

***De Novo* Synthesis of a 2-Acetamido-4-amino-2,4,6-trideoxy-D-galactose (AAT) Building Block for the Preparation of a *Bacteroides fragilis* A1 Polysaccharide Fragment**

Rajan Pragani, Pierre Stallforth, and Peter H. Seeberger\*

Max-Planck-Institute of Colloids and Interfaces

Department of Biomolecular Systems, Am Mühlenberg 1, 14476 Potsdam, Germany

and

Freie Universität Berlin

Institute for Chemistry and Biochemistry, Arnimallee 22, 14195 Berlin, Germany

e-mail: peter.seeberger@mpikg.mpg.de

**Supporting Information:**

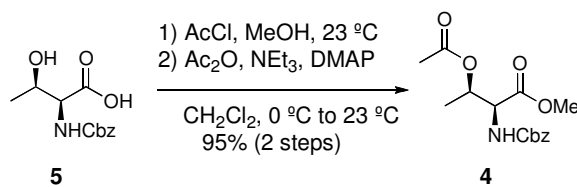
Experimental Procedures for *De Novo* Synthesis of a 2-Acetamido-4-amino-2,4,6-trideoxy-D-galactose (AAT) Building Block for the Preparation of a *Bacteroides fragilis* A1 Polysaccharide Fragment

**General Experimental Details.** Commercial grade reagents and solvents were used without further purification except as indicated below. Deionized water was obtained from an in-house purification system. All reactions were conducted under an Ar atmosphere. The term “concentrated under reduced pressure” refers to the removal of solvents and other volatile material using a rotary evaporator while maintaining a water bath temperature under 40 °C. The compounds purified by flash chromatography are further concentrated by the removal of residual solvent under high vacuum (<0.2 mbar).

**Physical Properties and Spectroscopic Measurements.**  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were measured with a Varian 400-MR, Bruker ECP 400, or Bruker AC 500 spectrometer. The proton signal of residual, non-deuterated solvent ( $\delta$  7.26 ppm for  $\text{CHCl}_3$ ) was used as an internal reference for  $^1\text{H}$  spectra. For  $^{13}\text{C}$  spectra, the chemical shifts are reported relative to the  $\delta$  77.36 ppm resonance of  $\text{CDCl}_3$ . Coupling constants are reported in Hertz (Hz).

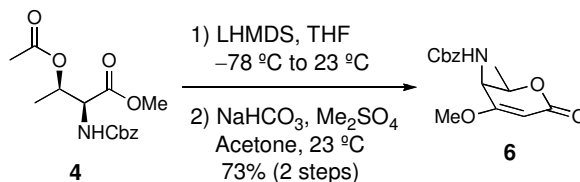
Infrared (IR) spectra were recorded as thin films on a Perkin Elmer Spectrum 100 FT-IR spectrophotometer. Optical rotations (OR) were measured with a Schmidt & Haensch UniPol L 1000 at a concentration (c) expressed in g/100 mL. High-resolution mass spectra (HRMS) were recorded with an Agilent 6210 ESI-TOF mass spectrometer at the Freie Universität Berlin, Mass Spectrometry Core Facility.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F<sub>254</sub> glass plates precoated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and by staining with Hanessian solution (ceric sulfate and ammonium molybdate in aqueous sulfuric acid) or potassium permanganate solution (potassium permanganate in basic aqueous solution). Column chromatography was performed using Kieselgel 60 (230-400 mesh) silica gel with a typical 50-100:1 weight ratio of silica gel to crude product.



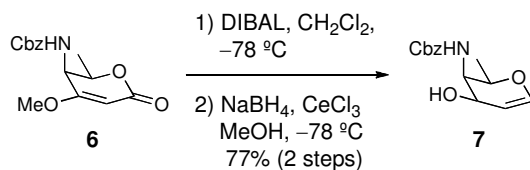
**(2*S*,3*R*)-Methyl 3-acetoxy-2-(benzyloxycarbonyl)amino butanoate (4):** To a solution of AcCl (4.63 mL, 65.2 mmol) in MeOH (70 mL) at 23 °C was added in one portion commercially available Cbz protected L-threonine **5** (15 g, 59.2 mmol). The mixture was then stirred at 23 °C for 3 h. The solution was concentrated. The resulting oil was dissolved in EtOAc (100 mL) and neutralized by addition of sat. aq. NaHCO<sub>3</sub> (100 mL). Following extraction with EtOAc (1 x 50 mL), the organic layer was washed with sat. aq. NaHCO<sub>3</sub> (1 x 100 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to yield 19.6 g of crude material.

The crude alcohol was then dissolved in CH<sub>2</sub>Cl<sub>2</sub> (70 mL), cooled to 0 °C, and treated with NEt<sub>3</sub> (12.4 mL, 89 mmol) and Ac<sub>2</sub>O (6.7 mL, 71.1 mmol). Finally, DMAP (362 mg, 2.96 mmol) was added and the mixture was warmed to 23 °C and stirred for 2 h. The reaction was quenched by addition of sat. aq. NaHCO<sub>3</sub> (100 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 mL). The combined organic extracts were washed with sat. aq. NaHCO<sub>3</sub> (2 x 100 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by flash chromatography (40:60 to 60:40 EtOAc/hexanes) to furnish acetate **4** (17.4 g, 56.3 mmol) in 95% yield as a clear oil:  $[\alpha]_D^{20} = +45.9^\circ$  ( $c = 2.1$ , CHCl<sub>3</sub>);  $R_f = 0.38$  (50:50 EtOAc/cyclohexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.39-7.30 (m, 5H), 5.47-5.38 (m, 2H), 5.16 (d,  $J = 12.0$  Hz, 1H), 5.13 (d,  $J = 12.0$  Hz, 1H), 4.48 (dd,  $J = 2.4, 9.6$  Hz, 1H), 3.73 (s, 3H), 1.91 (s, 3H), 1.30 (d,  $J = 6.4$  Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.7, 170.0, 156.8, 136.3, 128.9, 128.6, 128.5, 70.6, 67.6, 57.8, 53.0, 21.1, 17.3; IR (thin film) 3349, 2955, 1718, 1516, 1454, 1487, 1373, 1316, 1225, 1061, 997, 951, 740, 697 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>6</sub> (M+Na)<sup>+</sup> 332.1110, found 332.1089  $m/z$ .



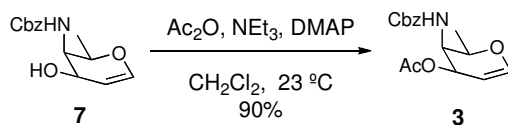
**(5*S*,6*R*)-5-((Benzyloxycarbonyl)amino)-4-(methoxy)-6-methyl-3,4-dihydropyran-2-one (6):** At  $-78\text{ }^{\circ}\text{C}$ , a 1M hexanes solution of LHMDs (46.4 mL, 46.4 mmol) was added to THF (33 mL). This solution was treated with slow addition of a solution of acetate **4** (7.0 g, 22.63 mmol) in THF (80 mL). After stirring for 30 min, the  $-78\text{ }^{\circ}\text{C}$  bath was removed, and the reaction was allowed to warm to room temperature. After an additional 1 h stirring, Et<sub>2</sub>O (100 mL) and 2M HCl (200 mL) were added. Following partitioning, the aqueous layer was extracted with Et<sub>2</sub>O (2 x 50 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to yield 7.7 g of the crude  $\beta$ -ketoester.

