Supporting Information - A

Synthesis of Tetrazole Fused Azepanes and Quantum Chemical Topology Study on the Mechanism of the Intramolecular Cycloaddition Reaction.

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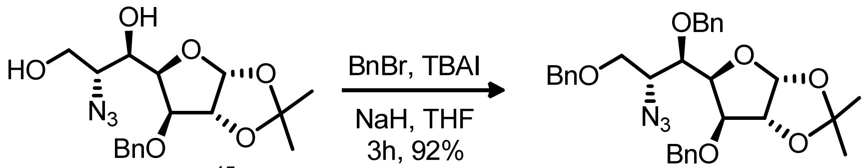
1. Experimental Procedures.

General.

Reactions were monitored by thin layer chromatography (TLC) on E. Merck silica gel plates (0.25 mm) and visualized using UV light (254 nm) and/or heating with phosphomolybdic acid/cerium sulfate(IV)/H2SO4 aq solution. Flash chromatography was performed on E. Merck silica gel (60, particle size 0.040–0.063 mm). NMR spectra were recorded on a Bruker Avance-400 or WP200SY spectrometers at room temperature. Chemical shifts (ppm) are reported relative to the residual solvent peak. Multiplicities are designated as: singlet (s), bs (broad single), doublet (d), triplet (t), multiplet (m), at (apparent triplet) and dt (double triplet) and Coupling constants *J* are expressed in Hertz units. NMR assignments were made using two-dimensional COSY and gHMQC experiments. NMR numbering for bicycled products followed that of the previous compounds. IR spectra of the azido compounds were recorded on a SHIMADZU FTIR-8300 and showed the N_3 typical band at 2324–2352 cm^{-1}. High resolution mass spectra (HRMS, FAB) were recorded in the Mass Spectrometry Service of the University of Seville. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

1.1 Synthesis of 6-azido-3,5,7-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-D-glycero-α-D-gluco-heptofuranose (16).

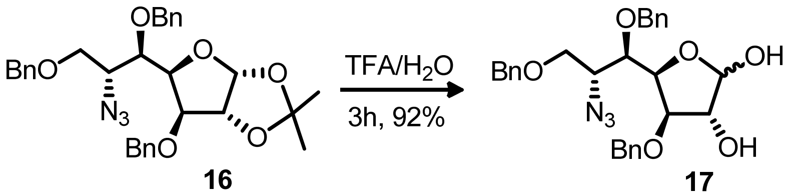


15[15] **16**

To a stirred solution of azide **15** (750 mg, 2.05 mmol) in dried THF (10 mL) at 0ºC, were added NaH 60% mineral oil (0.84 g), TBAI (3 mg) and BnBr (0.52 ml, 4.37 mmol) dropwise. After 3 h, solvent was evaporated and the residue dissolved in $CHCl_3$. The solution was washed with 5% aq. NaOH, dried (anh. $MgSO_4$) and concentrated under vacuum to give the tribenzylated **16** (1.02 g, 92%) as a colourless syrup. **Rf:** 0.3 (4:1 Hex/AcOEt). **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** 7.37-7.16 (m, 15H, *Ph*), 5.89 (d, 1H, *J* = 3.7 Hz, H-1), 4.77-4.47 (m, 6H, C*H₂*Ph), 4.43 (d, 1H, *J* = 4.3 Hz, H-2), 4.37 (d, 1H, *J* = 4.3 Hz, H-3), 4.23 (dd, 1H, *J* = 3.0 Hz, 9.3 Hz, H-6), 4.15-3.99 (m, 2H, H-4 and H-5), 3.80-3.74 (m, 2H, H-7a and H-7b), 1.44 and 1.30 (2s, 2x3H, 2CH_3). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** 137.3-127.2 (3 *Ph*), 111.9 [*C*$(CH_3)_2$], 105.19 (C-1), 82.00, 81.33 and 78.75 (C-2, C-3 and C-4), 76.64 (C-5), 73.50, 73.30 and 71.90 (*C*H_2Ph), 63.10 (C-6), 26.90 and 26.40 (2*C*H_3).

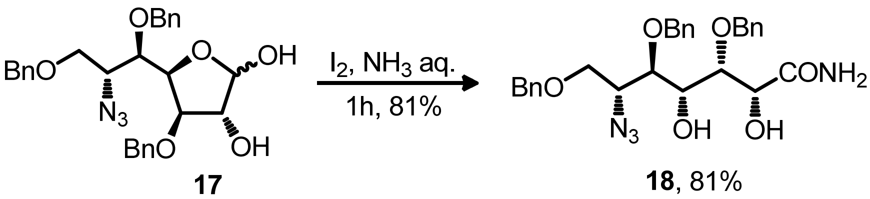
ref. 15: N. Oña, A. Romero-Carrasco and M. S. Pino-González, *Tetrahedron: Asymmetry* 2013, **24**, 156.

1.2 Synthesis of 6-azido-3,5,7-*O*-benzyl-6-deoxy-D-glycero-α-D-gluco-heptofuranose (17).



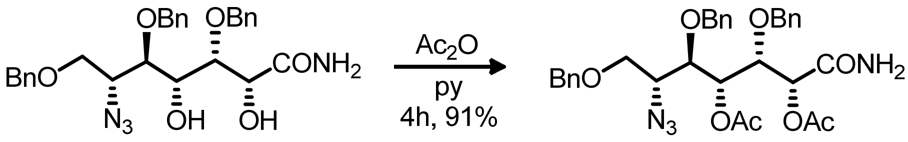
The protected azide **16** (840 mg, 1.53 mmol) was dissolved in 5 mL of TFA/H_2O (3:2) and stirred for 3h at r.t. Then, the mixture was concentrated and the residue purified by column chromatography to give pure **17** (710 mg, 92%) as a colourless syrup. **Rf:** 0.45 (1:1 Hex/AcOEt). **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** 7.61-7.16 (m, 15H, *Ph*), 5.47 (dd, 1H, *J* = 6.5 Hz, *J* = 4.1 Hz H-1), 4.82-4.33 (m, 8H, 3CH_2Ph, H-2, H-3), 4.32-3.60 (m, 3H, H-4, H-5, H6), 2.95-2.85 (m, 2H, H-7a and H-7b). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** 137.3-127.2 (3*Ph*), 79.2, 77.8, 74.1, 73.7 72.2 (C-1, C-2, C-3, C-4, C-5), 72.68, 69.35 and 69.02 (*C*H_2Ph), 63.24 (C-6).

1.3 Synthesis of (2R,3S,4R,5R,6R)-6-azido-3,5,7-tribenzyloxy-2,4-dihydroxyheptanamide (18).



To a solution of lactol **17** (515 mg, 1.01 mmol) in 28% aq NH_3 (10 mL) and THF (1 mL), was added I_2 (281 mg, 1.11 mmol). After stirring for 1h, a saturated solution of $Na_2S_2O_3$ was added and the mixture extracted with CH_2Cl_2 (2 x 25 mL). The combined organic solvents were dried ($MgSO_4$) and concentrated to give amide **18** (425 mg, 81%) as a colourless syrup. A minor product (19 mg, 4%) was isolated and identified as azido nitrile with a carbon less. **Rf:** 0.25 (1:1 Hex/AcOEt). **$[\alpha]_D^{26}$** -30.4 (c 0.8, CH_2Cl_2) **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** δ 7.42–7.17 (m, 15H, 3*Ph*), 6.81 (d, 1H, *J* = 3.0 Hz, N*H_2*), 6.27 (d, 1H, *J* = 2.9 Hz, N*H_2*), 4.68 (d, 1H, *J* = 11.2 Hz, *CH_2*Ph), 4.64 (d, 1H, *J* = 11.2 Hz, *CH_2*Ph), 4.56 (s, 2H, *CH_2*Ph), 4.41 (d, 1H, *J* = 11.2 Hz, *CH_2*Ph), 4.38 – 4.33 (m, 2H, *CH_2*Ph and H-2), 4.28–4.21 (m, 2H), 4.20 – 4.15 (m, 1H, H-6), 3.97 (t, 1H, *J* = 6.6 Hz, H-4), 3.83 (dd, 1H, *J* = 10.2, 4.1 Hz, H-7a), 3.77 – 3.71 (m, 2H, H-5 and H-7b), 3.65 (t, *J* = 6.2 Hz, 1H). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** δ 154.69 (C-1), 136.75–126.12 (*Ph*), 74.51 (C-3), 74.21 (C-4), 73.24 (*C*H_2Ph), 72.81 (C-5), 72.41 (*C*H_2Ph), 65.48 (C-2), 44.37 (C-6).

1.4 Synthesis of (2R,3S,4R,5R,6R)-6-azido-3,5,7-tribenzyloxy-2,4-diacetoxyheptanamide (20).

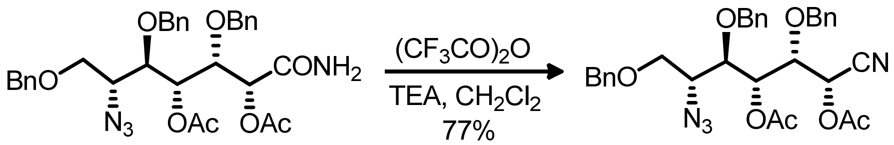


18 **20**

To a stirred solution of amide **18** (329 mg, 0.63 mmol) in Ac_2O (6.3 mL), at 0ºC, was added pyridine (101 μL, 1.26 mmol) dropwise. The reaction mixture was then allowed to warm to room temperature. After 4 h, DCM (30 mL) and a saturated NH_4Cl solution (20 mL) were added. The phases were then separated, and the aqueous phase was extracted with DCM (20 mL). The combined organic phases were dried (anh. $MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting colourless oil was purified by column chromatography to give pure **20** (350 mg, 92%).

Rf: 0.35 (1:1 Hex/AcOEt) **$[\alpha]_D^{28}$** -18.1 (c 1.5, CH_2Cl_2) **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** δ 7.42 – 7.16 (m, 15H, 3*Ph*), 6.35 and 6.21 (2 bs, 1H, N*H₂*), 5.46 (dd, 1H, *J* = 6.6, 3.4 Hz, H-2), 5.36 (d, 1H, *J* = 3.7 Hz, H-4), 4.68 and 4.60 (2d, 2x1H, *J* = 11.3 Hz, C*H*₂Ph), 4.56–4.52 (m, 3H, *CH₂*Ph), 4.44 (d, 1H, *J* = 11.0 Hz, *CH₂*Ph), 4.37 (dd, 1H, *J* = 6.7, 3.7 Hz, H-3), 3.84–3.73 (m, 3H, H-5, H-6 and H-7a), 3.69–3.60 (m, 1H, H-7b), 2.11 and 2.00 (2s, 2x3H, 2C*H*₃CO. **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** 170.19, 169.97 and 169.80 (2*C*OCH₃ and C-1), 138.08–124.60 (3*Ph*), 77.02 (C-4), 76.91 (C-2), 75.01, 73.41 and 73.04 (*C*H₂Ph), 72.09 (C-3), 71.17 (C-5), 69.81 (C-7) , 61.35 (C-6), 20.92 and 20.79 (2CO*C*H₃).

