

Supporting information

**First and Stereoselective Synthesis of an α -(2 \rightarrow 5)-Linked Disaccharide of
3-Deoxy-D-*manno*-oct-2-ulosonic Acid (Kdo)**

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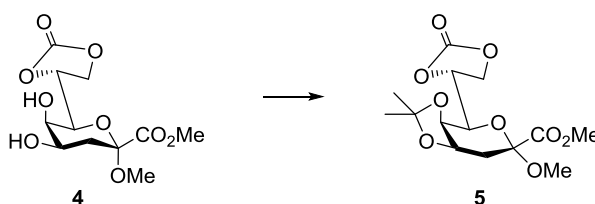
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1. General

All purchased chemicals were used without further purification unless stated otherwise. Solvents were dried over activated 4 Å (CH₂Cl₂, DMF, pyridine, toluene, acetone) molecular sieves. 2-Propanol for glycosylation was dried over 5 Å molecular sieves for 24 h. Anhydrous MeOH (secco solv) was purchased from Merck. Cation exchange resin DOWEX 50 H⁺ was regenerated by consecutive washing with HCl (3 M), water and anhydrous MeOH. Aqueous solutions of salts were saturated unless stated otherwise. Concentration of organic solutions was performed under reduced pressure < 40 °C. Optical rotations were measured with a Perkin-Elmer 243 B Polarimeter. $[\alpha]_D^{20}$ values are given in units of 10⁻¹deg cm²g⁻¹. Thin layer chromatography was performed on Merck precoated plates: generally on 5 x 10 cm, layer thickness 0.25 mm, Silica Gel 60F₂₅₄; alternatively on HP-TLC plates with 2.5 cm concentration zone (Merck). Spots were detected by dipping reagent (anisaldehyde-H₂SO₄). For column chromatography silica gel (0.040 – 0.063 mm) was used. HP-column chromatography was performed on a pre-packed column (YMC-Pack SIL-06, 0.005 mm, 250x20 mm). Size exclusion chromatography was performed on Bio-Gel® P-2 Gel extra fine < 45 μm (wet) (1 x 30 cm) and on pre-packed PD-10 columns (GE Healthcare, Sephadex™ G-25 M). NMR spectra were recorded with a Bruker Avance III 600 instrument (600.22 MHz for ¹H, 150.93 MHz for ¹³C and 564.77 MHz for ¹⁹F) at 300.15 K using standard Bruker NMR software unless stated otherwise. Alternatively, spectra were recorded with a Bruker DPX 300 instrument (300.13 MHz for ¹H, 75.47 MHz for ¹³C). ¹H NMR spectra were referenced to 7.26 (CDCl₃), 3.31 (MeOD), 2.08 (d₈-toluene) and 0.00 (D₂O, external calibration to 2,2-dimethyl-2-silapentane-5-sulfonic acid) ppm. ¹³C NMR spectra were referenced to 77.00 (CDCl₃), 49.00 (MeOD), 20.43 (d₈-toluene) and 67.40 (D₂O, external calibration to 1,4-dioxane) ppm. ¹⁹F NMR spectra were indirectly referenced according to IUPAC recommendations^{S1}. ESI-MS data were obtained on a Waters Micromass Q-TOF Ultima Global instrument.

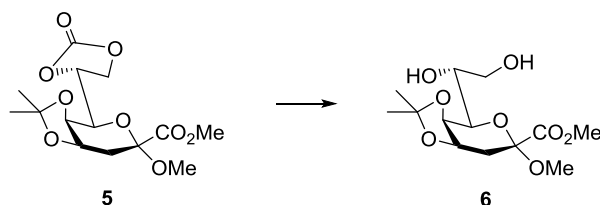
2. Synthesis and characterization of compounds

2.1 Methyl (methyl 7,8-*O*-carbonyl-3-deoxy-4,5-*O*-isopropylidene- α -D-manno-oct-2-ulopyranosid)onate (5)



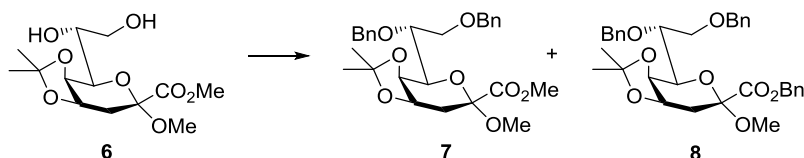
A solution of the known 7,8-O-carbonyl derivative **4**^{S2} (0.37 g, 1.27 mmol) in anhydrous CH₂Cl₂ (32 mL) and anhydrous acetone (0.65 mL) was treated with TMSOTf (0.29 mL, 1.58 mmol) at 0 °C under an atmosphere of argon. After 4 h at 0 °C triethylamine (0.4 mL) was added dropwise and after complete addition the solution was stirred for 10 min. The mixture was diluted with CH₂Cl₂ and washed with aq. NaHCO₃. The organic phase was dried (MgSO₄), filtered and concentrated. Filtration of the residue over silica gel (EtOAc) afforded **5** (0.40 g, 95%) as a colorless oil; [α]_D²⁰ + 71.5 (*c* 0.99, CHCl₃); R_f 0.51 (toluene/EtOAc 1:2); ¹H NMR (CDCl₃): δ 4.94 (ddd, 1H, *J*_{7,8b} 8.3, *J*_{7,8a} 7.0, *J*_{7,6} 3.3 Hz, H-7), 4.80 (dd, 1H, *J*_{8a,8b} 9.0 Hz, H-8a), 4.55 - 4.50 (m, 2H, H-4, H-8b), 4.21 (dd, 1H, *J*_{5,4} 7.6, *J*_{5,6} 2.0 Hz, H-5), 3.99 (dd, 1H, H-6), 3.78 (s, 3H, CO₂CH₃), 3.21 (s, 3H, OCH₃), 2.74 (dd, 1H, *J*_{3a,3b} 15.5, *J*_{3a,4} 4.4 Hz, H-3a), 1.88 (dd, 1H, *J*_{3b,4} 3.4 Hz, H-3b), 1.39 [s, 3H, C(CH₃)], 1.26 [s, 3H, C(CH₃)]; ¹³C NMR (CDCl₃): δ 168.69 (s, C-1), 154.67 [s, O(C=O)O], 109.95 [s, C(CH₃)₂], 97.78 (s, C-2), 75.53 (d, C-7), 71.63 (d, C-5), 70.00 (d, C-4), 69.61 (d, C-6), 65.86 (t, C-8), 52.45 (q, CO₂CH₃), 50.85 (q, OCH₃), 32.79 (t, C-3), 25.25 [q, C(CH₃)], 24.57 [q, C(CH₃)]; ESI-TOF HRMS: *m/z* = 350.1464; calcd for C₁₄H₂₀O₉NH₄⁺: 350.1446.

2.2 Methyl (methyl 3-deoxy-4,5-*O*-isopropylidene- α -D-manno-oct-2-ulopyranosid)onate (**6**)



A solution of 0.1 M methanolic sodium methoxide (4.0 mL, 0.40 mmol) was added dropwise to a solution of **5** (0.40 g, 1.20 mmol) in anhydrous MeOH (15 mL) and the mixture was stirred 14 h at ambient temperature. The solution was treated with ion exchange resin DOWEX 50 (H⁺ form) to give a neutral pH. The resin was filtered off, and concentration of the filtrate afforded pure **6**^{S3} (0.36 g, 97%) as a colorless oil; [α]_D²⁰ + 64.5 (*c* 1.16, CHCl₃); R_f 0.29 (toluene/EtOAc 1:2); ¹H NMR (MeOD): δ 4.51 (ddd, 1H, *J*_{4,5} 7.6, *J*_{4,3a} 4.1, *J*_{4,3b} 2.9 Hz, H-4), 4.38 (dd, 1H, *J*_{5,6} 1.8 Hz, H-5), 3.91 (ddd, 1H, *J*_{7,6} 8.9, *J*_{7,8b} 5.5, *J*_{7,8a} 2.9 Hz, H-7), 3.84 (dd, 1H, *J*_{8a,8b} 11.3 Hz, H-8a), 3.75 (s, 3H, CO₂CH₃), 3.65 (dd, 1H, H-8b), 3.62 (dd, 1H, H-6), 3.18 (s, 3H, OCH₃), 2.61 (dd, 1H, *J*_{3a,3b} 15.2 Hz, H-3a), 1.90 (dd, 1H, H-3b), 1.37 [s, 3H, C(CH₃)], 1.30 [s, 3H, C(CH₃)]; ¹³C NMR (MeOD, 75 MHz): δ 171.10 (s, C-1), 110.13 [s, C(CH₃)₂], 99.29 (s, C-2), 73.12 (d, C-5), 71.67 (d, C-6), 71.51 (d, C-4), 70.94 (d, C-7), 64.67 (t, C-8), 52.78 (q, CO₂CH₃), 50.97 (q, OCH₃), 33.79 (t, C-3), 26.09 [q, C(CH₃)], 25.12 [q, C(CH₃)]; ESI-TOF HRMS: *m/z* = 324.1655; calcd for C₁₃H₂₂O₈NH₄⁺: 324.1653.

2.3 Methyl (methyl 7,8-di-*O*-benzyl-3-deoxy-4,5-*O*-isopropylidene- α -D-manno-oct-2-ulo-pyranosid)onate (7) and benzyl (methyl 7,8-di-*O*-benzyl-3-deoxy-4,5-*O*-isopropylidene- α -D-manno-oct-2-ulo-pyranosid)onate (8)



NaH (0.18 g, 4.60 mmol) was added in small portions at 0 °C to a solution of **6** (0.35 g, 1.15 mmol) in anhydrous DMF (14 mL). After complete addition the mixture was stirred at 0 °C for 30 min. Then, BnBr (0.55 mL, 4.60 mmol) was added dropwise and after 3 h at ambient temperature the mixture was cooled to 0 °C and diluted with anhydrous CH₂Cl₂. Anhydrous MeOH (1.0 mL) was added dropwise and after completed addition the mixture was immediately subjected to extraction with CH₂Cl₂ and aq. NaHCO₃. The organic phase was dried (MgSO₄), filtered and concentrated. Column chromatography (SiO₂, toluene/EtOAc 15:1) afforded partly separated^{S4} methyl ester **7** and benzyl ester **8** (0.33 g; **7**: 54%; **8**: 5%) as colorless oils. Additionally, a mixture of different mono-benzylated compounds could be isolated (~18%).

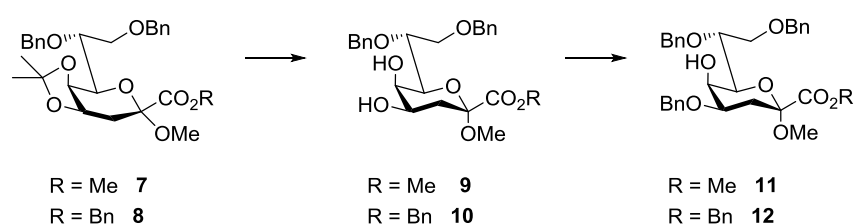
To improve the yield, **6** (22.0 mg, 0.072 mmol) was dissolved in anhydrous DMF (1.0 mL) and treated with NaH (17 mg, 0.431 mmol) at ambient temperature for 30 min. After dropwise addition of BnBr (51 μ L, 0.431 mmol), the mixture was stirred for 5 h before it was cooled to 0 °C and diluted with anhydrous CH₂Cl₂. MeOH (0.1 mL) was added dropwise followed by immediate extraction with CH₂Cl₂ and aq. NaHCO₃. The organic phase was further washed with brine, dried (MgSO₄), filtered and concentrated. Column chromatography (SiO₂, toluene/EtOAc 15:1) provided benzyl ester **8** (13.3 mg, 33%) and methyl ester **7** (16.1 mg, 46%) as a mixture. Thus, by increasing the amount of NaH and BnBr from 2 eq. to 3 eq./ free hydroxyl group and performing deprotonation with NaH at ambient temperature instead of 0 °C monobenzylation could be avoided and the yield was increased from 59% to 79%.

8: [α]_D²⁰ + 31.7 (*c* 0.74, CHCl₃); R_f 0.57 (toluene/EtOAc 5:1); ¹H NMR (CDCl₃): δ 7.41 - 7.25 (m, 15H, Ar), 5.25 (d, 1H, *J* 12.4 Hz, CHHPh), 5.20 (d, 1H, *J* 12.4 Hz, CHHPh), 4.75 (d, 1H, *J* 11.1 Hz, CHHPh), 4.65 (d, 1H, *J* 11.1 Hz, CHHPh), 4.59 (d, 1H, *J* 12.1 Hz, CHHPh), 4.55 (d, 1H, *J* 12.1 Hz, CHHPh), 4.48 (ddd, 1H, *J*_{4,5} 7.0, *J*_{4,3a} 5.5, *J*_{4,3b} 4.1 Hz, H-4), 4.40 (dd, 1H, *J*_{5,6} 2.0 Hz, H-5), 4.00 (ddd, 1H, *J*_{7,6} 9.4, *J*_{7,8b} 4.2, *J*_{7,8a} 2.1 Hz, H-7), 3.91 (dd, 1H, H-6), 3.82 (dd, 1H, *J*_{8a,8b} 10.5 Hz, H-8a), 3.73 (dd, 1H, H-8b), 3.09 (s, 3H, OCH₃), 2.50 (dd, 1H, *J*_{3a,3b} 14.8 Hz, H-3a), 1.97 (dd, 1H, H-3b), 1.39 [s, 3H, C(CH₃)], 1.32 [s, 3H, C(CH₃)]; ¹³C NMR (CDCl₃): δ 168.17 (s, C-1), 138.60, 138.44 and 135.54 (3 x s, 3C, Ar), 128.46, 128.35, 128.27, 128.20, 128.07, 127.57, 127.54 and 127.43 (8 x d, 15C, Ar), 108.96 [s, C(CH₃)₂], 98.20 (s, C-2), 76.65 (d, C-7), 73.39 (t, CH₂Ph), 72.97 (t, CH₂Ph), 71.38 (d, C-5), 70.08 (d, C-4), 69.30 (t, C-8), 68.74 (d, C-6), 66.99 (t, CH₂Ph), 50.61 (q, OCH₃), 33.43 (t, C-3),

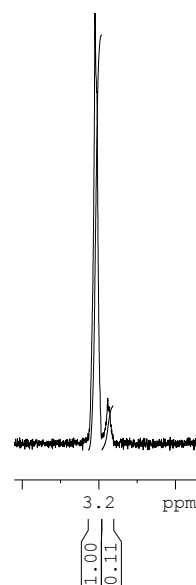
26.35 [q, C(CH₃)], 25.43 [q, C(CH₃)]; ESI-TOF HRMS: m/z = 585.2457; calcd for C₃₃H₃₈O₈Na⁺: 585.2459.

7: [α]_D²⁰ + 33.0 (*c* 0.84, CHCl₃); R_f 0.45 (toluene/EtOAc 5:1); ¹H NMR (CDCl₃): δ 7.37 - 7.25 (m, 10H, Ar), 4.75 (d, 1H, *J* 11.2 Hz, CHHPh), 4.65 (d, 1H, *J* 11.2 Hz, CHHPh), 4.61 (d, 1H, *J* 12.2 Hz, CHHPh), 4.57 (d, 1H, *J* 12.2 Hz, CHHPh), 4.48 (ddd, 1H, *J*_{4,5} 7.1, *J*_{4,3a} 5.3, *J*_{4,3b} 3.9 Hz, H-4), 4.41 (dd, 1H, *J*_{5,6} 1.9 Hz, H-5), 4.00 (ddd, 1H, *J*_{7,6} 9.6, *J*_{7,8b} 4.3, *J*_{7,8a} 2.0 Hz, H-7), 3.91 (dd, 1H, H-6), 3.82 (dd, 1H, *J*_{8a,8b} 10.4 Hz, H-8a), 3.78 (s, 3H, CO₂CH₃), 3.74 (dd, 1H, H-8b), 3.15 (s, 3H, OCH₃), 2.50 (dd, 1H, *J*_{3a,3b} 14.8 Hz, H-3a), 1.95 (dd, 1H, H-3b), 1.44 [s, 3H, C(CH₃)], 1.33 [s, 3H, C(CH₃)]; ¹³C NMR (CDCl₃): δ 169.04 (s, C-1), 138.57 and 138.43 (2 x s, 2C, Ar), 128.27, 128.21, 128.09, 127.60, 127.56 and 127.46 (6 x d, 10C, Ar), 108.95 [s, C(CH₃)₂], 98.32 (s, C-2), 76.60 (d, C-7), 73.42 (t, CH₂Ph), 72.99 (t, CH₂Ph), 71.39 (d, C-5), 70.05 (d, C-4), 69.26 (t, C-8), 68.81 (d, C-6), 52.35 (q, CO₂CH₃), 50.67 (q, OCH₃), 33.52 (t, C-3), 26.28 [q, C(CH₃)], 25.36 [q, C(CH₃)]; ESI-TOF HRMS: m/z = 509.2143; calcd for C₂₇H₃₄O₈Na⁺: 509.2146.

2.4 Methyl (methyl 4,7,8-tri-*O*-benzyl-3-deoxy- α -D-manno-oct-2-ulopyranosid)onate (**11**) and benzyl (methyl 4,7,8-tri-*O*-benzyl-3-deoxy- α -D-manno-oct-2-ulopyranosid)onate (**12**)



The 9:1 (ratio derived by ¹H NMR) mixture of **7** and **8** (0.37 g, 0.756 mmol) was dissolved in anhydrous MeOH (15 mL) and treated with *p*-toluenesulfonic acid (0.03 g, 0.15 mmol) at ambient temperature for 18 h. Triethylamine (0.3 mL) was added dropwise and after 10 min the solvent was removed *in vacuo*. Silica gel filtration of the residue using 5:1 toluene/EtOAc (to elute traces of remaining starting material) followed by 9:1 EtOAc/EtOH provided a mixture of **9** and **10** (0.31 g, 90%) as a colorless oil.



A solution of this mixture (0.31 g, 0.680 mmol) in anhydrous toluene (10 mL) containing dibutyltin oxide (0.19 g, 0.75 mmol) was refluxed in a Dean-Stark apparatus for 3 h. The solution was allowed to cool to room temperature before BnBr (0.40 mL, 3.39 mmol), tetra-*n*-butylammonium iodide (0.28 g,

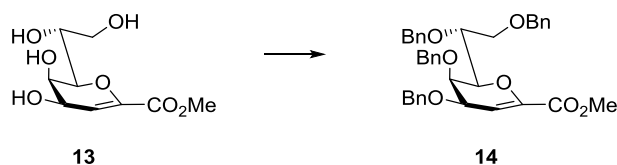
0.75 mmol) and anhydrous DMF (1.05 mL, 13.55 mmol) were added successively and the mixture was kept at 60 °C for 14 h. The mixture was cooled to rt, then diluted with EtOAc and washed sequentially with 1 M aq. HCl, aq. NaHCO₃, aq. Na₂S₂O₃ (5 w/w%) and brine. The organic layer was dried (MgSO₄), filtered over Celite and concentrated. The crude mixture was purified by column chromatography (SiO₂, toluene/EtOAc 9:1→5:1) yielding **12** (0.04 g, 8%) as the faster migrating compound followed by **11** (0.21 g, 52%). Yields were calculated for 2 steps and were based on the relative amounts of **7** and **8** in the mixture.

To obtain the methyl ester **11** from benzyl ester **12**, the latter compound (22 mg, 0.036 mmol) was treated with a 0.1 M methanolic sodium methoxide (0.43 mL, 0.043 mmol) in anhydrous MeOH (2 mL) under argon for 2 h. Neutralization of the solution by addition of ion exchange resin DOWEX 50 (H⁺ form), filtration and concentration of the filtrate gave a residue which was subjected to elution on silica gel (toluene/EtOAc 5:1) affording the methyl ester **11** (19 mg, 98%)

12: colorless oil; [α]_D²⁰ + 35.5 (*c* 0.63, CHCl₃); R_f 0.20 (toluene/EtOAc 9:1); ¹H NMR (CDCl₃): δ 7.38 - 7.26 (m, 20H, Ar), 5.25 (d, 1H, *J* 12.4 Hz, CHHPh), 5.20 (d, 1H, *J* 12.4 Hz, CHHPh), 4.73 (d, 1H, *J* 11.5 Hz, CHHPh), 4.68 (d, 1H, *J* 11.5 Hz, CHHPh), 4.58 (s, 2H, CH₂Ph), 4.56 (d, 1H, *J* 12.3 Hz, CHHPh), 4.51 (d, 1H, *J* 12.3 Hz, CHHPh), 4.23 - 4.20 (m, 1H, H-5), 4.02 (ddd, 1H, *J*_{7,6} 8.6, *J*_{7,8b} 3.8, *J*_{7,8a} 3.1 Hz, H-7), 3.88 (ddd, 1H, *J*_{4,3ax} 11.7, *J*_{4,3eq} 5.0, *J*_{4,5} 2.8 Hz, H-4), 3.80 (dd, 1H, *J*_{6,5} 0.9 Hz, H-6), 3.78 (dd, 1H, *J*_{8a,8b} 10.6 Hz, H-8a), 3.72 (dd, 1H, H-8b), 3.14 (s, 3H, OCH₃), 2.38 - 2.35 (m, 1H, OH), 2.23 - 2.18 (m, 1H, H-3eq), 2.04 (dd, 1H, *J*_{3ax,3eq} 12.8 Hz, H-3ax); ¹³C NMR (CDCl₃, 75 MHz): δ 167.86 (s, C-1), 138.34, 138.22, 137.93 and 135.40 (4 x s, 4C, Ar), 128.57, 128.50, 128.38, 128.33, 128.30, 128.19, 128.07, 127.84, 127.69, 127.64 and 127.54 (11 x d, 20C, Ar), 99.15 (s, C-2), 76.15 (d, C-7), 73.37 (t, CH₂Ph), 73.28 (d, C-4), 73.03 (t, CH₂Ph), 70.32 (t, CH₂Ph), 70.22 (d, C-6), 68.58 (t, C-8), 67.08 (t, CH₂Ph), 63.93 (d, C-5), 50.94 (q, OCH₃), 32.08 (t, C-3); ESI-TOF HRMS: *m/z* = 635.2619; calcd for C₃₇H₄₀O₈Na⁺: 635.2615.

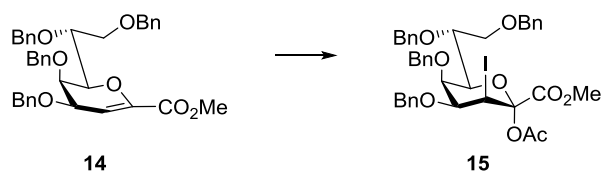
11: colorless oil; [α]_D²⁰ + 39.4 (*c* 1.14, CHCl₃); R_f 0.10 (toluene/EtOAc 9:1); ¹H NMR (CDCl₃): δ 7.37 - 7.26 (m, 15H, Ar), 4.74 (d, 1H, *J* 11.3 Hz, CHHPh), 4.67 (d, 1H, *J* 11.3 Hz, CHHPh), 4.60 (d, 1H, *J* 11.9 Hz, CHHPh), 4.59 (d, 1H, *J* 12.1 Hz, CHHPh), 4.58 (d, 1H, *J* 11.9 Hz, CHHPh), 4.53 (d, 1H, *J* 12.1 Hz, CHHPh), 4.24 - 4.22 (m, 1H, H-5), 4.01 (ddd, 1H, *J*_{7,6} 8.9, *J*_{7,8b} 3.8, *J*_{7,8a} 2.8 Hz, H-7), 3.89 (ddd, 1H, *J*_{4,3ax} 11.6, *J*_{4,3eq} 5.0, *J*_{4,5} 2.8 Hz, H-4), 3.81 (d, 1H, H-6), 3.79 (s, 3H, CO₂CH₃), 3.78 (dd, 1H, *J*_{8a,8b} 10.5 Hz H-8a), 3.72 (dd, 1H, H-8b), 3.18 (s, 3H, OCH₃), 2.33 - 2.31 (m, 1H, OH), 2.21 - 2.17 (m, 1H, H-3eq), 2.03 (dd, 1H, *J*_{3ax,3eq} 12.7 Hz, H-3ax); ¹³C NMR (CDCl₃): δ 168.71 (s, C-1), 138.38, 138.26 and 137.95 (3 x s, 3C, Ar), 128.53, 128.36, 128.32, 128.10, 127.87, 127.72, 127.68 and 127.56 (8 x d, 15C, Ar), 99.31 (s, C-2), 76.05 (d, C-7), 73.39 (t, CH₂Ph), 73.18 (d, C-4), 73.01 (t, CH₂Ph), 70.31 (t, CH₂Ph), 70.23 (t, C-6), 68.55 (t, C-8), 63.98 (d, C-5), 52.53 (q, CO₂CH₃), 50.99 (q, OCH₃), 32.22 (t, C-3); ESI-TOF HRMS: *m/z* = 554.2744; calcd for C₃₁H₃₆O₈NH₄⁺: 554.2748.

2.5. Methyl 2,6-anhydro-4,5,7,8-tetra-*O*-benzyl-3-deoxy-*D*-manno-oct-2-enosonate (**14**)



A solution of glycal **13**^{S2} (0.30 g, 1.30 mmol) in anhydrous DMF (14.0 mL) was treated with NaH (60% dispersion in mineral oil; 0.42 g, 10.38 mmol) at 0 °C for 30 min. Benzyl bromide (1.23 mL, 10.38 mmol) was added dropwise and stirring at ambient temperature was continued for 2 h. At 0 °C the mixture was diluted with anhydrous CH₂Cl₂ (15 mL) and treated with anhydrous MeOH (1 mL). The reaction mixture was swiftly partitioned between CH₂Cl₂ and ice-cold 1 M aq. HCl, the aqueous phase was re-extracted with CH₂Cl₂ and the combined organic extracts were washed with aq. NaHCO₃ and brine successively. Drying (MgSO₄), filtration and concentration of the filtrate afforded a crude product which was purified by column chromatography (SiO₂, toluene/EtOAc 50:1 → 10:1) yielding **14** (0.60 g, 77%) as a colorless oil: $[\alpha]_D^{20} - 32.2$ (*c* 1.02, CHCl₃); *R*_f 0.81 (toluene/EtOAc 3:1); ¹H NMR (CDCl₃): δ 7.37 - 7.20 (m, 20H, Ar), 6.10 (app. t, 1H, *J*_{3,4} = *J*_{3,5} 2.1 Hz, H-3), 5.03 (d, 1H, *J* 11.6 Hz, *CHHP*h), 4.71 (d, 1H, *J* 12.0 Hz, *CHHP*h), 4.66 (d, 1H, *J* 11.3 Hz, *CHHP*h), 4.63 (d, 1H, *J* 12.0 Hz, *CHHP*h), 4.58 (s, 2H, *CH*₂Ph), 4.55 (d, 1H, *J* 11.6 Hz, *CHHP*h), 4.41 - 4.39 (m, 1H, H-4), 4.28 (d, 1H, *J* 11.3 Hz, *CHHP*h), 4.26 - 4.25 (m, 1H, H-5), 4.10 - 4.07 (m, 1H, H-6), 4.01 (ddd, 1H, *J*_{7,6} 9.3, *J*_{7,8b} 3.8, *J*_{7,8a} 2.1 Hz, H-7), 3.91 (dd, 1H, *J*_{8a,8b} 10.6 Hz, H-8a), 3.77 - 3.74 (m, 4H, H-8b, CO₂CH₃); ¹³C NMR (CDCl₃): δ 162.48 (s, C-1), 143.88 (s, C-2), 138.84, 138.41, 138.11 and 137.85 (4 x s, 4C, Ar), 128.48, 128.36, 128.30, 128.18, 127.91, 127.78, 127.70, 127.64, 127.49 and 127.36 (10 x d, 20C, Ar), 109.64 (d, C-3), 76.12 (d, C-6), 75.40 (d, C-7), 74.28 (t, *CH*₂Ph), 73.99 (d, C-4), 73.46 (t, *CH*₂Ph), 71.79 (t, *CH*₂Ph), 71.01 (t, *CH*₂Ph), 68.51 (d, C-5), 67.97 (t, C-8), 52.09 (q, CO₂CH₃); ESI-TOF HRMS: *m/z* = 612.2956; calcd for C₃₇H₃₈O₇NH₄⁺: 612.2956.