The crude  $\beta$ -ketoester was then dissolved in acetone (57 mL) and treated with Me<sub>2</sub>SO<sub>4</sub> (1.72 mL, 22.63 mmol) followed by K<sub>2</sub>CO<sub>3</sub> (4.83 g, 33.9 mmol). After stirring for 5 h, H<sub>2</sub>O (200 mL) and Et<sub>2</sub>O (50 mL) were added, and the Et<sub>2</sub>O and acetone were removed by a rotary evaporator. The mixture was filtered over Celite with Et<sub>2</sub>O and concentrated. To the mixture was added Et<sub>2</sub>O (200 mL), which was partitioned. The aqueous layer was further extracted with Et<sub>2</sub>O (2 x 75 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to yield 7.1 g of the crude diketone. The crude oil was purified by flash chromatography (50:50 to 70:30 EtOAc/cyclohexane) to give enone **6** (4.82 g, 16.6 mmol) in 73% yield over 2 steps as a white foam:  $[\alpha]_{\text{D}}^{20} = -163.1^{\circ}$  ( $c = 2.1$ , CHCl<sub>3</sub>);  $R_f = 0.30$  (60:40 EtOAc/cyclohexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.35-7.27 (m, 5H), 5.63 (d,  $J = 10.0$  Hz, 1H), 5.15 (s, 1H), 5.15 (d,  $J = 12.0$  Hz, 1H), 5.10 (d,  $J = 12.0$  Hz, 1H), 4.53 (m, 1H), 4.35 (dd,  $J = 2.8, 10.0$  Hz, 1H), 3.72 (s, 3H), 1.34 (d,  $J = 6.4$  Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.9, 166.56, 156.8, 136.4, 128.8, 128.5, 128.2, 92.0, 75.0, 67.6, 56.7, 50.5, 16.0; IR (thin film) 3296, 3034, 2986, 2942, 1690, 1630, 1529, 1455, 1389, 1372, 1319, 1286, 1221, 1061, 1029, 998, 976, 834, 750, 697 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>5</sub> (M+Na)<sup>+</sup> 314.1004, found 314.0991  $m/z$ .



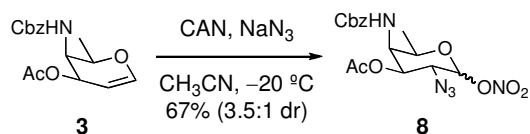
**4-(Benzyloxycarbonyl)amino-4,6-dideoxy-D-galactal (7):** To enone **6** (4.82 g, 16.55 mmol) in THF (55.0 mL) at  $-78\text{ }^{\circ}\text{C}$  was added 1M DIBAL in cyclohexanes (34.7 mL, 34.7 mmol). The solution was stirred for 30 min. and then, quenched with MeOH (5 mL) at  $-78\text{ }^{\circ}\text{C}$ . Upon addition of  $\text{CH}_2\text{Cl}_2$  (5 mL),  $\text{Et}_2\text{O}$  (100 mL), and 1M HCl (150 mL), the mixture was warmed to  $23\text{ }^{\circ}\text{C}$  and stirred vigorously for 1 h. Following partitioning, the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (2 x 50 mL). The combined organic extracts were washed with sat. aq.  $\text{NaHCO}_3$  (2 x 100 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure to yield 3.3 g of the crude enone.

The crude enone and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (3.08 g, 8.27 mmol) were then dissolved in MeOH (55.0 mL). After cooling the solution to  $-78\text{ }^{\circ}\text{C}$ ,  $\text{NaBH}_4$  (0.63 g, 16.55 mmol) was added, and the mixture was stirred for 30 min. at  $-78\text{ }^{\circ}\text{C}$ . The mixture was diluted with  $\text{Et}_2\text{O}$  (150 mL) and then, quenched by dropwise addition of  $\text{H}_2\text{O}$  (10 mL) at  $-78\text{ }^{\circ}\text{C}$ , followed by addition of sat. aq.  $\text{NH}_4\text{Cl}$  (150 mL). The mixture was partitioned and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (2 x 50 mL). The combined organic extracts were washed with sat. aq.  $\text{NaHCO}_3$  (2 x 100 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The crude product was purified by flash chromatography (40:60 to 50:50 EtOAc/hexanes) to furnish alcohol **7** (3.34 g, 12.69 mmol) in 77% yield as a clear oil over 2 steps:  $[\alpha]_{\text{D}}^{20} = -4.4^{\circ}$  ( $c = 1.4$ ,  $\text{CHCl}_3$ );  $R_f = 0.31$  (60:40 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.37-7.28 (m, 5H), 6.30 (dd,  $J = 1.2, 6.4$  Hz, 1H), 5.15 (d,  $J = 12.0$  Hz, 1H), 5.09 (d,  $J = 12.0$  Hz, 1H), 4.65 (dt,  $J = 1.6, 6.0$  Hz, 1H), 4.53 (bs, 1H), 4.09 (q,  $J = 6.4$  Hz, 1H), 4.00 (dd,  $J = 5.2, 9.6$  Hz, 1H), 2.81 (bs, 1H), 1.25 (d,  $J = 6.4$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  158.2, 144.9, 136.4, 128.8, 128.5, 128.4, 103.8, 73.1, 67.5, 64.7, 51.9, 17.2; IR (thin film) 3415, 3065, 3032, 2981, 2937, 2897, 1705, 1644, 1515, 1318, 1229, 1094, 1070, 1027, 743, 697  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{17}\text{NO}_4$  ( $\text{M}+\text{Na}$ ) $^{+}$  286.1055, found 286.1048  $m/z$ .



**3-O-Acetyl-4-(benzyloxycarbonyl)amino-4,6-dideoxy-D-galactal (3):** Alcohol **7** (5.1 g, 19.37 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (48.4 mL) at  $0\text{ }^{\circ}\text{C}$  was treated with  $\text{NEt}_3$  (4.05

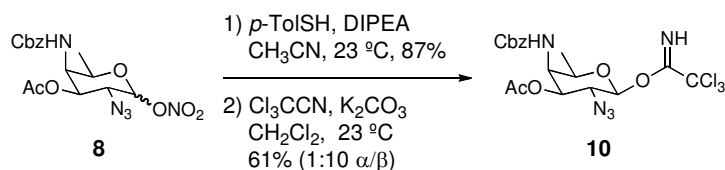
mL, 29.1 mmol) and Ac<sub>2</sub>O (2.19 mL, 23.2 mmol). Finally, DMAP (118 mg, 0.97 mmol) was added, the mixture was allowed to warm to 23 °C, and was stirred for 2 h. The reaction was quenched by addition of sat. aq. NaHCO<sub>3</sub> (200 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL), washed with sat. aq. NaCl (1 x 100 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by flash chromatography (30:70 to 40:60 EtOAc/cyclohexane) to furnish acetate **3** (5.35 g, 17.5 mmol) in 90% yield as a clear oil. This compound has been previously synthesized by an alternative route,<sup>1</sup> and our characterization data were consistent with the previously reported data: [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +14.9° (c = 1.0, CHCl<sub>3</sub>); R<sub>f</sub> = 0.43 (40:60 EtOAc/cyclohexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.37-7.28 (m, 5H), 6.41 (dd, *J* = 1.6, 6.4 Hz, 1H), 5.49 (m, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 4.63 (dt, *J* = 1.6, 6.0 Hz, 1H), 4.20 (m, 2H), 1.92 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  170.8, 157.2, 146.6, 136.8, 128.8, 128.5, 128.4, 100.0, 73.2, 67.2, 66.6, 48.6, 21.1, 17.1; IR (thin film) 3429, 3351, 3067, 3036, 2984, 2938, 1726, 1646, 1509, 1229, 1088, 1031, 742, 699 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>5</sub> (M+Na)<sup>+</sup> 328.1161, found 328.1142 *m/z*.



