Synthesis of a Six-Carbon Sialic Acid Using an Indium-Mediated Coupling

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Supporting Information

Methyl (*S*)-3-(4-methoxyphenyl)methoxy-2-(*N*-phenylmethoxycarbonyl)aminopropanoate (8). A solution of compound **7** (3.42 g, 13.5 mmol) in CH_2Cl_2 (115 mL) was treated with a solution of *para*-methoxybenzyl trichloroacetimidate (5.50 g, 20.3 mmol dissolved in 20 mL CH_2Cl_2). The reaction mixture was cooled to -78 °C for 45 min followed by the addition of TMSOTf (0.24 mL, 1.3 mmol). The reaction mixture was stirred for 75 min and then quenched with saturated $NaHCO_3$ (5.0 mL), after which it was warmed to rt and washed with saturated $NaHCO_3$ (1 100 mL) and then water (2 × 100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to provide a crude yellow syrup, which was purified by flash chromatography (hexanes:EtOAc 3:1) to afford compound **8** (4.07 g, 81%) as a clear syrup. $[\alpha]^{25}_D$ +11.4 (c 1.2, $CHCl_3$); IR (thin film) 3346, 3033, 2953, 1725, 1612, 1586 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5 H), 7.16 (d, 2 H, *J* = 8.7 Hz), 6.89 (d, 2 H, *J* = 8.5 Hz), 5.59 (d, 1 H, *J* = 8.7 Hz), 5.10 (s, 2 H), 4.48-4.43 (m, 2 H, H-2), 4.39 (d, 1 H, *J* = 11.7 Hz), 3.84 (dd, 1 H, *J* = 3.2, 9.5 Hz), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.65 (dd, 1 H, *J* = 3.2, 9.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ

170.8, 159.3, 155.9, 136.2, 129.4, 129.2, 128.4, 128.1, 128.0, 113.7, 72.8, 69.3, 66.9, 55.2, 54.3, 52.4; HRMS (EI) calcd for $C_{20}H_{23}NO_6$ (M^+) 373.1525, found 373.1534.

(*S*)-3-(4-methoxyphenyl)methoxy-2-(*N*-Phenylmethoxycarbonyl)amino-1-propanol (9). A solution of compound **8** (3.69 g, 9.88 mmol) in Et_2O (100 mL) was treated with $LiBH_4$ (0.32 g, 14.8 mmol) and CH_3OH (0.62 mL, 15.3 mmol). The reaction mixture was heated to reflux for 15 min, cooled to rt, and quenched with saturated NH_4Cl (5.0 mL). The reaction was diluted with EtOAc (100 mL) and washed with water (2 × 100 mL) and brine (1 × 100 mL), successively. The solution was dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting crude syrup was purified by flash chromatography (hexanes:EtOAc 3:2 → 2:1) to give compound **9** (3.02 g, 88%) as a clear syrup. $[\alpha]^{25}_D$ +13.0 (c 0.8, $CHCl_3$); IR (thin film) 3408, 3033, 2953, 1700, 1612, 1586 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5 H), 7.22-7.18 (m, 2 H), 6.87-6.84 (m, 2 H), 5.47 (d, 1 H, *J* = 7.2 Hz), 4.43 (d, 1 H, *J* = 11.5 Hz), 4.41 (d, 1 H, *J* = 11.5 Hz), 3.87-3.80 (m, 1 H), 3.80-3.73 (m, 4 H), 3.66 (dd, 1 H, *J* = 4.6, 11.1 Hz), 3.62-3.53 (m, 2 H), 2.50 (br s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 156.4, 136.3, 129.5, 129.3, 128.4, 128.0, 128.0, 113.8, 73.0, 70.0, 66.8, 63.4, 55.2, 51.9; HRMS (EI) calcd for $C_{19}H_{23}NO_5$ (M^+) 345.1576, found 375.1564.