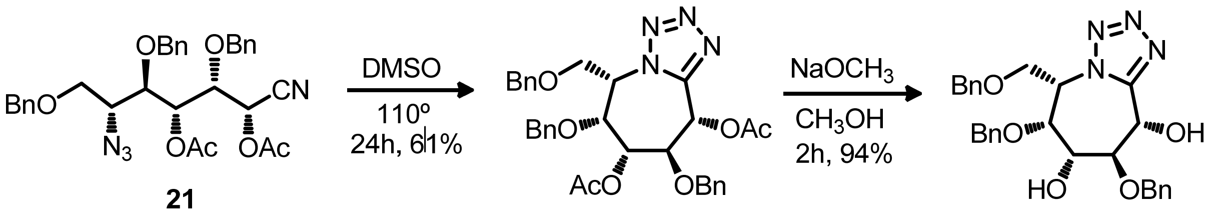
1.5 Synthesis of (2S,3R,4R,5R,6R)-6-azido-3,5,7-tribenzyloxy-2,4-diacetoxyheptanonitrile (21).



20 **21**

To a stirred solution of **20** (335 mg, 0.55 mmol) in DCM (5.5 mL) were added TEA anh. (0.15 mL, 1.1 mmol) and TFAA (0.08 mL, 0.6 mmol). After 4h, a saturated NH_4Cl solution (10 mL) was added. The phases were then separated and the aqueous phase extracted with DCM (2x20 mL). The organic phase was washed with water (10 mL). The combined organic phases were dried (anh. $MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting colourless syrup was purified by column chromatography to give pure **21** (238 mg, 74%). **Rf:** 0.4 (2:1 Hex/AcOEt). **$[\alpha]_D^{28}$** +12.5 (c 1.5, CH_2Cl_2) **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** 7.43–7.24 (m, 15H, 3Ph), 5.61 (d, 1H, *J* = 6.3 Hz, H-2), 5.48 (dd, 1H, *J* = 5.1, 3.5 Hz, H-4), 4.70 – 4.49 (m, 6H, 3*CH2*Ph), 4.12 (dd, 1H, *J* = 6.4, 3.5 Hz, H-3), 3.95 – 3.86 (m, 2H, H-5 and H-6), 3.83 (dd, 1H, *J* = 10.1, 2.7 Hz, H-7a), 3.70 (dd, 1H, *J* = 10.1, 6.7 Hz, H-7b), 2.15 and 2.06 (2s, 2x3H, 2 C*H*₃CO). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** 169.91 and 168.68 (2*C*OCH₃), 138.42–126.59 (3*Ph*), 115.25 (C-1), 77.34 (C-5), 75.51 (C-3), 74.29, 74.00 and 73.47 (C*H*₂Ph), 69.98 (C-4), 69.52 (C-7), 61.68 (C-6), 60.23 (C-2), 21.09 and 20.28 (COC*H*₃).

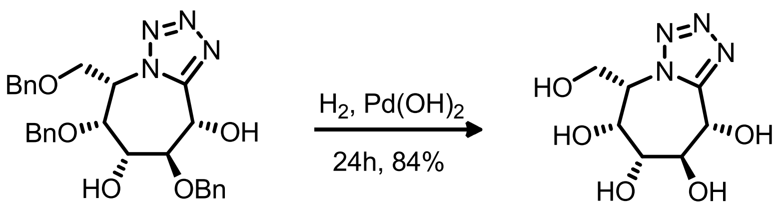
1.6 Cycloaddition to tetrazole azepane 22 and deacetylation. Synthesis of tetrazole azepane 23



21 22 23

In a sealed tube with Ar atmosphere and stirring was placed **21** (241 mg, 0.41 mmol) in anh. DMSO (8.2 mL). After heating at 140 ºC for 24 h, the mixture is allowed to warm to room temperature and CH_2Cl_2 (25 mL) was added. The organic extracts are washed with saturated solution of NH_4Cl, dried (anh. $MgSO_4$) and concentrated to give **22** (146 mg, 61%) as a colourless syrup that was characterized as the tetrazolo azepane **22**.To a solution of **22** (142 mg, 0.24 mmol) in anh. MeOH (2.4 mL) was added with stirring CH_3ONa (26 mg, 0.48 mmol). After 2h the mixture was concentrated and the residue purified by flash chromatography to give **23** (113 mg, 94%) as a colourless syrup. **Rf:** 0.4 (1:3 Hex/AcOEt). **$[\alpha]_D^{27}$** +3.2 (c 0.6, CH_2Cl_2). **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** δ 7.40–7.10 (m, 15H, 3*Ph*), 5.25 (d, 1H, *J* = 8.3 Hz, H-2), 5.10 (dt, 1H, *J* = 6.6, 4.0 Hz, H-6), 4.99 (d, 1H, *J* = 11.3 Hz, *CH₂*Ph), 4.68 (d, 1H, *J* = 11.4 Hz, C*H₂*Ph), 4.60 (d, 1H, *J* = 11.8 Hz, *CH₂*Ph), 4.53 (d, 1H, *J* = 11.6 Hz, *CH₂*Ph), 4.44 (d, 1H, *J* = 12.0 Hz, *CH₂*Ph), 4.37 (d, 1H, *J* = 12.0 Hz, *CH₂*Ph), 4.27 (dd, 1H, *J* = 6.8, 1.6 Hz, H-4), 4.20 (dd, 1H, *J* = 6.6, 1.6 Hz, H-5), 3.95 (dd, 1H, *J* = 8.3, 6.8 Hz, H-3), 3.86 (dd, 1H, *J* = 10.4, 4.2 Hz, H-7a), 3.80 (dd, 1H, *J* = 10.4, 3.8 Hz, H-7b). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** δ 154.95 (C-1), 138.55 – 123.25 (3*Ph*), 80.03 (C-3), 75.56 (C-5), 74.99, 73.55 and 73.12 (*C*H_2Ph), 72.22 (C-4), 67.70 (C-2), 67.54 (C-7), 59.47 (C-6).

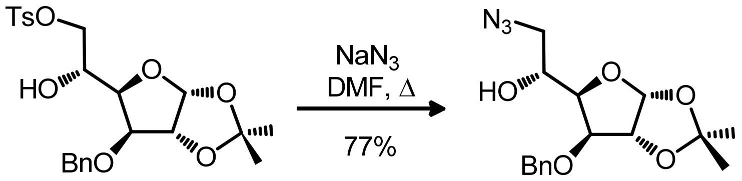
1.7 Deprotection of benzylated 23 to tetrazolopolyhydroxyazepane 13



23 13

The tetrazolo **23** (108 mg, 0.21 mmol) was dissolved in MeOH (10 mL) and $Pd(OH)_2$ (16 mg, 0.11 mmol) was added. The mixture was hydrogenated under a pressure of 45 psi for 48 h and then filtered throught Celite®. Solvent was evaporated and water was added to the crude product to be purified throught Cartridge, Sep-Pak® C18. Filtrates were concentrated under vacuum giving the tetrazolopolyhydroxyazepane **13** (41 mg, 84%) as a white solid. m.p. = 92-95ºC. $[\alpha]_D^{27}$ +4.7(0.8 c, MeOH). **IR (ν, cm-1):** 3313, 2464, 2399, 1468, 1433, 1262, 1061. **^{1}H-RMN (D_2O, 400 MHz, δ ppm):** δ 5.03 (ddd, 1H, *J* = 6.5, 4.8 Hz, H-6), 4.94 (d, 1H, *J* = 9.7 Hz, H-2), 4.33 (dd, 1H, *J* = 5.3, 2.0 Hz, H-5), 3.90 – 3.75 (m, 3H, H-7a, H-7b and H-4), 3.81 (dd, 1H, *J* = 9.7, 8.6 Hz, H-3). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)** and **DEPT-135** data: δ 157.69 (C-1), 74.95 (C-4, CH), 73.68 (C-3, CH), 71.93 (C-5, CH), 69.19 (C-2, CH) , 66.93 (C-6, CH), 61.82 (C-7, CH_2). **FAB-HRMS (NBA):** m/z 255.0697, $[M+Na]^+$ calcd. for $C_7H_{12}N_4O_5Na$ 255.0700.

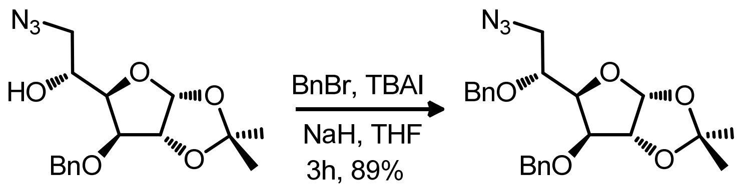
1.8 Synthesis of 6-azido-6-deoxy-3-*O*-benzyl-1,2-*O*-isopropyliden-α-D-glucofuranose (25).



24 **25**

To a stirred solution of **24** (6.66 g, 14.33 mmol) in DMF (140 mL) was added NaN_3 (1.024 g, 15.76 mmol) and the mixture refluxed for 2h. The reaction is left to reach r.t. and a saturated NH_4Cl solution (100 mL) was added. The phases were then separated and the aqueous phase extracted with DCM (2x150 mL). The combined organic extracts were washed with water (100 mL), dried (anh. $MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting syrup was purified by column chromatography to give pure **25** (3.78 g, 77%) as a colourless syrup. **Rf:** 0.75 (1:1 Hex/AcOEt) **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** 7.41–7.27 (m, 5H, *Ph*), 5.92 (d, 1H, *J* = 3.8 Hz, H-1), 4.74 (d, 1H, *J* = 11.8 Hz, CH_2Ph), 4.63 (d, 1H, *J* = 3.8 Hz, H-1), 4.53 (d, 1H, *J* = 11.8 Hz, CH_2*Ph*), 4.15 – 4.04 (m, 4H, H-2, H-3, H-4, H-5), 3.57–3.39 (m, 1H, H-6), 2.36 – 2.28 (m, 1H, OH), 1.49 and 1.33 (s, 6H, C*Me*$_2$). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** 138.41–122.97 (*Ph*), 112.00 [*C*(CH_3)$_2$], 105.24 (C-1), 82.11, 81.61 and 79.97 (C-2, C-3 and C-4), 72.11(*C*H_2Ph), 68.47 (C-5), 54.52 (C-6), 26.83 and 26.31 (C*Me*$_2$).

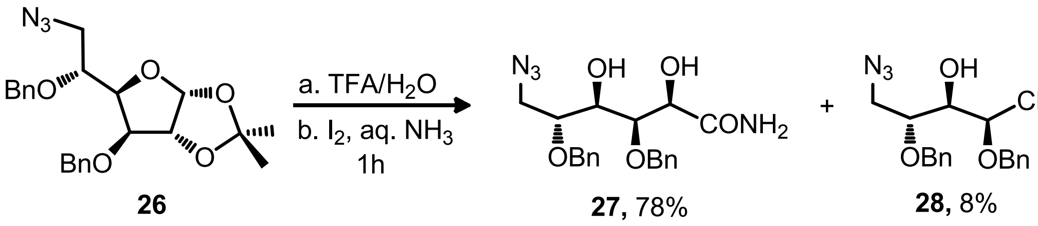
1.9 Synthesis of 6-azido-6-deoxy-3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (26).



