Supporting Information

Chemical synthesis of C6-tetrazole D-mannose building blocks and access to a bioisostere of mannuronic acid 1-phosphate

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S1. General Experimental

All reagents and solvents which were available commercially were purchased from Acros, Alfa Aesar, Fisher Scientific, Sigma Aldrich or TCI. All reactions in non-aqueous solvents were conducted in oven dried glassware with a magnetic stirring device under an inert atmosphere of nitrogen passed through a drying column using a vacuum manifold. Solvents were purified by passing through activated alumina columns and used directly from a Pure Solv-MD solvent purification system and were transferred under nitrogen. Reactions were followed by thin layer chromatography (TLC) using Merck silica gel 60F254 analytical plates (aluminium support) and were developed using short wave UV radiation (245 nm) and 5% sulfuric acid in methanol/Δ. Purification via flash column chromatography was conducted manually using Sigma Aldrich silica gel 60 (0.043-0.063 mm) under a positive pressure of compressed air or via automation using a Büchi Reveletis X2 with pre-packed silica cartridges. Purification via strong ion exchange (SAX) chromatography was conducted on a Bio-Rad Biologic LP system using a Bio-Scale Mini UNOsphere Q (strong anion exchange) cartridge (column volume = 5 mL): flow rate (3.0 mL/min), 0 → 100% 1.0 M NH₄HCO₃ over 33 min. Optical activities were recorded on an automatic Rudolph Autopol I or Bellingham and Stanley ADP430 polarimeter (concentration in g/100mL). ¹H NMR spectra were recorded at 400 MHz, ¹³C NMR spectra at 100 MHz and ³¹P NMR spectra at 161 MHz respectively using Bruker AV-III spectrometers. ¹H NMR resonances were assigned with the aid of gDQCOSY. ¹³C NMR resonances were assigned with the aid of gHSQCAD. Coupling constants are reported in Hertz. Chemical shifts (δ, in ppm) are standardised against the deuterated solvent peak. NMR data were analysed using Mestrenova or iNMR software. ¹H NMR splitting patterns were assigned as follows: br. s (broad singlet), s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), app. t (apparent triplet), t (triplet), quartet (q) or m (multiplet and/or multiple resonances). HRMS (ESI) were obtained on Agilent 6530 Q-TOF, LQT Orbitrap XL1 or Waters (Xevo, G2-XS TOF or G2-S ASAP) Micromass LCT spectrometers using a methanol mobile phase in positive/negative ionisation modes, as appropriate.
S2. Experimental procedures for compounds 2-21

S2.1. 3-Propionitrile (phenyl 2,3-di-O-benzyl-1-thio-α-D-mannopyranoside) amide 2

To a stirred solution of 1 (100 mg, 0.21 mmol, 1.0 equiv.), PyBOP (280 mg, 0.53 mmol, 2.5 equiv.) and DIPEA (75 µL, d = 0.742, 0.43 mmol, 2.0 equiv.) in CH₂Cl₂ (2 mL), was added 3-aminopropionitrile (24 µL, d = 0.952, 0.32 mmol, 1.5 equiv.) in CH₂Cl₂ (0.1 mL) at 0 °C. The mixture was left stirring for 40 min. and was diluted with CH₂Cl₂ (10 mL). The organic layer was washed 1.0 M aq. HCl (2 x 10 mL), sat. aq. NaHCO₃ solution (2 x 10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification using silica gel flash column chromatography, eluting with EtOAc/toluene (100/1, 5/95, 10/90, 20/80) afforded 2 as a white solid (51 mg, 0.1 mmol, 47%). Rf 0.29 (EtOAc/toluene, 3/7); [α]D²⁰ +56.4 (c. 7.5, CHCl₃); mp: 102-105 °C; ¹H NMR (400 MHz; CDCl₃) δ 7.40 – 7.29 (15 H, m, Ar-H), 6.87 (1 H, t, J = 6.1 Hz, C(O)N(H)CH₂CH₂C≡N), 5.45 (1 H, d, J = 1.5 Hz, H₁), 4.88 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.72 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.68 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.64 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.53 (1 H, d, J = 9.8 Hz, H₃), 4.38 (1 H, s, C4-OH), 4.26 (1 H, app. t, J = 9.5 Hz, H₄), 3.94 (1 H, dd, J = 2.8, 1.8 Hz, H₂), 3.77 (1 H, dd, J = 9.3, 3.0 Hz, H₅), 3.64 (1 H, td, J = 12.6, 6.2 Hz, C(O)N(H)CH₂CH₂C≡N), 3.39 (1 H, ddt, J = 13.8, 7.8, 5.9 Hz, C(O)N(H)CH₂CH₂C≡N), 2.66 (1 H, dd, J = 11.7, 5.0 Hz, C(O)N(H)CH₂CH₂CN), 2.61 – 2.51 (1 H, m, C(O)N(H)CH₂CH₂C≡N); ¹³C NMR (101 MHz; CDCl₃) δ 172.1 (C(O)N(H)CH₂CH₂C≡N), 138.4 (C₉), 137.8 (C₉), 132.8 (C₉), 132.4, 129.4, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 117.4 (C(O)N(H)CH₂CH₂C≡N), 86.8 (C₁), 78.5 (C₃), 77.2 (C₂), 73.3 (CH₂Ph), 73.1 (CH₂Ph), 70.9 (C₅), 69.8 (C₄), 35.1 (C(O)N(H)CH₂CH₂C≡N), 18.3 (C(O)N(H)CH₂CH₂C≡N); HRMS (ES⁺) m/z [Found: (M+NH₄)⁺ 536.2217 C₂₉H₃₄N₃O₅S requires (M+NH₄)⁺, 536.2219]; IR νmax/cm⁻¹ 3401 (w, N-Hamide), 2249 (w, C=≡N), 1655, 1530 (s, C=Oamide), 1496, 1454 (m, C=C aromatic), 1102 (C=N).

S2.1.1. Elimination by-product 3

Elimination by-product 3 was isolated from the crude mixture containing 2 and as a colourless oil (46 mg, 90 µmol, 44%). Rf 0.32 (EtOAc/toluene, 3/7); [α]D²⁰ +72.0 (c. 7.5, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 7.49 – 7.28 (15 H, m, Ar-H), 6.73 (1 H, t, J = 6.2 Hz, C(O)N(H)CH₂CH₂C≡N), 6.23 (1 H, dd, J = 3.5, 0.9 Hz, H₄), 5.59 (1 H, d, J = 5.3 Hz, H₁), 4.70 (1 H, d, J = 12.1 Hz, CH₂Ph), 4.69 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.64 (1 H, d, J = 12.1 Hz, CH₂Ph), 4.60 (1 H, d, J = 11.9 CH₂Ph), 4.29 (1 H, app. t, J = 3.8 Hz, H₃), 3.85 (1 H, ddt, J = 5.1, 4.1, 0.9 Hz, H₂), 3.62 – 3.43 (2 H, m, C(O)N(H)CH₂CH₂C≡N), 2.69 – 2.52 (2 H, m, C(O)N(H)CH₂CH₂C≡N); ¹³C NMR (101 MHz; CDCl₃) δ 161.5 (C(O)N(H)CH₂CH₂C≡N), 143.6 (C₅), 137.8 (C₉), 137.5 (C₉), 133.4 (C₉), 131.9, 129.4, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 117.9 (C(O)N(H)CH₂CH₂C≡N), 106.1 (C₄), 85.1 (C₁), 72.81 (C₂), 72.5 (CH₂Ph), 71.2 (CH₂Ph), 68.3 (C₃), 35.6 (C(O)N(H)CH₂CH₂C≡N), 18.2 (C(O)N(H)CH₂CH₂C≡N); HRMS (ES⁺) m/z [Found:...
Na completion, the mixture was cooled down to room temperature, diluted with EtOAc (50 equiv.) were added. The mixture was heated to 120 °C and TMSN₃ (M+NH₄)⁺, 74.2 (C₅), 72.4 (C₂), 72.1 (C₃), 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 117.6 (C(O)N(H)CH), 68.7 (C₄), 35.3 (C(O)N(H)CH₂CH₂C≡N), 25.8 (C(CH₃)₃), 18.0 (C(CH₃)₂), -4.8 (Si(CH₃)₃), -5.0 (Si(CH₃)₂); HRMS (ES⁺) m/z [Found: (M+NH₄)⁺ 650.3082 C₃₅H₆₈N₃O₅SSi requires (M+NH₄)⁺, 650.3078]; IR νmax/cm⁻¹ 3217 (w, N-Hamide), 2255 (w, C≡N), 1678, 1659 (s, C=Oamide), 1496, 1455 (m, C=C aromatic), 1243 (s, Si-C), 1096 (s, C-N), 1068 (s, Si-O).

S2.2. 3-propionitrile (phenyl 4-O-t-butyldimethylsilyl 2,3-di-O-benzyl-1-thio-α-D-mannopyranoside) amide 4

To a mixture of 2 (50 mg, 0.1 mmol, 1.0 equiv.), imidazole (20 mg, 0.29 mmol, 3.0 equiv.) and DMAP (5.9 mg, 50 µmol, 0.5 equiv.) in DMF (1 mL) was added TBDMSOTf (66 µL, d = 1.151, 0.29 mmol, 3.0 equiv.) dropwise. The reaction mixture was left stirring overnight at room temperature and was quenched with H₂O (0.1 mL). The mixture was concentrated under reduced pressure, and the remaining crude was reconstituted in CH₂Cl₂ (10 mL) and H₂O (5 mL). The organic layer was washed, separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure to furnish a colourless oil. Purification by silica gel flash column chromatography, eluting with EtOAc/hexane (0/100, 10/90, 20/80) afforded 4 as a white solid (50 mg, 79 µmol, 80%). Rf 0.46 (EtOAc/hexane, 1/2); [α]D +14.0 (c. 1.0, CHCl₃); mp: 119 °C; ¹H NMR (400 MHz; CDCl₃) δ 7.67 – 7.23 (15 H, m, Ar-H), 6.29 (1 H, t, J = 6.1 Hz, C(O)N(H)CH₂CH₂C≡N), 5.35 (1 H, d, J = 7.4 Hz, H₁), 4.57 (1 H, d, J = 12.1 Hz, CH₂Ph), 4.56 (1 H, d, J = 11.8 Hz, CH₂Ph), 4.50 (1 H, app. t, J = 3.4 Hz, H₄), 4.49 (1 H, d, J = 11.8 Hz, CH₂Ph), 4.47 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.19 (1 H, d, J = 3.9 Hz, H₅), 3.81 (1 H, dd, J = 7.3, 2.6 Hz, H₂), 3.56 (1 H, dd, J = 5.2, 2.6 Hz, H₃), 3.28 (1 H, dq, J = 13.1, 6.6 Hz, C(O)N(H)CH₂CH₂C≡N), 3.19 (1 H, td, J = 13.2, 6.5 Hz, C(O)N(H)CH₂CH₂C≡N), 2.31 (1 H, dt, J = 16.6, 6.6 Hz, C(O)N(H)CH₂CH₂C≡N), 2.25 – 2.12 (1 H, m, C(O)N(H)CH₂CH₂C≡N), 0.80 (9 H, s, C(CH₃)₃), 0.00 (3 H, s, Si(CH₃)₂), -0.08 (3 H, s, Si(CH₃)₂); ¹³C NMR (101 MHz; CDCl₃) δ 169.3 (C(O)N(H)CH₂CH₂C≡N), 137.9 (C₆), 137.8 (C₅), 133.5 (C₄), 133.0, 129.2, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 117.6 (C(O)N(H)CH₂CH₂C≡N), 84.1 (C₁), 77.5 (C₅), 74.2 (C₂), 72.4 (CH₂Ph), 72.4 (CH₂Ph), 68.7 (C₄), 35.3 (C(O)N(H)CH₂CH₂C≡N), 25.8 (C(CH₃)₃), 18.0 (C(CH₃)₂), -4.8 (Si(CH₃)₃), -5.0 (Si(CH₃)₂); HRMS (ES⁺) m/z [Found: (M+NH₄)⁺ 650.3082 C₃₅H₆₈N₃O₅SSi requires (M+NH₄)⁺, 650.3078]; IR νmax/cm⁻¹ 3217 (w, N-Hamide), 2255 (w, C≡N), 1678, 1659 (s, C=Oamide), 1496, 1455 (m, C=C aromatic), 1243 (s, Si-C), 1096 (s, C-N), 1068 (s, Si-O).