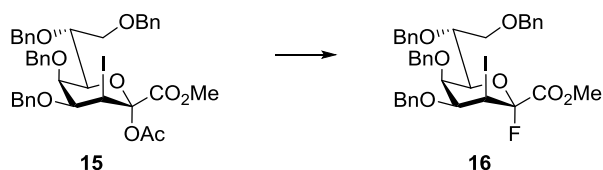
2.6. Methyl 2-*O*-acetyl-4,5,7,8-tetra-*O*-benzyl-3-deoxy-3-iodo-*D*-glycero- α -*D*-talo-oct-2-ulopyranosonate (**15**)



A solution of **14** (0.45 g, 0.755 mmol) in glacial acetic acid (30.0 mL) was treated with *N*-iodosuccinimide (0.48 g, 2.114 mmol) at ambient temperature for 1 h. The solution was poured onto ice-cold aq. sat. NaHCO₃ solution. After gas evolution had ceased, the aqueous phase was extracted with CHCl₃ (2 x). The combined organic phases were washed successively with aq. NaHCO₃, aq.

Na₂S₂O₃ (5 w/w%) and brine. The organic phase was dried (Na₂SO₄), filtered and concentrated. The crude product was purified by column chromatography to give the diaxial product **15** (0.49 g, 83%) as a colorless oil; $[\alpha]_D^{20} + 2.4$ (*c* 0.54, CHCl₃); R_f 0.37 (*n*-hexane/EtOAc 3:1); ¹H NMR (CDCl₃): δ 7.44 - 7.41 (m, 2H, Ar), 7.40 - 7.36 (m, 4H, Ar), 7.34 - 7.20 (m, 12H, Ar), 7.17 - 7.13 (m, 2H, Ar), 5.29 (d, 1H, *J* 11.5 Hz, CHHPH), 4.79 (d, 1H, *J* 11.6 Hz, CHHPH), 4.56 (dd, 1H, *J*_{3,4} 4.5, *J*_{3,5} 0.9 Hz, H-3), 4.53 (d, 1H, *J* 11.9 Hz, CHHPH), 4.50 - 4.45 (m, 3H, 1 x CHHPH, 2 x CHHPH), 4.35 (d, 1H, *J* 12.2 Hz, CHHPH), 4.27 - 4.23 (m, 2H, CHHPH, H-5), 4.15 - 4.11 (m, 1H, H-6), 4.02 - 3.99 (m, 1H, H-7), 3.87 (s, 3H, CO₂CH₃), 3.70 (dd, 1H, *J*_{8a,8b} 10.6, *J*_{8a,7} 2.0 Hz, H-8a), 3.62 - 3.58 (m, 2H, H-4, H-8b), 1.81 (s, 3H, COCH₃); ¹³C NMR (CDCl₃): δ 167.39 (s, COCH₃), 166.72 (s, C-1), 138.95, 138.57, 138.08 and 137.22 (4 x s, 4C, Ar), 128.53, 128.29, 128.23, 128.06, 127.94, 127.76, 127.67, 127.65, 127.61, 127.42 and 127.19 (11 x d, 20C, Ar), 99.24 (s, C-2), 75.12 (d, C-7), 74.08 (t, CH₂Ph), 73.78 (d, C-4), 73.00 (t, CH₂Ph), 71.99 (d, C-5), 71.72 (d, C-6), 71.61 (t, CH₂Ph), 70.29 (t, CH₂Ph), 66.27 (t, C-8), 52.98 (q, CO₂CH₃), 23.79 (d, C-3), 20.04 (q, COCH₃); ESI-TOF HRMS: *m/z* = 798.2134; calcd for C₃₉H₄₁IO₉NH₄⁺: 798.2134.

2.7. Methyl (4,5,7,8-tetra-*O*-benzyl-3-deoxy-3-iodo-*D*-glycero-*α*-*D*-talo-oct-2-ulopyranosyl)onate fluoride (**16**)



A solution of **15** (1.07 g, 1.37 mmol) in anhydrous CH₂Cl₂ (10.0 mL) was treated with hydrogen fluoride pyridine (ca. 70% HF, ca. 30% pyridine; 0.65 mL) at -15 °C and allowed to warm up to 0 °C over period of 1 h in a sealed Teflon flask. Ice-cold water (10 mL) was added, the phases were mixed thoroughly followed by separation. The aqueous phase was once again extracted with CH₂Cl₂ and the combined organic extracts were washed with aq. sat. NaHCO₃ solution, dried (MgSO₄), filtered and concentrated. The crude product was swiftly purified by flash chromatography (SiO₂, *n*-hexane/EtOAc 3:1) affording **16** (0.97 g, 96%) as a colorless oil; $[\alpha]_D^{20} - 9.5$ (*c* 0.47, CHCl₃); R_f 0.54 (toluene/EtOAc 9:1); ¹H NMR (CDCl₃): δ 7.44 - 7.20 (m, 18H, Ar), 7.18 - 7.15 (m, 2H, Ar), 5.30 (d, 1H, *J* 11.5 Hz, CHHPH), 4.78 (d, 1H, *J* 11.6 Hz, CHHPH), 4.70 (app. t, 1H, H-3), 4.62 (d, 1H, *J* 11.3 Hz, CHHPH), 4.57 (d, 1H, *J* 12.3 Hz, CHHPH), 4.50 (2d, 2H, *J* 11.9 Hz, 2 x CHHPH), 4.40 (d, 1H, *J* 11.6 Hz, CHHPH), 4.31 (dd, 1H, *J*_{6,7} 9.5, *J*_{6,5} 1.8 Hz, H-6), 4.28 - 4.25 (m, 2H, CHHPH, H-5), 4.09 - 4.06 (m, 1H, H-7), 3.87 (s, 3H, CO₂CH₃), 3.80 (dd, 1H, *J*_{8a,8b} 10.8, *J*_{8a,7} 2.0 Hz, H-8a), 3.68 (dd, 1H, *J*_{8b,7} 3.6 Hz, H-8b), 3.59 (dd, 1H, *J*_{4,3} 4.5, *J*_{4,5} 2.8 Hz, H-4); ¹³C NMR (CDCl₃): δ 164.37 (ds, *J*_{C-1,F} 28.9 Hz, C-1), 138.84, 138.35, 138.23 and 137.07 (4 x s, 4C, Ar), 128.56, 128.24, 128.20, 128.04, 128.01, 127.69, 127.64, 127.62, 127.55, 127.50, 127.40 and 127.15 (12 x d, 20C, Ar), 109.64 (ds, *J*_{C-2,F} 227.3 Hz, C-2),

75.48 (d, C-7), 74.06 (t, CH₂Ph), 73.39 (t, CH₂Ph), 73.13 (d, C-4), 72.99 (dd, $J_{C-6,F}$ 3.7 Hz, C-6), 72.01 (t, CH₂Ph), 71.92 (d, C-5), 70.44 (t, CH₂Ph), 67.70 (t, C-8), 53.18 (q, CO₂CH₃), 20.79 (dd, $J_{C-3,F}$ 31.8 Hz, C-3); ¹⁹F NMR (CDCl₃): δ -100.43 (d, $J_{F,H-3}$ 5.6 Hz); ESI-TOF HRMS: m/z = 763.1535; calcd for C₃₇H₃₈FIO₇Na⁺: 763.1538.

2.7.1. Epimerization

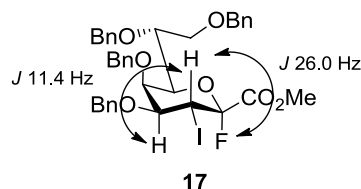


Figure S1: Structure of **17** with coupling constants $J_{H_{3ax}-H_4}$ and $J_{H_{3ax}-F_{ax}}$

When **15** was treated with a 10-fold amount of hydrogen fluoride pyridine (as described under 2.7) between 0 °C and ambient temperature, a ~2:1 mixture of **16** and the 3-iodo-epimer **17** (Fig. S1) was obtained after chromatography in significantly lower yield (~70%). The presence of two signals (-100.4 ppm for **16** and -124.1 ppm for **17**) in the ¹⁹F spectrum (Fig. S2) revealed two fluorinated species. The ¹H NMR spectrum (Fig. S3) showed a signal at 4.85 ppm of the minor compound split into a dd with $J_{H-3ax,F-ax} \sim 26.0$ Hz and $J_{H-3ax,4} \sim 11.4$ Hz. The large coupling constant confirmed the *trans*-diaxial relationship between H-3 and the anomeric fluoride, which was further supported by the large coupling between H-3 and the axial H-4. The carbon signal of C-3 at 26.6 ppm was identified by an HSQC experiment and confirmed the position of the iodo substituent.

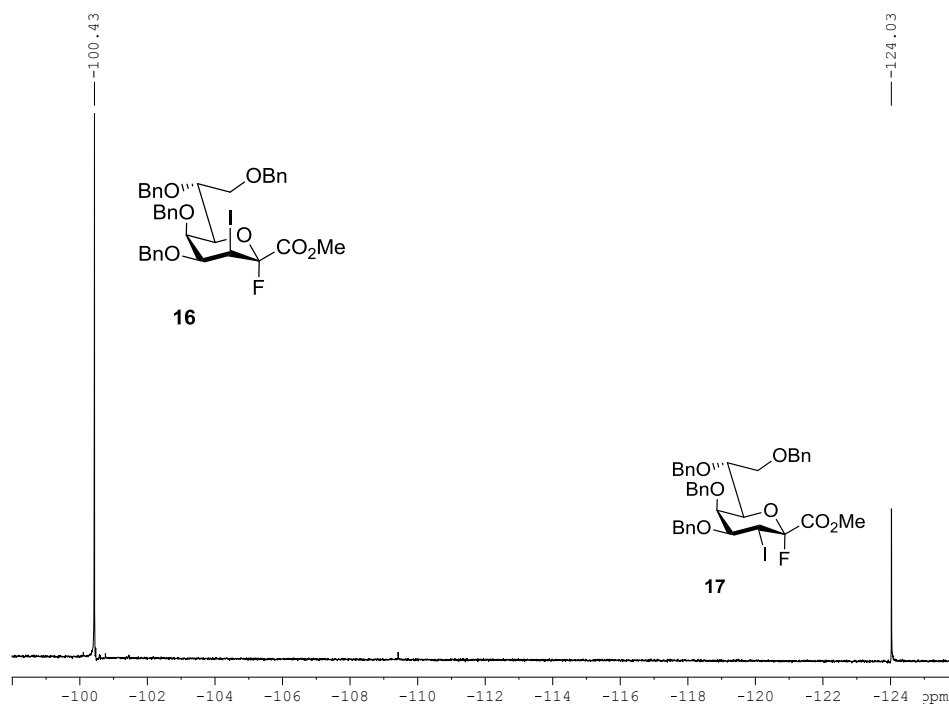


Figure S2: ¹⁹F NMR (CDCl₃, 565 MHz) of a mixture of donor **16** and its 3-iodo-epimer **17**

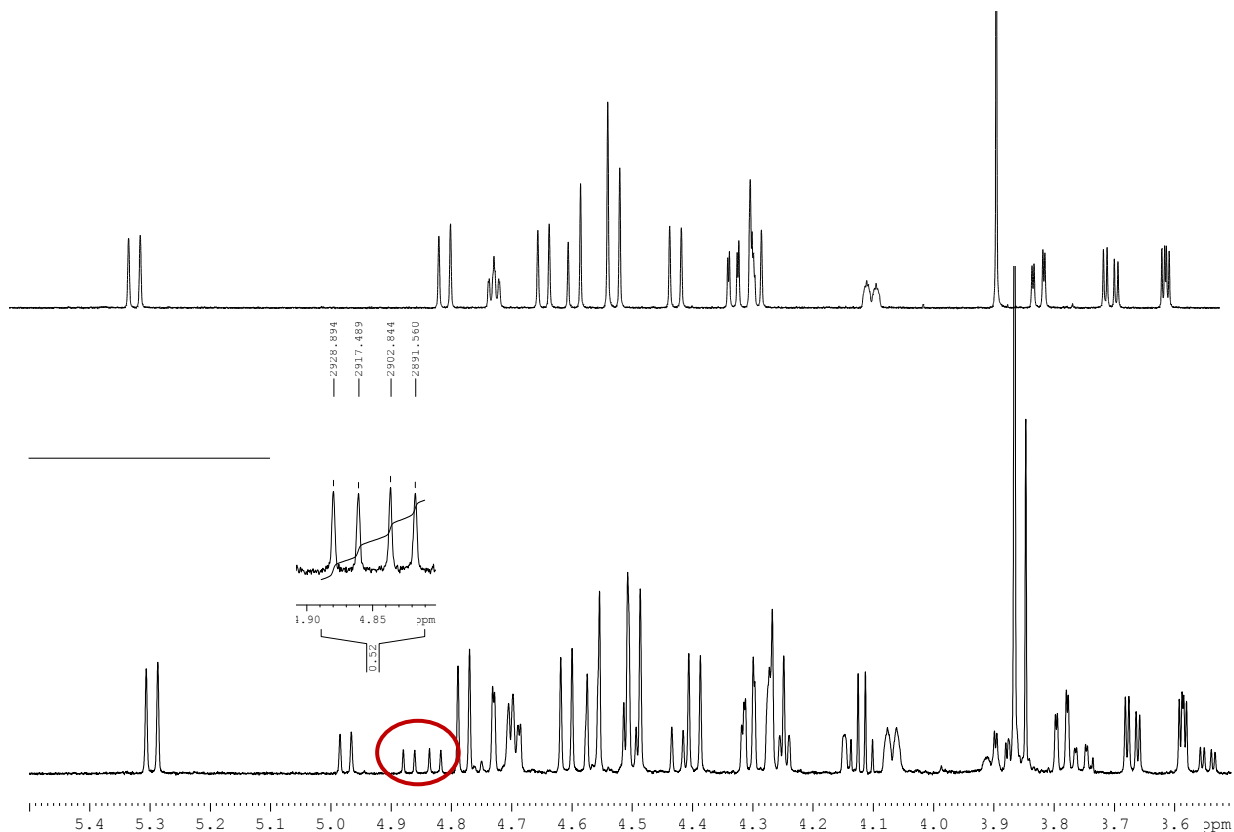
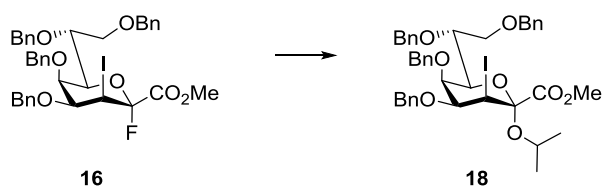


Figure S3: ^1H NMR spectra (CDCl_3 , 600 MHz) of pure **16** (top) and a mixture of **16** and **17** (bottom)

2.8. Model reaction of fluoride donor (**16**) with 2-propanol



2.8.1. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as promotor

A mixture of pre-dried fluoride donor **16** (21.4 mg, 0.029 mmol) and anhydrous 2-propanol (4.5 μL , 0.058 mmol) in anhydrous CH_2Cl_2 (0.7 mL) containing ground molecular sieves (3 Å, 50 mg) was stirred at ambient temperature for 1 h. After cooling to -60°C , $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (11.9 μL , 0.058 mmol, ~46% BF_3 basis) was added dropwise and the mixture was kept at -60°C for 15 min. The mixture was warmed up to -40°C quickly and kept at this temperature again for 15 min. The procedure was repeated at a temperature of -20°C and -10°C . After 15 min at each temperature a sample was taken, which

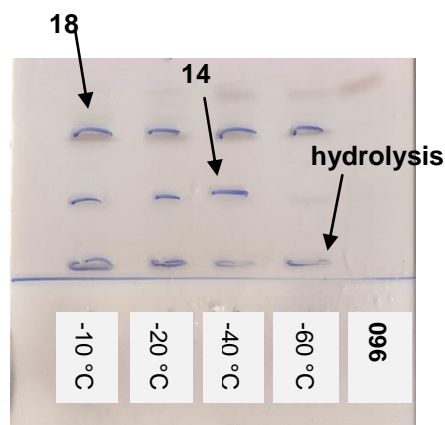


Figure S4: TLC analysis of temperature-dependent activation of donor **16**

was immediately added to a cold solution of triethylamine in CH₂Cl₂. TLC analysis after each step showed, that the donor had been converted already at -60 °C (Fig. S4). Thus, a much higher reactivity was observed than for the acetylated pendant described recently.^{S2} The reaction mixture was diluted with CH₂Cl₂ and washed with aq. sat. NaHCO₃ solution, aq. Na₂S₂O₃ (5 w/w%) solution and water successively. The organic layer was dried (MgSO₄), filtered and concentrated. The crude product was purified by column chromatography (SiO₂, toluene/EtOAc 40:1) affording **18** (15.9 mg, 70%) in sufficient purity for further reactions.

2.8.2. Cp₂ZrCl₂/AgClO₄ as promotor

To examine the reactivity of donor **16**, it was converted under milder conditions (Cp₂ZrCl₂/AgClO₄). Under an atmosphere of argon a suspension of **16** (15.0 mg, 0.020 mmol) and 2-propanol (3.1 μL, 0.041 mmol) in anhydrous CH₂Cl₂ (1.0 mL) containing ground molecular sieves (4 Å, 50 mg) was stirred at ambient temperature for 1 h. Then, AgClO₄ (9.1 mg, 0.041) and Cp₂ZrCl₂ (11.8 mg, 0.041 mmol) were added sequentially at 0 °C and the mixture was stirred at ambient temperature for 24 h. After addition of aq. NaHCO₃ (5 mL) the mixture was filtered over a pad of Celite and rinsed with CH₂Cl₂. The filtrate was subjected to phase separation and the organic phase was thoroughly washed successively with aq. Na₂S₂O₃ (5 w/w%) and water. The organic phase was dried (MgSO₄), filtered and concentrated. Purification by column chromatography (SiO₂, toluene/EtOAc 50:1) provided **18** (11.7 mg, 74%).

2.8.3. Addition of base

The addition of triethylamine as base (1.5 eq/ eq donor **16**) during glycosylation drastically reduced the reactivity of the donor. With BF₃·Et₂O as promotor, the temperature had to be raised to 0°C to get conversion. With Cp₂ZrCl₂/AgClO₄ as promotor couple no reaction took place in the presence of triethylamine even after 2 d.

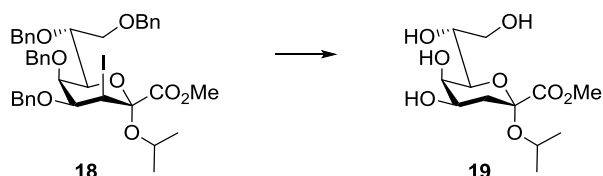
2.8.4. Methyl (propan-2-yl 4,5,7,8-tetra-*O*-benzyl-3-deoxy-3-iodo-*D*-glycero-*α*-*D*-talo-oct-2-ulopyranosid)onate (**18**)

Colorless oil; [α]_D²⁰ - 7.8 (c 0.78, CHCl₃); R_f 0.29 (toluene/EtOAc 50:1, HP-TLC); ¹H NMR (CDCl₃): δ 7.43 - 7.41 (m, 2H, Ar), 7.39 - 7.18 (m, 16H, Ar), 7.16 - 7.14 (m, 2H, Ar), 5.35 (d, 1H, *J* 11.6 Hz, CHHPh), 4.78 (d, 1H, *J* 11.5 Hz, CHHPh), 4.60 (dd, 1H, *J*_{3,4} 4.2, *J*_{3,5} 1.1 Hz, H-3), 4.55 (d, 1H, *J* 12.1 Hz, CHHPh), 4.53 (d, 1H, *J* 11.9 Hz, CHHPh), 4.47 (d, 1H, *J* 11.4 Hz, CHHPh), 4.46 (d, 1H, *J* 12.1 Hz, CHHPh), 4.37 (d, 1H, *J* 11.7 Hz, CHHPh), 4.25 (d, 1H, *J* 11.1 Hz, CHHPh), 4.20 - 4.19 (m, 1H, H-5), 4.11 (app. td, 1H, *J*_{7,6} 9.3, *J*_{7,8a} ~ *J*_{7,8b} 2.5 Hz, H-7), 4.08 (dd, 1H, *J*_{6,5} 2.0 Hz, H-6), 4.00 [hept, 1H, *J* 6.1 Hz, CH(CH₃)₂], 3.83 (s, 3H, CO₂CH₃), 3.81 - 3.77 (m, 2H, H-8a, H-8b), 3.66 (dd, 1H, *J*_{4,5} 3.0 Hz, H-4), 1.04 [d, 3H, *J* 6.1 Hz, CH(CH₃)], 0.97 [d, 3H, *J* 6.1 Hz, CH(CH₃)]; ¹³C NMR (CDCl₃): δ 167.94 (s, C-1), 139.29, 138.41, 138.33 and 137.70 (4 x s, 4C, Ar), 128.42, 128.25, 128.24, 127.96, 127.75, 127.72, 127.67, 127.62, 127.55, 127.51, 127.48 and 126.94 (12 x d, 20C, Ar), 100.65 (s, C-2),

76.10 (d, C-7), 74.19 (d, C-4), 74.02 (t, CH₂Ph), 73.35 (t, CH₂Ph), 72.71 (d, C-5), 72.04 (t, CH₂Ph), 71.15 (d, C-6), 70.23 (t, CH₂Ph), 67.99 [d, CH(CH₃)₂], 67.76 (t, C-8), 52.36 (q, CO₂CH₃), 26.39 (d, C-3), 23.74 [q, 1C, CH(CH₃)], 21.80 [q, 1C, CH(CH₃)]; ESI-TOF HRMS: m/z = 803.2052; calcd for C₄₀H₄₅IO₈Na⁺: 803.2051.

2.8.5. Methyl (propan-2-yl 3-deoxy- α -D-manno-oct-2-ulopyranosid)onate (**19**)

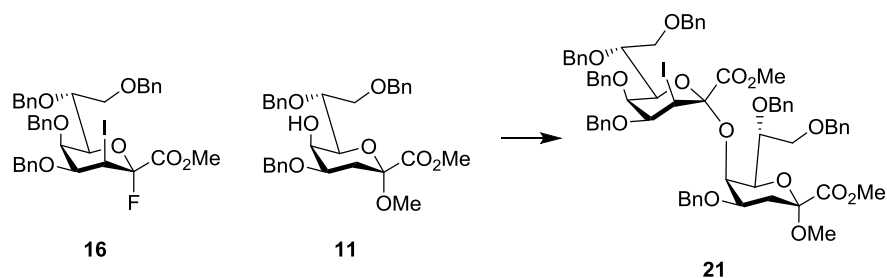
Dehalogenation and deprotection:



Iodo compound **18** (18.4 mg, 0.024 mmol) was dissolved in anhydrous MeOH (2.0 mL) and sodium acetate (3.9 mg, 0.047 mmol) was added to the stirred solution. The atmosphere was exchanged to argon, Pd(OH)₂ on carbon (20%, 3 mg) was added and the atmosphere was successively exchanged to argon and hydrogen. After hydrogenation for 1 h at ambient temperature the mixture was filtered *via* a syringe filter, rinsed with MeOH and the filtrate was concentrated. The yellow residue was dissolved in CH₂Cl₂ and washed with aq. Na₂S₂O₃ (5 w/w%, 2 x) and water (2 x). The organic phase was dried (MgSO₄), filtered and concentrated. The crude product was directly debenzylated in anhydrous MeOH (2.0 mL) over Pd on carbon (10%, 3 mg) at ambient temperature for 3 h. Filtration and concentration of the filtrate afforded **19** (6.3 mg, 91%). Colorless oil; $[\alpha]_D^{20} + 56.2$ (c 0.62, MeOH); R_f 0.25 (EtOAc/EtOH 19:1); ¹H NMR (MeOD): δ 4.02 - 3.91 [m, 4H, CH(CH₃)₂, H-4, H-5, H-7], 3.85 (dd, 1H, $J_{8a,8b}$ 11.3, $J_{8a,7}$ 4.1 Hz, H-8a), 3.76 (s, 3H, CO₂CH₃), 3.68 (dd, 1H, $J_{6,7}$ 8.2, $J_{6,5}$ 1.2 Hz, H-6), 3.63 (dd, 1H, $J_{8b,7}$ 5.8 Hz, H-8b), 2.06 (ddd, 1H, $J_{3eq,3ax}$ 12.8, $J_{3eq,4}$ 4.9, $J_{3eq,5}$ 0.9 Hz, H-3_{eq}), 1.87 (dd, 1H, $J_{3ax,4}$ 11.9 Hz, H-3_{ax}), 1.17 [d, 3H, J 6.3 Hz, CH(CH₃)], 1.02 [d, 3H, J 6.3 Hz, CH(CH₃)]; ¹³C NMR (MeOD): δ 171.36 (s, C-1), 99.34 (s, C-2), 74.07 (d, C-6), 71.23 (d, C-7), 67.77, 67.65, 67.30 [3 x d, 3C, C-4, C-5, CH(CH₃)₂], 64.76 (t, C-8), 52.79 (q, CO₂CH₃), 36.13 (t, C-3), 24.20 [q, CH(CH₃)], 22.88 [q, CH(CH₃)]; ESI-TOF HRMS: m/z = 317.1234; calcd for C₁₂H₂₂O₈Na⁺: 317.1207.

For determination of the anomeric configuration of **19**, latter compound (ca. 6 mg) was dissolved in anhydrous pyridine (2 mL) and treated with acetic anhydride (0.2 mL) at ambient temperature over night. Excessive reagent was destroyed at 0 °C by addition of anhydrous MeOH (1 mL) and after 10 min the mixture was coevaporated with toluene (3x). Column chromatography (SiO₂, *n*-hexane/EtOAc 1:1) of the crude residue afforded the known methyl (propan-2-yl 4,5,7,8-tetra-*O*-acetyl-3-deoxy- α -D-manno-oct-2-ulopyranosid)onate^{S2} verifying the α -configuration of **19**.

