**Novel Efficient Routes to Heparin Monosaccharides, and Disaccharides Achieved
via Regio- and Stereoselective Glycosidation**

Henry N. Yu, Jun-ichi Furukawa, Tsuyoshi Ikeda and Chi-Huey Wong*

Department of Chemistry and Skaggs Institute for Chemical Biology, The Scripps
Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

General. All chemicals were purchased as reagent grade and used without further purification. Dichloromethane (CH_2Cl_2), toluene, and acetonitrile (CH_3CN) were distilled over calcium hydride whereas tetrahydrofuran (THF) and ether (Et_2O) were distilled over sodium/benzophenone ketyl. Anhydrous DMF was purchased from a commercial source. Molecular sieves (MS) used for glycosylation were AW-300, which was ground into powdered form before use. Reactions were monitored with analytical thin-layer chromatography (TLC) on silica gel 60 F254 plates and visualized under UV (254 nm) and/or by staining with 5% sulfuric acid or acidic ceric ammonium molybdate. ^1H NMR spectra were recorded on a 400- or 500-Hz NMR spectrometer at 20 °C. Chemical shift (in ppm) was determined relative to either tetramethylsilane in deuterated chloroform (δ 0 ppm) or acetone in deuterated water (δ 2.05 ppm). Coupling constant(s) in hertz (Hz) were measured from one-dimensional spectra. ^{13}C Attached Proton Test (C-Apt) spectra were obtained with NMR-400 or NMR 500 spectrometer and were calibrated with CDCl_3 (δ 77.00 ppm). Mass spectra were obtained by the analytical services of this department.

Methyl 1,2,3,4-tetra-*O*-acetyl-5-*C*-bromo- α -D-glucopuranosyluronate (6a) - A suspension of methyl 1,2,3,4-tetra-*O*-acetyl- α -D-glucopyranuroate **5a** (4.7 g, 12.5 mmol) and *N*-bromosuccinimide (3.5 g, 19.7 mmol) in dry CCl₄ (160 mL) was stirred for 45 min under irradiation with two 250 W tungsten light blubs (reflux). The mixture was cooled to room temperature and filtered by Celite, and the solvent was removed by evaporation. Short column chromatography (5:1 toluene-EtOAc) of residue gave the amorphous compound **6a** (4.0 g, 70 %); ¹H NMR: δ 6.54 (d, 1H, *J* 4.1, H-1), 5.81 (dd, 1H, *J* 9.9, 10.3, H-3), 5.31 (d, 1H, *J* 9.4, H-4), 5.19 (dd, 1H, *J* 4.1, 10.3, H-2), 3.83 (s, 3H, COOCH₃), 2.21, 2.11, 2.06, 2.05 (s x 4, 12H, 4 x Ac); ¹³C NMR (CDCl₃): δ 169.5, 169.3, 168.8, 168.5, 164.7 (C=O x 5), 89.4 (C-1), 87.1 (C-5), 69.7 (C-4), 67.8 (C-2), 66.9 (C-3), 54.1 (OCH₃), 21.1, 20.6, 20.6, 20.5 (Ac x 4); *m/z* (High Res. MALDI-FTMS) calcd for C₁₅H₁₉BrO₁₁Na (M+Na⁺) 477.0003, found: 477.0003.

Methyl 1,2,3,4-tetra-*O*-acetyl-5-*C*-bromo- β -D-glucopuranosyluronate (6b) – Compound **5b** was converted to **6b** as described above. ¹H NMR: δ 6.28 (d, 1H, *J* 8.6, H-1), 5.54 (t, 1H, *J* 9.5, H-3), 5.33 (d, 1H, *J* 9.4, H-4), 5.25 (dd, 1H, *J* 8.8, 9.7, H-2), 3.83 (s, 3H, COOCH₃), 2.28, 2.21, 2.06, 2.03 (s x 4, 12H, 4 x Ac).