### **3-O-Acetyl-2-azido-4-(benzyloxycarbonyl)amino-2,4,6-dideoxy-D-galacto**

**pyranosyl nitrate (8):** Acetate **3** (2.4 g, 7.9 mmol) dissolved in CH<sub>3</sub>CN (39.3 mL) at –25 °C was treated with cerium ammonium nitrate (12.9 g, 23.6 mmol) followed by NaN<sub>3</sub> (767 mg, 11.8 mmol). Then, the mixture was stirred vigorously for 8 h between –20 °C and –25 °C. The reaction was diluted with cold Et<sub>2</sub>O (100 mL). The organic layer was then washed with cold H<sub>2</sub>O (3 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by flash chromatography (20:80 EtOAc/hexanes) to furnish nitrate **8** (2.14 g, 5.23 mmol) in 67% yield as a white foam. The nitrate mixture is made of three components: two *galacto* (2:1  $\alpha/\beta$ -anomeric mixture) and one *talo* ( $\alpha$ -anomer) configured azides (3.5:1 dr *galacto/talo*). This mixture could not be separated by silica chromatography. Nitrate **8** has been previously

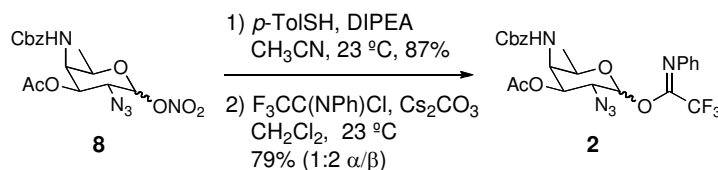
synthesized,<sup>1</sup> and our characterization data were consistent with the previously reported data. The material appears to be slightly unstable to silica gel:  $[\alpha]_D^{20} = +100.5^\circ$  ( $c = 1.2$ ,  $\text{CHCl}_3$ );  $R_f = 0.62$  (40:60 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  6.23 (d,  $J = 4.4$  Hz, 1H; *galacto*  $\alpha$ -nitrate), 6.15 (d,  $J = 0.8$  Hz, 1H; *talo*  $\alpha$ -nitrate), 5.50 (d,  $J = 8.8$  Hz, 1H; *galacto*  $\beta$ -nitrate);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  170.3, 170.2, 169.8, 157.2, 156.9, 156.8, 136.9, 136.4, 128.9, 128.9, 128.7, 128.7, 128.4, 128.4, 128.4, 128.1, 98.6, 98.5, 97.2, 73.8, 71.2, 70.6, 69.1, 68.4, 67.8, 67.6, 67.5, 67.2, 57.7, 57.3, 56.2, 52.5, 51.9, 51.3, 20.9, 20.9, 20.6, 16.8, 16.6, 16.5; IR (thin film) 3425, 3336, 3067, 3035, 2988, 2940, 2117, 1750, 1721, 1657, 1521, 1370, 1329, 1274, 1224, 1135, 1086, 1029, 824  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{19}\text{N}_5\text{O}_8$  ( $\text{M}+\text{H}$ )<sup>+</sup> 410.1312, found 410.1320  $m/z$ .



**3-*O*-Acetyl-2-azido-4-(benzyloxycarbonyl)amino-2,4,6-dideoxy- $\beta$ -D-galactopyranosyl trichloroacetimidate (10):** Nitrate **8** (402 mg, 0.982 mmol) dissolved in  $\text{CH}_3\text{CN}$  (9.82 mL) at 0  $^\circ\text{C}$  was treated with *p*-thiocresol (244 mg, 1.96 mmol). Then, DIPEA (172  $\mu\text{L}$ , 0.982 mmol) was added and the mixture was stirred for 1 h at 23  $^\circ\text{C}$ . The reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (30:70 to 50:50 EtOAc/hexanes) to furnish the lactol as a mixture of isomers as a white foamy solid (310 mg, 0.851 mmol) in 87% yield.

The lactol (80 mg, 0.220 mmol) was then added as a  $\text{CH}_2\text{Cl}_2$  (2.20 mL) solution to previously dried  $\text{K}_2\text{CO}_3$  (152 mg, 1.10 mmol). To this mixture was added  $\text{Cl}_3\text{CCN}$  (176  $\mu\text{L}$ , 1.76 mmol), and the mixture was stirred vigorously over 8 h at 23  $^\circ\text{C}$ . The mixture was then filtered over basic Celite with  $\text{CH}_2\text{Cl}_2$  and concentrated. The crude oil was then purified by column chromatography (25:75 to 30:70 to 40:60 EtOAc/hexanes) to yield imidate **10** (68 mg, 0.134 mmol) in 61% yield as an inseparable 1:10  $\alpha/\beta$  mixture. This compound has been previously synthesized,<sup>1</sup> and our characterization data were consistent with the previously reported data:  $[\alpha]_D^{20} = +6.3^\circ$  ( $c = 1.7$ ,  $\text{CHCl}_3$ );  $R_f = 0.41$  (40:60 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.77 (s, 1H), 7.39-7.29 (m,

5H), 5.63 (d,  $J$  = 8.4 Hz, 1H), 5.18 (d,  $J$  = 12.0 Hz, 1H), 5.13 (d,  $J$  = 9.6 Hz, 1H), 5.07 (d,  $J$  = 12.0 Hz, 1H), 4.82 (dd,  $J$  = 4.0, 6.4 Hz, 1H), 4.21 (dd,  $J$  = 3.2, 10.0 Hz, 1H), 3.91 (q,  $J$  = 6.4 Hz, 1H), 3.74 (dd,  $J$  = 8.8, 10.8 Hz, 1H), 2.01 (s, 3H), 1.27 (d,  $J$  = 6.4 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  170.4, 161.0, 156.8, 136.5, 128.9, 128.7, 128.5, 97.3, 90.7, 73.3, 71.0, 67.5, 52.2, 21.0, 16.9, 16.8; IR (thin film) 3436, 3343, 3067, 3031, 2984, 2940, 2115, 1746, 1720, 1678, 1513, 1297, 1270, 1227, 1053, 835, 797  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{20}^{35}\text{Cl}_3\text{N}_5\text{O}_6$  ( $\text{M}+\text{Na}$ ) $^+$  530.0377, found 530.0375  $m/z$ .

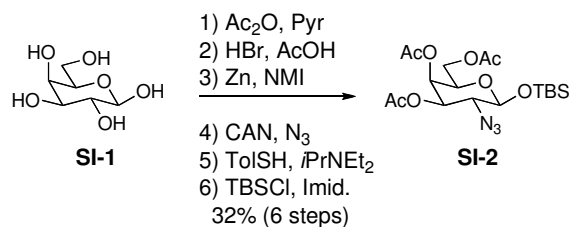


**3-*O*-Acetyl-2-azido-4-(benzyloxycarbonyl)amino-2,4,6-dideoxy-D-galactopyranosyl *N*-phenyltrifluoroacetimidate (2):** Nitrate **8** was converted to the lactol in the same way as for the synthesis of the trichloroimidate (**10**).