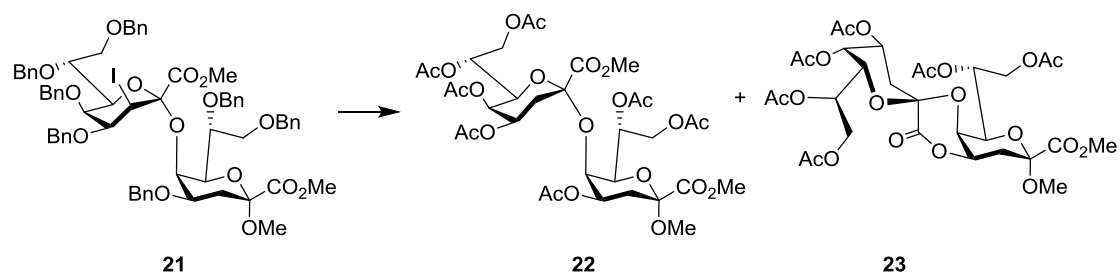
2.9. Methyl (4,5,7,8-tetra-*O*-benzyl-3-deoxy-3-iodo- α -D-glycero- α -D-talo-oct-2-ulopyranosyl)onate-(2 \rightarrow 5)-methyl (methyl 4,7,8-tri-*O*-benzyl-3-deoxy- α -D-manno-oct-2-ulopyranosid)onate (21**)**



A mixture of pre-dried starting materials **11** (38.0 mg, 0.071 mmol) and **16** (78.7 mg, 0.106 mmol) in anhydrous toluene (7.6 mL) containing ground molecular sieves (3 Å, 350 mg) was stirred at ambient temperature for 2 h. The suspension was cooled to -40 °C (MeCN/dry ice) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (29.1 μL , 0.142 mmol, ~46% BF_3 basis) was added dropwise. The mixture was allowed to warm to -15 °C over 2 h and was kept between -20 °C and -10 °C for additional 1.5 h (Note: for TLC analysis, samples were immediately treated with triethylamine in CH_2Cl_2 to avoid degradation). The mixture was cooled to -30 °C and a solution of triethylamine (0.1 mL) in anhydrous toluene (0.9 mL) was slowly added. During addition, the color of the solution turned orange and finally to a pale yellow. After complete addition the mixture was stirred at -30 °C for further 5 min. Then, the solution was poured onto an ice-cold aq. sat. NaHCO_3 solution (10 mL) and was quickly extracted with EtOAc (40 mL). The aqueous phase was once again washed with EtOAc (10 mL) and the combined organic phases were washed successively with ice-cold aq. $\text{Na}_2\text{S}_2\text{O}_3$ (5 w/w%) solution and brine. Drying (MgSO_4), filtration and swift concentration afforded a crude product which was purified by column chromatography (SiO_2 , *n*-hexane/EtOAc 3:1) yielding **21** (63.0 mg, 71%) as a colorless oil; $[\alpha]_{\text{D}}^{20} + 16.3$ (*c* 0.60, CHCl_3); R_f 0.32 (*n*-hexane/EtOAc 4:1, HP-TLC); ^1H NMR (d_8 -toluene, 323.15 K): δ 7.64 - 7.61 (m, 2H, Ar), 7.41 - 7.38 (m, 2H, Ar), 7.31 - 7.27 (m, 4H, Ar), 7.24 - 7.19 (m, 8H, Ar), 7.17 - 6.99 (m, 19H, Ar), 5.38 (d, 1H, J 12.0 Hz, *CHHPh*), 4.98 - 4.96 (m, 1H, H-5), 4.84 (dd, $J_{6',7'}$ 9.1, $J_{6',5'}$ 1.7 Hz, H-6'), 4.77 (d, 1H, J 10.9 Hz, *CHHPh*), 4.73 (d, 1H, J 10.9 Hz, *CHHPh*), 4.71 (dd, 1H, $J_{3',4'}$ 4.2, $J_{3',5'}$ 0.7 Hz, H-3'), 4.53 (d, 1H, J 11.1 Hz, *CHHPh*), 4.37 (d, 1H, J 11.8 Hz, *CHHPh*), 4.34 (d, 1H, J 11.8 Hz, *CHHPh*), 4.33 (d, 1H, J 12.0 Hz, *CHHPh*), 4.22 (d, 1H, J 11.1 Hz, *CHHPh*), 4.22 (d, 1H, J 11.6 Hz, *CHHPh*), 4.17 - 4.10 (m, 3H, H-7', CH_2Ph), 4.07 (d, 1H, J 10.7 Hz, *CHHPh*), 4.06 (d, 1H, J 11.6 Hz, *CHHPh*), 4.00 (d, 1H, J 10.7 Hz, *CHHPh*), 3.98 - 3.96 (m, 1H, H-5'), 3.92 - 3.87 (m, 3H, H-4', H-6, H-8a), 3.83 (dd, 1H, $J_{8b,8a}$ 10.4, $J_{8b,7}$ 2.9 Hz, H-8b), 3.77 (dd, 1H, $J_{8'a,8'b}$ 10.4, $J_{8'a,7'}$ 3.5 Hz, H-8'a), 3.76 - 3.69 (m, 2H, H-7, H-8'b), 3.49 (s, 3H, CO_2CH_3), 3.40 (s, 3H, CO_2CH_3), 3.39 - 3.35 (m, 1H, H-4), 3.26 (s, 3H, OCH_3), 2.25 - 2.22 (m, 2H, H-3_{ax}, H-3_{eq}); ^{13}C NMR (d_8 -toluene, 323.15 K)^{S5}: δ 168.39 (s, C-1), 167.87 (s, C-1'), 140.39, 139.96, 139.69, 139.06, 138.82 and 138.60 (6 x s, Ar), 129.25, 128.97, 128.64, 128.62, 128.56, 128.54, 128.48, 128.44, 128.31, 127.96, 127.95, 127.71, 127.68, 127.53, 127.11 and 125.47 (16 x d, Ar), 102.12 (s, C-2'), 99.84 (s, C-2), 77.48 (d, C-7'), 76.49 (d, C-

7), 75.24 (d, C-4), 74.43 (t, CH₂Ph), 74.21 and 73.21 (2 x d, C-4', C-5'), 73.72 (t, CH₂Ph), 73.27 (t, CH₂Ph), 72.35 and 72.05 (2 x d, C-6, C-6'), 72.28 (t, CH₂Ph), 71.67 (t, CH₂Ph), 71.10 (t, CH₂Ph), 70.58 (t, CH₂Ph), 69.41 (d, C-5), 69.15 (t, C-8'), 68.45 (t, C-8), 51.82 (q, CO₂CH₃), 51.72 (q, CO₂CH₃), 51.16 (q, OCH₃), 33.28 (t, C-3), 28.80 (d, C-3'); ESI-TOF HRMS: $m/z = 1274.4332$; calcd for C₆₈H₇₃IO₁₅NH₄⁺: 1274.4332.

2.10. Methyl (4,5,7,8-tetra-*O*-acetyl-3-deoxy- α -D-manno-oct-2-ulopyranosyl)onate-(2 \rightarrow 5)-methyl (methyl 4,7,8-tri-*O*-acetyl-3-deoxy- α -D-manno-oct-2-ulopyranosid)onate (22**) and [4,5,7,8-tetra-*O*-acetyl-3-deoxy- α -D-manno-oct-2-ulopyranosylono-(1'-4)-lactone]-(2 \rightarrow 5)-methyl (methyl 4,7,8-tri-*O*-acetyl-3-deoxy- α -D-manno-oct-2-ulopyranosid)onate (**23**)**



Disaccharide **21** (63.0 mg, 0.050 mmol) was dissolved in anhydrous MeOH (5 mL) and sodium acetate (41.0 mg, 0.501 mmol) was added in one portion. The atmosphere was exchanged to argon by consecutive evacuation and flushing with inert gas. Then, Pd(OH)₂/C (20%, 63 mg) was added to the solution followed by exchange of atmosphere to argon and finally to hydrogen. After 1 h at ambient temperature the suspension was filtered via a syringe filter and rinsed with anhydrous MeOH. Swift concentration afforded a yellow residue which was partitioned between ice-cold aq. sat. NaHCO₃ solution (10 mL) and EtOAc (30 mL). The aqueous phase was once again extracted with EtOAc (10 mL) and the combined organic phases were washed successively with aq. Na₂S₂O₃ (5 w/w%, 2x) solution and brine (2 x). Drying (MgSO₄), filtration and concentration provided a colourless oil which was dissolved in anhydrous MeOH (5 mL) and treated with hydrogen on Pd/C (10%, 10 mg) after exchange of atmosphere as described above. After 20 h at ambient temperature the catalyst was filtered off via a syringe filter and rinsed with anhydrous MeOH. The filtrate was concentrated, the residue taken up in anhydrous pyridine (2 mL), cooled to 0°C and treated with acetic anhydride (0.4 mL) and 4-(*N,N*-dimethylamino)-pyridine (3 mg). After 24 h at ambient temperature excessive reagent was destroyed by dropwise addition of anhydrous MeOH (2 mL) at 0 °C and the solution was kept at this temperature for 5 min. Coevaporation with toluene (3 x) provided a crude product which was purified by HP-column chromatography (SiO₂, toluene/EtOAc 2:1) providing a mixture of **23** and **22** (3.5 mg of **23**, 10%; 20.0 mg of mixture in a ratio of **22** : **23** of 10 : 1, 51%; total: 61%, see Fig. S5).

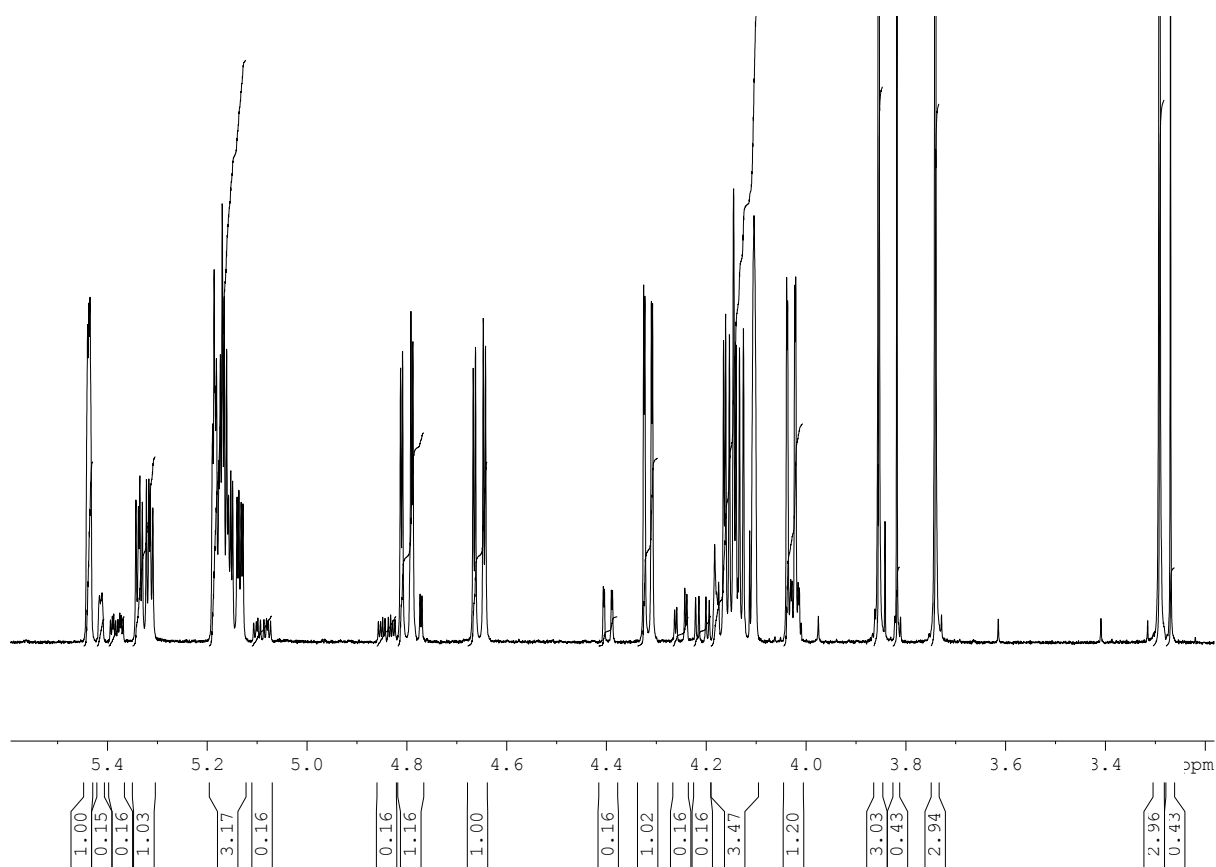


Figure S5: ^1H NMR (CDCl_3) of mixture of **22** and lactone **23**

Partial separation of this mixture (9.9 mg, 10:1 ratio of **22**:**23**) was obtained by normal-phase HP chromatography (*n*-hexane/EtOAc 2:1) giving a small fraction of pure **22**^{S6} (1.2 mg, 12%) for spectroscopic analysis. ^1H NMR analysis of the minor compound (Fig. S6) strongly suggested the expected formation of an interresidue lactone, based on the absence of one methyl ester signal and the presence of six acetyl groups only. The presence of the 1'-4 lactone was furthermore evident from the ^{13}C NMR signals, which showed a pronounced low-field shift of C-4 (ca. +5 ppm) as well as a high-field shift (ca. -6 ppm) of C-5 in comparison to the C-4 and C-5 signals of **22**. Thus, the lactone was formed between O-4 of the proximal Kdo and C-1' forming a six-membered ring. This assignment was further supported by the fact that saponification of the mixture yielded an identical product.

22: ^1H NMR (600 MHz, CDCl_3): δ 5.45 - 5.43 (m, 1H, H-5'), 5.33 (ddd, 1H, J 12.6, J 4.6, J 3.0 Hz, H-4'), 5.20 - 5.13 (m, 3H, H-4, H-7, H-7'), 4.80 (dd, 1H, J 12.5, J 2.3 Hz, H-8a), 4.66 (dd, 1H, J 12.0, J 2.7 Hz, H-8'a), 4.32 (dd, 1H, J 9.3, J 1.3 Hz, H-6'), 4.16 (dd, 1H, J 12.3, J 2.6 Hz, H-8b), 4.14 (dd, 1H, J 12.0, J 4.7 Hz, H-8'b), 4.12 - 4.10 (m, 1H, H-5), 4.03 (dd, 1H, J 9.8, J 1.1 Hz, H-6), 3.86 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 3.29 (s, 3H, OCH_3), 2.29 (ddd, 1H, J 12.9, J 4.7, J 0.8 Hz, H-3'eq), 2.14 (s, 3H, COCH_3), 2.13 (app t, 1H, J 12.5 Hz, H-3ax), 2.09 (s, 3H, COCH_3), 2.09 - 2.05 (m, 1H, H-3eq), 2.064 (s, 3H, COCH_3), 2.055 (s, 3H, COCH_3), 2.05 (s, 3H, COCH_3), 2.00 (s, 3H, COCH_3), 1.99 (app t, 1H, J 12.8 Hz, H-3'ax), 1.99 (s, 3H, COCH_3); ^{13}C NMR (150 MHz, CDCl_3): δ

170.91, 170.63, 170.42, 170.34, 170.14, 170.08 and 169.78 (7 x s, 7C, COCH₃), 167.49 and 166.60 (2 x s, 2C, C-1, C-1'), 100.88 (s, C-2'), 98.76 (s, C-2), 70.80 (d, C-5), 69.39 (d, 2C, C-6, C-6'), 68.26, 68.21 and 68.14 (3 x d, 3C, C-4, C-7, C-7'), 66.12 (d, C-4'), 64.56 (d, C-5'), 62.26 (t, C-8'), 61.37 (d, C-8), 52.76 and 52.65 (2 x q, 2C, CO₂CH₃), 51.15 (q, OCH₃), 33.70 (t, C-3'), 32.37 (t, C-3), 21.38, 21.11, 20.85, 20.77, 20.73, 20.69 and 20.63 (7 x q, 7C, COCH₃).

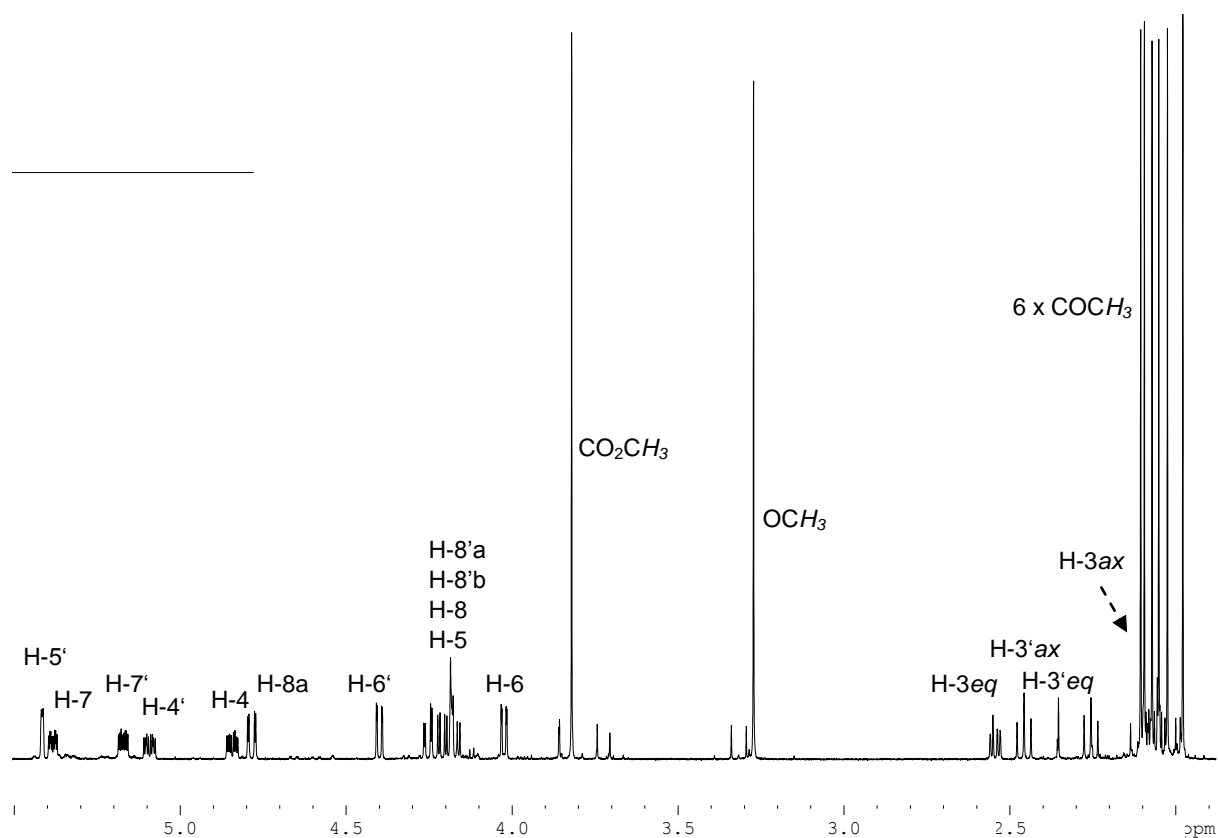
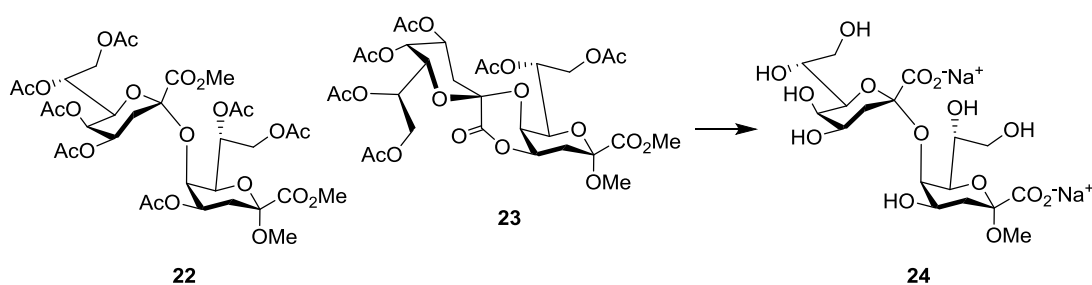


Figure S6: ¹H NMR (CDCl₃) of lactone **23**

2.11. Sodium (3-deoxy- α -D-manno-oct-2-ulopyranosyl)onate-(2 \rightarrow 5)-sodium (methyl 3-deoxy- α -D-manno-oct-2-ulopyranosid)onate (**24**)



A solution of **22** and **23** (9.4 mg, 0.012 mmol) in anhydrous MeOH (1.0 mL) was treated with 0.1 M sodium methoxide (60 μ L in anhydrous) at ambient temperature for 16 h followed by neutralization using ion exchange resin DOWEX 50 (H⁺ form). The resin was filtered off, rinsed with anhydrous

MeOH and the solvent was removed under reduced pressure. The residue was dissolved in water (1.0 mL) and was treated with 0.1 M aq. NaOH (1.0 mL) at 0 °C for 2 h and at ambient temperature for 4 h. The solution was made neutral by adding DOWEX 50 resin (H⁺ form), followed by filtration and freeze-drying of the filtrate. The residue was desalted on a PD-10 column (H₂O) to afford **24** as a colorless amorphous solid (5.6 mg, ca. 90%; minor impurity present; Fig. S7).

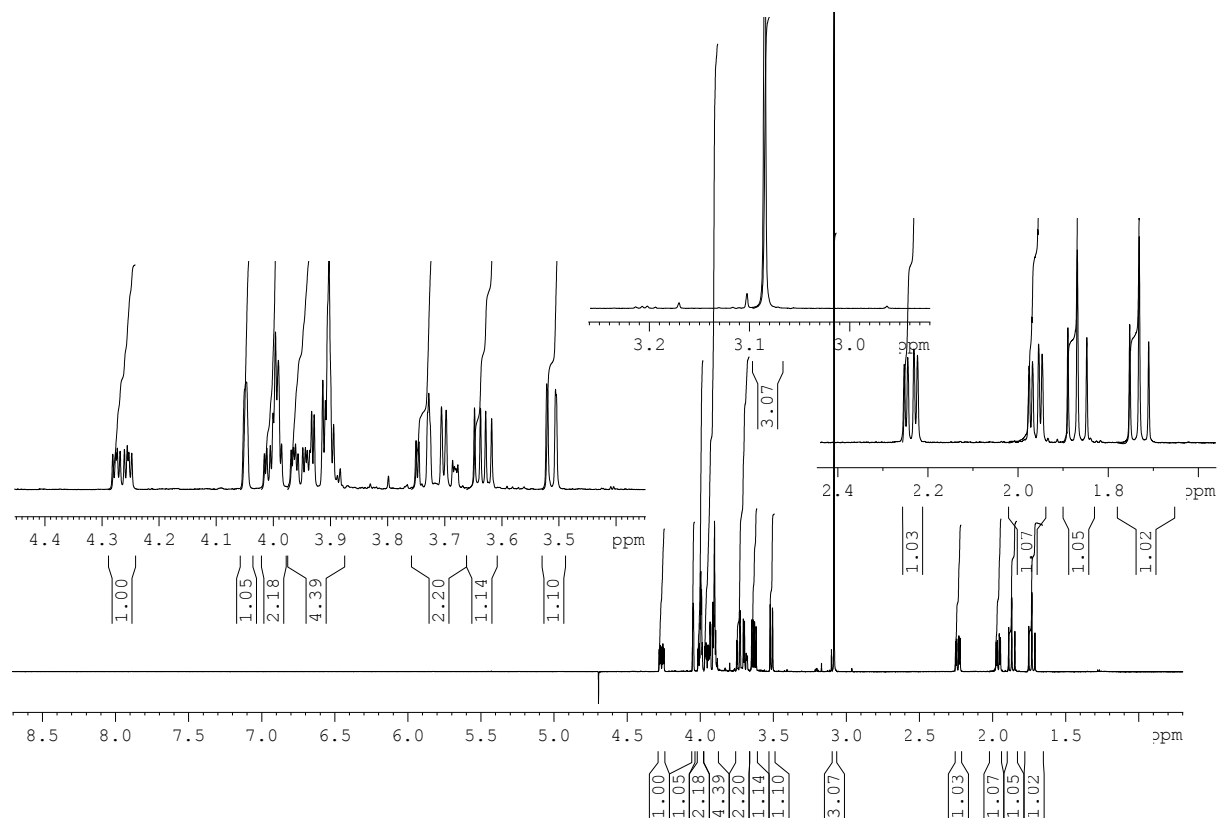


Figure S7: ¹H NMR (D₂O, pH ~ 7) of disaccharide **24** with minor impurity

2.12. Preparation of an analytically pure sample of (**24**)

A small fraction of pure **22** (ca. 1.2 mg) was deacetylated and saponified according to the described method under 2.11. to give the disaccharide **24** cleanly as colorless amorphous solid; $[\alpha]_D^{20} + 70.4$ (*c* 0.66, H₂O); ¹H NMR (D₂O, pH ~ 7): δ 4.26 (ddd, 1H, $J_{4',3'ax}$ 12.2, $J_{4',3'eq}$ 4.7, $J_{4',5'}$ 3.0 Hz, H-4'), 4.06 - 4.04 (m, 1H, H-5), 4.02 - 3.98 (m, 2H, H-5', H-7), 3.95 (ddd, 1H, $J_{4,3ax}$ 12.2, $J_{4,3eq}$ 4.2, $J_{4,5}$ 2.5 Hz, H-4), 3.92 (dd, 1H, $J_{8a,8b}$ 11.7, $J_{8a,7}$ 2.7 Hz, H-8a), 3.91 - 3.88 (m, 2H, H-6', H-7'), 3.75 - 3.72 (m, 1H, H-8'a), 3.71 - 3.67 (m, 1H, H-8'b), 3.63 (dd, 1H, $J_{8b,7}$ 6.1 Hz, H-8b), 3.51 (dd, 1H, $J_{6,7}$ 9.2, $J_{6,5}$ 0.8 Hz, H-6), 3.08 (s, 3H, OCH₃), 2.24 (dd, 1H, $J_{3'eq,3'ax}$ ~ 12.9 Hz, H-3'eq), 1.96 (dd, 1H, $J_{3eq,3ax}$ ~ 12.8 Hz, H-3eq), 1.87 (app t, 1H, H-3'ax), 1.73 (app t, 1H, H-3ax); ¹³C NMR (D₂O, pH ~ 7): δ 175.89 (s, C-1), 174.73 (s, C-1'), 102.92 (s, C-2'), 101.26 (s, C-2), 74.21 (d, C-5), 72.94 (d, C-6), 72.70 (d, C-6'), 71.46 (d, C-7'), 70.13 (d, C-7), 67.63 (d, C-5'), 66.59 (d, C-4), 66.31 (d, C-4'), 63.36 (t, C-8), 63.22 (t,

C-8'), 51.38 (q, OCH₃), 36.61 (t, C-3'), 35.87 (t, C-3); ESI-TOF HRMS: $m/z = 495.1305$; calcd for C₁₇H₂₈O₁₅Na⁺: 495.1320.