S2.3. Phenyl 2,3-di-O-benzyl-4-O-t-tert-butyldimethylsilyl-6-C-(1H-tetrazol-5-yl)-1-thio-α-D-mannopyranoside 5

Propionitrile 4 (60 mg, 0.11 mmol, 1.0 equiv.) was dissolved in toluene (10 mL) and TMSN₃ (84 µL, d = 0.872, 0.64 mmol, 6.0 equiv.) and Bu₂SnO (11 mg, 43 µmol, 0.4 equiv.) were added. The mixture was heated to 120 °C and stirred for 16 h. Upon completion, the mixture was cooled down to room temperature, diluted with EtOAc (50 mL) and washed with 0.1 M aq. HCl solution (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of this crude material by silica gel flash column chromatography, eluting with MeOH/CH₂Cl₂ (0/100,
1/99, 2/98) afforded 5 as a brown oil (34 mg, 56 µmol, 51%). R₆ 0.71 (MeOH/CH₂Cl₂, 1/2); [α]D²² +88.7 (c. 1.75, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 7.47 – 7.26 (15 H, m, Ar-H), 5.64 (1 H, d, J = 8.9 Hz, H₆), 5.45 (1 H, d, J = 1.8 Hz, H₂), 4.74 (1 H, d, J = 11.7 Hz, CH₂Ph), 4.73 (1 H, d, J = 11.8 Hz, CH₂Ph), 4.69 (1 H, d, J = 11.7 Hz, CH₂Ph), 4.65 (1 H, d, J = 11.8 Hz, CH₂Ph), 4.41 (1 H, app. t, J = 8.8 Hz, H₄), 4.09 (1 H, app. t, J = 2.6 Hz, H₂), 3.84 (1 H, dd, J = 8.6, 2.8 Hz, H₃), 0.78 (9 H, s, C(CH₃)₃), 0.00 (3 H, s, Si(CH₃)₂); ¹³C NMR (101 MHz; CDCl₃) δ 155.8 (Cq tetrazole), 137.6 (C₉), 137.1 (Cq), 132.8 (Cq), 132.2, 129.2, 128.6, 128.5, 128.3, 128.1, 128.0, 86.8 (C₁), 79.7 (C₃), 76.5 (C₂), 73.3 (CH₂Ph), 72.7 (CH₂Ph), 71.0 (C₄), 68.5 (C₅), 25.6 (C(CH₃)₃), 17.9 (C(CH₃)₃), -4.3 (Si(CH₃)₂), -5.9 (Si(CH₃)₂); HRMS (ES⁺) m/z [Found: (M+H)⁺ 605.2628 C₃₂H₄¹N₄O₄SSi requires (M+H)⁺ 605.2618].

S2.4. Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-1-thio-α-D-mannopyranoside 7

S2.4.1. Phenyl 2,3-di-O-benzyl-6-O-benzoyl-1-thio-α-D-mannopyranoside

To a stirred solution of 6¹ (1.0 g, 2.21 mmol, 1.0 equiv.), pyridine (357 µL, d = 0.978, 4.42 mmol, 2.0 equiv.), DMAP (81 mg, 0.7 mmol, 0.3 equiv.) in CH₂Cl₂ (10 mL) was added BzCl dropwise (269 µL, d = 1.211, 2.32 mmol, 1.05 equiv.) at 0 °C. The reaction was left stirring overnight at room temperature, and diluted with CH₂Cl₂ (15 mL). The mixture was washed with 1.0 M aq. HCl (10 mL), sat. aq. NaHCO₃ (10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by Revelers® automated silica gel flash column chromatography (liquid injection onto column), eluting with EtOAc/hexane (0/100, 5/95 and 10/90) afforded phenyl 2,3-di-O-benzyl-6-O-benzoyl-1-thio-α-D-mannopyranoside as a colourless oil (1.1 g, 2.0 mmol, 90%). R₆ 0.37 (EtOAc/hexane, 1/2); [α]D²² +48.2 (c. 7.5, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 8.03 – 7.19 (20 H, m, Ar-H), 5.65 (1 H, d, J = 1.3 Hz, H₁), 4.69 (1 H, d, J = 12.1 Hz, CH₂Ph-attached to C₂), 4.65 – 4.59 (2 H, m, H₆a,b), 4.61 (1 H, d, J = 12.7 Hz, CH₂Ph-attached to C₂), 4.55 (1 H, d, J = 10.5 Hz, CH₂Ph-attached to C₃), 4.52 (1 H, d, J = 10.1 Hz, CH₂Ph-attached to C₃), 4.43 (1 H, dt, J = 9.6, 3.9 Hz, H₅), 4.15 (1 H, dd, J = 9.6 Hz, H₄), 4.04 (1 H, dd, J = 3.0, 1.6 Hz, H₂), 3.73 (1 H, dd, J = 9.5, 3.0 Hz, H₃), 2.64 (1 H, br. s, C₄-OH); ¹³C NMR (101 MHz; CDCl₃) δ 166.7 (C(O)Ph), 137.8 (Cq), 137.7 (Cq), 134.1 (Cq), 133.0 (C₂), 131.5, 130.1, 129.8, 129.1, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.5, 85.7 (C₁), 79.6 (C₃), 75.7 (C₂), 72.1 (CH₂Ph), 71.9 (CH₂Ph), 71.7 (C₅), 66.9 (C₄), 64.1 (C₆); HRMS (ES⁺) m/z [Found: (M+NH₄)⁺ 574.2257 C₃₃H₃₂O₆SNH₄ requires (M+NH₄)⁺, 574.2258]; IR νmax/cm⁻¹ 3477 (br. s, C₄-OH), 1718 (s, C=O) ester, 1273 (s, C-O) ester, 1070 (s, C-O ether), 1025 (s, C-OH).

S2.4.2. Phenyl 2,3-di-O-benzyl-4-O-tert-butyldimethylsilyl-6-O-benzoyl-1-thio-α-D-mannopyranoside

To a mixture of phenyl 2,3-di-O-benzyl-6-O-benzoyl-1-thio-α-D-mannopyranoside (900 mg, 1.62 mmol, 1.0 equiv.), imidazole (330 mg, 4.85 mmol, 3.0 equiv.) and DMAP
(99 mg, 0.81 mmol, 0.5 equiv.) in DMF (10 mL) was added TBDMSOTf (1.1 mL, d = 1.151, 4.85 mmol, 3.0 equiv.) dropwise. The reaction mixture was left stirring overnight at room temperature and was quenched with H₂O (2 mL). The mixture was concentrated under reduced pressure, and the remaining crude was reconstituted in CH₂Cl₂ (50 mL) and H₂O (30 mL). The organic layer was washed, separated, dried over MgSO₄, filtered and concentrated under reduced pressure to furnish a colourless oil. Purification by silica gel flash column chromatography, eluting with EtOAc/hexane (0/100, 5/95, 10/90) afforded phenyl 2,3-di-O-benzyl-4-O-tert-butyldimethylsilyl-6-O-benzoyl-1-thio-α-D-mannopyranoside, as a colourless oil (846 mg, 1.27 mmol, 78%). Rf 0.75 (EtOAc/hexane, 1/2); [α]₂⁰° +57.8 (c. 1.37, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 7.96 – 7.10 (20 H, m, Ar-H), 5.54 (1 H, d, J = 1.7, H₁), 4.61 (1 H, dd, J = 11.6, 1.8 Hz, H₆bb), 4.57 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.57 (1 H, s, J = 11.9 Hz, CH₂Ph), 4.52 (1 H, d, J = 11.8 Hz, CH₂Ph), 4.50 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.39 (1 H, dd, J = 11.6, 5.8 Hz, H₆a), 4.35 – 4.29 (1 H, m, H₅), 4.19 (1 H, t, J = 9.1 Hz, H₄), 3.91 (1 H, dd, J = 2.7, 2.0 Hz, H₂), 3.61 (1 H, dd, J = 8.9, 2.9 Hz, H₃), 0.82 (9 H, s, C(CH₃)₃), 0.00 (6 H, d, J = 1.5 Hz, Si(CH₃)₂); ¹³C NMR (101 MHz; CDCl₃) δ 166.4 (C(O)Ph), 138.1 (Cₐ), 138.1 (Cₐ), 132.8 (Cₐ), 131.3 (Cₐ), 130.1, 129.7, 129.0, 128.3, 128.3, 127.9, 127.6, 127.6, 127.5, 127.3, 85.7 (C1), 80.3 (C₃), 76.2 (C2), 72.6 (C5), 72.1 (CH₃Ph), 71.8 (CH₂Ph), 68.2 (C4), 64.2 (C6), 26.0 (C(CH₃)₃), 18.2 (C(CH₃)₃), -3.8 (Si(CH₃)₂), -5.0 (Si(CH₃)₂); HRMS (ES⁺) m/z [Found: (M+NH₄)⁺ 688.3127 C₃₉H₅₀NO₆SSi requires (M+NH₄)⁺, 688.3123]; IR υmax/cm⁻¹ 1713 (s, C=Oester), 1276 (m, C-Oether), 1253 (m, Si-C), 1096 (s, Si-O), 1024 (m, C-Oether).