The lactol (250 mg, 0.69 mmol) in  $\text{CH}_2\text{Cl}_2$  (6.86 mL) at 0  $^\circ\text{C}$  was treated with  $\text{F}_3\text{CC}(\text{NPh})\text{Cl}$  (425 mg, 2.09 mmol) and then,  $\text{Cs}_2\text{CO}_3$  (447 mg, 1.37 mmol). The mixture was warmed to 23  $^\circ\text{C}$  and stirred for 4 h. The mixture was then diluted with cyclohexanes, filtered over Celite, and concentrated. The crude oil was then purified by column chromatography (15:85 to 35:65 EtOAc/hexanes) to yield *N*-phenyl trifluoroimidate **2** (291 mg, 0.543 mmol) in 79% yield as a foamy white solid and as a 2:1 mixture of  $\alpha/\beta$  anomers:  $[\alpha]_{\text{D}}^{20} = +50.2^\circ$  ( $c = 1.7$ ,  $\text{CHCl}_3$ );  $R_f = 0.37$  and  $0.49$  (50:50 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\alpha$ -anomer:  $\delta$  7.40-7.29 (m, 7H), 7.18-7.11 (m, 1H), 6.85 (d,  $J$  = 7.6 Hz, 2H), 5.21-5.03 (m, 3H) 5.15 (d,  $J$  = 4.4 Hz, 1H), 4.82-4.73 (m, 1H), 4.20-4.14 (m, 1H), 3.80-3.60 (m, 2H), 2.00 (s, 3H), 1.24 (d,  $J$  = 6.4 Hz, 3H);  $\beta$ -anomer:  $\delta$  7.40-7.29 (m, 7H), 7.18-7.11 (m, 1H), 6.85 (d,  $J$  = 7.6 Hz, 2H), 5.74 (d,  $J$  = 10.4 Hz, 1H), 5.51 (bs, 1H), 5.21-5.03 (m, 2H), 5.00-4.94 (m, 1H), 4.37-4.32 (m, 1H), 4.20-4.14 (m, 1H), 4.09-4.03 (m, 1H), 2.03 (s, 3H), 1.30-1.20 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  170.4, 170.2, 157.3, 156.8, 143.3, 143.2, 137.0, 136.5, 129.2, 129.2, 128.9, 128.9, 128.8, 128.7, 128.5, 128.4, 128.4, 128.1, 125.1, 125.0, 119.6, 119.5, 96.0, 94.9, 73.2, 72.7, 71.1, 68.8, 67.5, 67.2, 60.4, 60.2, 52.1, 51.1, 21.0, 20.9, 16.7, 16.7; IR (thin



film) 3417, 3351, 3063, 3035, 2984, 2939, 2116, 1718, 1597, 1514, 1454, 1315, 1211, 1163, 1074, 1040, 1029, 906, 777, 752, 696  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{24}\text{F}_3\text{N}_5\text{O}_6$  ( $\text{M}+\text{Na}$ )<sup>+</sup> 558.1576, found 558.1575  $m/z$ .



***tert*-Butyldimethylsilyl 3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy- $\beta$ -D-galactopyranoside (SI-2):** The first four steps were run according to Kihlberg's procedure.<sup>2</sup> Galactose **SI-1** (20.0 g, 111 mmol) was dissolved in  $\text{Ac}_2\text{O}$  (100 mL, 1060 mmol) and pyridine (100 mL, 1236 mmol) and stirred for 12 h. The mixture was concentrated and then, the remaining pyridine was azeotroped off with toluene (3 x 100 mL) and placed on high vacuum to afford 46 g of the crude acetate.

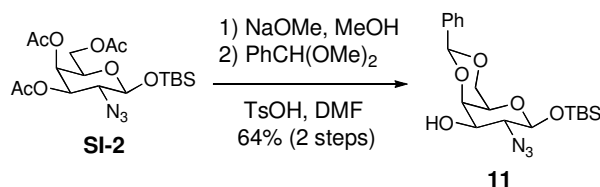
The crude acetate and  $\text{Ac}_2\text{O}$  (5.24 mL, 55.5 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (111 mL) at 0  $^\circ\text{C}$  was then, treated with 33% HBr in AcOH (91 mL, 555 mmol). The mixture was allowed to warm to room temperature and stirred for 3 h. Then, the mixture was diluted in  $\text{CH}_2\text{Cl}_2$  (150 mL) and poured into ice-cold water (250 mL). The organic layer was then washed with ice cold sat. aq.  $\text{NaHCO}_3$  (4 x 200 mL), sat. aq. NaCl (1 x 200 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure to yield 46 g of the crude bromide.

A small amount of the crude bromide (~1.3 g) dissolved in EtOAc (2 mL) was added first to a refluxing mixture (100  $^\circ\text{C}$ ) of Zn (36.3 g, 554 mmol), NMI (8.84 mL, 111 mmol), and EtOAc (300 mL) that was being mechanically stirred. After stirring for 10 min., the rest of the crude acetate (~44.7 g) in EtOAc (68 mL) was added by slow dropwise addition. Following addition, the mixture was refluxed for an additional 30 min and cooled to room temperature. The solution was then decanted away from the excess zinc using EtOAc to rinse, and the organic layers were washed with  $\text{H}_2\text{O}$  (1 x 250 mL), sat. aq.  $\text{NaHCO}_3$  (2 x 250 mL), sat aq. NaCl (1 x 250 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure.

The crude glycal dissolved in CH<sub>3</sub>CN (370 mL) at –25 °C under mechanical stirring was treated with ceric ammonium nitrate (152 g, 277 mmol) followed by NaN<sub>3</sub> (9.0 g, 139 mmol). After vigorously stirring between –20 °C and –25 °C for 6 h, cold Et<sub>2</sub>O (400 mL) was added. The cold organic layer was washed with ice cold H<sub>2</sub>O (3 x 400 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to yield 30.5 g of crude material as a faint yellow foam.

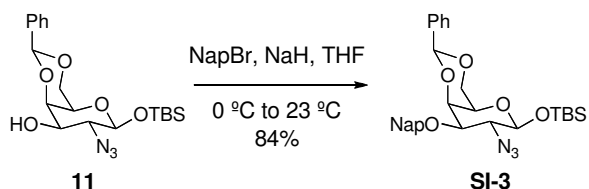
The crude nitrate dissolved in CH<sub>3</sub>CN (222 mL) at 0 °C was treated with *p*-thiocresol (16.5 g, 133 mmol). Then, DIPEA (8.59 g, 66.5 mmol) was added and the mixture was stirred for 1 h at 0 °C. The reaction was concentrated under reduced pressure. The crude product was run through a plug of silica gel (20:80 to 40:60 EtOAc/cyclohexane) to furnish 25.5 g of the crude lactol.