(*S*)-2-(*N*-Benzyloxycarbonyl)amino-3-(4-methoxyphenyl)methoxypropanal (10). A solution of compound **9** (2.67 g, 7.74 mmol) in CH_2Cl_2 (79 mL) was treated with Dess-Martin periodinane (3.63 g, 8.56 mmol). The reaction mixture was stirred at rt for 3 h, after which it was concentrated to a volume of approximately 3 mL and purified by flash chromatography (hexanes:EtOAc 3:1 → 2:1) to afford compound **9** (2.48 g, 93%) as a clear syrup. $[\alpha]^{25}_D$ +28.1 (c 0.8, $CHCl_3$); IR (thin film) 3334, 3033, 2934, 1716, 1612, 1586 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1 H), 7.38-7.29 (m, 5 H), 7.18-7.15 (m, 2 H), 6.87-6.83 (m, 2 H), 5.61 (d, 1 H, *J* = 7.4 Hz), 5.18 (s, 2 H), 4.43 (d, 1 H, *J* = 11.7 Hz), 4.41 (d, 1 H, *J* = 11.5 Hz), 4.37-4.33 (m, 1

H), 3.97 (dd, 1 H, J = 3.0, 9.7 Hz), 3.78 (s, 3 H), 3.68 (dd, 1 H, J = 4.2, 9.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5, 159.4, 156.1, 136.0, 129.3, 129.1, 128.5, 128.2, 128.1, 113.8, 73.2, 67.1, 67.1, 60.3, 55.2; HRMS (CI) calcd for $C_{19}H_{22}NO_5$ (M - H^+) 342.1342, found 342.1333.

Indium-Mediated Allyl Addition. A solution of compound **10** (2.31 g, 6.73 mmol) in 1:1 THF:H_2O (68 mL) was treated with methyl (bromomethyl)acrylate **11** (0.98 mL, 8.15 mmol) and indium (0.850 g, 7.40 mmol). The reaction mixture was stirred for 4.5 h and then filtered through Celite. The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude syrup was purified by flash chromatography (hexanes:EtOAc 3:1 → 3:2 hexanes:EtOAc) to give compound **12** (1.52 g, 51%) as a white solid and compound **13** (1.10 g, 37%) also as a white solid.

Methyl 2-((2*S*,3*S*)-2-hydroxy-4-(4-methoxyphenyl)methoxy-3-(*N*-phenylmethoxycarbonyl)amino)butylpropenoate (12). $[\alpha]^{25}_D$ +4.5 (c 1.1, $CHCl_3$); IR (thin film) 3424, 2952, 1718, 1630, 1612 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5 H), 7.20-7.16 (m, 2 H), 6.85-6.82 (m, 2 H), 6.22 (s, 1 H), 5.64 (s, 1 H), 5.44 (d, 1 H, J = 9.1 Hz), 5.09 (s, 2 H), 4.43 (d, 1 H, J = 11.5 Hz), 4.40 (d, 1 H, J = 11.3 Hz), 4.09-4.06 (m, 1 H), 3.79-3.77 (m, 4 H, H-4), 3.72 (s, 3 H), 3.65-3.60 (m, 2 H), 3.27 (d, 1 H, J = 1.8 Hz), 2.51-2.46 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 159.3, 156.4, 136.6, 136.4, 129.4, 129.3, 128.5, 128.4, 128.1, 128.0, 113.8, 73.2, 72.0, 70.9, 66.8, 55.2, 53.0, 52.0, 37.1; HRMS (CI) calcd for $C_{24}H_{30}NO_7$ (M + H^+) 444.2022, found 444.2016.

Methyl 2-((2*R*,3*S*)-2-hydroxy-4-(4-methoxyphenyl)methoxy-3-(*N*-phenylmethoxycarbonyl)amino)butylpropenoate (13). $[\alpha]^{25}_D$ +16.4 (c 0.2, $CHCl_3$); IR (thin film) 3354, 2950, 1715, 1612 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.29 (m, 5 H), 7.22-7.19 (m, 2 H), 6.87-6.83 (m, 2 H), 6.23 (s, 1 H), 5.64 (s, 1 H), 5.48 (d, 1 H, J = 8.5 Hz), 5.08 (s, 2 H),

4.44 (d, 1 H, J = 11.5 Hz), 4.40 (d, 1 H, J = 11.5 Hz), 3.84-3.78 (m, 5 H), 3.74-3.71 (m, 4 H), 3.60 (dd, 1 H, J = 3.0), 3.12 (d, 1 H, J = 7.2 Hz), 2.58 (dd, 1 H, J = 3.6, 14.3 Hz), 2.38 (dd, 1 H, J = 9.1, 14.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 159.4, 156.2, 136.8, 136.4, 129.4, 128.5, 128.1, 128.0, 113.9, 73.2, 72.0, 69.3, 66.8, 55.2, 54.0, 52.0, 37.1; HRMS (CI) calcd for $C_{24}H_{30}NO_7$ (M + H^+) 444.2022, found 444.2023.

Methyl 2-((2*S*,3*S*)-2-benzoyloxy-4-(4-methoxyphenyl)methoxy-3-(*N*-phenylmethoxycarbonyl)amino)butylpropenoate (14).