S2.4.3. Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-1-thio-α-D-mannopyranoside 7

To a stirred solution of phenyl 2,3-di-O-benzyl-4-O-tert-butyldimethylsilyl-6-O-benzoyl-1-thio-α-D-mannopyranoside (800 mg, 1.19 mmol, 1.0 equiv.) in anhydrous MeOH and THF (7 mL, 1/1 v/v), Na (14 mg, 0.60 mmol, 0.5 equiv.) dissolved in anhydrous MeOH (2 mL) was added dropwise at room temperature. The mixture was stirred overnight, then neutralised with ion exchange Amberlite 120 (H⁺) resin (approximately 0.7 g, 10 min), filtered, and concentrated under reduced pressure. Purification by silica gel flash column chromatography, eluting with Et₂O/hexane (0/100, 5/95, 10/90) afforded 7 as a colourless oil (596 mg, 1.07 mmol, 90%). Rf 0.69 (EtOAc/hexane, 1/2); [α]₂° +81.3 (c. 1.0, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 7.35 – 7.13 (15 H, m, Ar-H), 5.37 (1 H, d, J = 1.8 Hz, H₁), 4.51 (2 H, d, J = 12.5 Hz, CH₂Ph), 4.49 (1 H, d, J = 11.8 Hz, CH₂Ph), 4.44 (1 H, d, J = 11.9 Hz, CH₂Ph), 4.02 – 3.96 (1 H, m, H₄), 3.96 – 3.91 (1 H, m, H₅), 3.82 (1 H, dd, J = 2.8, 2.0 Hz, H₂), 3.72 (1 H, ddd, J 11.5, 6.6, 2.4 Hz, H₆bb), 3.64 (1 H, ddd, J = 11.6, 6.5, 5.2 Hz, H₆a), 3.53 (1 H, dd, J = 8.4, 2.9 Hz, H₃), 1.70 (1 H, t, J = 6.6 Hz, C₆-OH), 0.78 (9 H, s, C(CH₃)₃), 0.00 (3 H, s, Si(CH₃)₂), -0.05 (3 H, s, Si(CH₃)₂); ¹³C NMR (101 MHz; CDCl₃) δ 138.1 (Cₐ), 138.0 (Cₐ), 134.0 (Cₐ), 132.0, 129.1, 128.4, 128.3, 127.9, 127.7, 127.7, 127.6, 86.2 (C1), 80.4 (C₃), 76.4 (C₂), 74.8 (C₅), 72.5 (CH₂Ph), 72.0 (CH₂Ph), 67.9 (C₄), 62.2 (C₆), 26.0 (C(CH₃)₃), 18.2 (C(CH₃)₃), -3.8 (Si(CH₃)₂), -4.9
(Si(CH₃)₂); **HRMS (ES⁺) m/z** [Found: (M+NH₄)⁺ 584.2875 C₃₂H₄₆NO₅SSi requires (M+NH₄)⁺, 584.2850]; **IR νmax/cm⁻¹** 1454 (w, C=C aromatic), 1248 (m, C-Si), 1084 (s, Si-O).

S2.5. C-6 oxime thioglycoside 8

**S2.5.1. C6-aldehyde thioglycoside intermediate**

To a stirred solution of 7 (60 mg, 0.11 mmol, 1.0 equiv.) in DMSO (1 mL) was added Et₃N (44 µL, d = 0.726, 0.32 mmol, 3.0 equiv.) and sulfur trioxide pyridine complex (51 mg, 0.32 mmol, 3.0 equiv.) at room temperature. The reaction mixture was left stirring for 1 h before it was diluted with EtOAc (30 mL) and H₂O (20 mL). The whole was extracted with EtOAc (3 x 15 mL) and the extracts were washed with H₂O (6 x 20 mL) and brine (20 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude aldehyde was obtained as a colourless oil (60 mg, 0.11 mmol, 98%) and used immediately in the next step, without further purification. Rf 0.684 (EtOAc/hexane, 1/2); [α]D²⁻ 14.4 (c. 0.33, CHCl₃); **¹H NMR (400 MHz; CDCl₃) δ** 9.77 (1 H, s, CHO), 7.56 – 7.25 (15 H, m, Ar-H), 5.56 (1 H, d, J = 6.4 Hz, H₁), 4.57 (1 H, d, J = 11.9 Hz, CH₂Ph), 4.52 (2 H, s, CH₂Ph), 4.43 (1 H, d, J = 11.9 Hz, CH₂Ph), 4.26 – 4.20 (2 H, m, H₄, H₅), 3.83 (1 H, dd, J = 6.2, 2.3 Hz, H₂), 3.60 (1 H, dd, J = 5.8, 2.5 Hz, H₃), 0.82 (9 H, s, C(CH₃)₃), 0.00 (3 H, s, Si(CH₃)₂); **¹³C NMR (101 MHz; CDCl₃) δ** 198.0 (CHO), 137.8 (C₁), 137.6 (C₄), 133.5 (C₉), 132.4, 131.8, 129.0, 128.5, 128.4, 128.0, 127.9, 127.8, 127.5, 83.8 (C₁), 81.15 (C₅), 77.2 (C₃), 73.8 (C₂), 72.5 (CH₂Ph), 72.3 (CH₂Ph), 68.9 (C₄), 25.7 (C(CH₃)₃), 18.0 (C(CH₃)₃), -4.6 (Si(CH₃)₂), -5.0 (Si(CH₃)₂); **HRMS (ES⁺) m/z** [Found: (M+NH₄)⁺ 582.2723 C₃₂H₄₄NO₅SSi requires (M+NH₄)⁺, 582.2704].

S2.5.2. C-6 oxime thioglycoside 8

The crude C-6 aldehyde (4.5 g, 7.97 mmol, 1.0 equiv.) was dissolved in THF (790 mL) and a solution of H₂NOH.HCl (554 mg, 7.97 mmol, 1.0 equiv.) dissolved in H₂O (15 mL) was added dropwise. The mixture was cooled to 0 °C and a solution of Na₂CO₃ (1.0 g, 9.56 mmol, 1.2 equiv.) dissolved in H₂O (9.5 mL) was added dropwise. The solution was slowly warmed to room temperature and stirred for 24 h. The mixture was diluted with H₂O (30 mL) and then extracted with EtOAc (4 x 300 mL). The organic layers were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The obtained crude oil was purified using silica gel flash column chromatography, eluting with Et₂O/petroleum ether (0/100, 5/95, 10/90, 20/80) to furnish 8 as a colourless oil. Cis and trans (1/6.7) were isolated separately (major isomer: 2.82 g, 4.86 mmol, 71%, minor isomer: 416 mg, 0.72 mmol, 9%) and both were used in the next step; Major isomer Rf 0.78; minor isomer Rf 0.68; (EtOAc/petroleum ether, 1/2); major: [α]D²⁰ +57.7 (c. 0.46, CHCl₃); minor: [α]D²⁰ +41.3 (c. 1.0, CHCl₃); **¹H NMR (400 MHz; CDCl₃) Major isomer δ** 7.46 – 7.17 (16 H, m, Ar-H, HCl=N), 5.40 (1 H, d, J = 1.8 Hz, H₁), 4.58 (1 H, d, J = 10.5 Hz, CH₂Ph), 4.57 (1 H, m, H₅), 4.55 (1 H, d, J = 10.1 Hz, CH₂Ph), 4.54 (1 H, d, J = 12.4 Hz, CH₂Ph).
Hz, CH₂Ph), 4.50 (1 H, d, J = 11.9 Hz, CH₂Ph), 4.06 (1 H, app. t, J = 9.0 Hz, H₄), 3.89 – 3.86 (1 H, m, H₂), 3.59 (1 H, dd, J = 8.9, 2.9 Hz, H₃), 0.81 (9 H, s, C(CH₃)₃), 0.00 (3 H, s, Si(CH₂)₂), -0.01 (3 H, s, Si(CH₂)₂); ¹³C NMR (101 MHz; CDCl₃) δ 149.3 (HC≡N), 138.1 (C₁), 137.9 (C₉), 134.0 (C₉), 131.9, 129.1, 128.4, 128.4, 127.9, 127.85, 127.8, 127.7, 127.6, 86.3 (C₁), 79.8 (C₃), 76.3 (C₂), 72.5 (C₅), 72.5 (CH₂Ph), 72.2 (CH₂Ph), 69.8 (C₄), 25.8 (C(CH₃)₂), 18.1 (C(CH₃)₃), -4.0 (Si(CH₃)₂), -4.6 (Si(CH₃)₂); HRMS (ES⁺) m/z [Found: (M+NH₄)⁺ 597.2815 C₃₂H₄₅N₂O₅SSi requires (M+NH₄)⁺, 597.2813].

S2.6. C-6 nitrile thioglycoside 9

Oxime 8 (120 mg, 0.21 mmol, 1.0 equiv.) was dissolved in dry acetonitrile (21 mL) and POCl₃ (19 µL, d = 1.645, 0.21 mmol, 1.0 equiv.) was added at room temperature. The solution was stirred for 5 min. at room temperature, heated up to 65 °C and then stirred for 3 h. The reaction was quenched with sat. aq. NaHCO₃ solution (20 mL) and extracted with EtOAc (3 x 60 mL). The organic layers were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified using silica gel flash column chromatography, eluting with Et₂O/petroleum ether (0/100, 5/95, 10/90, 20/80) to furnish 9 as a yellow oil (47 mg, 84 µmol, 40%). Rₐ 0.90 (EtOAc/hexane, 1/2); [α]₂⁰° +39.4 (c. 0.53, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 7.44 – 7.21 (15 H, m, Ar-H), 5.45 (1 H, d, J = 3.0 Hz, H₁), 4.76 (1 H, d, J = 8.3 Hz, H₃), 4.60 (1 H, d, J = 11.9 Hz, CH₂Ph), 4.58 (1 H, d, J = 12.1 Hz, CH₂Ph), 4.55 (1 H, d, J = 12.1 Hz, CH₂Ph), 4.53 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.21 (1 H, app. t, J = 8.2 Hz, H₄), 3.84 (1 H, app. t, J = 2.9 Hz, H₂), 3.49 (1 H, dd, J = 8.2, 2.9 Hz, H₃), 0.89 (9 H, s, C(CH₃)₃), 0.18 (3 H, s, Si(CH₃)₂), 0.05 (3 H, s, Si(CH₃)₂); ¹³C NMR (101 MHz; CDCl₃) δ 137.5 (C₁), 137.1 (C₉), 132.9 (C₀), 131.5, 129.4, 129.3, 129.1, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.6, 127.2, 124.4, 117.0 (C≡N), 85.9 (C₁), 78.8 (C₃), 75.3 (C₂), 72.6 (CH₂Ph), 72.5 (CH₂Ph), 69.4 (C₄), 64.7 (C₅), 25.8 (C(CH₃)₃), 18.0 (C(CH₃)₃), -4.1 (Si(CH₃)₂), -4.8 (Si(CH₃)₂); HRMS (ES⁺) m/z [Found: (M+NH₄)⁺ 579.2732 C₃₂H₄₅N₂O₅SSi requires (M+NH₄)⁺, 579.2707].