The crude lactol in CH<sub>2</sub>Cl<sub>2</sub> (222 mL) at 0 °C was treated with imidazole (9.05 g, 133 mmol) and then, TBSCl (11.7 g, 78 mmol). The mixture was then warmed to 23 °C and stirred for 3 h. Then, the mixture was quenched with sat. aq. NH<sub>4</sub>Cl (300 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL), and the organic layer was washed with water (3 x 200 mL), sat. aq. NaCl (1 x 200 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to give 34 g of crude material. The crude oil was purified by silica gel chromatography (10:90 to 20:80 EtOAc/cyclohexane) to provide TBS ether **SI-2** (14.6 g, 32.8 mmol) in 30% yield over 6 steps. Our characterization data were consistent with previously reported data.<sup>3</sup>



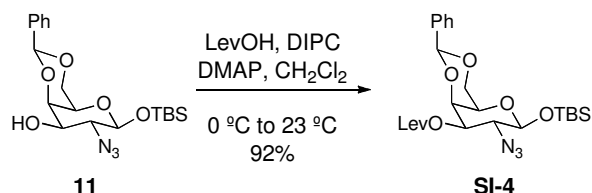
***tert*-Butyldimethylsilyl 2-Azido-4,6-benzylidene-2-deoxy-β-D-galactopyranoside (11):** The peracetylated **SI-2** (6 g, 13.47 mmol) was then dissolved in MeOH (80 mL), and a solution of NaOMe (15 mg, 0.27 mmol) in MeOH (10 mL) was slowly added to the mixture at 23 °C. The reaction was stirred overnight and subsequently, treated with IR+ 4 Amberlite Resin (~300 mg), filtered, and concentrated under reduced pressure. The crude material was coevaporated with chloroform (1 x 150 mL).

The crude triol in DMF (90 mL) was then treated with  $\text{PhCH(OMe)}_2$  (6.06 mL, 40.4 mmol) and then,  $\text{TsOH}\cdot\text{H}_2\text{O}$  (51 mg, 0.27 mmol). The solution was warmed to 50 °C, stirred for 4 h, and recooled to 23 °C. Then, the mixture was quenched with  $\text{NEt}_3$  (0.5 mL) and concentrated to a crude oil. The crude oil was purified by silica gel chromatography (20:80 to 30:70 EtOAc/cyclohexane) to afford alcohol **11** (3.5 g, 8.6 mmol) in 64% yield over 2 steps as a clear oil. Our characterization data were consistent with previously reported data.<sup>4</sup>

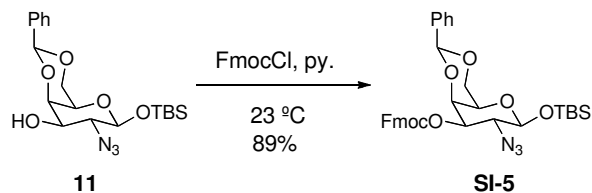


***tert*-Butyldimethylsilyl 2-Azido-4,6-benzylidene-2-deoxy-3-*O*-naphthyl- $\beta$ -D-galactopyranoside (SI-3):** Alcohol **11** (1.9 g, 4.66 mmol) in THF (23.3 mL) at 0 °C was treated with 60% NaH (261 mg, 6.53 mmol) and then, NapBr (1.08 g, 4.90 mmol). The mixture was allowed to warm to at 23 °C and stirred for 12 h. After diluting with  $\text{Et}_2\text{O}$  (100 mL) in an ice bath, the mixture was quenched with 100 mL  $\text{H}_2\text{O}$ . The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (2 x 50 mL), and the combined organic extracts were washed with sat. aq. NaCl (1 x 100 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The crude product was purified by flash chromatography (10:90 to 20:80 EtOAc/hexanes) to furnish naphthyl ether **SI-3** (2.15 g, 3.93 mmol) in 84% yield as a foamy white solid:  $[\alpha]_D^{20} = +3.7^\circ$  ( $c = 2.1$ ,  $\text{CHCl}_3$ );  $R_f = 0.57$  (40:60 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.88-7.77 (m, 4H), 7.58-7.55 (m, 3H), 7.52-7.47 (m, 2H), 7.43-7.35 (m, 3H), 5.46 (s, 1H), 4.93 (d,  $J = 12.4$  Hz, 1H), 4.89 (d,  $J = 12.4$  Hz, 1H), 4.52 (d,  $J = 7.6$  Hz, 1H), 4.23 (dd,  $J = 1.2, 12.4$  Hz, 1H), 4.07 (d,  $J = 3.2$  Hz, 1H), 3.97 (dd,  $J = 1.6, 12.4$  Hz, 1H), 3.82 (d,  $J = 8.0, 10.4$  Hz, 1H), 3.36 (d,  $J = 3.6, 10.4$  Hz, 1H), 3.24 (bs, 1H), 0.97 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  138.1, 135.7, 133.5, 133.4, 129.4, 128.6, 128.6, 128.2, 128.1, 126.9, 126.8, 126.5, 126.4, 126.1, 101.5, 97.7, 77.7, 73.0, 72.0, 69.6, 66.8, 64.9, 26.1, 18.4, -3.7, -4.5; IR (thin film) 3059, 2952, 2929, 2857, 2110, 1461, 1400, 1364, 1284, 1252, 1172, 1106,

1087, 1059, 996, 836, 819, 783, 756, 697  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_5\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$  570.2400, found 570.2393  $m/z$ .

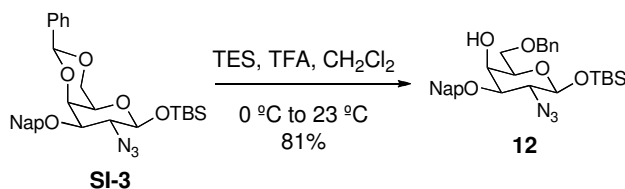


***tert*-Butyldimethylsilyl 2-Azido-4,6-benzylidene-2-deoxy-3-*O*-levulinoyl- $\beta$ -D-galactopyranoside (SI-4):** Alcohol **11** (551 mg, 1.35 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (6.7 mL) at 0  $^\circ\text{C}$  was treated with DMAP (248 mg, 2.03 mmol), DIPC (394  $\mu\text{L}$ , 2.03 mmol), and then, LevOH (235 mg, 2.03 mmol). The mixture was allowed to warm to 23  $^\circ\text{C}$  and then, stirred for 3 h. The mixture was diluted with 1:2 cyclohexane/EtOAc and run through a plug of silica gel. After concentrating the material, the crude product was purified by flash chromatography (30:70 to 40:60 EtOAc/hexanes) to furnish Lev protected **SI-4** (627 mg, 1.24 mmol) in 92% yield as a clear oil and as a inseparable 1:12  $\alpha/\beta$  isomer mixture:  $[\alpha]_{\text{D}}^{20} = +28.9^\circ$  ( $c = 2.1$ ,  $\text{CHCl}_3$ );  $R_f = 0.31$  (40:60 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.52 (d,  $J = 6.5$  Hz, 2H), 7.42-7.33 (m, 3H), 5.50 (s, 1H), 4.70 (dd,  $J = 3.5, 11.0$  Hz, 1H), 4.62 (d,  $J = 7.5$  Hz, 1H), 4.27-4.22 (m, 2H), 4.03 (d,  $J = 12.0$  Hz, 1H), 3.80 (dd,  $J = 7.5, 11.0$  Hz, 1H), 3.42 (s, 1H), 2.75 (t,  $J = 6.0$  Hz, 2H), 2.67-2.62 (m, 2H), 2.09 (s, 3H), 0.95 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  206.5, 172.4, 137.9, 129.4, 128.5, 126.6, 101.2, 97.6, 73.0, 72.1, 69.4, 66.6, 63.0, 38.2, 30.0, 28.4, 26.0, 18.3,  $-3.8$ ,  $-4.6$ ; IR (thin film) 2952, 2930, 2888, 2858, 2112, 1740, 1720, 1405, 1367, 1284, 1252, 1156, 1096, 1058, 1001, 837, 817, 783  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{35}\text{N}_3\text{O}_7\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$  528.2142, found 528.2136  $m/z$ .