3. References for SI

^{S1} Harris, R. K.; Becker, E. D.; De Menezes, S. M. C.; Goodfellow, R.; Granger, P. *Pure Appl. Chem.* **2001**, *73*, 1795-1818.

^{S2} Pokorny, B.; Kosma, P. *Chem. Eur. J.* **2014**, in press (doi: 10.1002/chem.201405424)

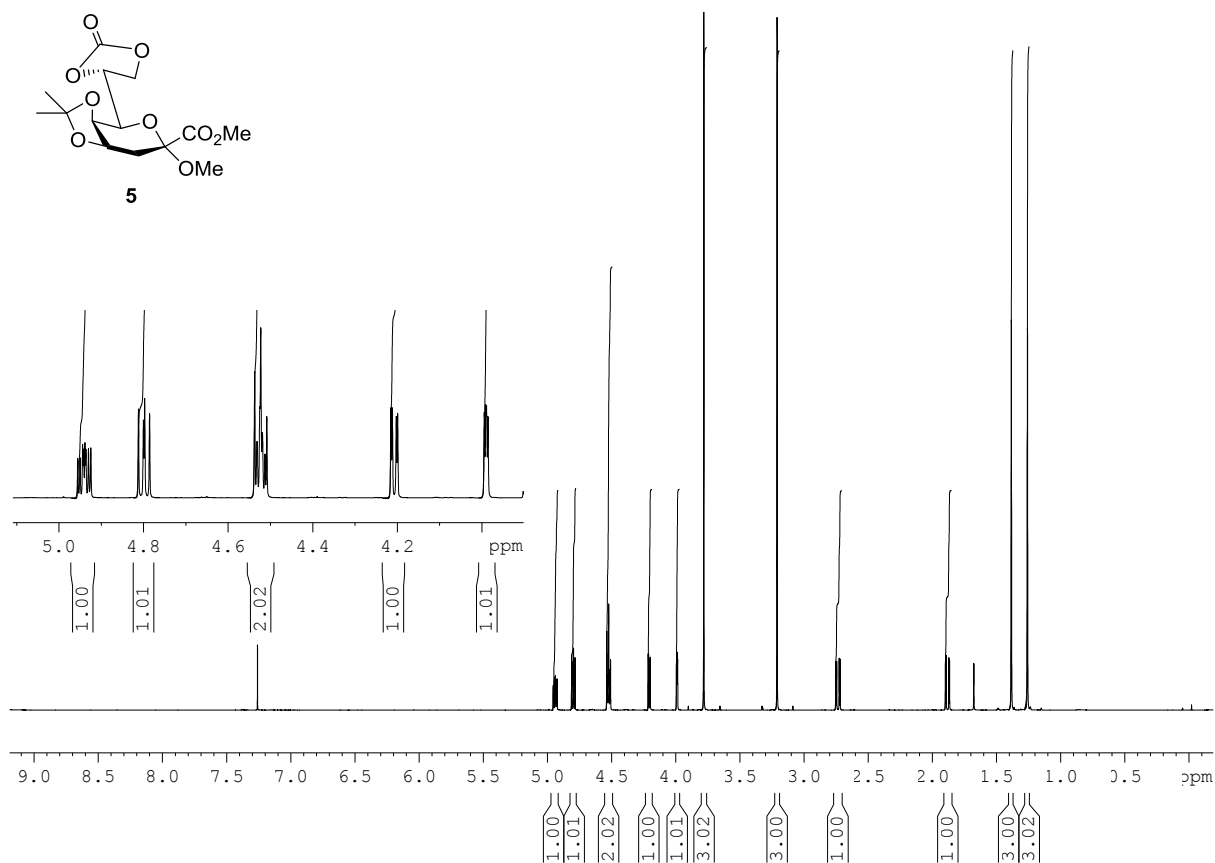
^{S3} Charon, D.; Auzanneau, F.-I.; Mérinne, C.; Szabo, L. *Tetrahedron Lett.* **1987**, *28*, 1393-1396; published NMR data in CDCl₃; measured: $[\alpha]_D^{20} + 64.5$ (c 1.16, CHCl₃), lit: +56 (c 1, CHCl₃).

^{S4} Pure fractions were used for characterization of **8** and **7**. The yield was calculated from the ratio determined by ¹H NMR. For further reactions **8** and **7** were combined as the conversion from **9** towards **11** was known to also yield some benzyl ester **12** via partial transesterification. Thus, separation of benzyl and methyl ester was performed after the last step of the acceptor synthesis (**11** and **12**).

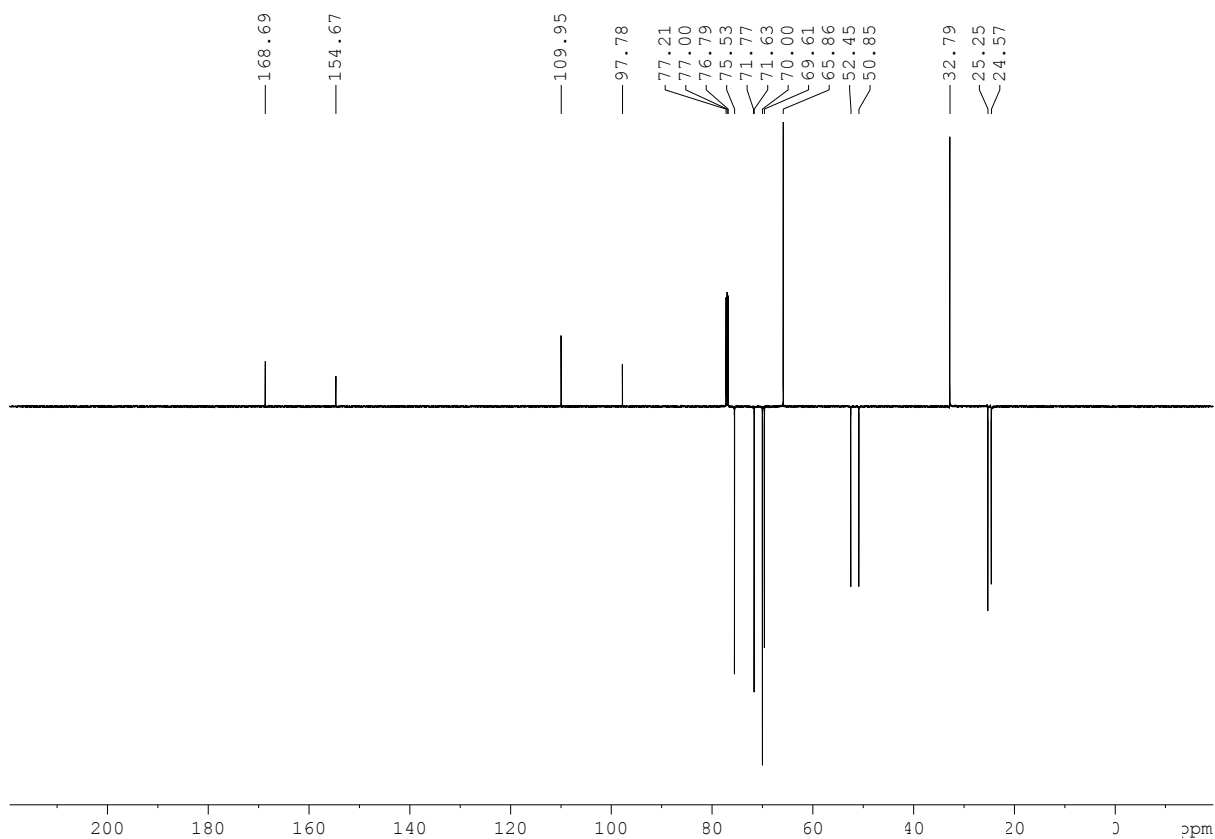
^{S5} Product signals might be overlapping with d₈-tol

^{S6} Colorless oil; ¹H NMR (CDCl₃): δ 5.45 - 5.43 (m, 1H, H-5'), 5.33 (ddd, 1H, J 12.6, J 4.6, J 3.0 Hz, H-4'), 5.20 - 5.13 (m, 3H, H-4, H-7, H-7'), 4.80 (dd, 1H, J 12.5, J 2.3 Hz, H-8a), 4.66 (dd, 1H, J 12.0, J 2.7 Hz, H-8'a), 4.32 (dd, 1H, J 9.3, J 1.3 Hz, H-6'), 4.16 (dd, 1H, J 12.3, J 2.6 Hz, H-8b), 4.14 (dd, 1H, J 12.0, J 4.7 Hz, H-8'b), 4.12 - 4.10 (m, 1H, H-5), 4.03 (dd, 1H, J 9.8, J 1.1 Hz, H-6), 3.86 (s, 3H, CO₂CH₃), 3.74 (s, 3H, CO₂CH₃), 3.29 (s, 3H, OCH₃), 2.29 (ddd, 1H, J 12.9, J 4.7, J 0.8 Hz, H-3'eq), 2.14 (s, 3H, COCH₃), 2.13 (app t, 1H, J 12.5 Hz, H-3ax), 2.09 (s, 3H, COCH₃), 2.09 - 2.05 (m, 1H, H-3eq), 2.064 (s, 3H, COCH₃), 2.055 (s, 3H, COCH₃), 2.05 (s, 3H, COCH₃), 2.00 (s, 3H, COCH₃), 1.99 (app t, 1H, J 12.8 Hz, H-3'ax), 1.99 (s, 3H, COCH₃); ¹³C NMR (CDCl₃): δ 170.91, 170.63, 170.42, 170.34, 170.14, 170.08 and 169.78 (7 x s, 7C, COCH₃), 167.49 and 166.60 (2 x s, 2C, C-1, C-1'), 100.88 (s, C-2'), 98.76 (s, C-2), 70.80 (d, C-5), 69.39 (d, 2C, C-6, C-6'), 68.26, 68.21 and 68.14 (3 x d, 3C, C-4, C-7, C-7'), 66.12 (d, C-4'), 64.56 (d, C-5'), 62.26 (t, C-8'), 61.37 (d, C-8), 52.76 and 52.65 (2 x q, 2C, CO₂CH₃), 51.15 (q, OCH₃), 33.70 (t, C-3'), 32.37 (t, C-3), 21.38, 21.11, 20.85, 20.77, 20.73, 20.69 and 20.63 (7 x q, 7C, COCH₃).

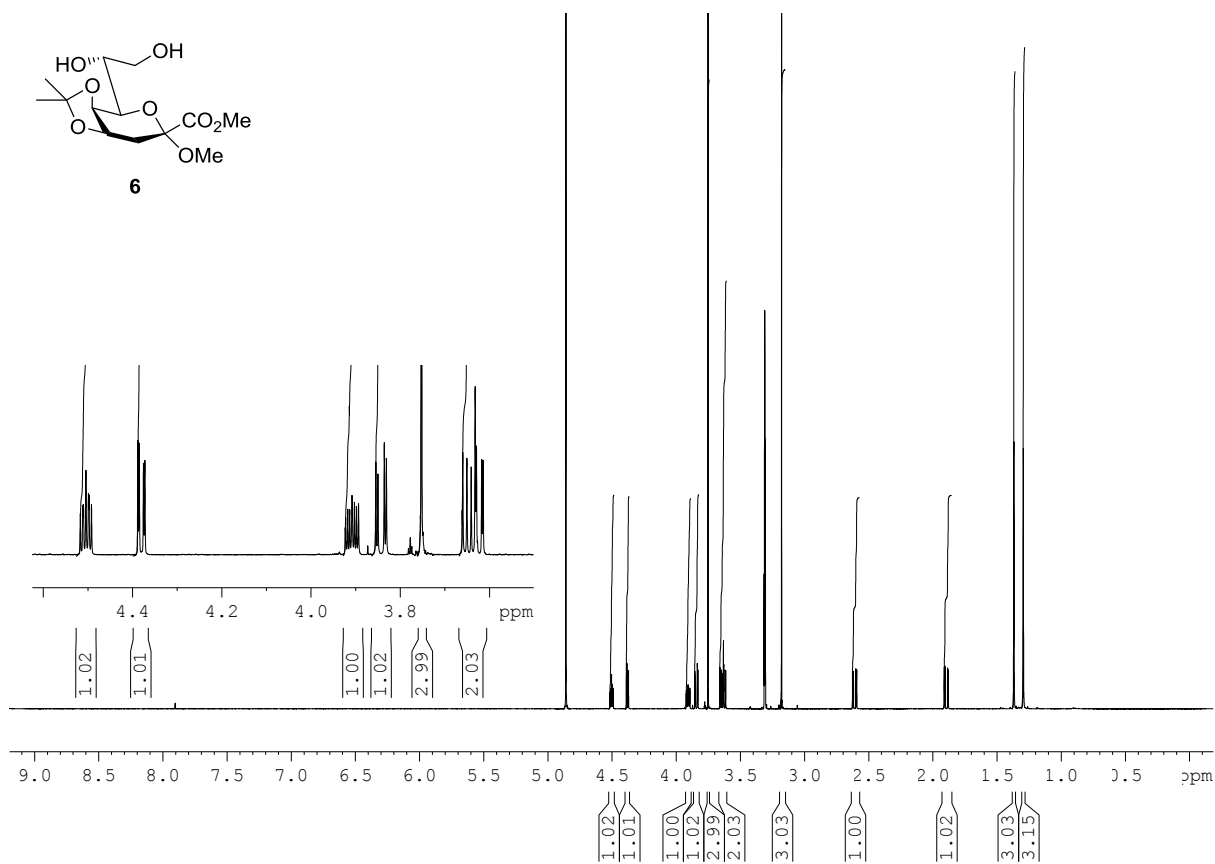
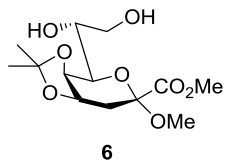
4. NMR spectra of compounds 5-8, 11-12, 14-16, 18, 19, 21, 22 and 24