S2.6.1. 4-postion deprotected by-product 10

Alcohol 10 was also isolated as a yellow oil (24 mg, 54 µmol, 26%) from the crude mixture containing 9. Rₐ 0.82 (EtOAc/hexane, 1/2); [α]₂⁰° +15.4 (c. 0.95, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 7.41 – 7.28 (15 H, m, Ar-H), 5.51 (1 H, d, J = 1.7 Hz, H₁), 4.87 (1 H, d, J = 9.8 Hz, H₃), 4.66 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.60 (1 H, d, J = 12.0 Hz, CH₂Ph), 4.57 (1 H, d, J = 12.2 Hz, CH₂Ph), 4.55 (1 H, d, J = 11.8 Hz, CH₂Ph), 4.32 (1 H, app. t, J = 9.6 Hz, H₄), 3.96 (1 H, dd, J = 2.7, 2.0 Hz, H₂), 3.57 (1 H, dd, J = 9.3, 2.9 Hz, H₃), 2.92 (1 H, br. s, C₄-OH); ¹³C NMR (101 MHz; CDCl₃) δ 137.3 (C₁), 137.2 (C₉), 132.7 (C₀), 131.5, 129.4, 128.7, 128.6, 128.3, 128.3, 128.1, 128.0, 128.0, 116.6 (C≡N), 86.6 (C₁), 78.4 (C₃), 75.4 (C₂), 72.5 (CH₂Ph), 72.4 (CH₂Ph), 68.3 (C₄), 63.1 (C₃); HRMS (ES⁺) m/z [Found: (M+NH₄)⁺ 465.1857 C₂₆H₂₉N₂O₄S requires (M+NH₄)⁺, 465.1843].
S2.7. PMB-protected C-6 tetrazole thioglycosides 11 and 12

To a stirred solution of 5 (130 mg, 0.21 mmol, 1.0 equiv.) in DMF (2 mL) was added successively, KI (53 mg, 0.32 mmol, 1.5 equiv.), K$_2$CO$_3$ (44 mg, 0.32 mmol, 1.5 equiv.) and PMBCl (58 µL, d = 1.155, 0.43 mmol, 2.0 equiv.). The reaction was left stirring for 4 h and was diluted with CH$_2$Cl$_2$ (10 mL). The organic layer was washed with 10% aq. Na$_2$S$_2$O$_3$ solution (10 mL) and brine (10 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified using silica gel flash column chromatography, eluting with acetone/toluene (1/250, 1/150, 1/100) to furnish isomers 11 and 12 (80 mg, 0.11 mmol, 53%) as oils.

S2.7.1. Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-6-C-(1-para-methoxybenzyl-tetrazol-5-yl)-1-thio-α-D-mannopyranoside 11

N$_1$-regioisomer 11 was isolated as a yellow oil (42 mg, 58 µmol, 28%). R$_t$ 0.42 (acetone/toluene, 1/50); [α]$_D^{22}$ +25.4 (c. 0.53, CHCl$_3$); $^1$H NMR (400 MHz; CDCl$_3$) δ 7.56 – 7.39 (16 H, m, Ar-H), 7.36 (2 H, d, J = 8.7 Hz, Ar-H PMB), 5.76 (1 H, d, J = 1.8 Hz, H$_1$), 5.68 (1 H, d, J = 9.4 Hz, H$_5$), 5.66 (1 H, d, J = 15.0 Hz, CH$_2$Ph-PMB), 5.63 (1 H, d, J = 15.0 Hz, CH$_2$Ph-PMB), 4.83 (1 H, d, J = 11.6 Hz, CH$_2$Ph-attached to C2), 4.81 (1 H, d, J = 12.0 Hz, CH$_2$Ph-attached to C3), 4.78 (1 H, d, J = 11.1 Hz, CH$_2$Ph-attached to C2), 4.75 (1 H, d, J = 11.7 Hz, CH$_2$Ph-attached to C3), 4.59 (1 H, app. t, J = 9.4 Hz, H$_4$), 4.22 – 4.19 (1 H, m, H$_2$), 3.87 (3 H, s, OCH$_3$), 3.86 – 3.84 (1 H, m, H$_3$), 0.79 (9 H, s, C(CH$_3$)$_3$), 0.00 (3 H, s, Si(CH$_3$)$_2$), -0.53 (3 H, s, Si(CH$_3$)$_2$); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 159.7 (C$_1$), 152.0 (C$_q$ PMB), 152.0 (C$_q$ tetrazole), 137.8 (C$_q$), 137.5 (C$_q$), 133.5 (C$_q$), 131.1 (C$_q$), 129.9, 129.2, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 125.7, 114.1, 86.5 (C1), 80.1 (C3), 76.4 (C2), 72.9 (CH$_2$Ph-attached to C2), 72.1 (CH$_2$Ph-attached to C3), 70.0 (C4), 67.7 (C5), 55.2 (CH$_2$Ph PMB), 50.8 (OCH$_3$), 25.6 (C(CH$_3$)$_3$), 17.8 (C(CH$_3$)$_3$), -4.5 (Si(CH$_3$)$_2$), -6.1 (Si(CH$_3$)$_2$); $^{13}$C-GATED (101 MHz; CDCl$_3$): 86.5 ($^{13}$C$_{C1,H1}$ =172 Hz, C1); HRMS (ES$^+$) m/z [Found: (M+H)$^+$ 725.3177 C$_{49}$H$_{49}$NaO$_5$Si requires (M+H)$^+$, 725.3187].

S2.7.2. Phenyl2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-6-C-(2-para-methoxybenzyl-tetrazol-5-yl)-1-thio-α-D-mannopyranoside 12

N$_1$-regioisomer 12 was isolated as a yellow oil (38 mg, 52 µmol, 25%). R$_t$ 0.48 (acetone/toluene, 1/50); [α]$_D^{22}$ +40.6 (c. 0.86, CHCl$_3$); $^1$H NMR (400 MHz; CDCl$_3$) δ 7.43 – 7.21 (18 H, m, Ar-H), 6.87 (2 H, d, J = 8.7 Hz, Ar-H PMB), 5.67 (1 H, d, J = 14.1 Hz, CH$_2$Ph-PMB), 5.62 (1 H, d, J = 14.0 Hz, CH$_2$Ph-PMB), 5.56 (1 H, d, J = 1.9 Hz, H$_1$), 5.40 (1 H, d, J = 9.2 Hz, H$_3$), 4.67 (1 H, d, J = 12.3 Hz, CH$_2$Ph-attached to C2), 4.60 (1 H, app. t, J = 9.1 Hz, H$_4$), 4.57 (1 H, d, J = 12.4 Hz, CH$_2$Ph-attached to C2), 4.56 (1 H, d, J = 12.9 Hz, CH$_2$Ph-attached to C3), 4.52 (1 H, d, J = 12.0 Hz, CH$_2$Ph-attached to C3), 4.01 – 3.99
(1 H, m, H2), 3.79 (3 H, s, OCH3), 3.70 (1 H, dd, J = 8.9, 2.9 Hz, H3), 0.50 (9 H, s, C(CH3)3), -0.11 (3 H, s, Si(CH3)2), -0.55 (3 H, s, Si(CH3)2); 13C NMR (101 MHz; CDCl3) δ 164.4 (Cq tetrazole), 160.1 (Cq PMB), 138.0 (Cq), 133.9 (Cq), 131.8 (Cq), 130.6 (Cq), 129.0, 128.3, 128.3, 127.8, 127.7, 127.6, 127.5, 125.0, 114.3, 86.5 (C1), 80.2 (C3), 75.7 (C2), 72.1 (CH2Ph-attached to C2), 71.6 (CH2Ph-attached to C3), 70.4 (C4), 69.1 (C5), 56.5 (CH2Ph PMB), 55.3 (OCH3), 25.5 (C(CH3)3), 17.7 (C(CH3)3), -4.1 (Si(CH3)2), -5.9 (Si(CH3)2); HRMS (ES+) m/z [Found: (M+H)+ 725.3192 C40H50N4O5Si requires (M+H)+, 725.3187].

S2.8. Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-6-C-(1H-tetrazol-5-yl)-1-thio-α-d-mannopyranoside triethylammonium salt

To a stirred solution of 5 (75 mg, 0.12 mmol, 1.0 equiv.) in CH2Cl2 (1 mL) was added Et3N (17 µL, d = 0.726, 0.12 mmol, 1.0 equiv.). The reaction was left stirring for 1 h and then was dried in vacuo, giving the title compound as a yellow oil (80 mg, 0.11 mmol, 94%). [α]D2+ = -42.2 (c 0.46, CHCl3); 1H NMR (400 MHz; CDCl3) δ 7.51 – 7.26 (15 H, m, Ar-H), 5.62 (1 H, d, J = 9.3 Hz, H5), 5.56 (1 H, d, J = 1.5 Hz, H1), 4.77 (1 H, d, J = 11.9 Hz, CH2Ph), 4.74 (1 H, d, J = 11.8 Hz, CH2Ph), 4.71 (1 H, d, J = 12.0 Hz, CH2Ph), 4.67 (1 H, d, J = 11.3 Hz, CH2Ph), 4.53 (1 H, app. t, J = 9.1 Hz, H4), 4.13 (1 H, app. t, J = 2.2 Hz), 3.86 (1 H, dd, J = 8.9, 2.9 Hz, H3), 3.05 (6 H, q, J = 7.3 Hz, N(CH2CH3)3), 1.23 (9 H, t, J = 7.3 Hz, N(CH2CH3)3), 0.75 (9 H, s, C(CH3)3), 0.00 (3 H, s, Si(CH3)2), -0.43 (3 H, s, Si(CH3)2); 13C NMR (101 MHz; CDCl3) δ 159.6 (Cq tetrazole), 138.2 (Cq), 138.1 (Cq), 134.3 (Cq), 131.9, 128.9, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6, 127.4, 86.9 (C1), 81.0 (C3), 77.2 (C2), 73.1 (CH2Ph), 72.3 (CH2Ph), 71.7 (C4), 69.8 (C5), 45.2 (N(CH2CH3)3), 25.7 (C(CH3)3), 17.9 (C(CH3)3), 8.5 (N(CH2CH3)3), -4.4 (Si(CH3)2), -5.9 (Si(CH3)2).