25 **26**

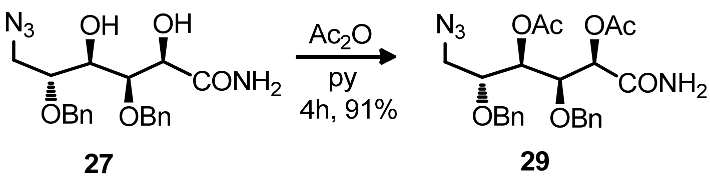
To a stirred solution of azide **5** (4,41 g, 13.15 mmol) in THF (120 mL) at 0ºC, were added NaH 60% mineral oil, (525 mg), TBAI (100 mg, 0.27 mmol) and BnBr (2,05 ml, 17.23 mmol) dropwise. After 3 h, solvent is evaporated and the residue dissolved in CH_2Cl_2 (100 mL). The mixture is washed with aq. 5% NaOH (2 x 50 mL), dried (MgSO4) and concentrated under vacuum to give the dibenzylated **29** (4.97 g, 89%) as a colourless syrup. **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** 7.46–7.11 (m, 10H, 2*Ph*), 5.91 (d, 1H, *J* = 3.9 Hz, H-1), 4.74 – 4.49 (m, 2H, 2C*H*$_2$Ph and H-2), 4.30 (dd, 1H, *J* = 9.0, 3.1 Hz, H-4), 4.13 (d, 1H, *J* = 3.1 Hz, H-3), 4.03 (ddd, 1H, *J* = 9.0, 5.1, 2.6 Hz, H-5), 3.68 (dd, 1H, *J* = 13.2, 2.6 Hz, H-6a), 3.46 (dd, 1H, *J* = 13.2, 5.1 Hz, H-6b), 1.52 and 1.33 (s, 2x3H, 2C*H*$_3$). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** 137.93–127.27 (2*Ph*), 112.10 [*C*(CH_3)$_2$], 105.11 (C-1), 81.78, 81.70 and 79.33 (C-2, C-3 and C-4), 75.39, 72.76 and 71.96 (2C*H*$_2$Ph and C-5), 52.19 (C-6), 26.93 and 26.46 (2CH_3).

1.10 Synthesis of (2R,3S,4R,5R)-6-azido-3,5-dibenzyloxy-2,4-dihydroxyhexanamide (27).



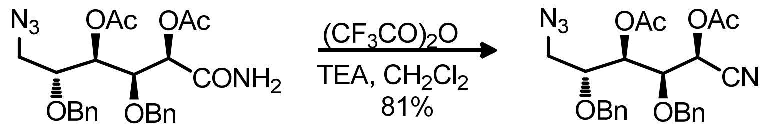
A solution of azide **26** (510 mg, 1.20 mmol) in TFA/H_2O (18 mL, 3:2) was stirred at room temperature for 3 h. Evaporation of the solvent gave 435 mg of crude product, which is used in the next step without purification. The crude product was dissolved in a mixture of 28% aq. NH_3 (11.2 mL) and THF (1.1 mL), and then **I_2** (312 mg, 1.23 mmol) was added. After stirring for 1h the reaction mixture was diluted with aq. saturated $Na_2S_2O_3$ (15 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The extracts were dried ($MgSO_4$), concentrated and purified on column chromatography to give **27** (374 mg, 78%, two steps) as a colourless syrup. A minor les polar compound (8%) was isolated and identified as azido nitrile **28** (See NMR assignment in spectra in Supporting-B document). Compound **27** had **$[\alpha]_D^{28}$:** -34.5 (c 1.5, CH_2Cl_2) **Rf:** 0.2 (1:3 Hexanes/AcOEt). **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** 7.39–7.16 (m, 10H, 2*Ph*), 6.82 and 6.21 (2s, 2x1H, CON*H₂*), 4.62 (2d, 2H, 2 H, C*H₂*Ph), 4.38 (d, 1H, *J* = 11.2 Hz, C*H₂*Ph), 4.34 (d, 1H, *J* = 11.3 Hz, C*H₂*Ph), 4.22 (bs, 2H, H-2 and H-3), 3.95 (d, 1H, *J* = 7.9 Hz, H-4), 3.66 (dd, 1H, *J* = 13.0, 2.9 Hz, H-6a), 3.61 (m, 1H, H- 5), 3.44 (dd, 1H, *J* = 13.0, 3.7 Hz, H-6b). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)** and **DEPT-135** data: 175.50 (C-1), 137.41, 137.15 and 128.50–128.10 (2*Ph*), 77.91 (C-5, CH), 77.06 (C-3, CH), 74.07 (*C*H_2Ph), 72.54 (C-2, CH), 71.85 (*C*H_2-Ph), 71.76 (C-4, CH), 49.07 (C-6, *C*H_2).

1.11 Synthesis of (2R,3S,4R,5R)-6-azido-3,5-dibenzyloxy-2,4-diacetoxyhexanamide (29).



To a stirred solution of **27** (377 mg, 0.95 mmol) in Ac_2O (9.4 mL), cooled up to 0ºC, was added py (159 μL, 1.97 mmol) dropwise. The reaction mixture was then left to reach room temperature. After 4 h, DCM (40 mL) and saturated aq. NH_4Cl solution (30 mL) were added. The phases were then separated, and the aqueous phase was extracted with DCM (30 mL). The combined organic phases were dried (anh. $MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting colourless oil was purified by column chromatography to give pure **29** (416 mg, 91%). **Rf:** 0.25 (1:1 Hexanes/AcOEt). **$[\alpha]_D^{27}$:** -11.8 (c 1.6, CH_2Cl_2). **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** δ 7.40–7.20 (m, 10H, 2 Ph), 6.35 and 5.95 (N*H₂*), 5.40 (t, 1H, *J* = 5.5 Hz, H-4), 5.28 (d, 1H, *J* = 4.2 Hz, H-2), 4.69 (d, 1H, *J* = 11.3 Hz, C*H₂*Ph), 4.59 – 4.48 (m, 3H, C*H₂*Ph), 4.13 (dd, 1H, *J* = 5.7, 4.2 Hz, H-3), 3.82 (q, 1H, *J* = 4.9 Hz, H-5), 3.46 – 3.33 (m, 2H, H-6a and H-6b), 2.13 and 2.04 (2s, 2x3H, C*H3*). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** δ 170.27, 169.77 and 169.72 (2 x *C*OCH_3 and C-1), 140.42 – 121.18 (2Ph), 76.87 and 76.81 (C-3 and C-5), 75.04 and 72.20 (*C*H_2Ph), 71.58 (C-2), 70.73 (C-4), 50.63 (C-6), 20.86 and 20.77 (CO*C*H_3).

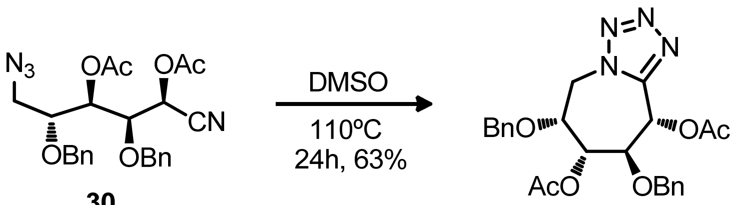
1.12 Synthesis of nitrile 30



29 **30**

To a solution of **29** (407 mg, 0.84 moles) in DCM (8.4 mL), anh. TEA (0.23 mL, 1.68 mmol) and TFAA (0.13 mL, 0.92 mmol) were added with stirring. After 4h, a saturated NH_4Cl solution (15 mL) was added. The phases were then separated and the aqueous phase extracted with DCM (2x25 mL). The organic phase was washed with water (10 mL). The combined organic phases were dried (anh. $MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting colourless syrup was purified by column chromatography to give pure **30** (317 mg, 81%). **Rf:** 0.35 (2:1 Hexanes/AcOEt). **$[\alpha]_D^{27}$:** +29.3 (c 1.3, CH_2Cl_2). **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** δ 7.41 – 7.28 (m, 10H, *Ph*), 5.49 (d, 1H, *J* = 6.3 Hz, H-2), 5.38 (dd, 1H, *J* = 7.5, 2.5 Hz, H-4), 4.69 (d, 1H, *J* = 11.3 Hz, CH_2Ph), 4.62 and 4.57 (2d, 2x1H, *J* = 11.7 Hz, CH_2Ph), 4.42 (d, 1H, *J* = 11.3 Hz, CH_2Ph), 4.07 (dd, 1H, *J* = 6.3, 2.5 Hz, H-3), 3.87 (ddd, 1H, *J* = 7.5, 5.0, 3.5 Hz, H-5), 3.59 (dd, 1H, *J* = 13.4, 3.5 Hz, H-6a), 3.31 (dd, 1H, *J* = 13.4, 5.0 Hz, H-6b), 2.17 and 2.10 (2s, 2x3H, CH_3).**^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** δ 169.9 and 168.6 (2$COCH_3$), 137.0, 136.5 and 129-127 (2Ph), 115.08 (C-1), 76.15 (C-5), 74.75 (C-3), 74.27 and 72.56 (CH_2Ph), 69.52 (C-4), 59.47 (C-2), 50.50 (C-6), 21.01 and 20.28 (CH_3).

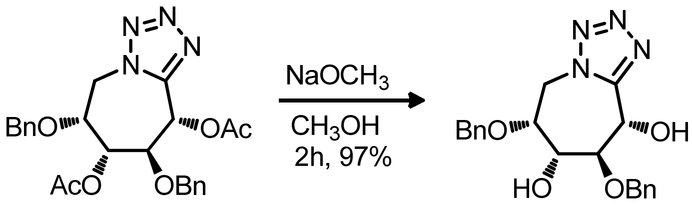
1.13 Cycloaddition to tetrazole 31.



30 **31**

In a sealed tube with Ar atmosphere and stirring was placed **30** (308 mg, 0.66 mmol) in anh. DMSO (12.8 mL). After heating at 140 ºC for 24 h, the mixture was allowed to warm to room temperature and CH_2Cl_2 (30 mL) was added. The organic extracts are washed with saturated solution of NH_4Cl, dried (anh. MgSO4) and concentrated to give **31** (193 mg, 63 %) as a colourless syrup. **Rf:** 0.65 (1:1 Hexanes/AcOEt). **$[\alpha]_D^{27}$:** +10.9 (c 2.8, CH_2Cl_2). **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** 7.40 – 7.20 (m, 10H, 2*Ph*), 6.32 (d, 1H, *J* = 6.9 Hz, H-2), 5.47 (dd, 1H, *J* = 6.5, 1.9 Hz, H-4), 4.90 (dd, 1H, *J* = 14.4, 9.1 Hz, H-6), 4.72 (d, 1H, *J* = 11.5 Hz, CH_2Ph), 4.62 (dd, 1H, *J* = 14.4, 1.9 Hz, H-6´), 4.61 (d, 1H, *J* = 11.5 Hz, CH_2Ph), 4.52 (s, 1H, CH_2Ph), 4.25 (at, 1H, *J* = 6.7 Hz, H-3), 3.96 (dt, 1H, H-5), 2.12 and 2.04 (2s, 2x3H, 2CH_3). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** δ 169.52 and 168.90 ($COCH_3$), 151.27 (C-1), 136.60, 136.30 and 128.70-127.90 (2*Ph*), 74.63 (CH_2Ph), 73.14 (C-3), 72.74 (C-4), 71.94 (CH_2Ph), 71.45 (C-5), 65.26 (C-2), 45.96 (C-6), 20.78 and 20.51 (2CH_3).

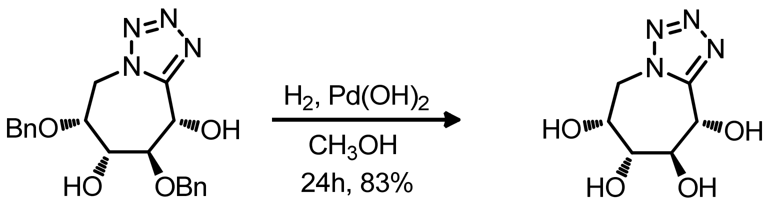
1.14 Deacetylation of tetrazole 31.