By acylation of *Syn* Diastereomer 12. A solution of compound **12** (1.36 g, 3.07 mmol) in CH_2Cl_2 (31 mL) was treated with Et_3N (0.92 mL, 6.60 mmol), Bz_2O (0.766 g, 3.38 mmol), and 4-dimethylaminopyridine (0.0380g, 0.311 mmol), successively. The reaction mixture was stirred for 24 h and then washed with saturated $NaHCO_3$ (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude syrup was purified by flash chromatography (hexanes:EtOAc 3:1) to provide compound **14** (1.20 g, 71%) as a clear oil.

By Mitsunobu Inversion of *Anti* Diastereomer 13. A solution of **13** (0.0286 g, 0.0648 mmol) in THF (1.5 mL) was treated with $PhCO_2H$ (0.0200 g, 0.164 mmol) and then PPh_3 (0.0514 g, 0.196 mmol). The solution was cooled to –23 °C for 15 min and then di-*tert*-butylazodicarboxylate (0.0540 g, 0.234 mmol) was added. The reaction mixture was stirred at -23 °C for 3 h, warmed to rt, and stirred overnight. To the reaction mixture was added an additional $PhCO_2H$ (0.0200 g, 0.164 mmol) and PPh_3 (0.0520 g, 0.198 mmol). The solution was again cooled to –23 °C and di-*tert*-butylazodicarboxylate (0.0520 g, 0.226 mmol) was added. The solution was stirred at -23 °C for 3 h, warmed to rt, and stirred for an additional 6 h. The reaction mixture was washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL), after which the solution was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude syrup was purified by flash chromatography (hexanes:EtOAc 4:1 → 2:1) to afford compound **14**

(0.0226 g, 64%) as a clear syrup. $[\alpha]^{25}_D$ -15.2 (c 1.4, $CHCl_3$); IR (thin film) 3349, 3032, 2951, 1722, 1630 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, 2 H, *J* = 7.3 Hz), 7.53 (t, 1 H, *J* = 7.3 Hz), 7.38 (t, 2 H, *J* = 7.8 Hz), 7.34-7.26 (m, 5 H), 7.15-7.09 (m, 2 H), 6.76-6.72 (m, 2 H), 6.16 (s, 1 H), 5.64-5.58 (m, 2 H), 5.18 (d, 1 H, *J* = 9.7 Hz), 5.06 (d, 1 H, *J* = 12.3 Hz), 5.03 (d, 1 H, *J* = 12.1 Hz), 4.37 (s, 2 H), 4.18-4.12 (m, 1 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.55 (dd, 1 H, *J* = 4.4, 9.5 Hz), 3.46 (dd, 1 H, *J* = 5.8, 9.5 Hz), 2.79 (dd, 1 H, *J* = 4.0, 14.1 Hz), 2.68 (dd, 1 H, *J* = 8.9, 14.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 165.7, 159.0, 156.2, 136.2, 135.7, 132.9, 129.8, 129.6, 129.6, 129.3, 128.5, 128.3, 128.1, 128.1, 113.6, 72.9, 72.0, 69.3, 66.9, 55.1, 53.1, 52.0, 34.5; HRMS (EI) calcd for $C_{31}H_{34}NO_8$ (M + H^+) 548.2284, found 548.2276.

Methyl 2-((2*S*,3*S*)-2-benzoyloxy-4-hydroxy-3-(*N*-phenylmethoxycarbonyl)amino)butylpropenoate (15). A solution of compound **14** (1.19 g, 2.17 mmol) in 18:1 CH_2Cl_2:H_2O (19 mL) was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (0.742 g, 3.27 mmol). The reaction mixture was stirred for 1.5 h, after which it was washed with saturated $NaHCO_3$ (2 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude syrup was purified by flash chromatography (hexanes: EtOAc 3:2) to give compound **15** (0.820 g, 88%) as a clear syrup. $[\alpha]^{25}_D$ -59.3 (c 1.3, $CHCl_3$); IR (thin film) 3355, 3033, 2952, 1721, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2 H), 7.56 (t, 1 H, *J* = 7.4 Hz), 7.42 (t, 2 H, *J* = 7.7 Hz), 7.36-7.27 (m , 5 H), 6.18 (s, 1 H), 5.64 (s, 1 H), 5.61-5.57 (m ,1 H), 5.10-5.02 (m, 3 H), 4.10-4.04 (m, 1 H), 3.74-3.68 (m, 4 H), 3.52-3.46 (m, 1 H), 2.82-2.74 (m, 2 H), 2.62 (t, 1 H, *J* = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 166.6, 156.4, 136.1, 135.5, 133.5, 129.8, 129.1, 128.6, 128.5, 128.3, 128.2, 71.6, 67.2, 55.0, 52.1, 34.5, 29.7; HRMS (FAB+) calcd for $C_{31}H_{34}NO_8$ (M + H^+) 428.1709, found 428.1694.