S2.9. Bn-protected C-6 tetrazole thioglycosides 13 and 14

To a stirred solution of phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-6-C-(1H-tetrazol-5-yl)-1-thio-α-d-mannopyranoside triethylammonium salt (80 mg, 0.11 mmol, 1.0 equiv.) in DMF (1.1 mL) was added BnBr (20 µL, d = 1.438, 0.17 mmol, 1.5 equiv.). The reaction was left stirring for 3 h and was diluted with CH2Cl2 (10 mL). The organic layer was washed with brine (10 mL), dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was purified using silica gel flash column chromatography, eluting with acetone/toluene (1/250, 1/150, 1/100) to furnish the inseparable isomers 13 and 14 as colourless oil in 1/1.2 ratio (24 mg, 34 µmol, 31%). Rf 0.80 (EtOAc/petroleum ether, 1/50); 1H NMR (400 MHz; CDCl3) δ 7.41 – 7.18 (40 H, m, Ar-H), 5.73 (1 H, d, J = 14.3 Hz, CH2Ph benzyl tetrazole, N2-isomer), 5.68 (1 H, d, J = 14.2 Hz, CH2Ph benzyl tetrazole, N2-isomer), 5.57 (1 H, d, J = 2.7 Hz, H1 N1-isomer), 5.56 (1 H, d, J = 2.4 Hz, H1 N2-isomer), 5.54 (2 H, d, J = 1.9 Hz, CH2Ph benzyl tetrazole, N1-isomer), 5.50 (1 H, d, J = 9.5 Hz, H5 N1-isomer), 5.40 (1 H, d, J = 9.2 Hz, H5 N2-isomer), 4.67 (1 H, d, J = 12.2 Hz, CH2Ph), 4.65 (1 H, d, J = 11.6 Hz, CH2Ph), 4.63 (1 H, d, J =
12.2 Hz, \( CH_2Ph \)), 4.61 (1 H, d, \( J = 11.9 \) Hz, \( CH_2Ph \)), 4.60 (1 H, m, H, N2-isomer) 4.59 (1 H, d, \( J = 11.7 \) Hz, \( CH_2Ph \)), 4.57 (1 H, d, \( J = 12.3 \) Hz, \( CH_2Ph \)), 4.54 (2 H, s, \( CH_2Ph \)), 4.43 (1 H, app. t, \( J = 9.1 \) Hz, H4 N1-isomer), 4.04 (1 H, app. t, \( J = 2.8 \) Hz, H2 N1-isomer), 4.00 (1 H, app. t, \( J = 2.6 \) Hz, H2 N2-isomer), 3.70 (1 H, dd, \( J = 8.9 \), 2.9 Hz, H3 N1 and N2-isomers), 0.63 (9 H, s, C(CH3)3), 0.51 (9 H, s, C(CH3)3), -0.11 (3 H, s, Si(CH3)2), -0.17 (3 H, s, Si(CH3)2), -0.54 (3 H, s, Si(CH3)2), -0.68 (3 H, s, Si(CH3)2); \(^{13}C\) NMR (101 MHz; CDCl3) 164.5 (Cq tetrazole, N2-isomer), 152.3 (Cq tetrazole, N1-isomer), 138.0 (Cq), 137.9 (Cq), 137.8 (Cq), 137.5 (Cq), 134.5 (Cq), 133.9 (Cq), 133.6 (Cq), 133.5 (Cq), 132.8, 131.8, 131.0, 129.2, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 86.5 (C1, N1 or N2-isomer), 86.4 (C1, N1 or N2-isomer), 80.2 (C3, N1 or N2-isomer), 80.1 (C3, N1 or N2-isomer), 76.3 (C2, N1-isomer), 75.7 (C2, N2-isomer), 72.9 (CH2Ph), 72.1 (2C, CH2Ph), 71.6 (CH2Ph), 70.4 (C4, N2-isomer), 69.9 (C4, N1-isomer), 69.1 (C5, N2-isomer), 67.8 (C5, N1-isomer), 56.9 (CH2Ph tetrazole, N2-isomer), 51.2 (CH2Ph tetrazole, N1-isomer), 25.6 (C(CH3)3), 25.5 (C(CH3)3), 17.8 (C(CH3)3), 17.7 (C(CH3)3), -4.2 (Si(CH3)2), -4.5 (Si(CH3)2), -5.9 (Si(CH3)2), -6.0 (Si(CH3)2); \(^{13}C\).GATED (101 MHz; CDCl3): 86.5 and 86.4 (\(^1J\)C1-H1 = 168 Hz, C1); HRMS (ES\(^{+}\)) m/z [Found: (M+H\(^{+}\)) 695.3084 C\(_{39}\)H\(_{47}\)N\(_{4}\)O\(_{4}\)SSi requires (M+H\(^{+}\)) 695.3082].

S2.10. C-6 nitrile thioglycoside 16

S2.10.1. C-6 aldehyde thioglycoside intermediate

To a stirred solution of 15\(^2\) (420 mg, 0.77 mmol, 1.0 equiv.) in dimethyl sulfoxide (7.7 mL) was added Et\(_3\)N (323 μL, d = 0.726, 2.32 mmol, 3.0 equiv.) and sulfur trioxide pyridine complex (369 mg, 2.32 mmol, 3.0 equiv.) at room temperature. The reaction mixture was left stirring for 1 h before it was diluted with EtOAc (25 mL) and H\(_2\)O (20 mL). The whole was extracted with EtOAc (3 x 20 mL) and the extracts were washed with H\(_2\)O (5 x 30 mL) and brine (2 x 30 mL). The organic layer was dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The crude aldehyde was obtained as a yellow oil (400 mg, 0.74 mmol, 96%) and was carried on the next step without further purification. R\(_f\) 0.83 (EtOAc/hexane, 1/2); [α]\(^D\)\(_{20}\) +40.5 (c. 1.0, CHCl3); \(^{1}H\) NMR (400 MHz; CDCl3) δ 9.73 (1 H, s, CHO), 7.49 – 7.27 (20 H, m, Ar-H), 5.59 (1 H, t, \( J = 6.3 \) Hz, H1), 4.69 (1 H, d, \( J = 12.9 \) Hz, CH2Ph), 4.63 (1 H, d, \( J = 12.8 \) Hz, CH2Ph), 4.59 (2 H, d, \( J = 12.0 \) Hz, CH2Ph), 4.55 (1 H, d, \( J = 11.9 \) Hz, CH2Ph), 4.54 (1 H, d, \( J = 12.5 \) Hz, CH2Ph), 4.49 (1 H, d, \( J = 7.7 \) Hz, H3), 4.08 (1 H, app. t, \( J = 7.7 \) Hz, H4), 3.94 – 3.91 (1 H, m, H2), 3.87 (1 H, dd, \( J = 7.6 \), 2.8 Hz, H3); \(^{13}C\) NMR (101 MHz; CDCl3) δ 197.6 (CHO), 137.6 (Cq), 137.6 (Cq), 137.6 (Cq), 133.5 (Cq), 131.6, 129.1, 128.5, 128.4, 128.0, 128.0, 128.0, 127.9, 127.9, 127.6, 84.9 (C1), 77.4 (C3), 77.2 (C5), 75.0 (C2), 74.7 (C4), 74.3 (CH2Ph), 72.3 (CH2Ph), 72.2 (CH2Ph). These data were consistent with literature values.\(^2\)
S2.10.2 C-6 oxime thioglycoside intermediate

The crude aldehyde from the previous step (4.72 g, 8.73 mmol, 1.0 equiv.) was dissolved in THF (873 mL) and a solution of H₂NOH.HCl (606 mg, 8.73 mmol, 1.0 equiv.) dissolved in H₂O (17.5 mL) was added dropwise. The mixture was cooled to 0 °C and a solution of Na₂CO₃ (1.1 g, 10.5 mmol, 1.2 equiv.) dissolved in H₂O (10.5 mL) was added dropwise. The solution was slowly warmed to room temperature and stirred for 24 h. The mixture was diluted with H₂O (200 mL) and then extracted with EtOAc (4 x 400 mL). The organic layers were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The obtained crude oil was purified using silica gel flash column chromatography, eluting with EtOAc/petroleum ether (0/100, 5/95, 10/90, 20/80) to furnish the title compound as a colourless oil. *cis* and *trans* (1/7) isomers were isolated separately (major isomer: 3.8 g, 6.54 mmol, 78%, minor isomer: 550 mg, 0.99 mmol, 11%) and both were used for the next step. Major isomer R₁ 0.70; minor isomer R₁ 0.62 (EtOAc/petroleum ether, 1/2); major: [α]₀° +87.7 (c. 3.1, CHCl₃); ¹H NMR (400 MHz; CDCl₃) major isomer δ 7.46 (1 H, d, J = 6.5 Hz, HC=N); 7.47 – 7.25 (20 H, m, Ar-H), 5.49 (1 H, d, J = 1.5 Hz, H₁), 4.86 (1 H, d, J = 10.9 Hz, CH₂Ph), 4.73 (1 H, dd, J = 10.5, 5.6 Hz, H₃), 4.68 (1 H, d, J = 12.4 Hz, CH₂Ph), 4.66 (1 H, d, J = 11.7 Hz, CH₂Ph), 4.65 (1 H, d, J = 10.7 Hz, CH₂Ph), 4.64 (1 H, d, J = 12.3 Hz, CH₂Ph), 4.61 (1 H, d, J = 11.7 Hz, CH₂Ph), 4.01 (1 H, app. t, J = 9.4 Hz, H₄), 4.01– 3.98 (1 H, m, H₂), 3.87 (1 H, dd, J = 9.2, 2.9 Hz, H₃); ¹³C NMR (101 MHz; CDCl₃) δ 148.7 (HC=N), 138.1 (C₅), 137.7 (C₄), 133.9 (C₉), 129.1, 128.4, 128.4, 128.3, 128.5, 128.0, 127.8, 127.8, 127.8, 127.6, 86.1 (C¹), 79.5 (C₃), 76.4 (1 C, C₂ or C₄), 76.3 (1 C, C₂ or C₄), 75.1 (CH₂Ph), 72.4 (CH₂Ph), 72.3 (CH₂Ph), 70.6 (C₅); HRMS (ES⁺) m/z [Found: (M+Na)⁺ 578.1993, C₃₅H₃₃NO₅SNa requires (M+Na)⁺, 578.1977].