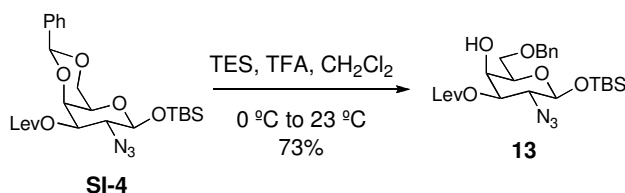


***tert*-Butyldimethylsilyl 2-Azido-4,6-benzylidene-2-deoxy-3-*O*-fluorenylmethoxy carbonyl- $\beta$ -D-galactopyranoside (SI-5):** Alcohol **11** (593 mg, 1.46 mmol) was treated with pyridine (7.3 mL) and then, FmocCl (753 mg, 2.91 mmol). The mixture was stirred for 2 h, concentrated, and then, co-evaporated with toluene (1 x 20 mL). The crude oil was diluted with EtOAc (100 mL), washed with H<sub>2</sub>O (2 x 100 mL), sat. aq. NaHCO<sub>3</sub> (1 x 100 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by flash chromatography (10:90 to 20:80 EtOAc/hexanes) to furnish Fmoc **SI-5** (820 mg, 1.30 mmol) in 89% yield as a foamy white solid:  $[\alpha]_D^{20} = +17.1^\circ$  ( $c = 2.8$ , CHCl<sub>3</sub>);  $R_f = 0.57$  (40:60 EtOAc/cyclohexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.78 (t,  $J = 6.5$  Hz, 2H), 7.64 (d,  $J = 7.0$  Hz, 2H), 7.60-7.57 (m, 2H), 7.46-7.39 (m, 5H), 7.32-7.27 (m, 2H), 5.55 (s, 1H), 4.68 (dd,  $J = 2.0, 7.5$  Hz, 1H), 4.58 (dt,  $J = 3.0, 11.0$  Hz, 1H), 4.51-4.46 (m, 2H), 4.37-4.27 (m, 3H), 4.06 (d,  $J = 12.5$  Hz, 1H), 3.95 (ddd,  $J = 3.5, 7.5, 11.0$  Hz, 1H), 3.44 (s, 1H), 1.05 (m, 9H), 0.27-0.20 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta$  154.7, 143.5, 143.4, 141.6, 141.5, 137.8, 129.4, 128.5, 128.2, 127.5, 127.5, 126.6, 125.5, 125.5, 120.4, 101.1, 97.7, 75.6, 72.7, 70.6, 69.3, 66.5, 63.0, 46.9, 26.0, 18.3, -3.8, -4.6; IR (thin film) 3067, 3039, 3019, 2954, 2930, 2884, 2857, 2113, 1746, 1451, 1389, 1367, 1255, 1174, 1092, 1057, 996, 984, 836, 820, 784, 757, 739 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>34</sub>H<sub>39</sub>N<sub>3</sub>O<sub>7</sub>Si (M+Na)<sup>+</sup> 652.2455, found 652.2474  $m/z$ .

**General Procedure for the Benzylidene Reduction to Synthesize Alcohols 12, 13, and 14:** The benzylidene compound (1 equiv) and TES (6 equiv) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) at 0 °C was treated TFA (6 equiv), dropwise. The mixture was allowed to warm to 23 °C and stirred for 3 h. The solution was quenched with sat. aq. NaHCO<sub>3</sub> (1 x) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x). The combined organic layers were washed with sat. aq. NaHCO<sub>3</sub> (1 x), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by flash chromatography.

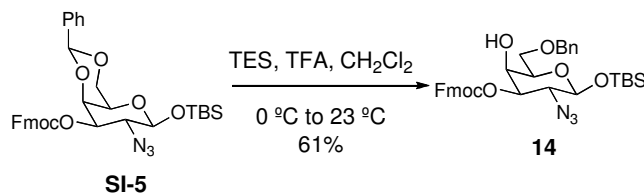


***tert*-Butyldimethylsilyl 2-Azido-6-*O*-benzyl-2-deoxy-3-*O*-naphthyl-β-D-galactopyranoside (12):** Nap **SI-3** (1.8 g, 3.29 mmol) furnished alcohol **12** (1.46 g, 2.66 mmol) in 81% yield (10:90 to 20:80 EtOAc/hexanes) as a solid:  $[\alpha]_D^{20} = -28.9^\circ$  ( $c = 1.8$ ,  $\text{CHCl}_3$ );  $R_f = 0.57$  (40:60 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.90-7.82 (m, 4H), 7.57-7.48 (m, 3H), 7.38-7.27 (m, 5H), 4.90 (d,  $J = 12.0$  Hz, 1H), 4.86 (d,  $J = 12.0$  Hz, 1H), 4.58 (s, 2H), 4.46 (d,  $J = 7.6$  Hz, 1H), 4.02 (d,  $J = 4.0$  Hz, 1H), 3.80 (dd,  $J = 6.0$ , 10.0 Hz, 1H), 3.71 (dd,  $J = 6.0$ , 10.0 Hz, 1H), 3.63 (dd,  $J = 7.6$ , 10.0 Hz, 1H), 3.51 (dd,  $J = 6.0$ , 6.0 Hz, 1H), 3.30 (dd,  $J = 3.2$ , 10.4 Hz, 1H), 2.58 (bs, 1H), 0.96 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  138.2, 135.1, 133.5, 133.5, 128.8, 128.7, 128.3, 128.1, 128.1, 128.0, 127.2, 126.6, 126.5, 126.1, 97.7, 79.0, 74.0, 73.6, 72.5, 69.6, 66.2, 65.6, 26.0, 18.3,  $-3.8$ ,  $-4.9$ ; IR (thin film) 3473, 3059, 3031, 2952, 2929, 2884, 2858, 2110, 1471, 1462, 1454, 1391, 1365, 1282, 1253, 1100, 1071, 837, 818, 783, 751  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{30}\text{H}_{39}\text{N}_3\text{O}_5\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$  572.2557, found 572.2536  $m/z$ .



