Supporting Information

Enhancing Glycan Stability via Site-Selective Fluorination: Modulating Substrate Orientation by Molecular Design.

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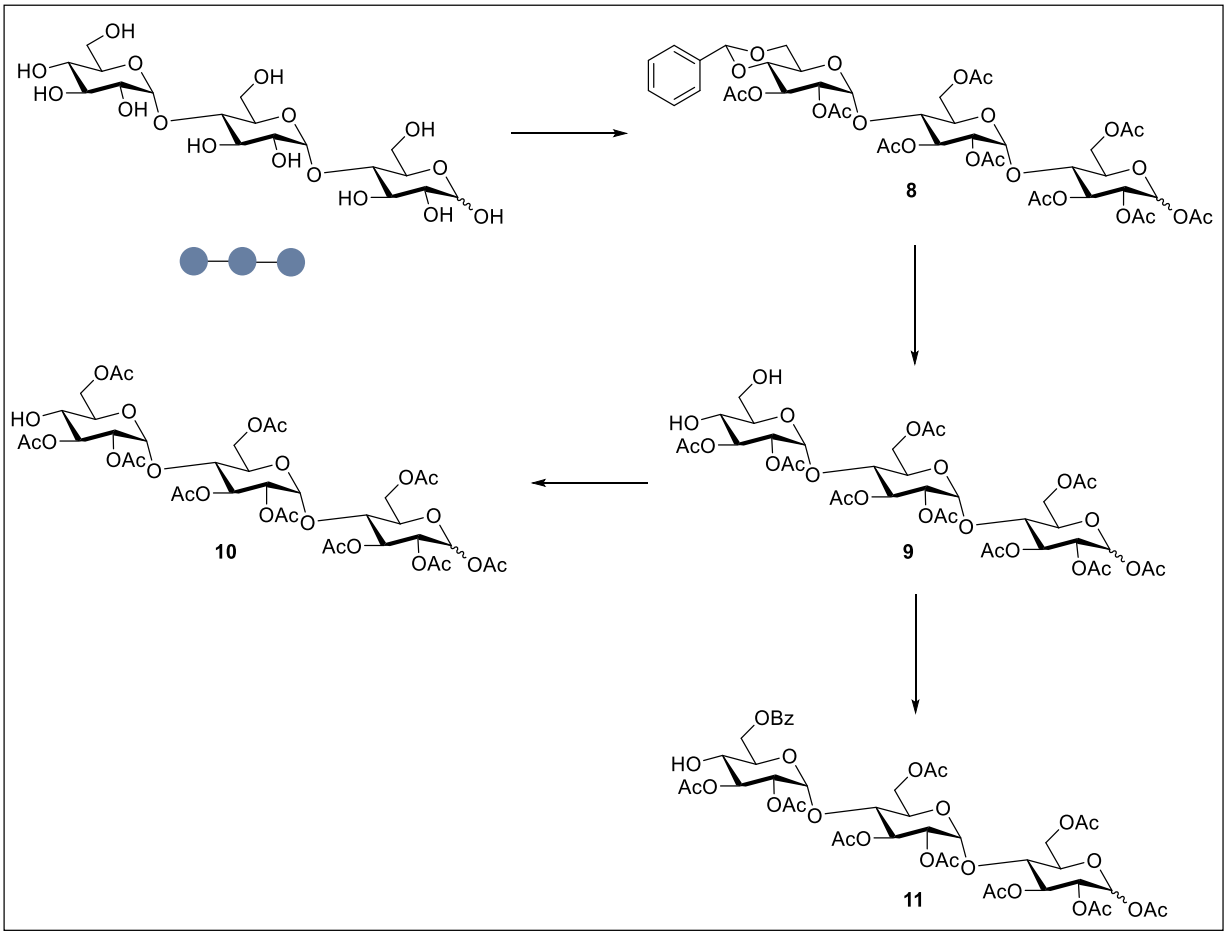
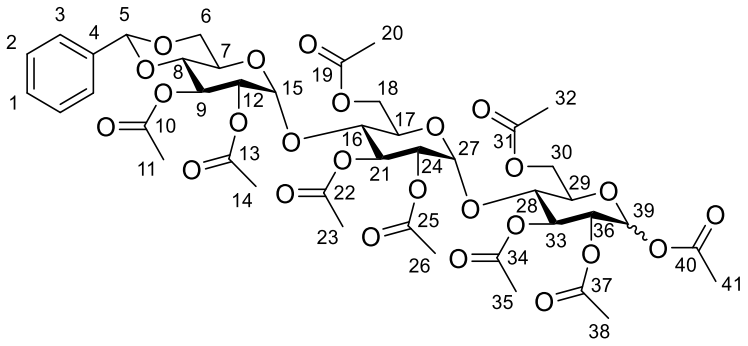
1 General Information

All chemicals were purchased as reagent grade and used without further purification. Solvents for purification (extraction and chromatography) were purchased as technical grade and distilled on the rotary evaporator prior to use. Anhydrous CH_2Cl_2 and THF were obtained by passing them over a column packed with Al_2O_3 (pellets, 3mm) under an atmosphere of Argon. For column chromatography SiO_2-60 (230-400 mesh ASTM; *Fluka*) was used as stationary phase. Analytical thin layer chromatography (TLC) was performed on aluminium foil pre-coated with SiO_2-60 F_{254} (*Merck*) and visualized with UV-light (254 nm), $KMnO_4$ or anisaldehyde solution followed by heating. Concentration under reduced pressure was performed at ≈10 mbar and 50 °C, drying at ≈10-2 mbar and rt unless stated otherwise. ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded by the NMR service at the Institute of Organic Chemistry (WWU Münster) on a *Bruker AV 300 MHz*, a *Bruker AV 400 MHz*, *Agilent DD2 500 MHz* or an *Agilent DD2 600 MHz* spectrometer at rt. Chemical shifts δ are reported in ppm relative to the residual solvent (relative to $\delta^1H(SiMe_4) = 0$ and $\delta^{13}C(SiMe_4) = 0$) and external for $\delta^{19}F(CFCl_3) = 0$, respectively. Coupling constants *J* are reported in Hz and are recorded to the nearest 0.1 Hz. The resonance multiplicity is abbreviated as: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and b (broad). Assignments of unknown compounds are supported by DEPT, COSY, HMBC, HSQC, TOCSY and NOESY NMR experiments. IR spectra were recorded on a *Perkin-Elmer 100 FT-IR* spectrometer. Absorption maxima are reported in wavenumbers (cm^{-1}) and reported as strong (s), medium (m) or weak (w). Specific optical rotations were obtained using a *JASCO P 2000* polarimeter. High-resolution mass spectra were performed by the MS service at the Institute of Organic Chemistry (WWU Münster): HR-MS (ESI) on a *Bruker Daltonics MicroTof*; HR-MS (APCI) on a *Thermo Scientific Orbitrap LTQ XL*.

2 Experimental Section



2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (8)



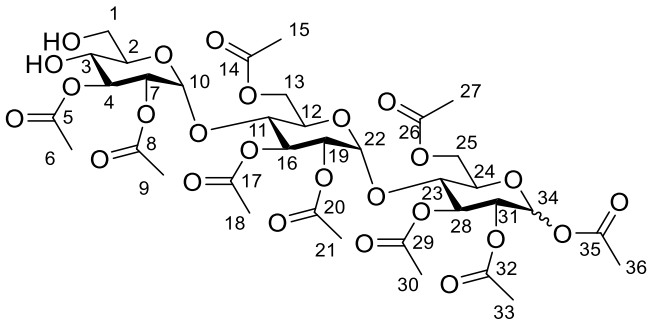
Maltotriose (350 mg, 0.694 mmol, 1.0 eq) was dissolved in dry DMF (7 ml), *p*TsOH · H_2O (26 mg, 0.138 mmol, 0.1 eq) was added and then ca. half of the volume was evaporated under reduced pressure. Then benzaldehyde dimethylacetal (158 mg, 156 µL, 1.041 mmol, 1.5 eq)

and MS4Å were added and the reaction mixture was allowed to stir at 50 °C for 4 h under a pressure of 150 mbar. After this time, the solvent was removed under reduced pressure and the residue was filtered through silica gel (ethyl acetate:methanol:water, 8:2:1 → 7:2:1) to obtain 4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α,β-D-glucopyranose as a white solid (310 mg), which was used without further purification. To a solution of the crude product (800 mg, 1.351 mmol, 1.0 eq) in pyridine (20 mL) were added Ac_2O (8 mL) and DMAP (50 mg, 0.409 mmol, 0.3 eq). The reaction mixture was allowed to stir for 4 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (100 mL), poured into a beaker containing sat. aq. $NaHCO_3$ (200 mL) and allowed to stir for 30 min. The mixture was then diluted with CH_2Cl_2, extracted with sat. aq. $NaHCO_3$ (3 x 100 mL) and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Residual pyridine was co-evaporated with toluene (3 x 20 mL) and the crude product was purified by silica gel column chromatography (cyclohexane:ethyl acetate, 1:1) to obtain 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-O-acetyl-α,β-D-glucopyranose (**8**) (907 mg, 69%) as a colorless foam (α:β = 1:1).

R_f 0.30 (cyclohexane:ethyl acetate, 1:1); IR υ_{max} (neat)/cm^{-1} = 2952 (w), 1742 (s), 1432 (w), 1368 (m), 1209 (s), 1149 (m), 1027 (s), 939 (m), 903 (m), 757 (m), 733 (m), 700 (m); **^{1}H-NMR** (600 MHz, $CDCl_3$, 300 K, ppm): 7.42 (4H, dd, *J* = 6.9, 2.8 Hz, H3), 7.36-7.32 (6H, m, H1, H2), 6.24 (1H, d, *J* = 3.8 Hz, H39$^{\alpha}$), 5.74 (1H, d, *J* = 8.0 Hz, H39$^{\beta}$), 5.51 (1H, t, *J* = 9.5 Hz, H33$^{\alpha}$), 5.47 (1H, s, H5$^{\alpha}$), 5.46 (1H, s, H5$^{\beta}$), 5.46-5.37 (4H, m, H9$^{\alpha}$, H9$^{\beta}$, H21$^{\alpha}$, H21$^{\beta}$), 5.37 (1H, d, *J* = 4.2 Hz, H15$^{\alpha}$), 5.35 (1H, d, *J* = 4.2 Hz, H15$^{\beta}$), 5.31-5.27 (2H, m, H27$^{\beta}$, H33$^{\beta}$), 5.26 (1H, d, *J* = 4.1 Hz, H27$^{\alpha}$), 4.98-4.92 (2H, m, H36$^{\alpha}$, H36$^{\beta}$), 4.87 (2H, ddd, *J* = 10.1, 4.1, 1.2 Hz, H12$^{\alpha}$, H12$^{\beta}$), 4.75 (2H, ddd, *J* = 10.5, 6.7, 4.1 Hz, H24$^{\alpha}$, H24$^{\beta}$), 4.51 (4H, dtd, *J* = 27.4, 12.5, 12.1, 2.1 Hz, H18$^{\alpha}$, H18$^{\beta}$, H30$^{\alpha}$, H30$^{\beta}$), 4.32-4.26 (2H, m, H30'$^{\alpha}$, H30'$^{\beta}$), 4.24 (2H, dd, *J* = 10.4, 4.6 Hz, H6$^{\alpha}$, H6$^{\beta}$), 4.20 (2H, dd, *J* = 12.4, 2.7 Hz, H18'$^{\alpha}$, H18'$^{\beta}$), 4.13 (1H, dt, *J* = 9.9, 3.0 Hz, H29$^{\alpha}$), 4.02 (2H, td, *J* = 9.2, 5.4 Hz, H28$^{\beta}$, H28$^{\alpha}$), 3.99-3.90 (4H, m, H16$^{\alpha}$, H16$^{\beta}$, H17$^{\alpha}$, H17$^{\beta}$), 3.89-3.80 (3H, m, H29$^{\beta}$, H7$^{\alpha}$, H7$^{\beta}$), 3.71 (2H, td, *J* = 10.2, 2.8 Hz, H6'$^{\alpha}$, H6'$^{\beta}$), 3.61 (2H, td, *J* = 9.7, 2.2 Hz, H8$^{\alpha}$, H8$^{\beta}$), 2.22, 2.17, 2.16, 2.12, 2.12, 2.09, 2.07, 2.07, 2.04, 2.03, 2.03, 2.02, 2.02, 2.00, 2.00, 1.99, 1.99, 1.98 (54H, 18s, H11$^{\alpha+\beta}$, H14$^{\alpha+\beta}$, H20$^{\alpha+\beta}$, H23$^{\alpha+\beta}$, H26$^{\alpha+\beta}$, H32$^{\alpha+\beta}$, H35$^{\alpha+\beta}$, H38$^{\alpha+\beta}$, H41$^{\alpha+\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$, 299 K, ppm): δ = 171.0, 171.0, 170.8, 170.8, 170.5, 170.5, 170.3, 170.3, 170.1,

169.9, 169.9, 169.7, 169.7, 169.6 ($C10^{\alpha+\beta}$, $C13^{\alpha+\beta}$, $C19^{\alpha+\beta}$, $C22^{\alpha+\beta}$, $C25^{\alpha+\beta}$, $C31^{\alpha+\beta}$, $C34^{\alpha+\beta}$, $C37^{\alpha+\beta}$), 169.1 ($C40^{\alpha}$), 168.9 ($C40^{\beta}$), 136.8 ($C4^{\alpha}$), 136.8 ($C4^{\beta}$), 129.3 ($C1^{\alpha}$), 129.2 ($C1^{\beta}$), 128.3 ($C2^{\alpha}$), 128.3 ($C2^{\beta}$), 126.4 ($C3^{\alpha}$), 126.3 ($C3^{\beta}$), 101.8 ($C5^{\alpha+\beta}$), 96.6 ($C15^{\alpha}$), 96.5 ($C15^{\beta}$), 96.1 ($C27^{\alpha}$), 96.0 ($C27^{\beta}$), 91.4 ($C39^{\beta}$), 89.0 ($C39^{\alpha}$), 78.9 ($C8^{\alpha+\beta}$), 75.3 ($C33^{\beta}$), 73.4 ($C28^{\beta}$), 73.3 ($C28^{\alpha}$), 73.1 ($C29^{\beta}$), 72.5 ($C16^{\alpha}$), 72.4 ($C16^{\beta}$), 72.3 ($C33^{\alpha}$), 72.0 ($C21^{\alpha}$), 71.9 ($C21^{\beta}$), 71.2 ($C36^{\beta}$), 71.0 ($C12^{\alpha}$), 71.0 ($C12^{\beta}$), 70.7 ($C24^{\alpha}$), 70.6 ($C24^{\beta}$), 70.4 ($C29^{\alpha}$), 69.9 ($C36^{\alpha}$), 69.3 ($C17^{\alpha}$), 69.3 ($C17^{\beta}$), 68.6 ($C6^{\alpha}$), 68.6 ($C6^{\beta}$), 68.6 ($C9^{\alpha}$), 68.6 ($C9^{\beta}$), 63.9 ($C7^{\alpha}$), 63.9 ($C7^{\beta}$), 62.6 ($C30^{\beta}$), 62.5 ($C30^{\alpha}$), 62.2 ($C18^{\alpha}$), 62.2 ($C18^{\beta}$), 21.2, 21.1, 21.0, 21.0, 21.0, 20.9, 20.9, 20.9, 20.9, 20.7, 20.7, 20.7, 20.7, 20.6 ($C11^{\alpha+\beta}$, $C14^{\alpha+\beta}$, $C20^{\alpha+\beta}$, $C23^{\alpha+\beta}$, $C26^{\alpha+\beta}$, $C32^{\alpha+\beta}$, $C35^{\alpha+\beta}$, $C38^{\alpha+\beta}$, $C41^{\alpha+\beta}$); HR-ESI-MS: *m*/*z*: 993.2856 ([*M*+Na]$^+$, calcd. for $C_{43}H_{54}O_{25}Na^+$: 993.2846). Analytical data in agreement with the literature.[1]

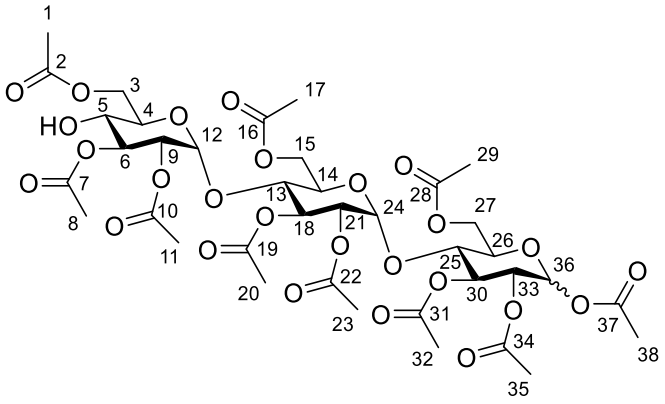
2,3-Di-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (9)



2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-O-acetyl-α,β-D-glucopyranose (**8**) (4.040 g, 4.17 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (45 mL). To this, water (0.6 mL) and trifluoroacetic acid (6 mL) were added and the reaction mixture was allowed to stir at RT for 1 h. After full conversion of the starting material (determined by TLC), the reaction mixture was quenched with trimethylamine (16 mL). All volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate:cyclohexane, 2:1) to obtain 2,3-di-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-O-acetyl-α,β-D-glucopyranose (**9**) (3.605 g, 98%) as a colourless foam (α:β = 1:1).

R_f 0.33 (ethyl acetate); IR υ_{max} (neat)/cm^{-1} = 3478 (w), 2946 (w), 1739 (s), 1432 (w), 1369 (m), 1210 (s), 1160 (m), 1137 (m), 1025 (s), 938 (m), 898 (m), 769 (w); **^{1}H-NMR** (600 MHz, $CDCl_3$, 300 K, ppm): δ = 6.24 (1H, d, *J* = 3.7 Hz, H34$^{\alpha}$), 5.74 (1H, d, *J* = 8.1 Hz, H34$^{\beta}$), 5.52 (1H, dd, *J* = 10.1, 9.0 Hz, H28$^{\alpha}$), 5.43-5.36 (2H, m, H16$^{\alpha}$, H16$^{\beta}$), 5.33 (1H, d, *J* = 4.0 Hz, H10$^{\beta}$), 5.32-5.29 (3H, m, H10$^{\alpha}$, H22$^{\beta}$, H28$^{\beta}$), 5.28 (1H, d, *J* = 4.0 Hz, H22$^{\alpha}$), 5.20 (2H, ddd, *J* = 10.5, 8.9, 6.4 Hz, H4$^{\alpha}$, H4$^{\beta}$), 4.99-4.93 (2H, m, H31$^{\alpha}$, H31$^{\beta}$), 4.75 (4H, dddd, *J* = 10.4, 9.8, 4.9, 2.9 Hz, H7$^{\alpha}$, H7$^{\beta}$, H19$^{\alpha}$, H19$^{\beta}$), 4.48-4.44 (4H, m, H13$^{\alpha}$, H13$^{\beta}$, H25$^{\alpha}$, H25$^{\beta}$), 4.26 (2H, ddd, *J* = 12.3, 9.6, 4.2 Hz, H25'$^{\alpha}$, H25'$^{\beta}$), 4.20 (2H, ddd, *J* = 12.2, 5.2, 3.1 Hz, H13'$^{\alpha}$, H13'$^{\beta}$), 4.17-4.13 (1H, m, H24$^{\alpha}$), 4.00 (2H, ddd, *J* = 9.6, 8.8, 7.6 Hz, H23$^{\alpha}$, H23$^{\beta}$), 3.95-3.90 (4H m, H11$^{\alpha}$, H11$^{\beta}$, H12$^{\alpha}$, H12$^{\beta}$), 3.90-3.86 (1H, m, H24$^{\beta}$), 3.86-3.78 (4H, m, H1$^{\alpha}$, H1$^{\beta}$, H1'$^{\alpha}$, H1'$^{\beta}$), 3.69-3.61 (4H, m, H2$^{\alpha}$, H2$^{\beta}$, H3$^{\alpha}$, H3$^{\beta}$), 2.23, 2.16, 2.16, 2.14, 2.14, 2.10, 2.09, 2.08, 2.06, 2.06, 2.05, 2.02, 2.01, 2.01, 2.00, 2.00, 2.00, 1.98 (54H, 18s, H6$^{\alpha+\beta}$, H9$^{\alpha+\beta}$, H15$^{\alpha+\beta}$, H18$^{\alpha+\beta}$, H21$^{\alpha+\beta}$, H27$^{\alpha+\beta}$, H30$^{\alpha+\beta}$, H33$^{\alpha+\beta}$, H36$^{\alpha+\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$, 299 K, ppm): δ = 171.5, 171.0, 171.0, 171.0, 170.9, 170.9, 170.8, 170.8, 170.1, 170.0, 170.7, 169.9, 169.8, 169.8 (C5$^{\alpha+\beta}$, C8$^{\alpha+\beta}$, C14$^{\alpha+\beta}$, C17$^{\alpha+\beta}$, C20$^{\alpha+\beta}$, C26$^{\alpha+\beta}$, C29$^{\alpha+\beta}$, C32$^{\alpha+\beta}$), 169.1 (C35$^{\alpha}$), 168.9 (C35$^{\beta}$), 96.1 (C10$^{\alpha}$), 96.1 (C10$^{\beta}$), 95.9 (C22$^{\alpha}$), 95.9 (C22$^{\beta}$), 91.5 (C34$^{\beta}$), 89.0 (C1$^{\alpha}$), 75.3 (C28$^{\beta}$), 73.2 (C23$^{\beta}$), 73.1 (C24$^{\beta}$), 73.1 (C23$^{\alpha}$), 72.9 (C3$^{\alpha}$), 72.8 (C3$^{\beta}$), 72.7 (C11$^{\beta}$), 72.6 (C11$^{\alpha}$), 72.4 (C4$^{\beta}$), 72.3 (C4$^{\alpha}$), 72.3 (C28$^{\alpha}$), 72.0 (C16$^{\beta}$), 71.9 (C16$^{\alpha}$), 71.1 (C31$^{\beta}$), 70.6 (C7$^{\alpha}$), 70.6 (C7$^{\beta}$), 70.4 (C19$^{\beta}$), 70.4 (C19$^{\alpha}$), 70.3 (C24$^{\alpha}$), 70.1 (C2$^{\alpha}$), 70.1 (C2$^{\beta}$), 69.9 (C31$^{\alpha}$), 69.5 (C12$^{\alpha}$, C12$^{\beta}$), 63.0 (C25$^{\beta}$), 62.9 (C25$^{\alpha}$), 62.7 (C13$^{\beta}$), 62.6 (C13$^{\alpha}$), 62.4 (C1$^{\alpha}$, C1$^{\beta}$), 21.2 (OAc), 21.1 (OAc), 21.0 (OAc) , 21.0 (OAc), 21.0 (OAc), 21.0 (OAc), 20.8 (OAc), 20.8 (OAc), 20.8 (OAc), 20.7 (OAc), 20.7 (OAc), 20.6 (OAc), 21.2, 21.1, 21.0, 21.0, 21.0, 21.0, 20.8, 20.8, 20.8, 20.7, 20.7, 20.6, (C6$^{\alpha+\beta}$, C9$^{\alpha+\beta}$, C15$^{\alpha+\beta}$, C18$^{\alpha+\beta}$, C21$^{\alpha+\beta}$, C37$^{\alpha+\beta}$, C30$^{\alpha+\beta}$, C33$^{\alpha+\beta}$, C36$^{\alpha+\beta}$); HR-ESI-MS: *m*/*z*: 905.2505 ([*M*+Na]$^+$, calcd. for $C_{36}H_{50}O_{25}Na^+$: 905.2533).[2]

2,3,6-Tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (10)

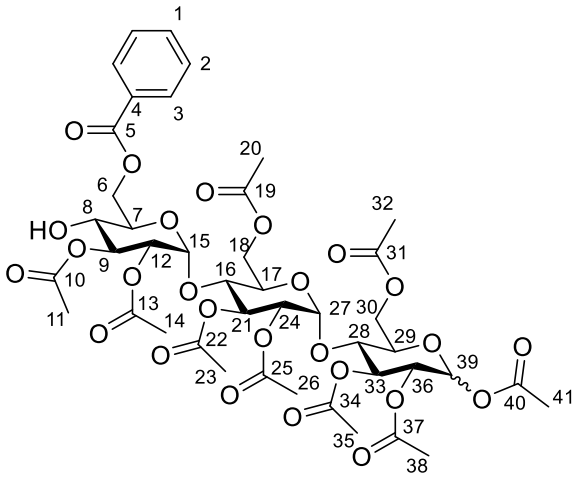


To a solution of HOBt (169 mg, 1.25 mmol, 1.1 eq) in CH_2Cl_2 (15 mL) triethylamine (172 mg, 236 µL, 1.70 mmol, 1.5 eq) and acetyl chloride (98 mg, 89 µL, 1.25 mmol, 1.1 eq) were added and the resulting mixture was allowed to stir for 30 min at RT. After this time, 2,3-di-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**9**) (1000 mg, 1.13 mmol, 1.0 eq) was added and the reaction mixture was stirred for 18 h at RT. After full conversion (determined by TLC), the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:1 → 2:1 → 3:1) to obtain 2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**10**) (794 mg, 76%) as a colourless foam (α:β = 1:1).

R_f 0.29 (ethyl acetate:cyclohexane, 2:1); IR υ_{max} (neat)/cm^{-1} = 3477 (w), 2966 (w), 1739 (s), 1434 (w), 1368 (m), 1211 (s), 1158 (m), 1140 (m), 1025 (s), 939 (m), 898 (m), 769 (s), 732 (s), 693 (s); **^{1}H-NMR** (600 MHz, $CDCl_3$, 300 K, ppm): δ = 6.24 (0.5H, d, *J* = 3.7 Hz, H36$^{\alpha}$), 5.74 (0.5H, d, *J* = 8.1 Hz, H36$^{\beta}$), 5.51 (0.5H, dd, *J* = 10.1, 8.9 Hz, H30$^{\alpha}$), 5.38 (1H, dd, *J* = 10.3, 8.3 Hz, H18), 5.35 (0.5H, d, *J* = 4.0 Hz, H12$^{\beta}$), 5.33 (0.5H, d, *J* = 4.0 Hz, H12$^{\alpha}$), 5.31-5.27 (1H, m, H24$^{\beta}$, H30$^{\beta}$), 5.26 (0.5H, d, *J* = 4.1 Hz, H24$^{\alpha}$), 5.20 (1H, ddd, *J* = 10.6, 9.4, 7.3 Hz, H6$^{\alpha+\beta}$), 4.95 (0.5H, t, *J* = 9.1 Hz, H33$^{\beta}$), 4.94 (0.5H, dd, *J* = 10.2, 3.6 Hz, H33$^{\alpha}$), 4.78 (1H, ddd, *J* = 10.5, 4.0, 2.1 Hz, H9$^{\alpha+\beta}$), 4.72 (0.5H, dd, *J* = 10.3, 3.8 Hz, H21$^{\alpha}$), 4.71 (0.5H, dd, *J* = 10.3, 3.9 Hz, H21$^{\beta}$), 4.50-4.33 (3H, m, H3$^{\alpha+\beta}$, H15$^{\alpha+\beta}$, H27$^{\alpha+\beta}$), 4.27 (0.5H, dd, *J* = 12.2, 4.4 Hz, H27'$^{\beta}$), 4.25 (0.5H, dd, *J* = 12.3, 4.0 Hz, H27'$^{\alpha}$), 4.21 (1H, ddd, *J* = 12.4, 3.6, 2.4 Hz, H3'$^{\alpha+\beta}$), 4.17-4-11 (1.5H, m, H15'$^{\alpha+\beta}$, H26$^{\alpha}$), 4.00 (0.5H, t, *J* = 9.4 Hz, H25$^{\alpha}$), 3.98 (0.5H, t, *J* = 9.4 Hz, H25$^{\beta}$), 3.95-3.85 (2.5H, m, H13$^{\alpha+\beta}$, H14$^{\alpha+\beta}$,

H26$^{\beta}$), 3.77 (1H, ddd, *J* = 12.2, 5.7, 3.0 Hz, H4$^{\alpha+\beta}$), 3.51 (1H, t, *J* = 10.1 Hz, H5$^{\alpha+\beta}$), 3.06 (1H, br s, 5-OH), 2.22, 2.15, 2.14, 2.14, 2.13, 2.12, 2.11, 2.09, 2.07, 2.07, 2.05, 2.05, 2.03, 2.01, 1.99, 1.99, 1.99, 1.99, 1.98, 1.97 (30H, 20s, H1$^{\alpha+\beta}$, H8$^{\alpha+\beta}$, H11$^{\alpha+\beta}$, H17$^{\alpha+\beta}$, H20$^{\alpha+\beta}$, H23$^{\alpha+\beta}$, H29$^{\alpha+\beta}$, H32$^{\alpha+\beta}$, H35$^{\alpha+\beta}$, H38$^{\alpha+\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$, 299 K, ppm): δ = 171.6, 171.6 , 171.2, 171.2, 170.9, 170.9, 170.8, 170.8, 170.8, 170.8, 170.8, 170.6, 170.5, 170.1, 170.0, 170.0, 169.9, 169.8, 169.7 (C2$^{\alpha+\beta}$, C7$^{\alpha+\beta}$, C10$^{\alpha+\beta}$, C16$^{\alpha+\beta}$, C19$^{\alpha+\beta}$, C22$^{\alpha+\beta}$, C28$^{\alpha+\beta}$, C31$^{\alpha+\beta}$, C34$^{\alpha+\beta}$), 169.1 (C37$^{\alpha}$), 168.9 (C37$^{\beta}$), 96.2 (C12$^{\beta}$), 96.1 (C12$^{\alpha}$), 95.9 (C24$^{\beta}$), 95.9 (C24$^{\alpha}$), 91.4 (C36$^{\beta}$), 89.0 (C36$^{\alpha}$), 75.3 (C30$^{\beta}$), 73.4 (C25$^{\beta}$), 73.2 (C25$^{\alpha}$), 73.1 (C26$^{\beta}$), 72.9(C13$^{\alpha}$), 72.8 (C13$^{\beta}$), 72.3 (C30$^{\alpha}$), 72.1 (C18$^{\beta}$), 72.0 (C18$^{\alpha}$), 71.9 (C6$^{\beta}$), 71.9 (C6$^{\alpha}$), 71.4 (C4$^{\alpha+\beta}$), 71.1 (C33$^{\beta}$), 70.7 (C21$^{\beta}$), 70.6 (C21$^{\alpha}$), 70.3 (C26$^{\alpha}$), 70.2 (C9$^{\beta}$), 70.1 (C9$^{\alpha}$), 69.9 (C33$^{\alpha}$), 69.5 (C14$^{\alpha+\beta}$), 69.0 (C5$^{\beta}$), 68.9 (C5$^{\alpha}$), 62.9 (C27$^{\alpha}$), 62.8 (C27$^{\beta}$), 62.6 (C15$^{\alpha}$), 62.6 (C3$^{\alpha}$), 62.6 (C15$^{\beta}$), 62.5 (C3$^{\beta}$), 21.2 (C38$^{\alpha}$), 21.1, 21.0, 21.0, 21.0, 21.0, 21.0, 21.0, 21.0, 21.0, 21.0, 21.0, 20.9, 20.9, 20.8, 20.8, 20.8, 20.7, 20.7, 20.6 (C38$^{\beta}$, C1$^{\alpha+\beta}$, C8$^{\alpha+\beta}$, C11$^{\alpha+\beta}$, C17$^{\alpha+\beta}$, C20$^{\alpha+\beta}$, C23$^{\alpha+\beta}$, C29$^{\alpha+\beta}$, C32$^{\alpha+\beta}$, C35$^{\alpha+\beta}$); HR-ESI-MS: *m*/*z*: 947.2608 ([*M*+Na]$^{+}$, calcd. for $C_{38}H_{52}O_{26}Na^{+}$: 947.2639).[3]

2,3-Di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyrano-syl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (11)

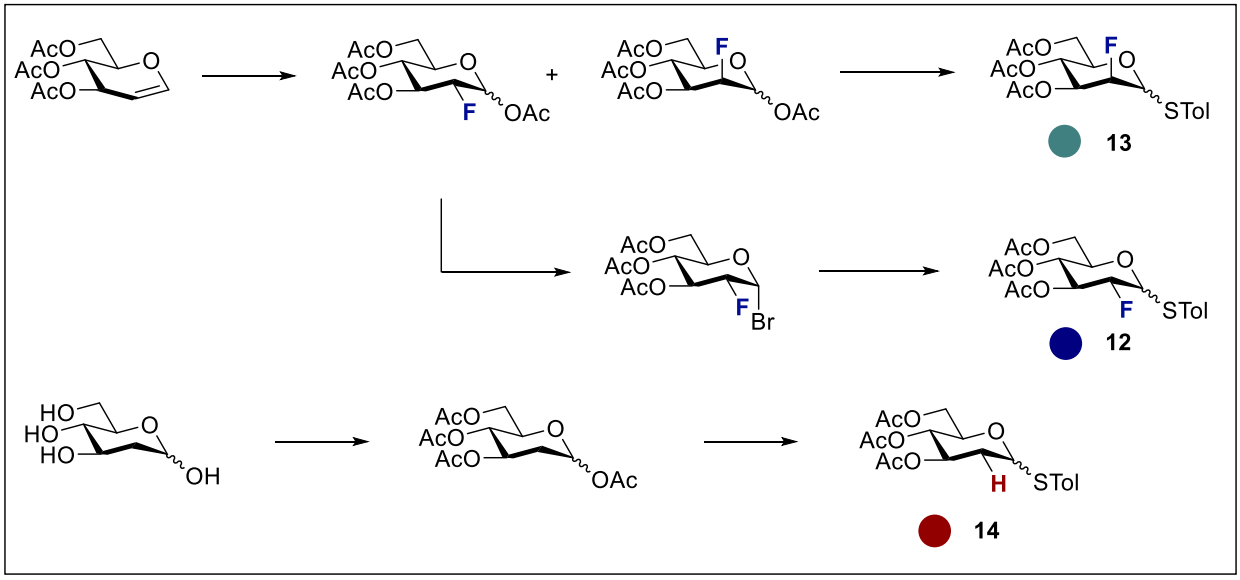


2,3-Di-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyrano-syl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**9**) (365 mg, 0.41 mmol, 1.0 eq) was dissolved in pyridine (6 mL) and the solution was cooled to -10 °C (methanol icebath) under an argon atmosphere. Benzoylchloride (93 mg, 76 µL, 0.66 mmol, 1.6 eq) was added dropwise and the reaction mixture was stirred for 3 h at -10 °C until full conversion of the starting material. After

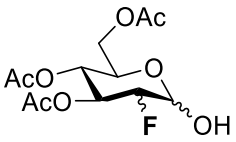
this time, the reaction was quenched by adding methanol (2 mL) and diluted with CH_2Cl_2 (15 mL). The reaction mixture was washed with aq. sat. $NaHCO_3$ (3 x 20 mL) and water (20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatographie (ethyl acetate:cyclohexane, 1:1 → 3:2) to obtain 2,3-di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyrano-syl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**11**) (233 mg, 57%) as a white foam.

R_f 0.24 (ethyl acetate:cyclohexane, 1:1); IR υ_{max} (neat)/cm^{-1} = 3474 (w), 2929 (w), 1743 (s), 1431 (w), 1368 (m), 1315 (w), 1212 (s), 1142 (m), 1116 (m), 1026 (s), 938 (m), 896 (m), 770 (w); **^{1}H-NMR** (600 MHz, $CDCl_3$, 299 K, ppm): δ = 8.06-8.03 (4H, m, H3$^\alpha$, H3$^\beta$), 7.60-7.56 (2H, m, H1$^\alpha$, H1$^\beta$), 7.47-7.43 (4H, m, H2$^\alpha$, H2$^\beta$), 6.23 (1H, d, *J* = 3.7 Hz, 39$^\alpha$), 5.73 (1H, d, *J* = 8.1 Hz, 39$^\beta$), 5.50 (1H, dd, *J* = 10.1, 9.0 Hz, 33$^\alpha$), 5.42-5.37 (2H, m, H21$^\alpha$, H21$^\beta$), 5.36 (1H, d, *J* = 4.2 Hz, H15$^\alpha$), 5.34 (1H, d, *J* = 4.0 Hz, H15$^\beta$), 5.30-5.27 (2H, m, H27$^\alpha$, H33$^\beta$), 5.28-5.24 (2H, m, H9$^\alpha$, H9$^\beta$), 5.26-5.24 (1H, m, H27$^\beta$), 4.97-4.92 (2H, m, H36$^\alpha$, H36$^\beta$), 4.79 (2H, ddd, *J* = 10.5, 4.0, 2.0 Hz, H12$^\alpha$, H12$^\beta$), 4.74 (2H, dt, *J* = 12.3, 3.6 Hz, H6$^\alpha$, H6$^\beta$), 4.73-4.68 (2H, m, H24$^\alpha$, H24$^\beta$), 4.50 (2H, ddd, *J* = 12.3, 4.7, 1.8 Hz, H18$^\alpha$, H18$^\beta$), 4.47 (2H, dt, *J* = 12.3, 2.0 Hz, H6$^{\alpha\prime}$, H6$^{\beta\prime}$), 4.46-4.42 (2H, m, H30$^\alpha$, H30$^\beta$), 4.28-4.22 (2H, m, H30$^{\alpha\prime}$, H30$^{\beta\prime}$), 4.16 (2H, dt, *J* = 12.2, 3.5 Hz, H18$^{\alpha\prime}$, H18$^{\beta\prime}$), 4.12 (1H, dt, *J* = 10.0, 3.2 Hz, H29$^\alpha$), 4.02-3.96 (2H, m, H28$^\alpha$, H28$^\beta$), 3.96-3.92 (4H, m, H16$^\alpha$, H16$^\beta$, H17$^\alpha$, H17$^\beta$), 3.91-3-86 (2H, m, H7$^\alpha$, H7$^\beta$), 3.87-3.84 (1H, m, H29$^\beta$), 3.62 (2H, *J* = 9.7, 2.2 Hz, H8$^\alpha$, H8$^\beta$), 2.21 (3H, s, H41$^\alpha$), 2.16 (3H, s, CH_3), 2.15 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.08 (3H, s, H41$^\beta$), 2.06 (3H, s, CH_3), 2.06 (3H, s, CH_3), 2.05 (6H, s, CH_3, CH_3), 2.03 (3H, s, CH_3), 2.00 (3H, s, CH_3), 1.99 (3H, s, CH_3), 1.99 (3H, s, CH_3), 1.99 (3H, s, CH_3), 1.98 (3H, s, CH_3), 1.97 (3H, s, CH_3), 1.97 (3H, s, CH_3); **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$, 300 K, ppm): δ = 171.1 (OCO) 171.1 (OCO), 170 .9 (OCO), 170.9 (OCO), 170.8 (OCO), 170.8 (OCO), 170.8 (OCO), 170.7 (OCO), 170.6 (OCO), 170.6 (OCO), 170.1 (OCO), 170.0 (OCO), 170.0 (OCO), 169.9 (OCO), 169.7 (OCO), 169.1 (C40$^\alpha$), 168.9 (C40$^\beta$), 167.0 (C5$^\alpha$, C5$^\beta$), 133.5 (C1$^\alpha$, C1$^\beta$), 129.9 (C3$^\alpha$, C3$^\beta$), 128.6 (C2$^\alpha$, C2$^\beta$), 96.1 (C15$^\beta$), 96.0 (C15$^\alpha$), 95.9 (C27$^\alpha$), 95.9 (C27$^\beta$), 91.4 (C39$^\beta$), 89.0 (C39$^\alpha$), 75.3 (C33$^\beta$), 73.4 (C28$^\beta$), 73.2 (C28$^\alpha$), 73.1 (C29$^\beta$), 72.5 (C16$^\beta$), 72.4 (C16$^\alpha$), 72.3 (C33$^\alpha$), 72.0 (C21$^\alpha$), 71.9 (C21$^\beta$), 71.8 (C9$^\beta$), 71.8 (C9$^\alpha$), 71.6 (C7$^\alpha$, C7$^\beta$), 71.1 (C36$^\beta$), 70.7 (C24$^\alpha$), 70.6 (C24$^\beta$), 70.3 (C12$^\alpha$), 70.3 (C12$^\beta$), 70.3 (C29$^\alpha$), 69.8 (C36$^\alpha$), 69.4 (C17$^\alpha$, C17$^\beta$), 68.9 (C8$^\beta$), 68.9 (C8$^\alpha$), 62.9 (C30$^\beta$), 62.8 (C30$^\alpha$), 62.8 (C6$^\alpha$, C6$^\beta$), 62.5 (C18$^\beta$), 62.4 (C18$^\alpha$), 21.1 (CH_3), 21.0 (CH_3), 21.0 (CH_3), 21.0 (CH_3),

20.9 (CH_3), 20.9 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 20.5 (CH_3); HR-ESI-MS: *m*/*z*: 1009.2804 ([*M*+Na]$^+$, calcd. for $C_{43}H_{54}O_{26}Na^+$: 1009.2796).