Methyl 1,2,3,4-tetra-*O*-acetyl- α -L-idopyranuroate (7a) - A mixture of bromide **6a** (3.9 g, 8.5 mmol) and tributyltin hydride (4.5 mL, 16.7 mmol) in dry benzene was stirred at 80 °C under Ar, AIBN (47 mg, 0.29 mmol) was added to the solution. The reaction was stirred for 2 h and allowed to cool to room temperature. The solvent was evaporated and residue was diluted with EtOAc and saturated potassium fluoride was added. The mixture

was filtered by celite pad. The filtrate was washed with saturated aqueous NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) and concentrated. Column chromatography (2:1 toluene-EtOAc) of residue gave amorphous compound **7a** (4.0 g, 70 %). ¹H NMR: δ 6.05 (d, 1H, *J* 1.8, H-1), 5.28 (t, 1H, *J* 3.3, 3.7, H-3), 5.10 (ddd, 1H, *J* 0.7, 2.9, 2.6, H-4), 5.19 (ddd, 1H, *J* 0.7, 1.8, 2.9, H-2), 4.72 (d, 1H, *J* 2.2, H-5), 3.78 (s, 3H, COOCH₃), 2.17, 2.14, 2.11, 2.09 (s x 4, 12H, 4 x Ac); ¹³C NMR (CDCl₃): δ 169.4, 169.2, 168.6, 168.1, 166.8 (C=O x 5), 89.7 (C-1), 73.3 (C-5), 67.2 (C-3), 66.2 (C-4), 65.2 (C-2), 52.7 (OCH₃), 20.7, 20.7, 20.7, 20.5 (Ac x 4); m/z (High Res. MALDI-FTMS) calcd for C₁₅H₂₀O₁₁Na (M+Na⁺) 399.08985, found: 399.0887.

Methyl 1,2,3,4-tetra-*O*-acetyl-β-L-idopyranuroate (7b) – Compound **6b** was converted to **7b** (53%) as described above. ¹H NMR: δ 6.29 (dd, 1H, *J*_{1,3} 1.3, 1.9 H-1), 5.18 (t, 1H, *J* 3.6, H-4), 5.16 (td, 1H, *J*_{1,3} 1.0, 4.0, H-3), 4.88 (d, 1H, *J* 2.5, H-5), 4.86 (ddd, 1H, *J*_{2,4} 1.0, 2.3, 3.4, H-2), 3.80 (s, 3H, COOCH₃), 2.13, 2.12, 2.11, 2.09 (s x 4, 12H, 4 x Ac); m/z (High Res. MALDI-FTMS) calcd for C₁₅H₂₀O₁₁Na (M+Na⁺) 399.0898, found: 399.0897.

Methyl (2,3,4-tetra-*O*-acetyl-α-L-idopyranosyl bromide)uroate (8) - A solution of acetylated iduronic acid **7a** (1.5 g, 4.0 mmol) in 30% HBr solution in acetic acid (20 mL) was stirred for 2 h at 0 °C to room temperature. The mixture was evaporated with toluene. The residue was diluted with EtOAc and washed with cold saturated aqueous NaHCO₃ and brine. The organic layer extraction was dried (Na₂SO₄) and concentrate to give the bromide **8** (1.6 g, quant). Spectral data were in good agreement with those reported.^{13a}

Methyl 3,4-di-*O*-acetyl-1,2-*O*-(*S*)-ethylidene- α -L-idopyranuroate (9**)** - To solution of bromide **8** (1.5 g, 3.8 mmol) in MeCN (40 mL), NaBH₄ (0.9 g, 23.8 mmol) was added at 0 °C and stirred for 2 h at room temperature. The reaction mixture was filtered by Celite pad and concentrated. Chromatography of the residue on silica gel with Hexane:EtOAc (2:1) gave the 1,2-acetal derivative **9** (0.96 g, 70 %). ¹H NMR: δ 5.42 (t, 1H, *J* 2.2, H-3), 5.37 (t, 1H, *J* 2.6, H-1), 5.34 (q, 1H, *J* 4.75, CH), 5.08 (m, 1H, H-4), 4.45 (d, 1H, *J* 1.45, H-5), 3.78 (s, 3H, COOCH₃), 3.76 (bs, 1H, H-2), 2.15, 2.07 (s x 2, 6 H, 2 x Ac), 1.54 (d, 1H, *J* 4.75, CH₃). ¹³C NMR (CDCl₃): δ 169.6, 168.4, 167.5, (C=O x 3), 104.5, 95.6 (C-1), 75.0 (C-5), 70.3, 66.5, 66.4, 52.6 (OCH₃), 21.7, 20.7, 20.5; *m/z* (High Res. MALDI-FTMS) calcd for C₁₃H₁₈O₉Na (M+Na⁺) 341.0843, found: 341.0840.