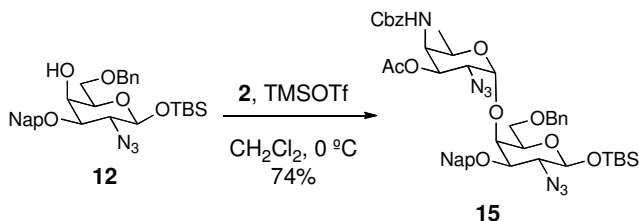
***tert*-Butyldimethylsilyl 2-Azido-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-β-D-galactopyranoside (13):** Lev **SI-4** (560 mg, 1.11 mmol) gave alcohol **13** (408 mg, 0.80 mmol) in 73% yield (30:70 to 40:60 EtOAc/hexanes) as a clear oil and as an inseparable 1:12  $\alpha/\beta$  isomer mixture:  $[\alpha]_D^{20} = +10.1^\circ$  ( $c = 1.5$ ,  $\text{CHCl}_3$ );  $R_f = 0.31$  (40:60 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.33-7.24 (m, 5H), 4.58 (dd,  $J = 3.0$ , 11.0 Hz, 1H), 4.55-4.52 (m, 3H), 4.08 (d,  $J = 3.0$  Hz, 1H), 3.77-3.66 (m, 3H), 3.60 (t,  $J = 5.0$  Hz, 1H), 3.24 (bs, 1H), 2.87-2.72 (m, 2H), 2.68-2.52 (m, 2H), 2.16 (s, 3H), 0.93 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  207.9, 172.2, 138.0, 128.6, 127.9, 127.8, 97.7, 74.1, 73.8, 73.5, 69.7, 66.7, 63.4, 38.5, 30.0, 28.4, 25.8, 18.2,

−4.0, −5.0; IR (thin film) 3470, 2948, 2930, 2858, 2113, 1740, 1718, 1363, 1254, 1153, 1072, 838, 784, 751  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{37}\text{N}_3\text{O}_7\text{Si}$  ( $\text{M}+\text{Na}$ ) $^{+}$  530.2298, found 530.2243  $m/z$ .

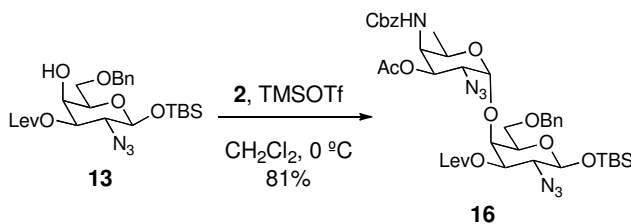


***tert*-Butyldimethylsilyl 2-Azido-6-*O*-benzyl-2-deoxy-3-*O*-fluorenylmethoxy carbonyl- $\beta$ -D-galactopyranoside (**14**):** Fmoc **SI-5** (750 mg, 1.19 mmol) afforded alcohol **14** (457 mg, 0.72 mmol) in 61% yield (10:90 to 15:85 EtOAc/hexanes) as a foamy solid:  $[\alpha]_{\text{D}}^{20} = -0.7^{\circ}$  ( $c = 2.2$ ,  $\text{CHCl}_3$ );  $R_f = 0.57$  (40:60 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.79 (d,  $J = 7.5$  Hz, 2H), 7.66 (dd,  $J = 7.0$  Hz, 2H), 7.43 (dd,  $J = 7.5$ , 7.5 Hz, 2H), 7.40–7.30 (m, 7H), 4.60 (s, 1H), 4.59 (s, 2H), 4.56–4.49 (m, 2H), 4.46 (dd,  $J = 7.0$ , 10.5 Hz, 1H), 4.31 (dd,  $J = 7.0$ , 7.0 Hz, 1H), 4.16 (s, 1H), 3.83–3.76 (m, 2H), 3.73 (dd,  $J = 5.0$ , 10.0 Hz, 1H), 3.61 (dd,  $J = 10.0$ , 10.0 Hz, 1H), 2.76 (s, 1H), 0.98 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  154.4, 143.3, 143.3, 141.4, 141.4, 137.6, 128.6, 128.1, 128.0, 127.8, 127.4, 127.3, 125.4, 125.3, 120.2, 120.2, 97.8, 77.1, 73.9, 72.9, 70.4, 69.5, 67.2, 63.4, 46.8, 25.7, 18.1, −4.1, −5.0; IR (thin film) 3472, 3065, 3035, 2952, 2930, 2858, 2114, 1749, 1451, 1390, 1258, 1102, 1072, 982, 838, 784, 758, 739  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{34}\text{H}_{41}\text{N}_3\text{O}_7\text{Si}$  ( $\text{M}+\text{Na}$ ) $^{+}$  654.2611, found 654.2605  $m/z$ .

**Optimized Procedure for the  $\alpha$ -Selective Glycosylation between Building Block 2 and Alcohols **12**, **13**, and **14**:** The glycosylating agent (1.5 equiv) and nucleophile (1 equiv) were coevaporated with toluene (3 x), and dried by high vacuum for 1 h. The mixture was then dissolved in  $\text{CH}_2\text{Cl}_2$  (0.02 M) and was cooled to 0  $^{\circ}\text{C}$ . After treatment with a  $\text{CH}_2\text{Cl}_2$  solution of TMSOTf (0.1 equiv), the mixture was stirred at 0  $^{\circ}\text{C}$  for 1 h. The mixture was then quenched with pyridine and concentrated under reduced pressure. The crude disaccharide was purified by flash chromatography.



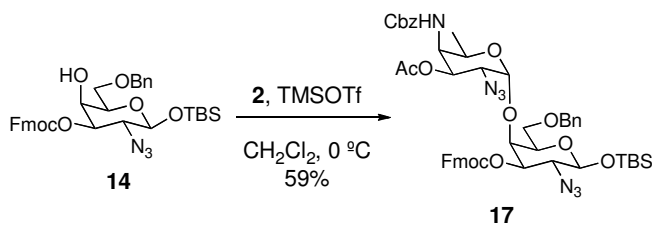
***tert*-Butyldimethylsilyl 2-Azido-6-*O*-benzyl-2-deoxy-3-*O*-naphthyl- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-3-*O*-acetyl-2-azido-4-(benzyloxycarbonyl)amino-2,4,6-dideoxy- $\alpha$ -D-galactopyranoside (15):** Building block **2** (58.4 mg, 0.109 mmol) and nucleophile **12** (40 mg, 0.073 mmol) gave disaccharide **15** (48.2 mg, 0.054 mmol) in 74% yield (15:85 to 20:80 EtOAc/hexanes):  $[\alpha]_D^{20} = +95.8^\circ$  ( $c = 1.6$ ,  $\text{CHCl}_3$ );  $R_f = 0.19$  (20:80 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.87-7.81 (m, 4H), 7.54-7.46 (m, 3H), 7.40-7.28 (m, 10H), 5.30 (dd,  $J = 3.6, 11.2$  Hz, 1H), 5.15 (d,  $J = 12.4$  Hz, 1H), 5.03 (d,  $J = 12.4$  Hz, 1H), 4.93 (d,  $J = 12.4$  Hz, 1H), 4.91 (d,  $J = 3.6$  Hz, 1H), 4.83 (d,  $J = 12.4$  Hz, 1H), 4.69 (q,  $J = 6.4$  Hz, 1H), 4.52 (d,  $J = 12.0$  Hz, 1H), 4.49 (d,  $J = 12.0$  Hz, 1H), 4.41 (d,  $J = 7.6$  Hz, 1H), 4.18 (dd,  $J = 2.0, 9.6$  Hz, 1H), 4.09 (d,  $J = 2.8$  Hz, 1H), 3.91 (t,  $J = 9.2$  Hz, 1H), 3.66 (dd,  $J = 7.6, 10.4$  Hz, 1H), 3.54 (dd,  $J = 5.6, 9.2$  Hz, 1H), 3.44 (dd,  $J = 5.6, 9.2$  Hz, 1H), 3.31 (dd,  $J = 4.0, 11.2$  Hz, 1H), 3.18 (dd,  $J = 2.8, 10.8$  Hz, 1H), 2.01 (s, 3H), 0.91 (s, 9H), 0.84 (d,  $J = 6.0$  Hz, 1H), 0.11 (s, 3H), 0.11 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  170.6, 156.9, 137.9, 136.7, 135.4, 133.5, 133.4, 128.9, 128.9, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 126.9, 126.6, 126.4, 125.9, 99.1, 98.0, 78.3, 73.8, 73.1, 70.2, 67.4, 67.3, 65.8, 65.1, 58.2, 53.1, 26.0, 21.2, 18.3, 16.6, -3.9, -4.7; IR (thin film) 3343, 3061, 3032, 2930, 2858, 2110, 1752, 1711, 1509, 1342, 1273, 1256, 1226, 1154, 1116, 1095, 1079, 1034, 840, 820, 782, 750, 698  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{46}\text{H}_{57}\text{N}_7\text{O}_{10}\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$  918.3834, found 918.3858  $m/z$ .