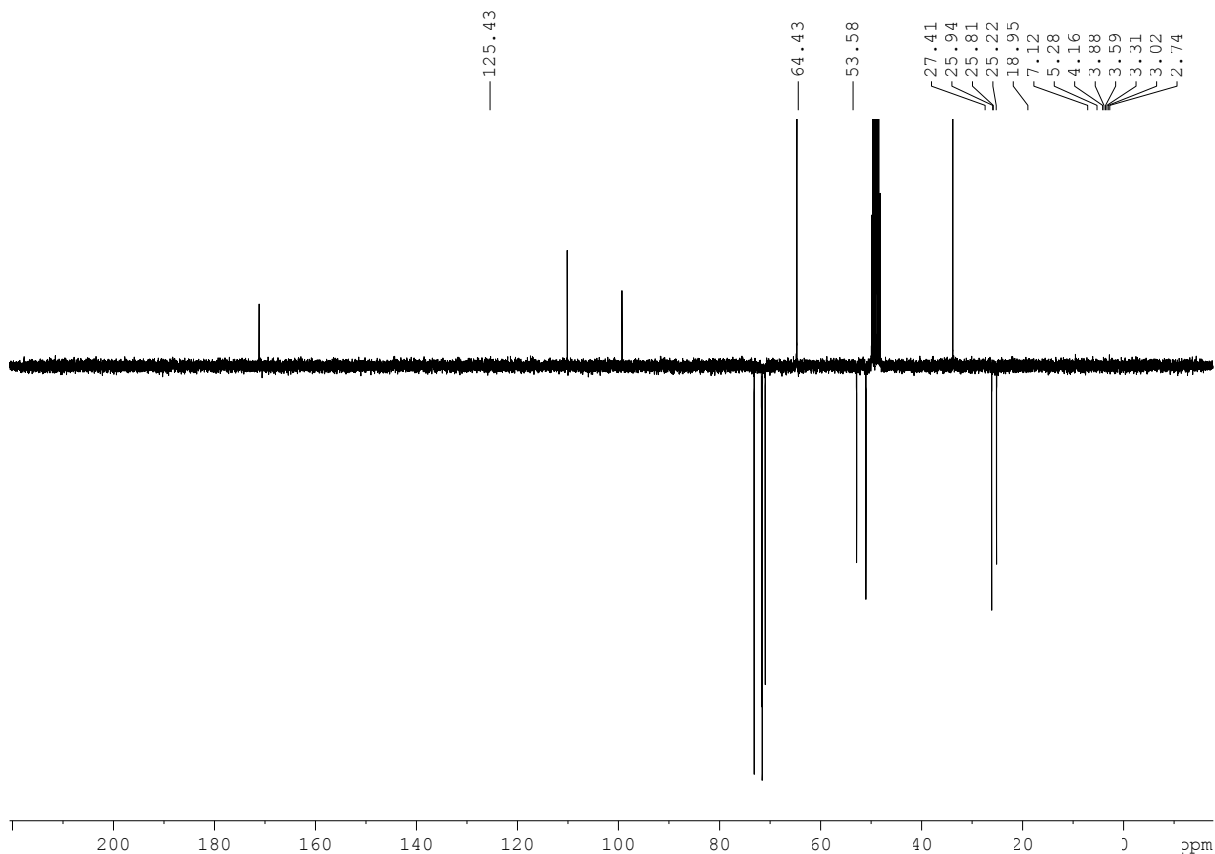
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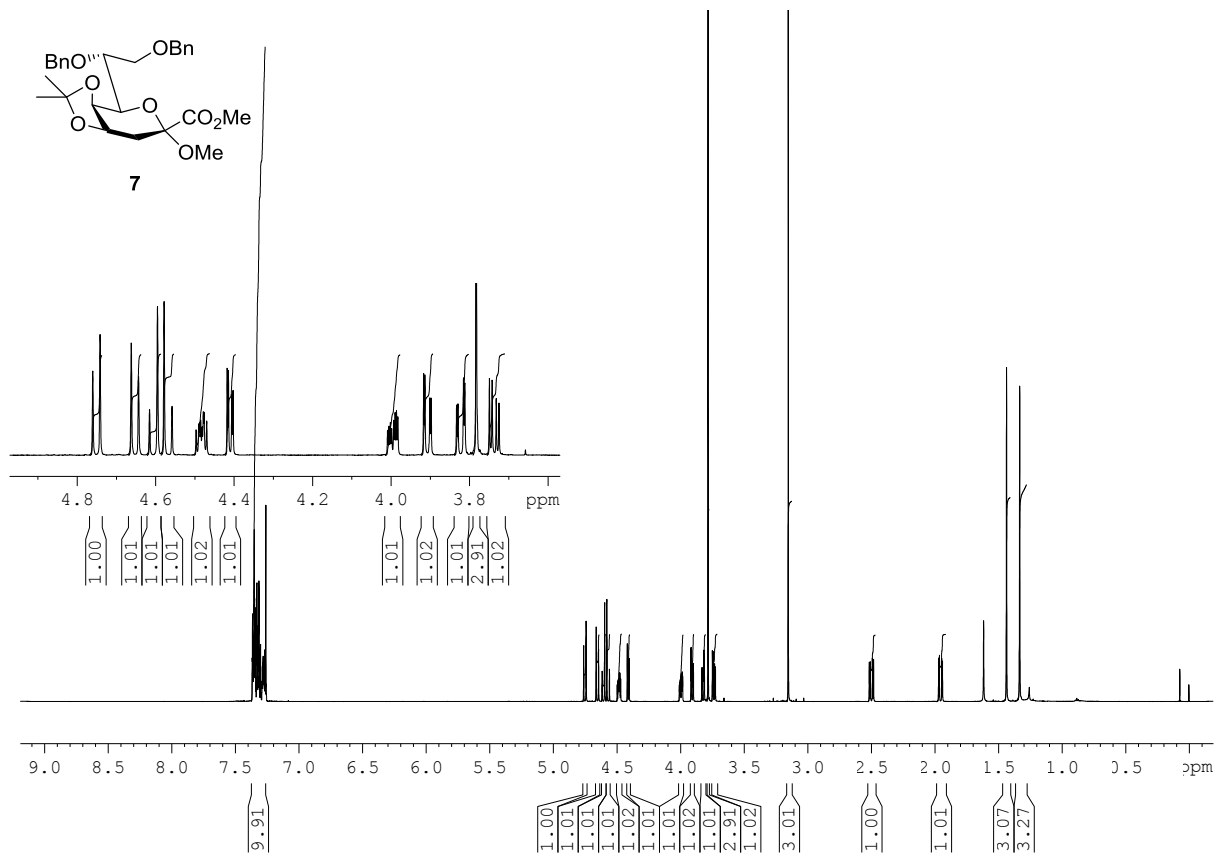
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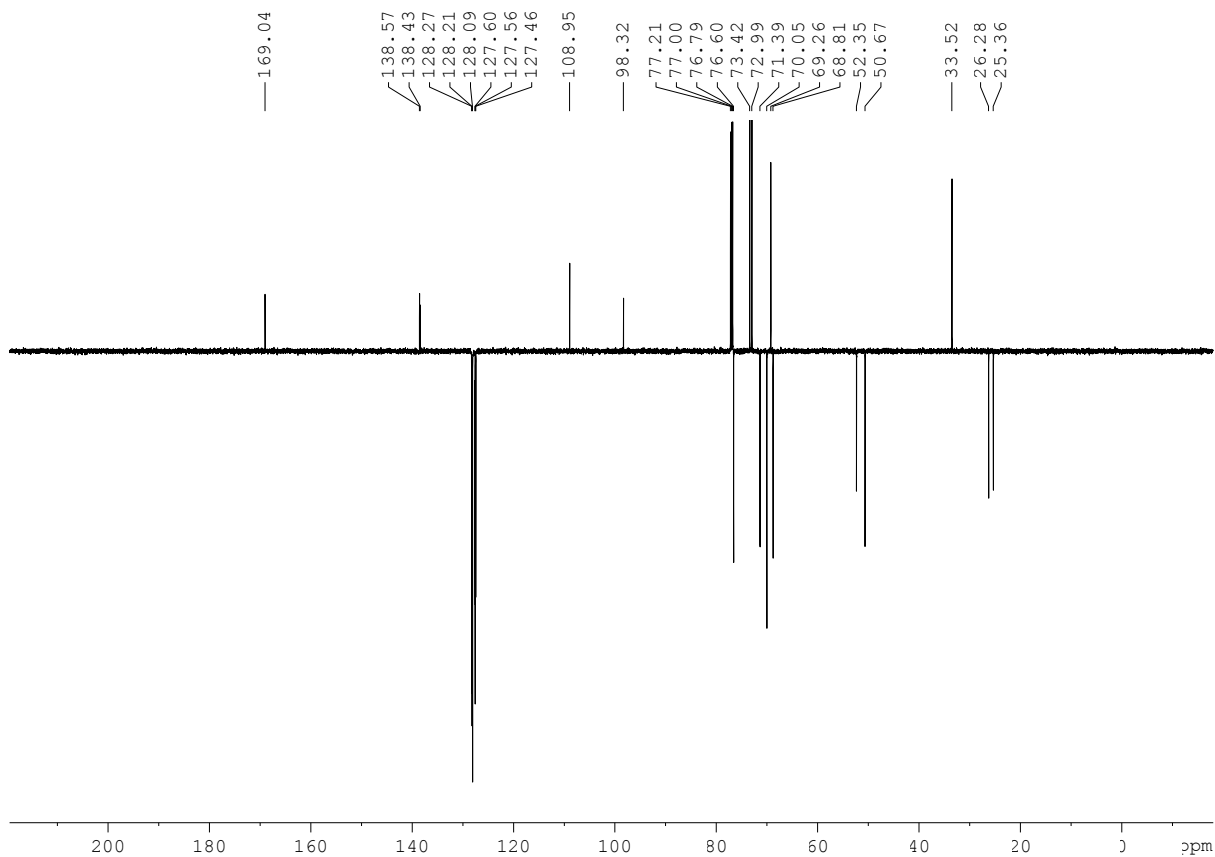
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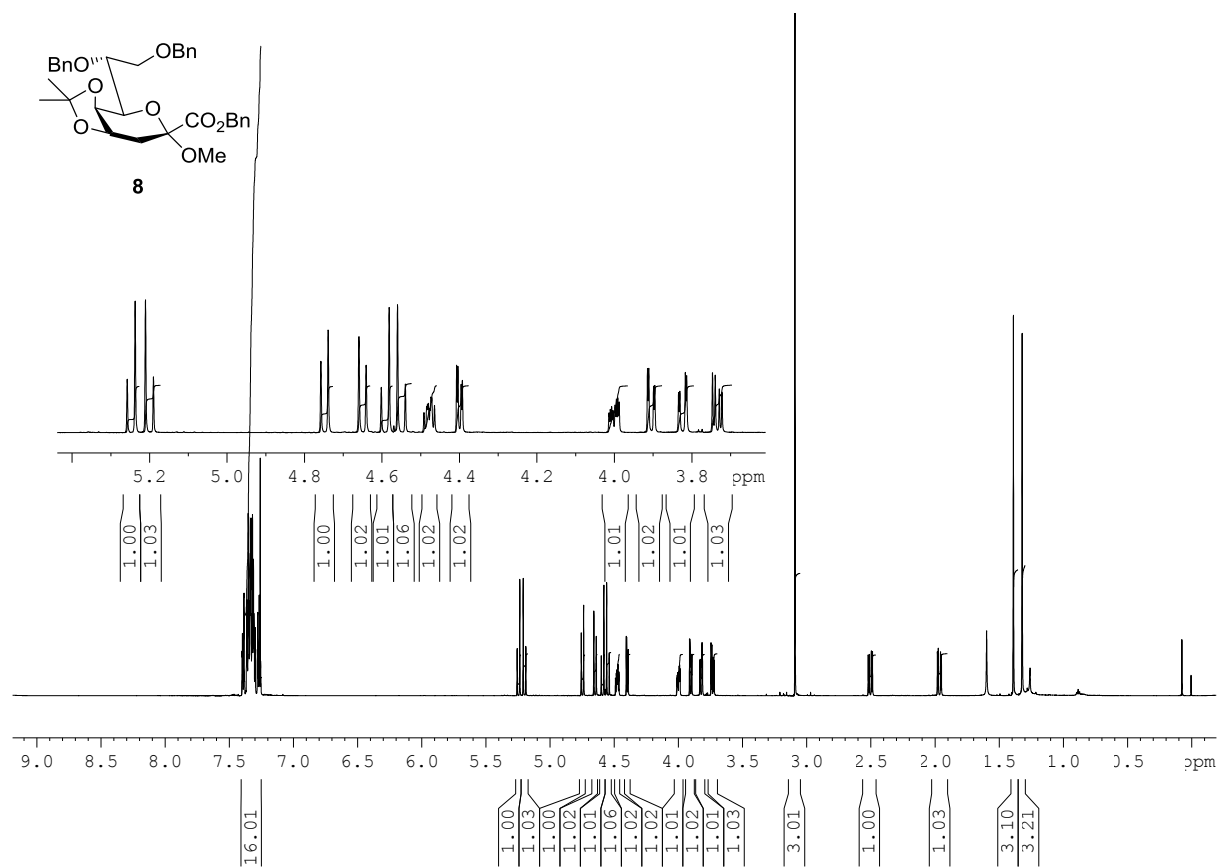
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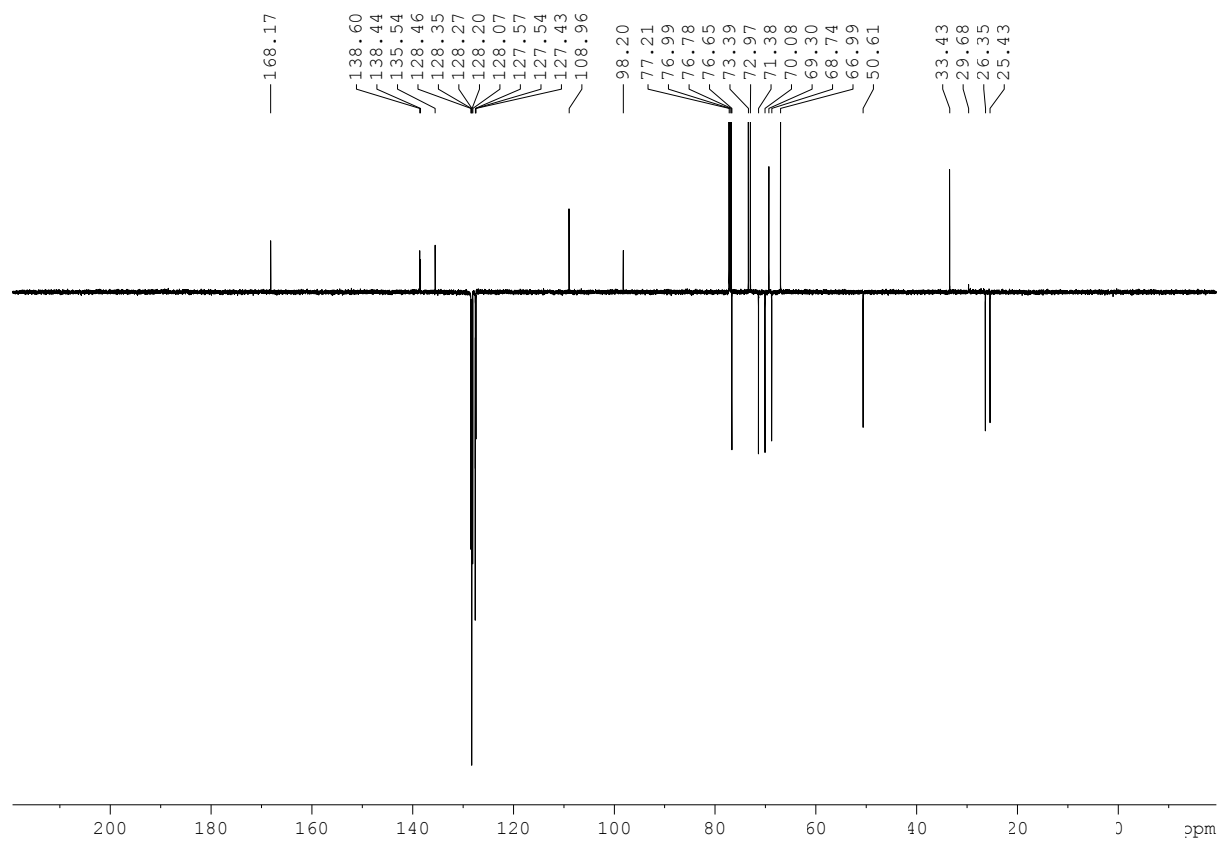
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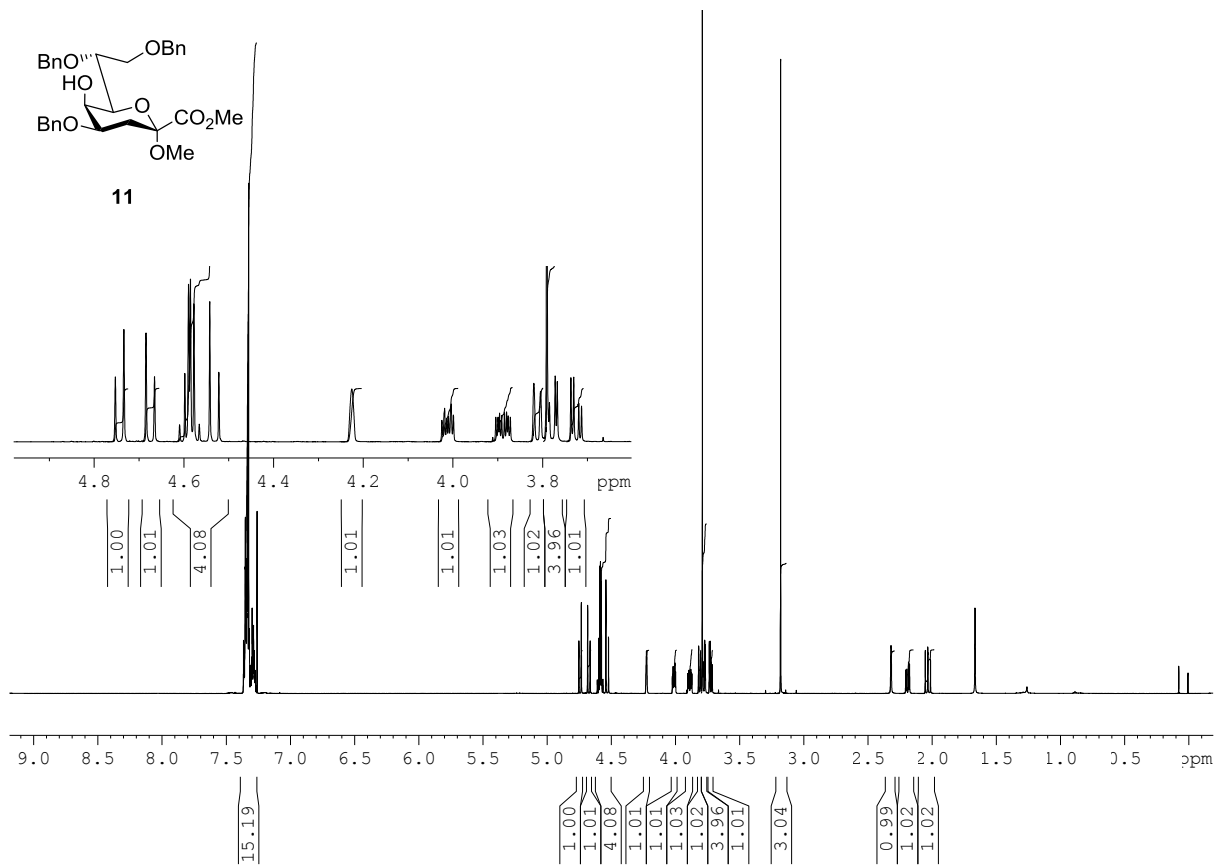
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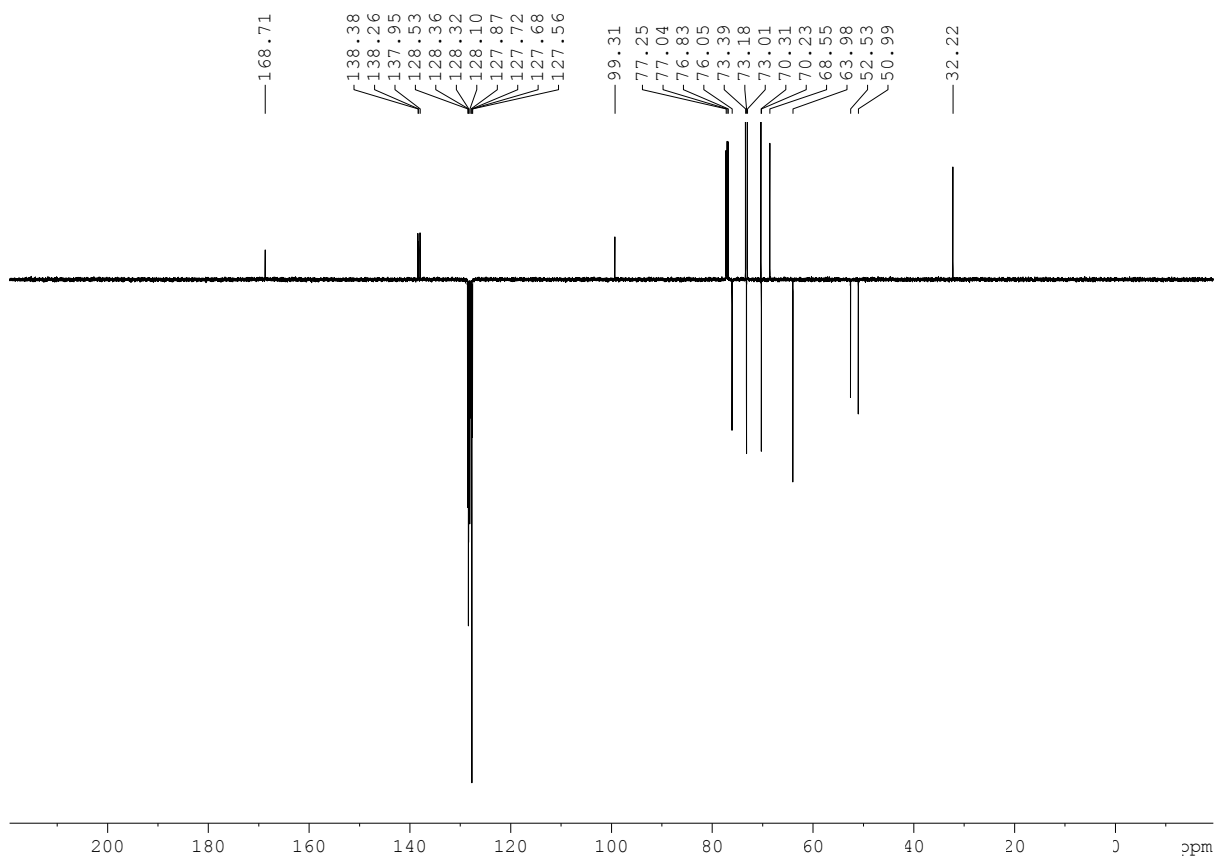
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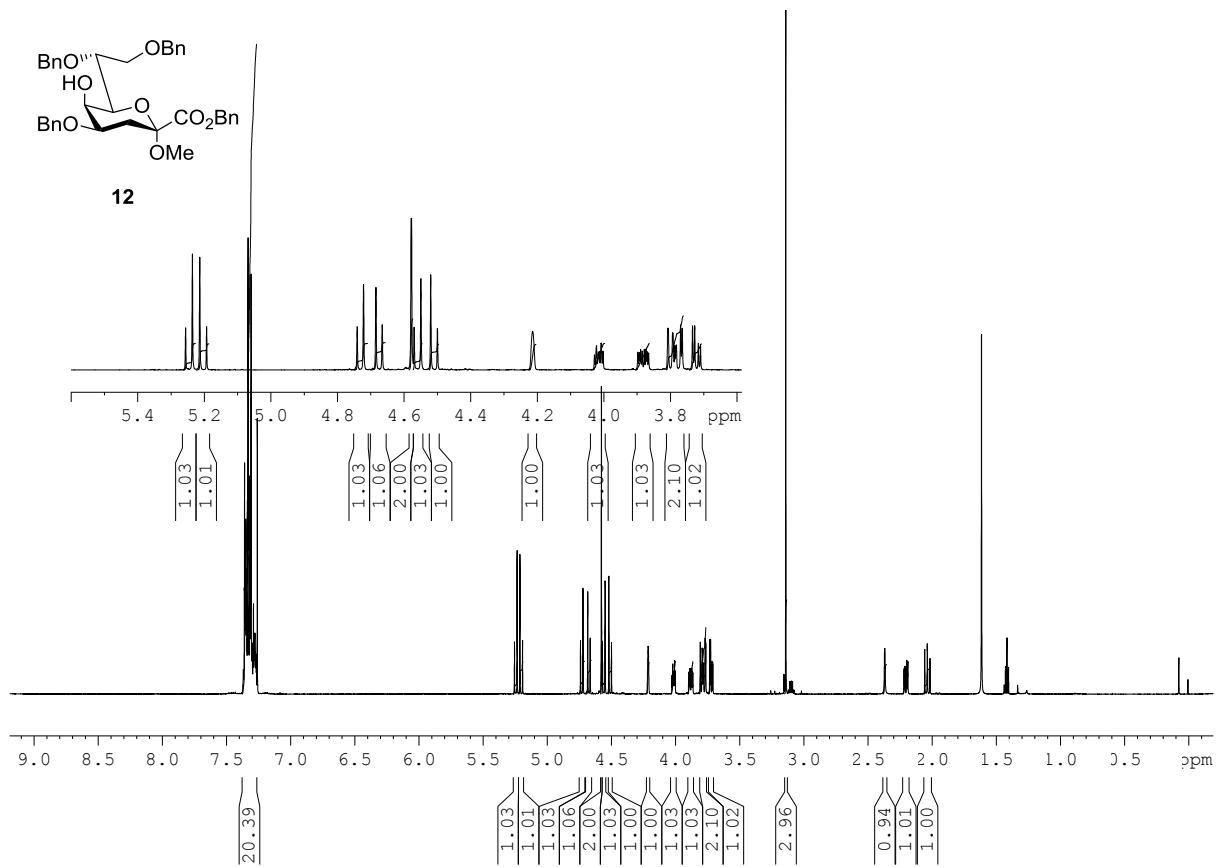
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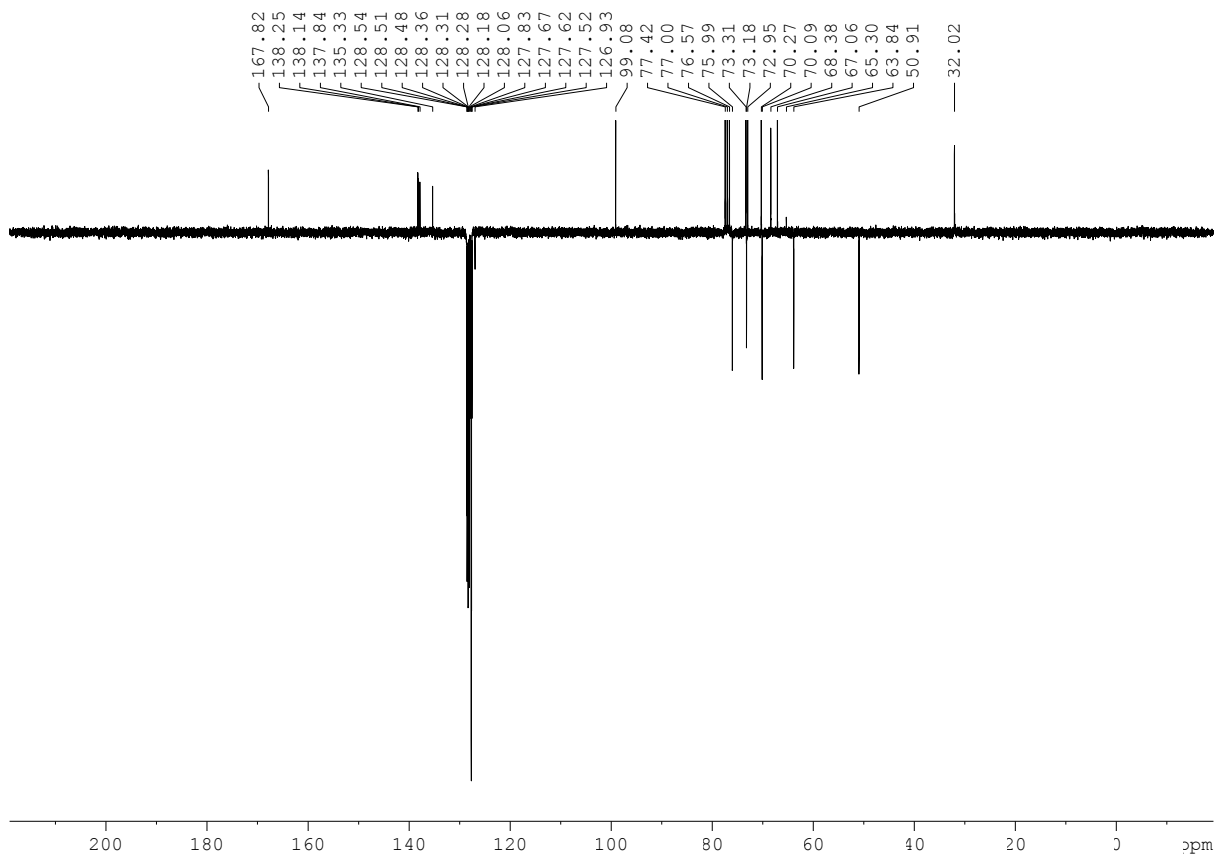
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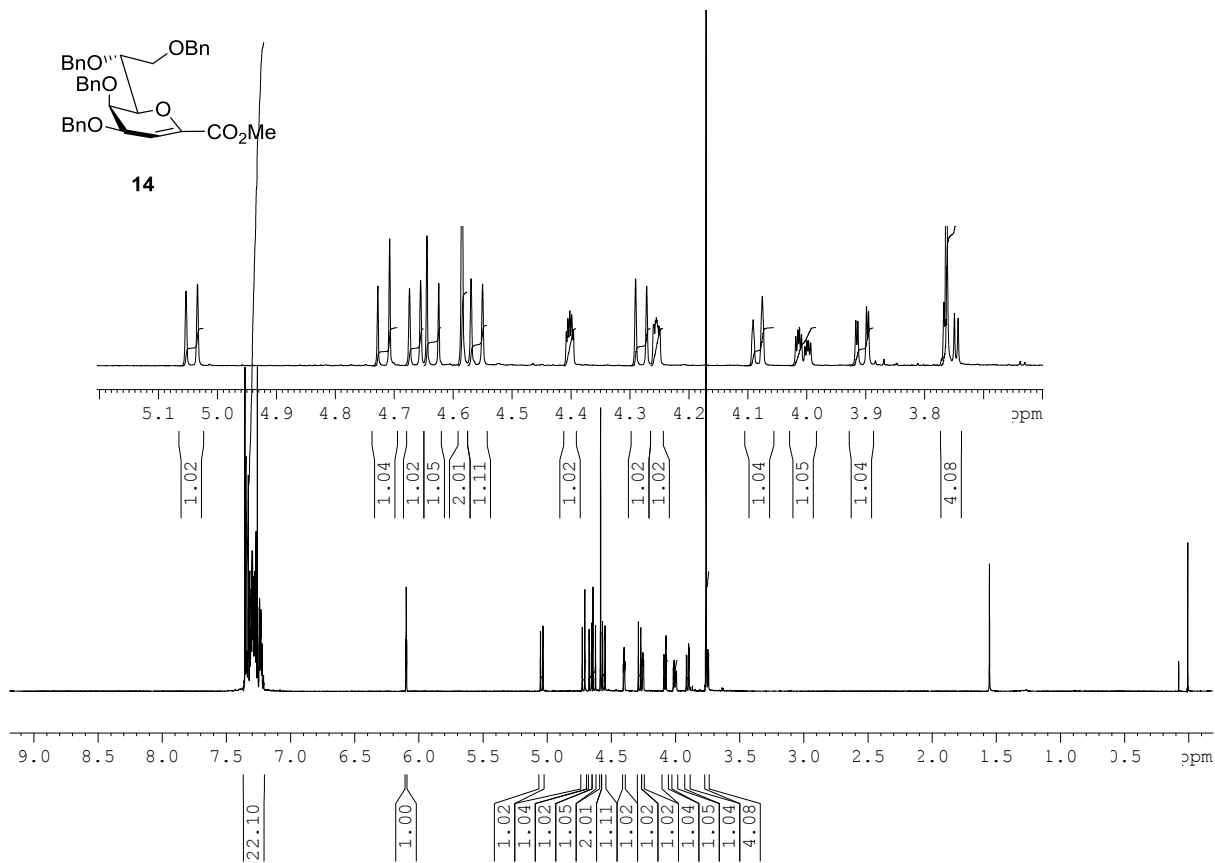
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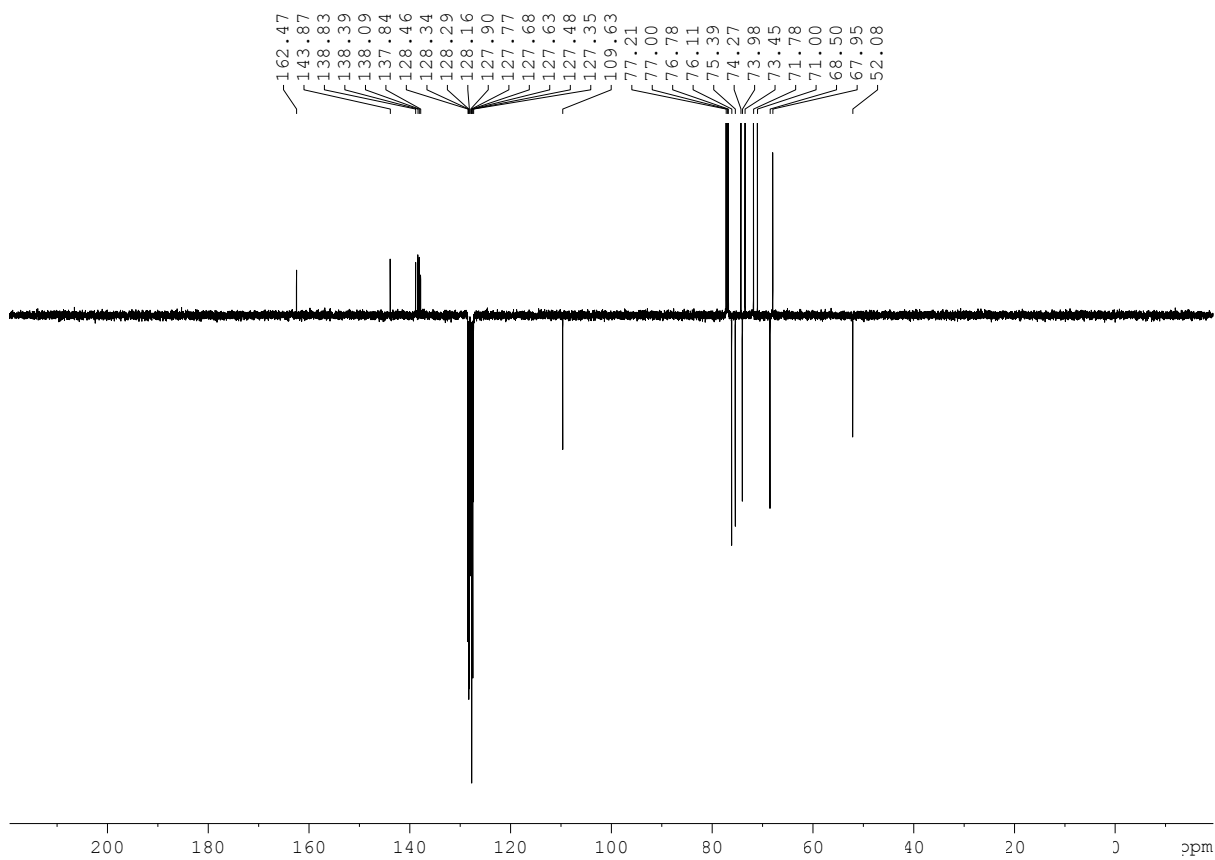
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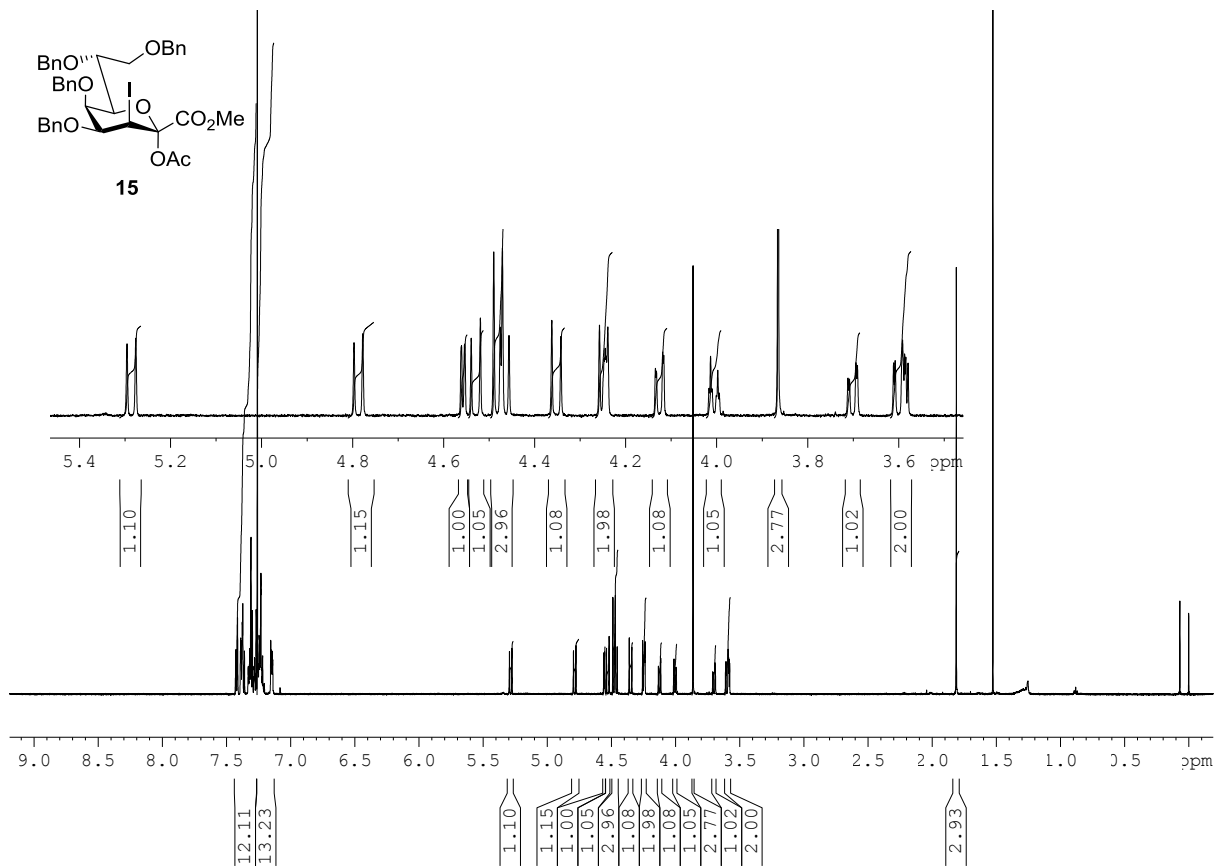
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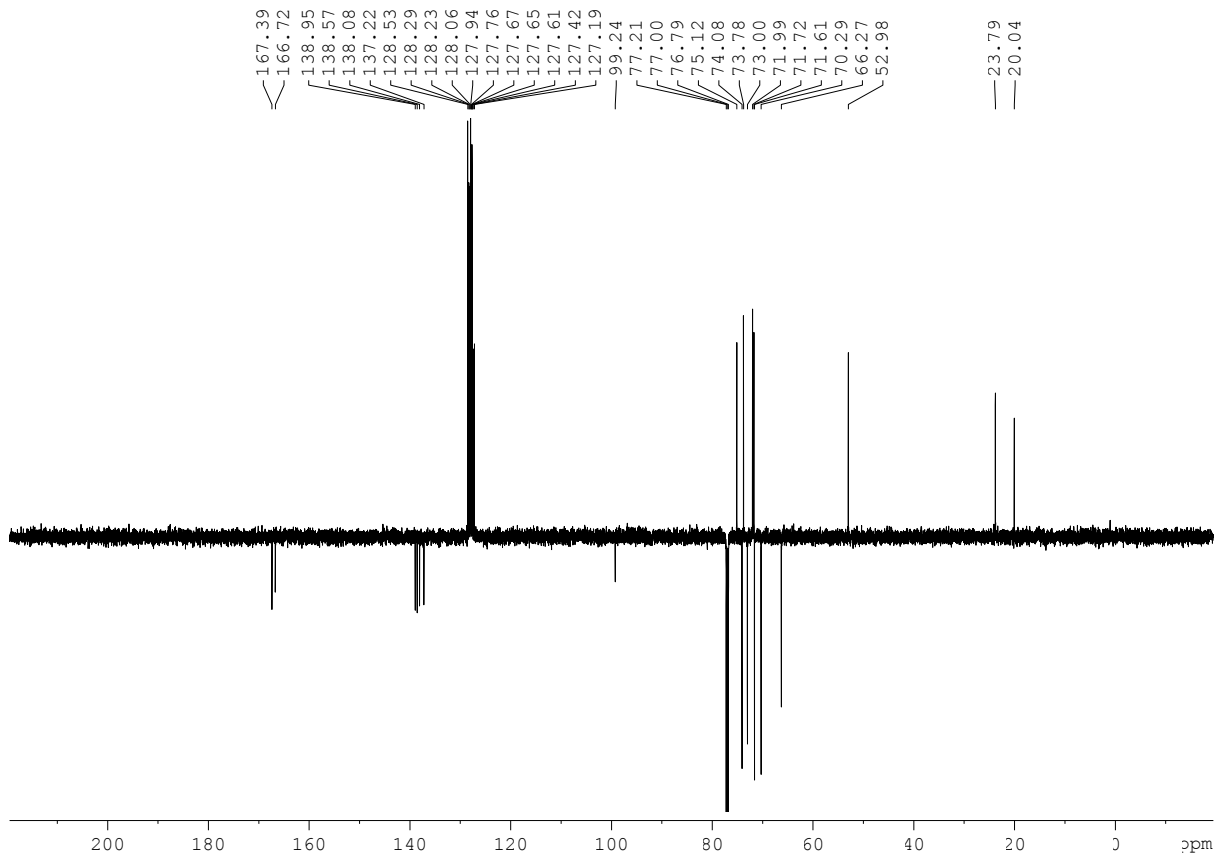
^{13}C NMR (CDCl₃, 150 MHz)