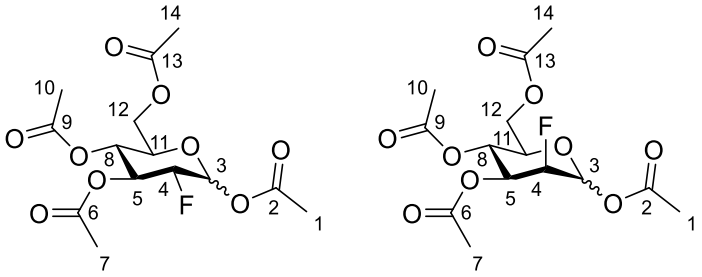
2-Deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-D-manno/glucopyranose



SelectFluor™ (17.70 g, 50.5 mmol, 1.2 eq.) was added at to a solution of tri-*O*-acetyl-D-glucal (11.45 g, 42.1 mmol, 1.0 eq.) in acetone (183 mL) and water (38 mL). The solution was stirred for 22 h at RT and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and a sat. aq. solution of NaHCO3. The aq. phase was extracted twice with CH_2Cl_2 and the combined organic phases dried over Na2SO4, filtered and evaporated under reduced pressure. Purification by flash column chromatography (ethyl acetate:cyclohexane, 1:2) afforded an inseparable mixture of the gluco- and manno-configured products. This mixture was used directly in the next step without any further purification.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranose and

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-D-mannopyranose

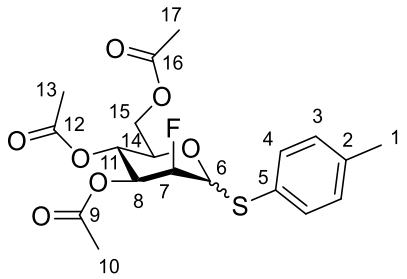


To a solution of 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-D-manno-/glucopyranose (7.92 g, 25.7 mmol, 1.0 eq) in pyridine (90 mL) acetic anhydride (9.70 mL, 10.5 g, 102.8 mmol, 4.0 eq) and DMAP (315 mg, 2.57 mmol, 0.1 eq) were added and the reaction mixture was allowed to stir for 4 h at RT. After full conversion of the start material (determined by TLC), the mixture was diluted with CH_2Cl_2, poured into a beaker with sat. aq. $NaHCO_3$ and stirred for 30 min. After this time, the organic layer was washed three times with sat. aq. $NaHCO_3$ and water, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:3) to obtain 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranose (3.22 g, 36% over two steps, α:β = 1.9:1) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-mannopyranose (4.64 g, 52% over two steps, mainly α) as colorless oils.[4]

glucopyranose: R_f 0.40 (ethyl acetate:cyclohexane, 2:3); **^{1}H-NMR** (300 MHz, $CDCl_3$, 299 K, ppm): δ = 6.41 (1H, d, *J* = 4.0 Hz, H3$^\alpha$), 5.77 (1H, dd, *J* = 8.1, 3.2 Hz, H3$^\beta$), 5.54 (1H, dt, *J* = 12.2, 9.6 Hz, H5$^\alpha$), 5.54 (1H, dt, *J* = 14.3, 9.3 Hz, H5$^\beta$), 5.08 (1H, t, *J* = 10.0 Hz, H8$^\alpha$), 5.06 (1H, t, *J* = 9.8 Hz, H8$^\beta$), 4.64 (1H, ddd, *J* = 48.5, 9.6, 4.0 Hz, H4$^\alpha$), 4.44 (1H, ddd, *J* = 50.8, 9.1, 8.2 Hz, H4$^\beta$), 4.32-4.24 (2H, m, H12$^\beta$, H12$^\alpha$), 4.12-4.01 (3H, m, H11$^\alpha$, H12'$^\beta$, H12'$^\beta$), 3.85 (1H, ddd, *J* = 10.1, 4.5, 2.2 Hz, H11$^\beta$), 2.19 (3H, s, CH_3), 2.17 (3H, s, CH_3), 2.08 (6H, s, CH_3), 2.07 (6H, s, CH_3), 2.03 (3H, s, CH_3), 2.03 (3H, s, CH_3); HR-ESI-MS: *m/z*: 373.0916 ([*M*+Na]$^+$, calcd. for $C_{14}H_{19}O_9FNa^+$: 373.0905). mannopyranose: R_f 0.28 (ethyl acetate:cyclohexane, 2:3); **^{1}H-NMR** (300 MHz, $CDCl_3$, 299 K, ppm): δ = 6.26 (1H, dd, *J* = 6.6, 2.1 Hz, H3$^\alpha$), 5.41 (1H, td, *J* = 10.1, 1.2 Hz, H8$^\alpha$), 5.25 (1H, ddd, *J* = 27.7, 10.2, 2.6 Hz, H5$^\alpha$), 4.74 (1H, dt, *J* = 48.7, 2.4 Hz, H34$^\alpha$), 4.27 (1H, dd, *J* = 12.4, 4.3 Hz, H12$^\alpha$), 4.13-4.01 (2H, m, H12$^\alpha$, H11$^\alpha$), 2.16 (3H, s, CH_3), 2.10 (3H,

s, CH_3), 2.08 (3H, s, CH_3), 2.04 (3H, s, CH_3); HR-ESI-MS: *m*/*z*: 373.0920 ([*M*+Na]$^+$, calcd. for $C_{14}H_{19}O_9FNa^+$: 373.0905). The data are in agreement with the available literature values.

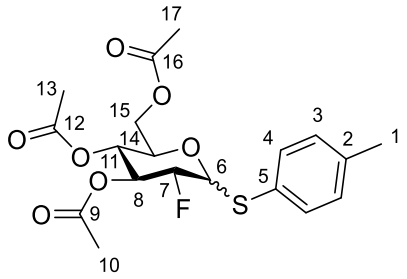
3,4,6-Tri-*O*-acetyl-1,2-dideoxy-1-(*p*-tolylthio)-2-fluoro-α,β-D-mannopyranose (13)



To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-mannopyranose (320 mg, 0.91 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (5 mL) *p*-toluenethiol (124 mg, 1.00 mmol, 1.1 eq) and $BF_3{\cdot}OEt_2$ (411 mg, 278 µL, 3.38 mmol, 2.4 eq) were added and the reaction mixture was allowed to stir 2 h at RT under an argon atmosphere. After this time, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with sat. aq. $NaHCO_3$ (2x25 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:9 → 1:7) to obtain 3,4,6-tri-*O*-acetyl-1,2-dideoxy-1-(*p*-tolylthio)-2-fluoro-α,β-D-mannopyranose (**13**) (266 mg, 70%) as a colorless solid (α only)

R_f 0.49 (ethyl acetate:hexane, 1:1); **^{1}H-NMR** (300 MHz, $CDCl_3$, 299 K, ppm): δ = 7.41-7.35 (2H, m, H4), 7.17-7.11 (2H, m, H3), 5.58 (1H, dd, *J* = 14.4, 1.8 Hz, H6), 5.39 (1H, td, *J* = 10.1, 1.0 Hz, H11), 5.22 (1H, ddd, *J* = 28.0, 10.0, 2.5 Hz, H8), 5.04 (1H, ddd, *J* = 49.9, 2.5, 1.8 Hz, H7), 4.52 (1H, ddd, *J* = 10.0, 5.3, 2.3 Hz, H14), 4.30 (1H, dd, *J* = 12.3, 5.3 Hz, H15), 4.11 (1H, dd, *J* = 12.3, 2.3 Hz, H15'), 2.34 (3H, s, tol-CH_3), 2.11 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.07 (3H, s, CH_3); HR-ESI-MS: *m*/*z*: 437.1034 ([*M*+Na]$^+$, calcd. for $C_{19}H_{23}O_7SFNa^+$: 437.1041). The data are in agreement with the available literature values.[5]

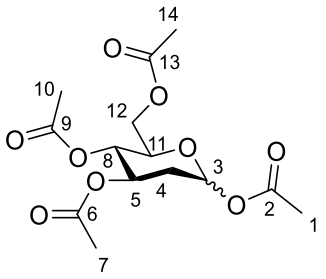
3,4,6-Tri-*O*-acetyl-1,2-dideoxy-1-(*p*-tolylthio)-2-fluoro-α,β-D-glucopyranose (12)



1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-D-glucoopyranose (400 mg, 1.14 mmol, 1.0 eq) was dissolved in anhydrous CH_2Cl_2 (4 mL) and cooled to 0 °C. To this, HBr (876 µL, 462 mg, 5.71 mmol, 5.0 eq, 33% sol in acetic acid) was added and the resulting solution was stirred for 16 h at RT. After this time, the mixture was poured into ice water, diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure and co-evaporated with toluene. The crude product was dissolved in anhydrous CH_2Cl_2 (5 mL) and *p*-toluenethiol (212 mg, 1.71 mmol, 1.5 eq) and a solution of TBAB (73 mg, 0.23 mmol, 0.2 eq) in water (1.5 mL) were added. The resulting emulsion was cooled to 0 °C and subsequently, a solution of KOH (127 mg, 2.28 mmol, 2.0 eq) in water (3.5 mL) was added over 10 min. The emulsion was vigorously stirred for 3 h. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:6) to obtain 3,4,6-tri-*O*-acetyl-1,2-dideoxy-1-(*p*-tolylthio)-2-fluoro-α,β-D-glucopyranose (**12**) (329 mg, 70%) as a colorless solid (α:β = 8:92).

R_f 0.48 (ethyl acetate:cyclohexane, 1:1); **^{1}H-NMR** (300 MHz, $CDCl_3$, 299 K, ppm): δ = 7.49-7.43 (2H, m, H4), 7.17-7.11 (2H, m, H3), 5.30 (1H, dt, *J* = 14.1, 9.1 Hz, H8), 4.92 (t, *J* = 9.8 Hz, H11), 4.62 (1H, dd, *J* = 9.8, 1.7 Hz, H6), 4.20-4.17 (2H, m, H15, H15'), 4.13 (1H, ddd, *J* = 49.2, 9.7, 8.9 Hz, H7), 3.71 (1H, ddd, *J* = 10.1, 4.4, 3.0 Hz, H14), 2.37 (3H, s, Tol-CH_3), 2.08 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.02 (3H, s, CH_3); HR-ESI-MS: *m*/*z*: 437.1039 ([*M*+Na]$^+$, calcd. for $C_{19}H_{23}O_7SFNa^+$: 437.1041). The data are in agreement with the available literature values.[6]

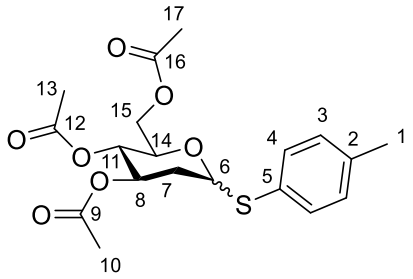
1,3,4,6-Tetra-*O*-acetyl-2-deoxy-D-glucopyranose



To a solution of 2-deoxy-D-glucose (1.03 g, 6.11 mmol, 1.0 eq) in pyridine (17 mL) acetic anhydride (5.77 mL, 6.23 g, 61.1 mmol, 10.0 eq) and DMAP (75 mg, 0.61 mmol, 0.1 eq) were added and the reaction mixture was allowed to stir for 2 h at RT. After full conversion of the starting material (determined by TLC), the mixture was diluted with CH_2Cl_2, poured into a beaker with sat. aq. $NaHCO_3$ and stirred for 30 min. After this time, the organic layer was washed three times with sat. aq. $NaHCO_3$ and water, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:2) to obtain 1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucopyranose (1.96 g, 97%) as a colorless solid (α:β = 1:6).

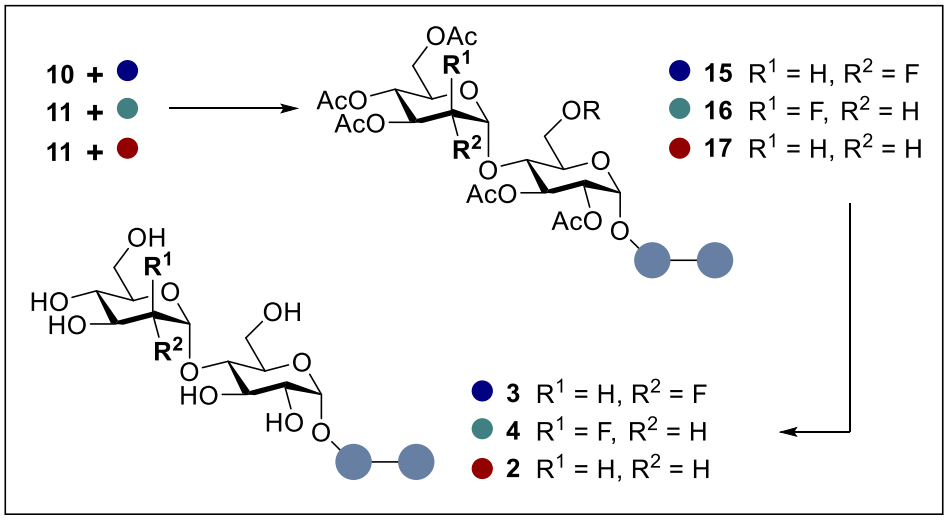
R_f 0.20 (ethyl acetate:cyclohexane, 1:2); **^{1}H-NMR** (400 MHz, $CDCl_3$, 299 K, ppm): δ = 5.78 (1H, dd, *J* = 10.0, 2.3 Hz, H3), 5.10-4.98 (2H, m, H5, H8), 4.31 (1H, dd, *J* = 12.5, 4.7 Hz, H12), 4.07 (1H, dd, *J* = 12.4, 2.3 Hz, H12'), 3.73 (1H, ddd, *J* = 9.4, 4.6, 2.2 Hz, H11), 2.34 (1H, ddd, *J* = 12.6, 4.9, 2.3 Hz, $H4_{eq}$), 2.10 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.03 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.85 (1H, ddd, *J* = 12.5, 11.2, 10.0 Hz, $H4_{ax}$), only the β-anomer was characterized; HR-ESI-MS: *m*/*z*: 355.1033 ([*M*+Na]$^+$, calcd. for $C_{14}H_{20}O_9Na^+$: 355.1000). The data are in agreement with the available literature values.[7]

3,4,6-Tri-*O*-acetyl-1,2-dideoxy-1-(*p*-tolylthio)-α,β-D-glucopyranose (14)



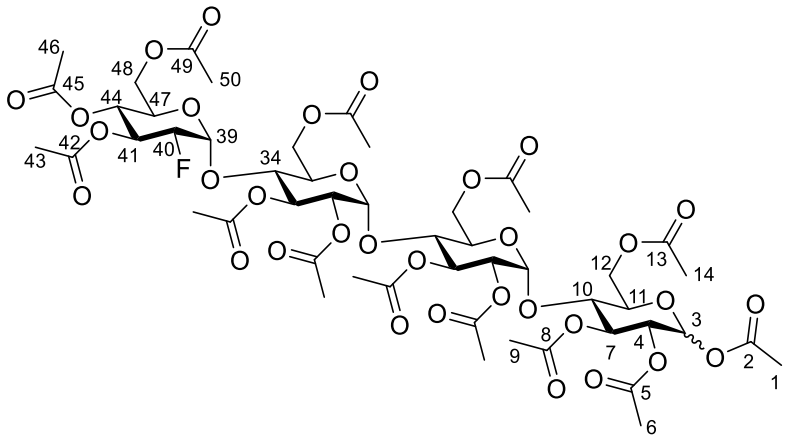
To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-α,β-D-glucopyranose (495 mg, 1.41 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (8 mL) *p*-toluenethiol (193 mg, 1.55 mmol, 1.1 eq) and $BF_3{\cdot}OEt_2$ (480 mg, 430 µL, 3.38 mmol, 2.4 eq) were added and the reaction mixture was allowed to stir 90 min at RT under an argon atmosphere. After this time, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with sat. aq. $NaHCO_3$ (2x25 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:6) to obtain 3,4,6-tri-*O*-acetyl-1,2-dideoxy-1-(*p*-tolylthio)-α,β-D-glucopyranose (**14**) (559 mg, 99%) as a yellowish solid (α:β = 8:92).

R_f 0.13 (ethyl acetate:cyclohexane, 1:6); $[\alpha]_D^{25}$ +257.4 (c 0.5, $CHCl_3$); IR υ_{max} (neat)/cm^{-1} = 2951 (w), 1742 (s), 1497 (w), 1439 (w), 1365 (m), 1330 (w), 1299 (w), 1250 (m), 1217 (s), 1132 (w), 1084 (m), 1050 (s), 982 (m), 941 (m), 916 (m), 904 (m), 886 (m), 861 (m), 813 (s), 764 (w); **^{1}H-NMR** (400 MHz, $CDCl_3$, 299 K, ppm): δ = 7.42-7.38 (2H, m, H4), 7.14-7.09 (2H, m, H3), 5.01 (1H, ddd, *J* = 10.9, 9.4, 5.2 Hz, H8), 4.94 (1H, t, *J* = 9.5 Hz), 4.73 (1H, dd, *J* = 11.9, 2.0 Hz, H6), 4.23 (1H, dd, *J* = 12.2, 5.4 Hz, H15), 4.12 (1H, dd, *J* = 12.2, 2.4 Hz, H15'), 3.62 (1H, ddd, *J* = 9.6, 5.4, 2.4 Hz, H14), 2.41 (1H, ddd, *J* = 13.0, 5.2, 2.1 Hz, H7), 2.34 (3H, s, H1), 2.07 (3H, s, H17), 2.02 (3H, s, H13), 2.00 (3H, s, H10), 1.80 (1H, ddd, *J* = 12.9, 11.8, 11.0 Hz, H7'); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$, 299 K, ppm): δ = 170.8 (C16), 170.4 (C9), 169.9 (C12), 138.5 (C2), 133.3 (C4), 129.8 (C3), 128.9 (C5), 82.3 (C6), 76.0 (C14), 71.9 (C8), 68.9 (C11), 62.8 (C15), 36.3 (C7), 21.3 (C1), 21.0 (C10), 20.9 (C17), 20.8 (C13), only the β-anomer was characterized; HR-ESI-MS: *m*/*z*: 419.1126 ([*M*+Na]$^+$, calcd. for $C_{19}H_{24}O_7SNa^+$: 419.1135).



All sonication glycosylation reactions were performed following literature known procedures.[8]

2-Deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose

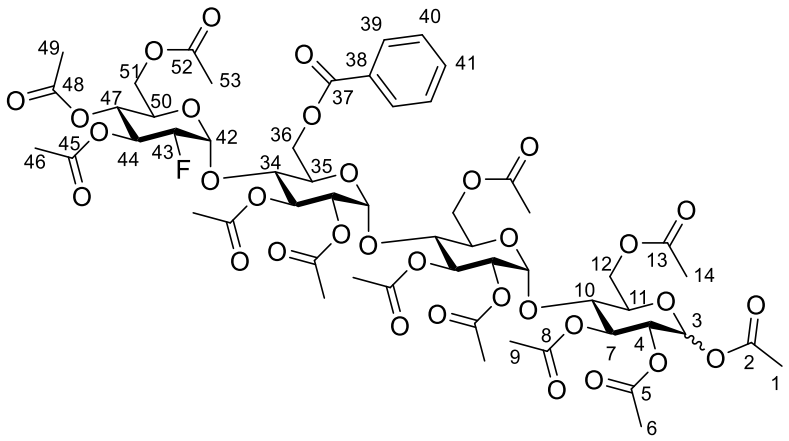


To 2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**10**) (100 mg, 0.108 mmol, 1.0 eq) dissolved in anhydrous CH_2Cl_2 (2 mL) 3,4,6-tri-*O*-acetyl-1,2-dideoxy-2-fluoro-1-(*p*-tolylthio)-α,β-D-glucopyranose (**12**) (50 mg, 0.119 mmol, 1.1 eq) and 3 Å molecular sieves were added and the mixture was stirred for 15 min under an argon atmosphere. After this time, NIS (29 mg, 0.129 mmol, 1.2 eq) and TMSOTf (4 mg, 3 µL, 0.016 mmol, 0.15 eq) and the reaction mixture

sonicated for 15 minutes. Subsequently, the reaction was quenched by addition of Na_2SO_4 (s) and $NaHCO_3$ (s). The resulting suspension was allowed to stir for several minutes until it turned yellow, filtered, concentrated under reduced pressure and purified by silica gel column chromatographie (CH_2Cl_2:acetone, 10:1) to obtain 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (38 mg, 32%) as a colourless foam (α:β = 1.6:1).

R_f 0.24 (CH_2Cl_2:acetone, 9:1); IR υ_{max} (neat)/cm^{-1} = 2926 (w), 1740 (s), 1598 (w), 1509 (w), 1433 (w), 1367 (m), 1209 (s), 1162 (m), 1026 (s), 942 (m), 896 (m), 757 (w); selected resonances: **^{1}H-NMR** (600 MHz, $CDCl_3$, 299 K, ppm): δ = 6.24 (1H, d, *J* = 3.7 Hz, H3$^{\alpha}$), 5.75 (1H, d, *J* = 8.1 Hz, H3$^{\beta}$), 5.50 (1H, dd, *J* = 10.1, 8.8 Hz, H7$^{\alpha}$), 5.39 (2H, dt, *J* =11.3, 9.9 Hz, H41$^{\alpha+\beta}$), 5.29 (1H, t, *J* = 9.0 Hz, H7$^{\beta}$), 5.20 (2H, d, *J* = 4.2 Hz, H39$^{\alpha+\beta}$), 4.98 (2H, t, *J* = 9.7 Hz, H44$^{\alpha+\beta}$), 4.96 (1H, t, *J* = 8.5 Hz, H4$^{\beta}$), 4.95 (1H, dd, *J* = 10.2, 3.6 Hz, H4$^{\alpha}$), 4.47 (1H, dd, *J* = 12.6, 3.1 Hz, H12$^{\alpha}$), 4.46-4.43 (1H, m, H12$^{\beta}$), 4.45 (2H, ddd, *J* = 49.6, 9.8, 4.0 Hz, H40$^{\alpha+\beta}$), 4.36 (1H, dd, *J* = 12.4, 4.4 Hz, H12'$^{\beta}$), 4.33 (1H, dd, *J* = 12.6, 3.8 Hz, H12'$^{\alpha}$), 4.25 (2H, dd, *J* = 12.4, 4.0 Hz, H48$^{\alpha+\beta}$), 4.14 (1H, dt, *J* = 10.0, 3.3 Hz, H11$^{\alpha}$), 4.08 (2H, ddd, *J* = 10.0, 4.2, 2.1 Hz, H47$^{\alpha+\beta}$), 4.07-4.03 (2H, m, H48$^{\alpha+\beta}$), 4.00 (1H, t, *J* = 9.3 Hz, H10$^{\alpha}$), 4.00 (1H, t, *J* = 8.9 Hz, H10$^{\beta}$), 3.90-3.86 (1H, m, H11$^{\beta}$), 3.80 (1H, t, *J* = 9.6 Hz, H34$^{\alpha}$), 3.80 (1H, t, *J* = 9.6 Hz, H34$^{\beta}$), 2.23 (3H, s, H1$^{\alpha}$), 2.09 (3H, s, H1$^{\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$, 299 K, ppm): δ = 169.0 (C2$^{\alpha}$), 168.7 (C2$^{\beta}$), 98.7 (d, *J* = 21.2 Hz, C39$^{\alpha+\beta}$), 91.3 (C3$^{\beta}$), 88.8 (C3$^{\alpha}$), 87.0 (d, *J* = 194.4 Hz, C40$^{\alpha+\beta}$), 78.3 (C34$^{\beta}$), 78.2 (C34$^{\alpha}$), 75.1 (C7$^{\beta}$), 73.7 (C10$^{\beta}$), 73.6 (C10$^{\alpha}$), 73.1 (C11$^{\beta}$), 72.2 (C7$^{\alpha}$), 71.0 (C4$^{\beta}$), 70.2 (C11$^{\alpha}$), 69.7 (C4$^{\alpha}$), 68.6 (C47$^{\alpha+\beta}$), 67.6 (d, *J* = 7.5 Hz, C44$^{\alpha+\beta}$), 62.7 (C12$^{\beta}$), 62.6 (C12$^{\alpha}$), 61.4 (C48$^{\alpha+\beta}$), 21.0 (C1$^{\alpha}$), 20.8 (C1$^{\beta}$); **^{19}F-NMR** (564 MHz, $CDCl_3$, 299 K, ppm): δ = -199.83 (ddd, *J* = 49.7, 11.4, 1.8 Hz, F$^{\alpha+\beta}$); HR-ESI-MS: *m*/*z*: 1237.3416 ([*M*+Na]$^+$, calcd. for $C_{50}H_{67}O_{33}FNa^+$: 1237.3441).

2-Deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (15)

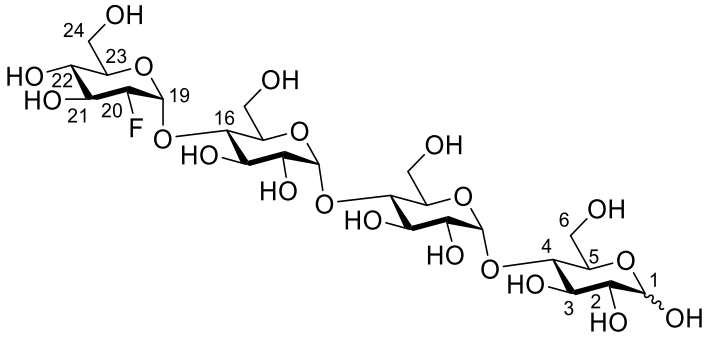


To 2,3-di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**11**) (65 mg, 0.066 mmol, 1.0 eq) dissolved in anhydrous CH_2Cl_2 (3 mL) 3,4,6-tri-*O*-acetyl-1,2-dideoxy-2-fluoro-1-(*p*-tolylthio)-α,β-D-glucopyranose (**12**) (30 mg, 0.073 mmol, 1.1 eq) and 3 Å molecular sieves were added and the mixture was stirred for 15 min under an argon atmosphere. After this time, NIS (18 mg, 0.079 mmol, 1.2 eq) and TMSOTf (3 mg, 2 µL, 0.011 mmol, 0.15 eq) and the reaction mixture sonicated for 15 minutes. Subsequently, the reaction was quenched by addition of Na_2SO_4 (s) and $NaHCO_3$ (s). The resulting suspension was allowed to stir for several minutes until it turned yellow, filtered, concentrated under reduced pressure and by silica gel column chromatographie twice, principally with CH_2Cl_2:acetone (8.5:1) and secondly with ethyl acetate:cyclohexane (1:1) to obtain 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**15**) (28 mg, 33%) as a colourless foam (α:β = 1.6:1).

R_f 0.20 (CH_2Cl_2:acetone, 9:1); IR υ_{max} (neat)/cm^{-1} = 2923 (w), 2853 (w), 1742 (s), 1716 (s), 1452 (w), 1367 (m), 1211 (s), 1171 (m), 1026 (s), 943 (m), 895 (m), 805 (w), 715 (m); selected resonances: **^{1}H-NMR** (600 MHz, MeOD-d_4, 299 K, ppm): δ = 8.09-8.07 (4H,m, H39$^{\alpha+\beta}$), 7.66-7.62 (2H, m, H41$^{\alpha+\beta}$), 7.54-7.50 (4H, m, H40$^{\alpha+\beta}$), 6.22 (1H, d, *J* = 3.7 Hz, H3$^{\alpha}$), 5.82 (1H, d, *J* = 8.1 Hz, H3$^{\beta}$), 5.51 (1H, dd, *J* = 10.3, 9.0 Hz, H7$^{\alpha}$), 5.39 (1H, t, *J* = 8.6 Hz, H7$^{\beta}$), 5.39 (2H, dt,

J = 11.6, 9.7 Hz, H44$^{\alpha+\beta}$), 5.37 (2H, d, *J* = 4.0 Hz, H42$^{\alpha+\beta}$), 4.97 (2H, t, *J* = 9.7 Hz, H47$^{\alpha+\beta}$), 4.96 (1H, dd, *J* = 10.2, 3.7 Hz, H4$^{\alpha}$), 4.93 (1H, t, *J* = 8.6 Hz, H4$^{\beta}$), 4.80 (2H, dd, *J* = 12.4, 1.9 Hz, H36$^{\alpha+\beta}$), 4.59 (2H, ddd, *J* = 49.3, 9.9, 4.0 Hz, H43$^{\alpha+\beta}$), 4.53 (2H, dd, *J* = 12.4, 4.2 Hz, H39'$^{\alpha+\beta}$), 4.23-4.19 (2H, m, H35$^{\alpha+\beta}$), 4.21 (2H, ddd, *J* = 10.1, 4.4, 2.1 Hz, H50$^{\alpha+\beta}$), 4.19 (2H, dd, *J* = 12.2, 4.8 Hz, H51$^{\alpha+\beta}$), 4.07 (1H, t, *J* = 9.6 Hz, H34$^{\alpha}$), 4.07 (1H, t, *J* = 9.5 Hz, H34$^{\beta}$), 4.04 (2H, dd, *J* = 12.2, 2.1 Hz, H39$^{\alpha+\beta}$), 2.20 (3H, s, H1$^{\alpha}$), 2.07 (3H, s, H1$^{\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, MeOD-d$_4$, 299 K, ppm): δ = 170.8 (C2$^{\alpha}$), 170.4 (C2$^{\beta}$), 167.6 (C37$^{\alpha+\beta}$), 134.6 (C41$^{\alpha+\beta}$), 131.0 (C38$^{\alpha+\beta}$), 130.8 (C39$^{\alpha+\beta}$), 129.8 (C40$^{\alpha+\beta}$), 100.3 (d, *J* = 20.9 Hz, C42$^{\alpha+\beta}$), 92.7 (C3$^{\beta}$), 90.2 (C3$^{\alpha}$), 88.5 (d, *J* = 192.2, C43$^{\alpha+\beta}$), 80.0 (C34$^{\beta}$), 80.0 (C34$^{\alpha}$), 76.2 (C7$^{\beta}$), 73.3 (C7$^{\alpha}$), 72.4 (C4$^{\beta}$), 71.6 (d, *J* = 19.6 Hz, C44$^{\alpha+\beta}$), 71.3 (C4$^{\alpha}$), 69.8 (C50$^{\alpha+\beta}$), 69.3 (d, *J* = 8.2 Hz, C47$^{\alpha+\beta}$), 64.7 (C36$^{\alpha+\beta}$), 63.2 (C51$^{\alpha+\beta}$); **^{19}F-NMR** (564 MHz, MeOD-d$_4$, 299 K, ppm): δ = -201.10 (dd, *J* = 49.3, 11.6 Hz, F$^{\alpha+\beta}$); LR-ESI-MS: *m*/*z*: 1299.66 ([*M*+Na]$^+$, calcd. for $C_{55}H_{69}O_{33}FNa^+$: 1299.36).

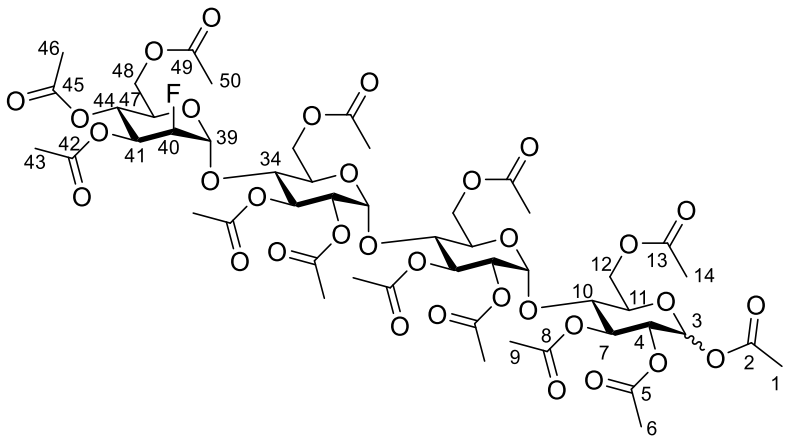
2-Deoxy-2-fluoro-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α,β-D-glucopyranose (3)



To a solution of 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**15**) (45 mg, 0.035 mmol, 1.0 eq) in methanol (2 mL) NaOMe (1 mg, 0.018 mmol, 0.5 eq) was added and the reaction mixture was allowed to stir at RT for2 h. After this time, the mixture was neutralized with Amberlyst® H$^+$, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:methanol:water, 7:2:1) to obtain 2-deoxy-2-fluoro-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α,β-D-glucopyranose (**3**) (16 mg, 69%) as a colourless foam (α:β = 1:1.6).

R_f 0.10 (ethyl acetate:methanol:water, 6:2:1); IR υ_{max} (neat)/cm^{-1} = 3292 (m), 2924 (w), 1646 (w), 1362 (w), 1259 (w), 1147 (m), 1075 (s), 1014 (s), 931 (m), 846 (m), 762 (m); selected resonances: **^{1}H-NMR** (600 MHz, D_2O, 299 K, ppm): δ = 5.72 (2H, d, *J* = 4.1 Hz, H19$^{\alpha+\beta}$), 5.25 (1H, d, *J* = 3.8 Hz, H1$^{\alpha}$), 4.68 (1H, d, *J* = 8.0 Hz, H1$^{\beta}$), 4.48 (2H, ddd, *J* = 49.4, 9.7, 4.1 Hz, H20$^{\alpha+\beta}$), 3.85-3.78 (2H, m, H21$^{\alpha+\beta}$), 3.59 (1H, dd, *J* = 10.0, 3.8 Hz, H2$^{\alpha}$), 3.30 (1H, dd, *J* = 9.5 Hz, H2$^{\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, D_2O, 299 K, ppm): δ = 96.4 (d, *J* = 20.5 Hz, C19$^{\alpha+\beta}$), 95.7 (C1$^{\beta}$), 91.8 (C1$^{\alpha}$), 89.8 (d, *J* = 187.1 Hz, C20$^{\alpha+\beta}$), 73.9 (C2$^{\beta}$), 71.2 (C2$^{\alpha}$); **^{19}F-NMR** (564 MHz, D_2O, 299 K, ppm): δ = -199.68 (dd, *J* = 49.31, 12.68 Hz, F$^{\alpha+\beta}$); HR-ESI-MS: *m*/*z*: 691.2059 ([*M*+Na]$^+$, calcd. for $C_{24}H_{41}O_{20}FNa^+$: 691.2067).

2-Deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (16)

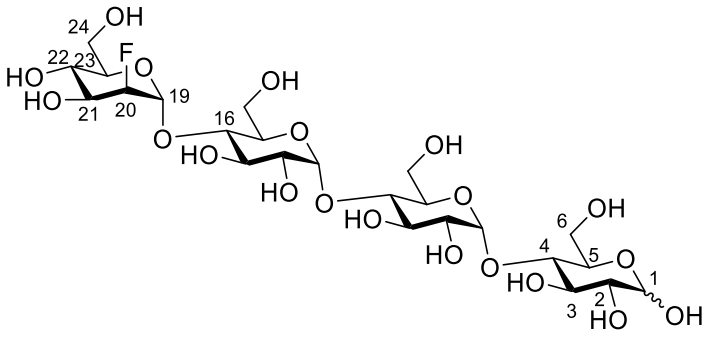


To 2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**10**) (126 mg, 0.136 mmol, 1.0 eq) dissolved in anhydrous CH_2Cl_2 (3 mL) 3,4,6-tri-*O*-acetyl-1,2-dideoxy-2-fluoro-1-(*p*-tolylthio)-α,β-D-mannopyranose (**13**) (62 mg, 0.119 mmol, 1.1 eq) and 3 Å molecular sieves were added and the mixture was stirred for 15 min under an argon atmosphere. After this time, NIS (37 mg, 0.163 mmol, 1.2 eq) and TMSOTf (6 mg, 5 µL, 0.027 mmol, 0.2 eq) and the reaction mixture sonicated for 15 minutes. Subsequently, the reaction was quenched by addition of Na_2SO_4 (s) and $NaHCO_3$ (s). The resulting suspension was allowed to stir for several minutes until it turned yellow, filtered, concentrated under reduced pressure and purified by silica gel column

chromatographie twice, firstly with CH_2Cl_2:acetone (10:1) and secondly with ethyl acetate:cyclohexane (1:1) to obtain 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**16**) (82 mg, 50%) as a colourless foam (α:β = 1.9:1).

R_f 0.23 (CH_2Cl_2:acetone, 9:1); IR υ_{max} (neat)/cm^{-1} = 2967 (w), 1740 (s), 1434 (w), 1368 (m), 1210 (s), 1140 (m), 1028 (s), 940 (m), 895 (m), 810 (w), 769 (w), 700 (w); selected resonances: **^{1}H-NMR** (600 MHz, benzene-d_6, 299 K, ppm): δ = 6.39 (1H, d, *J* = 3.7 HZ, H3$^\alpha$), 5.76 (1H, td, *J* = 10.1, 0.7 Hz, H44$^\alpha$), 5.75 (1H, d, *J* = 8.2 Hz, H3$^\beta$), 5.74 (1H, t, *J* = 9.8 Hz, H44$^\beta$), 5.33 (1H, ddd, *J* = 28.3, 10.0, 2.6 Hz, H41$^\alpha$), 5.31 (1H, ddd, *J* = 28.3, 10.1, 2.6 Hz, H41$^\beta$), 5.16 (1H, dd, *J* = 7.4, 2.1 Hz, H39$^\alpha$), 5.14 (1H, dd, *J* = 7.5, 2.1 Hz, H39$^\beta$), 5.11 (1H, dd, *J* = 9.3, 8.3 Hz, H4$^\beta$), 4.99 (1H, dd, *J* = 10.2, 3.7 Hz, H4$^\alpha$), 4.85 (1H, dt, *J* = 50.2, 2.4 Hz, H40$^\alpha$), 4.83 (1H, dt, *J* = 50.3, 2.4 Hz, H40$^\beta$), 4.45-4.40 (1H, m, H48$^{\alpha+\beta}$), 4.39-4.35 (1H, m, H48'$^{\alpha+\beta}$), 4.21 (1H, ddd, *J* = 10.1, 4.2, 2.1 Hz, H47$^\alpha$), 4.20-4.16 (1H, m, H47$^\beta$), 3.69 (1H, t, *J* = 9.6 Hz, H34$^\alpha$), 3.68 (1H, t, *J* = 9.6 Hz, H34$^\beta$), 1.51 (3H, s, H1$^\alpha$), 1.46 (3H, s, H1$^\beta$); **^{13}C{^{1}H}-NMR** (151 MHz, benzene-d_6, 299 K, ppm): δ = 168.1 (C2$^\beta$), 168.1 (C2$^\alpha$), 99.3 (d, *J* = 29.9 Hz, C39$^\alpha$), 99.3 (d, *J* = 29.8 Hz, C39$^\beta$), 91.2 (C3$^\beta$), 88.9 (C3$^\alpha$), 87.2 (d, *J* = 180.9 Hz, C40$^{\alpha+\beta}$), 77.0 (C34$^\beta$), 77.0 (C34$^\beta$), 71.3 (C4$^\beta$), 70.4 (C47$^\alpha$), 70.4 (C47$^\beta$), 69.9 (C4$^\alpha$), 69.8 (d, *J* = 17.0 Hz, C41$^{\alpha+\beta}$), 65.3 (C44$^{\alpha+\beta}$), 61.6 (C48$^\alpha$), 61.5 (C48$^\beta$), 19.8 (C1$^\alpha$), 19.7 (C1$^\beta$); **^{19}F-NMR** (564 MHz, benzene-d_6, 299 K, ppm): δ = -201.40 (ddd, *J* = 50.2, 28.3, 7.5 Hz, F$^\alpha$), -201.41 (ddd, *J* = 50.3, 28.3, 7.5 Hz, F$^\beta$); HR-ESI-MS: *m*/*z*: 1237.3461 ([*M*+Na]$^+$, calcd. for $C_{50}H_{67}O_{33}FNa^+$: 1237.3441).