Methyl 1,2-*O*-(*S*)-ethylidene- α -L-idopyranuroate (10**)** - To solution of acetate **9** (487 mg, 1.5 mmol) in MeOH (20 mL), NaOMe (cat.) was added and stirred for 3 h. The reaction was neutralized by DOWEX 650C, filtered and concentrated. Chromatography of the residue on silica gel with Hexane:EtOAc (2:1) gave derivative **10** (402 mg, 95 %). ¹H NMR: δ 5.40 (d, 1H, *J* 2.0, H-1), 5.28 (q, 1H, *J* 5.0, CH), 4.55 (bs, 1H, H-5), 4.48 (m, 1H, H-3), 3.96-3.99 (m, 1H, *J* 12.1, H-4), 3.84 (dd, 1H, *J* 2.0, H-2), 3.77 (s, 3H, COOCH₃), 3.06 (d, 1H, *J* 12.1, 4-OH), 2.45 (m, 1H, 3-OH), 1.56 (d, 1H, *J* 5.0, CH₃); ¹³C NMR (CDCl₃): δ 169.7 (C=O), 103.9 (CH), 95.5 (C-1), 78.4 (C-2), 71.4 (C-5), 69.6 (C-4), 66.7 (C-3), 52.5 (OCH₃), 21.7 (CH₃); *m/z* (High Res. MALDI-FTMS) calcd for C₉H₁₄O₇Na (M+Na⁺) 257.0632, found: 257.0630.

***p*-methylphenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-*p*-methoxybenzyl-1-thio- β -D-glucopyranoside (11)** – To a mixture of mannoside **32** (640mg, 1.29 mmol) in pyridine-dichloromethane (1:1, 12 mL) at -15 °C under argon, was added liquid trifluoromethanesulfonic anhydride (1 mL). The reaction was allowed to warm to room temperature. The reaction was diluted with EtOAc and quenched with a few drops of H₂O. The mixture was then washed with HCl (2 N), NaHCO₃, and brine. The organic layer was dried over Na₂SO₄ and concentrated in *vacuo*. The residue was then stirred in anhydrous DMF at 0 °C under argon. Solid NaN₃ (422 mg, 6.48 mmol) was added. The reaction was allowed to warm to room temperature and proceed overnight. The reaction was diluted with EtOAc, washed with H₂O. The organic layer was dried over Na₂SO₄ and concentrated in *vacuo*. The resulting residue was purified by column chromatography (3% EtOAc in toluene) to give **11** (537 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ 7.49 – 6.84 (m, 9H, PMB + Ph), 5.55 (s, 1H, *CH*Ph), 4.83 (d, 1H, *J* 10.5, PMB), 4.70 (d, 1H, *J* 10.5, PMB), 4.40 (d, 1H, *J* 10.3, H-1), 4.17 (dd, 1H, *J* 4.8, 10.5, H-6a), 3.77 (overlapped, 4H, H-6b + OMe), 3.63 ('t', 1H, *J* 8.6, H-3), 3.57 ('t', 1H, *J* 9.1, H-4), 3.42 (d't', 1H, *J* 5.1, 9.7, H-5), 3.30 (dd, 1H, *J* 8.9, 10.1, H-2), 2.33 (s, 3H, Tol). ¹³C (400 MHz, CDCl₃) δ 159.7, 139.4, 137.4, 134.8, 134.3, 130.3, 130.1, 129.9, 129.7, 129.3, 128.5, 126.6, 126.2, 114.1, 114.0, 101.4, 86.7, 81.5, 80.8, 75.1, 10.7, 68.7, 64.6, 55.5, 21.4. *m/z* (High Res. MALDI-FTMS) calcd C₂₈H₂₉N₃O₅SN⁺: 542.1720, found: 542.1722.

Methyl 4-*O*-acetyl-1,2-*O*-(*S*)-ethylidene- β -L-idopyranosyluronate (16) – Under argon, Mg(OMe)₂ (25 μ L, 6-10 wt.%) was added dropwise to a stirred solution of **9** (30 mg, 94.3 μ mol) in anhydrous MeOH-dichloromethane (1:1, 1 mL) at 0 °C, and reaction was

continued for 2.5 h. MeOH (10 mL) was added and the mixture was neutralized to pH 7 with H⁺ resin. After filtration, the mixture was concentrated. The residue was purified by chromatography on silica using toluene - EtOAc (1:1 v/v) as eluent to give compound **16** (23 mg, 88%) and **9** (3.6 mg, 12%). ¹H NMR (400 MHz, CDCl₃) δ 5.41 (d, *J* 2.6, 1H, H-1), 5.33 (q, 1H, *J* 5.0, CHCH₃), 5.02 (ddd, 1H, *J* 1.3, 1.3, 2.6, H-4), 4.61 (d, 1H, *J* 1.5, H-5), 4.45 (‘t’, 1H, *J* 2.5 H-3), 3.83 (m, 1H, H-2), 3.80 (s, 3H, CO₂CH₃), 2.12 (s, 3H, OAc), 1.10 (d, 3H, *J* 5.0, CHCH₃). ¹³C (400 MHz, CDCl₃) δ 169.9, 167.6, 104.4, 95.9, 77.7, 70.0, 69.7, 65.6, 52.8, 22.0, 21.1; m/z (High Res. MALDI-FTMS) calcd C₁₁H₁₆O₈Na⁺: 299.0737, found: 299.0735.