31 **32**

To a stirred solution of tetrazole **31** (180 mg, 0.38 mmol) in anh. MeOH (3.8 mL) was added $NaOCH_3$ (41 mg, 0.76 mmol). After 2h, the mixture was concentrated and the crude syrup purified by flash chromatography to afford **32** (141 mg, 97%) as a colourless syrup. **Rf:** 0.3 (1:3 Hexanes/AcOEt). **$[\alpha]_D^{28}$:** +6.4 (c 0.7, CH_2Cl_2). **^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm):** 7.42–6.94 (m, 10H, 2*Ph*), 5.44 (d, 1H, *J* = 5.8 Hz, H-2), 4.72 (m, H-6a, H-6b), 4.65 and 4.44 (2d, 2x1H, *J* = 11.7 Hz, C*H*₂Ph), 4.58 (2d, 2x1H, *J* = 12.10 Hz, C*H*₂Ph), 4.34 (dd, 1H, *J* = 5.8, 1.7 Hz, H-4), 4.17 (t, 1H, *J* = 5.8 Hz, H-3), 3.89 (ddd, 1H, *J* = 8.8, 3.8, 1.7 Hz, H-5). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm):** δ 154.66 (C-1), 136.59 (2C) and 128.68–127.91 (2*Ph*), 74.46 (C-3), 74.15 (C-4), 73.18 (CH_2Ph), 72.75 (C-5), 72.35 (CH_2Ph), 65.42 (C-2), 44.31 (C-6).

1.15 Deprotection of 32 to tetrazolopolyhydroxyazepane 14



32 **14**

The tetrazolo **32** (129 mg, 0.33 mmol) was dissolved in MeOH (10 mL) and $Pd(OH)_2$ (25 mg, 0.18 mmol) was added. The mixture was hydrogenated under a pressure of 45 psi for 48 h and then filtered through Celite®. Solvent was evaporated and water was added to the crude product which was purified through Cartridge, Sep-Pak® C18. Filtrates were concentrated under vacuum giving the tetrazolopolyhydroxyazepane **14** (55 mg, 83%) as a white solid. **$[\alpha]_D^{28}$** +1.4 (c 0.5, MeOH). **p.f. =** 83-86 ºC. **IR (ν, cm^{-1}):** 3342, 2477, 2327, 1651, 1431, 1257, 1068. **^{1}H-RMN (D_2O, 400 MHz, δ ppm):** 4.71 (d,1H, *J* = 9.1 Hz, H-2), 4.67 (d, 1H, *J* = 15.0, 6.0 Hz, H-6a), 4.17 (d, 1H, *J* = 15.0 Hz, $J_{5,6'}$= 0, H-6b), 4.12 (dd, 1H, *J* = 6.0, 2.2 Hz, H-5), 3.63 (dd, 1H, *J* = 9.1, 2.2 Hz, H-4), 3.42 (t, 1H, *J* = 9.1 Hz, H-3). **^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)** and **DEPT-135** data: 157.84 (C-1), 77.65 (C-4, CH), 72.63 (C-5, CH), 70.29 (C-3, CH), 68.74 (C-2, CH), 51.46 (C-6, CH_2). **FAB-HRMS (NBA):** m/e 225.0606, $[M+Na]^+$ calcd. for $C_6H_{10}N_4O_4Na$ 225.0600.

2. Computational data.

2.1. Transition State (TS) in the cyclization process to form tetrazole 22 from azido nirile 21

Table S1.- Values for the charge density, $\rho(\mathbf{r})$, and the Laplacian of charge density, $L = -\nabla^2\rho(\mathbf{r})$, computed at the outlined BCP´s of **figure 5** (also enclosed in manuscript). A combination of low charge density with a negative and also low value of *L* confirms the closed-shell interaction between the atoms connected by each Bond Critical Point (BCP).

BCP	α	β	γ	δ	ε	ζ
$\rho(\mathbf{r})$	0,00470	0,00750	0,00340	0,01035	0,01064	0,01410
$L = -\nabla^2\rho(\mathbf{r})$	-0,00380	-0,00613	-0,00253	-0,00908	-0,01037	-0,01353

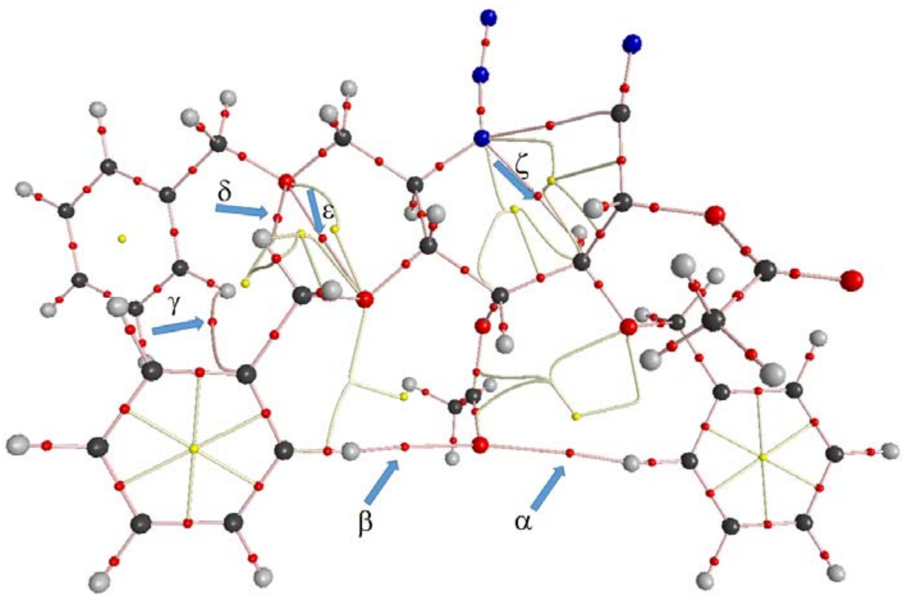


Figure 5. The computed LC-wPBE(DMSO)/6-311++G(d,p)//LC-wPBE(DMSO)/6-31G(d) molecular graph. The closed-shell relevant interactions have been indicated with blue arrows.

```
Coordinates (TS)
6                    -0.86883   1.91843  -0.41989
6                    -0.43586   0.75002   0.47463
6                     2.3551    1.89559   1.00566
6                     0.84938   0.0615    0.01168
6                     2.12892   0.87737  -0.14480
7                     0.15348   2.95194  -0.24056
6                     1.85902   3.24408   0.62102
7                     2.12169   4.39778   0.53740
7                     0.51052   5.14649  -0.52473
7                    -0.04336   4.13405  -0.60851
8                     3.74009   2.061     1.23571
8                     3.17101  -0.06297  -0.16515
8                     0.59205  -0.51633  -1.26641
8                    -1.40454  -0.26762   0.49560
1                    -0.88609   1.58383  -1.46241
1                    -0.2793    1.1426    1.48860
1                     1.84906   1.57843   1.92148
1                     1.0529   -0.74358   0.72242
1                     2.09385   1.42162  -1.09534
```

6	4.43241	1.22637	2.05529
6	4.17729	0.17878	-1.13955
6	0.63768	-1.85717	-1.38384
6	-2.19814	-0.34503	1.66689
6	3.67323	0.32	2.97990
8	5.63362	1.30101	2.01828
1	3.07768	-0.401	2.41766
1	3.01208	0.88863	3.63896
6	5.15826	-0.96211	-1.12493
6	4.7279	-2.27021	-0.91686
6	5.63689	-3.31857	-0.94463
6	-2.85491	-1.6982	1.74223
6	-2.166	-2.84747	1.36344
6	-2.76674	-4.09343	1.47864
6	0.29287	-2.27579	-2.77988
8	0.91925	-2.60347	-0.47572
1	0.40816	-3.35376	-2.87892
1	0.93774	-1.76145	-3.49508
1	-0.73955	-1.99309	-2.99850
6	-2.24548	2.48181	-0.06755
1	-2.35663	3.46762	-0.54150
1	-2.33294	2.62809	1.02024
6	6.98305	-3.07294	-1.18737
6	7.41667	-1.77081	-1.39625
6	6.50805	-0.72083	-1.35894
1	4.68865	1.12516	-0.93309
1	3.70316	0.2584	-2.12737
1	3.67695	-2.46377	-0.72387
1	5.29164	-4.33491	-0.77702
1	7.6927	-3.89493	-1.20975
1	8.46785	-1.56823	-1.58017
1	6.85435	0.29854	-1.51122
6	-4.05848	-4.206	1.97919
6	-4.74921	-3.06325	2.35896
6	-4.1504	-1.81593	2.23539
1	-2.96266	0.43914	1.66362
1	-1.56193	-0.19532	2.55052
1	-1.15879	-2.76157	0.96679
1	-2.22196	-4.98355	1.17637
1	-4.52634	-5.1822	2.06902
1	-5.7616	-3.14004	2.74510
1	-4.7004	-0.92271	2.52193
1	4.39927	-0.21833	3.58670
8	-3.22726	1.60879	-0.55108
6	-4.53116	2.10478	-0.36098
1	-4.69832	2.32391	0.70493
1	-4.66195	3.05056	-0.90719
6	-5.53621	1.08773	-0.83529
6	-6.85893	1.47316	-1.04059
6	-5.17477	-0.23754	-1.04817
6	-7.80788	0.54658	-1.44700
1	-7.14922	2.50951	-0.88263
6	-6.12498	-1.16517	-1.45912
1	-4.14427	-0.53762	-0.88949
6	-7.44266	-0.77801	-1.65877
1	-8.83588	0.86065	-1.60407
1	-5.83086	-2.19822	-1.62263
1	-8.18388	-1.50405	-1.98015

Energies reported relative to the TS energy of -1983.983652

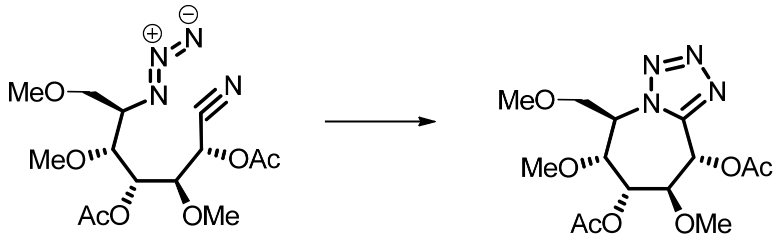
Summary of reaction path following

	Energy	RxCoord
1	-0.03249	-8.77246
2	-0.03212	-8.42189
3	-0.03171	-8.07640
4	-0.03124	-7.72724
5	-0.03071	-7.37647
6	-0.03011	-7.02468
7	-0.02944	-6.67524
8	-0.02870	-6.33175
9	-0.02785	-5.98047
10	-0.02692	-5.63467
11	-0.02587	-5.28335
12	-0.02469	-4.93090
13	-0.02339	-4.57954
14	-0.02196	-4.22726
15	-0.02039	-3.87706
16	-0.01867	-3.52515
17	-0.01679	-3.17297
18	-0.01476	-2.82064
19	-0.01259	-2.46820
20	-0.01032	-2.11570
21	-0.00800	-1.76313
22	-0.00571	-1.41050
23	-0.00358	-1.05782
24	-0.00176	-0.70510
25	-0.00049	-0.35234
26	0.00000	0.00000
27	-0.00058	0.35216
28	-0.00249	0.70508
29	-0.00593	1.05797
30	-0.01100	1.41090
31	-0.01767	1.76382
32	-0.02576	2.11674
33	-0.03500	2.46966
34	-0.04501	2.82256
35	-0.05537	3.17544
36	-0.06562	3.52831
37	-0.07520	3.88117
38	-0.08342	4.23393
39	-0.08948	4.58258
40	-0.09290	4.88474
41	-0.09533	5.19745
42	-0.09750	5.53773
43	-0.09939	5.88367
44	-0.10103	6.23123
45	-0.10245	6.58095
46	-0.10367	6.93137
47	-0.10471	7.28243
48	-0.10557	7.63156
49	-0.10626	7.97934
50	-0.10682	8.32567
51	-0.10726	8.66929

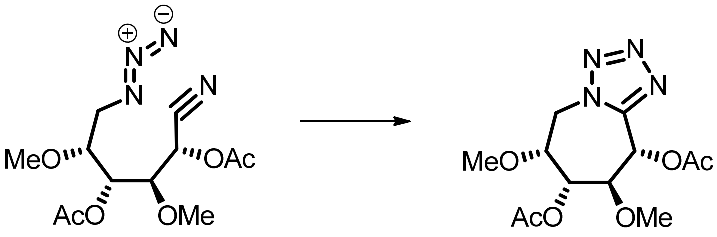
2.2. Cyclization processes to form tetrazoles 34 and 36 from azido nitriles 33 and 35.