Methyl 4-*O*-benzoyl-3,5-dideoxy-5-(*N*-phenylmethoxycarbonyl)amino-α-L-*threo*-2-hexulopyranosonate (16). A solution of compound **15** (0.0256 g, 0.0597 mmol) was cooled to -78 °C for 20 min. Ozone was bubbled through the solution for 15 min and then the reaction was quenched with dimethylsulfide (0.30 mL). The solution was stirred at -78 °C for 40 min, warmed to rt, and stirred overnight. The reaction mixture was concentrated under vacuum and the crude syrup was purified by flash chromatography (hexanes: EtOAc 2:1) to provide compound **16** (0.0217g, 84%) as a white foam. $[\alpha]^{25}_D$ +9.4 (c 1.1, $CHCl_3$); IR (thin film) 3356, 2955, 1718, 1702, 1654, 1648, 1636 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) (10:1 α:β mixture of anomers, NMR data for the major anomer reported) δ 7.92-7.88 (m, 2 H), 7.52 (t, 1 H, J = 7.4 Hz), 7.37 (t, 2 H, J = 7.7 Hz), 7.12-7.04 (m, 5 H), 5.29 (dt, J = 5.0, 11.3 Hz), 4.98 (d, 1 H, J = 12.3 Hz), 4.86 (d, 1 H, J = 12.5 Hz), 3.89 (dt, J = 5.0, 10.3 Hz), 3.80 (t, 1 H, J = 10.7 Hz), 3.74 (dd, 1 H, J = 5.6, 10.9 Hz), 3.68 (s, 3 H), 2.34 (dd, 1 H, J = 4.8, 12.5 Hz), 1.97 (dd, 1 H, J = 11.3, 12.5 Hz); ^{13}C NMR (126 MHz, CD_3OD) δ 171.4, 167.4, 158.6, 138.2, 134.4, 131.2, 130.7, 129.6, 129.3, 128.8, 128.5, 96.5, 71.8, 67.4, 63.1, 53.2, 52.4, 38.0; HRMS (CI) calcd for $C_{22}H_{22}NO_8$ ($M - H^+$) 428.1345, found 428.1321.

Methyl 5-acetamido-4-*O*-benzoyl-3,5-dideoxy-α-L-*threo*-2-hexulopyranosonate (17α). A solution of compound **16** (0.398 g, 0.928 mmol) in Ac_2O (5.0 mL) was treated with a catalytic amount of 10% Pd-C. Hydrogen was bubbled through the reaction mixture for approximately 10 min and then the reaction was placed under 1 atm of H_2. The reaction mixture was stirred vigorously for 5 h, filtered through Celite with methanol rinses, and then concentrated under vacuum. The crude foam was purified by flash chromatography (hexanes:EtOAc 1:3) to give compound **17** (0.252 g, 81%) as a while foam. $[\alpha]^{25}_D$ -32.1 (c 1.26, $CHCl_3$); IR (thin film) 3364, 3012, 2955, 1748, 1721, 1644 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) (10:1 α:β mixture of anomers, NMR data for the major anomer reported) δ 7.91-7.88 (m, 2 H),

7.50 (t, 1 H, J = 7.5 Hz), 7.37 (t, 2 H, J = 8.0 Hz), 5.29 (dt, 1 H, J =5.0, 10.5 Hz), 4.14 (dt, 1 H, J = 5.8, 10.1 Hz), 3.79-3.70 (m, 2 H), 3.66 (s, 3 H), 2.33 (dd, 1 H, J = 5.0, 12.7 Hz), 1.97 (dd, 1 H, J = 11.1, 12.7 Hz), 1.76 (s, 3 H); ^{13}C NMR (126 MHz, CD_3OD) δ 173.5, 171.3, 167.3, 134.4, 131.2, 130.6, 129.6, 96.5, 71.5, 62.5, 53.2, 50.6, 37.8, 22.6; HRMS (EI) calcd for $C_{16}H_{19}NO_7$ (M^+) 337.1162, found 337.1151.