Methyl 4-*O*-acetyl-3-*O*-benzoyl-1,2-*O*-(*S*)-ethylidene-β-L-idopyranosyluronate (17**) –**

Under argon, benzoyl chloride (200 μL) was added dropwise to a stirred solution of **16** (22 mg, 80 μmol) in pyridine (1 mL) at 0 °C. The reaction was continued at room temperature for 30 min. The mixture was concentrated and the resulting residue was purified by chromatography on silica using toluene - EtOAc (7:3 v/v) as eluent to give compound **17** (26 mg, 86%). ¹H NMR (400 MHz, CDCl₃) δ 8.13-7.48 (m, 5H, Bz), 5.68 (d, *J* 1.8, 1H, H-1), 5.45 (d, 1H, *J* 2.3 H-3), 5.38 (q, 1H, *J* 4.8, CHCH₃), 5.25 (dd, 1H, *J* 1.5, 2.5, H-4), 4.52 (s, 1H, H-5), 3.82 (s, 1H, H-2), 3.78 (s, 3H, CO₂CH₃), 2.11 (s, 3H, OAc), 1.07 (d, 3H, *J* 5.0, CHCH₃). ¹³C (400 MHz, CDCl₃) δ 167.0, 167.8, 164.3, 134.1, 134.0, 130.4, 130.1, 128.9, 128.7, 104.9, 96.0, 75.4, 70.8, 67.2, 66.8, 52.9, 22.0, 20.9; m/z (High Res. MALDI-FTMS) calcd C₁₈H₂₀O₉Na⁺: 403.0999, found: 403.1004.

Methyl 4-*O*-acetyl-3-*O*-pivaloyl-1,2-*O*-(*S*)-ethylidene- β -L-idopyranosyluronate (18**) -**

Under argon, trimethyl acetyl chloride (150 μ L) was added dropwise to a stirred solution of **16** (22 mg, 80 μ mol) and DMAP (cat.) in pyridine (1 mL) at 0 °C. The ice-bath was removed and reaction was continued at room temperature for 12 h. The mixture was concentrated and the resulting residue was purified by chromatography on silica using toluene - EtOAc (5:1 v/v) as eluent to give compound **18** (23 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ 5.40 ('t', 1H, *J* 2.3, H-3), 5.35 (q, 1H, *J* 4.8, CHCH₃), 5.33 (d, 1H, *J* 2.8, H-1), 5.06 (dd, 1H, *J* 1.3, 2.4, H-4), 4.43 (d, 1H, *J* 1.3, H-5), 3.78 (s, 3H, CO₂CH₃), 3.71 (s, 1H, H-2), 2.08 (s, 3H, OAc), 1.55 (d, 3H, *J* 4.7, CHCH₃), 1.24 (s, 9H, Piv); ¹³C (400 MHz, CDCl₃) δ 176.0, 169.8, 167.8, 104.9, 96.0, 75.3, 70.7, 66.7, 66.3, 52.8, 39.0, 27.2, 22.0, 20.8; m/z (High Res. MALDI-FTMS) calcd C₁₆H₂₄O₉Na⁺: 383.1313, found: 383.1313.

Methyl 3,4-di-*O*-acetyl-1,2-*O*-ethylidene- α -D-glucopuranosyluronate (20**)** – To a stirring mixture of bromide **19** (50 mg, 126 μ mol), tetrabutylammonium iodide (30 mg, 81 μ mol) and activated 3 Å molecular sieves in anhydrous CH₃CN (2 mL), solid NaBH₄ (30 mg, 793 μ mol) was added. The reaction was heated at 40 °C for 16 h. The mixture was then diluted with dichloromethane and filtered. After evaporation, the residue was purified by chromatography on silica using toluene - EtOAc (7:3 v/v) as eluent to give compound **20** (4 mg, 10%). ¹H NMR (400 MHz, CDCl₃) δ 5.64 (d, 1H, *J* 4.9, H-1), 5.20 (dd, 1H, *J* 2.9, 4.7, H-3), 5.11 (dd, 1H, *J* 2.8, 9.0, H-4), 5.07 (q, 1H, *J* 4.9, CHCH₃), 4.37 (d, 1H, *J* 8.8 H-5), 4.02 (dd, 1H, *J* 3.0, 4.5, H-2), 3.71 (s, 3H, CO₂CH₃), 2.08 (s, 3H,

OAc), 2.06 (s, 3H, OAc), 1.50 (d, 3H, J 4.9, CHCH_3). (High Res. MALDI-FTMS) calcd $\text{C}_{13}\text{H}_{18}\text{O}_9\text{Na}^+$: 341.0843, found: 341.0845.