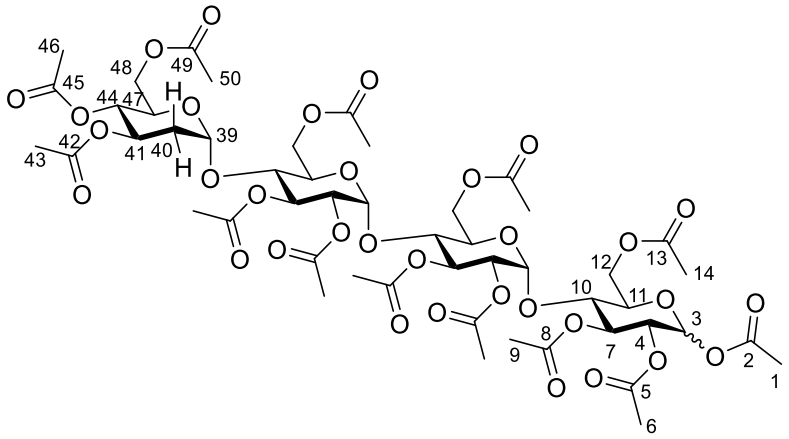
2-Deoxy-2-fluoro-α-D-mannopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α,β-D-glucopyranose (4)



To a solution of 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**16**) (59 mg, 0.049 mmol, 1.0 eq) in methanol (3 mL) NaOMe (1 mg, 0.01 mmol, 0.2 eq) was added and the reaction mixture was allowed to stir at RT for1 h. After this time, the mixture was neutralized with Amberlyst H^+, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:methanol:water, 8:2:1) to obtain 2-deoxy-2-fluoro-α-D-mannopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α,β-D-glucopyranose (**4**) (28 mg, 86%) as a colourless foam (α:β = 1:1.5).

R_f 0.15 (ethyl acetate:methanol:water, 6:2:1); IR υ_{max} (neat)/cm^{-1} = 3314 (m), 2931 (w), 1643 (w), 1563 (w), 1408 (w), 1362 (w), 1249 (w), 1143 (m), 1014 (s), 928 (m), 878 (m), 813 (m), 767 (m); selected resonances **^{1}H-NMR** (600 MHz, D_2O, 299 K, ppm): δ = 5.51 (2H, dd, *J* = 7.7, 2.0 Hz, H19$^{\alpha+\beta}$), 5.25 (1H, d, *J* = 3.8 Hz, H1$^{\alpha}$), 4.90 (2H, dt, *J* = 49.4, 2.3 Hz, H20$^{\alpha+\beta}$), 4.67 (1H, d, *J* = 8.0 Hz, H1$^{\beta}$), 3.99 (1H, t, *J* = 9.4 Hz, H3$^{\alpha}$), 3.96-3.87 (2H, m, H21$^{\alpha+\beta}$), 3.79 (1H, t, *J* = 9.4 Hz, H3$^{\beta}$), 3.78-3.75 (2H, m, H23$^{\alpha+\beta}$), 3.78-3.75 (2H, m, H22$^{\alpha+\beta}$), 3.70 (2H, t, *J* = 9.1 Hz, H16$^{\alpha+\beta}$), 3.68 (1H, t, *J* = 9.3 Hz, H4$^{\beta}$), 3.59 (1H, dd, *J* = 9.9, 3.8 Hz, H2$^{\alpha}$), 3.29 (1H, dd, *J* = 9.5, 8.0 Hz, H2$^{\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, D_2O, 299 K, ppm): δ = 98.5 (d, *J* = 30.2 Hz, C19$^{\alpha+\beta}$), 95.7 (C1$^{\beta}$), 91.8 (C1$^{\alpha}$), 89.6 (d, *J* = 173.4 Hz, C20$^{\alpha+\beta}$), 76.8 (C4$^{\beta}$), 76.4 (C16$^{\alpha+\beta}$), 76.1 (C3$^{\beta}$), 74.0 (C2$^{\beta}$), 73.6 (C23$^{\alpha+\beta}$), 73.2 (C3$^{\alpha}$), 71.2 (C2$^{\alpha}$), 69.5 (d, *J* = 17.4 Hz, C21$^{\alpha+\beta}$), 66.4 (C22$^{\alpha+\beta}$); **^{19}F-NMR** (564 MHz, D_2O, 299 K, ppm): δ = -203.34 (dddd, *J* = 49.4, 31.5, 7.6, 1.2 Hz, F$^{\alpha+\beta}$); HR-ESI-MS: *m*/*z*: 691.2088 ([*M*+Na]$^+$, calcd. for $C_{24}H_{41}O_{20}FNa^+$: 691.2067).

2-Deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (17)

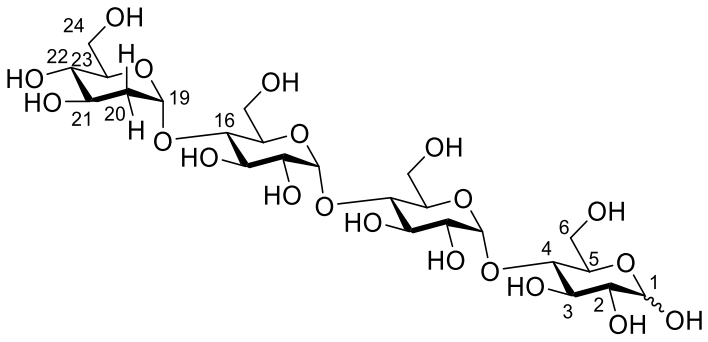


To 2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**10**) (112 mg, 0.121 mmol, 1.0 eq) dissolved in anhydrous CH_2Cl_2 (4 mL) 3,4,6-tri-*O*-acetyl-1,2-dideoxy-1-(*p*-tolylthio)-α,β-D-glucopyranose (**14**) (53 mg, 0.134 mmol, 1.1 eq) and 3 Å molecular sieves were added and the mixture was stirred for 15 min under an argon atmosphere. After this time, NIS (33 mg, 0.145 mmol, 1.2 eq) and TMSOTf (4 mg, 3 µL, 0.018 mmol, 0.15 eq) and the reaction mixture sonicated for 15 minutes. Subsequently, the reaction was quenched by addition of Na_2SO_4 (s) and $NaHCO_3$ (s). The resulting suspension was allowed to stir for several minutes until it turned yellow, filtered, concentrated under reduced pressure and purified by silica gel column chromatographie (CH_2Cl_2:acetone, 9:1) to obtain 2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**17**) (16 mg, 11%) as a colourless foam (α:β = 1.2:1).

R_f 0.15 (CH_2Cl_2:acetone, 9:1); IR υ_{max} (neat)/cm^{-1} = 3505 (w), 2962 (w), 1738 (s), 1433 (w), 1368 (m), 1210 (s), 1159 (m), 1025 (s), 939 (m), 897 (m), 768 (w); selected resonances: **^{1}H-NMR** (500 MHz, $CDCl_3$, 299 K, ppm): δ = 6.23 (1H, d, *J* = 3.7 Hz, H3$^{\alpha}$), 5.74 (1H, d, *J* = 8.0 Hz, H3$^{\beta}$), 5.50 (1H, dd, *J* = 10.1, 8.9 Hz, H7$^{\alpha}$), 5.29 (1H, t, *J* = 8.9 Hz, H7$^{\beta}$), 5.17 (2H, ddd, *J* = 11.5, 9.3, 5.2 Hz, H41$^{\alpha+\beta}$), 5.13-5.11 (2H, m, H39$^{\alpha+\beta}$), 4.96 (2H, t, *J* = 8.9 Hz, H44$^{\alpha+\beta}$), 4.95 (1H, t, *J* = 8.6 Hz, H4$^{\beta}$), 4.94 (1H, dd, *J* = 10.1, 3.7 Hz, H4$^{\alpha}$), 4.48-4.43 (2H, m, H12$^{\alpha+\beta}$), 4.35-4.28 (2H, m, H12'$^{\alpha+\beta}$),

4.28 (2H, dd, *J* = 12.5, 3.9 Hz, H48$^{\alpha+\beta}$), 4.14-4.10 (1H, m, H11$^{\alpha}$), 4.03-3.98 (2H, m, H48'$^{\alpha+\beta}$), 4.01 (1H, t, *J* = 9.4 Hz, H10$^{\alpha}$), 4.00 (1H, t, *J* = 9.2 Hz, H10$^{\beta}$), 3.97-3.93 (2H, m, H47$^{\alpha+\beta}$), 3.89-3.84 (1H, m, H11$^{\beta}$), 2.22 (3H, s, H1$^{\alpha}$), 2.10 (2H, dd, *J* = 13.2, 2.1 Hz, eq-H40$^{\alpha+\beta}$), 2.09 (3H, s, H1$^{\beta}$), 1.79 (2H, td, *J* = 12.6, 4.0 Hz, ax-H40$^{\alpha+\beta}$); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$, 299 K, ppm): δ = 168.9 (C2$^{\alpha}$), 168.7 (C2$^{\beta}$), 99.0 (C39$^{\alpha+\beta}$), 91.4 (C3$^{\alpha}$), 89.0 (C3$^{\beta}$), 75.3 (C7$^{\beta}$), 73.7 (C10$^{\beta}$), 73.6 (C10$^{\alpha}$), 73.1 (C11$^{\beta}$), 72.3 (C7$^{\alpha}$), 71.1 (C4$^{\beta}$), 70.3 (C11$^{\alpha}$), 69.9 (C4$^{\alpha}$), 69.4 (C47$^{\alpha+\beta}$), 69.0 (C44$^{\alpha+\beta}$), 68.5 (C41$^{\alpha+\beta}$), 62.8, 62.7 (C12$^{\alpha+\beta}$), 62.1 (C48$^{\alpha+\beta}$), 35.2 (C40$^{\alpha+\beta}$), 21.0 (C1$^{\alpha}$), 20.8 (C1$^{\beta}$); HR-ESI-MS: *m*/*z*: 1219.3570 ([*M*+Na]$^{+}$, calcd. for $C_{50}H_{68}O_{33}Na^{+}$: 1219.3535).

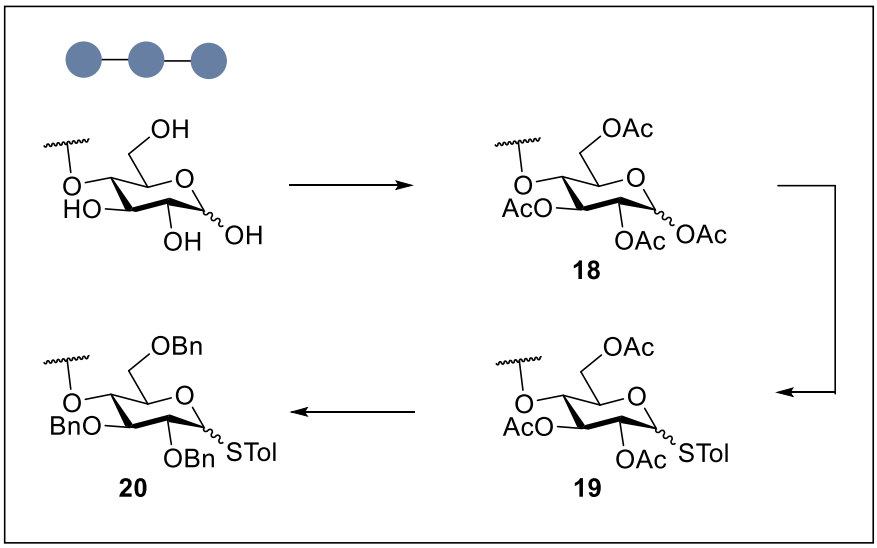
2-Deoxy-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α,β-D-glucopyranose (2)



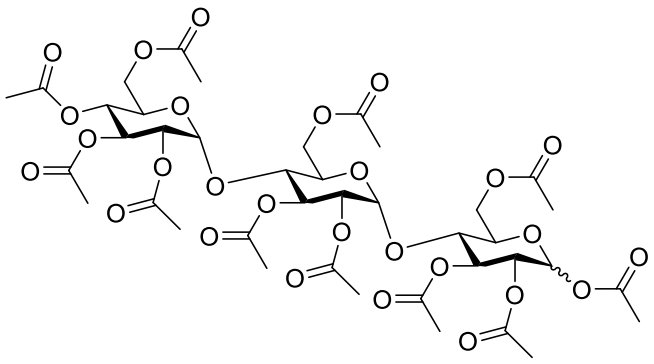
To a solution of 2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**17**) (28 mg, 0.023 mmol, 1.0 eq) in methanol (2 mL) NaOMe (1 mg, 0.01 mmol, 0.4 eq) was added and the reaction mixture was allowed to stir at RT for 16 h. After this time, the mixture was neutralized with Amberlyst H^{+}, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:methanol:water, 7:2:1) to obtain 2-deoxy-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α,β-D-glucopyranose (**2**) (14 mg, 94%) as a colourless foam (α:β = 1:1).

R_f 0.14 (ethyl acetate:methanol:water, 8:2:1); IR υ_{max} (neat)/cm^{-1} = 3306 (m), 2927 (w), 1645 (w), 1410 (w), 1362 (w), 1073 (s), 1015 (s), 547 (m), 764 (m); selected resonances: **^{1}H-NMR** (500 MHz, D_2O, 299 K, ppm): 5.51 (2H, d, *J* = 3.8 Hz, H19$^{\alpha+\beta}$), 5.10 (1H, d, *J* = 3.8 Hz, H1$^{\alpha}$), 4.49

(1H, d, *J* = 7.8 Hz, H1$^{\beta}$), 3.92 (1H, t, *J* = 9.3 Hz, H3$^{\alpha}$), 3.88-3.84 (2H, m, H24$^{\alpha+\beta}$), 3.81-3.74 (2H, m, H21$^{\alpha+\beta}$), 3.68-3.63 (2H, m, H24'$^{\alpha+\beta}$), 3.63-3.59 (2H, m, H23$^{\alpha+\beta}$), 3.57 (2H, t, *J* = 9.3 Hz, H16$^{\alpha+\beta}$), 3.21-3.18 (2H, m, H22$^{\alpha+\beta}$), 2.19 (2H, dd, *J* = 12.9, 5.1 Hz, eq-H20$^{\alpha+\beta}$), 1.60 (2H, ddd, *J* = 12.9, 11.7, 3.9 Hz, ax-H20$^{\alpha+\beta}$); **^{13}C{^{1}H}-NMR** (126 MHz, D_2O, 299 K, ppm): δ = 99.6 (C19$^{\alpha+\beta}$), 98.2 (C1$^{\beta}$), 93.9 (C1$^{\alpha}$), 76.1 (C16$^{\alpha+\beta}$), 75.0 (C23$^{\alpha+\beta}$), 74.7 (C3$^{\alpha}$), 73.4 (C22$^{\alpha+\beta}$), 69.8 (C21$^{\alpha+\beta}$), 63.0 (C24$^{\alpha+\beta}$), 39.0 (C20$^{\alpha+\beta}$); HR-ESI-MS: *m*/*z*: 673.2150 ([*M*+Na]$^{+}$, calcd. for $C_{24}H_{42}O_{20}Na^{+}$: 673.2162).



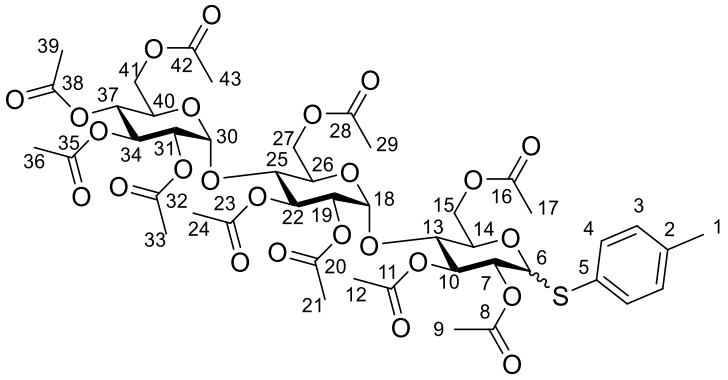
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (18)



To a solution of D-maltotriose (5.00 g, 9.92 mmol, 1.0 eq) in pyridine (40 mL) acetic anhydride (23.3 mL, 25.3 g, 247 mmol, 25.0 eq) and DMAP (365 mg, 2.97 mmol, 0.3 eq) were added and

the reaction mixture was allowed to stir for 4 h at RT. After full conversion of the start material determined by TLC, the mixture was diluted with CH_2Cl_2, poured into a beaker with sat. aq. $NaHCO_3$ and stirred for 30 min. After this time, the organic layer was washed three times with sat. aq. $NaHCO_3$ and water, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 3:2) to obtain 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**18**) (8.41 g, 88%) as a colorless solid which was used without any further purification (α:β = 1:1.1): HR-ESI-MS: *m*/*z*: 989.2752 ([*M*+Na]$^+$, calcd. for $C_{40}H_{54}O_{27}Na^+$: 989.2745).

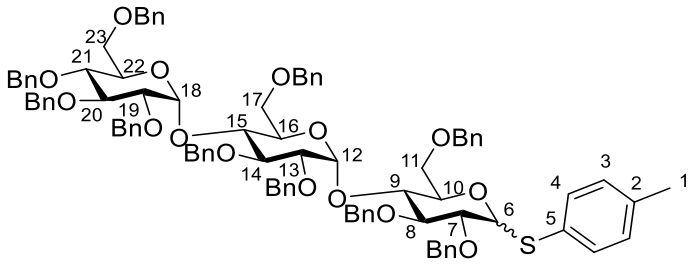
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-1-(*p*-tolylthio)-α,β-D-glucopyranose (19)



To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-1-α,β-D-glucopyranose (**18**) (497 mg, 0.51 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (10 mL) *p*-toluenethiol (70 mg, 0.56 mmol, 1.1 eq) and $BF_3{\cdot}OEt_2$ (175 mg, 156 µL, 1.23 mmol, 2.4 eq) were added and the reaction mixture was allowed to stir 23 h at RT under an argon atmosphere. After this time, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with sat. aq. $NaHCO_3$ (2x25 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:2) to obtain 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-1-(*p*-tolylthio)-α,β-D-glucopyranose (**19**) (414 mg, 78%) as a white solid (β only).

R_f 0.13 (ethyl acetate:cyclohexane, 3:4); IR υ_{max} (neat)/cm^{-1} = 2956 (w), 1740 (s), 1494 (w), 1432 (w), 1367 (m), 1210 (s), 1138 (m), 1026 (s), 944 (m), 898 (m), 809 (m), 766 (w); **^{1}H-NMR** (400 MHz, $CDCl_3$, 299 K, ppm): δ = 7.38-7.34 (2H, m, H4), 7.14-7.09 (2H, m, H3), 5.39 (1H, d, *J* = 4.1 Hz, H30), 5.39-5.35 (1H, m, H22), 5.37-5.31 (1H, m, H34), 5.29-5.24 (1H, m, H10), 5.23 (1H, d, *J* = 4.4 Hz, H18), 5.06 (1H, t, *J* = 9.9 Hz, H37), 4.84 (1H, dd, *J* = 10.5, 4.0 Hz, H31), 4.73 (1H, t, *J* = 9.9 Hz, H7), 4.73-4.69 (1H, m, H19), 4.64 (1H, d, *J* = 10.0 Hz, H6), 4.54 (1H, dd, *J* = 12.2, 2.8 Hz, H15), 4.45 (1H, dd, *J* = 12.7, 1.7 Hz, H27), 4.27 (1H, dd, *J* = 11.9, 4.2 Hz, H15'), 4.24 (1H, dd, *J* = 12.3, 3.7 Hz, H41), 4.16 (1H, dd, *J* = 12.2, 2.9 Hz, H27'), 4.04 (1H, dd, *J* = 12.4, 2.3 Hz, H41'), 3.96-3.92 (1H, m, H26), 3.95-3.91 (1H, m, H25), 3.93-3.90 (1H, m, H40), 3.88 (1H, t, *J* = 9.3 Hz, H13), 3.71 (1H, ddd, *J* = 9.7, 4.4, 2.7 Hz, H14), 2.34 (3H, s, H1), 2.15 (3H, s, H17), 2.14 (3H, s, H29), 2.09 (3H, s, H43), 2.05 (3H, s, H9), 2.04 (3H, s, H33), 2.02 (3H, s, H39), 2.00 (3H, s, H21), 1.99 (3H, s, H24), 1.99 (3H, s, H36), 1.95 (3H, s, H12); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$, 299 K, ppm): δ = 170.8 (C20), 170.7 (C32), 170.7 (C42), 170.5 (C16), 170.5 (C28), 170.2 (C11), 170.0 (C35), 169.8 (C23), 169.7 (C8), 169.6 (C38), 139.0 (C2), 134.4 (C4), 129.8 (C3), 127.1 (C5), 95.9 (C18), 95.8 (C30), 85.1 (C6), 76.6 (C10), 76.2 (C14), 73.6 (C13), 72.3 (C25), 71.8 (C22), 70.8 (C7), 70.6 (C19), 70.2 (C31), 69.5 (C34), 69.1 (C26), 68.6 (C40), 68.0 (C37), 63.0 (C15), 62.4 (C27), 61.5 (C41), 21.3 (C1), 20.9 (CH_3), 20.9 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 20.6 (CH_3), 20.6 (CH_3), 20.6 (CH_3); HR-ESI-MS: *m*/*z*: 1053.2909 ([*M*+Na]$^+$, calcd. for $C_{45}H_{58}O_{25}SNa^+$: 1053.2880).

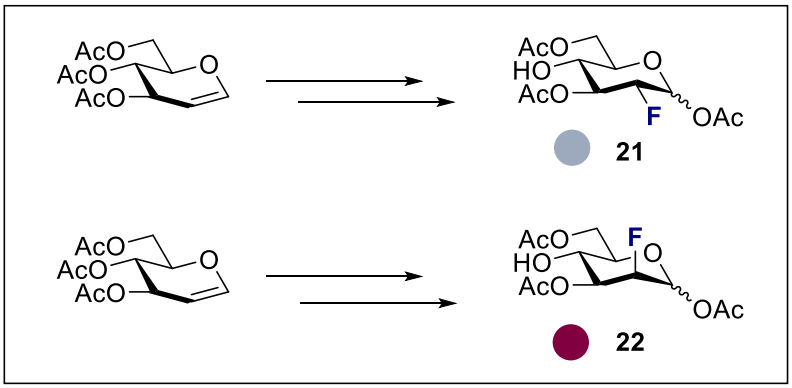
2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-1-(*p*-tolylthio)-α,β-D-glucopyranose (20)



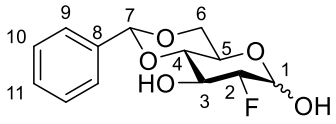
To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-1-(*p*-tolylthio)-α,β-D-glucopyranose (**19**) (2.669 g, 2.59 mmol, 1.0 eq) in methanol (35 mL) NaOMe (279 mg, 5.18 mmol, 2.0 eq) was added and the reaction mixture was allowed to stir at RT for 2 h. After this time, the mixture was

neutralized with Amberlyst® H^+, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:methanol:water, 8:2:1 → 7:2:1) to obtain α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-1-(*p*-tolylthio)-α,β-D-glucopyranose (1.453 g, 91%) which was used without any further purification. The crude product was dissolved in DMF (50 mL) and cooled to 0 °C. NaH (856 mg, 35.7 mmol, 15.0 eq) was slowly added and the suspension was stirred for 30 minutes at 0 °C. After this time, TBAI (87 mg, 0.24 mmol, 0.1 eq) and BnBr (6.109 g, 4.24 mL, 35.7 mmol, 15.0 eq) were added dropwise, the reaction mixture slowly allowed to warm to RT and stirred for 20 h. The reaction was quenched by the addition of MeOH (50 mL) and stirred for 15 min. The solvents were evaporated under reduced pressure, the residue dissolved in water and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:10) to obtain 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-1-(*p*-tolylthio)-α,β-D-glucopyranose (**20**) (2.751 g, 77%) as a colourless oil (α:β = 5:95).

R_f 0.41 (ethyl acetate:cyclohexane, 1:7); IR υ_{max} (neat)/cm^{-1} = 3063 (w), 3030 (w), 2865 (w), 1604 (w), 1495 (m), 1453 (m), 1396 (w), 1360 (m), 1270 (w), 1207 (w), 1138 (m), 1088 (s), 1038 (s), 1026 (s), 908 (m), 844 (w), 810 (m), 731 (s), 694 (s); **^{1}H-NMR** (600 MHz, $CDCl_3$, 299 K, ppm): δ = 7.53-7.50 (2H, m, H4), 7.05 (2H, d, *J* = 8.0 Hz, H3), 5.64 (1H, d, *J* = 3.6 Hz, H18), 5.53 (1H, d, *J* = 3.6 Hz, H12), 4.65 (1H, d, *J* = 9.8 Hz, H6), 4.07 (1H, t, *J* = 9.1 Hz, H9), 4.06 (1H, t, *J* = 9.0 Hz, H15), 4.04-4.00 (1H, m, H14), 3.94 (1H, t, *J* = 9.4 Hz, H20), 3.94-3.90 (1H, m, H16), 3.91 (1H, dd, *J* = 11.1, 4.2 Hz, H11), 3.84 (1H, dd, *J* = 11.1, 2.0 Hz, H'11), 3.81 (1H, t, *J* = 8.7 Hz, H8), 3.76 (1H, dt, *J* = 10.3, 2.5 Hz, H22), 3.74 (1H, dd, *J* = 10.9, 2.8 Hz, H17), 3.68 (1H, t, *J* = 9.5 Hz, H21), 3.59-3.55 (1H, m, H10), 3.56 (1H, t, *J* = 9.1 Hz, H7), 3.56 (1H, dd, *J* = 10.8, 2.9 Hz, H23), 3.55-3.53 (1H, m, H'17), 3.53 (1H, dd, *J* = 9.2, 3.6 Hz, H13), 3.50 (1H, dd, *J* = 9.8, 3.6 Hz, H19), 3.42 (1H, dd, *J* = 10.8, 2.0 Hz, H'23), 2.33 (3H, s, H1); **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$, 299 K, ppm): δ = 137.7 (C2), 132.8 (C4), 129.7 (C3), 129.7 (C5), 96.9 (C18), 96.8 (C12), 87.5 (C6), 86.6 (C8), 82.0 (C20), 81.5 (C14), 80.8 (C7), 79.6 (C19), 79.4 (C13), 78.9 (C10), 77.7 (C21), 73.7 (C9), 73.1 (C15), 71.0 (C22), 70.9 (C16), 69.1 (C11), 69.0 (C17), 68.2 (C23), 21.1 (C1); LR-ESI-MS: *m*/*z*: 1533.68 ([*M*+Na]$^+$, calcd. for $C_{95}H_{98}O_{15}SNa^+$: 1533.65).



4,6-*O*-Benzylidene-2-deoxy-2-fluoro-α,β-D-glucopyranose

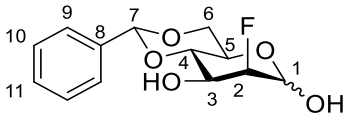


To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranose (1030 g, 2.94 mmol, 1.0 eq) in methanol (20 mL) NaOMe (79 mg, 1.47 mmol, 0.5 eq) was added and the reaction mixture was allowed to stir at RT for 3 h. After this time, the mixture was neutralized with Amberlyst® H^+, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:methanol, 10:1) to obtain 2-deoxy-2-fluoro-D-glucopyranose as a colorless solid which was used without any further purification. Subsequently, 2-deoxy-2-fluoro-D-glucopyranose was dissolved in dry MeCN (25 ml), *p*TsOH · H_2O (55 mg, 0.290 mmol, 0.1 eq), benzaldehyde dimethylacetal (1118 mg, 7.35 mmol, 2.5 eq) and MS4Å were added and the reaction mixture was allowed to stir for 3 h at 50 °C. After this time, the reaction was quenched by addition of NEt_3. The solvent was removed under reduced pressure, the residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:9 → 1:2 → 1:1.5) to obtain 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-glucopyranose (582 mg, 73% over two steps) as a colorless solid (α:β = 1:1).

R_f 0.17 (ethyl acetate:cyclohexane, 1:2); **^{1}H-NMR** (600 MHz, CD_2Cl_2, 299 K, ppm): δ = 7.51-7.45 (4H, m, H9$^{\alpha+\beta}$), 7.41-7.36 (6H, m, H10$^{\alpha+\beta}$, H11$^{\alpha+\beta}$), 5.53 (1H, s, H7$^{\alpha}$), 5.53 (1H, s, H7$^{\beta}$), 5.43 (1H, t, *J* = 3.4 Hz, , H1$^{\alpha}$), 4.88 (1H, br s, H1$^{\beta}$), 4.43 (1H, ddd, *J* = 48.9, 9.0, 3.9 Hz, H2$^{\alpha}$), 4.33 (1H, dd, *J* = 10.5, 4.9 Hz, H6$^{\beta}$), 4.30-4.23 (2H, m, H3$^{\alpha}$, H6$^{\alpha}$), 4.17 (1H, dt, *J* = 50.4, 8.2 Hz, H2$^{\beta}$), 4.07 (1H,

td, *J* = 9.9, 4.9 Hz, H5$^{\alpha}$), 4.00 (1H, dt, *J* = 14.9, 8.9 Hz, H3$^{\beta}$), 3.76 (1H, t, *J* = 10.2 Hz, H6'$^{\beta}$), 3.71 (1H, t, *J* = 10.3 Hz, H6'$^{\alpha}$), 3.57-3.45 (3H, m, H4$^{\alpha}$, H4$^{\beta}$, H5$^{\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, CD_2Cl_2, 299 K, ppm): δ = 136.8 (C8$^{\alpha}$), 136.6 (C8$^{\beta}$), 129.9 (C11$^{\beta}$), 129.8 (C11$^{\alpha}$), 128.8 (C10$^{\beta}$), 128.8 (C10$^{\alpha}$), 126.9 (C9$^{\alpha}$), 126.8 (C9$^{\beta}$), 102.5, 102.4 (C7$^{\alpha+\beta}$), 95.6 (d, *J* = 24.4 Hz, C1$^{\beta}$), 94.6 (d, *J* = 186.0 Hz, C2$^{\beta}$), 91.7 (d, *J* = 21.3 Hz, C1$^{\alpha}$), 91.4 (d, *J* = 189.6 Hz, C2$^{\alpha}$), 81.1 (d, *J* = 8.2 Hz, C4$^{\alpha}$), 80.5 (d, *J* = 9.0 Hz, C4$^{\beta}$), 72.8 (d, *J* = 19.5 Hz, C3$^{\beta}$), 69.6 (d, *J* = 19.1 Hz, C3$^{\alpha}$), 69.4 (C6$^{\alpha}$), 69.0 (C6$^{\beta}$), 66.9 (C5$^{\beta}$), 62.7 (C5$^{\alpha}$); **^{19}F-NMR** (564 MHz, CD_2Cl_2, 299 K, ppm): δ = -200.45 (dddd, *J* = 50.3, 14.8, 3.9, 1.1 Hz, F$^{\beta}$), -201.11 (dd, *J* = 48.9, 12.8 Hz, F$^{\alpha}$); HR-ESI-MS: *m*/*z*: 293.0806 ([*M*+Na]$^{+}$, calcd. for $C_{13}H_{15}O_5FNa^{+}$: 293.0796).

4,6-*O*-Benzylidene-2-deoxy-2-fluoro-α,β-D-mannopyranose

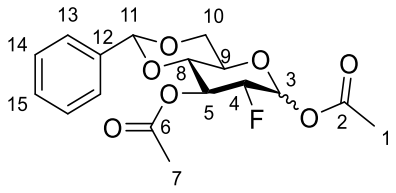


To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-mannopyranose (3.387 g, 9.67 mmol, 1.0 eq) in methanol (50 mL) NaOMe (260 mg, 4.81 mmol, 0.5 eq) was added and the reaction mixture was allowed to stir at RT for 3 h. After this time, the mixture was neutralized with Amberlyst® H^{+}, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:methanol, 10:1) to obtain 2-deoxy-2-fluoro-D-glucopyranose (940 mg, 99%) as a colorless solid (α:β = 6.8:1) which was used without any further purification. Subsequently 2-deoxy-2-fluoro-D-mannopyranose was dissolved in dry MeCN (60 ml), *p*TsOH · H_2O (182 mg, 0.96 mmol, 0.1 eq), benzaldehyde dimethylacetal (3.648 g, 23.96 mmol, 8.0 eq) and MS4Å were added and the reaction mixture was allowed to stir for 3 h at 50 °C. After this time, the reaction was quenched by addition of NEt_3. The solvent was removed under reduced pressure, the residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:9 → 1:2 → 1:1.5) to obtain 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-mannopyranose (1.833 g, 71% over two steps) as a colorless solid (α:β = 5:1).

R_f 0.30 (ethyl acetate:cyclohexane, 1:1); **^{1}H-NMR** (600 MHz, CD_2Cl_2, 299 K, ppm): δ = 7.50-7.46 (4H, m, H9$^{\alpha+\beta}$), 7.40-7.37 (6H, m, H10$^{\alpha+\beta}$, H11$^{\alpha+\beta}$), 5.58 (1H, s, H7$^{\alpha}$), 5.57 (1H, s, H7$^{\beta}$), 5.37 (1H,

ddd, *J* = 7.9, 4.0, 1.8 Hz, H1$^{\alpha}$), 4.85 (1H, ddd, *J* = 19.1, 11.1, 1.0 Hz, H1$^{\beta}$), 4.79 (1H, dd, *J* = 50.0, 1.0 Hz, H2$^{\beta}$), 4.77 (1H, ddd, *J* = 49.0, 2.8, 1.8 Hz, H2$^{\alpha}$), 4.33 (1H, dd, *J* = 10.5, 5.0 Hz, H6$^{\beta}$), 4.24 (1H, dd, *J* = 10.3, 5.0 Hz, H6$^{\alpha}$), 4.14 (1H, dddd, 28.0, 10.0, 5.8, 2.7 Hz, H3$^{\alpha}$), 4.04 (1H, dddt, *J* = 10.3, 9.5, 5.0, 0.8 Hz, H5$^{\alpha}$), 3.95-3.91 (1H, m, H3$^{\beta}$), 3.87 (1H, td, *J* = 9.8, 1.6 Hz, H4$^{\alpha}$), 3.81 (1H, t, *J* = 10.2 Hz, H6'$^{\beta}$), 3.79 (1H, t, *J* = 10.3 Hz, H6'$^{\alpha}$), 3.78 (1H, td, *J* = 9.7, 2.0 Hz, H4$^{\beta}$), 3.61 (1H, dd, *J* = 11.3, 2.5 Hz, C1$^{\beta}$-OH), 3.42 (1H, dddd, *J* = 10.1, 9.2, 5.1, 0.8 Hz, H5$^{\beta}$), 3.11 (1H, dd, *J* = 4.1, 3.0 Hz, C1$^{\alpha}$-OH), 2.62 (1H, d, *J* = 5.8 Hz, C3$^{\beta}$-OH), 2.47 (1H, d, *J* = 6.0 Hz, C3$^{\alpha}$-OH); **^{13}C{^{1}H}-NMR** (151 MHz, CD_2Cl_2, 299 K, ppm): δ = 138.0 (C8$^{\alpha}$), 137.8 (C8$^{\beta}$), 129.8 (C11$^{\beta}$), 129.7 (C11$^{\alpha}$), 128.8 (C10$^{\beta}$), 128.8 (C10$^{\alpha}$), 126.8 (C9$^{\alpha}$), 126.8 (C9$^{\beta}$), 102.7 (C7$^{\alpha}$), 102.6 (C7$^{\alpha}$), 94.1 (d, *J* = 17.4 Hz, C1$^{\beta}$), 93.6 (d, *J* = 31.5 Hz, C1$^{\alpha}$), 91.8 (d, *J* = 182.5 Hz, C2$^{\beta}$), 90.7 (d, *J* = 175.6 Hz, C2$^{\alpha}$), 79.4 (d, *J* = 1.7 Hz, C4$^{\alpha}$), 78.6 (d, *J* = 1.8 Hz, C4$^{\beta}$), 70.8 (d, *J* = 17.3 Hz, C3$^{\beta}$), 69.2 (C6$^{\alpha}$), 68.9 (C6$^{\beta}$), 68.2 (d, *J* = 17.1 Hz, C3$^{\alpha}$), 67.3 (C5$^{\beta}$), 64.2 (C5$^{\beta}$); **^{19}F-NMR** (564 MHz, CD_2Cl_2, 299 K, ppm): δ = 206.25 (dddt, *J* = 49.0, 28.1, 8.0, 1.6 Hz, F$^{\alpha}$), -224.54 (dddt, *J* = 49.3, 27.8, 18.9, 2.1 Hz, F$^{\beta}$); HR-ESI-MS: *m*/*z*: 293.0790 ([*M*+Na]$^{+}$, calcd. for $C_{13}H_{15}O_5FNa^{+}$: 293.0796).

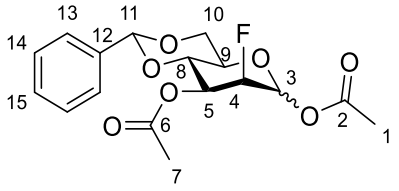
1,3-Di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-glucopyranose



To a solution of 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-glucopyranose (531 mg, 1.97 mmol, 1.0 eq) in pyridine (10 mL) acetic anhydride (1.50 mL, 15.73 mmol, 8.0 eq) and DMAP (25 mg, 0.20 mmol, 0.1 eq) were added and the reaction mixture was allowed to stir for 4 h at RT. After full conversion of the start material (determined by TLC), the mixture was diluted with CH_2Cl_2 (30 mL), poured into a beaker with sat. aq. $NaHCO_3$ (40 mL) and stirred for 30 min. After this time, the organic layer was washed with sat. aq. $NaHCO_3$ (3 x 30 mL) and water (30 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:6) to obtain 1,3-di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-glucopyranose (433 mg, 62%) as a white foam (α:β = 1:2).

R_f 0.21 (ethyl acetate:cyclohexane, 1:6); IR υ_{max} (neat)/cm^{-1} = 2914 (w), 1758 (s), 1745 (s), 1459 (w), 1421 (w), 1371 (m), 1315 (w), 1213 (s), 1183 (m), 1133 (m), 1097 (m), 1085 (m), 1065 (s) 1031 (s), 1013 (s), 981 (s), 963 (s), 948 (s), 922 (m), 877 (w), 770 (s), 726 (w), 699 (s); **^{1}H-NMR** (600 MHz, $CDCl_3$, 299 K, ppm): δ = 7.45-7.42 (4H, m, H13$^{\alpha+\beta}$), 7.40-7.34 (6H, m, H14 $^{\alpha+\beta}$, H15 $^{\alpha+\beta}$), 6.40 (1H, d, *J* = 4.0 Hz, H3$^{\alpha}$), 5.86 (1H, dd, *J* = 7.9, 4.2 Hz, H3$^{\beta}$), 5.68 (1H, dt, *J* = 11.4, 9.6 Hz, H5$^{\alpha}$), 5.54-5.48 (1H, m, H5$^{\beta}$), 5.50 (1H, s, H11$^{\alpha}$), 5.48 (1H, s, H11$^{\beta}$), 4.63 (1H, ddd, *J* = 48.1, 9.4, 4.1 Hz, H4$^{\alpha}$), 4.45 (1H, ddd, *J* = 50.2, 8.9, 7.9 Hz, H4$^{\beta}$), 4.39 (1H, dd, *J* = 10.3, 4.5 Hz, H10$^{\beta}$), 4.32 (1H, dd, *J* = 10.5, 4.9 Hz, H10$^{\alpha}$), 4.00 (1H, td, *J* = 9.8, 4.9 Hz, H9$^{\alpha}$), 3.76-3.70 (2H, m, H10'$^{\alpha+\beta}$), 3.70-3.66 (1H, m, H9$^{\beta}$), 3.67-3.63 (1H, m, H8$^{\beta}$), 3.65-3.60 (1H, m, H8$^{\alpha}$), 2.21 (3H, s, H1$^{\alpha}$), 2.18 (3H, s, H1$^{\beta}$), 2.14 (6H, s, H7$^{\alpha+\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$, 299 K, ppm): δ = 169.9 (C6$^{\alpha}$), 169.7 (C6$^{\beta}$), 169.2 (C2$^{\alpha}$), 168.9 (C2$^{\beta}$), 136.7 (C12$^{\alpha}$), 136.6 (C12$^{\beta}$), 129.4 (C15$^{\beta}$), 129.4 (C15$^{\alpha}$), 128.4 (C14$^{\alpha+\beta}$), 126.3 (C13$^{\beta}$), 126.3 (C13$^{\alpha}$), 136.7 (C11$^{\alpha}$), 136.6 (C11$^{\beta}$), 92.0 (d, *J* = 25.2 Hz, C3$^{\beta}$), 89.5 (d, *J* = 191.6 Hz, C4$^{\beta}$), 89.1 (d, *J* = 22.0 Hz, C3$^{\alpha}$), 87.2 (d, *J* = 195.7 Hz, C4$^{\alpha}$), 78.2 (d, *J* = 8.0 Hz, C8$^{\alpha}$), 77.9 (d, *J* = 8.2 Hz, C8$^{\beta}$), 71.6 (d, *J* = 19.9 Hz, C5$^{\beta}$), 69.6 (d, *J* = 19.8 Hz, C5$^{\alpha}$), 68.6 (C10$^{\alpha}$), 68.4 (C10$^{\beta}$), 67.2 (C9$^{\beta}$), 64.8 (C9$^{\alpha}$), 21.0 (C1$^{\alpha}$), 21.0 (C7$^{\alpha}$), 20.9 (C7$^{\beta}$), 20.9 (C1$^{\beta}$); **^{19}F-NMR** (564 MHz, $CDCl_3$, 299 K, ppm): δ = -201.12 (ddd, *J* = 50.7, 13.6, 0.5 Hz, F$^{\beta}$), -201.93 (ddd, *J* = 48.1, 11.5, 1.2 Hz, F$^{\alpha}$); HR-ESI-MS: *m*/*z*: 377.1002 ([*M*+Na]$^+$, calcd. for $C_{17}H_{19}O_7FNa^+$: 377.1007).