S2.10.3 C-6 nitrile thioglycoside 16

The previously synthesised oxime (4.35 g, 7.83 mmol, 1.0 equiv.) was dissolved in dry MeCN (783 mL) and POCl₃ (729 µL, d = 1.645, 7.83 mmol, 1.0 equiv.) was added at room temperature. The solution was stirred for 5 min. at room temperature, heated up to 65 °C and then stirred for 3 h. The reaction was quenched with sat. aq. NaHCO₃ solution (20 mL) and extracted with EtOAc (3 x 300 mL). The organic layers were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified using silica gel flash column chromatography, eluting with EtOAc/petroleum ether (0/100, 5/95, 10/90, 20/80) to furnish 16 as a yellow oil (2.5 g, 4.65 mmol, 59%). R₁ 0.76 (EtOAc/hexane, 1/2); [α]₀° +71.0 (c. 0.93, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 7.38 – 7.28 (20 H, m, Ar-H), 5.48 (1 H, d, J = 2.2 Hz, H₁), 4.88 (1 H, d, J = 12.9 Hz, CH₂Ph), 4.88 (1H, d, J = 9.7 Hz, H₅), 4.68 (1 H, d, J = 12.1 Hz, CH₂Ph), 4.66 (2 H, d, J = 11.6 Hz, CH₂Ph), 4.63 (1 H, d, J = 11.9 Hz, CH₂Ph), 4.60 (1 H, d, J = 11.7 Hz, CH₂Ph), 4.19 (1 H, app.t, J = 9.2 Hz, H₄), 3.93 (1 H, app. t, J = 2.6 Hz, H₂), 3.71 (1 H, dd, J = 8.9, 2.9 Hz, H₃); ¹³C NMR (101 MHz; CDCl₃) δ 137.5 (C₅), 137.3 (C₄), 137.2
(C₆), 132.7 (C₅), 131.5 (C₄), 129.3, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 117.1 (C≡N), 86.2 (C₁), 78.4 (C₃), 76.1 (C₄), 75.8 (C₂ or CH₃Ph), 75.7 (C₂ or CH₂Ph), 72.7 (CH₂Ph), 72.6 (CH₂Ph), 62.2 (C₅); HRMS (ES⁺) m/z [Found: (M+H)⁺ 538.2068 C₃₃H₃₃NO₄S requires (M+H)⁺, 538.2052].

S2.11. Phenyl 2,3,4-tri-O-benzyl-6-C-(1H-tetrazol-5-y1)-1-thio-α-D-mannopyranoside 17

C₆-nitrile thioglycoside 16 (2.5 g, 4.65 mmol, 1.0 equiv.) was dissolved in toluene (465 mL) and TMSN₃ (3.7 mL, d = 0.872, 27.9 mmol, 6.0 equiv.) and Bu₂SnO (463 mg, 1.86 mmol, 0.4 equiv.) were added. The mixture was heated to 120 °C and stirred for 16 h. Upon completion, the mixture was cooled down to room temperature, diluted with EtOAc (400 mL) and washed with 0.1 M aq. HCl (250 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification of the crude material by silica gel flash column chromatography, eluting with MeOH/CH₂Cl₂ (0/100, 2/98, 5/95) afforded 17 as a brown oil (1.5 g, 2.58 mmol, 55%). Rf 0.65 (MeOH/CH₂Cl₂, 1/9); [α]D⁰ +95.0 (c. 1.96, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 7.37 – 7.08 (20 H, m, Ar-H), 5.61 (1 H, d, J = 9.7 Hz, H₅), 5.54 (1 H, d, J = 1.7 Hz, H₁), 4.71 (2 H, d, J = 11.9 Hz, CH₂Ph), 4.70 (1 H, d, J = 10.5 Hz, CH₂Ph), 4.65 (2 H, d, J = 11.8 Hz, CH₂Ph), 4.38 (1 H, d, J = 10.7 Hz, CH₂Ph), 4.19 (1 H, app. t, J = 9.4 Hz, H₄), 4.08 (1 H, dd, J = 2.7, 2.1 Hz, H₂), 3.99 (1 H, dd, J = 9.2, 2.9 Hz, H₃); ¹³C NMR (101 MHz; CDCl₃) δ 155.0 (C₆ tetrazole), 137.6 (C₆), 137.1 (C₅), 137.0 (C₄), 132.8 (C₃), 132.0, 129.3, 128.7, 128.6, 128.6, 128.4, 128.4, 128.1, 128.1, 128.0, 127.9, 86.8 (C₁), 79.4 (C₃), 76.6 (C₂ and C₄), 75.0 (CH₂Ph), 73.3 (CH₂Ph), 72.8 (CH₂Ph), 66.5 (C₅); HRMS (ES⁺) m/z [Found: (M+H)⁺ 581.2251 C₃₃H₃₄NO₄S requires (M+H)⁺, 581.2223].

S2.12. PMB-protected C-6 tetrazole thioglycosides 18 and 19

To a stirred solution of 17 (920 mg, 1.37 mmol, 1.0 equiv.) in DMF (10 mL) was added successively, KI (341 mg, 2.06 mmol, 1.5 equiv.), K₂CO₃ (227 mg, 1.65 mmol, 1.2 equiv.) and PMBCl (279 µL, d = 1.155, 2.06 mmol, 1.5 equiv.). The reaction was left stirring for 16 h and was diluted with CH₂Cl₂ (30 mL). The organic layer was washed with 10% aq. Na₂S₂O₃ solution (30 mL) and brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified using silica gel flash column chromatography, eluting with EtOAc/petroleum ether (5/95, 10/90, 15/85) to furnish isomers 18 and 19 (732 mg, 1.04 mmol, 76%) as colourless oils.

S2.12.1. Phenyl 2,3,4-tri-O-benzyl-6-C-(1-para-methoxybenzyl-tetrazol-5-y1)-1-thio-α-D-mannopyranoside 18

N₁-regioisomer 18 was isolated as a yellow oil (374 mg, 0.53 mmol, 39%). Rf 0.72 (EtOAc/petroleum ether, 1/2); [α]D⁰ +48.5 (c. 2.75, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 7.39 – 6.95 (21 H, m, Ar-H), 7.00 (2 H, d, J = 8.8 Hz, Ar-H PMB), 6.65 (2 H, d, J = 8.8 Hz, Ar-H PMB), 5.61 (1 H, d, J = 1.6 Hz, H₁), 5.45 (1 H, d, J = 9.9 Hz, H₅), 5.28 (1 H, d, J =
15.0 Hz, CH₂Ph-PMB), 5.19 (1 H, d, J = 15.0 Hz, CH₂Ph-PMB), 4.72 (2 H, d, J = 12.5 Hz, CH₂Ph), 4.70 (1 H, d, J = 11.7 Hz, CH₂Ph), 4.67 (1 H, d, J = 11.0 Hz, CH₂Ph), 4.65 (1 H, d, J = 12.3 Hz, CH₂Ph), 4.45 (1 H, app. t, J = 9.6 Hz, H₄), 4.33 (1 H, d, J = 10.6 Hz, CH₂Ph), 4.08 (1 H, dd, J = 2.7, 2.0 Hz, H₂), 3.93 (1 H, dd, J = 9.2, 2.8 Hz, H₃), 3.70 (3 H, s, OCH₃); ¹³C NMR (101 MHz; CDCl₃) δ 159.6 (Cq PMB), 152.2 (Cq tetrazole), 137.8 (Cq), 137.5 (Cq), 137.5 (Cq), 133.3 (Cq), 129.3, 129.3, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 125.6, 114.1, 86.3 (C1), 79.7 (C3), 76.4 (C2), 76.0 (C4), 75.1 (CH₂Ph), 72.8 (CH₂Ph), 72.5 (CH₂Ph), 65.6 (C5), 55.2 (OCH₃), 50.5 (CH₂Ph PMB); ¹³C-GATED (101 MHz; CDCl₃): 86.3 ([³J₁₁H₁ =172 Hz, C1); HRMS (ES⁺) m/z [Found: (M+H)⁺ 701.2829 C₄₁H₄₂N₄O₄S requires (M+H)⁺, 701.2798).

S2.12.2. Phenyl 2,3,4-tri-O-benzyl-6-C-(2-para-methoxybenzyl-tetrazol-5-yl)-1-thio-α-d-mannopyranoside 19

N₂-regiosomer 19 was isolated as a yellow oil (355 mg, 0.51 mmol, 37%). Rf 0.73 (EtOAc/petroleum ether, 1/2); ¹H NMR (400 MHz; CDCl₃) δ 7.38 – 7.13 (21 H, m, Ar-H), 6.84 (2 H, d, J = 8.0 Hz, Ar-H PMB), 6.76 (2 H, d, J = 8.7 Hz, Ar-H PMB), 5.57 (1 H, d, J = 1.3 Hz, H₁), 5.52 (1 H, d, J = 9.9 Hz, H₅), 5.27 (1 H, d, J = 15.0 Hz, CH₂Ph-PMB), 5.18 (1 H, d, J = 15.0 Hz, CH₂Ph-PMB), 4.63 (1 H, d, J = 11.5 Hz, CH₂Ph), 4.63 (1 H, d, J = 11.6 Hz, CH₂Ph), 4.59 (1 H, d, J = 11.9 Hz, CH₂Ph), 4.58 (1 H, app. t, J = 9.9 Hz, H₄), 4.56 (1 H, d, J = 11.5 Hz, CH₂Ph), 4.08 – 4.06 (1 H, m, H₂), 3.94 (1 H, dd, J = 9.3, 1.2 Hz, H₃), 4.33 (1 H, d, J = 10.7 Hz, CH₂Ph), 4.23 (1 H, d, J = 10.8 Hz, CH₂Ph), 3.67 (1 H, s, OCH₃); ¹³C NMR (101 MHz; CDCl₃) δ 164.3 (Cq tetrazole), 160.0 (Cq PMB), 138.1 (Cq), 138.1 (Cq), 137.8 (Cq), 133.8 (Cq), 132.0 (Cq), 129.4, 129.3, 128.6, 128.5, 128.3, 128.1, 128.1, 127.9, 127.8, 127.7, 125.3, 114.3, 86.6 (C1), 79.8 (C3), 76.3 (C2), 76.0 (C4), 75.1 (CH₂Ph), 72.4 (CH₂Ph), 72.2 (CH₂Ph), 67.1 (C5), 56.5 (CH₂Ph PMB), 55.3 (OCH₃); ¹³C-GATED (101 MHz; CDCl₃): 86.6 ([³J₁₁H₁ =168 Hz, C1); HRMS (ES⁺) m/z [Found: (M+H)⁺ 701.2829 C₄₁H₄₂N₄O₄S requires (M+H)⁺, 701.2798).