Methyl 1,2-*O*-(*S*)-ethylidene- α -D-glucopuranosyluronate (25a) – A solution of NaOCl (8.1 mL, $d = 1.097$), saturated NaHCO_3 (5.8 mL) and brine (9.5 mL) at 0 °C was added dropwise for 2 h to a cooled solution of **24a** (500 mg, 2.42 mmol), TEMPO (12.9 mg, 0.83 mmol), sodium bromide (51 mg, 0.50 mmol), tetrabutylammonium chloride (64 mg, 0.23 mmol), in saturated NaHCO_3 (9.5 mL) and EtOAc (16 mL). The reaction was stirred overnight at 4 °C. The mixture was washed with EtOAc and extracted with H_2O (4 X). The aqueous layers was combined and acidified to pH 1 with HCl (2 N). The mixture was then concentrated, co-evaporated with toluene and dried in *vacuo*. The resulting residue was then stirred in anhydrous MeOH with H^+ resin for 36 h. The resin was removed by filtration and organic solvent removed. The residue was then diluted with EtOAc washed with H_2O . The organic layer was dried over Na_2SO_4 and concentrated in *vacuo*. The resulting residue was purified by column chromatography using toluene - EtOAc (1:9 v/v) as eluent to give compound **25a** (351 mg, 62%). ^1H NMR (400 MHz, CDCl_3) δ 5.71 (d, J 4.1, 1H, H-1), 5.54 (q, 1H, J 5.0, CHCH_3), 4.31 (d, 1H, J 7.3 H-5), 4.12 (dd, 1H, J 4.1, 5.7, H-2), 3.98 (dd, 1H, J 3.2, 5.9, H-3), 3.84 (m, 4H, H-4 + CO_2CH_3), 1.39 (d, 3H, J 4.8, CHCH_3). ^{13}C (400 MHz, CDCl_3) δ 171.0, 102.2, 96.5, 78.5, 76.9, 74.2, 70.6, 69.8, 52.8, 20.6; m/z (High Res. ESI) calcd $\text{C}_9\text{H}_{14}\text{O}_7\text{Cl}^-$: 269, found: 269.

Methyl 1,2-*O*-(*R*)-ethylidene- α -D-glucopuranosyluronate (25b) – Compound **24b** was converted to **25b** as described above. ^1H NMR (400 MHz, CDCl_3) δ 5.52 (d, J 3.7, 1H,

H-1), 5.18 (q, 1H, J 5.7, CHCH₃), 4.40 (d, 1H, J 6.7, H-5), 4.16 (m, 1H, H-3), 4.05 (dd, 1H, J 3.7, 6.7, H-2), 4.0 (m, 1H, H-4), 3.82 (s, 3H, CO₂CH₃), 1.50 (d, 3H, J 4.8, CHCH₃). ¹³C (400 MHz, CDCl₃) δ 171.2, 102.4, 95.8, 73.7, 73.4, 70.6, 70.3, 52.8, 20.6; m/z (GC/MS) calcd C₉H₁₄O₇⁺: 234, found: 234.

2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-*p*-methoxybenzyl- α -D-glucopyranosyl-

