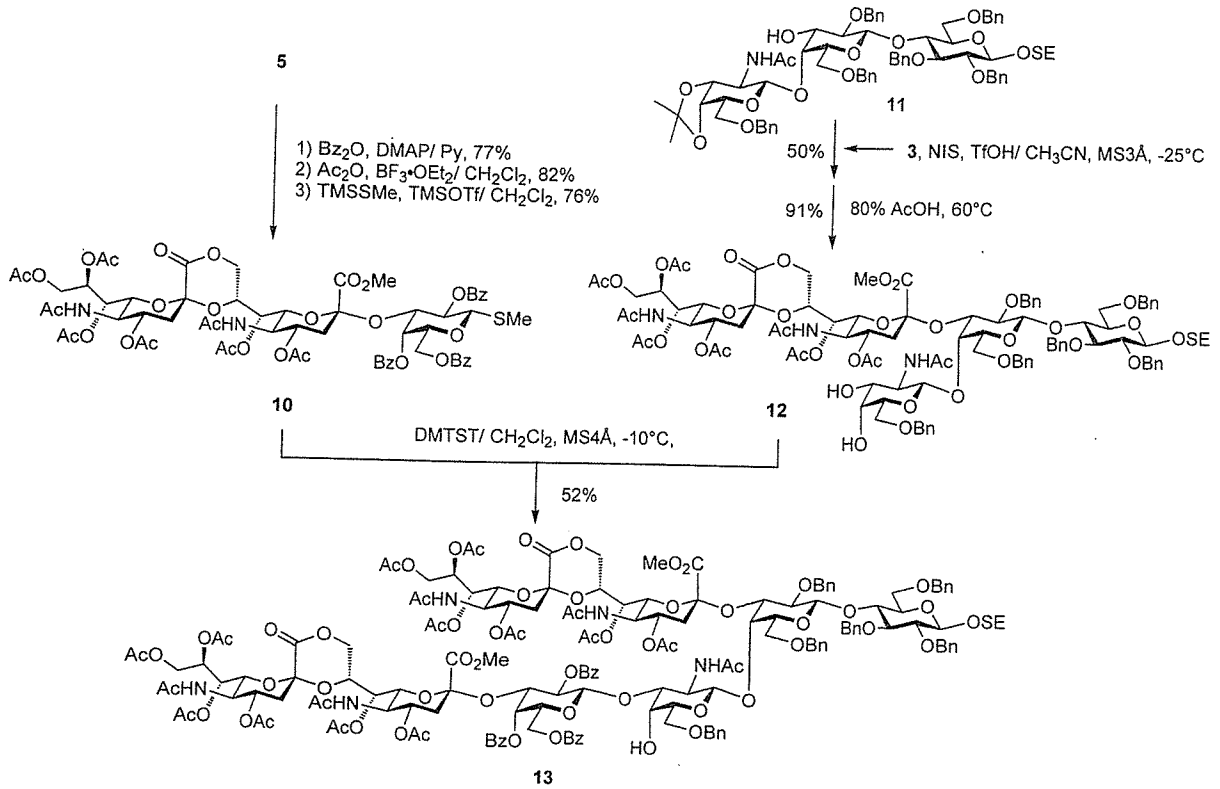
Scheme 4　Preparation of disialyl donor. Reagents and conditions: a) IR-120(H^+), MeOH/40 ℃, 2 d; b) Ac_2O, Py/40 ℃, 1 d, 84% (2 steps); c) PhSH, $BF_3 \cdot OEt_2/CH_2Cl_2$, RT, 12 h, 89%.

こうして得られた供与体３を種々の糖受容体4, 6, 7とのカップリング反応に供したところ，比較的良好な立体選択性と収率でα-ジシアロシドが得られた(スキーム５)[7]。

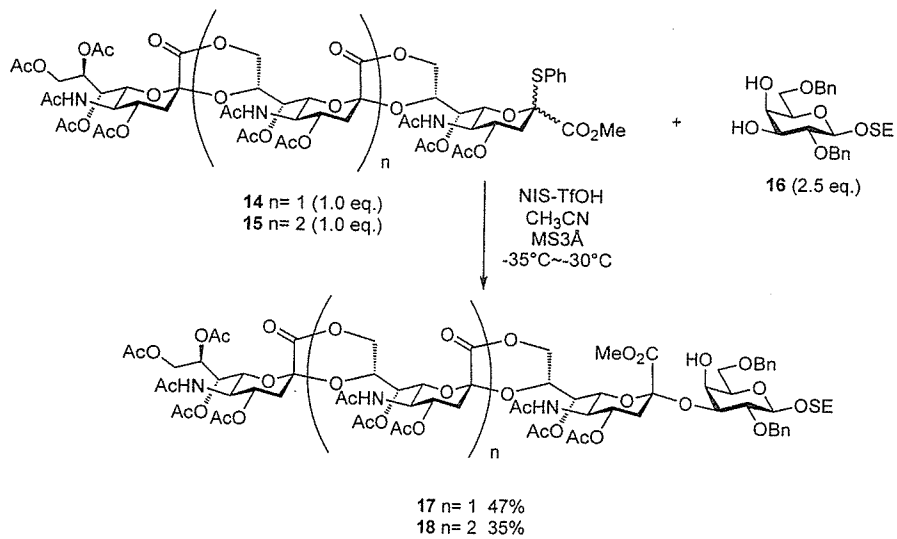
この結果をもとに，目的のGQ１b８糖部分を，収束的合成法によって構築することとし，ジシアル酸を含む非還元末端３糖と内部ジシアル酸を含む５糖部分に大きく分割した。まず，ジシアロ化反応を鍵反応として，それぞれのブロック10, 12を高収率で構築した後に，最



Scheme 5　α-Selective disialylation.



Scheme 6　Synthesis of ganglioside GQ 1 b.



Scheme 7　Tri- and tetra-sialylations.

終のブロックカップリングにより収率よく８糖部分を得ることができた。最後に，脂質の導入，保護基の脱保護を経て，GQ１ｂの世界初の全合成を達成した(スキーム6)[8]。

また，他のジシアル酸含有ガングリオシド，GD３，GD２，GT１b，GD１c，GT１aなどの合成もシアル酸二量体ユニットを利用する合成戦略により，達成された[9]。さらに我々のシアリル化反応は，シアル酸三量体，四量体の供与体14，15を用いた場合でも，比較的良好な収率でグリコシル化産物を得ることができ，本反応の広い応用範囲が示された(スキーム7)[10]。合成を達成したガングリオシドのうち，GT１ｂは，破傷風毒素の受容体，シグレック-7のリガンドとして機能することが知られている。我々は，種々のGT１ｂ類縁体をプローブとして合成し，対タンパク質との共結晶を用いたX線結晶解析によって，糖鎖-タンパク質相互作用の詳細な解明を共同研究によって進めている[11]。

3.　シアル酸部分修飾体を有する糖鎖の合成

上述した天然由来のオリゴシアル酸を利用した合成ブ