1,3-Di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-mannopyranose

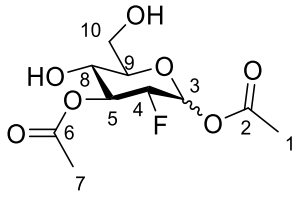


To a solution of 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-mannopyranose (650 mg, 2.40 mmol, 1.0 eq) in pyridine (10 mL) acetic anhydride (1.80 mL, 19.25 mmol, 8.0 eq) and DMAP (30 mg, 0.24 mmol, 0.1 eq) were added and the reaction mixture was allowed to stir for 2 h at RT. After full conversion of the start material (determined by TLC), the mixture was diluted with CH_2Cl_2 (30 mL), poured into a beaker with sat. aq. $NaHCO_3$ (40 mL) and stirred for 30 min. After this time, the organic layer was washed with sat. aq. $NaHCO_3$ (3 x 30 mL) and

water (30 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 1:4) to obtain 1,3-di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-mannopyranose (807 mg, 95 %) as a white foam (α:β = 5.2:1).

R_f 0.30 (ethyl acetate:cyclohexane, 1:4); IR υ_{max} (neat)/cm^{-1} = 2918 (w), 1758 (s), 1742 (s), 1459 (w), 1417 (w), 1371 (m), 1319 (w), 1217 (s), 1134 (m), 1086 (m), 1068 (s), 1053 (s), 1033 (s), 1014 (s), 978 (s), 967 (s), 948 (m), 922 (m), 896 (m), 879 (m), 769 (s), 726 (s), 700 (s); **^{1}H-NMR** (600 MHz, $CDCl_3$, 299 K, ppm): δ = 7.48-7.44 (2H, m, H13), 7.40-7.35 (3H, m, H14, H15), 6.25 (1H, dd, *J* = 7.4, 2.0 Hz, H3), 5.59 (1H, s, H11), 5.34 (1H, ddd, *J* = 26.5, 10.5, 2.8 Hz, H5), 4.84 (1H, ddd, *J* = 48.3, 2.7, 2.0 Hz, H4), 4.31 (1H, dd, *J* = 10.4, 4.8 Hz, H 10), 4.14 (1H, ddd, *J* = 10.7, 9.6, 1.4 Hz, H8), 4.01 (1H, ddd, *J* = 10.3, 9.5, 4.9 Hz, H9), 3.83 (1H, t, *J* = 10.3 Hz, H10'), 2.18 (3H, s, H1), 2.15 (3H, s, H7); **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$, 299 K, ppm): δ = 170.4, (C6), 168 (C2), 137.0 (C12), 129.4 (C15), 128.4 (C14), 126.3 (C13), 102.1 (C11), 90.9 (d, *J* = 33.0 Hz, C3), 86.8 (d, *J* = 180.9 Hz, C4), 75.4 (C8), 68.9 (d, *J* = 16.7 Hz, C5), 68.5 (C10), 66.1 (C9), 21.0 (C1), 21.0 (C7); **^{19}F-NMR** (564 MHz, $CDCl_3$, 299 K, ppm): δ = -203.30 (ddd, *J* = 48.2, 26.5, 7.4 Hz); only the α-anomer was characterized; HR-ESI-MS: *m*/*z*: 377.1005 ([*M*+Na]$^+$, calcd. for $C_{17}H_{19}O_7FNa^+$: 377.1007).

1,3-Di-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose

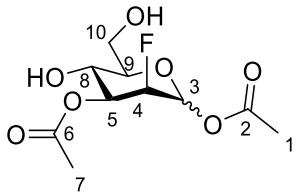


To a solution of 1,3-di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-glucopyranose (410 mg, 1.16 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) trifluoroacetic acid (2.0 mL) and water (0.2 mL) were added and the reaction mixture was allowed to stir at RT for 90 min. After full conversion of the start material determined by TLC, the mixture was quenched with triethylamine (3 mL) and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 2:1) to obtain 1,3-

di-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (299 mg, 97%) as a viscous colourless oil (α:β = 1:2).

R_f 0.19 (ethyl acetate:cyclohexane, 2:1); $[\alpha]_D^{25}$ +21.9 (c 1.0, MeOH); IR υ_{max} (neat)/cm^{-1} = 3413 (w), 2945 (w), 1743 (s), 1618 (w), 1435 (w), 1368 (m), 1215 (s), 1147 (m), 1122 (m), 1012 (s), 936 (m), 893 (m), 782 (m), 738 (s); **^{1}H-NMR** (500 MHz, MeOD-d$_4$, 299 K, ppm): δ = 6.38 (1H, d, *J* = 3.9 Hz, H3$^\alpha$), 5.83 (1H, dd, *J* = 8.1, 3.0 Hz, H3$^\beta$), 5.41 (1H, dt, *J* = 12.2, 9.5 Hz, H5$^\alpha$), 5.26 (1H, dt, *J* = 14.3, 9.2 Hz, H5$^\beta$), 4.60 (1H, ddd, *J* = 49.0, 9.7, 3.9 Hz, H4$^\alpha$), 4.34 (1H, ddd, *J* = 51.7, 9.2, 8.0 Hz, H4$^\beta$), 3.84 (1H, dd, *J* = 12.2, 2.2 Hz, H10$^\beta$), 3.82-3.79 (1H, m, H10$^\alpha$), 3.78-3.73 (1H, m, H9$^\alpha$), 3.75-3.70 (2H, m, H10'$^{\alpha+\beta}$), 3.65 (1H, t, *J* = 9.1 Hz, H8$^\alpha$), 3.63 (1H, t, *J* = 9.4 Hz, H8$^\beta$), 3.54 (1H, ddd, *J* = 9.9, 4.8, 2.2 HZ, H9$^\beta$), 2.19 (3H, s, H1$^\alpha$), 2.15 (3H, s, H7$^\beta$), 2.15 (3H, s, H7$^\alpha$), 2.14 (3H, s, H1$^\beta$); **^{13}C{^{1}H}-NMR** (126 MHz, MeOD-d$_4$, 299 K, ppm): δ = 172.2 (C6$^\alpha$), 171.9 (C6$^\beta$), 170.7 (C2$^\alpha$), 170.6 (C2$^\beta$), 92.8 (d, *J* = 23.8 Hz, C3$^\beta$), 90.3 (d, *J* = 22.4 Hz, C3$^\alpha$), 90.2 (d, *J* = 189.7 Hz, C4$^\beta$), 88.3 (d, *J* = 192.3 Hz, C4$^\alpha$), 78.7 (C9$^\beta$), 76.6 (d, *J* = 17.2 Hz, C5$^\beta$), 75.9 (C9$^\alpha$), 74.4 (d, *J* = 17.3 Hz, (C5$^\alpha$), 68.9 (d, *J* = 6.7 Hz, C8$^\beta$), 68.5 (d, *J* = 7.1 Hz, C8$^\alpha$), 61.2 (C10$^\alpha$), 61.2 (C10$^\beta$), 20.9 (C7$^\alpha$), 20.8 (C7$^\beta$), 20.7 (C1$^\alpha$), 20.7 (C1$^\beta$); **^{19}F-NMR** (282 MHz, MeOD-d$_4$, 299 K, ppm): δ = -203.36 (ddd, *J* = 51.7, 14.4, 3.0 Hz, F$^\beta$), -203.65 (ddd, *J* = 48.9, 12.2, 0.7 Hz, F$^\alpha$); HR-ESI-MS: *m*/*z*: 289.0693 ([*M*+Na]$^+$, calcd. for $C_{10}H_{15}O_7FNa^+$: 289.0694).

1,3-Di-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose

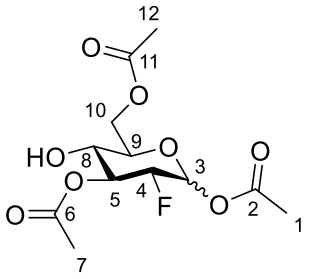


To a solution of 1,3-di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-mannopyranose (780 mg, 2.20 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) trifluoroacetic acid (3.20 mL) and water (0.32 mL) were added and the reaction mixture was allowed to stir at RT for 90 min. After full conversion of the start material (determined by TLC), the mixture was quenched with NEt_3 (5 mL) and the solvent was removed under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 2:1) to

obtain 1,3-di-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (578 mg, 99%) as a viscous colourless oil (α:β = 5:1).

R_f 0.18 (ethyl acetate:cyclohexane, 2:1); $[\alpha]_D^{25}$ +37.1 (c 1.0, MeOH); IR υ_{max} (neat)/cm^{-1} = 3399 (w), 2940 (w), 2516 (w), 1732 (s), 1678 (w), 1432 (w), 1372 (m), 1219 (s), 1148 (s), 1073 (s), 1017 (s), 967 (s), 836 (w), 801 (m), 721 (w); **^{1}H-NMR** (500 MHz, MeOD-d_4, 299 K, ppm): δ = 6.18 (1H, dd, *J* = 6.9, 2.1 Hz, H3$^\alpha$), 5.09 (1H,ddd, *J* = 29.2, 10.0, 2.6 Hz, H5$^\alpha$), 4.75 (1H, dt, *J* = 49.2, 2.4 Hz, H4$^\alpha$),3.91 (1H, t, *J* = 9.6 Hz, H8$^\alpha$), 3.84-3.80 (1H, m, H10$^\alpha$), 3.76-3.73 (1H, m, H10'$^\alpha$), 3.74-3.71 (1H, m, H9$^\alpha$), 2.14 (3H, s, H1$^\alpha$), 2.14 (3H, s, H7$^\alpha$); **^{13}C{^{1}H}-NMR** (126 MHz, MeOD-d_4, 299 K, ppm): δ = 172.2 (C6$^\alpha$), 170.2 (C6$^\alpha$), 91.8 (d, *J* = 31.2 Hz, C3$^\alpha$), 87.8 (d, *J* = 177.9 Hz, C4$^\alpha$), 77.0 (C9$^\alpha$), 73.5 (d, *J* = 16.9 Hz, C5$^\alpha$), 65.2 (d, *J* = 1.6 Hz, C8$^\alpha$), 62.0 (C10$^\alpha$), 20.7 (C7$^\alpha$), 20.7 (C1$^\alpha$); **^{19}F-NMR** (282 MHz, MeOD-d_4, 299 K, ppm): δ = -205.63 (dddt, *J* = 49.2, 29.2, 6.8, 0.9 Hz, F$^\alpha$), -221.24 (dddd, *J* = 52.0, 28.2, 19.7, 1.0 Hz, F$^\beta$); only the α-anomer was characterized; HR-ESI-MS: *m*/*z*: 289.0689 ([*M*+Na]$^+$, calcd. for $C_{10}H_{15}O_7FNa^+$: 289.0694).

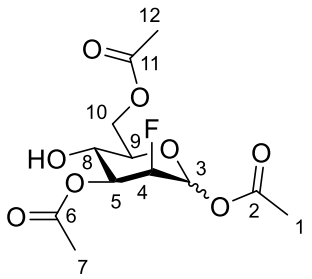
1,3,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (21)



To a solution of HOBt (216 mg, 1.60 mmol, 1.1 eq) in CH_2Cl_2 (14 mL) NEt_3 (220 mg, 302 µL, 2.19 mmol, 1.5 eq) and acetyl chloride (126 mg, 115 µL, 1.60 mmol, 1.1 eq) were added and the resulting mixture was allowed to stir for 30 min at RT. After this time, 1,3-di-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (388 mg, 1.46 mmol, 1.0 eq) was added and the reaction mixture was stirred for 23 h at RT. The solvent was removed under reduced pressure and the residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:cyclohexane, 3:4 → 1:1) to obtain 1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (**21**) (234 mg, 52%) as a colourless viscous oil (α:β = 1:1).

R_f 0.54 (ethyl acetate:cyclohexane, 2:1); $[\alpha]_D^{25}$ +10.4 (c 1.0, MeOH); IR υ_{max} (neat)/cm^{-1} = 3462 (w), 2953 (w), 1738 (s), 1433 (w), 1368 (m), 1211 (s), 1143 (m), 1072 (s), 1030 (s), 1011 (s), 937 (m), 915 (m); **^{1}H-NMR** (400 MHz, MeOD-d$_4$, 299 K, ppm): δ = 6.33 (1H, d, *J* = 6.3 Hz, H3$^\alpha$), 5.81 (1H, dd, *J* = 8.1, 5.8 Hz, H3$^\beta$), 5.39 (1H, dt, *J* = 12.2, 9.5 Hz, H5$^\alpha$), 5.26 (1H, dt, *J* = 14.3, 9.2 Hz, H5$^\beta$), 4.62 (1H, ddd, *J* = 48.8, 9.8, 4.0 Hz, H4$^\alpha$), 4.37 (1H, dd, *J* = 12.1, 2.2 Hz, H10$^\beta$), 4.34 (1H, ddd, *J* = 51.5, 9.3, 8.1 Hz, H4$^\beta$), 4.32 (1H, dd, *J* = 12.2, 2.3 Hz, H10$^\alpha$), 4.23 (1H, dd, *J* = 12.2, 5.0 Hz, H10'$^\alpha$), 4.21 (1H, dd, *J* = 12.1, 5.4 Hz, H10'$^\beta$), 3.94 (1H, ddd, *J* = 10.1, 5.2, 2.4 Hz, H9$^\alpha$), 3.75 (1H, ddd, *J* = 10.0, 5.4, 2.1 Hz, H9$^\alpha$), 3.61 (1H, t, *J* = 9.8 Hz, H8$^\alpha$), 3.57 (1H, t, *J* = 9.7 Hz, H8$^\beta$), 2.18 (3H, s, H1$^\alpha$), 2.13 (3H, s, H1$^\beta$), 2.13 (6H, s, H7$^\alpha$, H7$^\beta$), 2.05 (3H, s, H12$^\alpha$), 2.05 (3H, s, H12$^\beta$); **^{13}C{^{1}H}-NMR** (101 MHz, MeOD-d$_4$, 299 K, ppm): δ = 172.5 (C11$^\alpha$), 172.5 (C11$^\beta$), 172.0 (C6$^\alpha$), 171.8 (C6$^\beta$), 170.6 (C2$^\alpha$), 170.5 (C2$^\beta$), 92.7 (d, *J* = 21.1 Hz, C3$^\beta$), 90.2 (d, *J* = 22.4 Hz, C3$^\alpha$), 90.1 (d, *J* = 189.9 Hz, C4$^\alpha$), 88.1 (d, *J* = 192.4 Hz, C4$^\beta$), 76.3 (d, *J* = 17.4 Hz, C5$^\alpha$), 75.9 (d, *J* = 1.1 Hz, C9$^\beta$), 74.2 (d, *J* = 17.5 Hz, C5$^\beta$), 73.2 (d, *J* = 0.8 Hz, C9$^\alpha$), 69.2 (d, *J* = 7.2 Hz, C8$^\beta$), 68.8 (d, *J* = 7.2 Hz, C8$^\alpha$), 63.9 (C10$^\alpha$), 63.9 (C10$^\beta$), 20.8 (CH$_3$), 20.8 (CH$_3$),20.6 (CH$_3$), 20.6 (CH$_3$), 20.6(CH$_3$); **^{19}F-NMR** (376 MHz, MeOD-d$_4$, 299 K, ppm): δ = -202.39 (ddd, *J* = 51.5, 14.3, 3.1 Hz, F$^\beta$), -203.74 (ddd, *J* = 48.7, 12.2, 0.8 Hz, F$^\alpha$); HR-ESI-MS: *m*/*z*: 331.0806 ([*M*+Na]$^+$, calcd. for $C_{12}H_{17}O_8FNa^+$: 331.0800).

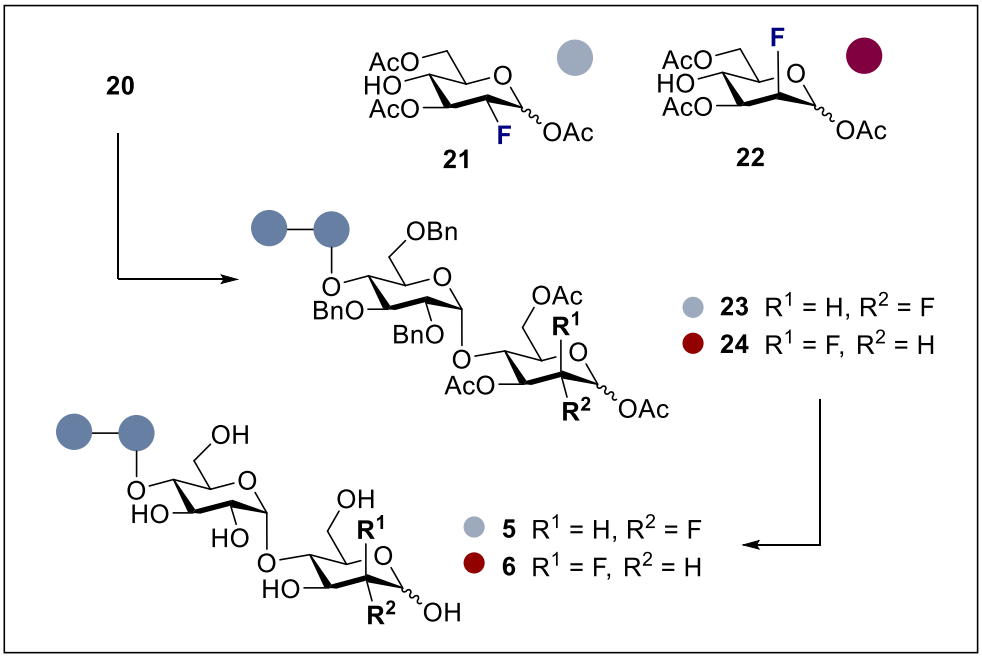
1,3,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (22)



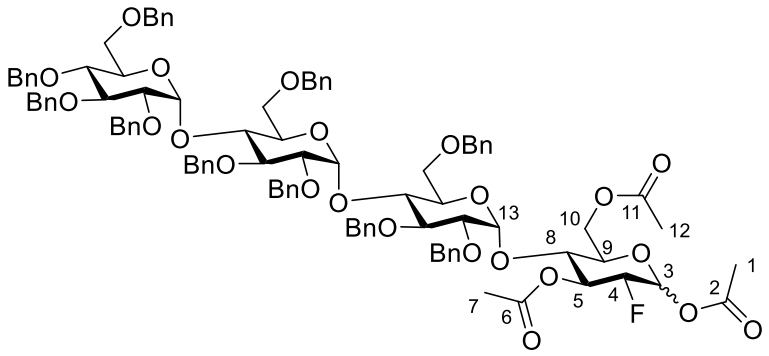
To a solution of HOBt (248 mg, 1.84 mmol, 1.2 eq) in CH_2Cl_2 (10 mL) NEt_3 (233 mg, 320 µL, 2.31 mmol, 1.5 eq) and acetyl chloride (144 mg, 131 µL, 1.84 mmol, 1.2 eq) were added and the resulting mixture was allowed to stir for 30 min at RT. After this time, 1,3-di-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (410 mg, 1.54 mmol, 1.0 eq) was added and the reaction mixture was stirred for 27 h at RT. The solvent was removed under reduced pressure and the residue was loaded onto silica and purified by silica gel column chromatography (ethyl

acetate:cyclohexane, 3:4 → 3:2) to obtain 1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (**22**) (175 mg, 37%) as a colourless viscous oil (α:β = 5:1).

R_f 0.51 (ethyl acetate:cyclohexane, 2:1); IR υ_{max} (neat)/cm^{-1} = 3464 (w), 2957 (w), 1734 (s), 1433 (w), 1371 (m), 1216 (s), 1148 (s), 1072 (s), 1017 (s), 968 (s), 922 (m), 811 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$, 299 K, ppm): δ = 6.24 (1H, dd, *J* = 6.7, 2.1 Hz, $H3^{\alpha}$), 5.13 (1H, dd, *J* = 28.3, 9.9, 2.6 Hz, $H5^{\alpha}$), 4.74 (1H, dt, *J* = 48.9, 2.3 Hz, $H4^{\alpha}$), 4.61-4.56 (1H, m, $H10^{\alpha}$), 4.26-4.22 (1H, m, $H10'^{\alpha}$), 3.92-3.89 (2H, m, $H8^{\alpha}$, $H9^{\alpha}$), 2.18 (3H, s, $H7^{\alpha}$), 2.15 (3H, s, $H1^{\alpha}$), 2.14 (3H, s, $H12^{\alpha}$); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$, 299 K, ppm): δ = 172.2 ($C11^{\alpha}$), 171.0 ($C6^{\alpha}$), 168.4 ($C2^{\alpha}$), 90.6 (d, *J* = 31.3 Hz, $C3^{\alpha}$), 86.3 (d, *J* = 180.5 Hz, $C4^{\alpha}$), 73.4 ($C9^{\alpha}$), 71.7 (d, *J* = 16.9 Hz, $C5^{\alpha}$), 64.8 (d, *J* = 1.6 Hz, $C8^{\alpha}$), 62.7 ($C10^{\alpha}$), 21.0 ($C7^{\alpha}$), 21.0 ($C1^{\alpha}$), 21.0 ($C12^{\alpha}$); **^{19}F-NMR** (282 MHz, MeOD-d_4, 299 K, ppm): δ = -205.80 (dddt, *J* = 49.3, 29.0, 6.8, 0.9 Hz, F^{α}), -221.25 (ddd, *J* = 51.9, 28.1, 19.6 Hz, F^{β}); only the α-anomer was characterized; HR-ESI-MS: *m/z*: 331.0806 ([*M*+Na]$^{+}$, calcd. for $C_{12}H_{17}O_8FNa^{+}$: 331.0800).



2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (23)

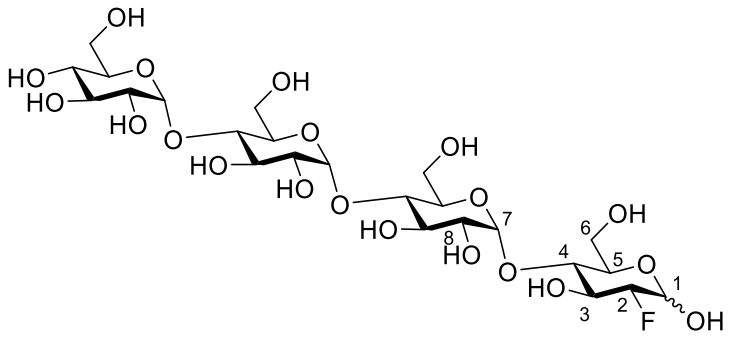


To 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-1-(*p*-tolylthio)-α,β-D-glucopyranose (**20**) (245 mg, 0.14 mmol, 1.0 eq) dissolved in anhydrous CH_2Cl_2 (4 mL) 1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glycopyranose (**21**) (42 mg, 0.16 mmol, 1.2 eq) and 3 Å molecular sieves were added and the mixture was stirred for 15 min under an argon atmosphere. After this time, NIS (37 mg, 0.16 mmol, 1.2 eq) and $BF_3{\cdot}OEt_2$ (19 mg, 18 µL, 0.14 mmol, 1.0 eq) were added and the reaction mixture was sonicated for 15 minutes. Subsequently, the reaction was quenched by addition of Na_2SO_4 (s) and $NaHCO_3$ (s). The resulting suspension was allowed to stir for several minutes until it turned clear, filtered, concentrated under reduced pressure and purified by silica gel column chromatographie twice, firstly with ethyl acetate:cyclohexane (1:7) and secondly with $CHCl_3$:acetone (80:1) to obtain 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (**23**) (47 mg, 21%) as a colourless foam (α:β = 1.5:1).

R_f 0.38 ($CHCl_3$:acetone, 60:1); IR υ_{max} (neat)/cm^{-1} = 3063 (w), 3031 (w), 2924 (w), 2867 (w), 1749 (m), 1496 (w), 1454 (w), 1363 (w), 1318 (w), 1213 (m), 1145 (m), 1075 (s), 1026 (s), 935 (m), 908 (m), 861 (w), 819 (w), 731 (s), 695 (s); selected resonances: **^{1}H-NMR** (600 MHz, $CDCl_3$, 299 K, ppm): δ = 6.38 (1H, d, *J* = 3.9 Hz, H3$^\alpha$), 5.76 (1H, dd, *J* = 8.0, 3.1 Hz, H3$^\beta$), 5.68 (1H, dt, *J* = 12.2, 9.5 Hz, H5$^\alpha$), 5.48 (1H, dt, *J* = 14.4, 8.8 Hz, H5$^\beta$), 4.72 (1H, d, *J* = 3.4 Hz, H13$^\alpha$), 4.67 (1H, d, *J* = 3.3 Hz, H13$^\beta$), 4.59 (1H, ddd, *J* = 48.9, 9.8, 3.9 Hz, H4$^\alpha$), 4.53-4.50 (1H, m, H10$^\beta$), 4.49-4.46 (1H, m H10$^\alpha$), 4.40 (1H, ddd, *J* = 51.2, 9.0, 8.2 Hz, H4$^\beta$), 4.34 (1H, dd, *J* = 12.6, 4.0 Hz,

H10'$^{\alpha}$), 4.29 (1H, dd, *J* = 12.8, 4.1 Hz, H10'$^{\beta}$), 4.00-3.96 (1H, m, H9$^{\alpha}$), 3.75 (1H, t, *J* = 9.6 Hz, H8$^{\alpha}$), 3.74-3.71 (1H, m H9$^{\beta}$), 3.73-3.70 (1H, m, H8$^{\beta}$), 2.23 (3H, s, H1$^{\alpha}$), 2.17 (3H, s, H1$^{\beta}$) 2.00 (3H, s, H7$^{\alpha}$), 1.99 (3H, s, H7$^{\beta}$), 1.96 (3H, s, H12$^{\alpha}$), 1.96 (3H, s, H12$^{\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$, 299 K, ppm): δ = 170.0 (C11$^{\beta}$), 170.0 (C11$^{\alpha}$), 169.8 (C6$^{\alpha}$), 169.6 (C6$^{\beta}$), 168.9 (C2$^{\alpha}$), 168.8 (C2$^{\beta}$), 99.6 (C13$^{\beta}$), 99.5 (C13$^{\alpha}$), 91.3 (C3$^{\beta}$), 88.4 (d, *J* = 192.0 Hz, C4$^{\beta}$), 88.3 (C3$^{\alpha}$), 86.5 (d, 194.6 Hz, C4$^{\alpha}$), 77.0 (C8$^{\beta}$), 76.6 (C8$^{\alpha}$), 73.0 (C5$^{\beta}$), 70.9 (C5$^{\alpha}$), 62.5 (C10$^{\beta}$), 62.4 (C10$^{\alpha}$), 21.1 (C7$^{\alpha}$), 21.0 (C7$^{\beta}$), 21.0 (C1$^{\alpha}$), 20.9 (C1$^{\beta}$), 20.8 (C12$^{\beta}$), 20.8 (C12$^{\alpha}$); **^{19}F-NMR** (564 MHz, $CDCl_3$, 299 K, ppm): δ = -200.44 (ddd, *J* = 51.2, 14.4, 3.1 Hz, F$^{\beta}$), -201.99 (dd, *J* 48.9, 12.2 Hz, F$^{\alpha}$); LR-ESI-MS: *m*/*z*: 1717.71 ([*M*+Na]$^{+}$, calcd. for $C_{100}H_{107}O_{23}FNa^{+}$: 1717.71).

α-D-Glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-2-deoxy-2-fluoro-α,β-D-glucopyranose (5)

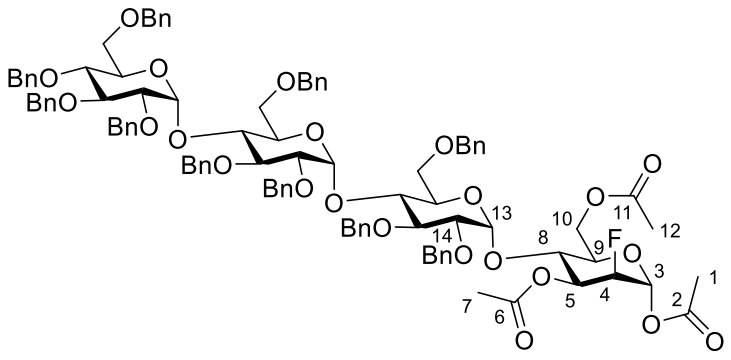


A flask with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (**23**) (112 mg, 0.07 mmol, 1.0 eq) and Pd/C (10% w/w) (70 mg, 0.07 mmol, 1.0 eq) was flushed with argon, then methanol (3 mL) and ethyl acetate (3 mL) were added. The argon atmosphere was replaced by hydrogen and the reaction mixture was allowed to stir at RT for 24 h. After this time, the reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure. The resulting crude product was dissolved in methanol (5 mL) and NaOMe (2 mg, 0.02 mmol, 0.3 eq) was added. The reaction mixture was stirred at RT for 2 h. After this time, the mixture was neutralized with Amberlyst® H^{+}, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:methanol:water, 8:2:1) to obtain α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-

(1→4)-2-deoxy-2-fluoro-α,β-D-glucopyranose (**5**) (39 mg, 88%) as a colourless foam (α:β = 1:1.2).

R_f 0.09 (EtOAc:methanol:water, 8:2:1); IR υ_{max} (neat)/cm^{-1} = 3274 (m), 2930 (w), 1643 (w), 1367 (w), 1204 (w), 1148 (m), 1074 (s), 1013 (s), 927 (m), 846 (m), 760 (m); selected resonances: **^{1}H-NMR** (600 MHz, D_2O, 299 K, ppm): δ = 5.46 (1H, d, *J* = 3.9 Hz, H1$^\alpha$), 5.45 (1H, d, *J* = 3.9 Hz, H7$^\beta$), 5.44 (1H, d, *J* = 3.9 Hz, H7$^\alpha$), 4.93 (1H, dd, *J* = 7.8, 2.3 Hz, H1$^\beta$), 4.46 (1H, ddd, *J* = 49.3, 9.6, 3.9 Hz, H2$^\alpha$), 4.26 (1H, dd, *J* = 13.6, 9.3 Hz, H3$^\alpha$), 4.21-4.07 (2H, m, H2$^\beta$, H3$^\beta$), 4.01-3.99 (1H, m, H5$^\alpha$), 3.93 (1H, dd, *J* = 12.3, 2.1 Hz, H6$^\beta$), 3.79 (1H, dd, *J* = 12.3, 5.2 Hz, H6'$^\beta$), 3.75 (1H, t, *J* = 9.2 Hz, H4$^\beta$), 3.75 (1H, t, *J* = 9.5 Hz, H4$^\alpha$), 3.68-3.64 (1H, m, H5$^\beta$), 3.64 (2H, dd, *J* = 10.1, 4.0 Hz, H8$^{\alpha+\beta}$); **^{13}C{^{1}H}-NMR** (151 MHz, D_2O, 299 K, ppm): δ = 99.4 (C7$^\alpha$), 99.2 (C7$^\beta$), 93.4 (d, *J* = 23.3 Hz, C1$^\beta$), 92.6 (d, *J* = 183.7 Hz, C2$^\beta$), 89.9 (d, *J* = 186.1 Hz, C2$^\alpha$), 89.4 (d, *J* = 21.4 Hz, C1$^\alpha$), 76.1 (d, *J* = 7.9 Hz, C4$^\alpha$), 75.9 (d, *J* = 7.7 Hz, C4$^\beta$), 74.5 (d, *J* = 0.7 Hz, C5$^\beta$), 74.4 (d, *J* = 17.8 Hz, C3$^\beta$), 71.5 (d, *J* = 18.2 Hz, C3$^\alpha$), 71.4, 71.3 (C7$^{\alpha+\beta}$), 69.7 (d, *J* = 0.9 Hz, (C5$^\alpha$), 60.4 (C6$^\beta$); **^{19}F-NMR** (564 MHz, D_2O, 299 K, ppm): δ = -199.95- -200.07 (m, F$^\beta$), -200.24 (dd, *J* = 49.3, 13.6 Hz, F$^\alpha$); LR-ESI-MS: *m*/*z*: 691.25 ([*M*+Na]$^+$, calcd. for $C_{24}H_{41}O_{20}FNa^+$: 691.21).

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (24)

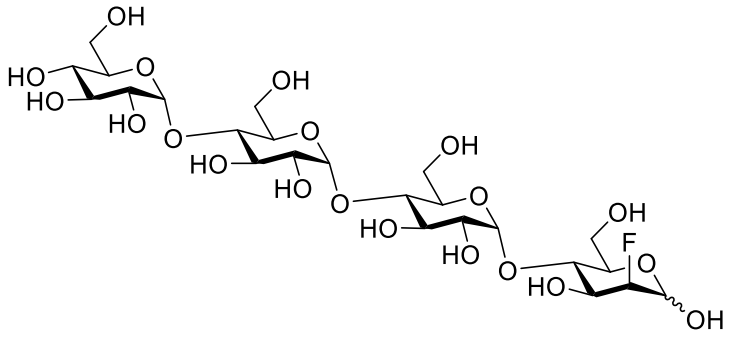


To 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-1-(*p*-tolylthio)-α,β-D-glucopyranose (**20**) (400 mg, 0.26 mmol, 1.1 eq) dissolved in anhydrous CH_2Cl_2 (5 mL) 1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (**22**) (74 mg, 0.24 mmol, 1.1 eq) and 3 Å molecular sieves were added and the

mixture was stirred for 15 min under an argon atmosphere. After this time, NIS (64 mg, 0.29 mmol, 1.2 eq) and $BF_3{\cdot}OEt_2$ (34 mg, 30 µL, 0.24 mmol, 1.0 eq) were added and the reaction mixture sonicated for 15 minutes. Subsequently, the reaction was quenched by addition of Na_2SO_4 (s) and $NaHCO_3$ (s). The resulting suspension was allowed to stir for several minutes until it turned yellow, filtered, concentrated under reduced pressure and purified by silica gel column chromatographie (ethyl acetate:cyclohexane, 1:7) to obtain 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (**24**) (100 mg, 25%) as a colourless foam (α:β = 98:2).

R_f 0.48 (ethyl acetate:cyclohexane, 1:2.5); IR υ_{max} (neat)/cm^{-1} = 3062 (w), 3030 (w), 2925 (w), 2857 (w), 1745 (m), 1606 (w), 1496 (w), 1453 (m), 1363 (m), 1298 (w), 1216 (m), 1149 (m), 1091 (s), 1026 (s), 909 (m), 860 (w), 817 (w), 733 (s), 695 (s); selected resonances: **^{1}H-NMR** (500 MHz, $CDCl_3$, 299 K, ppm): δ = 6.24 (1H, dd, *J* = 7.0, 2.4 Hz, H3), 5.41 (1H, ddd, *J* = 28.0, 9.3, 2.6 Hz, H5), 4.92 (1H, d, *J* = 3.5 Hz, H13), 4.76 (1H, dt, *J* = 48.9, 2.5 Hz, H4), 4.53-4.49 (1H, m, H10), 4.31 (1H, dd, *J* = 12.5, 4.1 Hz, H10'), 4.14 (1H, t, *J* = 9.5 Hz, H8), 4.03-3.98 (1H, m, H9), 3.54 (1H, dd, *J* = 9.5, 3.5 Hz, H14), 2.19 (3H, s, H1), 2.01 (3H, s, H7), 1.95 (3H, s, H12); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$, 299 K, ppm): δ = 170.4 (C11), 170.2 (C6), 168.6 (C2), 99.0 (C13), 90.1 (d, *J* = 30.8 Hz, C3), 86.5 (d, *J* = 180.2 Hz, C4), 80.5 (C14), 73.0 (C8), 72.1 (C9), 70.8 (d, *J* = 16.7 Hz, C5), 62.9 (C10), 21.2 (C7), 21.1 (C1), 20.9 (C12); **^{19}F-NMR** (282 MHz, $CDCl_3$, 299 K, ppm): δ = -203.80 (ddd, *J* = 49.0, 28.0, 7.0 Hz, F^{α}); LR-ESI-MS: *m/z*: 1717.51 ([*M*+Na]$^+$, calcd. for $C_{100}H_{107}O_{23}FNa^+$: 1717.71).

α-D-Glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-2-deoxy-2-fluoro-α,β-D-mannopyranose (6)



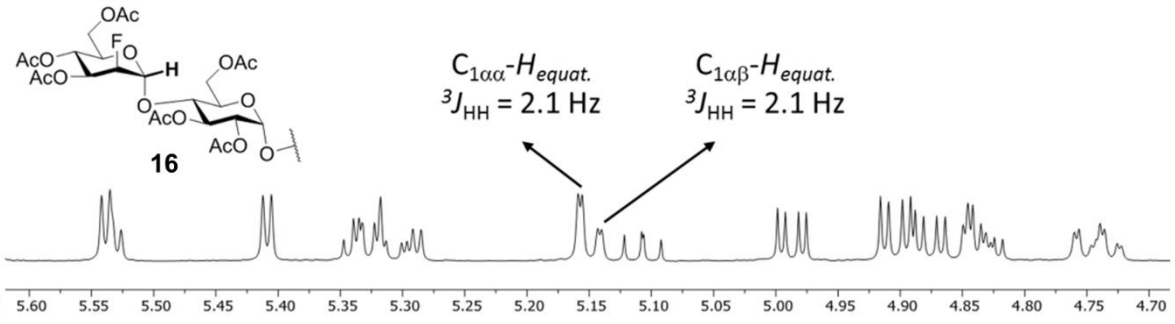
A flask with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (**24**) (99 mg, 0.06 mmol, 1.0 eq) and Pd/C (10% w/w) (60 mg, 0.06 mmol, 1.0 eq) was flushed with argon, then methanol (3 mL) and ethyl acetate (3 mL) were added. The argon atmosphere was replaced by hydrogen and the reaction mixture was allowed to stir at RT for 24 h. After this time, the reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure. The resulting crude product was dissolved in methanol (4 mL) and NaOMe (2 mg, 0.015 mmol, 0.3 eq) was added. The reaction mixture was stirred at RT for 2 h. After this time, the mixture was neutralized with Amberlyst® H^+, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by silica gel column chromatography (ethyl acetate:methanol:water, 8:2:1) to obtain α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-2-deoxy-2-fluoro-α,β-D-mannopyranose (**6**) (26 mg, 67%) as a colourless foam (α:β = 2.2:1).

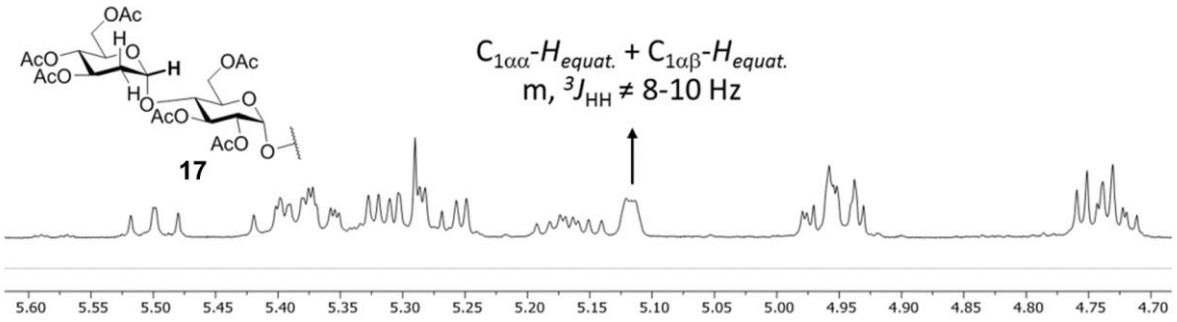
R_f 0.10 (ethyl acetate:methanol:water, 8:2:1); IR υ_{max} (neat)/cm^{-1} = 3274 (m), 2930 (w), 1643 (w), 1367 (w), 1204 (w), 1148 (m), 1074 (s), 1013 (s), 927 (m), 846 (m), 760 (m); **^{19}F-NMR** (564 MHz, D_2O, 299 K, ppm): δ = -204.64 (ddd, *J* = 49.2, 31.4, 7.5 Hz, F^{α}), -223.08 (ddd, *J* = 51.4, 31.1, 20.3 Hz, F^{β}); LR-ESI-MS: *m*/*z*: 691.28 ([*M*+Na]$^+$, calcd. for $C_{24}H_{41}O_{20}FNa^+$: 691.21).