***tert*-Butyldimethylsilyl 2-Azido-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-3-*O*-acetyl-2-azido-4-(benzyloxycarbonyl)amino-2,4,6-dideoxy- $\alpha$ -**



**D-galactopyranoside (16):** Building block **2** (49 mg, 0.092 mmol) and nucleophile **13** (31 mg, 0.061 mmol) afforded disaccharide **16** (42.2 mg, 0.050 mmol) in 81% yield (30:70 to 40:60 EtOAc/hexanes) and as a 1:12  $\alpha/\beta$  isomer mixture (for the galactosamine anomeric position; could not be separated by normal flash chromatography):  $[\alpha]_D^{20} = +82.5^\circ$  ( $c = 0.9$ ,  $\text{CHCl}_3$ );  $R_f = 0.13$  (30:70 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.39-7.27 (m, 10H), 5.27 (dd,  $J = 3.6, 11.2$  Hz, 1H), 5.18 (d,  $J = 12.4$  Hz, 1H), 5.07 (d,  $J = 12.4$  Hz, 1H), 4.95 (d,  $J = 9.6$  Hz, 1H), 4.88 (d,  $J = 3.6$  Hz, 1H), 4.75 (dd,  $J = 2.8, 11.2$  Hz, 1H), 4.55 (d,  $J = 7.6$  Hz, 1H), 4.54 (d,  $J = 12.4$  Hz, 1H), 4.47 (d,  $J = 12.0$  Hz, 1H), 4.28 (dd,  $J = 2.0, 9.6$  Hz, 1H), 4.09 (d,  $J = 2.8$  Hz, 1H), 3.86 (t,  $J = 8.8$  Hz, 1H), 3.62 (q,  $J = 7.2$ , 1H), 3.60-3.54 (m, 1H), 3.32 (dd,  $J = 4.0, 11.2$  Hz, 1H), 2.90-2.80 (m, 1H), 2.88-2.55 (m, 3H), 2.20 (s, 3H), 2.01 (s, 3H), 1.20 (d,  $J = 6.4$  Hz, 1H), 0.91 (s, 9H), 0.13 (s, 3H), 0.13 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  206.3, 172.4, 170.6, 156.9, 137.8, 136.7, 128.9, 128.8, 128.6, 128.3, 128.2, 128.2, 98.7, 98.0, 73.7, 73.6, 73.3, 72.4, 70.1, 67.4, 67.4, 65.1, 64.0, 58.1, 53.0, 38.1, 30.1, 28.3, 25.9, 25.9, 21.1, 18.2, 17.0, -3.9, -4.8; IR (thin film) 3356, 3065, 3032, 2954, 2932, 2858, 2112, 1747, 1720, 1524, 1365, 1227, 1152, 1117, 1076, 1044, 840, 784, 750, 740, 698  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{40}\text{H}_{55}\text{N}_7\text{O}_{12}\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$  876.3576, found 876.3568  $m/z$ .



***tert*-Butyldimethylsilyl**      **2-Azido-6-*O*-benzyl-2-deoxy-3-*O*-fluorenylmethoxy**  
**carbonyl- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-3-*O*-acetyl-2-azido-4-(benzyloxycarbonyl)**

**amino-2,4,6-dideoxy- $\alpha$ -D-galactopyranoside (17):** Building block **2** (36.9 mg, 0.069 mmol) and nucleophile **14** (29 mg, 0.046 mmol) furnished disaccharide **17** (26.5 mg, 0.027 mmol) in 59% yield (15:85 to 20:80 EtOAc/hexanes):  $[\alpha]_D^{20} = +94.9^\circ$  ( $c = 0.6$ ,  $\text{CHCl}_3$ );  $R_f = 0.42$  (30:70 EtOAc/cyclohexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.76 (d,  $J = 7.6$  Hz, 2H), 7.61 (dd,  $J = 7.6, 11.2$  Hz, 2H), 7.43-7.27 (m, 14H), 5.26 (dd,  $J = 3.6, 11.2$  Hz, 1H), 5.18 (d,  $J = 12.4$  Hz, 1H), 5.07 (d,  $J = 12.4$  Hz, 1H), 4.88 (d,  $J = 9.2$  Hz, 1H), 4.75

(d,  $J$  = 4.0 Hz, 1H), 4.63 (dd,  $J$  = 6.8, 10.4 Hz, 1H), 4.58-4.46 (m, 3H), 4.41 (dd,  $J$  = 6.8, 10.4 Hz, 1H), 4.24 (t,  $J$  = 6.8 Hz, 1H), 4.09 (d,  $J$  = 2.8 Hz, 1H), 3.91 (t,  $J$  = 8.4 Hz, 1H), 3.68 (dd,  $J$  = 7.2, 11.2 Hz, 1H), 3.63-3.54 (m, 2H), 3.31 (dd,  $J$  = 4.0, 11.2 Hz, 1H), 2.02 (s, 3H), 0.95 (d,  $J$  = 6.4 Hz, 1H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  170.7, 156.9, 154.9, 143.5, 143.2, 141.7, 141.7, 137.8, 136.7, 128.9, 128.9, 128.6, 128.4, 128.3, 128.2, 127.6, 127.6, 125.4, 125.3, 120.5, 120.4, 99.2, 98.1, 76.0, 73.8, 73.7, 73.0, 70.3, 70.3, 67.4, 67.1, 65.3, 63.7, 58.1, 53.1, 47.1, 25.9, 21.2, 18.3, 16.4, -3.9, -4.8; IR (thin film) 3358, 3065, 3032, 2954, 2931, 2884, 2860, 2112, 1750, 1727, 1505, 1452, 1258, 1158, 1115, 1079, 1037, 982, 840, 784, 740, 698  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{50}\text{H}_{59}\text{N}_7\text{O}_{12}\text{Si}$  ( $\text{M}+\text{Na}$ ) $^{+}$  1000.3889, found 1000.3882  $m/z$ .

---

## References

1. Smid, P.; Jörning, W. P. A.; van Duuren, A. M. G.; Boons, G. J. R. H.; van der Marel, G. A.; van Boom, J. H. *J. Carbohydr. Chem.* **1992**, *11*, 849.
2. Broddefalk, J.; Nilsson, U.; Kihlberg, J. *J. Carbohydr. Chem.* **1994**, *13*, 129.
3. Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244.
4. Grundler, G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1984**, *13*, 1826.