S2.13. 3-aminopropyl (6-C-tetrazol-5-yl)-α/β-d-mannopyranoside 20

S2.13.1. 3-(benzylxycarbonylamino) propyl (2,3,4-tri-O-benzyl-6-C-(2-para-methoxybenzyl-tetrazol-5-yl)-α/β-d-mannopyranoside

A solution of 18 and 19 (290 mg, 0.41 mmol, 1.0 equiv.) and 3-(benzylxycarbonylamino)-1-propanol (259 mg, 1.24 mmol, 3.0 equiv.) in in CH₂Cl₂ (4.1 mL) was stirred over activated MS4Å for 1 h before NIS (139 mg, 0.62 mmol, 1.5 equiv.) was added. The mixture was cooled to -40 °C before AgOTf (53 mg, 0.21 mmol, 0.5 equiv.) was added. The reaction was warmed up to 0 °C and stirred for 3 h. Upon completion, Et₃N was added until pH = 7, and subsequently diluted with CH₂Cl₂ (20 mL). The organic layer was washed with 10% aq. Na₂S₂O₃ solution (20 mL), brine (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Flash column chromatography, eluting with EtOAc/petroleum (30/70, 40/60 and 50/50) afforded the title
compound as a colourless oil in an anomeric mixture of $\alpha/\beta = 1/1$ ratio (110 mg, 0.14 mmol, 34%). Rf 0.66 (EtOAc/toluene, 3/7); $^1$H NMR (400 MHz; CDCl$_3$) 7.40 – 7.22 (23 H, m, Ar-H), 7.19 – 7.09 (6 H, m, Ar-H PMB), 6.83 – 6.73 (4 H, m, Ar-H PMB), 5.65 (1 H, d, $J = 14.4$ Hz, CH$_2$Ph PMB), 5.60 (1 H, d, $J = 14.6$ Hz, CH$_2$Ph PMB), 5.60 (1 H, d, $J = 14.6$ Hz, CH$_2$Ph PMB), 5.55 (1 H, d, $J = 14.4$ Hz, CH$_2$Ph PMB), 5.09 (1 H, d, $J = 12.0$ Hz, CH$_2$Ph), 5.03 (1 H, d, $J = 12.4$ Hz, CH$_2$Ph), 4.96 (1 H, d, $J = 12.6$ Hz, CH$_2$Ph), 4.92 (1 H, d, $J = 9.9$ Hz, $H_5$ $\alpha$-anomer), 4.85 (1 H, d, $J = 2.2$ Hz, $H_1$ $\alpha$-anomer), 4.83 (1 H, d, $J = 12.6$ Hz, CH$_2$Ph), 4.78 (1 H, d, $J = 12.5$ Hz, CH$_2$Ph), 4.73 (1 H, d, $J = 11.2$ Hz, CH$_2$Ph), 4.69 (2 H, d, $J = 10.7$ Hz, CH$_2$Ph), 4.63 (2 H, d, $J = 11.8$ Hz, CH$_2$Ph), 4.62 (1 H, d, $J = 9.6$ Hz, $H_5$ $\beta$-anomer), 4.59 (1 H, d, $J = 11.7$ Hz, CH$_2$Ph), 4.55 (1 H, d, $J = 3.0$ Hz, $H_1$ $\beta$-anomer), 4.53 (1 H, d, $J = 12.8$ Hz, CH$_2$Ph), 4.49 (2 H, app. t, $J = 9.7$ Hz, $H_4$ $\alpha$ and $\beta$-anomer), 4.47 (1 H, d, $J = 12.8$ Hz, CH$_2$Ph), 4.28 (1 H, d, $J = 10.7$ Hz, CH$_2$Ph), 4.24 (1 H, d, $J = 10.7$ Hz, CH$_2$Ph), 3.96 (1 H, d, $J = 2.7$ Hz, $H_2$ $\beta$-anomer), 3.95 (1 H, dd, $J = 9.4$, 2.9 Hz, $H_3$ $\alpha$-anomer), 3.93 – 3.88 (1 H, m, OCH$_2$CH$_2$CH$_2$NHCbz $\alpha$-anomer), 3.90 – 3.79 (2 H, m, $H_2$ $\alpha$-anomer, OCH$_2$CH$_2$CH$_2$NHCbz $\beta$-anomer), 3.72 (3 H, s, OCH$_3$ $\alpha$-anomer), 3.70 (3 H, s, OCH$_3$ $\beta$-anomer), 3.59 (1 H, dd, $J = 9.4$, 2.7 Hz, $H_3$ $\beta$-anomer), 3.56 – 3.50 (1 H, m, OCH$_2$CH$_2$CH$_2$NHCbz $\alpha$-anomer), 3.47 – 3.40 (1 H, m, OCH$_2$CH$_2$CH$_2$NHCbz $\beta$-anomer), 3.28 (4 H, m, OCH$_2$CH$_2$CH$_2$NHCbz $\alpha$ and $\beta$-anomer), 1.78 (4 H, dt, $J = 12.9$, 6.9 Hz, OCH$_2$CH$_2$CH$_2$NHCbz $\alpha$ and $\beta$-anomer); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 164.5 (C$_q$ tetrazole $\alpha$-anomer), 164.0 (C$_q$ tetrazole $\beta$-anomer), 160.0 (C$_q$ PMB), 156.4 (C=O CBz), 138.6 (C$_a$), 138.4 (2 C, C$_a$), 138.2 (2 C, C$_a$), 138.1 (C$_q$), 138.1 (C$_q$), 138.1 (C$_q$), 136.6 (C$_q$), 130.0 (C$_q$), 130.0 (C$_q$), 129.1, 128.5, 128.5, 128.4, 128.4, 128.1, 128.1, 128.0, 127.7, 127.7, 127.7, 127.6, 127.6, 127.4, 114.3, 102.2 (C1 $\beta$-anomer), 98.9 (C1 $\alpha$-anomer), 81.8 (C3 $\beta$-anomer), 79.9 (C3 $\alpha$-anomer), 77.2 (2 C, C$_a$, $\alpha$ and $\beta$-anomer), 75.0 (C2 $\alpha$-anomer), 74.8 (CH$_2$Ph), 74.2 (CH$_2$Ph), 74.2 (C2 $\beta$-anomer), 74.1 (CH$_2$Ph), 72.9 (CH$_2$Ph), 72.5 (2 C, CH$_2$Ph), 71.7 (CH$_2$Ph), 69.8 (C$_5$ $\beta$-anomer), 67.6 (OCH$_2$CH$_2$CH$_2$NHCbz $\alpha$-anomer), 66.6 (CH$_2$Ph), 66.4 (C$_5$ $\alpha$-anomer), 65.8 (OCH$_2$CH$_2$CH$_2$NHCbz $\beta$-anomer), 56.4 (2 C, CH$_2$Ph PMB), 55.2 (2 C, OCH$_3$), 38.4 (OCH$_2$CH$_2$CH$_2$NHCbz $\beta$-anomer), 38.2 (OCH$_2$CH$_2$CH$_2$NHCbz $\beta$-anomer), 29.7 (OCH$_2$CH$_2$CH$_2$NHCbz $\beta$-anomer), 29.5 (OCH$_2$CH$_2$CH$_2$NHCbz $\alpha$-anomer); $^{13}$C-GATED (101 MHz; CDCl$_3$): 102.2 ($^1$J$_{C1,H1}$ =156 Hz, C1 $\beta$-anomer); HRMS (ES$^+$) m/z [Found: (M+H)$^+$] 800.3693 C$_{46}$H$_{51}$N$_5$O$_8$ requires (M+H)$^+$, 800.3659.

S2.13.2. 3-aminopropyl (6-C-tetrazol-5-yl)-$\alpha$/-$\beta$-d-mannopyranoside 20

3-(benzoxycarbonylamino) propyl (2,3,4-tri-O-benzyl-6-C-(2-paramethoxybenzyl-tetrazol-5-yl)-$\alpha$/-$\beta$-d-mannopyranoside (30 mg, 38 µmol, 1.0 equiv.) was dissolved in a mixture of EtOH/THF (0.6 mL, 1.5/1 v/v), after which Pd/C (10%) (0.17 mg, 1.9 µmol, 0.5 equiv.), Pd(OH)$_2$/C (20%) (13 mg, 19 µmol, 0.5 equiv.) and 0.1 M aq. HCl (380 µL, 38 µmol, 1.0 equiv.) were added. The mixture was stirred for 56 h under an atmosphere of hydrogen (1 atm, balloon) at room temperature. TLC analysis (hexane/EtOAc, 1/2) showed complete conversion of starting material to a lower Rf spot.
The reaction mixture was filtered through Celite®, followed by solvent removal in vacuo to give white powder 20 in an anomic mixture of α/β = 3/1 (11 mg, 36 µmol, 96%). Rf 0.27 (H2O/MeCN, 1/2); 1H NMR (400 MHz; D2O) δ 4.86 (1 H, s, H1 α-anomer), 4.82 (1 H, d, J = 9.8 Hz, H5), 4.74 (1 H, s, H1 β-anomer), 4.61 (1 H, d, J = 9.9 Hz, H5 β-anomer), 4.15 (1 H, app. t, J = 9.9 Hz, H4 α-anomer), 4.08 (app. t, J = 9.9 Hz, H4 β-anomer), 4.03 (1 H, d, J = 3.2 Hz, H2 β-anomer), 4.01 – 3.98 (1 H, m, H2 α-anomer), 3.87 (1 H, dd, J = 9.8, 3.4 Hz, H3 α-anomer), 3.84 – 3.76 (2 H, m, OCH2CH2CH2NH3Cl α and β-anomer), 3.73 (1 H, dd, J = 9.8, 3.2 Hz, H3 β-anomer), 3.56 (2 H, ddd, J = 17.3, 9.7, 4.5 Hz, OCH2CH2CH2NH3Cl α and β-anomer), 3.17 – 3.07 (2 H, m, OCH2CH2CH2NH3Cl α-anomer), 3.02 (2 H, td, J = 12.6, 7.2 Hz, OCH2CH2CH2NH3Cl β-anomer), 1.99 (2 H, d, J = 13.6, 6.7 Hz, OCH2CH2CH2NH3Cl α-anomer), 1.91 – 1.82 (2 H, m, OCH2CH2CH2NH3.Cl β-anomer); 13C NMR (101 MHz; D2O) δ 160.1 (2 C, C3 tetrazole), 100.6 (C1 β-anomer), 100.5 (C1 α-anomer), 72.7 (C3 β-anomer), 70.5 (C3 α-anomer), 70.5 (C2 β-anomer), 70.2 (C5 β-anomer), 70.0 (C2 α-anomer), 69.6 (C4 β-anomer), 69.5 (C4 α-anomer), 67.6 (OCH2CH2CH2NH3.Cl β-anomer), 66.6 (C5 α-anomer), 65.3 (OCH2CH2CH2NH3.Cl α-anomer), 37.6 (OCH2CH2CH2NH3.Cl β-anomer), 37.4 (OCH2CH2CH2NH3.Cl α-anomer), 26.7 (OCH2CH2CH2NH3.Cl α-anomer), 26.6 (OCH2CH2CH2NH3.Cl β-anomer); 13C-GATED (101 MHz; D2O): 100.5 (‘J<sub>C1-H1</sub> = 172 Hz, C1 α-anomer); HRMS (ES+): m/z [Found: (M+H)+ 276.1309 C9H19N5O5 requires (M+H)+, 276.1308].