(1 $\rightarrow$ 4)-methyl 1,2-*O*-(*S*)-ethylidene- β -L-idopyranosyluronate (12) – To a stirring solution of donor **11** (35 mg, 67 μ mol), diol acceptor **10** (32 mg, 137 μ mol), NIS (20 mg, 87 μ mol) and MS in dry dichloromethane (1.5 mL) at -20 °C under argon, trifluoromethanesulfonic acid (0.6 μ L, 7 μ mol) was added. The mixture was allowed to warm to 10 °C. The reaction was quenched with saturated NaHCO₃ and diluted with dichloromethane. After filtration, the mixture was washed with saturated NaHCO₃, Na₂S₂O₃ (10%), H₂O, brine, and dried over Na₂SO₄. The organic layer was then concentrated and the resulting residue was purified by column chromatography using toluene - EtOAc (3:2 v/v) as eluent to give compound **12** (24 mg, 57%). ¹H NMR (400 MHz, CDCl₃) δ 7.48 – 6.82 (m, 9H, PMB + Ph), 5.50 (s, 1H, Ph), 5.33 (d, J 2.7, 1H, H-1), 5.25 (q, 1H, J 4.3, CHCH₃), 4.92 (d, 1H, J 3.3, H-1'), 4.79 (d, 1H, J 10.5, PMB), 4.62 (d, 1H, J 10.5, PMB), 4.53 (bs, 1H, H-5), 4.29 (dd, 1H, J 4.9, 10.0, H-6'a), 3.97 (m, 3H, H-4 + H-3' + H-6'b), 3.75 (m, 7H, H-2 + CO₂CH₃ + PMB), 3.61 (m, 2H, H-4' + H-5'), 3.35 (dd, J 3.5, 9.8, H-2'), 2.38 (d, 1H, J 9.2 3-OH), 1.68 (d, 3H, J 4.6, CHCH₃). m/z (High Res. MALDI-FTMS) calcd C₃₀H₃₅N₃O₁₂Na⁺: 652.2113, found: 652.2131.

2-azido-6-O-acetyl-3-O-benzyl-2-deoxy-4-O-levulinoyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-methyl 1,2-*O*-(*S*)-ethylidene- β -L-idopyranosyluronate (14) – To a stirring solution of donor **13** (116 mg, 214 μ mol), diol acceptor **10** (100 mg, 427 μ mol), NIS (62 mg, 276 μ mol) and MS in dry dichloromethane (5 mL) at -15 °C under argon, trifluoromethanesulfonic acid (cat.) was added. The mixture was allowed to warm to 10 °C. The reaction was quenched with saturated NaHCO₃ and diluted with dichloromethane. After filtration, the mixture was washed with saturated NaHCO₃, Na₂S₂O₃ (10%), H₂O, brine, and dried over Na₂SO₄. The organic layer was then concentrated and the resulting residue was purified by column chromatography using toluene - EtOAc (3:2 v/v) as eluent to give compound **14** (88 mg, 63%). ¹H NMR (400 MHz, CDCl₃) δ 7.32 (m, 5H, Ph), 5.38 (d, *J* 2.8, 1H, H-1), 5.30 (q, 1H, *J* 5.1, CHCH₃), 5.11 (dd, 1H, *J* 9.2, 10.3, H-4'), 5.03 (d, 1H, *J* 3.4, H-1'), 4.76 (d, 1H, *J* 11.0, Bn), 4.64 (d, 1H, *J* 11.0, Bn), 4.60 (dd, 1H, *J* 4.0, 6.5, H-3), 4.50 (d, 1H, *J* 2.0, H-5), 4.16 (dd, 1H, *J* 3.2, 7.4, H-6'a), 4.13 ('t', 1H, *J* 7.1, H-6'b), 4.04 (m, 2H, H-4 + H-5'), 3.95 (dd, 1H, *J* 9.4, 10.1, H-3'), 3.82 (dd, 1H, *J* 2.8, H-2), 3.79 (s, 3H, OMe), 3.36 (dd, *J* 3.4, 10.3, H-2'), 2.68 (t, 2H, *J* 6.4, Lev), 2.44 (m, 3H, 3-OH + Lev), 2.16 (s, 3H, Lev), 2.06 (s, 3H, Lev), 1.56 (d, 3H, *J* 5.0, CHCH₃). *m/z* (High Res. MALDI-FTMS) calcd C₂₉H₃₇N₃O₁₄Na⁺: 674.2168, found: 674.2150.

2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-*p*-methoxybenzyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-methyl 1,2-*O*-(*S*)-ethylidene- α -D-glucopuranosyluronate (26a) and 2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-*p*-methoxybenzyl- α -D-glucopyranosyl-(1 $\rightarrow$ 3)-methyl 1,2-*O*-(*S*)-ethylidene- α -D-glucopuranosyluronate (27a) – To a stirring solution of

donor **11** (49 mg, 94 μ mol), diol acceptor **25a** (44 mg, 188 μ mol), NIS (25 mg, 111 μ mol) and MS in dry dichloromethane (2 mL) at -20 °C under argon, trifluoromethanesulfonic acid (1 μ L, 11 μ mol) was added. The mixture was allowed to warm to 10 °C. The reaction was quenched with saturated NaHCO₃ and diluted with dichloromethane. After filtration, the mixture was washed with NaHCO₃, Na₂S₂O₃, H₂O, brine, and dried over Na₂SO₄. The organic layer was then concentrated and the resulting residue was purified by column chromatography using toluene - EtOAc (5:1 v/v) as eluent to give compound **27a** (18 mg, 30%) and **26a** (26 mg, 44%).