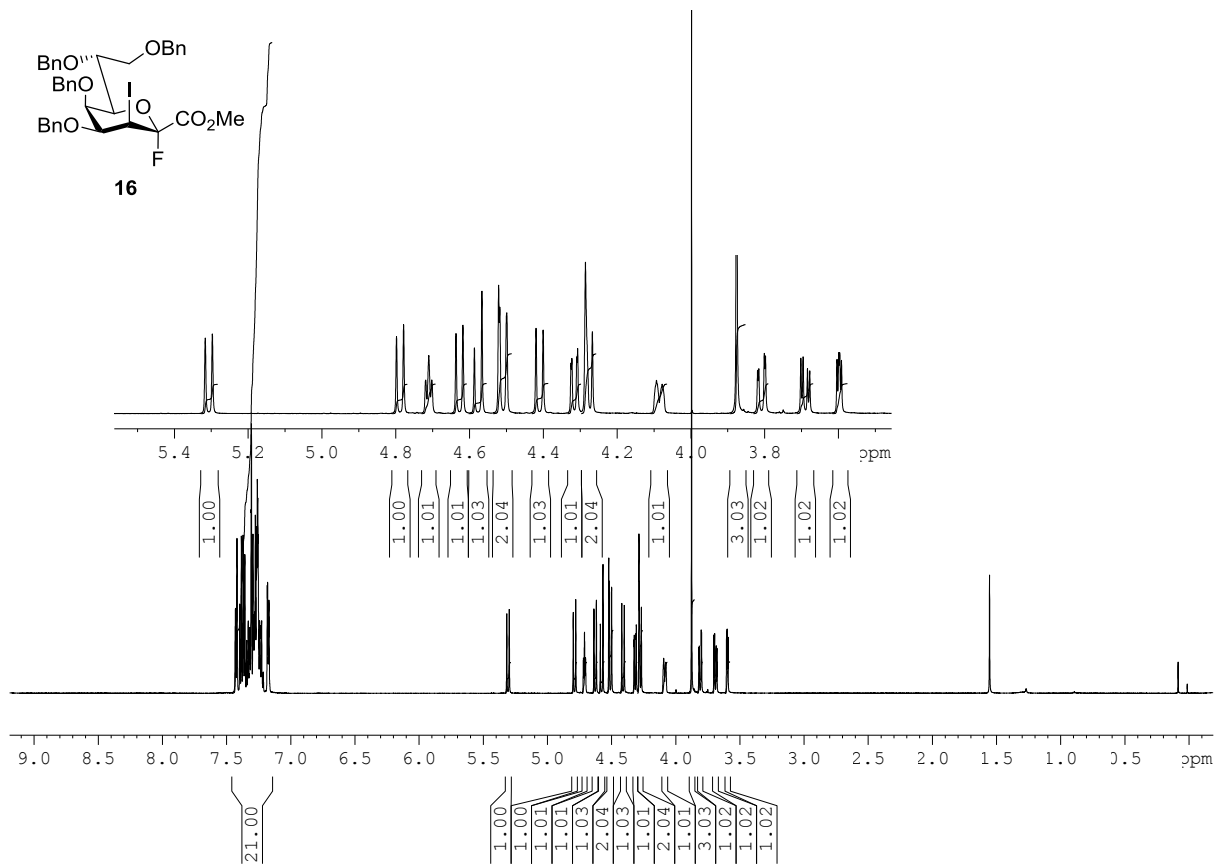
^{13}C NMR (CDCl₃, 150 MHz)



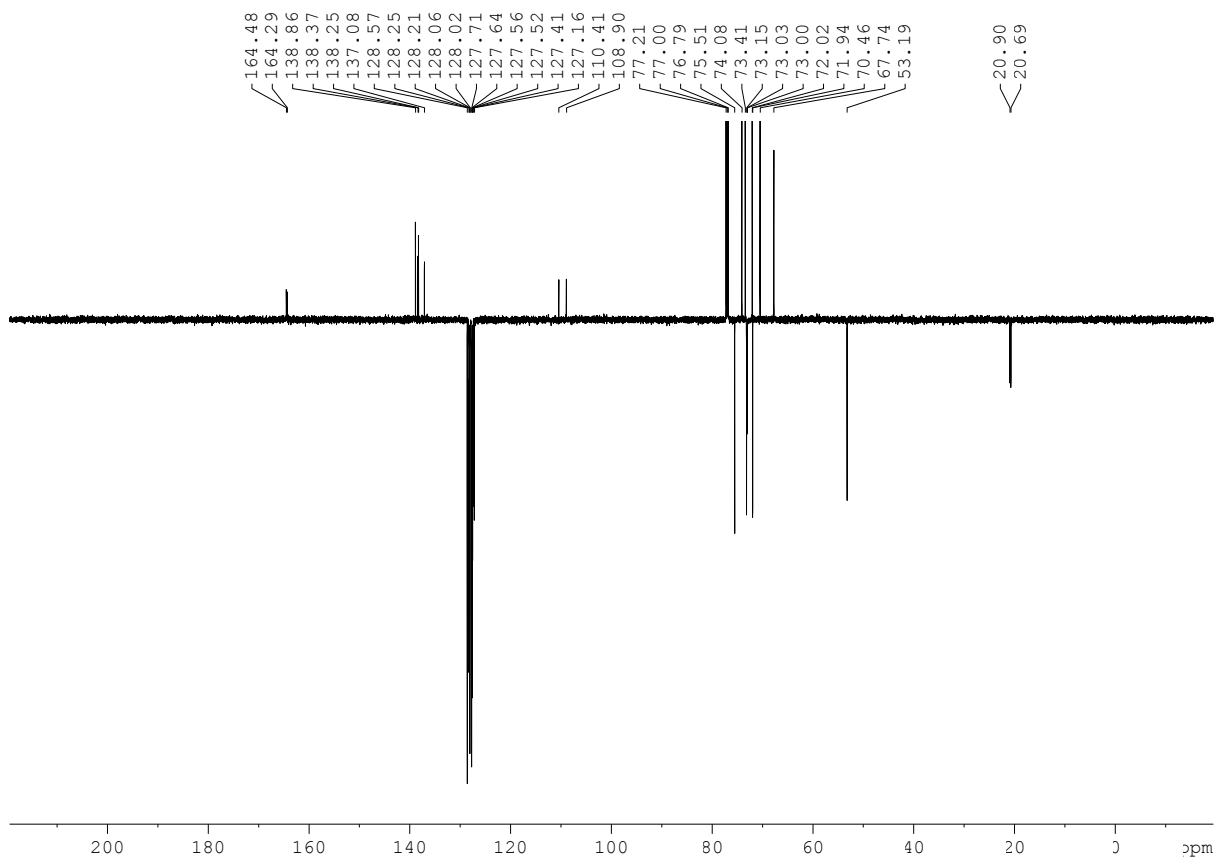
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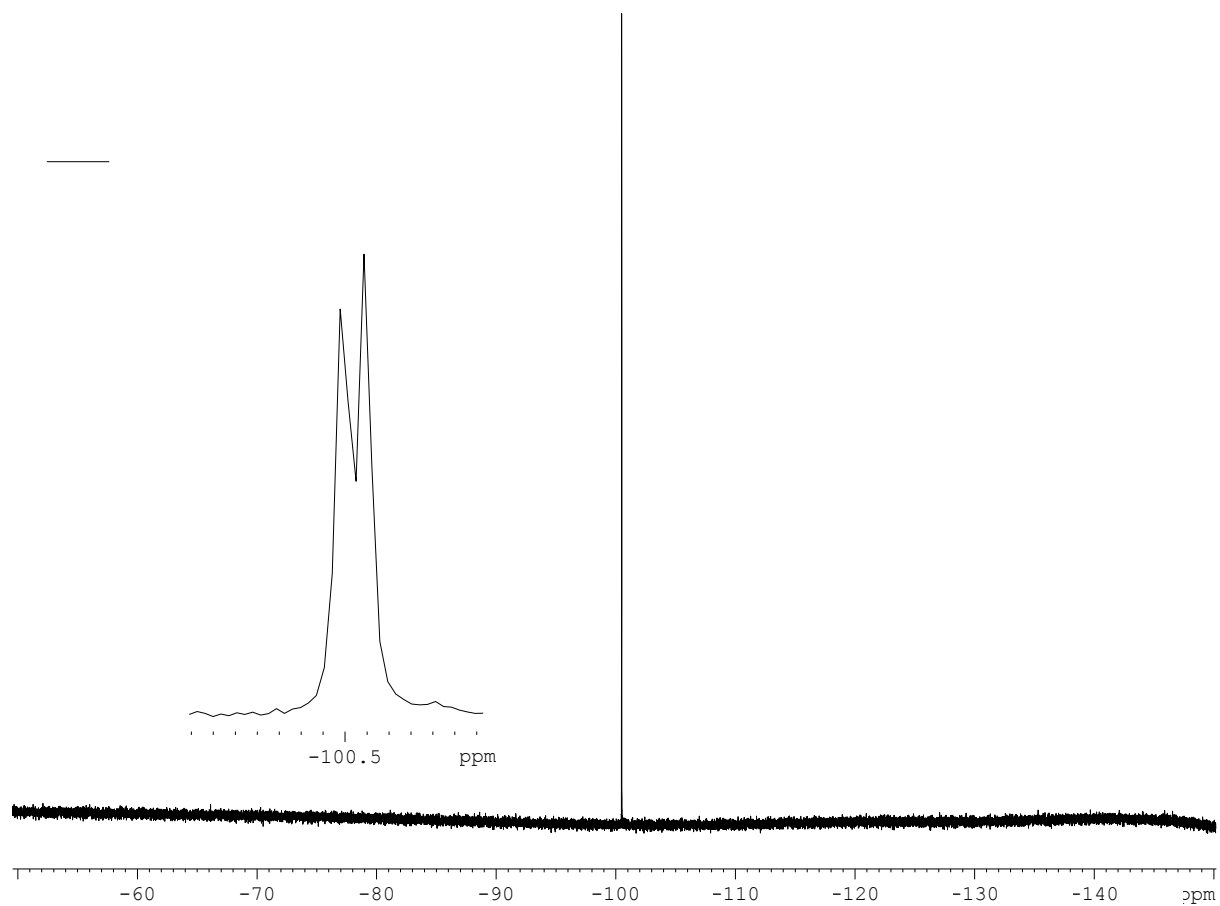
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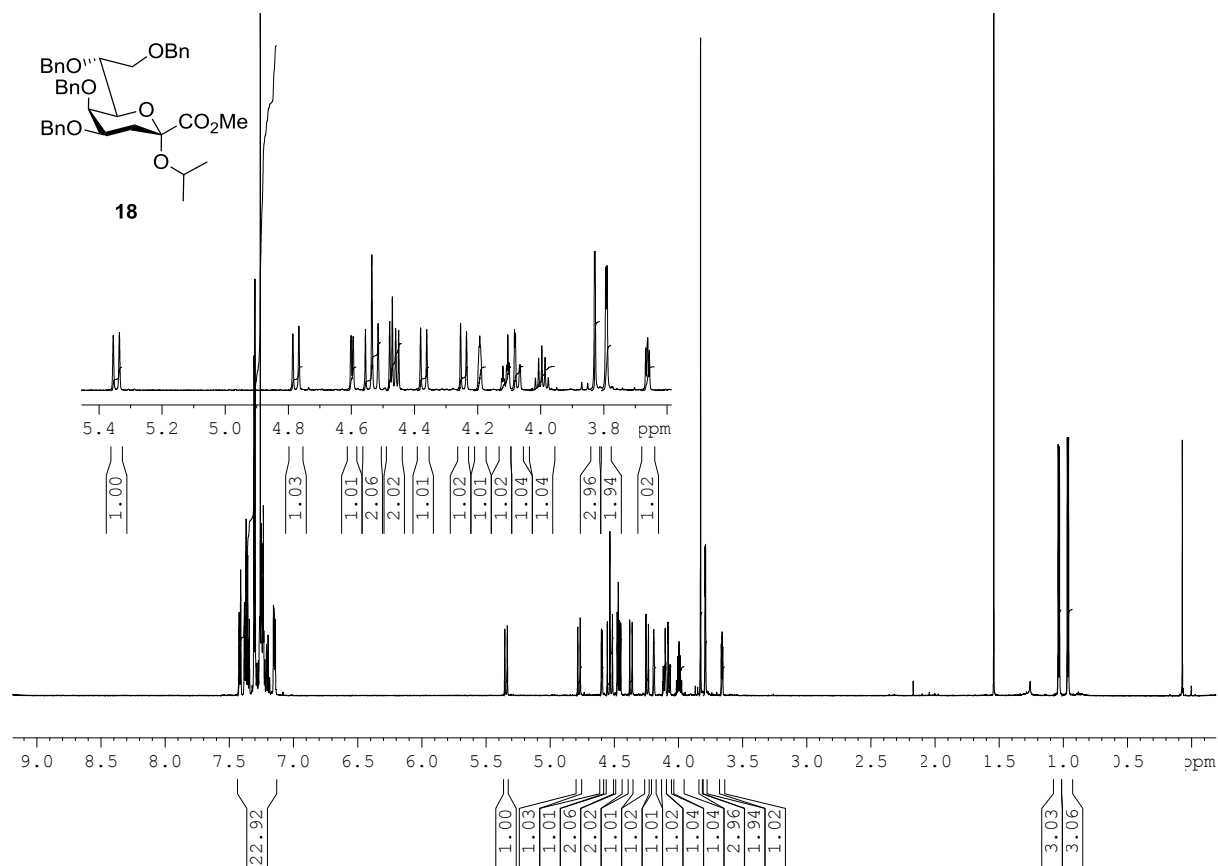
¹H NMR (CDCl₃, 600 MHz)



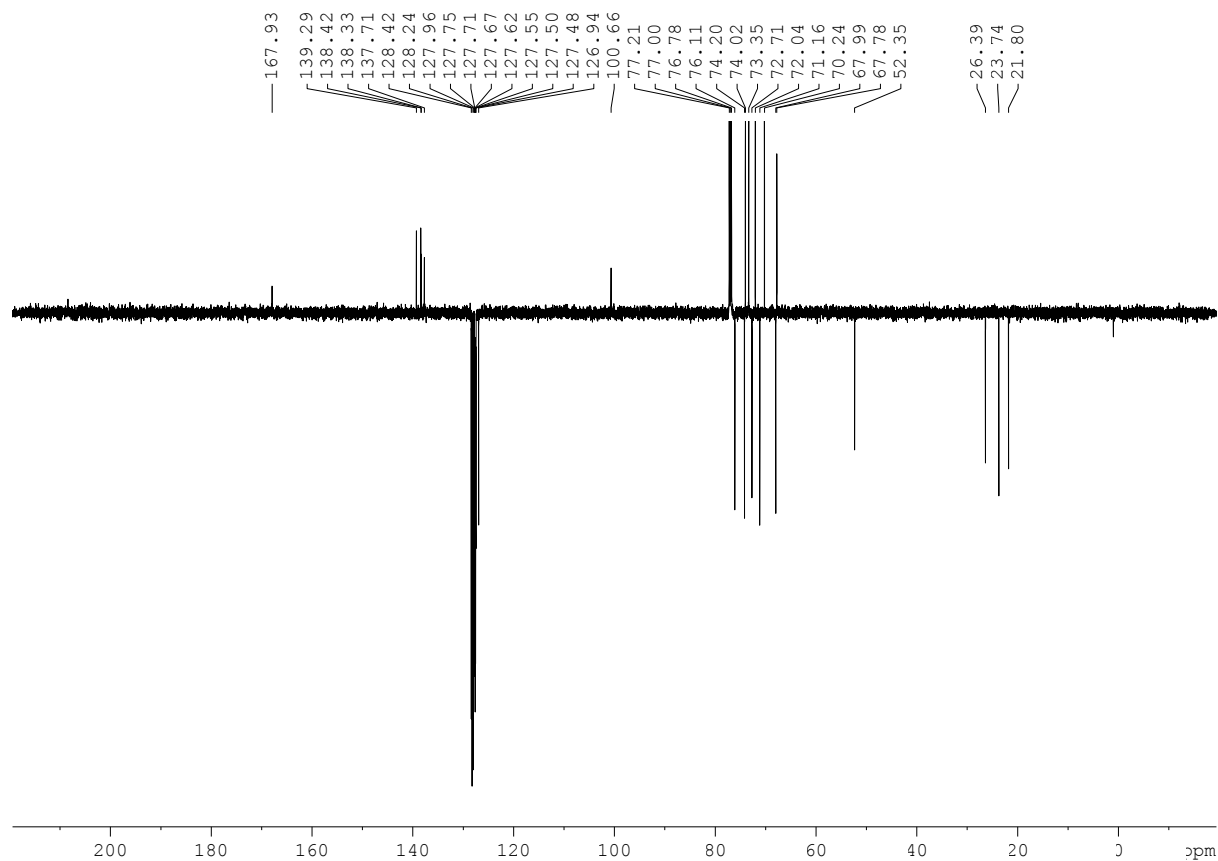
¹³C NMR (CDCl₃, 150 MHz)



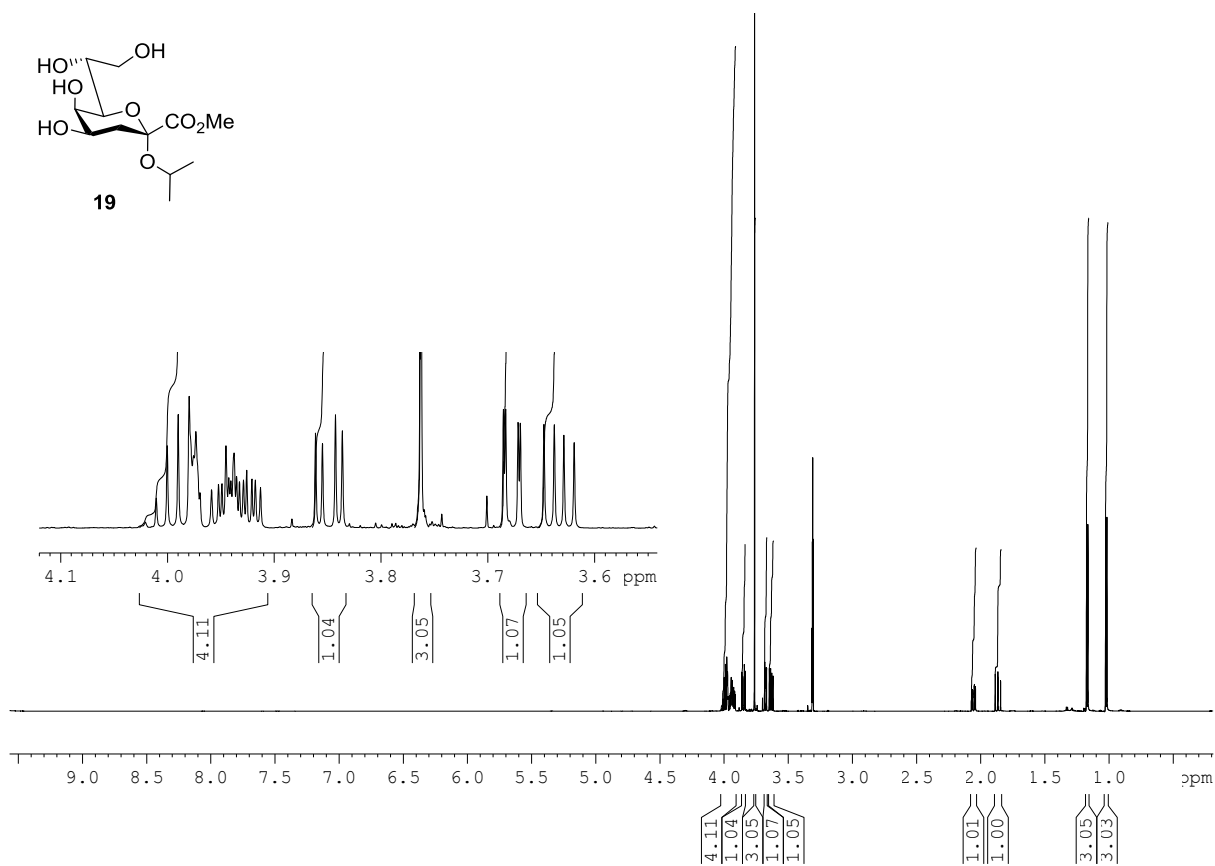
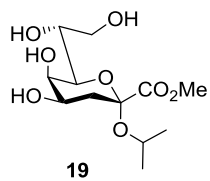
^{19}F NMR (CDCl_3 , 565 MHz)



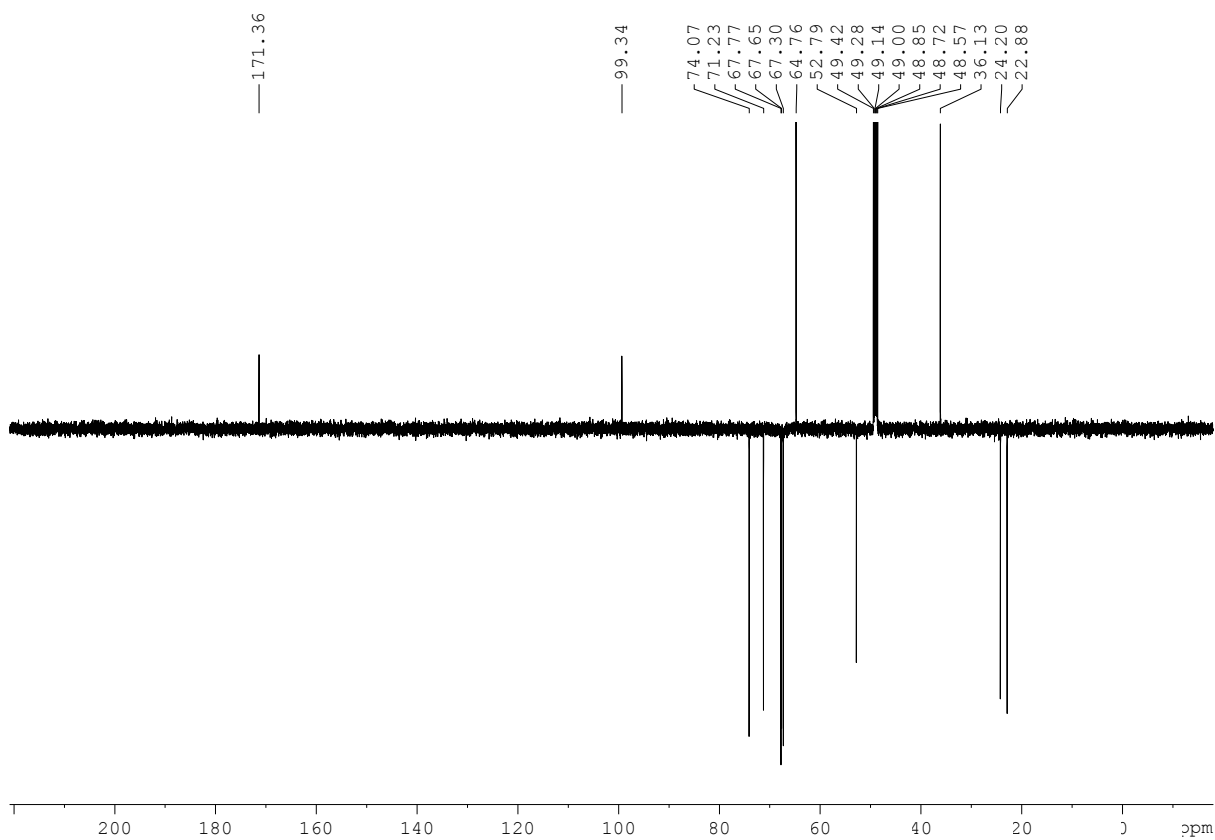
¹H NMR (CDCl₃, 600 MHz)