S2.14. (6-C-tetrazol-5-yl)-α-D-mannopyranoside 1-phosphate (bis-ammonium salt) 21

S2.14.1. Fully protected C-6 tetrazole 1-phosphates

A mixture of 18 and 19 (730 mg, 1.04 mmol, 1.0 equiv.) was stirred with activated MS4Å for 1h in CH2Cl2 (10 mL). Dibenzyl phosphate (580 mg, 2.08 mmol, 2.0 equiv.) was added, and the solution was stirred for further 30 min. before being cooled down to -30 °C. NIS (350 mg, 1.56 mmol, 1.5 equiv.) and AgOTf (133 mg, 0.52 mmol, 0.5 equiv.) were added successively and the reaction mixture was stirred for further 3.5 h, allowing the temperature to reach 0 °C. When TLC analysis indicated conversion to a lower Rf value, the reaction was quenched by the addition of Et3N (1.4 mL, d = 0.726, 10.4 mmol, 10.0 equiv.) and diluted with CH2Cl2 (50 mL). The organic layer was washed with 10% aq. Na2S2O3 solution (30 mL), brine (30 mL), dried over MgSO4, filtered and concentrated under reduced pressure. Flash column chromatography, eluting with EtOAc/toluene (5/95, 10/90 and 30/70) afforded the protected 1-phosphate regiosiomeric mixture as a colourless oil in a 50/50 ratio (650 mg, 0.75 mmol, 72%). Rf 0.66 (EtOAc/toluene, 3/7); 1H NMR (400 MHz; CDCl3) δ 7.38 – 7.27 (35 H, m, Ar-H), 7.14 (2 H, d, J = 7.2 Hz, Ar-H PMB), 7.07 (2 H, d, J = 8.7 Hz, Ar-H PMB), 6.93 (2 H, d, J = 6.7 Hz, Ar-H), 6.82 (2 H, d, J = 6.5 Hz, Ar-H), 6.75 (2 H, d, J = 8.8 Hz, Ar-H PMB), 6.65 (2 H, d, J = 8.8 Hz, Ar-H PMB), 5.76 (1 H, dd, J = 6.3, 1.8 Hz, H1 N2-isomer), 5.69 (1 H, dd, J = 6.3, 2.1 Hz, H1 N1-isomer), 5.65 (1 H, d, J = 14.0 Hz, CH2Ph PMB), 5.61 (1 H, d, J = 14.2 Hz, CH2Ph
filtered through Celite balloon) at room temperature for 24 h. TLC analysis (hexane/EtOAc, 1/2) showed
was stirred under an atmosphere of hydrogen (1 atm, 20% Pd(OH)$_2$/C) and lyophilisation afforded
_3^13C NMR (101 MHz; CDC$_3$) δ 163.8 (C$_3$ tetracazo N$_2$-isomer), 160.0 (C$_4$ PMB), 159.7 (C$_4$ PMB), 151.5 (C$_4$ tetracazo N$_1$-isomer), 138.1 (C$_4$), 138.0 (C$_4$), 137.9 (C$_4$), 137.7 (C$_4$), 137.4 (C$_4$), 137.4 (C$_4$), 135.6 (d, J = 6.7 Hz, C$_4$ OP(O)OBn), 135.5 (d, J = 6.7 Hz, C$_4$ OP(O)OBn), 135.2 (d, J = 6.2 Hz, C$_4$ OP(O)OBn), 135.1 (d, J = 6.4 Hz, C$_4$ OP(O)OBn), 130.0 (C$_4$), 129.6 (C$_4$), 128.9, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.4, 125.8, 125.2, 114.3, 114.2, 96.2 (d, J = 6.1 Hz, C$_1$ N$_2$-isomer), 96.1 (d, J = 6.1 Hz, C$_1$ N$_1$-isomer), 78.6 (C$_3$ N$_1$-isomer or N$_2$-isomer), 78.4 (C$_3$ N$_1$-isomer or N$_2$-isomer), 76.4 (C$_4$ N$_2$-isomer), 75.1 (2 C, CH$_2$Ph), 76.0 (C$_4$ N$_1$-isomer), 74.5 (d, J = 9.6 Hz, C$_2$ N$_1$-isomer), 74.3 (d, J = 9.3 Hz, C$_2$ N$_2$-isomer), 73.5 (CH$_2$Ph), 72.9 (CH$_2$Ph), 72.6 (CH$_2$Ph), 72.5 (CH$_2$Ph), 70.1 (d, J = 5.6 Hz, OP(O)OCH$_2$Ph), 70.0 (d, J = 5.7 Hz, OP(O)OCH$_2$Ph), 69.7 (d, J = 5.4 Hz, OP(O)OCH$_2$Ph), 69.6 (d, J = 5.5 Hz, OP(O)OCH$_2$Ph), 67.9 (C$_5$ N$_2$-isomer), 66.5 (C$_5$ N$_1$-isomer), 56.5 (CH$_2$Ph PMB), 55.2 (2 C, OCH$_3$), 50.4 (CH$_2$Ph PMB); $^{31}$P NMR δ$_P$ (162 MHz, CDC$_3$) -2.88 (s), -2.79 (s); HRMS (ES$^+$) m/z [Found: (M+H)$^+$ 869.3370 C$_{49}$H$_{51}$N$_4$O$_9$P (M+H)$^+$, 869.3315].

S2.14.2. (6-C-tetrazol-5-yl)-α-D-mannopyranoside 1-phosphate (bis-ammonium salt) 21

A suspension of the protected 1-phosphate regiosiomer mixture (190 mg, 0.22 mmol, 1.0 equiv.), 10% Pd/C (140 mg, 0.13 mmol, 0.6 equiv.), 20% Pd(OH)$_2$/C (92 mg, 0.13 mmol, 0.6 equiv.) and 5% aq. NaHCO$_3$ (739 μL, 0.44 mmol, 2.0 equiv.) in a mixture of EtOH/THF (4.4 mL, 1.5/1 v/v) was stirred under an atmosphere of hydrogen (1 atm, balloon) at room temperature for 24 h. TLC analysis (hexane/EtOAc, 1/2) showed complete conversion of starting material to a lower R$_f$ spot. The reaction mixture was filtered through Celite®, followed by solvent removal in vacuo. Purification via strong anion exchange chromatography was conducted manually using a Bio-Scale™ Mini UNOsphere™ Q (strong anion exchange) cartridge and lyophilisation afforded 21 as a white powder (53 mg, 0.16 mmol, 72%). R$_f$ 0.42 (H$_2$O/MeCN, 1/2); [α]$_D^{22}$ -3.0 (c. 1.0, H$_2$O); $^1$H NMR (400 MHz; D$_2$O) δ 5.41 (1 H, dd, J = 7.9, 1.7 Hz, H$_4$), 5.08 (1 H, d, J = 9.7 Hz,
H₅), 4.05 (1 H, app. t, J = 9.6 Hz, H₄), 4.02 – 3.97 (2 H, m, H₂ and H₃); ¹³C NMR (101 MHz; D₂O) δ 160.8 (C₉ tetrazole), 96.1 (C1), 70.5 (C2), 69.7 (C3), 69.4 (C4), 67.1 (C5); ³¹P NMR δ P (162 MHz, D₂O) -2.15 (s); HRMS (ES⁻) m/z [Found: (M-H)⁻ 297.0236 C₆H₁₀N₄O₈P requires (M-H)⁻ 297.0233].

S3. HMBC spectrum for N₁-protected tetrazole 11

δCH₂-RMe: 5.66 and 5.63 ppm

δH₅: 5.68 ppm

δH₄: 4.59 ppm

δC=N: 150.4 ppm
S4. References


S5. Spectral Data: $^1$H, $^{13}$C, $^{31}$P and HSQC NMR for compounds 2-5, 7-14, 16-18 and 20-21
3-propionitrile (phenyl 2,3-di-O-benzyl-1-thio-α-D-mannopyranoside) amide 2
Elimination by-product 3

[Chemical structure image]

[1H NMR spectrum]

[13C NMR spectrum]

Carbon X (CDCl₃) [δ (ppm)/J (Hz)]

-161.49
-117.88
-156.10
150.13
72.61
72.50
71.24
68.30
56.56
-18.24
3-propionitrile (phenyl 4-O-tert-butyl dimethylsilyl 2,3-di-O-benzyl-1-thio-α-Dmannopyranoside) amide 4
Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-6-C-(1H-tetrazol-5-yl)-1-thio-α-D-mannopyranoside 5
Phenyl 2,3-di-O-benzyl-6-O-benzoyl-1-thio-α-D-mannopyranoside
Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-6-O-benzoyl-1-thio-α-D-mannopyranoside
Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-1-thio-α-D-mannopyranoside 7
C6 aldehyde thioglycoside intermediate
C6 oxime thioglycoside 8
C6 nitrile thioglycoside 9

\[ \text{TBSO}_\text{BnO} \]

\[ \text{N} \]

\[ \text{OBn} \]

\[ \text{SPh} \]
4-Position deprotected by-product 10
Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-6-C-(1-para-methoxybenzyl-tetrazol-5-yl)-1-thio-α-D-mannopyranoside
Coupled HSQC

HMBC
Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-6-C-(2-para-methoxybenzyl-tetrazol-5-yl)-1-thio-α-D-mannopyranoside 12
Coupled HSQC

HMBC
Phenyl 2,3-di-O-benzyl-4-O-tert-butyl dimethylsilyl-6-C-(1H-tetrazol-5-yl)-1-thio-α-D-mannopyranoside triethylammonium salt
Bn protected C6-tetrazole thioglycosides 13 and 14
C-6 Aldehyde thioglycoside intermediate
C-6 Oxime thioglycoside intermediate

[Diagram of molecular structure and NMR spectrum]
C-6 nitrile thioglycoside 16
Phenyl 2,3,4-tri-O-benzyl-6-C-(1H-tetrazol-5-yl)-1-thio-α-D-mannopyranoside 17
Phenyl 2,3,4-tri-O-benzyl-6-C-(1-para-methoxybenzyl-tetrazol-5-yl)-1-thio-D-mannopyranoside
Coupled HSQC of $N_1$-isomer

[HSQC spectrum image]

Coupled HSQC of $N_2$-isomer

[HSQC spectrum image]
HMBC of both isomers
3-(benzylloxycarbonylamino) propyl (2,3,4-tri-O-benzyl-6-C-(2-para-methoxybenzyltetrazol-5-yl)-α/β-D-mannopyranoside

\[ \text{PMB-} \text{O} \text{Bn} \text{BnO} \text{BnO} \text{O} \text{NHCbz} \]

\[ \text{PMB-} \text{N} \text{N} \text{OBn} \text{BnO} \text{BnO} \text{O} \text{NHCbz} \]

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Coupled HSQC (showing only β-anomer $^1J_{C1-H1}$ coupling)
3-aminopropyl (6-C-tetrazol-5-yl)-α/β-D-mannopyranoside 20
Coupled HSQC
Fully protected C6-tetrazole 1-phosphates
$^{31}$P NMR
(6-C-tetrazol-5-yl)-1-phosphate-α-D-mannopyranoside 21
$^{31}$P NMR