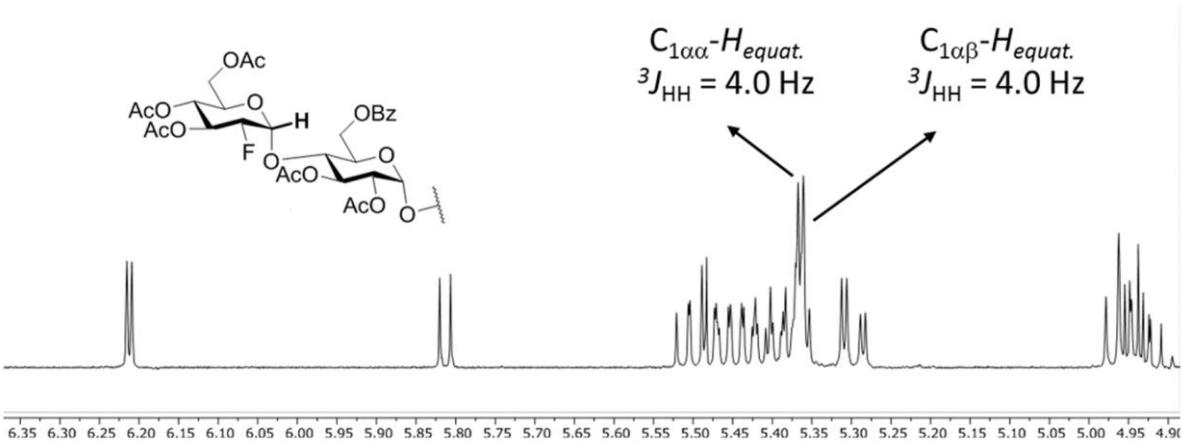
3 Determination of Configuration at the Anomeric Centre

Non-reducing end

$C_{1\alpha\alpha}$: C1α(non-reducing end)α(reducing end)

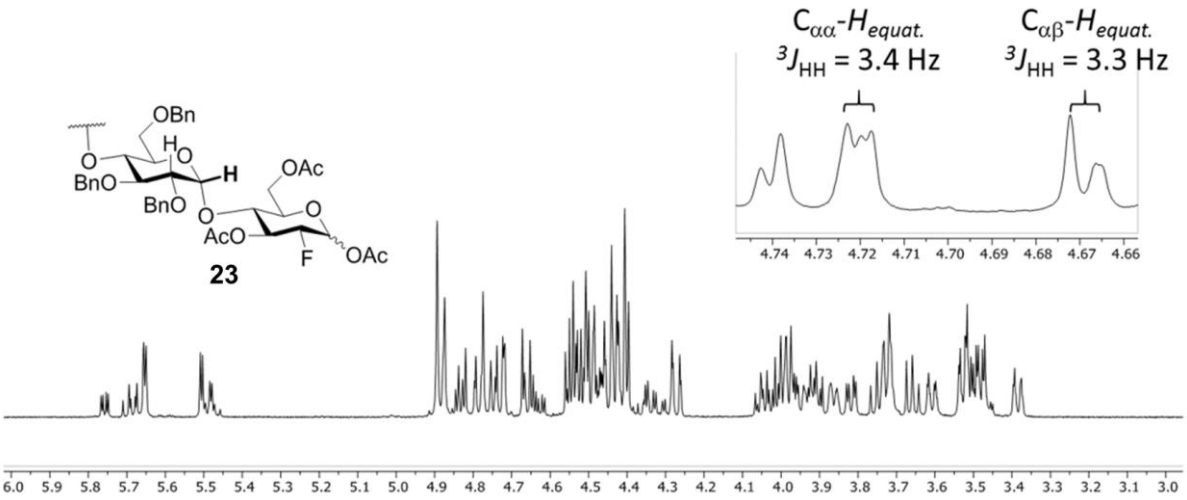


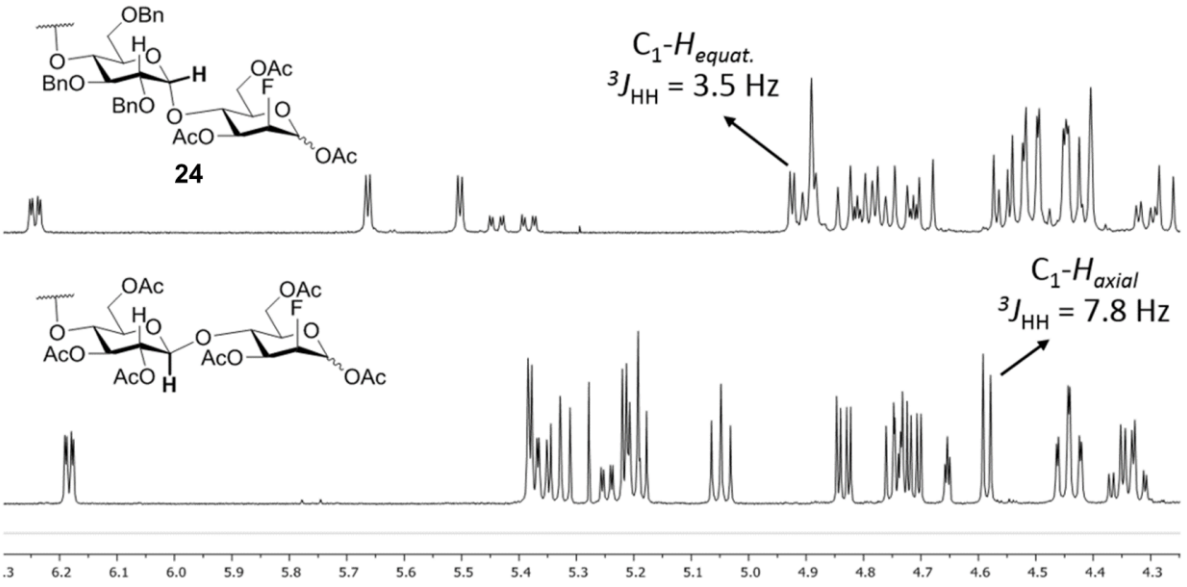




Reducing end

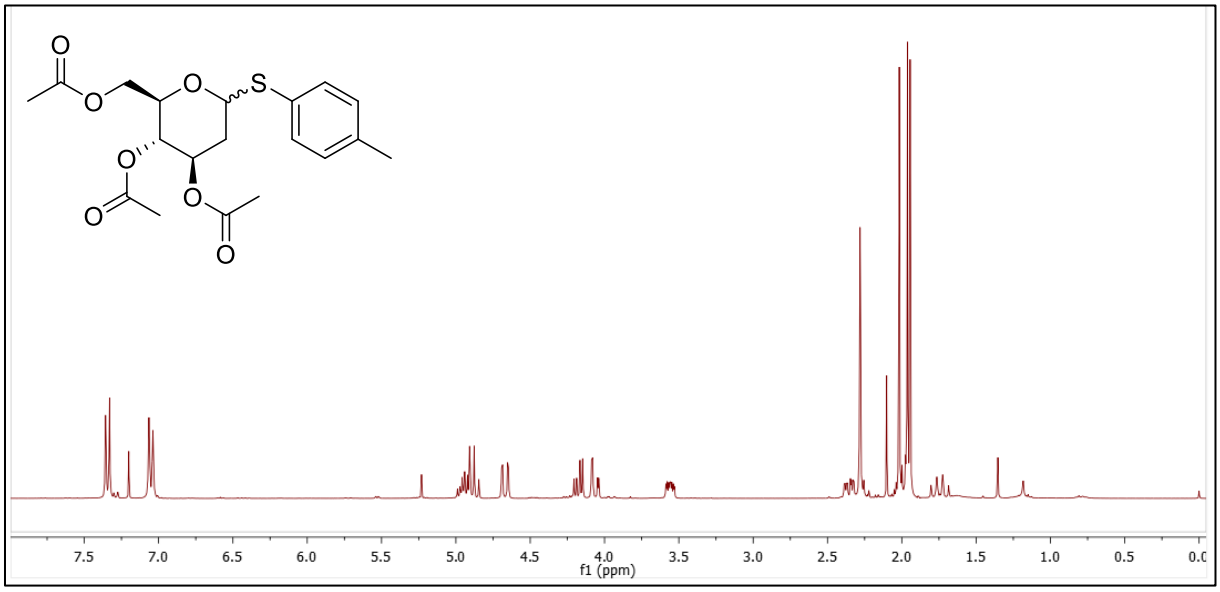
$C_{\alpha\alpha}$: Cα(non-reducing end)α(reducing end)



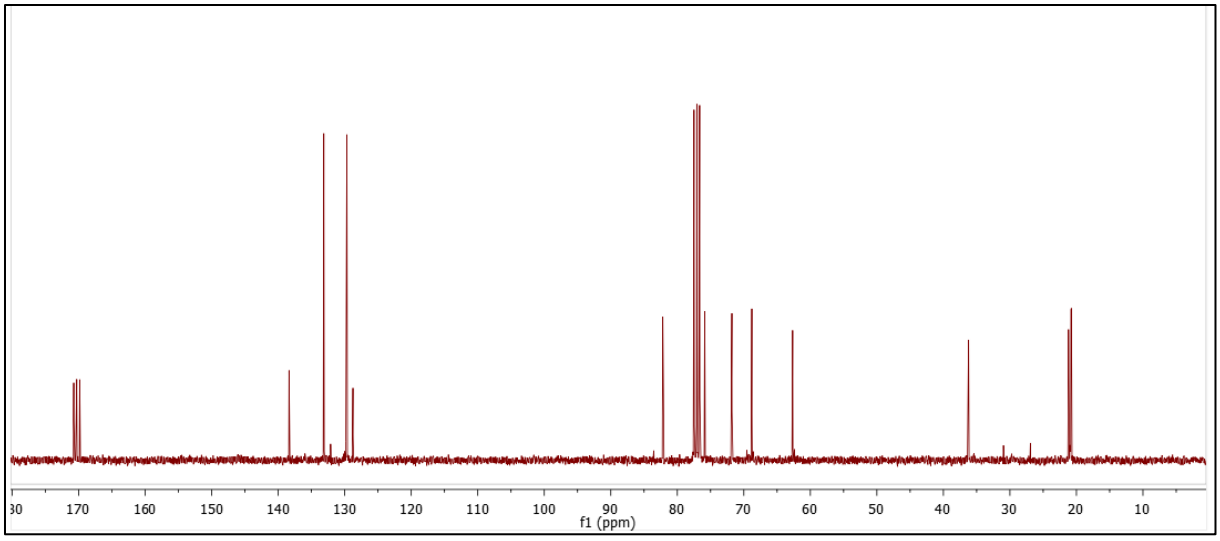


4 Selected NMR Spectra

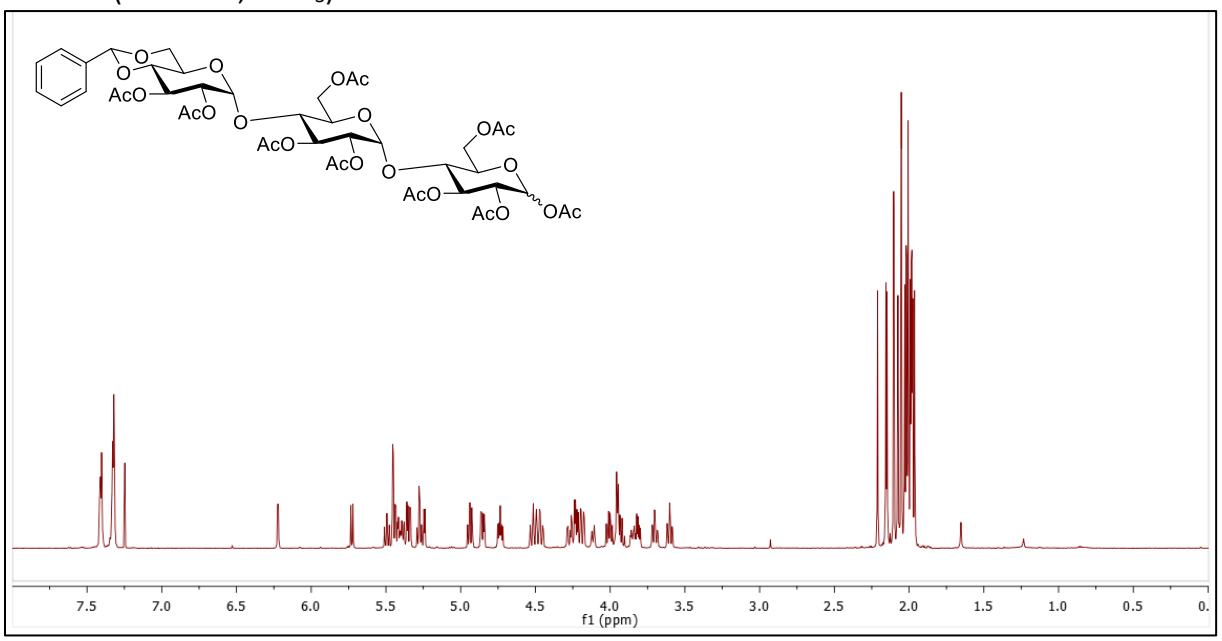
^{1}H NMR (400 MHz, $CDCl_3$)



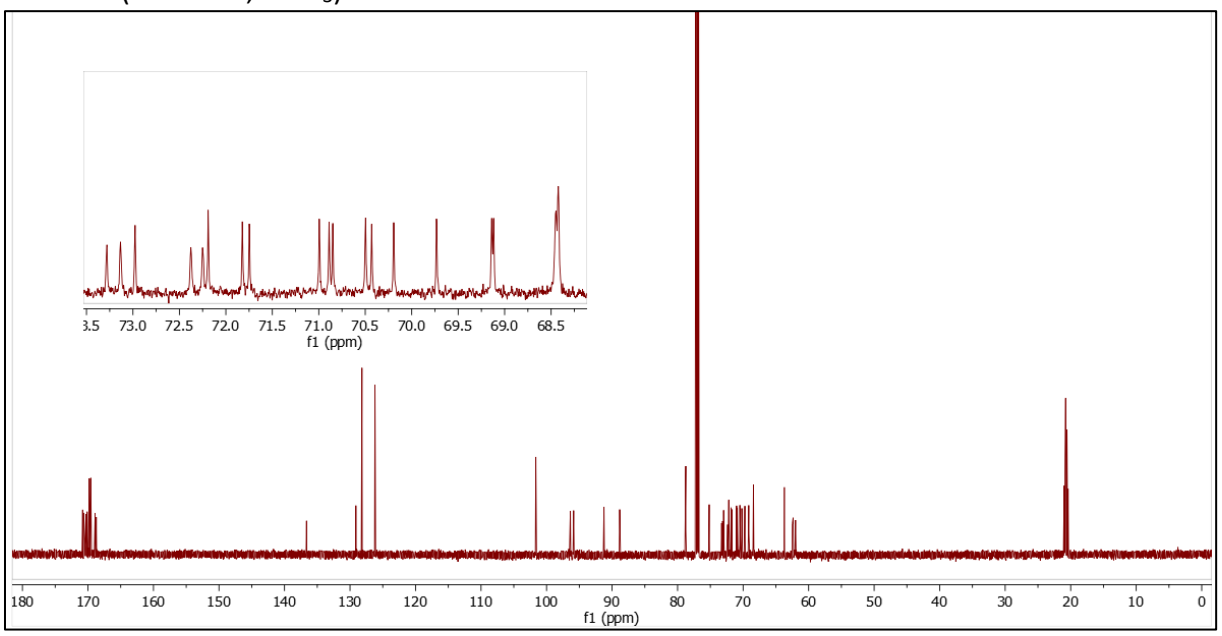
^{13}C NMR (101 MHz, $CDCl_3$)



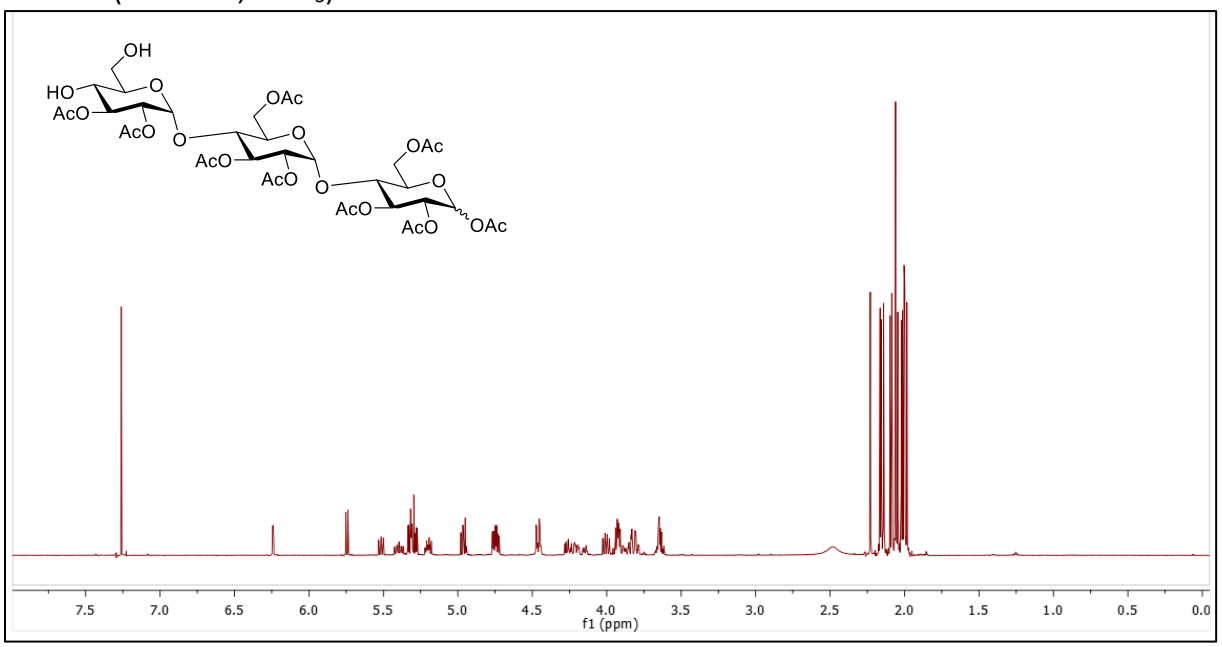
^{1}H NMR (600 MHz, $CDCl_3$)



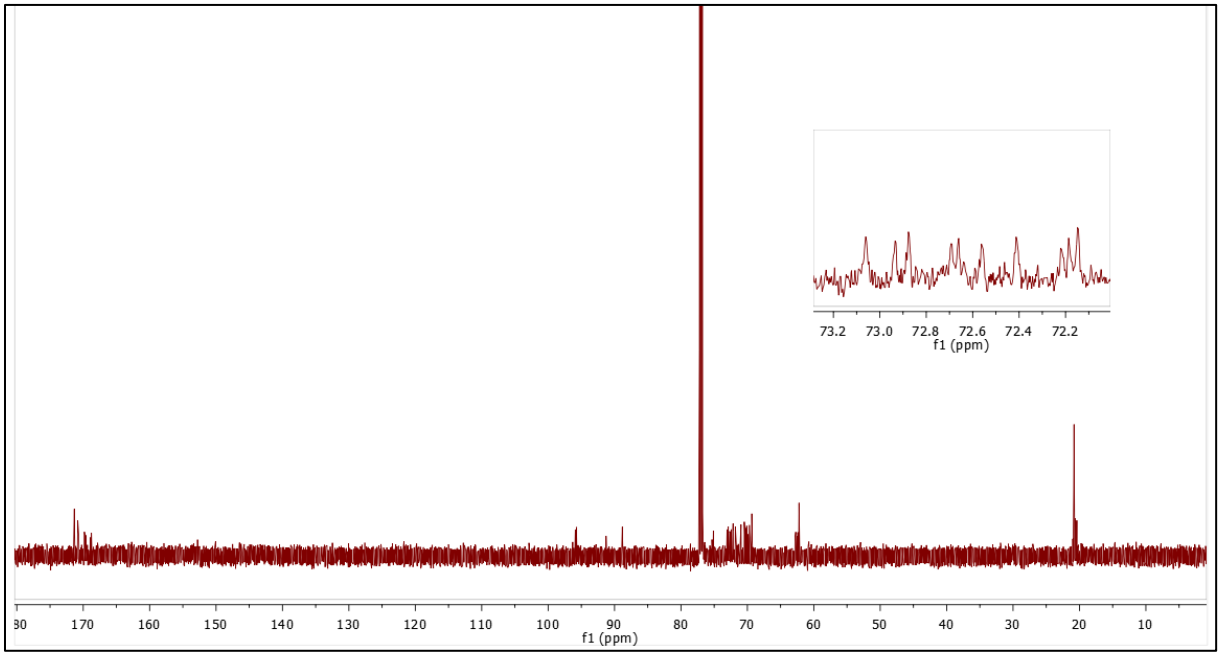
^{13}C NMR (151 MHz, $CDCl_3$)



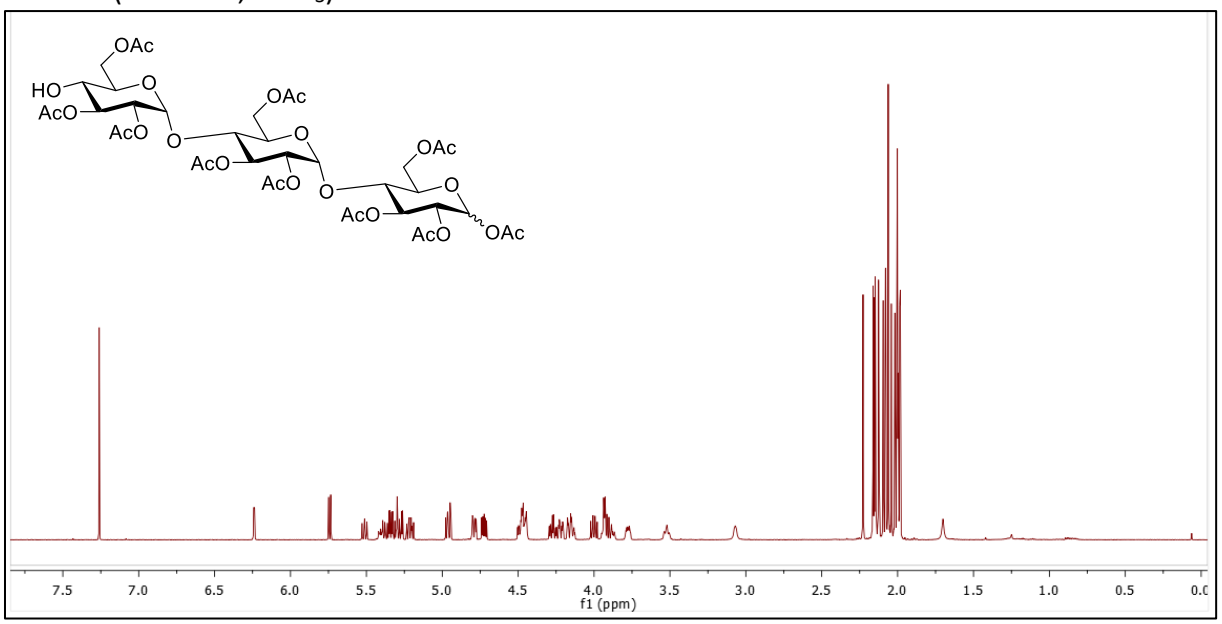
^{1}H NMR (600 MHz, $CDCl_3$)



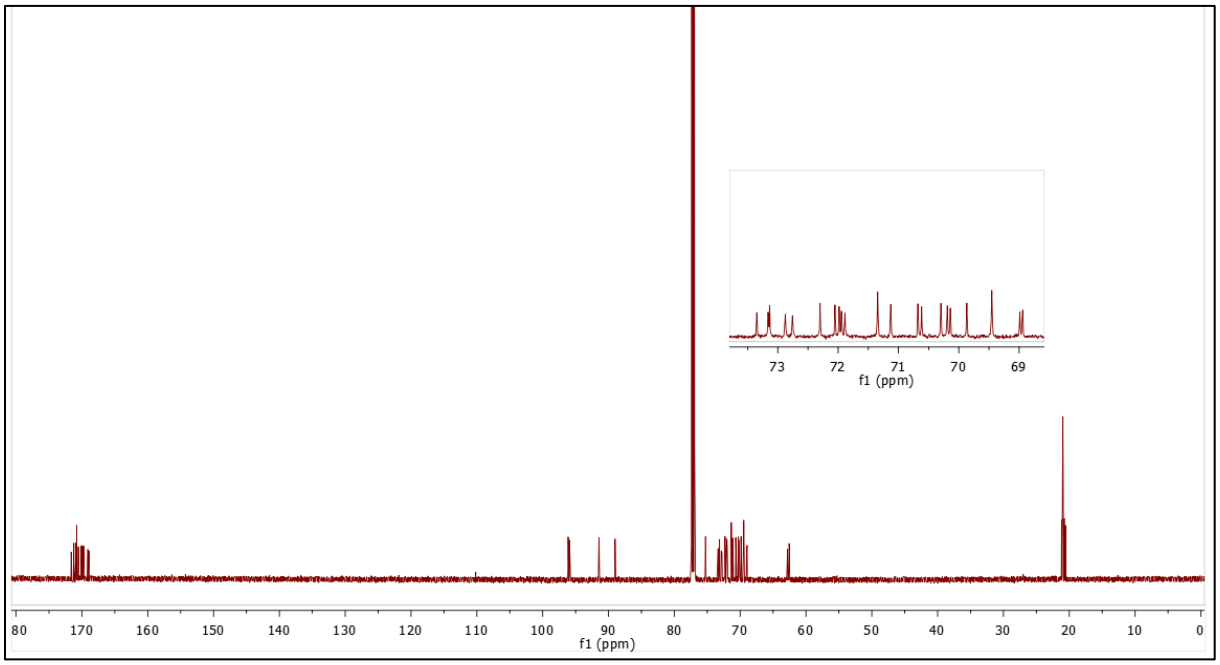
^{13}C NMR (151 MHz, $CDCl_3$)



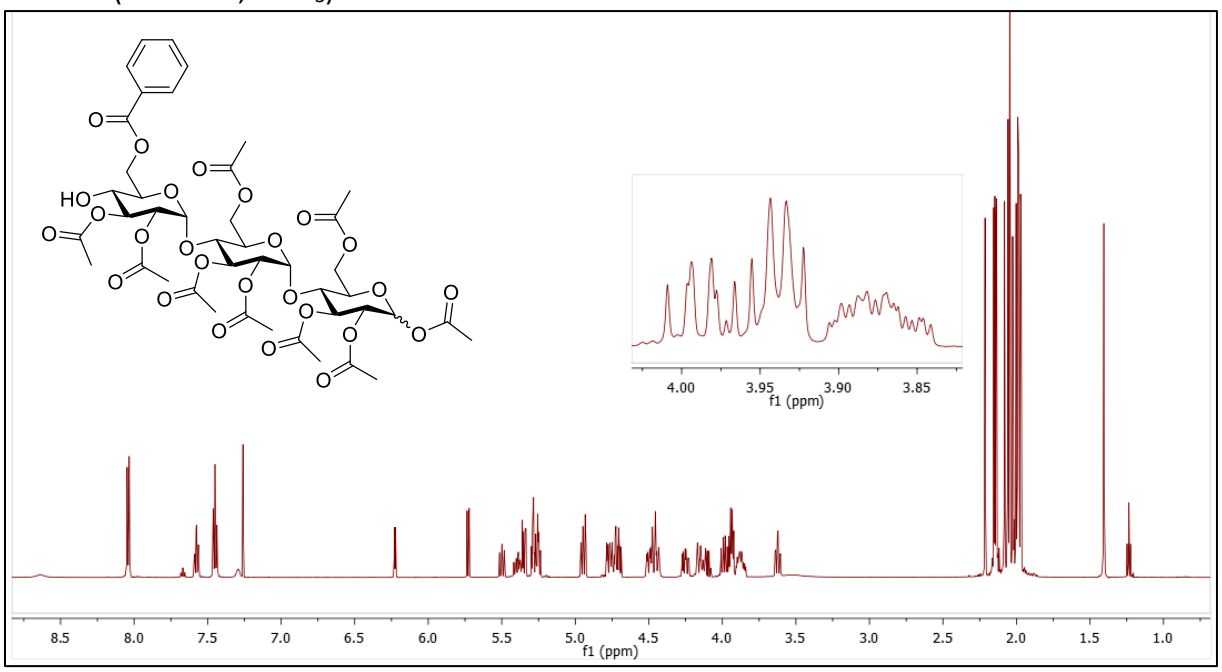
^{1}H NMR (600 MHz, $CDCl_3$)



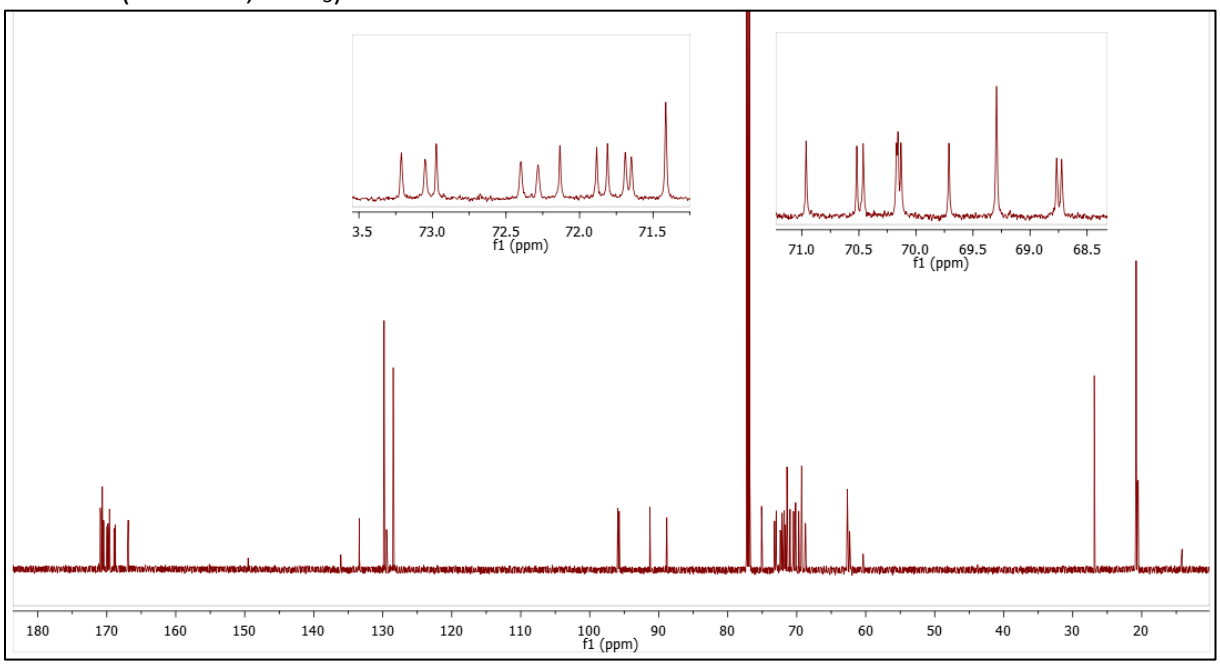
^{13}C NMR (151 MHz, $CDCl_3$)



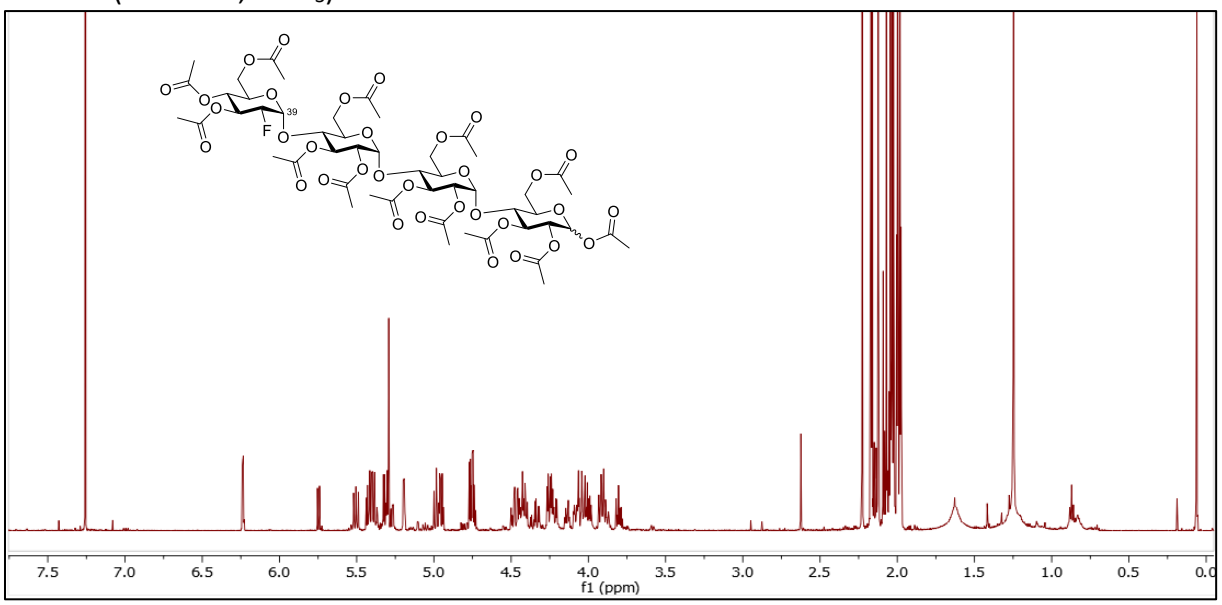
^{1}H NMR (600 MHz, $CDCl_3$)



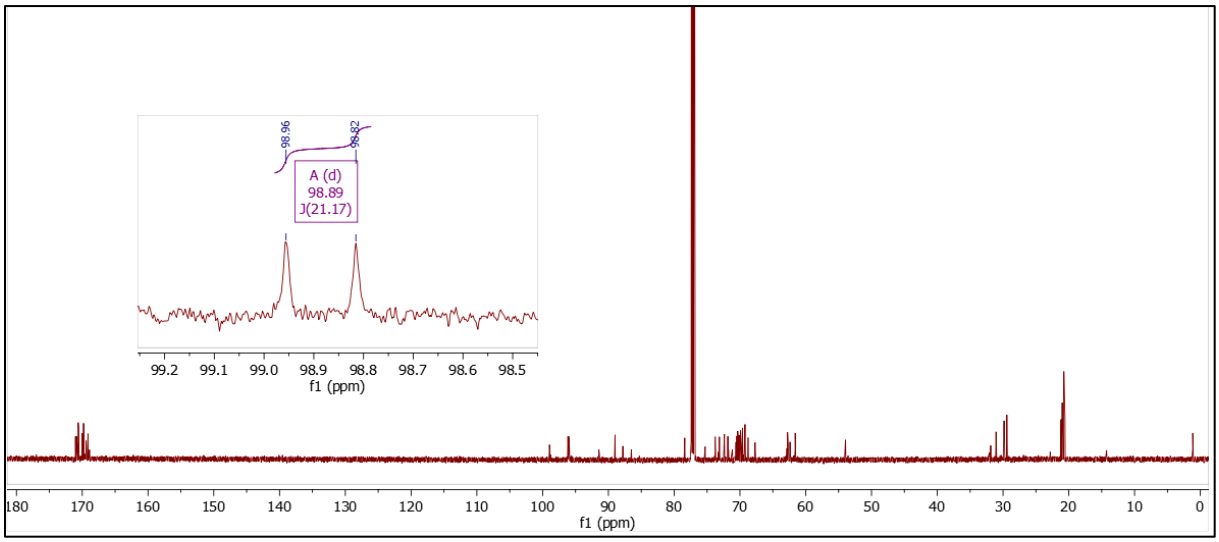
^{13}C NMR (151 MHz, $CDCl_3$)



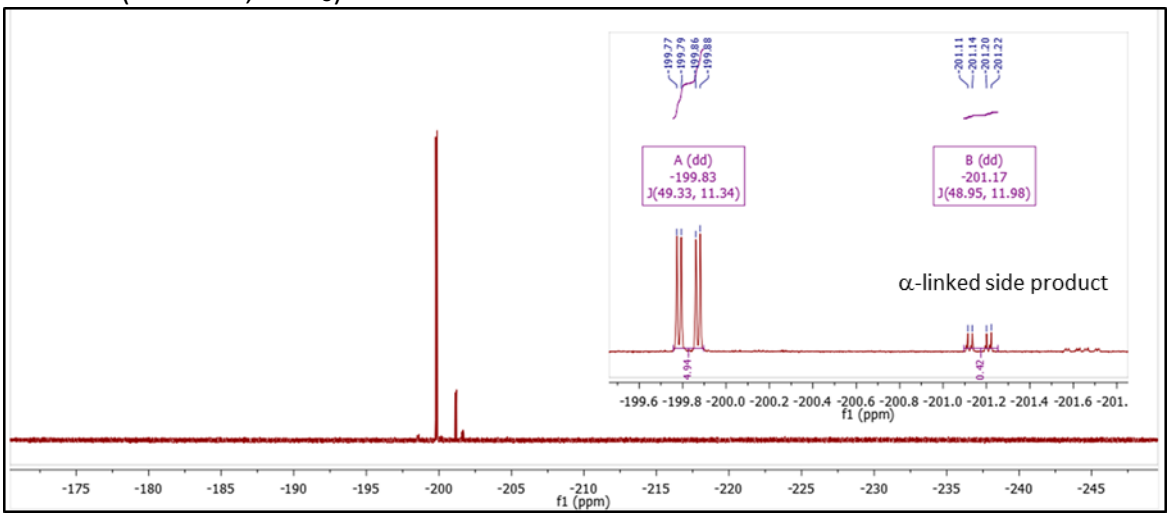
^{1}H NMR (600 MHz, $CDCl_3$)



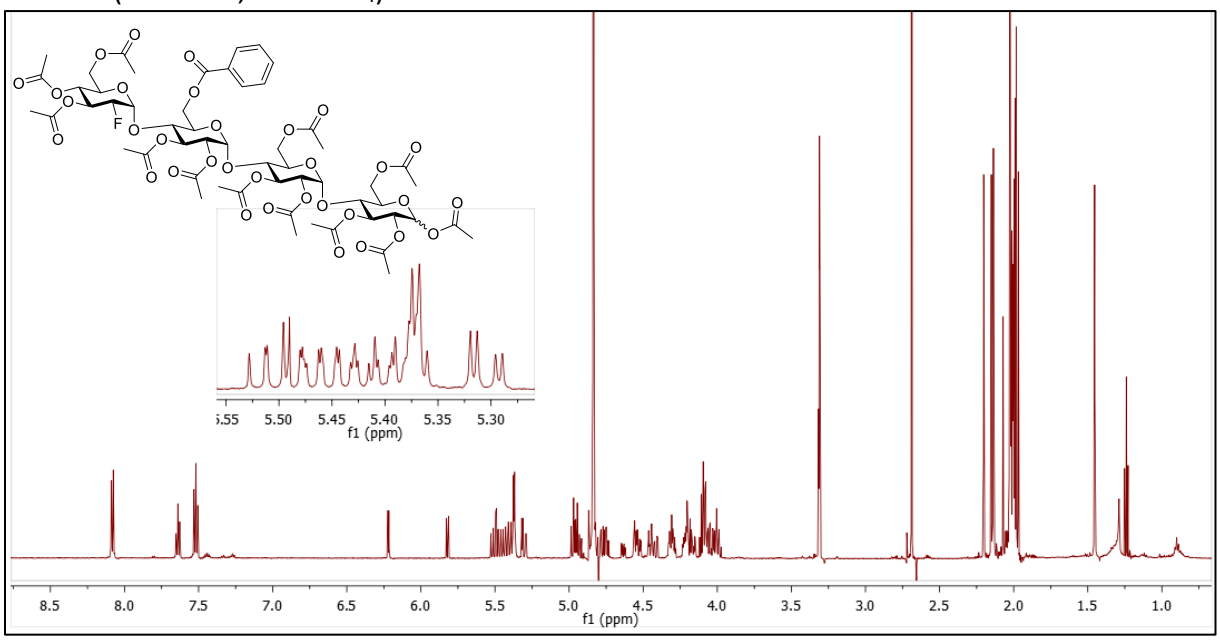
^{13}C NMR (151 MHz, $CDCl_3$)