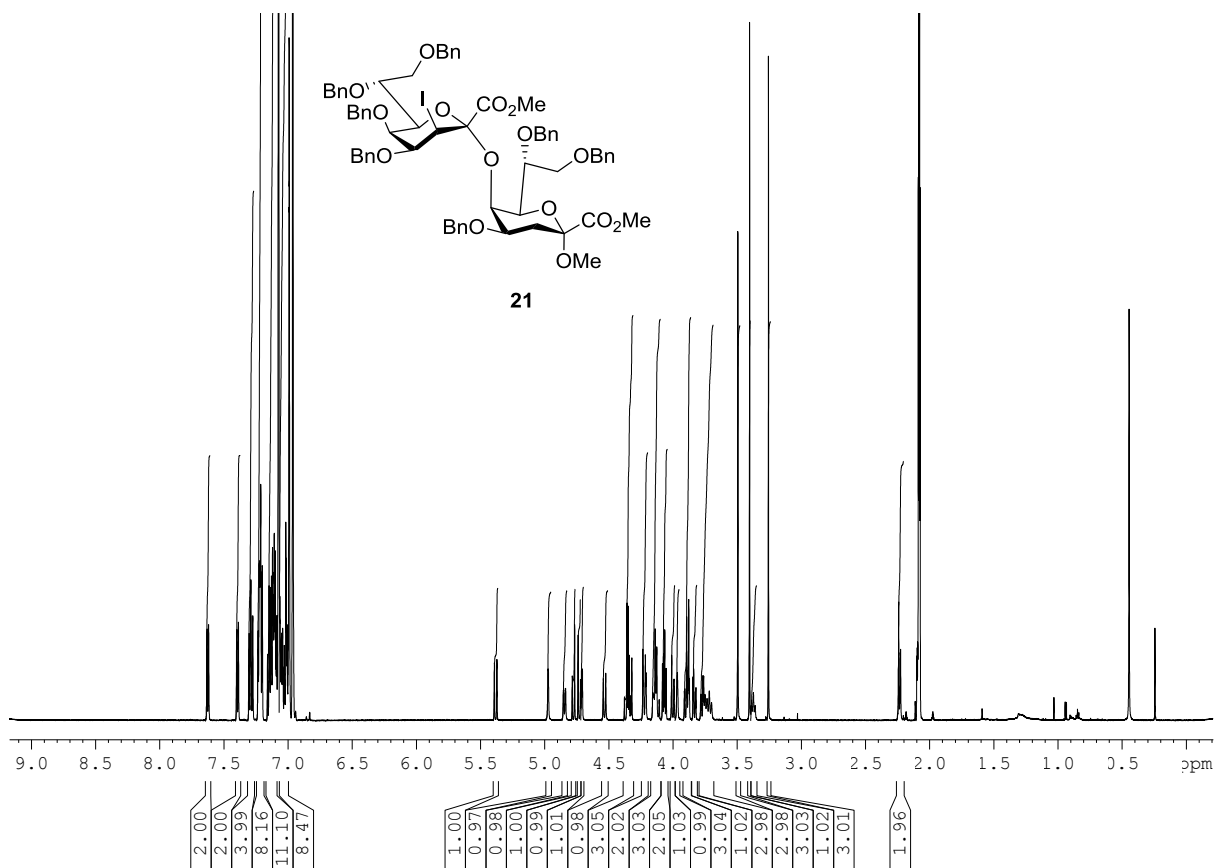
¹³C NMR (CDCl₃, 150 MHz)



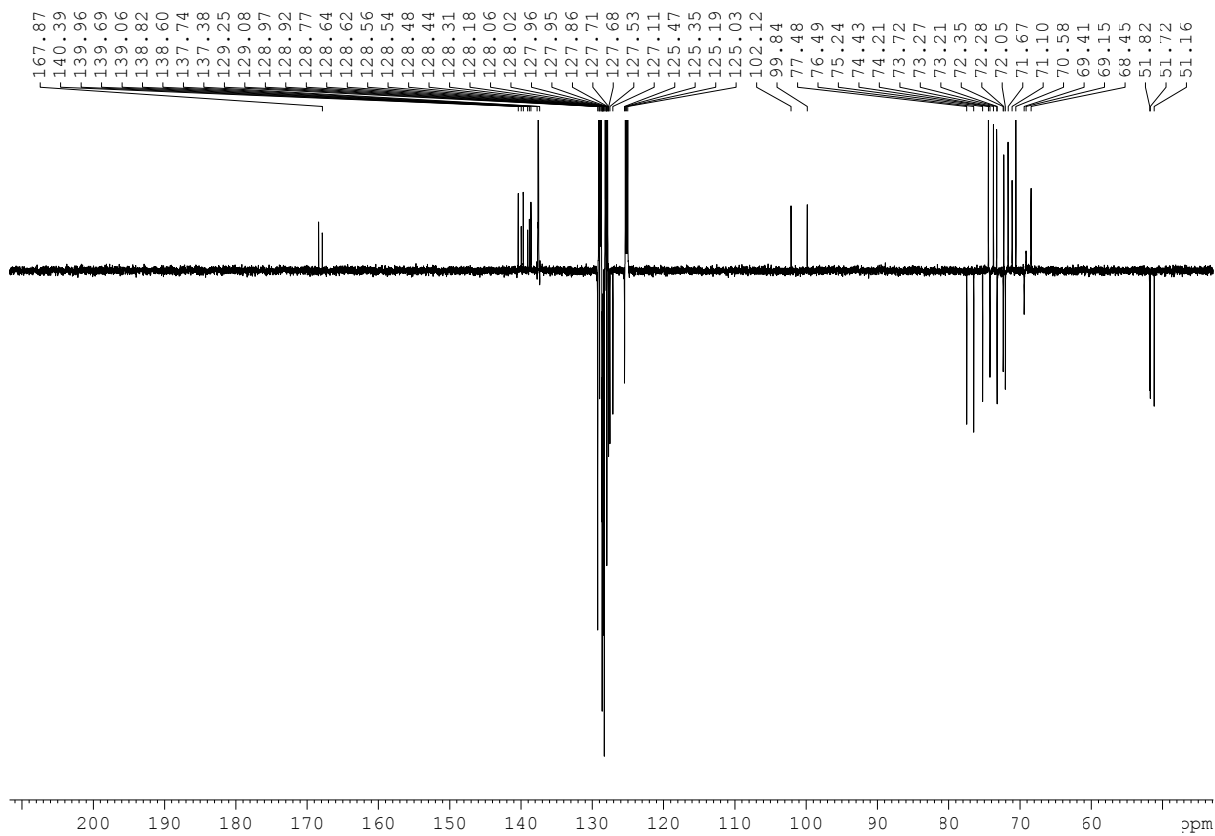
$^1\text{H NMR}$ (MeOD, 600 MHz)



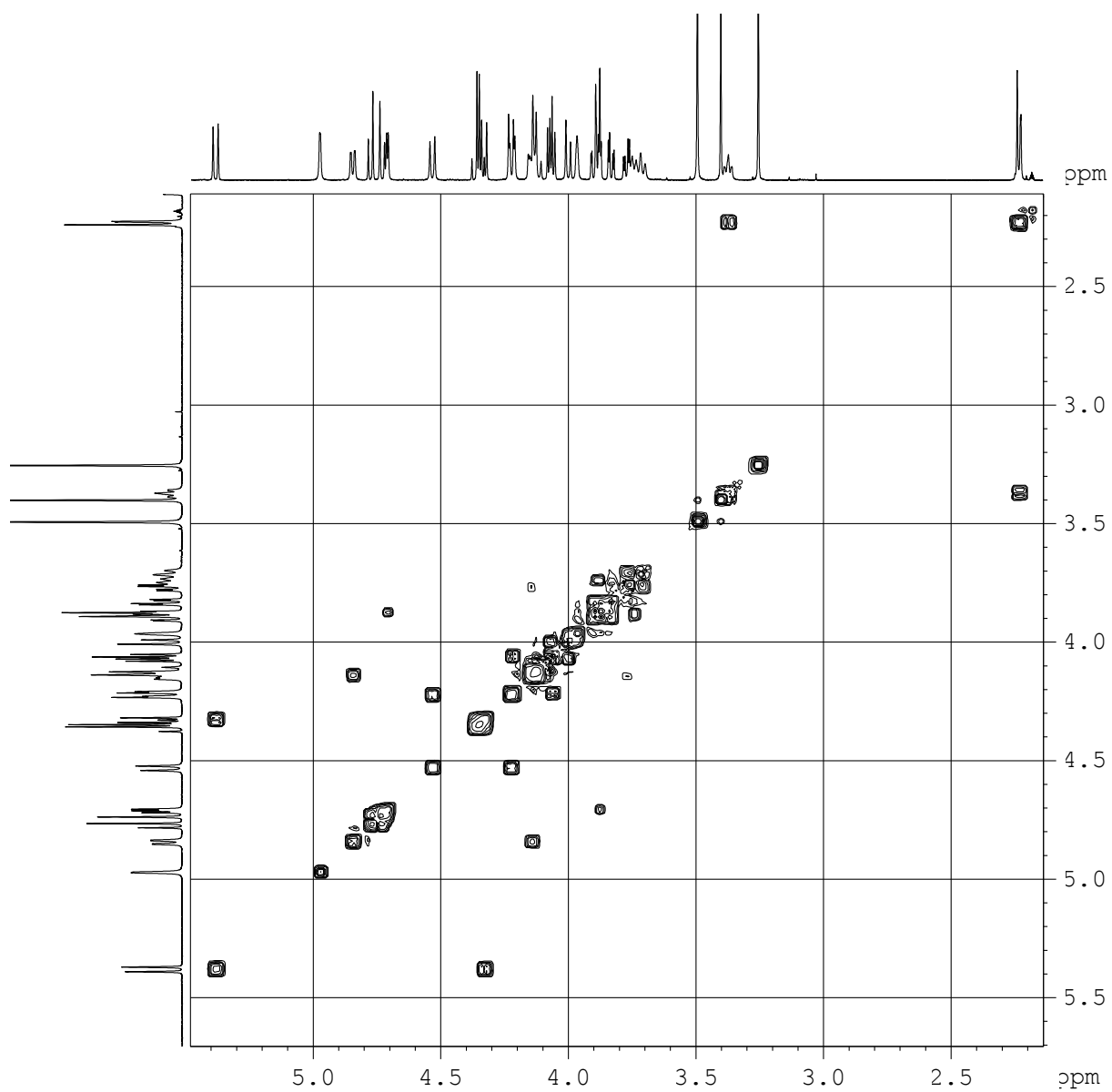
$^{13}\text{C NMR}$ (MeOD, 150 MHz)



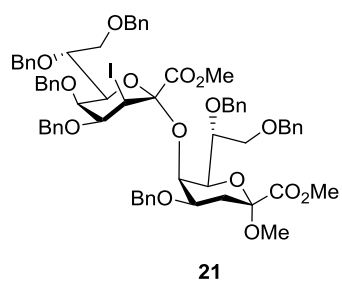
¹H NMR (d₈-toluene, 600 MHz, 323.15 K)

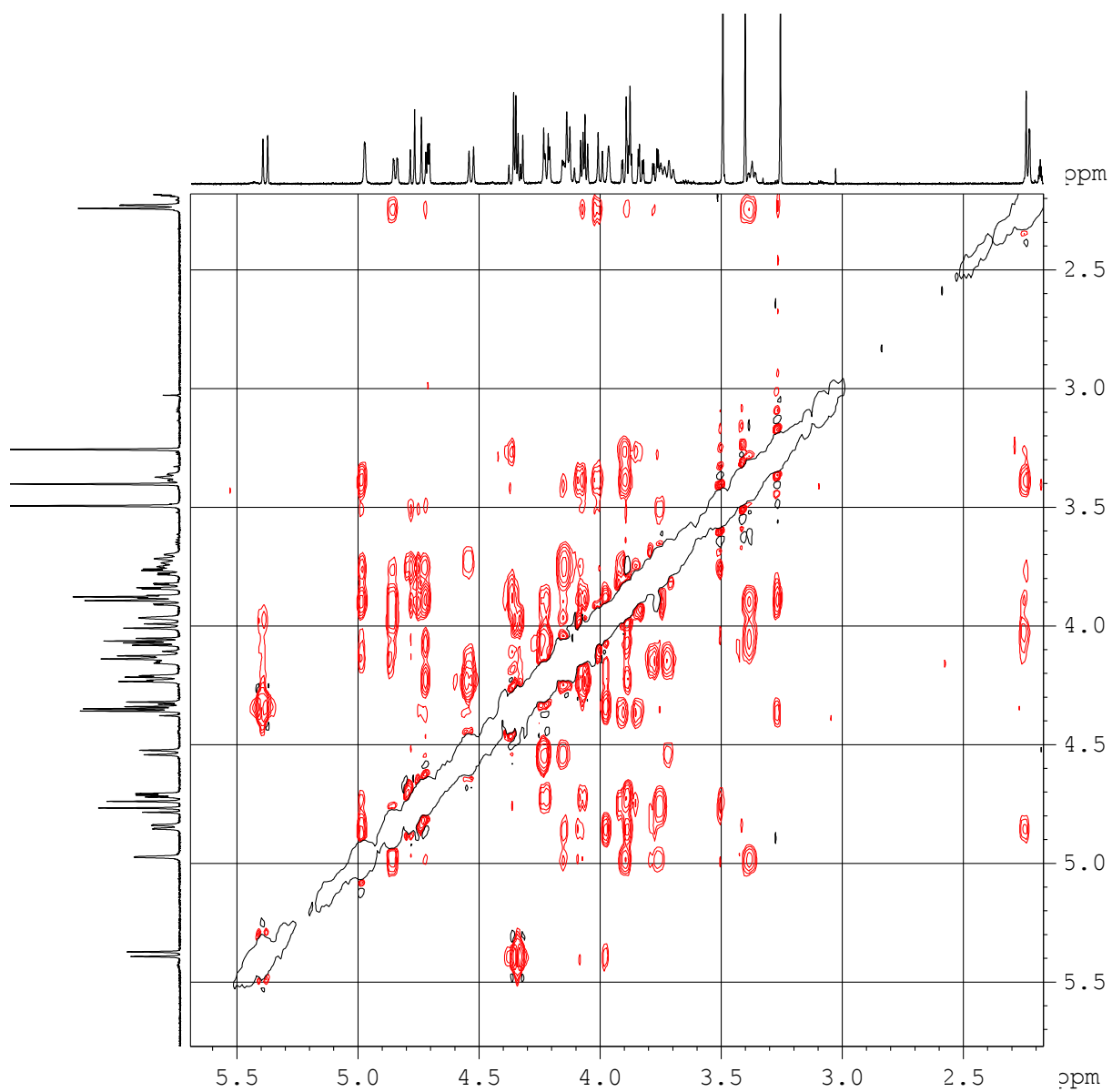


¹³C NMR (d₈-toluene, 150 MHz, 323.15 K)

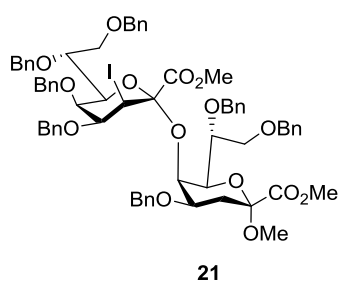


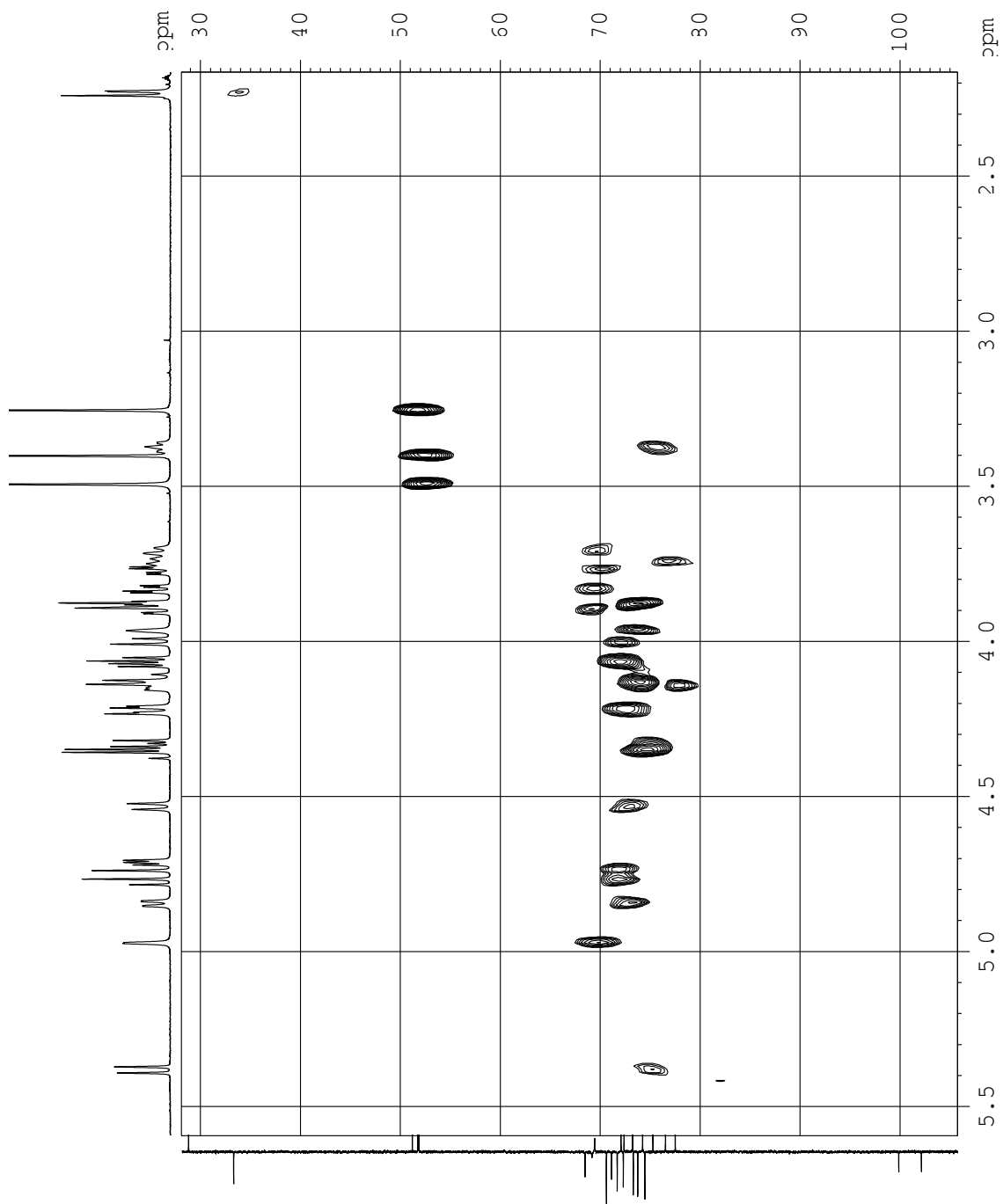
^1H - ^1H COSY (d_8 -toluene, 323.15 K)



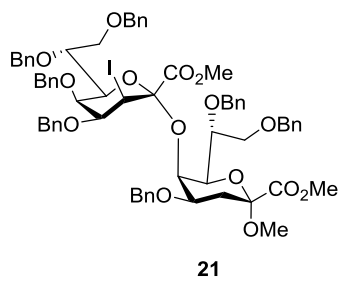


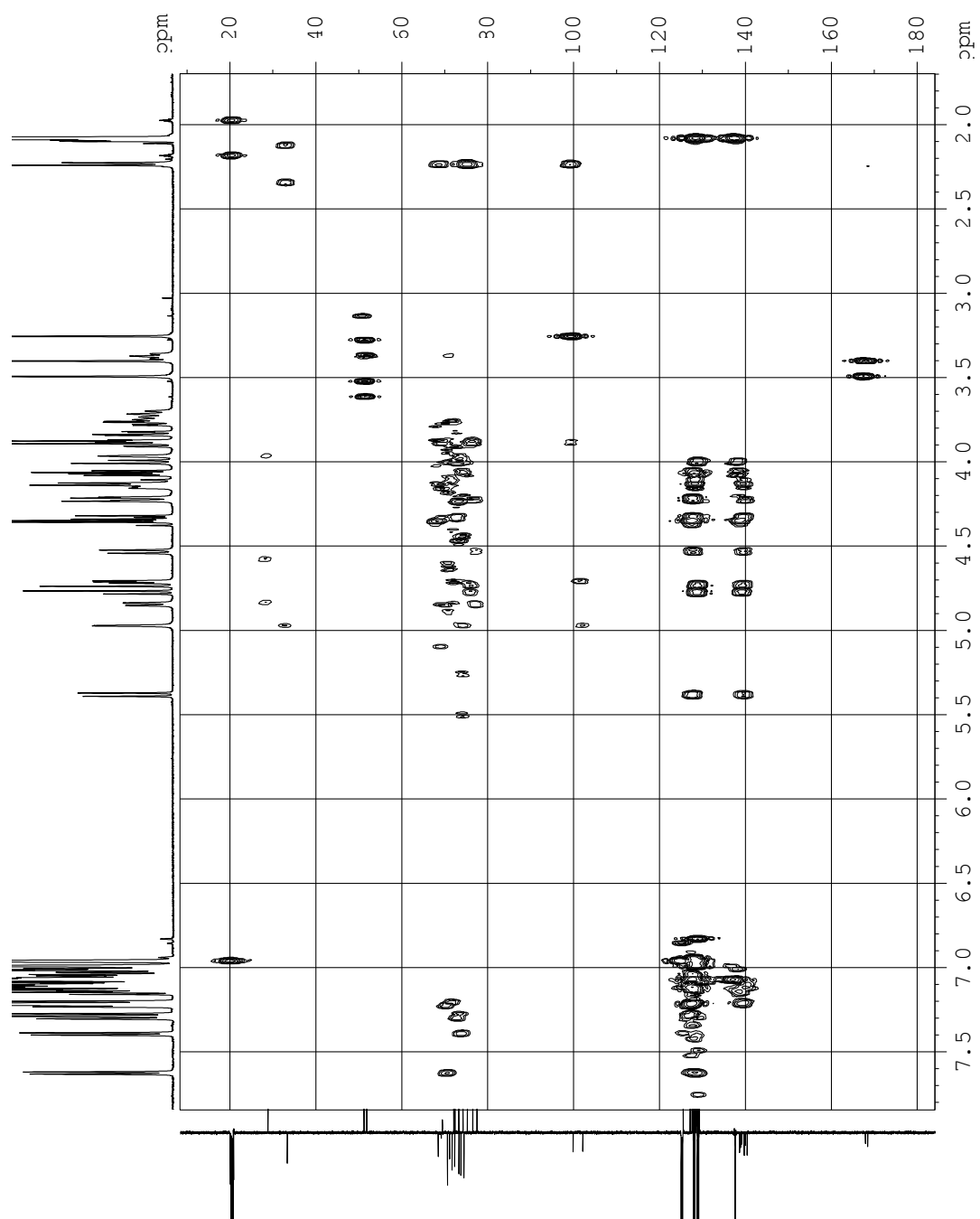
^1H - ^1H NOESY (d_8 -toluene, 323.15 K)



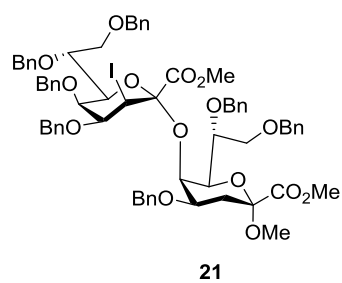


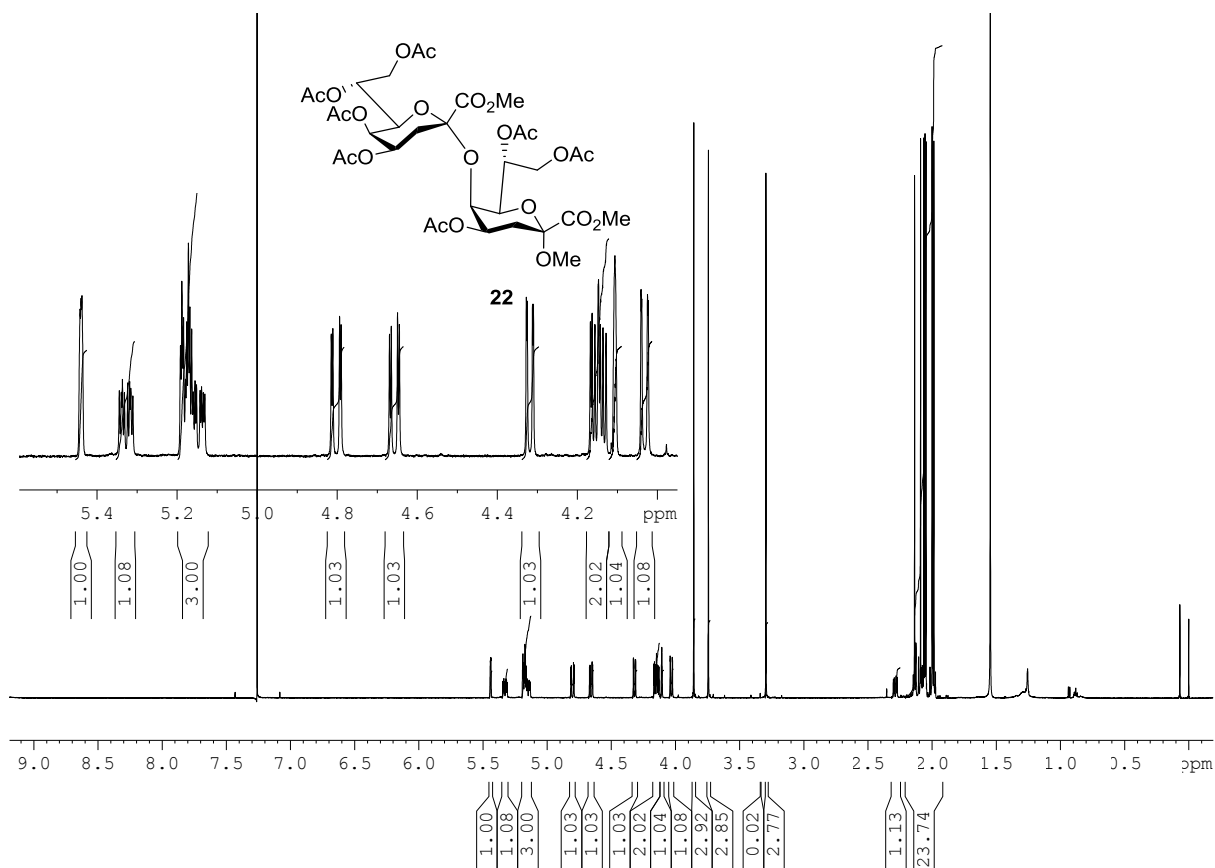
^1H - ^{13}C HSQC (d_8 -toluene, 323.15 K)