Table S2 Molecular graphs for selected points on the **IRC** for the azido nitriles **33** and **35** (Reactant, p1, p30, and p46) computed at LCwPBE(DMSO)/6-311++G(d,p)//LCwPBE(DMSO)/6-31G(d) theoretical level. The molecular graphs are constructed from CPs of the electronic charge density, $\rho(r)$, and trajectories of the gradient of $\rho(r)$, $\nabla\rho(r)$, red points stand for bond (3,-1) CPs, yellow for ring (3,+1)CPs and purple (not visible) for nuclear (3,-3)CPs .

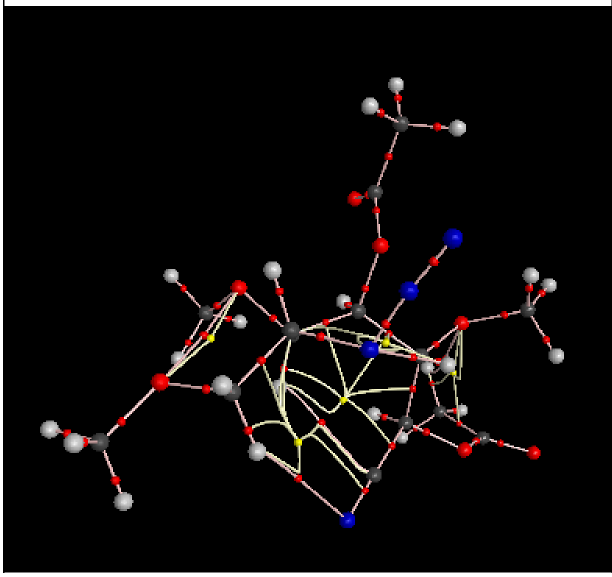
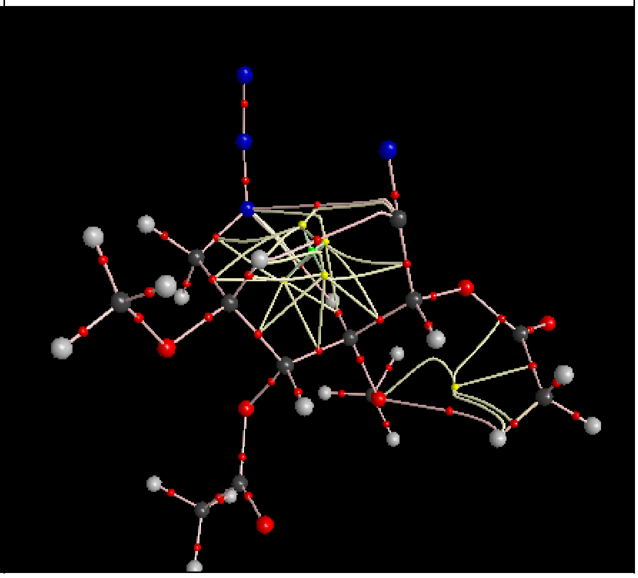
It can be observed the formation of the **N-C** bond before the **N-N** one due to the **pseudo concerted mechanism** in the formation of the tetrazole ring**.**

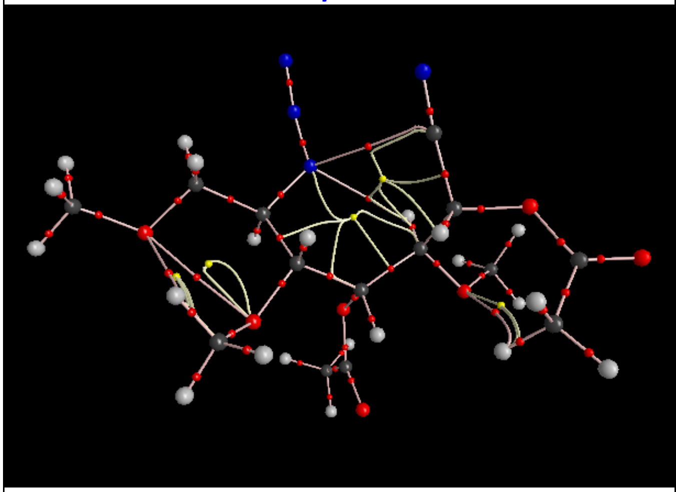
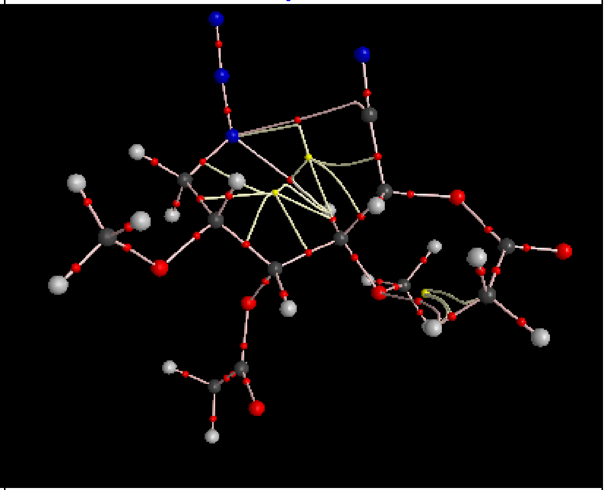
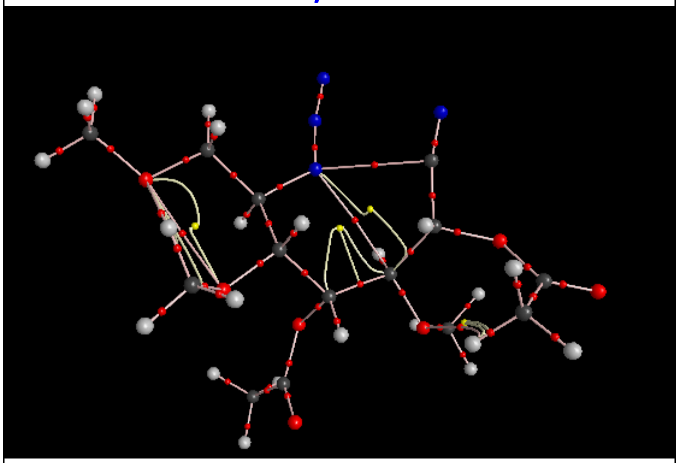
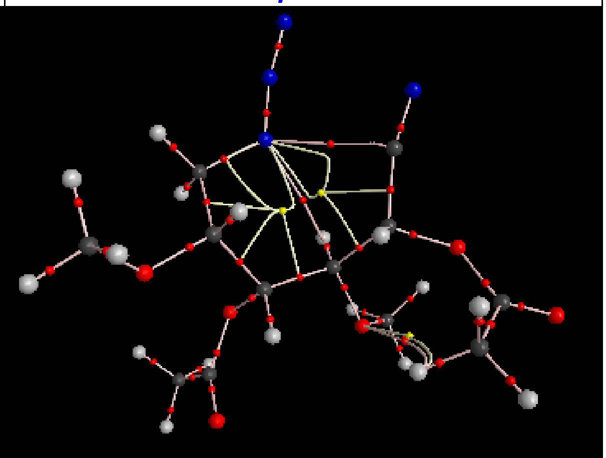
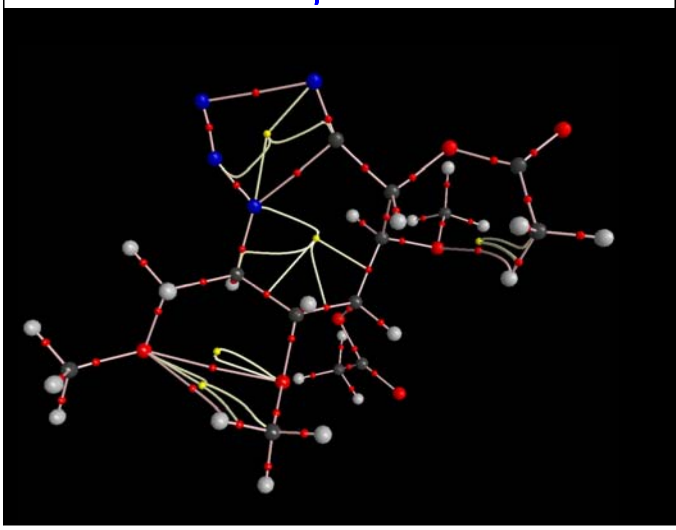
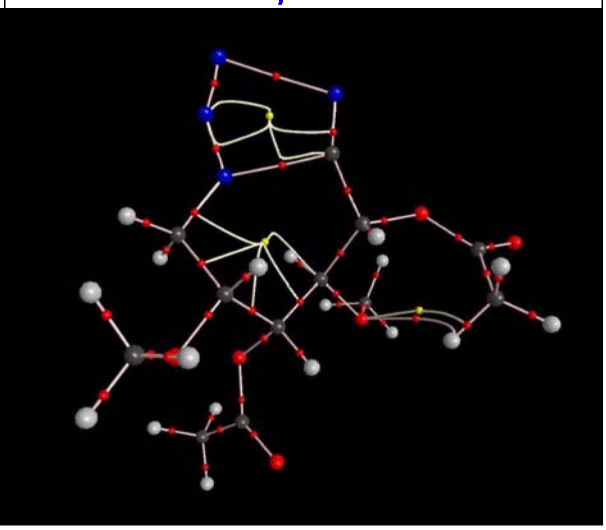