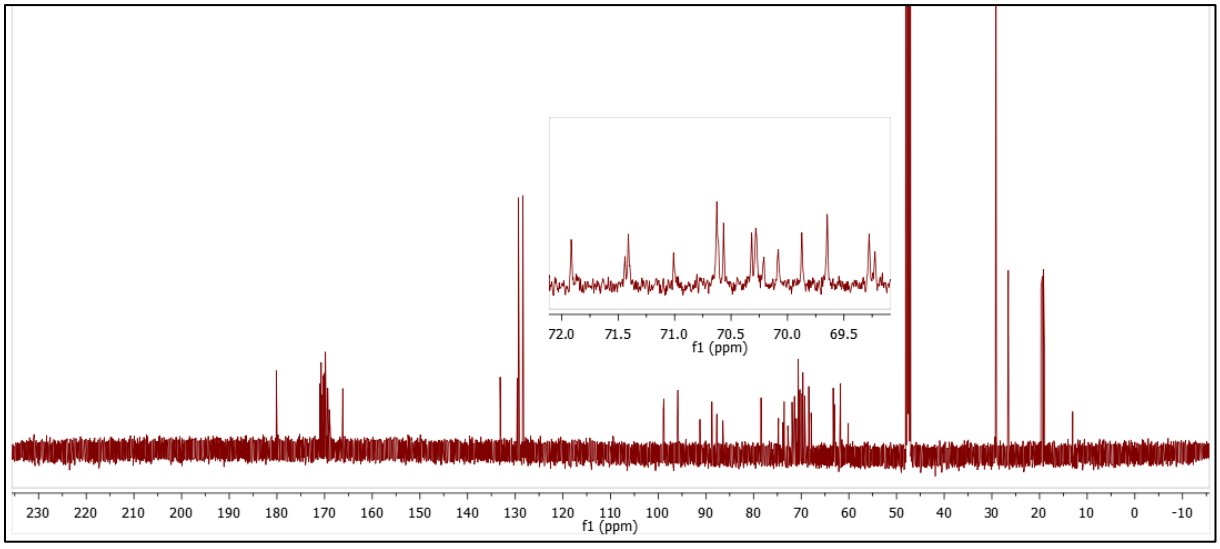
^{19}F NMR (564 MHz, $CDCl_3$)



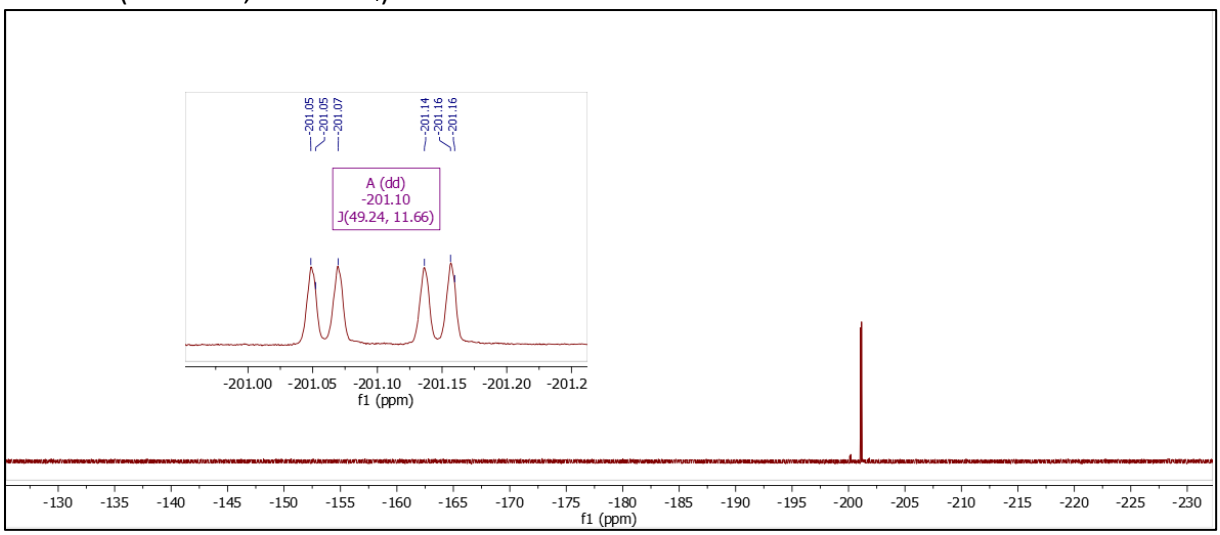
^{1}H NMR (600 MHz, MeOD-d_4)



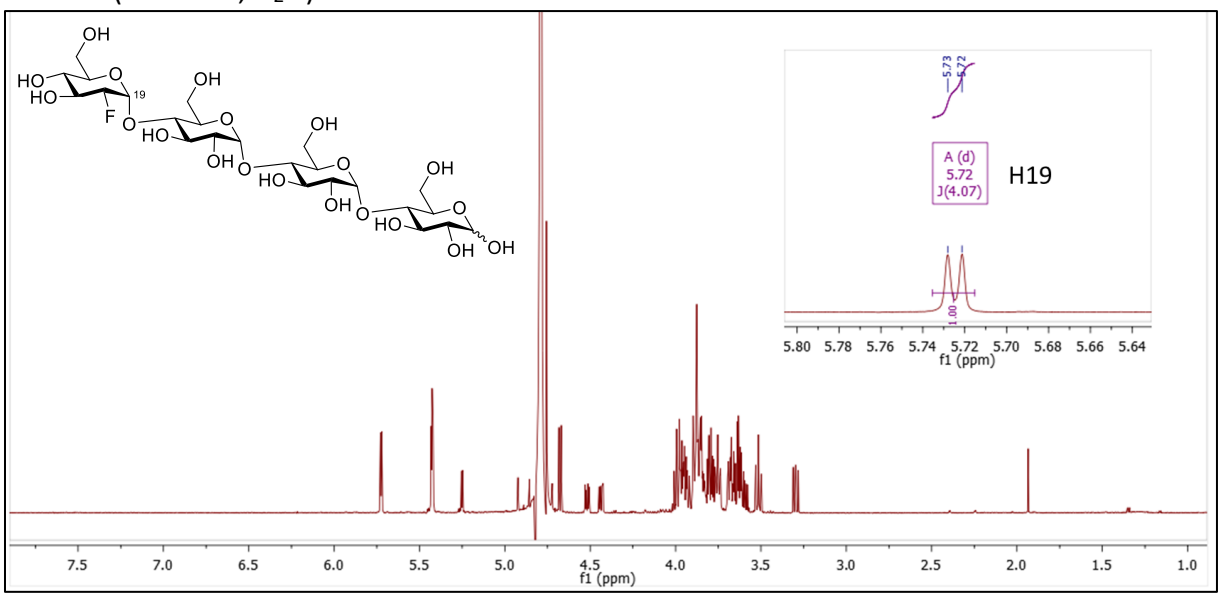
^{13}C NMR (151 MHz, MeOD-d_4)



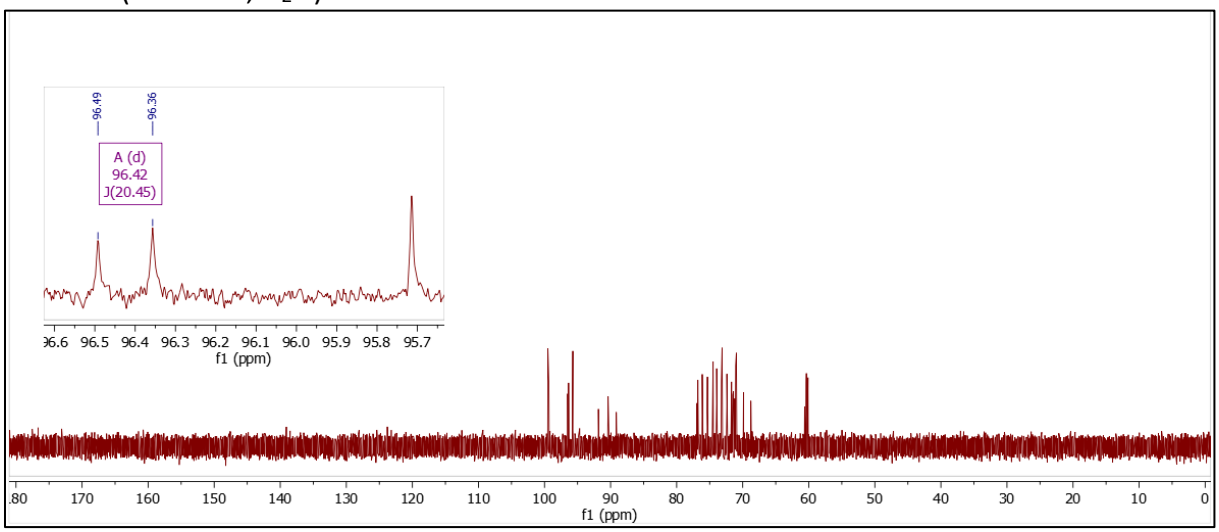
^{19}F NMR (564 MHz, MeOD-d_4)



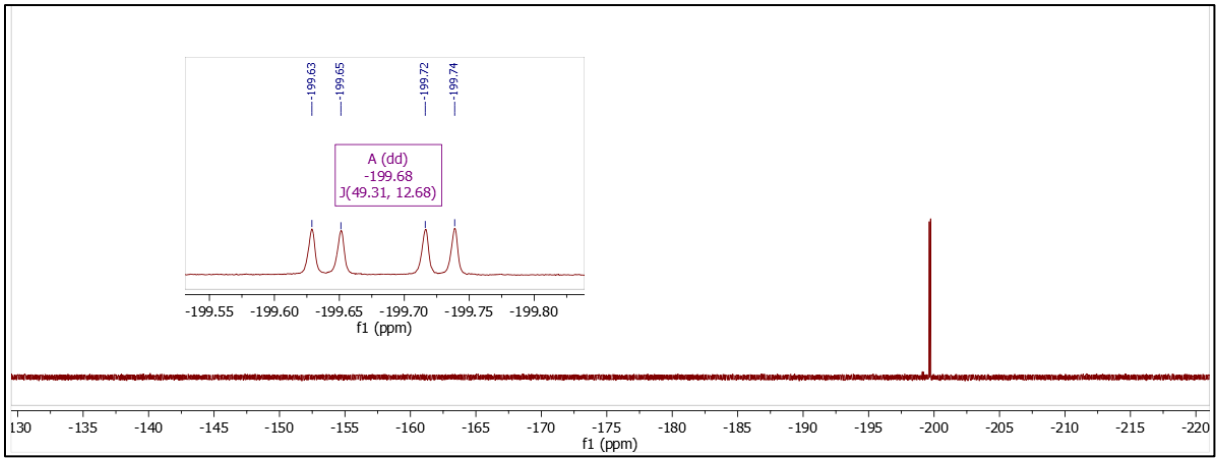
^{1}H NMR (600 MHz, D_2O)



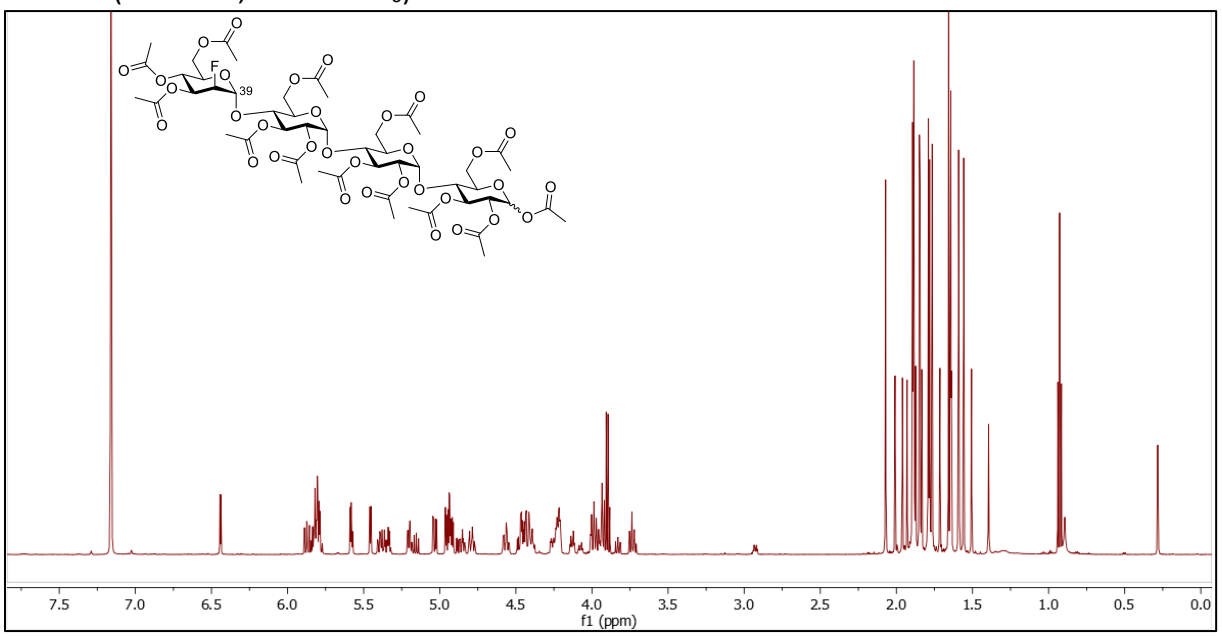
^{13}C NMR (151 MHz, D_2O)



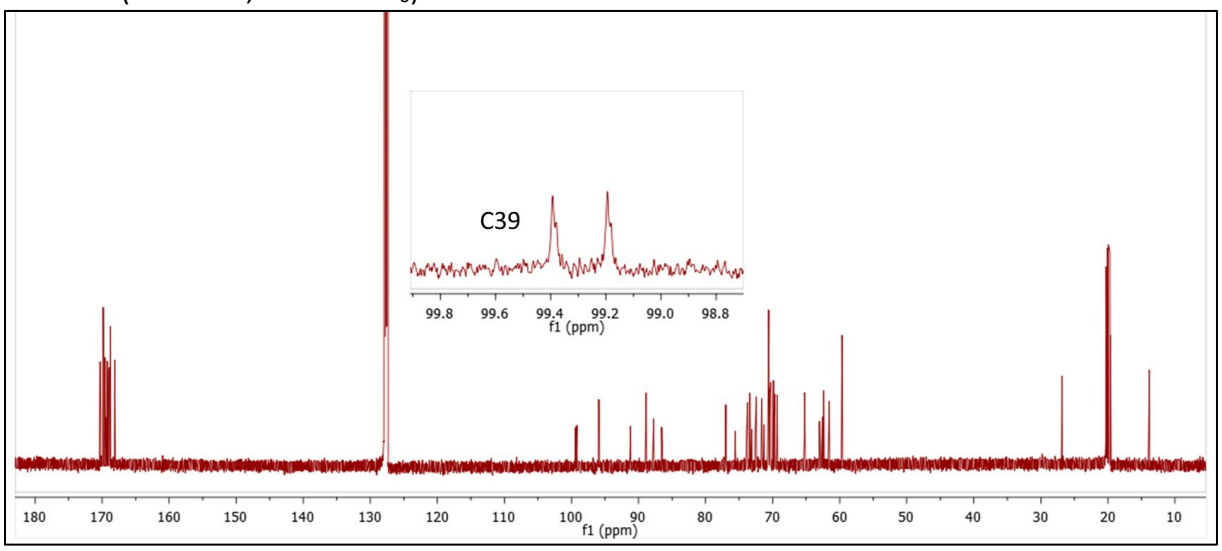
^{19}F NMR (564 MHz, D_2O)



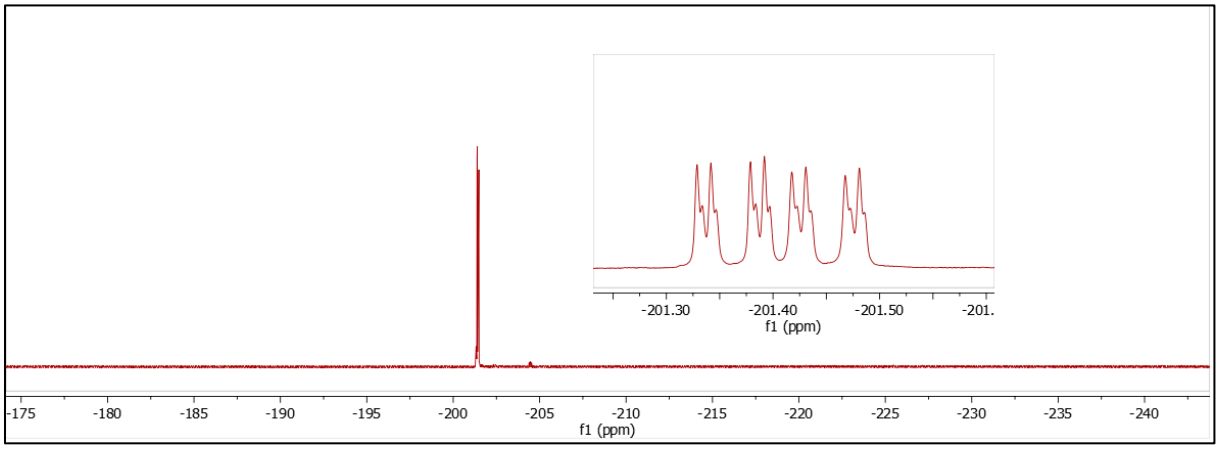
^{1}H NMR (600 MHz, benzene-d_6)



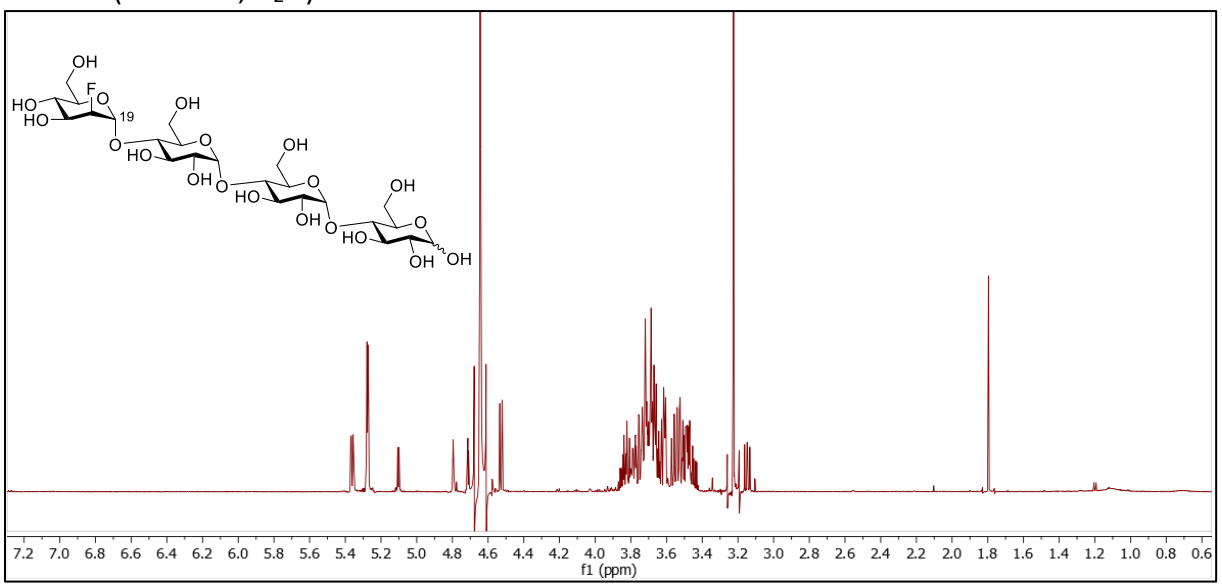
^{13}C NMR (151 MHz, benzene-d_6)



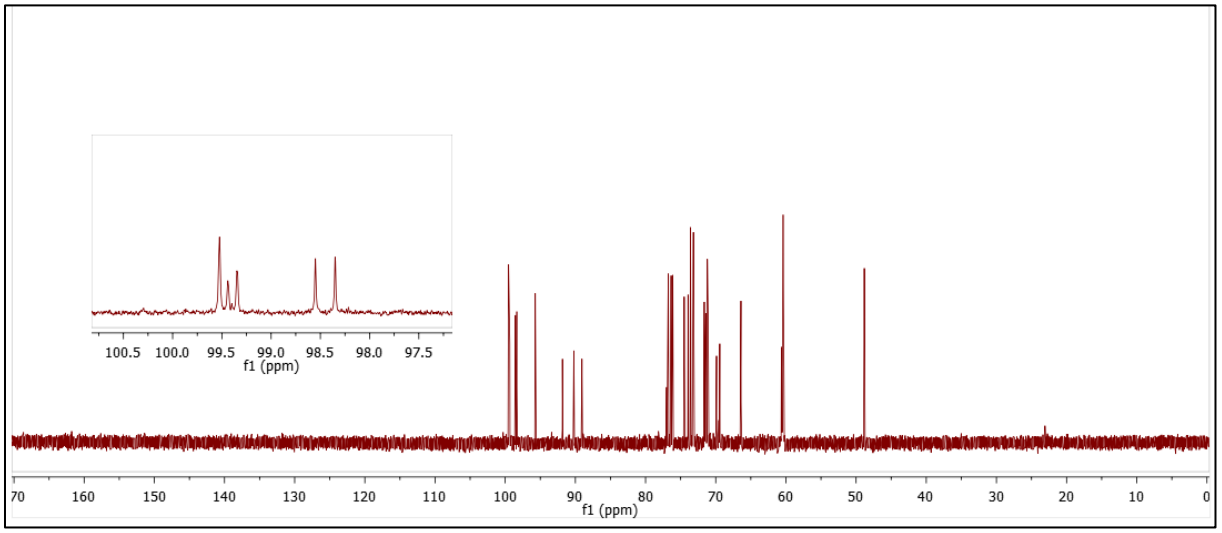
^{19}F NMR (564 MHz, benzene-d_6)



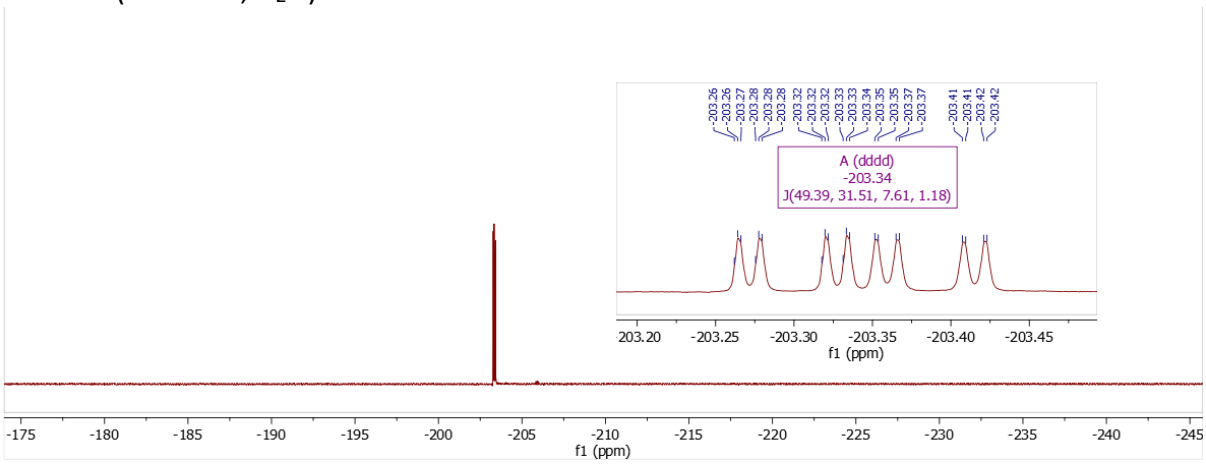
^{1}H NMR (600 MHz, D_2O)



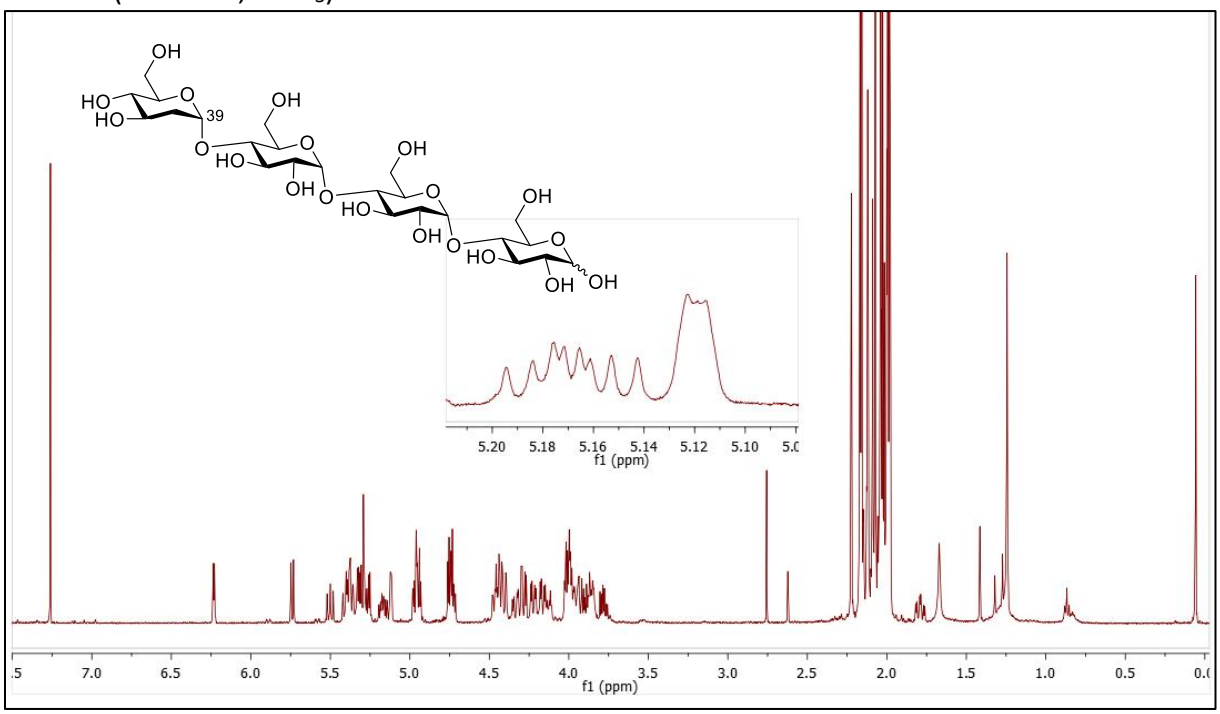
^{13}C NMR (151 MHz, D_2O)



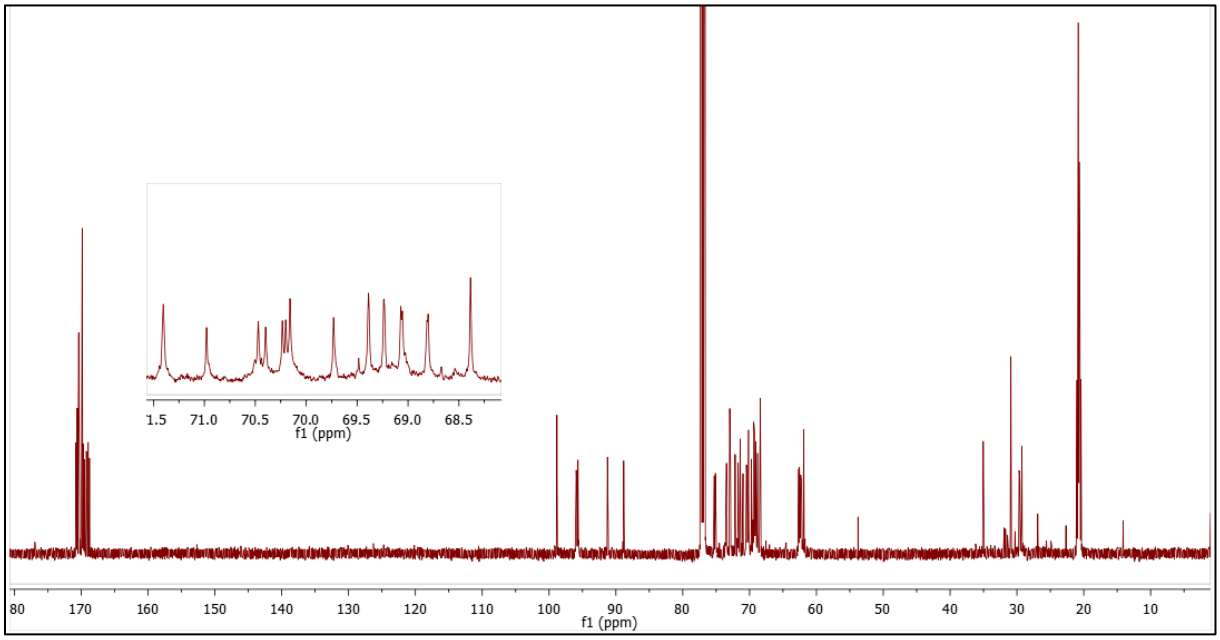
^{19}F NMR (564 MHz, D_2O)



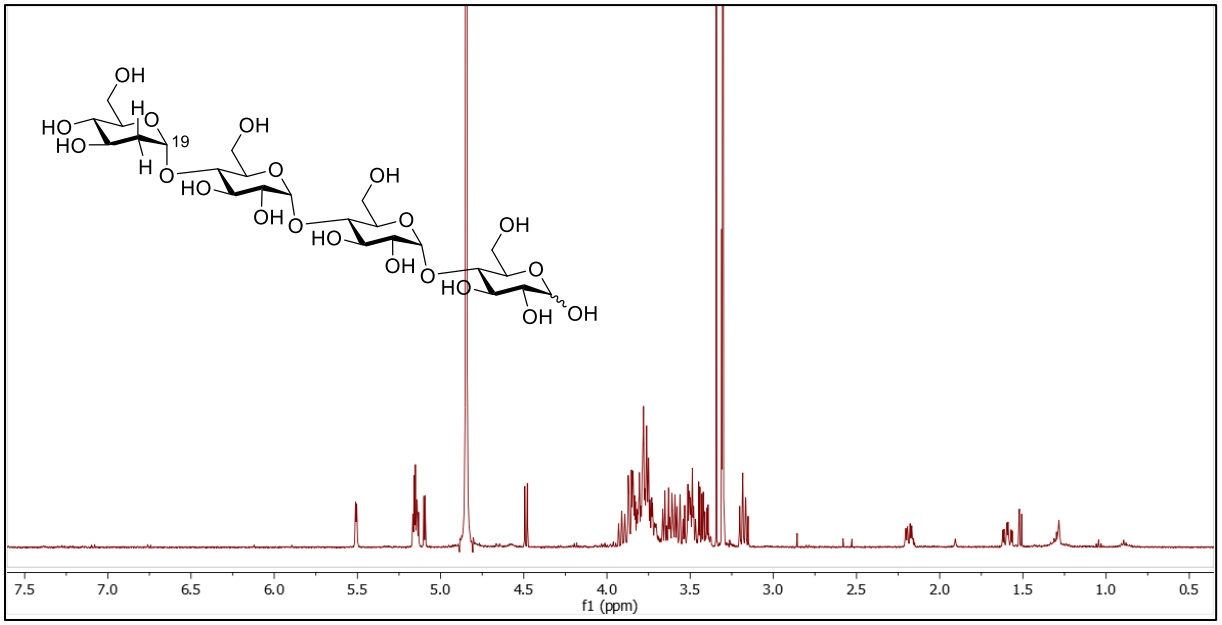
^{1}H NMR (600 MHz, $CDCl_3$)



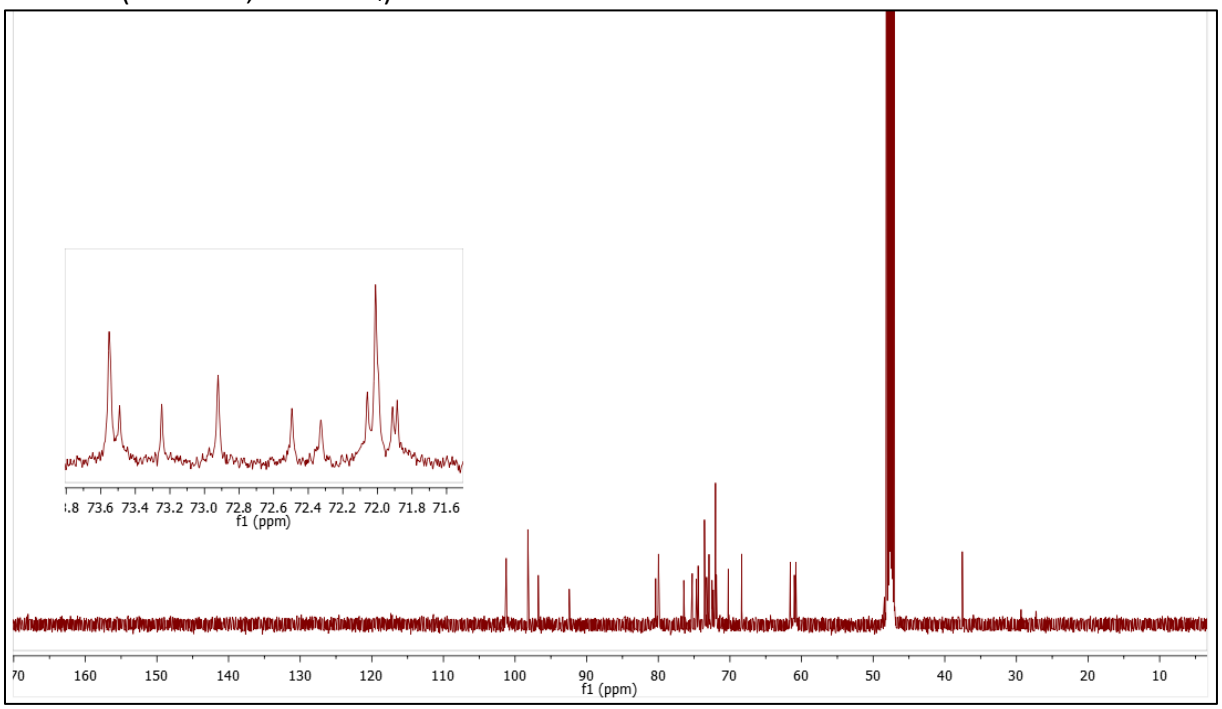
^{13}C NMR (151 MHz, $CDCl_3$)



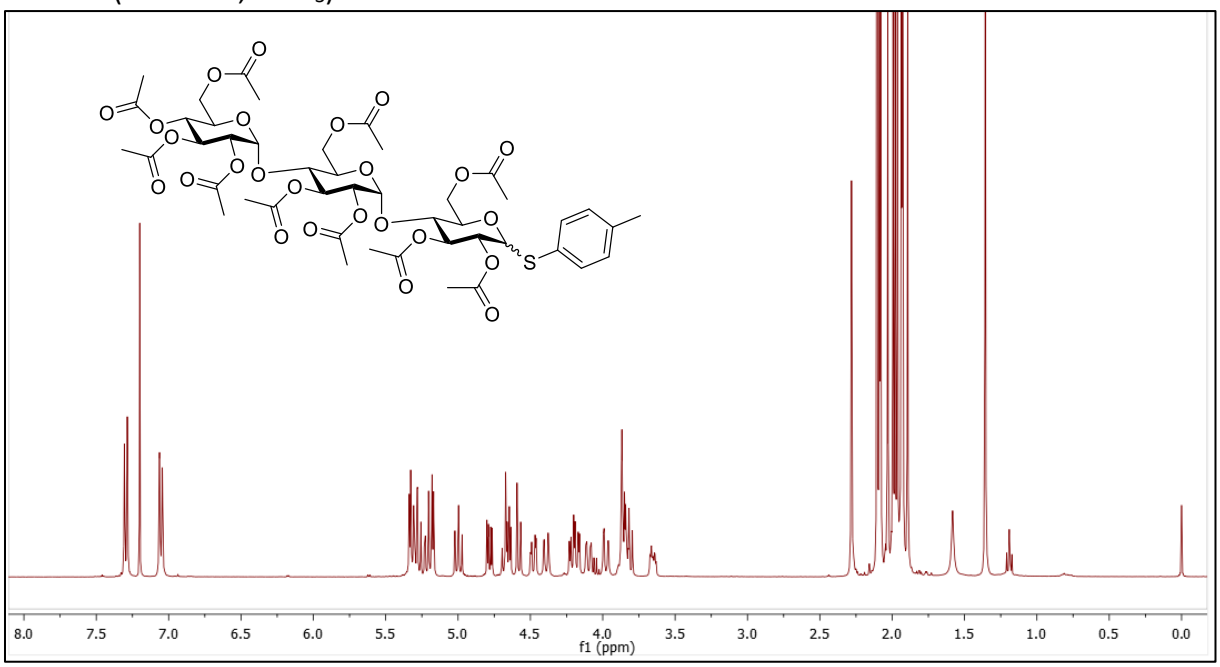
^{1}H NMR (500 MHz, MeOD-d_4)



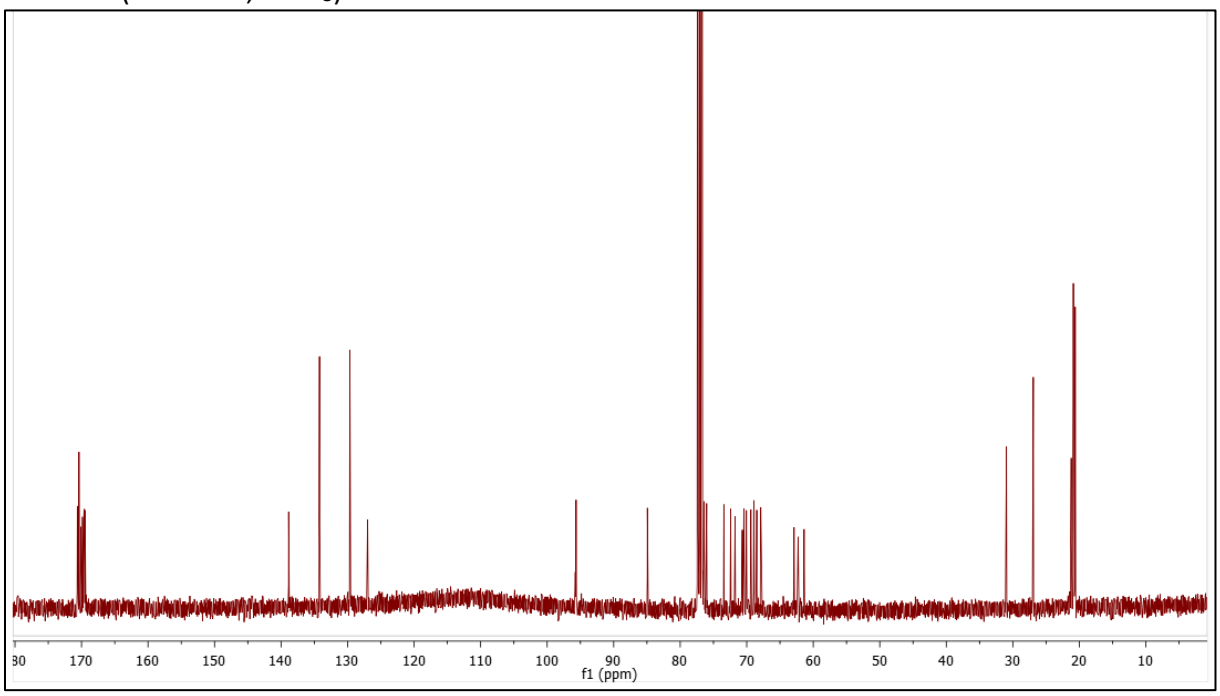
^{13}C NMR (126 MHz, MeOD-d_4)