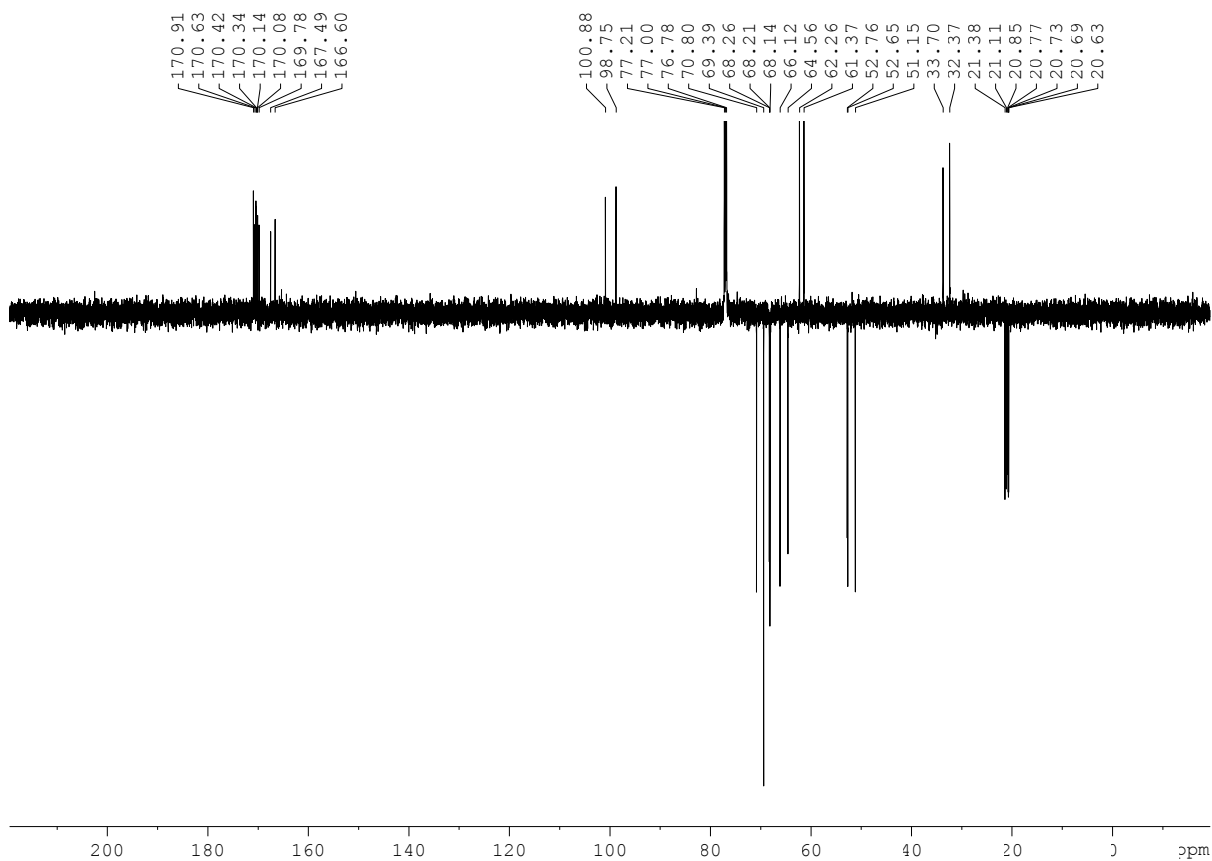


^1H - ^{13}C HMBC (d_8 -toluene, 323.15 K)

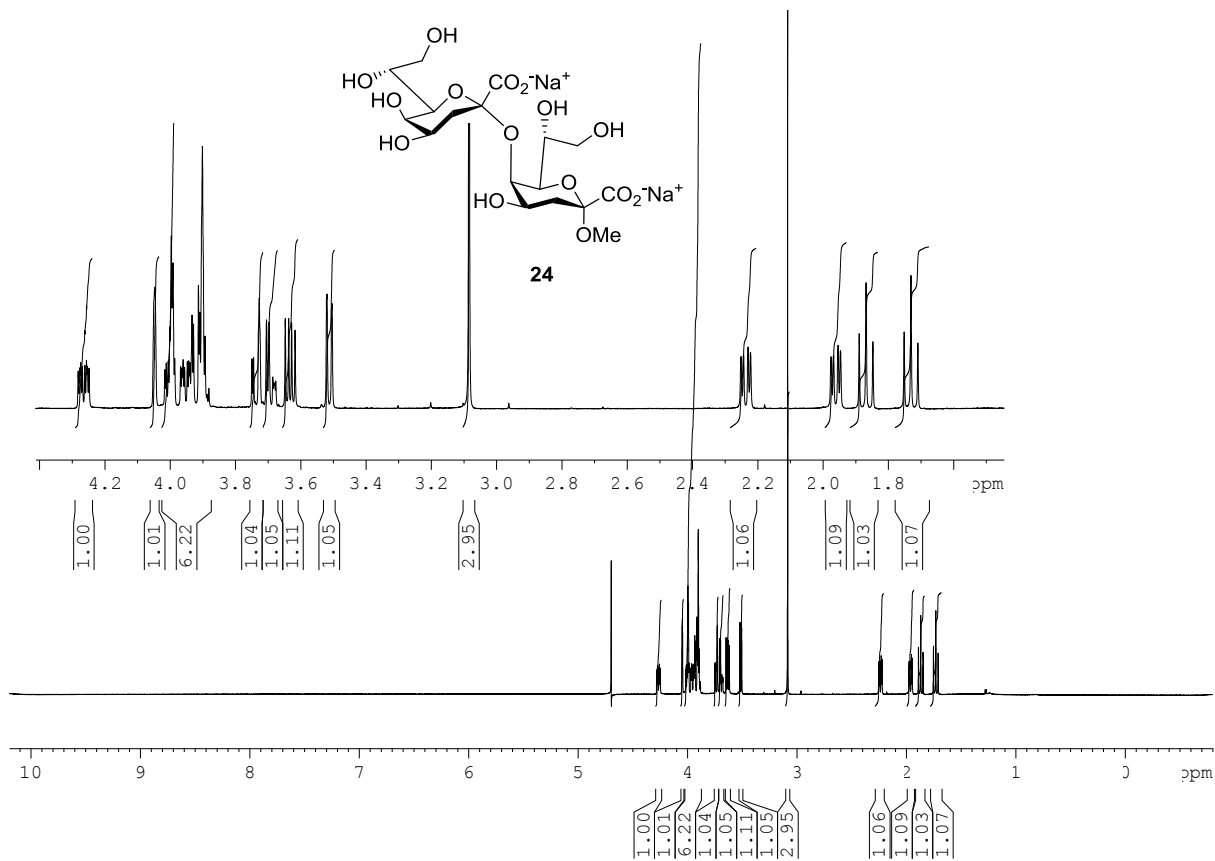




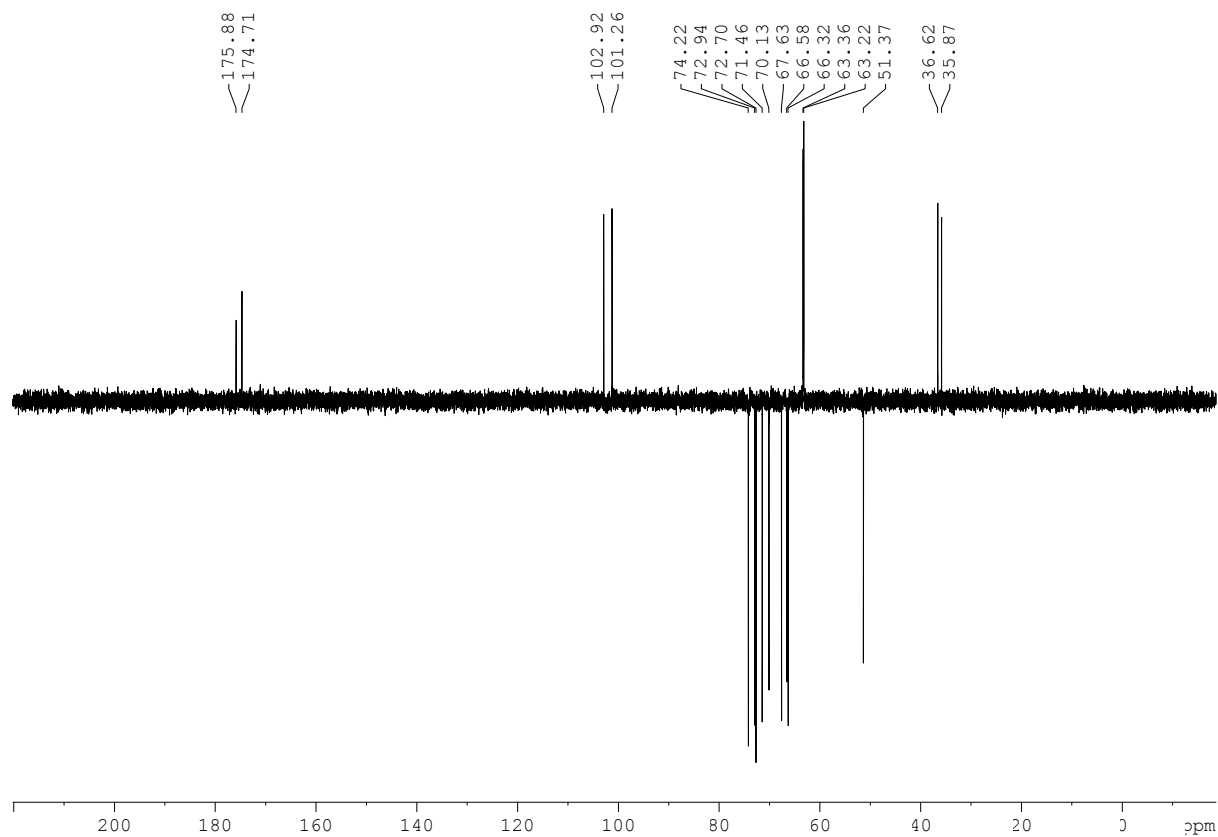
$^1\text{H NMR}$ (CDCl₃, 600 MHz)



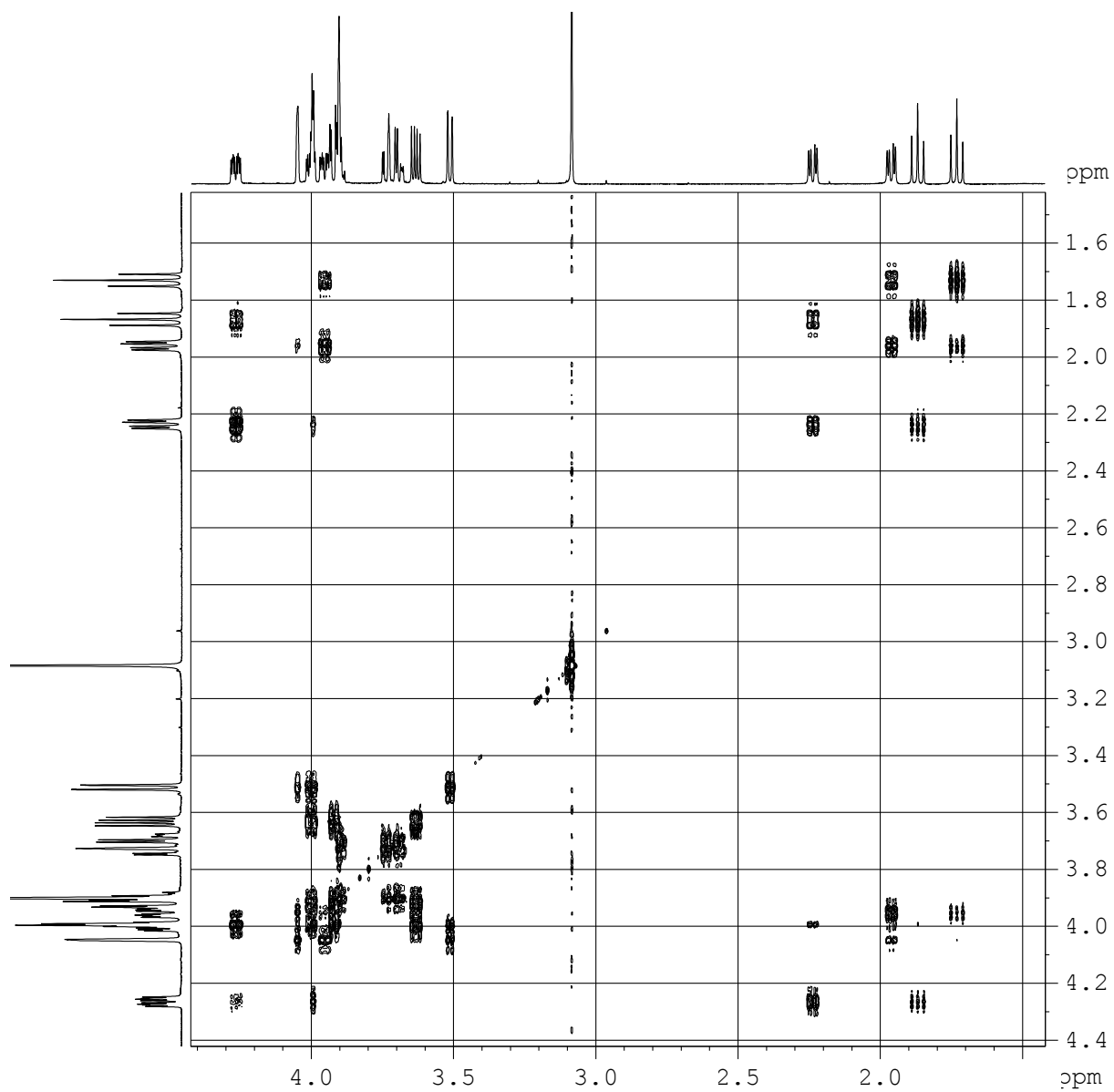
$^{13}\text{C NMR}$ (CDCl₃, 150 MHz)



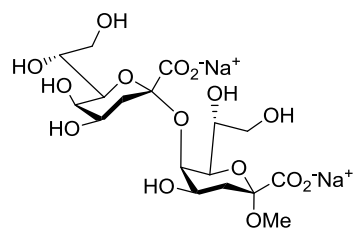
¹H NMR (D₂O, 600 MHz, pH ~ 7.0)



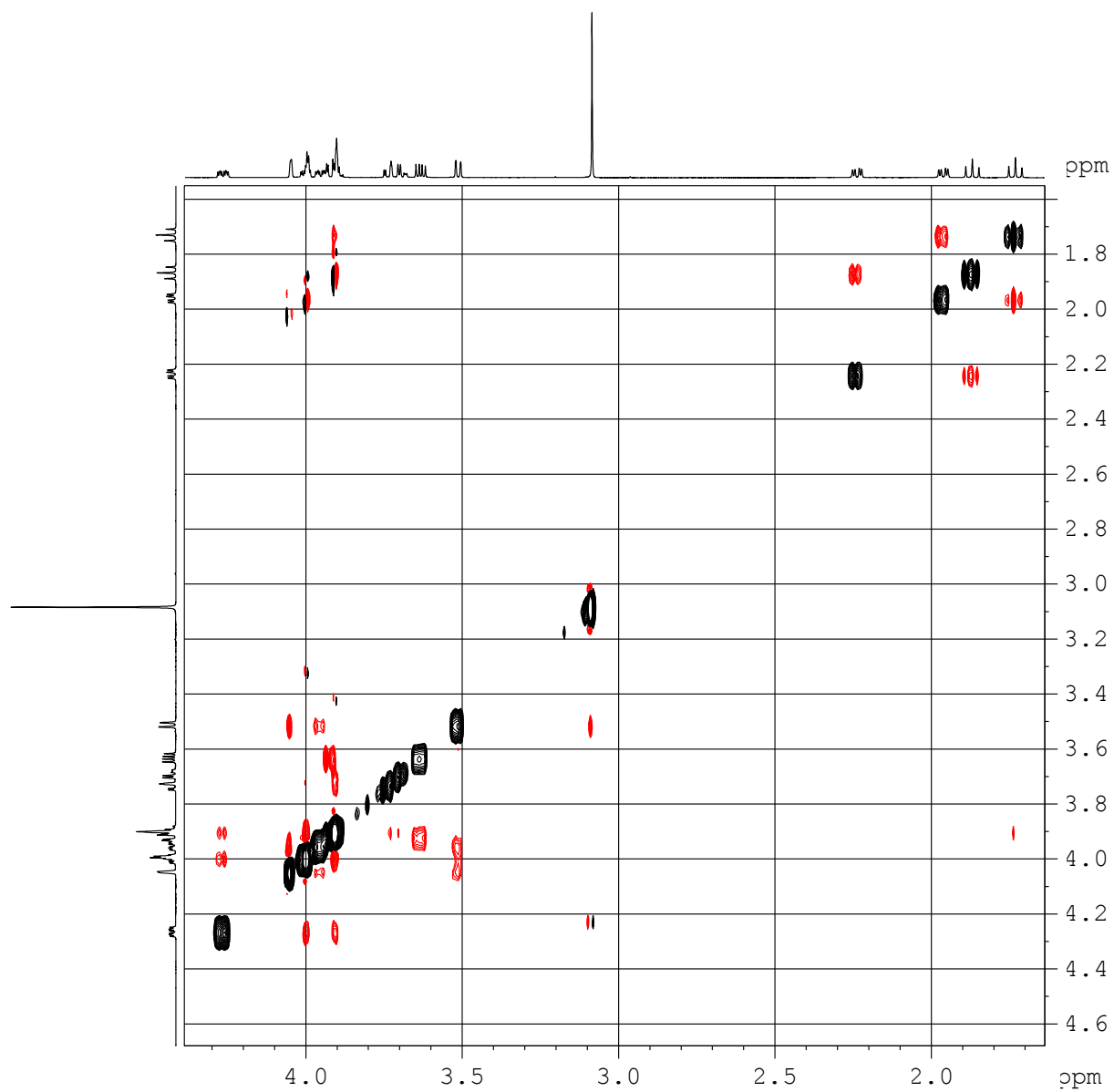
¹³C NMR (D₂O, 150 MHz, pH ~ 7.0)



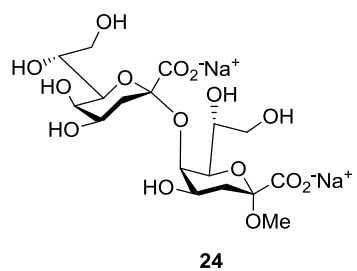
^1H - ^1H COSY (D_2O , $\text{pH} \sim 7.0$)

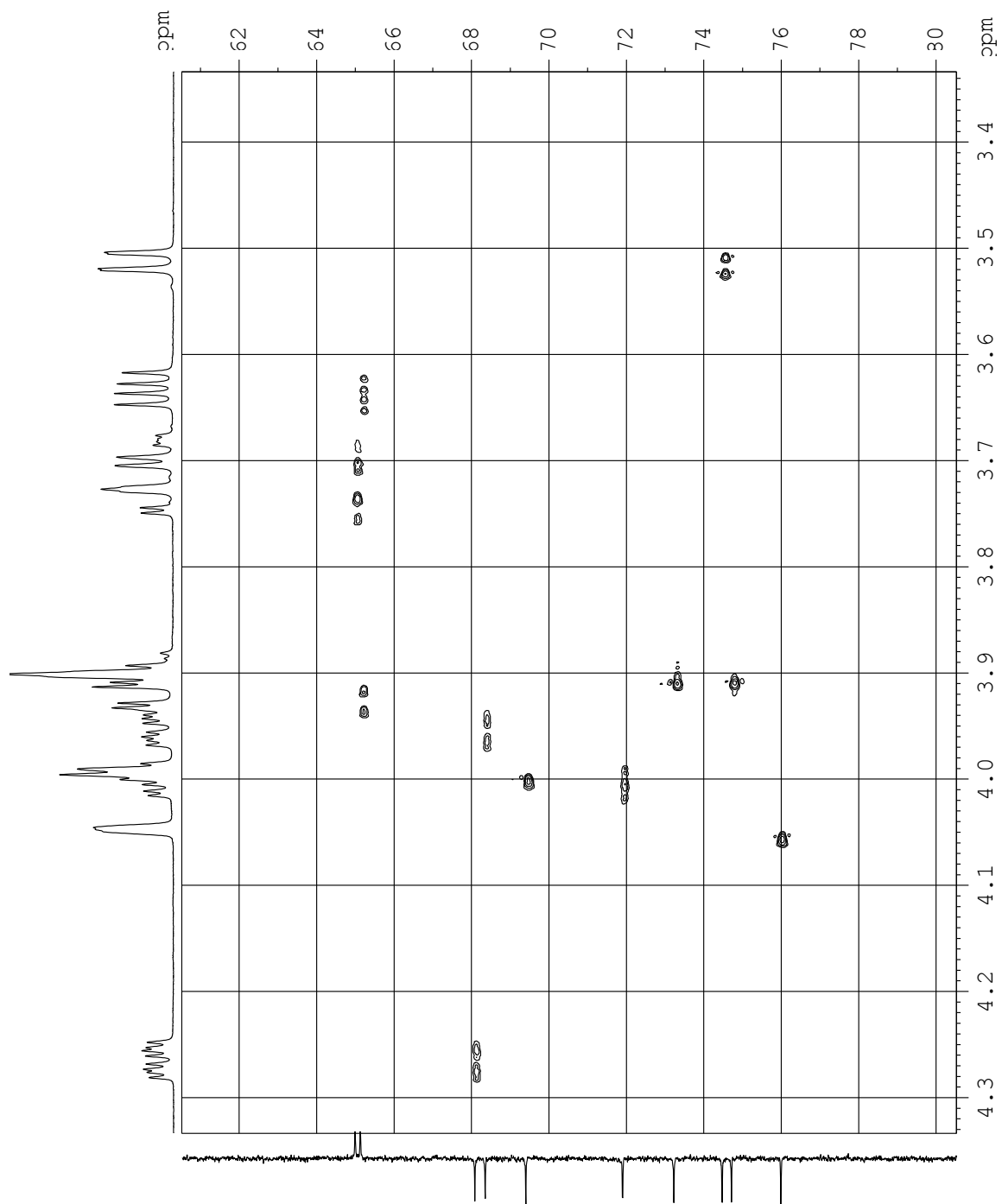


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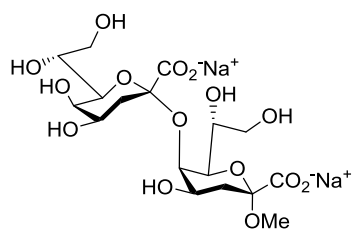


^1H - ^1H NOESY (D_2O , pH ~ 7.0)

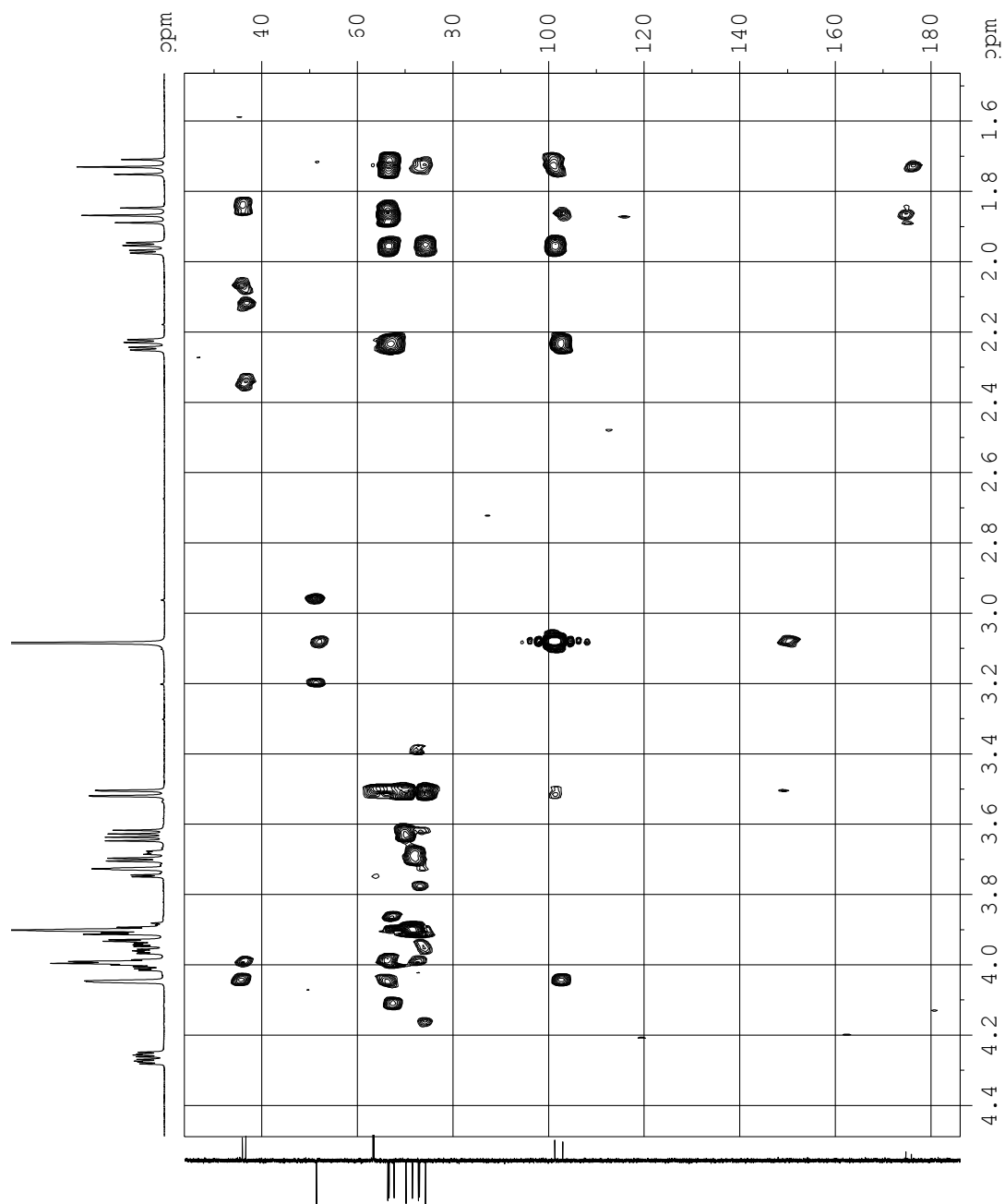




^1H - ^{13}C HSQC (D_2O , pH ~ 7.0)



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$^1\text{H}-^{13}\text{C}$ HMBC (D_2O , pH ~ 7.0)