Data for 26a ¹H NMR (400 MHz, CDCl₃) δ 7.50 – 6.83 (m, 9H, PMB + Ph), 5.69 (d, *J* 4.5, 1H, H-1), 5.58 (s, 1H, CHPh), 5.49 (q, 1H, *J* 4.7, CHCH₃), 5.12 (d, 1H, *J* 3.8, H-1'), 4.89 (d, 1H, *J* 10.5, PMB), 4.73 (d, 1H, *J* 10.5, PMB), 4.31 (d, 1H, *J* 8.2 Hz, H-5), 4.25 (dd, 1H, *J* 4.5, 10.0, H-6'a), 4.15 (dd, 1H, *J* 4.4, 6.9, H-2), 4.05 (ddd, 1H, *J* 2.6, 7.0, 9.7, H-3), 4.02 ('t', 1H, *J* 9.7, H-3'), 3.86 (m, 1H, H-5'), 3.80 (d, 6H, CO₂CH₃ + PMB), 3.70 (m, 4H, H-6b' + H-4'), 3.61 (dd, *J* 4.0, 10.0, H-2'), 2.04 (bs, 1H, 3-OH), 1.42 (d, 3H, *J* 5.0, CHCH₃). m/z (High Res. MALDI-FTMS) calcd C₃₀H₃₅N₃O₁₂SN⁺: 652.2113, found: 652.2114.

Data for 27a ¹H NMR (400 MHz, CDCl₃) δ 7.51 – 6.85 (m, 9H, PMB + Ph), 5.70 (d, *J* 4.3, 1H, H-1), 5.59 (s, 1H, CHPh), 5.50 (q, 1H, *J* 4.0, CHCH₃), 5.15 (d, 1H, *J* 3.7, H-1'), 4.89 (d, 1H, *J* 10.5, PMB), 4.74 (d, 1H, *J* 10.5, PMB), 4.28 (d, 1H, *J* 8.1Hz, H-5), 4.25 (dd, 1H, *J* 5.1, 10.3, H-6'a), 4.15 (dd, 1H, *J* 4.4, 6.3, H-2), 4.05 ('t', 1H, *J* 9.4, H-3'), 4.04 (overlapped, 1H, H-5'), 3.96 (d't', 1H, *J* 3.1, 8.2, H-4), 3.84 (dd, 1H, *J* 2.5, 6.3, H-3), 3.82 (s, 3H, CO₂CH₃), 3.80 (s, 3H, PMB), 3.76 (dd, 1H, *J* 3.1, 10.3, H-6'b), 3.71 ('t', 1H, *J* 9.5, H-4'), 3.54 (dd, *J* 3.8, 10.0, H-2'), 3.50 (d, 1H, *J* 3.5, 4-OH), 1.39 (d, 3H, *J* 4.5,

CHCH₃). m/z (High Res. MALDI-FTMS) calcd C₃₀H₃₅N₃O₁₂SNa⁺: 652.2113, found: 652.2121.

***p*-methylphenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-mannopyranoside (29)** – To an ice-cold solution of *p*-toluenethiol (26.6 g, 214 mmol) in anhydrous DMF (130 mL), was added *tert*-butoxide (14.4 g, 128 mmol), and the mixture was stirred for 15 min. A solution of bromide **28** (44 g, 107 mmol) in anhydrous THF (50 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated and the residue was diluted with EtOAc, washed with H₂O, brine, dried over anhydrous Na₂SO₄ and concentrated. Crystallization with EtOAc-hexane gave **29** (46 g, 94%). ¹H NMR (300 MHz, CD₃OD) δ 7.42 – 7.09 (m, 4H, Tol), 5.64 (dd, 1H, *J* 1.2, 3.6, H-2), 5.26 ('t', 1H, *J* 9.9, H-4), 5.03 (dd, 1H, *J* 3.6, 10.2, H-3), 4.83 (d, 1H, *J* 0.9, H-1), 4.25 (dd, 1H, *J* 6.3, 12, H-6a), 4.15 (dd, 1H, *J* 2.7, 12.3, H-6b), 3.66 (ddd, 1H, *J* 2.7, 6.6, 10.2, H-5), 2.34 (s, 3H, Tol), 2.21 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.98 (s, 3H, OAc). m/z (High Res. MALDI-FTMS) calcd C₂₁H₂₆O₉SNa⁺: 477.1190, found: 477.1190.