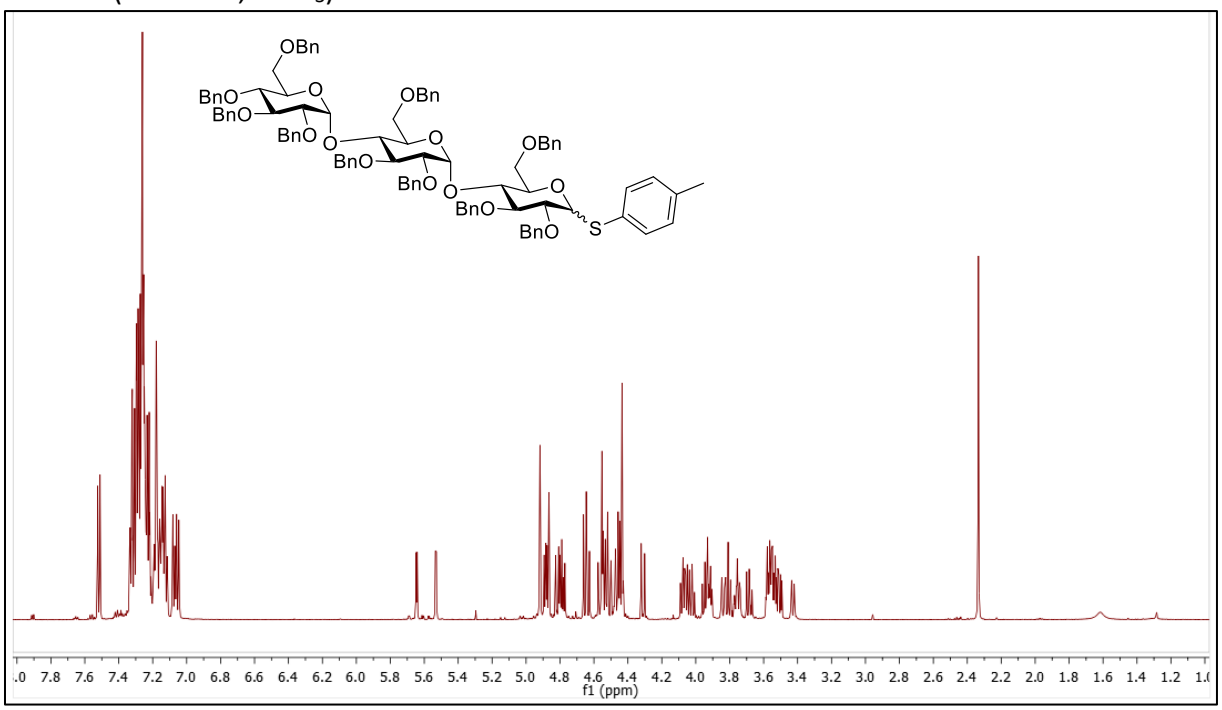
^{1}H NMR (400 MHz, $CDCl_3$)



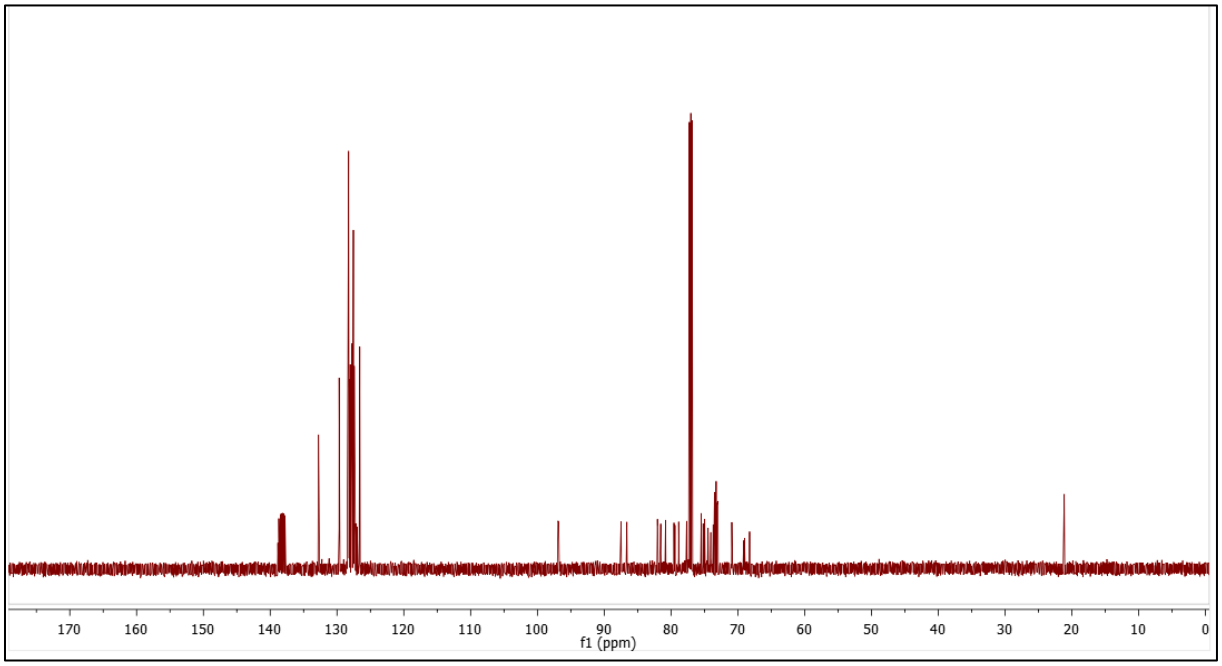
^{13}C NMR (101 MHz, $CDCl_3$)



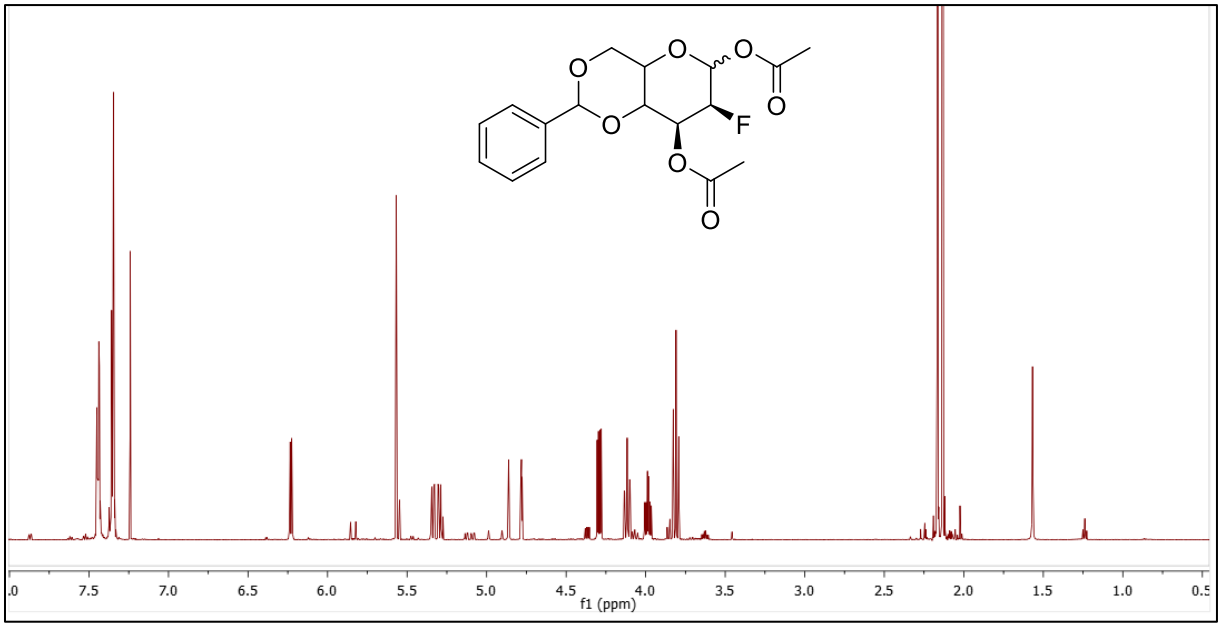
^{1}H NMR (600 MHz, $CDCl_3$)



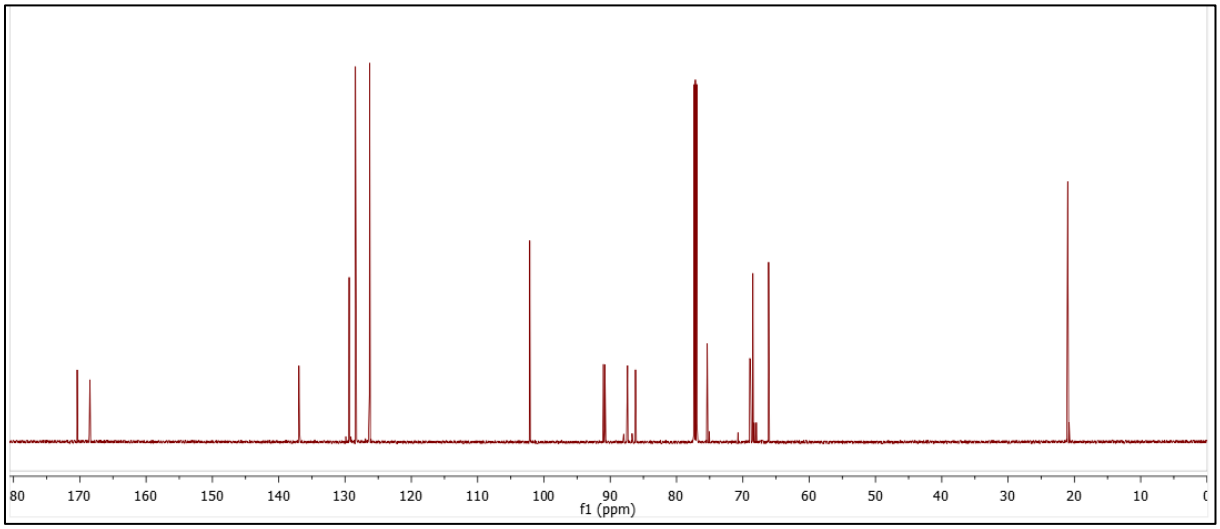
^{13}C NMR (151 MHz, $CDCl_3$)



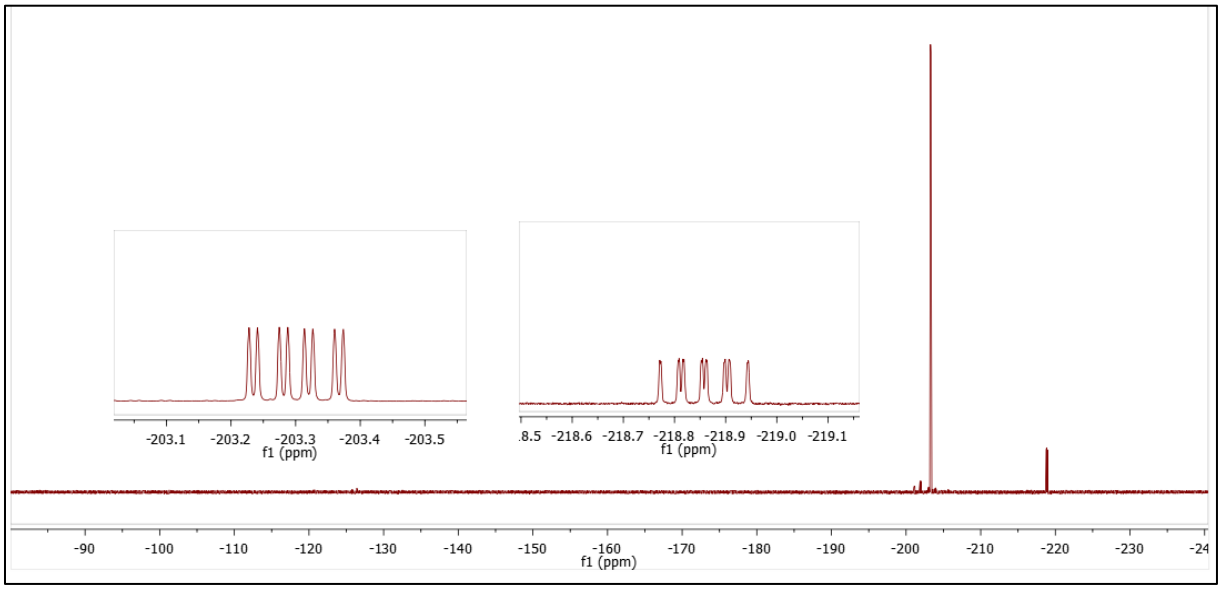
^{1}H NMR (600 MHz, $CDCl_3$)



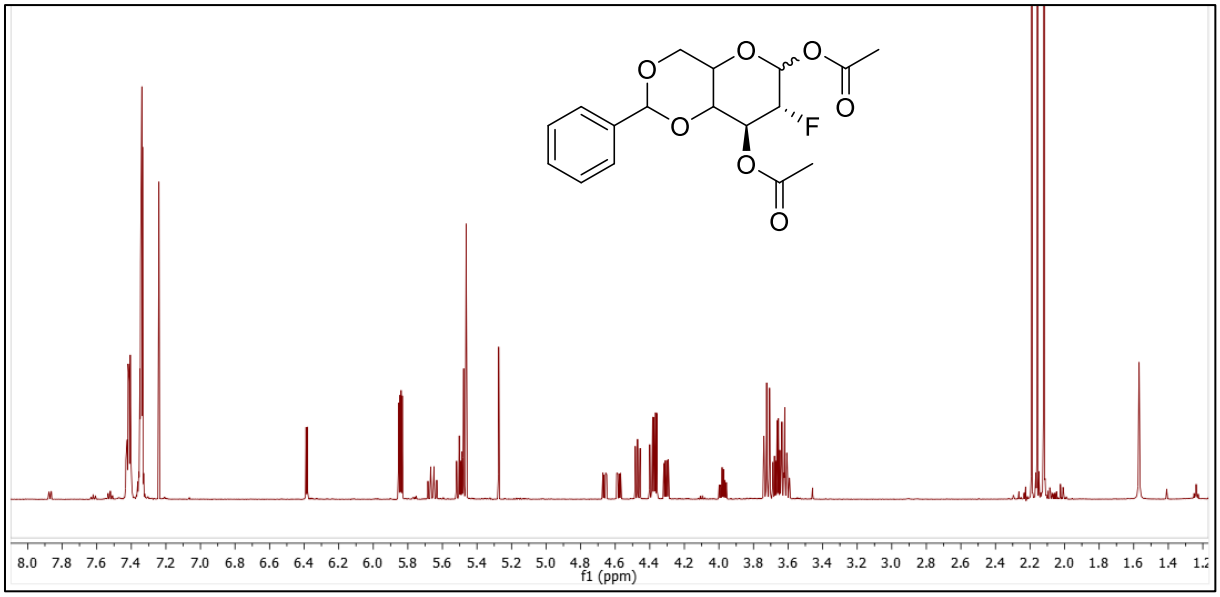
^{13}C NMR (151 MHz, $CDCl_3$)



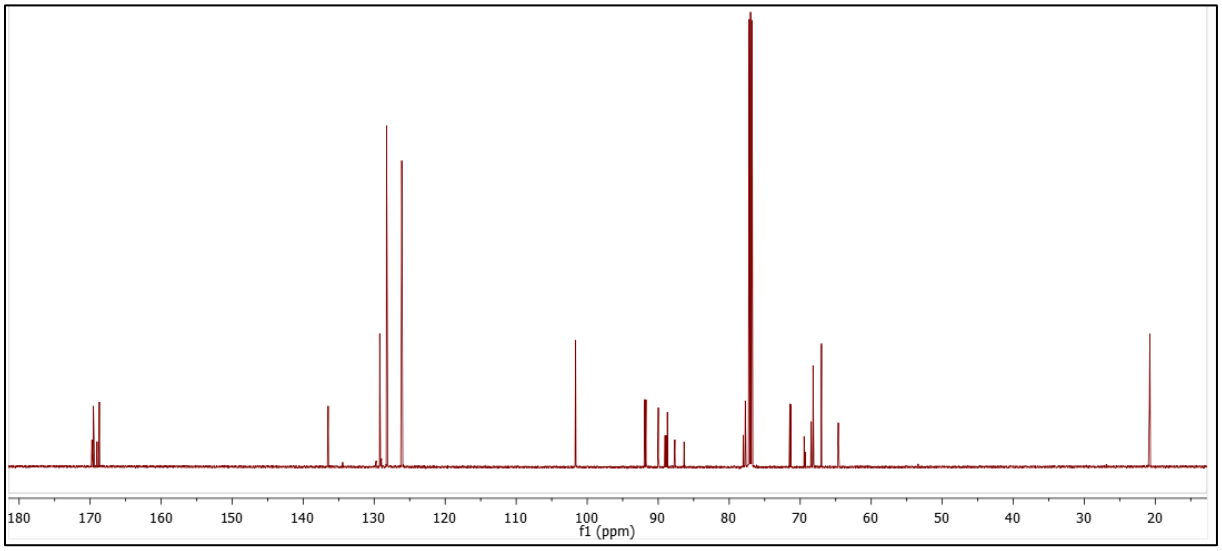
^{19}F NMR (564 MHz, $CDCl_3$)



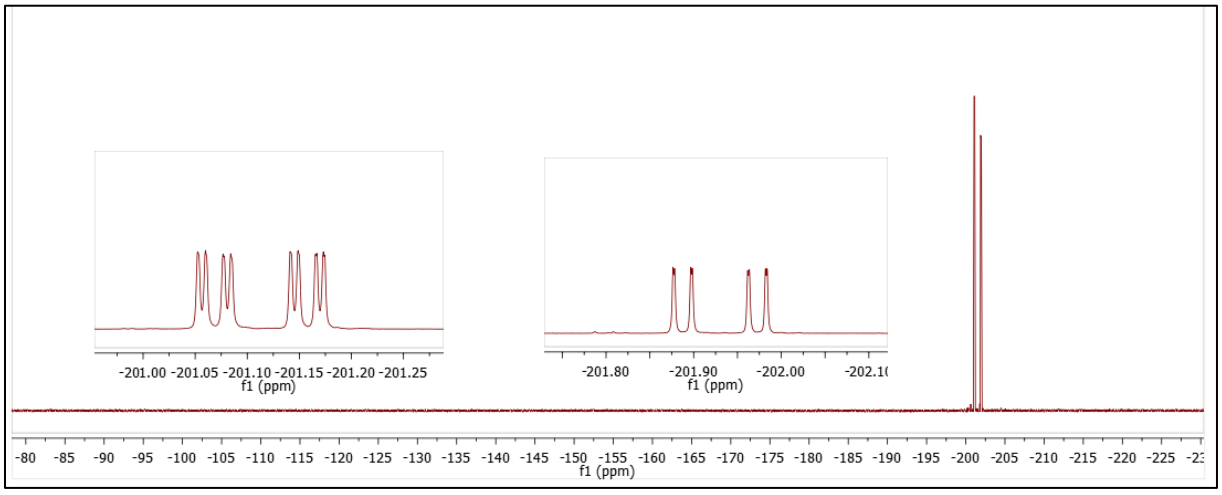
^{1}H NMR (600 MHz, $CDCl_3$)



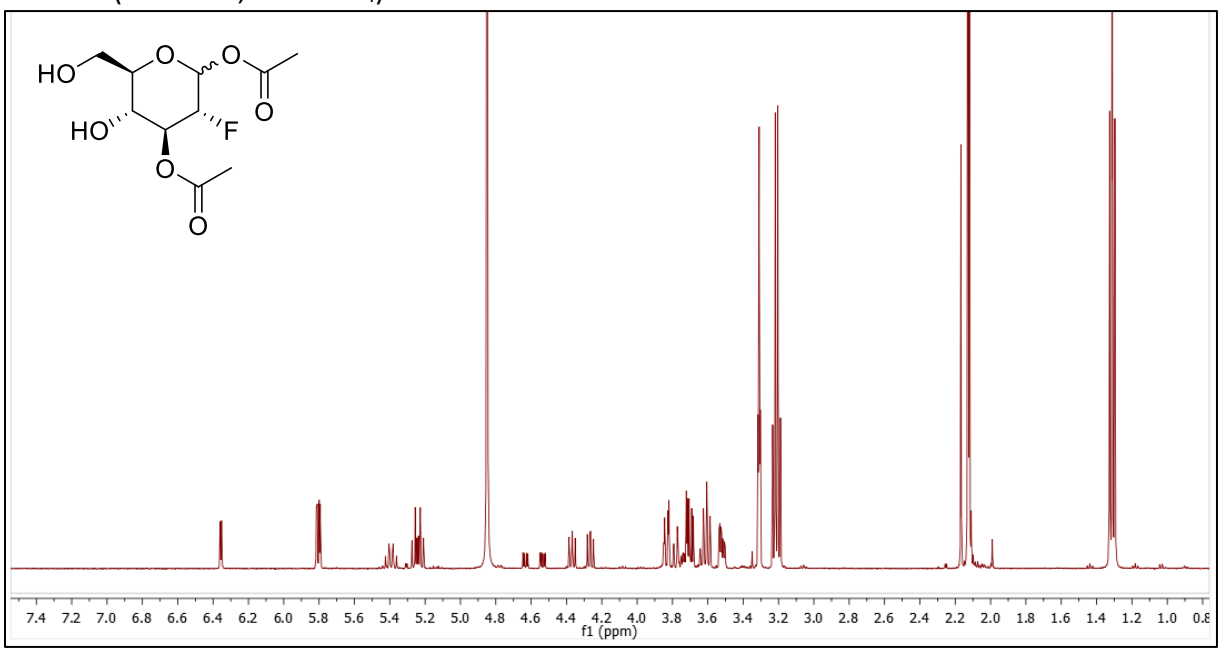
^{13}C NMR (151 MHz, $CDCl_3$)



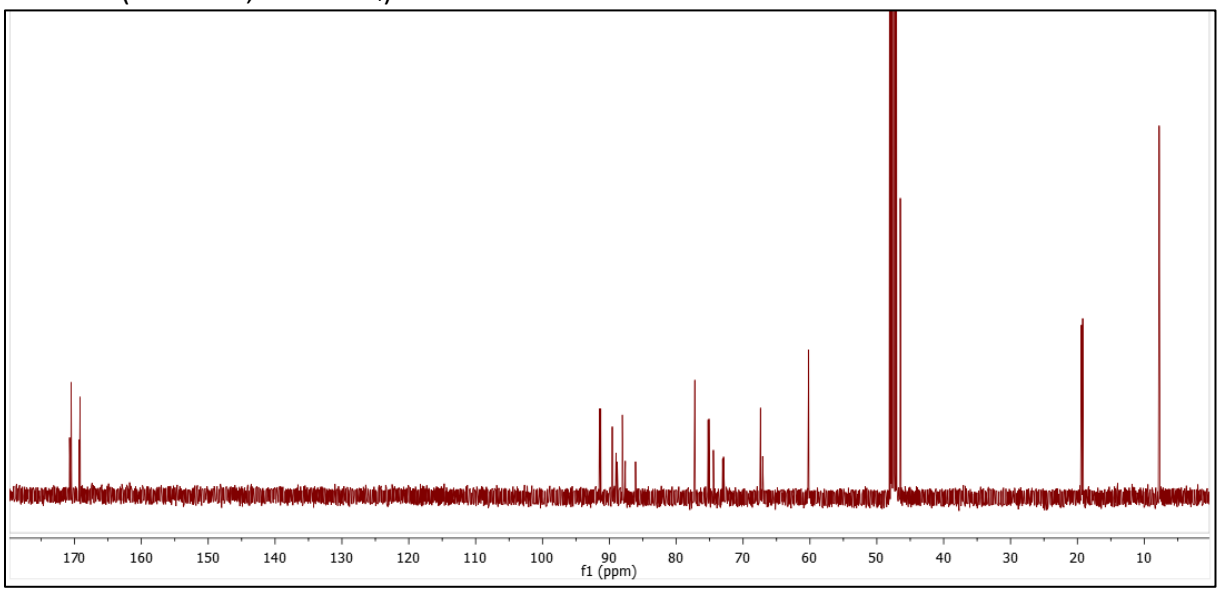
^{19}F NMR (564 MHz, $CDCl_3$)



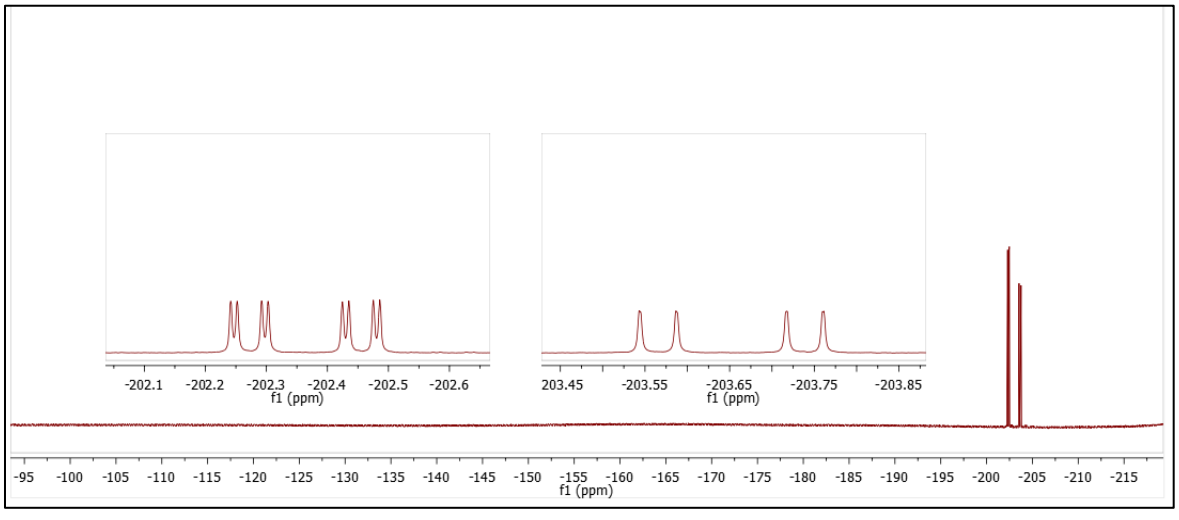
^{1}H NMR (500 MHz, MeOD-d_4)



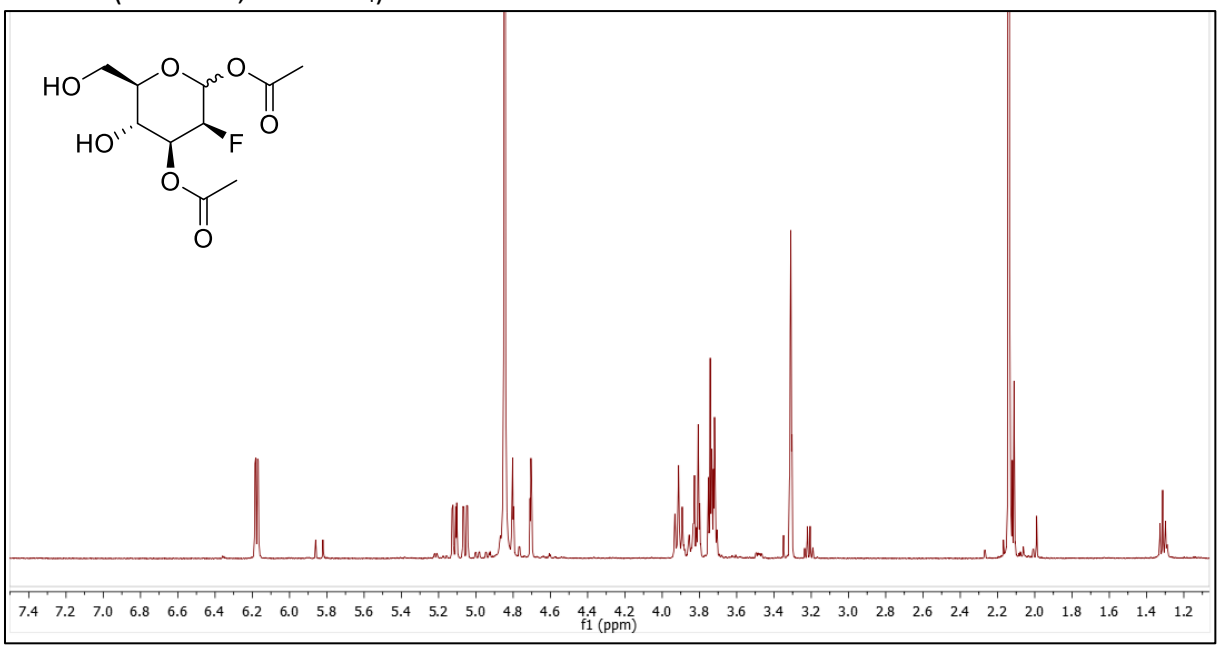
^{13}C NMR (126 MHz, MeOD-d_4)



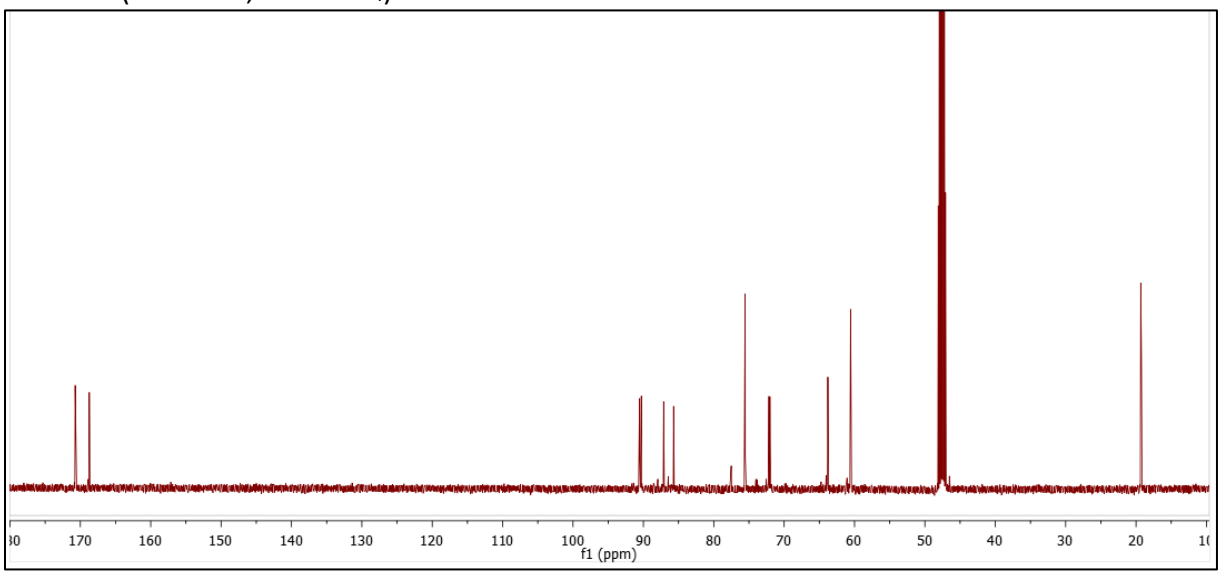
^{19}F NMR (282 MHz, MeOD-d_4)



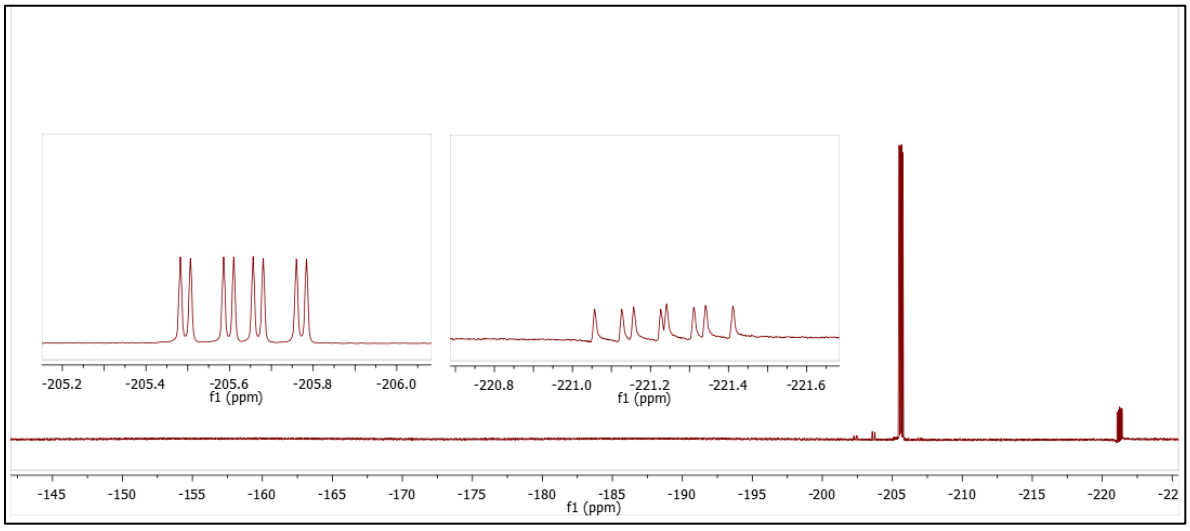
^{1}H NMR (500 MHz, MeOD-d_4)



^{13}C NMR (126 MHz, MeOD-d_4)



^{19}F NMR (282 MHz, MeOD-d_4)



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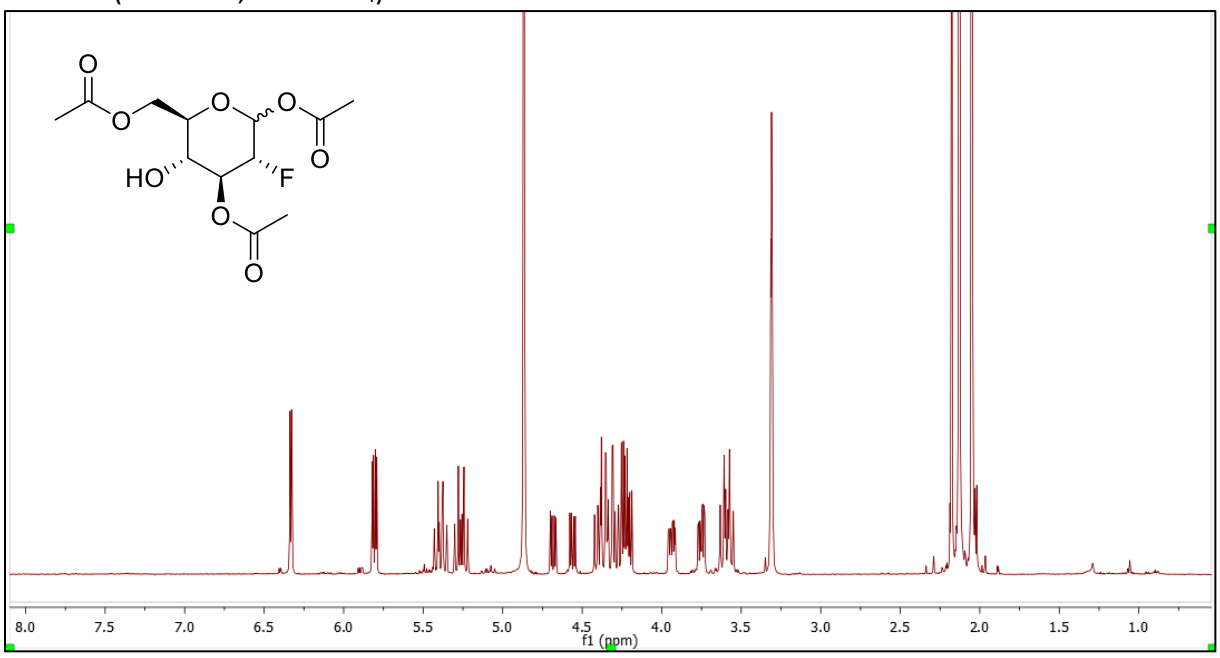

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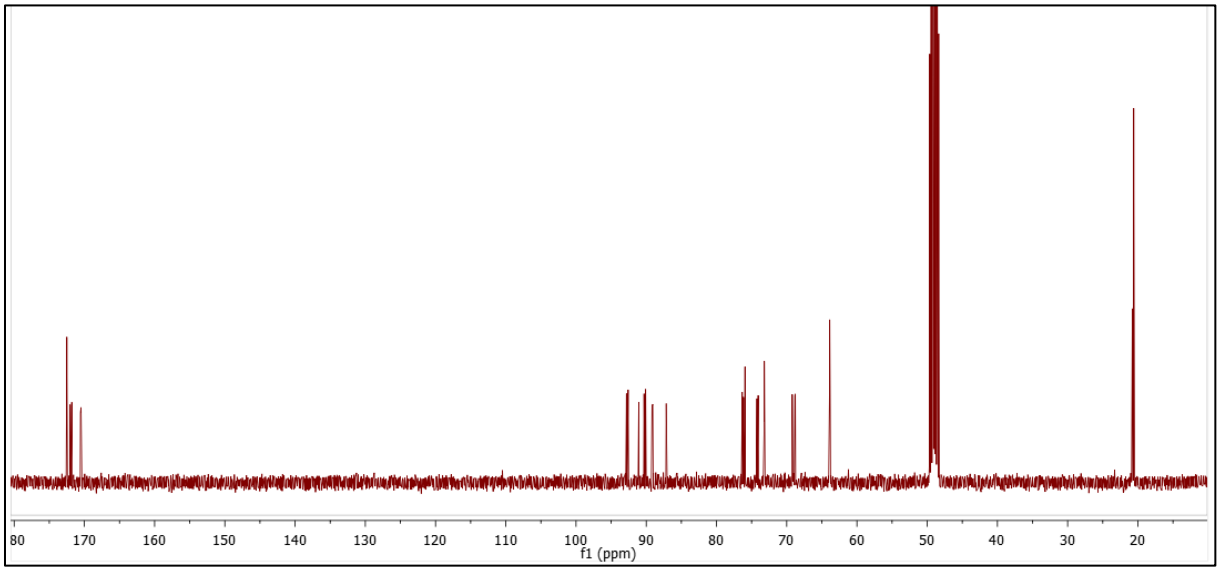
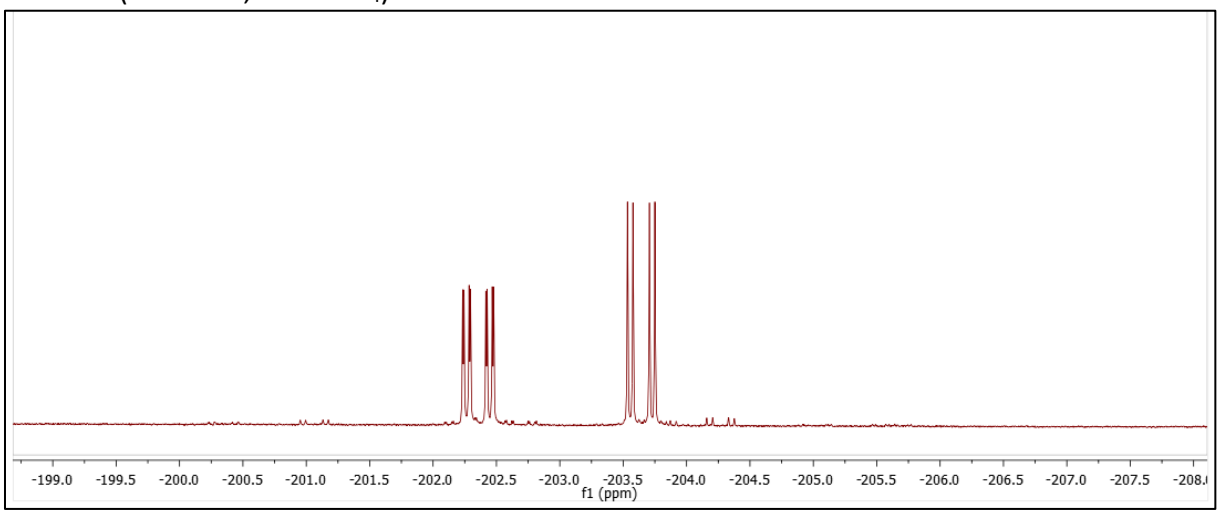
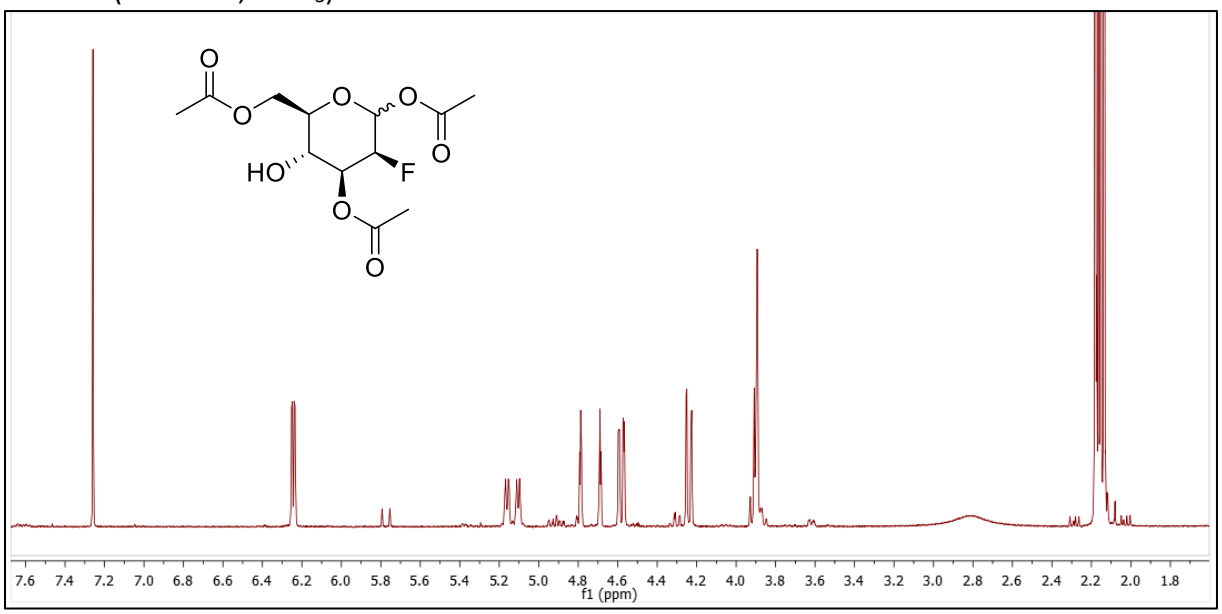