33 **34**



35 **36**

Reactant 33	Reactant 35
	

p1	p1
	
p30	**p30**
	
p46	**p46**
	

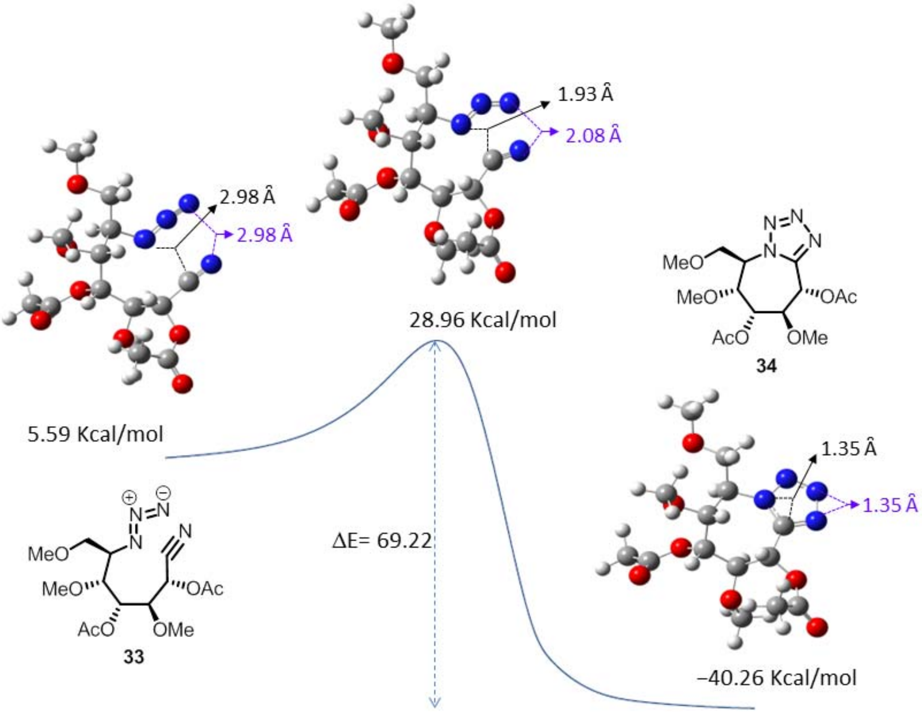


Figure S1. Some points of calculated Intrinsic Reaction Coordinate (IRC) for the cyclization reaction of **33** to **34.** Energies are relative to the preferred conformer obtained after full optimization of the starting compound. Interatomic distances: C-N (black) and N-N (violet).

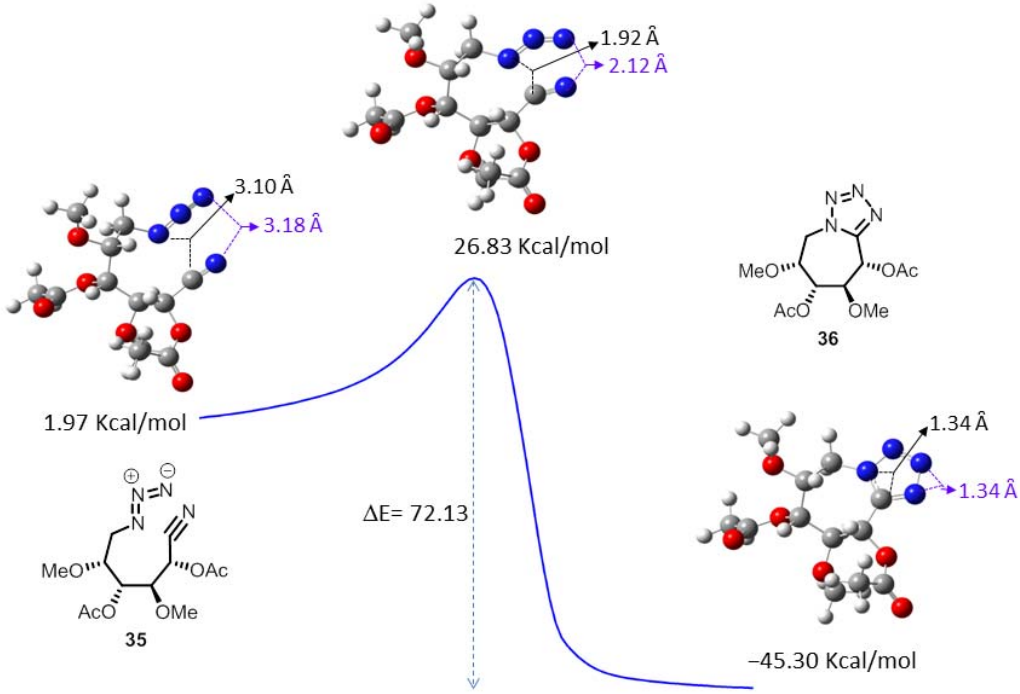


Figure S2. Some points of calculated Intrinsic Reaction Coordinate (IRC) for the cyclization reaction of **35** to **36.** Energies are relative to the preferred conformer obtained after full optimization of the starting compound. Interatomic distances: C-N (black) and N-N (violet).

Coordinates of the compounds 33 and 35 and Transition States (TS) in the cyclization processes to form tetrazoles 34 and 36 respectively.

Ciano nitrile 33

C	2.21373600	-0.04688200	-0.65949500
C	1.32592300	-0.19359700	0.59004200
C	-1.62119000	-1.39883800	0.06980700
C	-0.00817500	0.55615700	0.54107700
C	-1.17201900	0.03136800	-0.30318300
N	1.43683300	0.03453100	-1.90498100
C	-0.71585000	-2.43438900	-0.45421200
N	-0.01438800	-3.24836800	-0.87122000
N	1.34006400	2.10233000	-3.02275400
N	1.42090000	1.13658600	-2.44522500
O	-2.87479100	-1.65000400	-0.53462600
O	-2.26457700	0.87395100	-0.03733200
O	0.26397600	1.87309600	0.06160500
O	2.07877300	0.36212500	1.64630900
C	-4.04605600	-1.44141800	0.13163100
C	-2.81755900	1.49573000	-1.18581000
C	0.09736000	2.90857900	0.91198800
C	1.96029500	-0.34104700	2.86263900
C	-4.01302800	-1.24500000	1.61849100
O	-5.05163500	-1.46623700	-0.52778700
C	0.44898700	4.19939000	0.23757100
O	-0.28241800	2.78733900	2.05045600
C	3.13848900	-1.24540300	-0.83577500
O	3.82628400	-1.49498400	0.35960000
H	2.80314700	0.86315700	-0.51250700
H	1.14744000	-1.25856200	0.78433400
H	-1.66704700	-1.50911100	1.15685300
H	-0.37237600	0.64027200	1.56939300
H	-0.91741500	0.04925900	-1.36597800
H	-3.22380600	0.75405300	-1.88150000
H	-2.06533300	2.10530500	-1.69762500
H	-3.62464300	2.13929400	-0.83419700
H	2.34617800	-1.36159800	2.75798000
H	0.92168700	-0.38107500	3.21557200
H	2.55774100	0.19594600	3.60099800
H	-5.04229200	-1.16185000	1.96316200
H	-3.47416000	-0.33110900	1.87458300
H	-3.53762400	-2.09130200	2.12112100
H	0.30294900	5.02703800	0.92955100
H	-0.17677100	4.33806900	-0.64671100
H	1.48945200	4.17082200	-0.09352400
H	3.83853300	-1.04061100	-1.65913800
H	2.53058200	-2.11621400	-1.12457000
C	4.65493400	-2.62835400	0.25595800
H	5.41618300	-2.49780900	-0.52493700
H	4.07217700	-3.53090800	0.02745700
H	5.15156700	-2.75867900	1.21876100

TS to tetrazole 34

C	-2.16013828	0.47554594	-0.02168650
C	-1.34143428	-0.77373906	0.32295350
C	1.19930172	0.79224594	0.98178450
C	-0.04230028	-0.91789206	-0.47412050
C	0.99752872	0.19658194	-0.43889350
N	-1.34057828	1.61962294	0.38779350
C	0.38358072	2.02369094	1.15593750
N	0.39191772	3.16695594	1.47288950
N	-1.49545728	3.79991294	0.88876450
N	-1.83484328	2.76660694	0.49455550
O	2.54082072	1.20725294	1.14833750
O	2.19036172	-0.38311206	-0.89655950
O	-0.39227128	-1.08671406	-1.84551950
O	-2.06975028	-1.93901206	0.03743350
H	-2.32851528	0.50346294	-1.10345350
H	-1.09580428	-0.73110806	1.39320950
H	0.92371872	0.07206794	1.75677750
H	0.44024772	-1.83504406	-0.12572550
H	0.68565172	0.99958194	-1.11646650
C	3.50845072	0.34360494	1.55113250
C	2.93691972	0.43466394	-1.78253650
C	-0.17165128	-2.28905706	-2.41550650
C	-2.57136628	-2.63047006	1.16253150
C	3.10629872	-0.98429806	2.12425950
O	4.64835872	0.72229694	1.46258250
H	4.01388172	-1.50306506	2.42833050
H	2.58423272	-1.58838306	1.38051850
H	2.45998472	-0.85958106	2.99700050
H	3.25805772	1.36153294	-1.29793950
H	2.34833072	0.67272794	-2.67567250
H	3.81513172	-0.14239106	-2.07408150
H	-3.36737828	-2.06824106	1.65949550
H	-1.77267828	-2.85480306	1.87998750
H	-2.98574328	-3.56929306	0.79187250
C	-0.66231828	-2.29363506	-3.83138350
O	0.35007372	-3.21776406	-1.84873250
H	-0.41353228	-3.24262406	-4.30339850
H	-0.21146228	-1.46889806	-4.38698650
H	-1.74521928	-2.14928906	-3.84139250
C	-3.51243928	0.53175494	0.69172050
O	-4.40138128	-0.36561106	0.07148550
H	-3.89391628	1.55821394	0.62018350
H	-3.36986528	0.30500894	1.75820750
H	-5.27015628	-0.23796606	0.47486850

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C	-2.03076000	0.51935900	0.05733700
C	-1.30456400	-0.81616200	0.28437600
C	1.11119600	0.68018300	0.91717600
C	-0.03623300	-1.02624300	-0.54910200
C	1.04469200	0.04069300	-0.48278700
N	-1.22164400	1.63444600	0.58792000
C	0.05297800	1.73951100	1.00799400
N	0.25958500	2.97442200	1.39700200
N	-0.89735400	3.62078700	1.20721800
N	-1.78401900	2.84027600	0.72283300
O	2.35087100	1.32963500	1.07850500

O	2.26530800	-0.56993000	-0.80344800
O	-0.41334400	-1.15097200	-1.91577300
O	-2.14370000	-1.88223500	-0.06677800
H	-2.17168500	0.68456600	-1.01439200
H	-1.03726800	-0.88148300	1.34817400
H	0.96733300	-0.06920800	1.69958100
H	0.40404600	-1.97055100	-0.21998700
H	0.81750100	0.82899700	-1.21147300
C	3.43240700	0.67647700	1.57903400
C	3.05590100	0.15137200	-1.73555800
C	-0.27615000	-2.36087600	-2.49981900
C	-2.67815500	-2.62705000	1.00936700
C	3.23737300	-0.64396000	2.26723800
O	4.49852800	1.22535700	1.46766000
H	4.20655300	-0.96413900	2.64602700
H	2.86208400	-1.39298800	1.56771500
H	2.54000900	-0.55878200	3.10465000
H	3.33467800	1.13601900	-1.34794000
H	2.52281200	0.26922900	-2.68542800
H	3.95775500	-0.43886900	-1.90086400
H	-3.44135600	-2.06245900	1.55251600
H	-1.88959300	-2.94592000	1.70112600
H	-3.14307500	-3.51188600	0.57243300
C	-0.78674500	-2.32372600	-3.90740900
O	0.19963300	-3.32218300	-1.94747400
H	-0.59980500	-3.28100500	-4.39107800
H	-0.29736300	-1.52086500	-4.46245000
H	-1.85953700	-2.11728900	-3.89936800
C	-3.40032800	0.57320100	0.74482900
O	-4.31617000	-0.19127000	-0.00206100
H	-3.71692900	1.61779200	0.79153700
H	-3.29973000	0.20774100	1.77728600
H	-5.20263200	0.05941400	0.28886800