***p*-methylphenyl 1-thio-β-D-mannopyranoside (30)** – Compound **29** (20 g, 44 mmol) was suspended in dry MeOH (250 mL) and NaOMe (cat.) was added. The mixture was stirred overnight and neutralized to pH 1 with H⁺ resin. After filtration, the mixture was concentrated and crystallization with MeOH-H₂O at 4 °C afford **30** (11.5g, 92%) ¹H NMR (400 MHz, CD₃OD) δ 4.88 (d, 1H, *J* 1.2, H-1), 4.00 (dd, 1H, *J* 0.8, 3.6, H-2), 3.83 (dd, 1H, *J* 2.8, 12.4, H-6a), 3.69 (dd, 1H, *J* 5.6, 12.0, H-6b), 3.59 ('t', 1H, *J* 9.6, H-4),

3.45 (dd, 1H, J 3.6, 9.6, H-3), 3.22 (ddd, 1H, J 2.8, 6.0, 9.6, H-5), 2.34 (s, 3H, Tol). m/z (High Res. MALDI-FTMS) calcd $C_{13}H_{18}O_5SNa^+$: 309.0767, found: 309.0769.

***p*-methylphenyl 3-*O*-*p*-methoxybenzyl-1-thio- β -D-mannopyranoside (31)** – To a solution of **30** (2.3 g, 8.0 mmol) in anhydrous toluene (100 mL), was added di-*n*-butyltin oxide (2.2 g, 8.8 mmol); was refluxed with azeotropic removal of water for 6 h using Dean–Stark tube. The reaction was cooled to 60°C, tetra-*n*-butylammonium bromide (2.9 g, 8.9 mmol) and 4-methoxybenzyl chloride (1.7 mL, 12.5 mmol) were added the reaction was stirred for overnight at the same temperature. The mixture was concentrated and the residue was purified by column chromatography on silica gel (MeOH–EtOAc, 49:1 v/v), to give compound **31** (2.1 g, 65%). 1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 6.88 (m, 4H, PMB), 4.77 (d, 1H, J 1.2, H-1), 4.68 (d, 1H, J 11.2, PMB), 4.53 (d, 1H, J 11.6, PMB), 4.25 (dd, 1H, J 0.8, 3.2, H-2), 3.97 (‘t’, 1H, J 9.6, H-4), 3.86 (dd, 1H, J 3.6, 8.8, H-6a), 3.80 (s, 3H, OMe), 3.77 (dd, 1H, J 4.8, 8.5, H-6b), 3.41 (dd, 1H, J 3.2, 9.2, H-3), 3.22 (ddd, 1H, J 3.6, 4.8, 10.0, H-5), 2.33 (s, 3H, Tol). m/z (High Res. MALDI-FTMS) calcd $C_{21}H_{26}O_6SNa^+$: 429.1342, found: 429.1348.

***p*-methylphenyl 4,6-*O*-benzylidene-3-*O*-*p*-methoxybenzyl-1-thio- β -D-mannopyranoside (32)** – To a solution of compound **31** (1.9 g, 4.7 mmol) and benzaldehyde dimethyl acetal (2.1 mL, 14.0 mmol) in dry CH_3CN , was add camphor sulfonic acid (100mg, 0.43 mmol). The reaction was continued for 3.5 h and then quenched with triethyl amine. Concentration of the mixture followed by column chromatography on silica gel (toluene–EtOAc, 5:1 v/v), to give compound **32** (2.1 g,

89%). ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 6.85 (m, 9H, PMB + Ph), 5.60 (s, 1H, Ph), 4.80 (s, 1H, H-1), 4.77 (d, 1H, J 11.6, PMB), 4.67 (d, 1H, J 11.6, PMB), 4.31 (dd, 1H, J 5.2, 10.4, H-6a), 4.26 (d, 1H, J 3.2, H-2), 4.14 ('t', 1H, J 9.6, H-4), 3.91 ('t', 1H, J 10.4, H-6b), 3.80 (s, 3H, OMe), 3.66 (dd, 1H, J 3.2, 9.2, H-3), 3.22 (d't', 1H, J 4.8, 10.0, H-5), 2.33 (s, 3H, Tol). m/z (High Res. MALDI-FTMS) calcd $\text{C}_{28}\text{H}_{30}\text{O}_6\text{SNa}^+$: 517.1655, found: 517.1657.