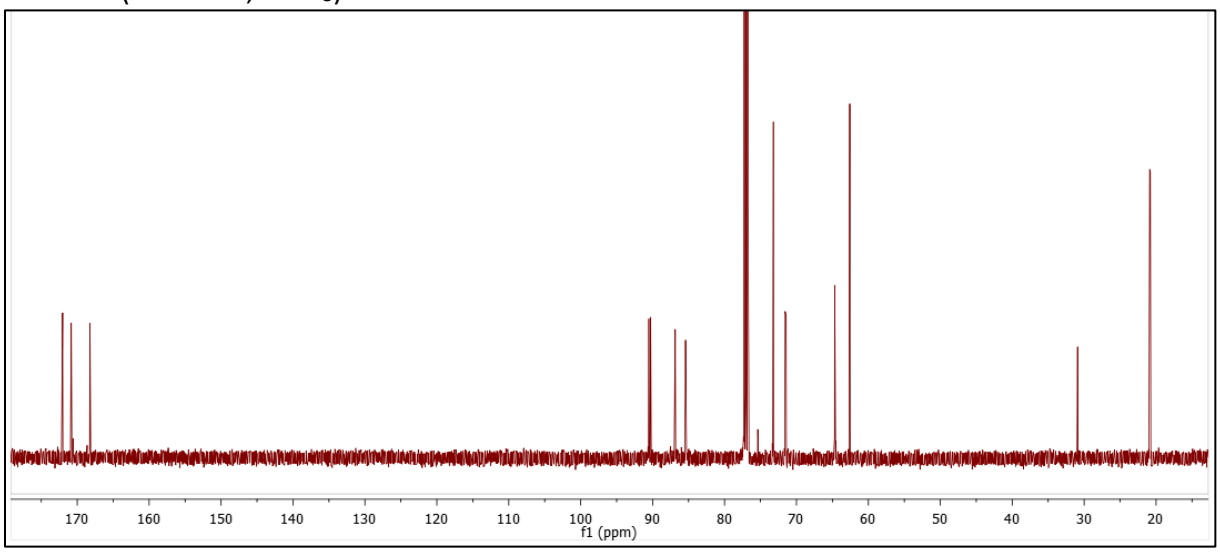
^{19}F NMR (282 MHz, MeOD-d_4)



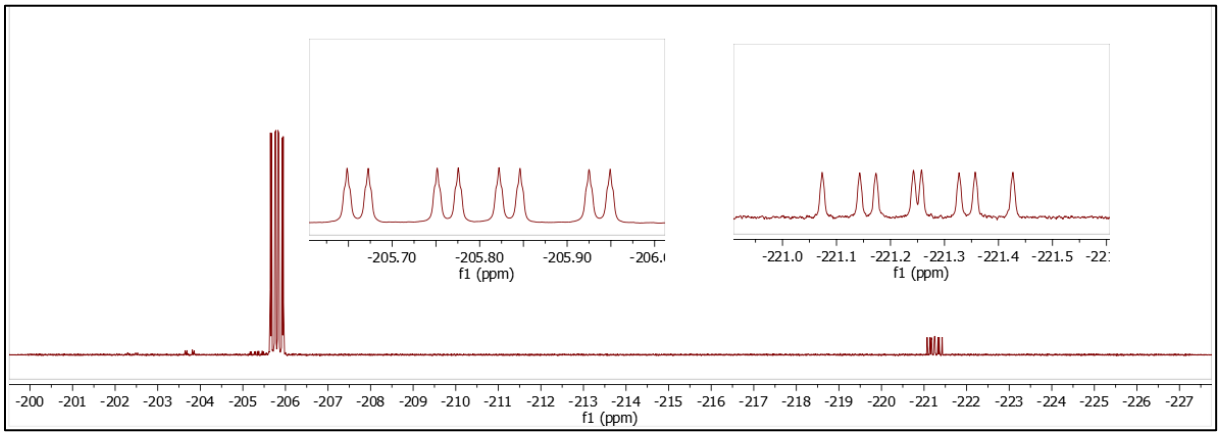
^{1}H NMR (500 MHz, $CDCl_3$)



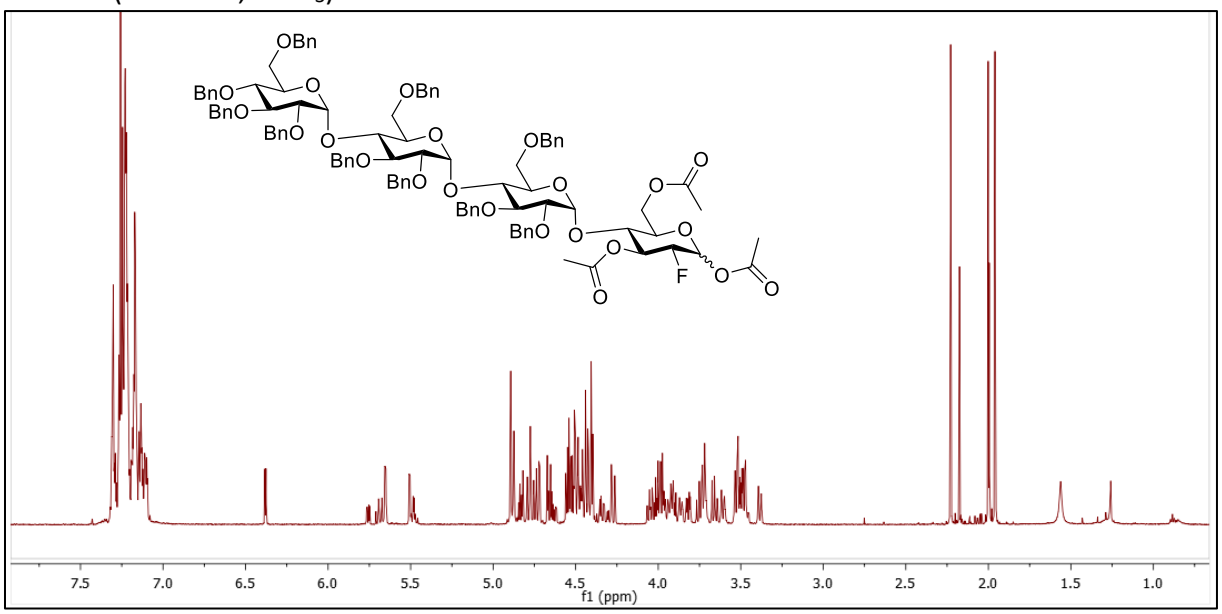
^{13}C NMR (126 MHz, $CDCl_3$)



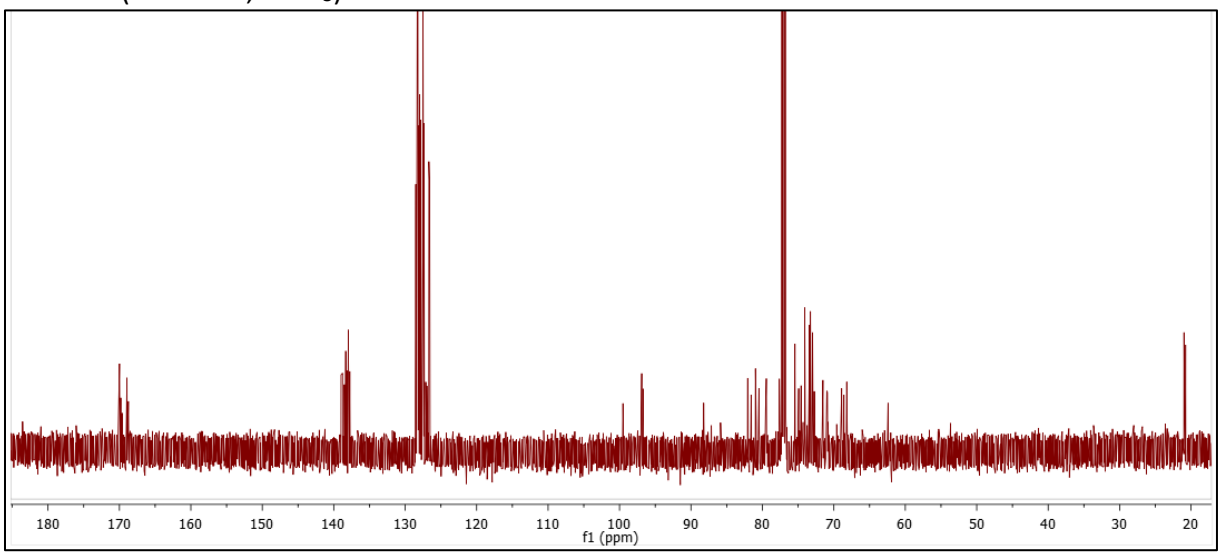
^{19}F NMR (282 MHz, $CDCl_3$)



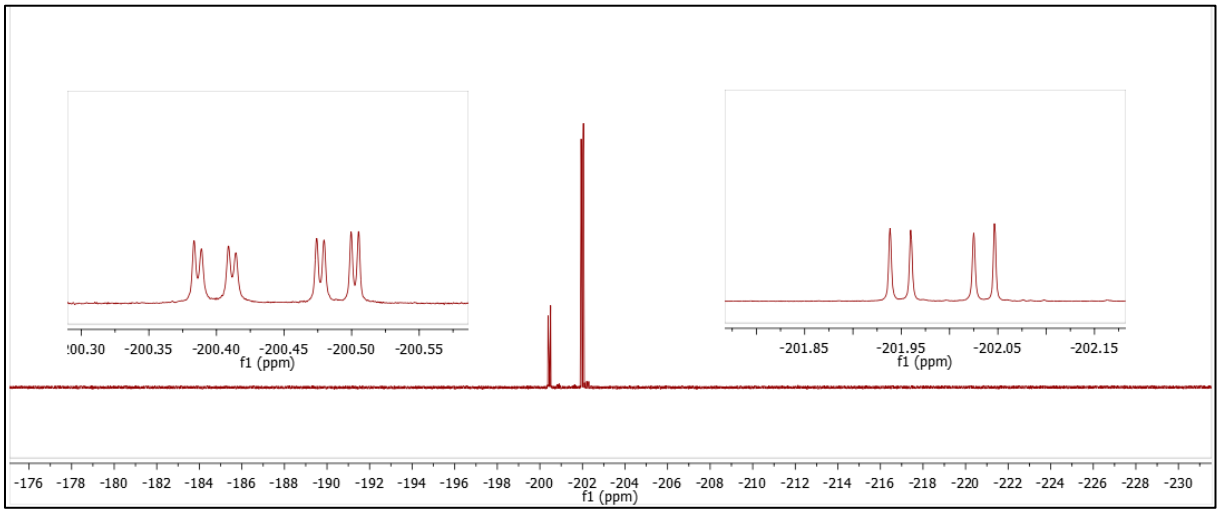
^{1}H NMR (600 MHz, $CDCl_3$)



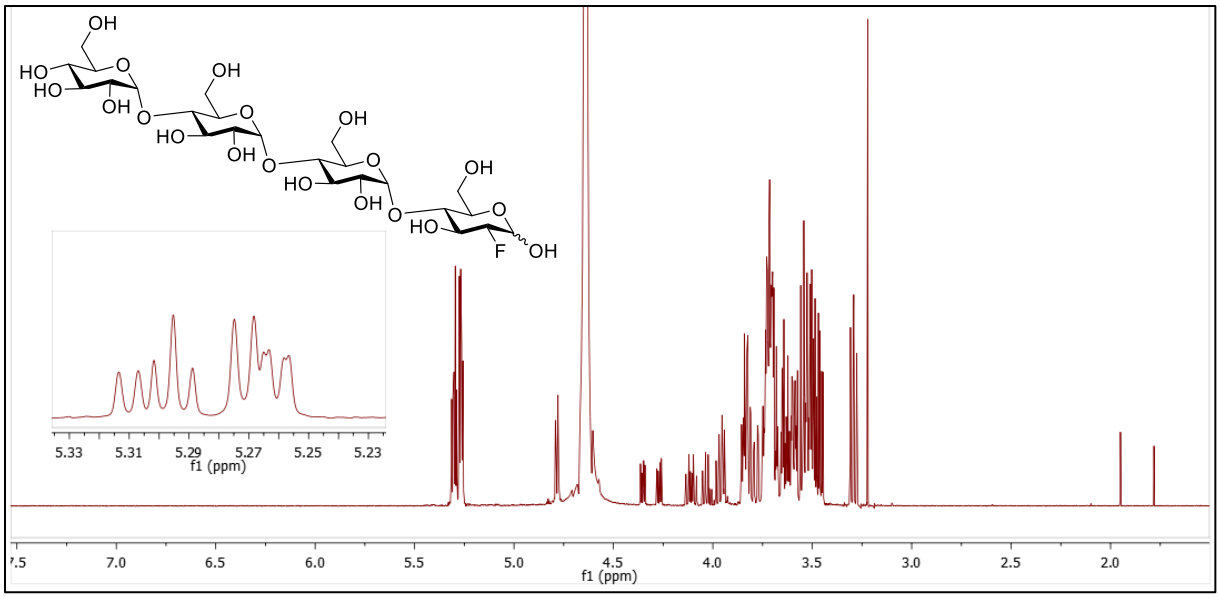
^{13}C NMR (151 MHz, $CDCl_3$)



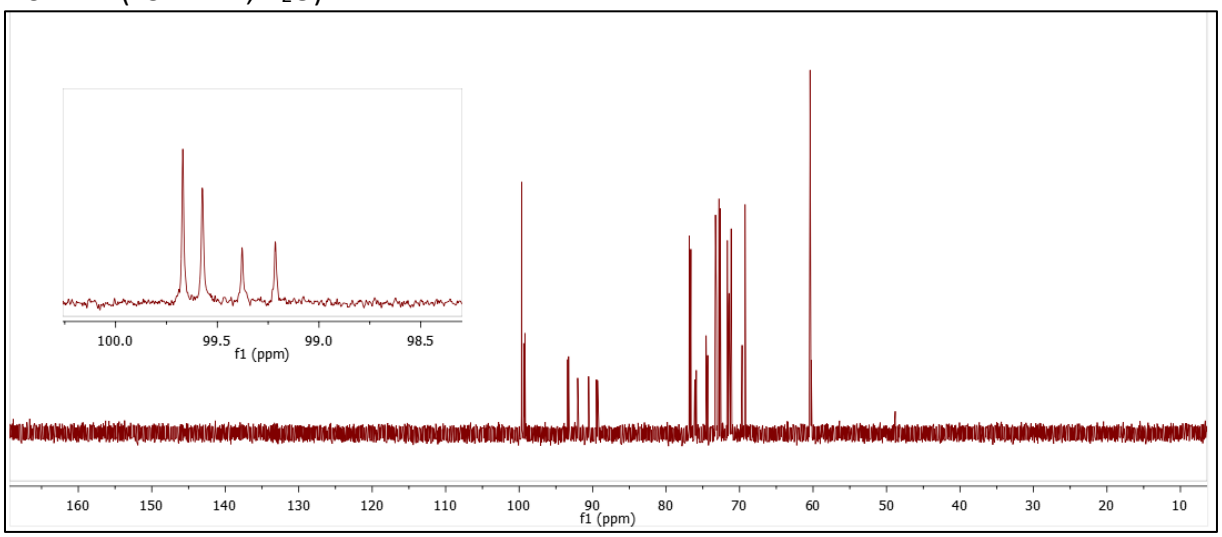
^{19}F NMR (564 MHz, $CDCl_3$)



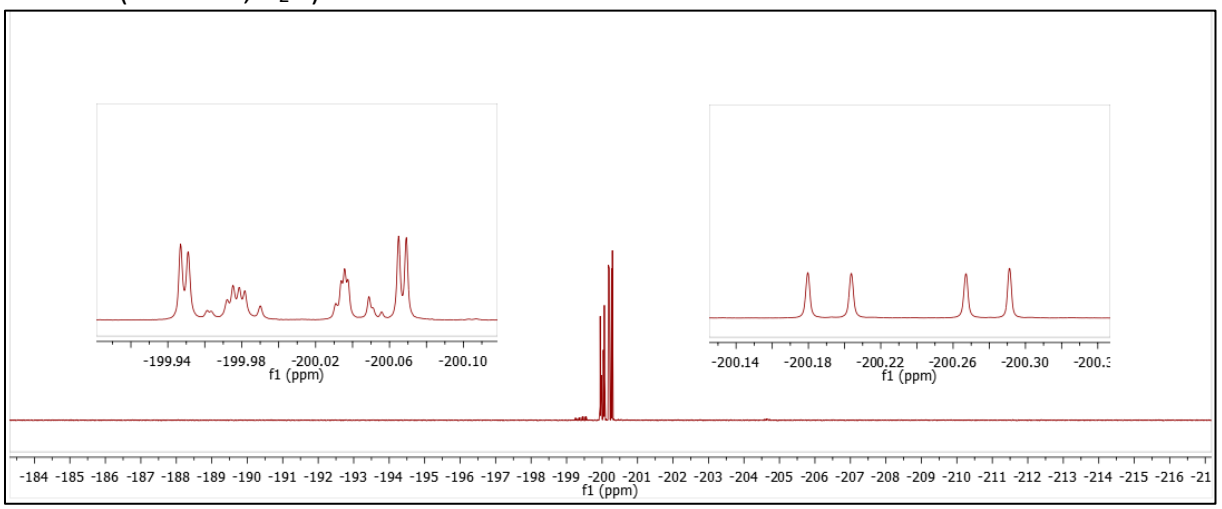
^{1}H NMR (600 MHz, D_2O)



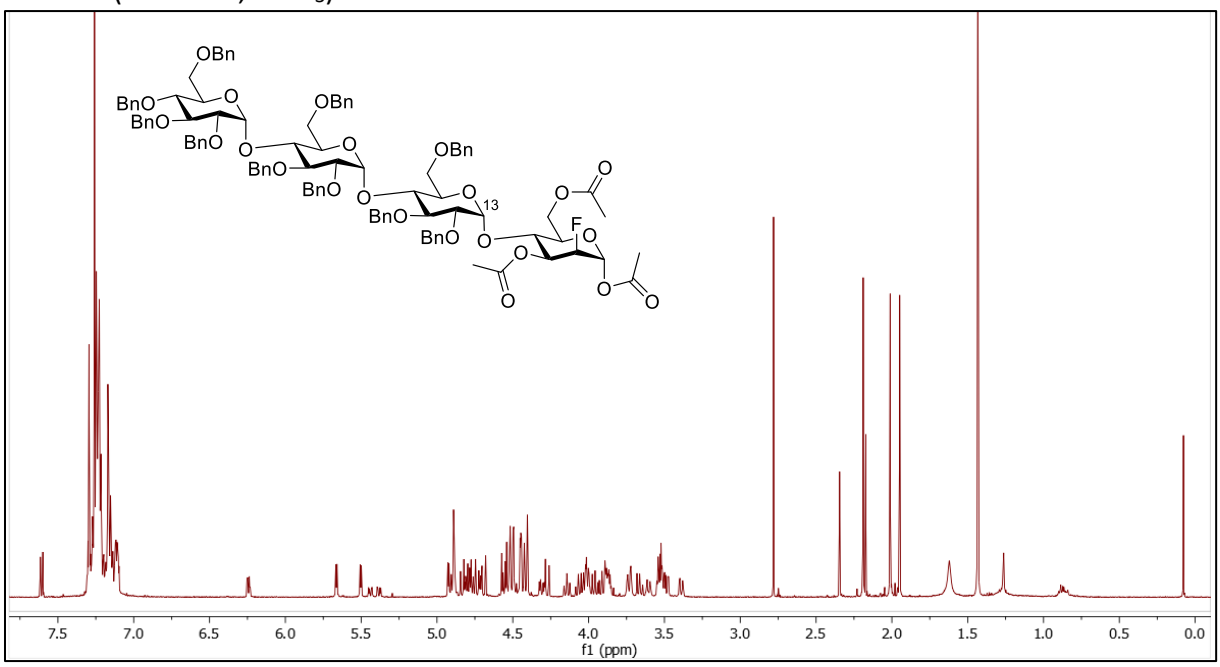
^{13}C NMR (151 MHz, D_2O)



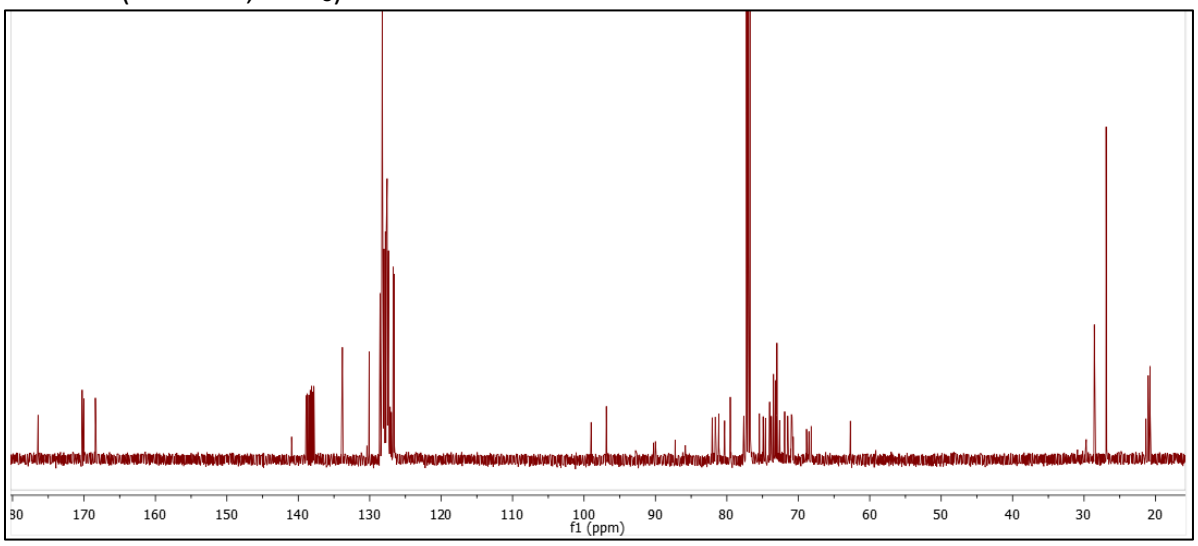
^{19}F NMR (564 MHz, D_2O)



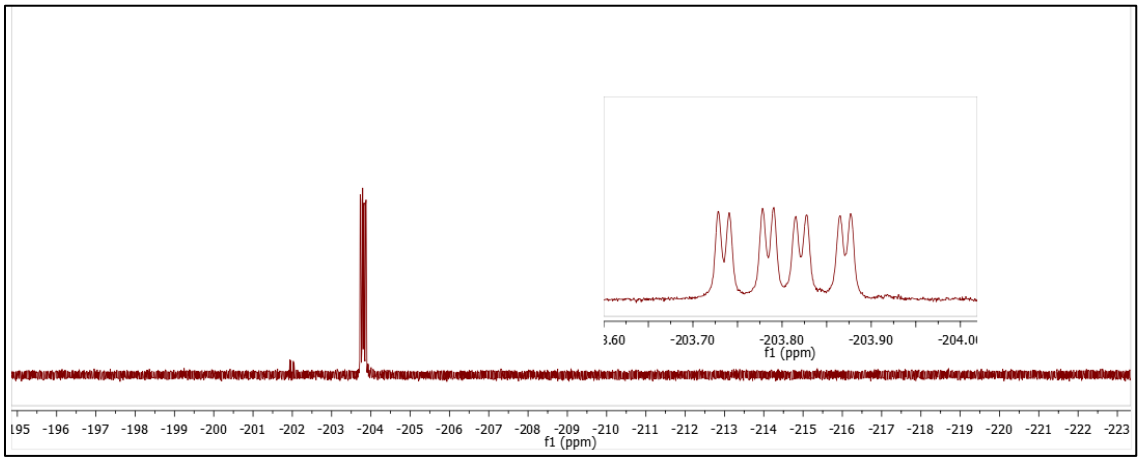
^{1}H NMR (500 MHz, $CDCl_3$)



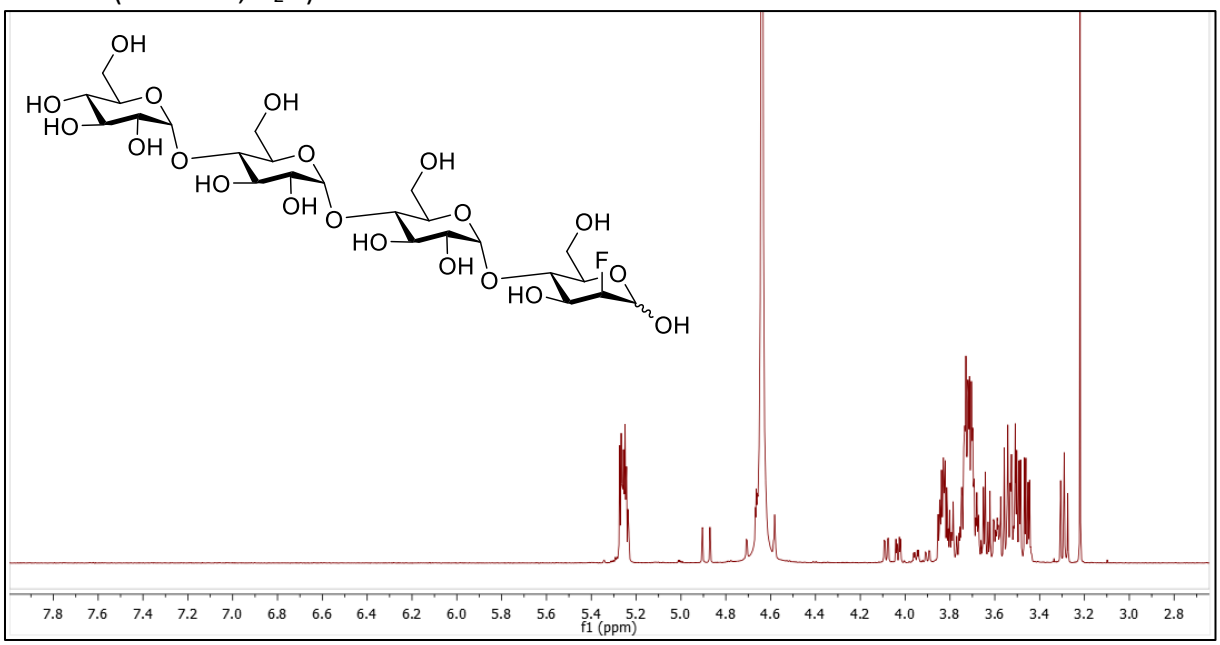
^{13}C NMR (126 MHz, $CDCl_3$)



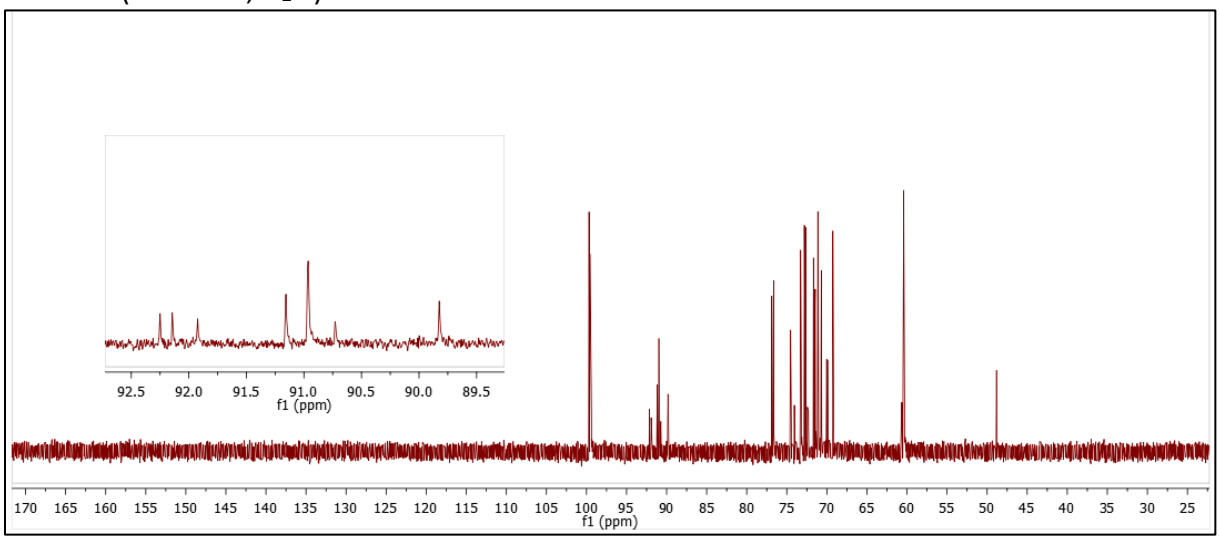
^{19}F NMR (564 MHz, $CDCl_3$)



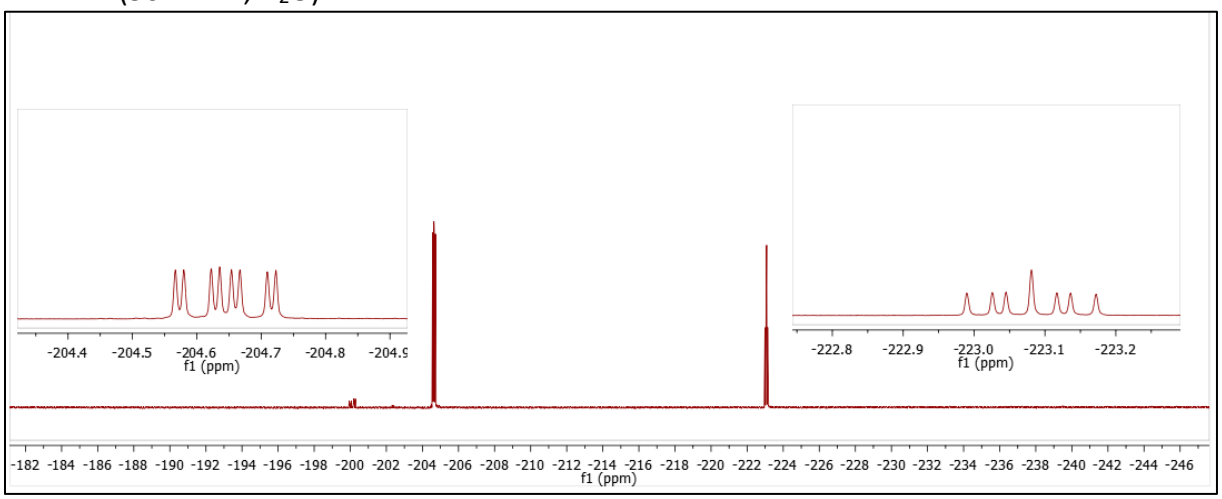
^{1}H NMR (600 MHz, D_2O)



^{13}C NMR (151 MHz, D_2O)



^{19}F NMR (564 MHz, D_2O)



5 Enzyme Assays

Enzymes and substrates: α-Amylase from porcine pancreas Type VI-B (EC 3.2.1.1; Lot no. SLBW1525), and α-glucosidases from *Saccharomyces cerevisiae* Type I (EC 3.2.1.20; Type VI; Lot no. SLBX6245) were obtained from Merck KGaA, Darmstadt, Germany. Enzymes were used without further purification in the kinetic studies. Maltotetraose was purchased from Biosynth Carbosynth Ltd.; Berkshire, United Kingdom. Maltotetraose derivatives were synthesized as described above. One unit is defined as the amount of enzyme required to liberate 1 µmol of glucose from maltotetraose per min at 37 °C.

Enzyme method: The stability of maltotetraose and five derivatives in murine (A) and human (B) serum (each pool of three different samples) was monitored by determining the liberation of glucose after incubation at 37 °C .For this purpose, 20 µL maltotetraose solution (20 mg/mL in water) or one of the derivatives was added to 200 µL serum at 37 °C. After incubation for 0, 10, 30, 120, 300 min, glucose levels were tested in 0.6 µL serum with a point-of-care glucose meter (ACCU-CHEK®-Inform II; Roche Diagnostics GmbH, modified glucose dehydrogenase electrochemical detection technique) using D-glucose as standard. Heat-inactivated serum (60 °C, 1 h) with 2000 U/L α-amylase (C) or 10 U/L acid-α-glucosidase (pH 4) (D) was incubated at 37 °C with 1 mg/mL maltotetraose or derivatives for 5, 30 and 60 min. The formation of glucose was analyzed according to the first experiment. Incubations were carried out in 1.5-mL microcentrifuge tubes in a shaking heating block thermostat (MHR23, HLC-Biotech, Bovenden, Germany) at 37 °C.

Linear-regression analysis of glucose formation as a function of time was performed with the software OriginPro/EnzymeKinetics from Originlab Corporation, Wellesley Hills, USA). Also this program was used for the determination of the kinetic parameters K_m and v_{max} to fit the initial rate data as a function of substrate concentration to the Michaelis–Menten equation. Five substrate concentrations were used ranging from approximately 0.2 to 6 times K_m.

Values of k_{cat} were determined by dividing v_{max} values by enzyme concentration using a molecular weight of 53,000 (amylase) and 63,000 (glucosidase). The catalyzed degradation of

maltotetraose was initiated by addition of 50–5000 Units and 1–100 U enzyme, respectively. Two S_o concentrations of around 0.1 × K_m were used to ensure that substrate hydrolysis was linear with time.

The kinetic parameters for the hydrolysis of compounds by α-amylase and α-glucosidase are summarized in Table 1. These were performed by quantitating the glucose formed as a reaction product using glucose dehydrogenase electrochemical detection technique.

Table.1: Key kinetic parameters and ΔΔ*G*‡ for hydrolysis of maltotetraose and derivates

Enzyme/Substrate	V_{max} (mM x U^{-1}x s^{-1})/ K_m (mM)	ΔΔG‡ (kJ x mol^{-1})
α-glucosidase		
substrate 1	4 x 10^{-4}	-
substrate 2	3.8 x 10^{-5}	1.9
substrate 3	2.1 x 10^{-5}	26.5
substrate 4	0.3 x 10^{-5}	29.2
substrate 5	1.5 x10^{-9}	52.2
substrate 6	2.7 x10^{-7}	48.2
α-amylase		
substrate 1	7.7 x 10^{-3}	-
substrate 2	3.1 x 10^{-4}	2.8
substrate 3	2.6 x 10^{-4}	23.4
substrate 4	3.8 x 10^{-4}	24.6
substrate 5	8.9 x10^{-4}	27.2
substrate 6	7.6 x10^{-4}	29.7

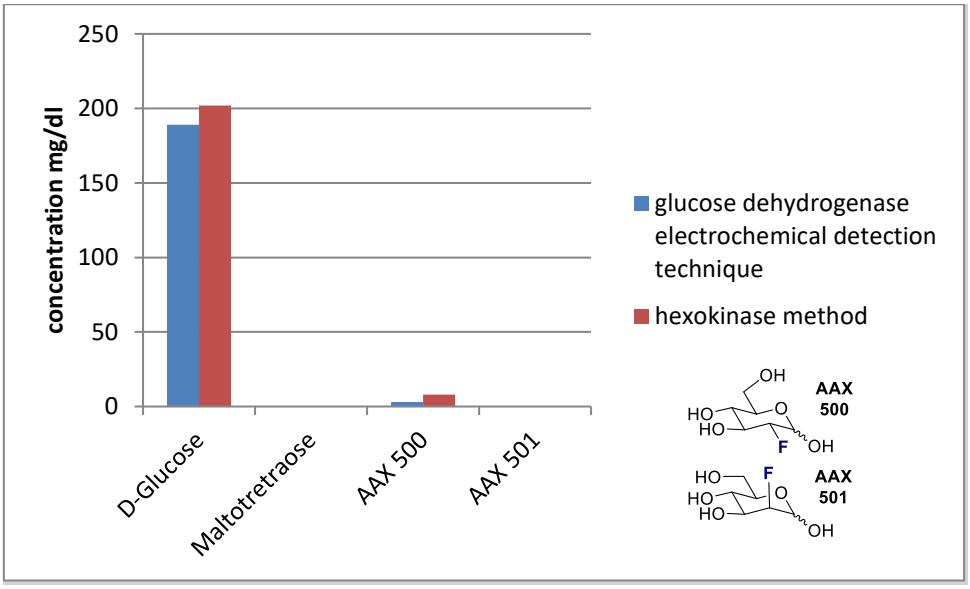
v_{max}/K_m ($s^{-1}\cdot U^{-1}$) = v_o/E_oS_o,; v_o initial reaction rate of hydrolysis , E_o enzyme amount in Units, S_o initial substrate concentration, determination at 37 °C in heat inactivated serum

$\Delta\Delta G‡=-RT\ln[(V_{max}/K_m)_{derivative}/(V_{max}/K_m)_{Maltotetraose}]$= activation energy increase due to the modified substrate (R gas constant; T absolute temperature) according to (Ref. 9)

v_{max} (the maximum reaction rate) and K_m (Michaelis constant; parameter of the enzyme's affinity for the substrate) were determined by fitting initial rates at different substrate concentrations from 0.1×K_m to 4×K_m to the Michaelis–Menten equation (2)

ΔΔG‡ resulted from v_{max}/K_m values quantified the energy contribution for stabilization the transitional state for a given probe in comparison to the model substrate **1**. ΔΔG‡ for the two fluoride-analogs at the non-reducing sugar ring (**3,4**) was in the range 23.1–29.2 kJ·mol−1 and for the fluorinated conjugates (**5,6**) between 27.2–52.2 kJ•mol^{-1} for the α-glucosidase and for

α-amylase (Tab. 1); the removal of the OH-group (**2**) from the non-reducing site decreased substrate hydrolysis for α-glucosidase and also for α-amylase.



A solution of 200mg/dl D-Glucose, Maltotetraose and the derivative AAX 500, 501 were measured with a point-of-care glucose meter (ACCU-CHEK®-Inform II; modified glucose dehydrogenase electrochemical detection technique) and with the hexokinase reference method with a Roche Cobas c702 chemistry analyzer, (both Roche Diagnostics GmbH, Mannheim, Germany).

6 X-ray Crystallographic Data

Table 1: Data collection and refinement statistics

	Alpha-Amylase
Data collection	
Space group	P 21 21 21
Cell dimensions	
a, *b*, *c* (Å)	51.87 72.73 135.21
α, β, γ (°)	90.00 90.00 90.00
Resolution (Å)	67.61 – 1.40 (1.48 – 1.40)
R_{merge}	0.043 (0.616)
$I / \sigma I$	17.8 (2.9)
Completeness (%)	99.8 (100.0)
Redundancy	6.3 (6.3)
Refinement	
Resolution (Å)	48.43 – 1.40
No. reflections	102448 (10138)
R_{work} / R_{free}	0.1420 / 0.1542
No. atoms	4436
Protein	3964
Ligand/ion	106
Water	366
B-factors	23.78
Protein	22.09
Ligand/ion	50.42
Water	34.34
R.m.s. deviations	
Bond lengths (Å)	0.012
Bond angles (°)	1.29

*Values in parentheses are for highest-resolution shell.

7 Literature

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