Ciano nitrile 35

C	-2.35788700	0.93578200	-0.84651200
C	-1.83284700	0.37416500	0.47815000
C	1.46152100	0.74879800	0.61773300
C	-0.69774900	-0.63706800	0.32076900
C	0.62591800	-0.16646200	-0.29727000
N	-1.40947300	1.86061300	-1.47703000
C	0.88176900	2.07793300	0.87042300
N	0.46465000	3.12883400	1.09544000
N	-1.75071900	4.17161000	-1.19381300
N	-1.63192800	3.05351800	-1.29278700
O	2.70333100	0.98715000	-0.01874900
O	1.42809400	-1.30581800	-0.48549300
O	-1.18414100	-1.67070300	-0.53283400
O	-2.87575500	-0.33486300	1.10992800
H	-3.32184900	1.42144600	-0.66855200
H	-2.52028500	0.11187400	-1.54270000
H	-1.49590100	1.19800700	1.11919700
H	1.58989500	0.25834900	1.58602800
H	-0.49652800	-1.07389100	1.30237500
H	0.44964300	0.34998800	-1.24557400
C	3.82789100	0.28862000	0.30478700
C	1.74967000	-1.57698700	-1.83931000
C	-1.24157800	-2.92452600	-0.03928900
C	-3.66192000	0.45656100	1.97601800

C	3.82736100	-0.56742600	1.53700700
O	4.77662900	0.43115400	-0.42095900
H	4.82485500	-0.98984000	1.64484600
H	3.10137800	-1.37706400	1.44253500
H	3.59179800	0.01845500	2.42928000
H	2.33043800	-0.75850400	-2.27826300
H	0.84368500	-1.74119400	-2.43130800
H	2.35174800	-2.48631100	-1.84114700
H	-4.14150600	1.29146700	1.45089000
H	-3.06088400	0.85743600	2.80150400
H	-4.43854100	-0.19276600	2.38226500
C	-1.77349000	-3.87122500	-1.07190200
O	-0.90560900	-3.22247900	1.08082200
H	-1.86694600	-4.86715200	-0.64211100
H	-1.09553900	-3.90168700	-1.92802600
H	-2.74550300	-3.52514600	-1.42925000

TS to tetrazole 36

C	-1.91174846	1.61009245	0.16075393
C	-1.54940146	0.40154345	1.01655393
C	1.39014054	0.56629645	0.21822993
C	-0.84751346	-0.70490155	0.23502493
C	0.39032354	-0.32338755	-0.57329007
N	-0.68018446	2.31247645	-0.17496107
C	1.21114954	2.02027445	-0.06226107
N	1.76824854	3.04432245	-0.28317307
N	0.13364954	4.35991945	-0.59340907
N	-0.65831446	3.53730445	-0.42075007
O	2.71495354	0.27532145	-0.18358707
O	0.99882354	-1.53736655	-0.92389707
O	-1.77745346	-1.23180955	-0.70727207
O	-2.71574446	-0.17489355	1.54535493
H	-2.57168846	2.26870845	0.72908793
H	-2.43067146	1.28198645	-0.74436007
H	-0.88794046	0.73223745	1.82977093
H	1.27788554	0.41300545	1.29556393
H	-0.57555446	-1.49767955	0.93639893
H	0.07493354	0.21460245	-1.47533907
C	3.42129554	-0.74190655	0.37314593
C	1.47680554	-1.59106955	-2.25779407
C	-2.22447546	-2.49097955	-0.52402407
C	-3.11389346	0.36944545	2.78744993
C	2.91512554	-1.37317855	1.63762393
O	4.45232654	-1.05024955	-0.16796207
H	3.64200854	-2.12145655	1.94902893
H	1.95291054	-1.86036755	1.47181393
H	2.80521754	-0.63280055	2.43423193
H	2.25383954	-0.84147055	-2.43516507
H	0.65522654	-1.44358155	-2.96766707
H	1.89859354	-2.58692055	-2.39773707
H	-3.32719846	1.44256245	2.71754793
H	-2.34540946	0.20918945	3.55333393
H	-4.02631546	-0.15034755	3.08169593
C	-3.22842346	-2.84787255	-1.57740407
O	-1.85433046	-3.21296855	0.36921293
H	-3.53563546	-3.88515855	-1.45529007
H	-2.79815846	-2.69900055	-2.56983707
H	-4.09775346	-2.19218355	-1.48942507

tetrazole 36

C	-1.72413700	1.58939600	0.06088100
C	-1.57452300	0.35515300	0.94924400
C	1.27558500	0.49876300	0.21744200
C	-0.91225500	-0.81957100	0.23289500
C	0.36355100	-0.49274200	-0.53438000
N	-0.46683400	2.31925800	-0.03972000
C	0.81010500	1.91441500	0.03062900
N	1.58037500	2.96830600	-0.10271800
N	0.75422600	4.01203700	-0.25368900
N	-0.47016600	3.64038800	-0.21477800
O	2.57534400	0.43076500	-0.32574900
O	1.04361800	-1.70139400	-0.74119800
O	-1.82802700	-1.33210600	-0.72905500
O	-2.83754300	-0.08778700	1.36342900
H	-2.44385900	2.28152300	0.49785600
H	-2.07137600	1.31216800	-0.93716800
H	-0.96109500	0.61897600	1.82295700
H	1.29415000	0.26695000	1.28613500
H	-0.69515200	-1.59950200	0.96568600
H	0.09052400	-0.04682100	-1.49970000
C	3.51207900	-0.41572900	0.17731300
C	1.47272900	-1.91350200	-2.07705100
C	-2.36792300	-2.54904200	-0.50367100
C	-3.29266100	0.51373800	2.56036000
C	3.27257200	-1.06338000	1.51075900
O	4.51171600	-0.57079000	-0.47604000
H	4.15883300	-1.64527800	1.75816800
H	2.40819800	-1.72863700	1.46820500
H	3.10803000	-0.31763300	2.29282800
H	2.18342300	-1.14483800	-2.39590900
H	0.61661900	-1.92783300	-2.76046600
H	1.96328300	-2.88720000	-2.09532800
H	-3.38671200	1.60170900	2.46379800
H	-2.61885900	0.28731200	3.39507200
H	-4.27698500	0.09369900	2.76853900
C	-3.35683200	-2.88935500	-1.57579800
O	-2.07614300	-3.24748100	0.43569700
H	-3.72312400	-3.90394400	-1.42861300
H	-2.89106100	-2.79700900	-2.55894400
H	-4.19188900	-2.18603800	-1.53524900

Energies of IRC to Tetrazole 34

Reaction path calculation complete.

Energies reported relative to the TS energy of -1252.057470

Summary of reaction path following

	Energy	RxCoord
1	-0.11052	-14.70165
2	-0.11047	-14.35121
3	-0.11041	-14.00076
4	-0.11035	-13.65031
5	-0.11027	-13.29984
6	-0.11019	-12.94937
7	-0.11009	-12.59890
8	-0.10998	-12.24844
9	-0.10986	-11.89798
10	-0.10973	-11.54752
11	-0.10959	-11.19706
12	-0.10943	-10.84662
13	-0.10926	-10.49619
14	-0.10907	-10.14580
15	-0.10887	-9.79547
16	-0.10864	-9.44525
17	-0.10839	-9.09523
18	-0.10810	-8.74562
19	-0.10776	-8.39644
20	-0.10732	-8.04725
21	-0.10675	-7.69763
22	-0.10602	-7.34764
23	-0.10510	-6.99743
24	-0.10397	-6.64715
25	-0.10261	-6.29688
26	-0.10099	-5.94671
27	-0.09908	-5.59667
28	-0.09682	-5.24696
29	-0.09403	-4.90053
30	-0.08986	-4.55520
31	-0.08335	-4.20549
32	-0.07488	-3.85514
33	-0.06519	-3.50471
34	-0.05493	-3.15428
35	-0.04461	-2.80384
36	-0.03467	-2.45337
37	-0.02552	-2.10290
38	-0.01751	-1.75241
39	-0.01091	-1.40191
40	-0.00588	-1.05142
41	-0.00247	-0.70094
42	-0.00057	-0.35050
43	0.00000	0.00000
44	-0.00049	0.34984
45	-0.00177	0.70026
46	-0.00359	1.05071
47	-0.00573	1.40116
48	-0.00803	1.75161
49	-0.01036	2.10205
50	-0.01265	2.45248
51	-0.01483	2.80290
52	-0.01688	3.15332
53	-0.01879	3.50375
54	-0.02055	3.85418
55	-0.02215	4.20461
56	-0.02360	4.55505
57	-0.02492	4.90549
58	-0.02610	5.25593
59	-0.02716	5.60637
60	-0.02811	5.95680
61	-0.02896	6.30723
62	-0.02971	6.65766
63	-0.03038	7.00807

64	-0.03097	7.35849
65	-0.03150	7.70890
66	-0.03197	8.05931
67	-0.03239	8.40970
68	-0.03276	8.76007
69	-0.03309	9.11043
70	-0.03339	9.46078
71	-0.03366	9.81112
72	-0.03391	10.16146
73	-0.03414	10.51181
74	-0.03435	10.86218
75	-0.03456	11.21258
76	-0.03475	11.56299
77	-0.03493	11.91343
78	-0.03511	12.26387
79	-0.03529	12.61433
80	-0.03545	12.96479
81	-0.03562	13.31525
82	-0.03578	13.66571
83	-0.03594	14.01617
84	-0.03610	14.36663
85	-0.03625	14.71710
86	-0.03640	15.06756
87	-0.03655	15.41803
88	-0.03670	15.76849
89	-0.03685	16.11896
90	-0.03700	16.46943
91	-0.03714	16.81991
92	-0.03729	17.17039
93	-0.03743	17.52088

Energies of IRC to Tetrazole 36

Reaction path calculation complete.

Energies reported relative to the TS energy of -1137.605658

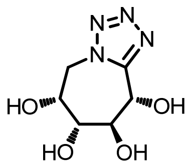
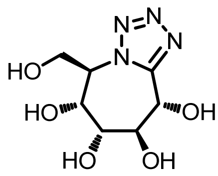
Summary of reaction path following

	Energy	RxCoord
1	-0.03961	-17.01899
2	-0.03945	-16.67860
3	-0.03930	-16.33820
4	-0.03913	-15.99780
5	-0.03895	-15.65740
6	-0.03876	-15.31699
7	-0.03857	-14.97658
8	-0.03836	-14.63617
9	-0.03815	-14.29576
10	-0.03792	-13.95534
11	-0.03769	-13.61492
12	-0.03744	-13.27450
13	-0.03718	-12.93408
14	-0.03690	-12.59366
15	-0.03661	-12.25325
16	-0.03631	-11.91283
17	-0.03600	-11.57243
18	-0.03567	-11.23202
19	-0.03533	-10.89162
20	-0.03497	-10.55123
21	-0.03459	-10.21085
22	-0.03419	-9.87048
23	-0.03377	-9.53011
24	-0.03333	-9.18975
25	-0.03286	-8.84939
26	-0.03236	-8.50903
27	-0.03183	-8.16867
28	-0.03126	-7.82832
29	-0.03064	-7.48796
30	-0.02997	-7.14761
31	-0.02925	-6.80726

32	-0.02847	-6.46690
33	-0.02762	-6.12655
34	-0.02670	-5.78619
35	-0.02570	-5.44584
36	-0.02461	-5.10548
37	-0.02342	-4.76511
38	-0.02212	-4.42475
39	-0.02071	-4.08438
40	-0.01919	-3.74403
41	-0.01753	-3.40368
42	-0.01574	-3.06334
43	-0.01382	-2.72300
44	-0.01179	-2.38266
45	-0.00966	-2.04232
46	-0.00749	-1.70197
47	-0.00535	-1.36160
48	-0.00335	-1.02121
49	-0.00166	-0.68082
50	-0.00046	-0.34045
51	0.00000	0.00000
52	-0.00054	0.34040
53	-0.00234	0.68079
54	-0.00556	1.02120
55	-0.01032	1.36162
56	-0.01658	1.70205
57	-0.02419	2.04246
58	-0.03292	2.38286
59	-0.04245	2.72323
60	-0.05248	3.06358
61	-0.06268	3.40392
62	-0.07272	3.74426
63	-0.08217	4.08462
64	-0.09048	4.42497
65	-0.09687	4.76493
66	-0.10074	5.09999
67	-0.10300	5.43359
68	-0.10481	5.77319
69	-0.10634	6.11327
70	-0.10763	6.45347
71	-0.10872	6.79370
72	-0.10962	7.13386
73	-0.11035	7.47388
74	-0.11093	7.81367
75	-0.11140	8.15320
76	-0.11177	8.49262
77	-0.11207	8.83218
78	-0.11233	9.17199
79	-0.11257	9.51201
80	-0.11278	9.85218
81	-0.11297	10.19245
82	-0.11315	10.53279
83	-0.11332	10.87318
84	-0.11348	11.21359
85	-0.11363	11.55401
86	-0.11377	11.89443
87	-0.11390	12.23485
88	-0.11402	12.57528
89	-0.11414	12.91572
90	-0.11425	13.25616
91	-0.11435	13.59660
92	-0.11445	13.93705
93	-0.11454	14.27750
94	-0.11462	14.61795
95	-0.11470	14.95837
96	-0.11477	15.29879
97	-0.11484	15.63920
98	-0.11490	15.97959
99	-0.11495	16.31998

3-Inhibitory activity against glycosidases.

Inhibitory activity of glycotetrazoles **13** and **14** was evaluated against 11 commercial glycosidases* with negative results except for **14** β-glucosidase from almonds and for **13** with β-galactosidase from *Aspergillus orizae,* with weak although selective results.

	Percentage Inhibition (1mM)	
Glycosidases	 **14**	 **13**
1. α-L-fucosidase (bovine kidney)	–	–
2. α-galactosidase (coffee beans)	–	–
3. β-galactosidase (*Escherichia coli*) 4. β-galactosidase (*Aspergillus orizae*)	– 16%	– –
5. α-glucosidase (yeast) 6. α-glucosidase (rice)	– –	– –
7. amiloglucosidase (Asper*gillus niger*)	–	–
8. β-glucosidase (almonds)	–	38%
9. α-mannosidase (beans)	–	–
10. β-mannosidase (snail)	–	–
11. β-*N*-acetylglucosaminidase (beans)	–	–

* Tests were carried out by Dr. I. Robina group, (Organic Chemistry Department) University of Seville.

Supporting Information - B

Synthesis of Tetrazole-Fused Azepanes and Quantum Chemical Topology Study on the Mechanism of the Intramolecular Cycloaddition Reaction.

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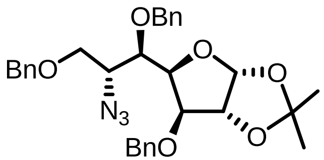
Contents: NMR spectra of the synthesized compounds



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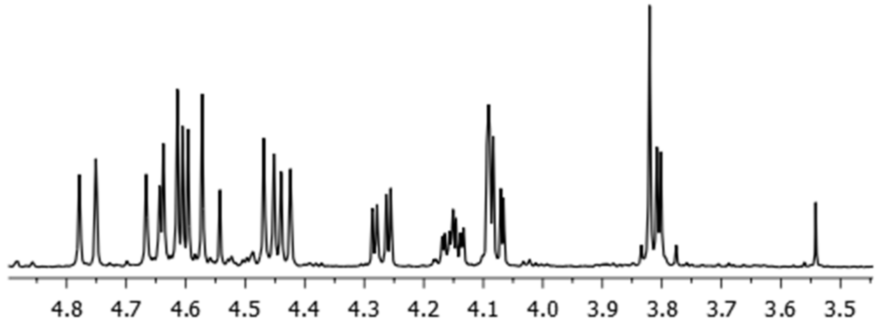
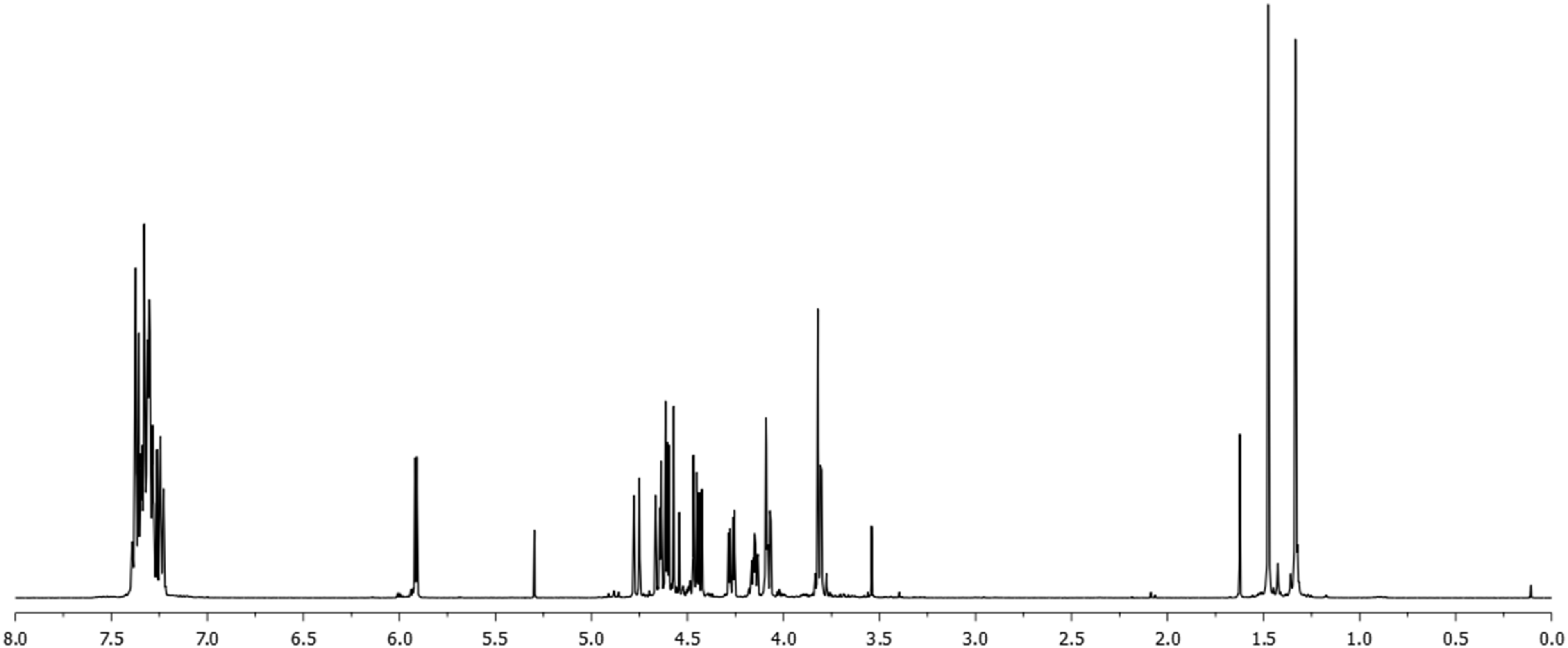
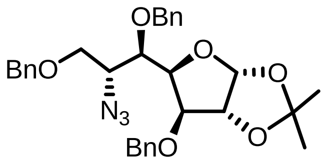




^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



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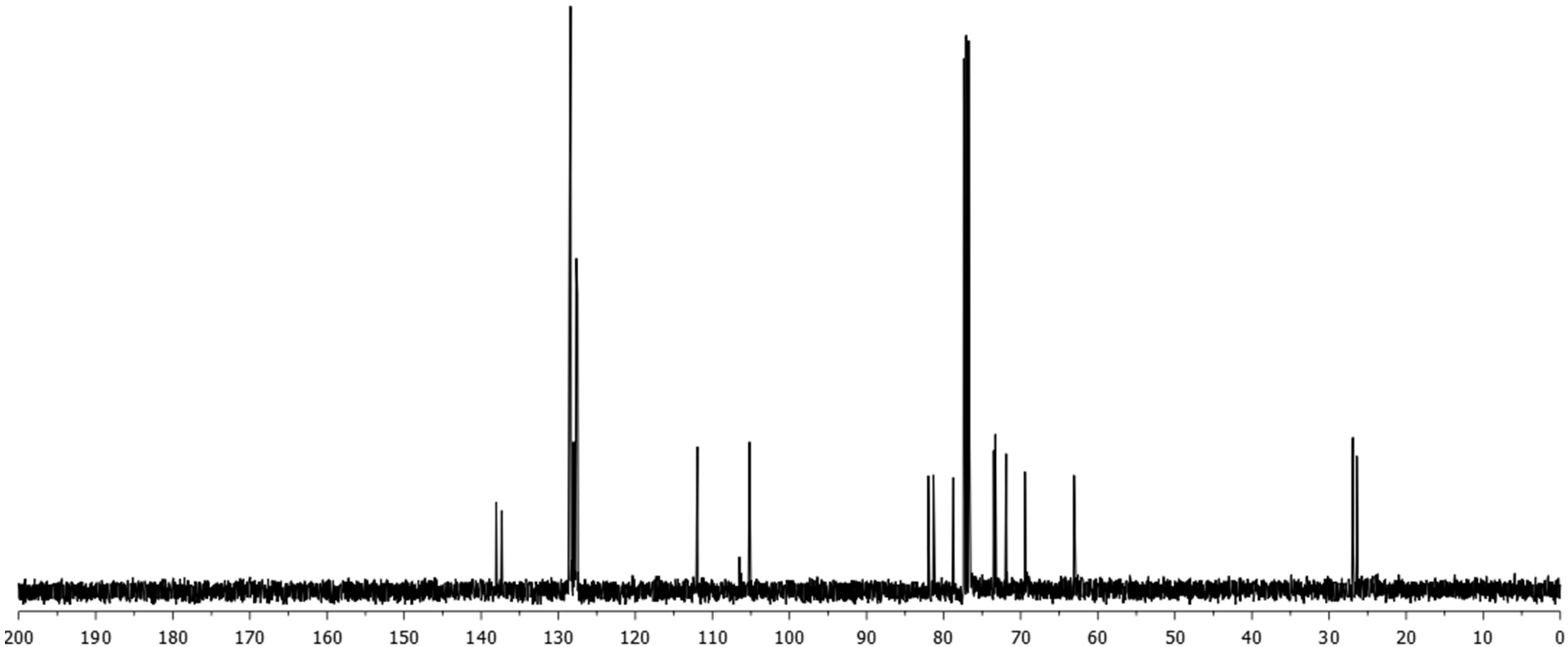
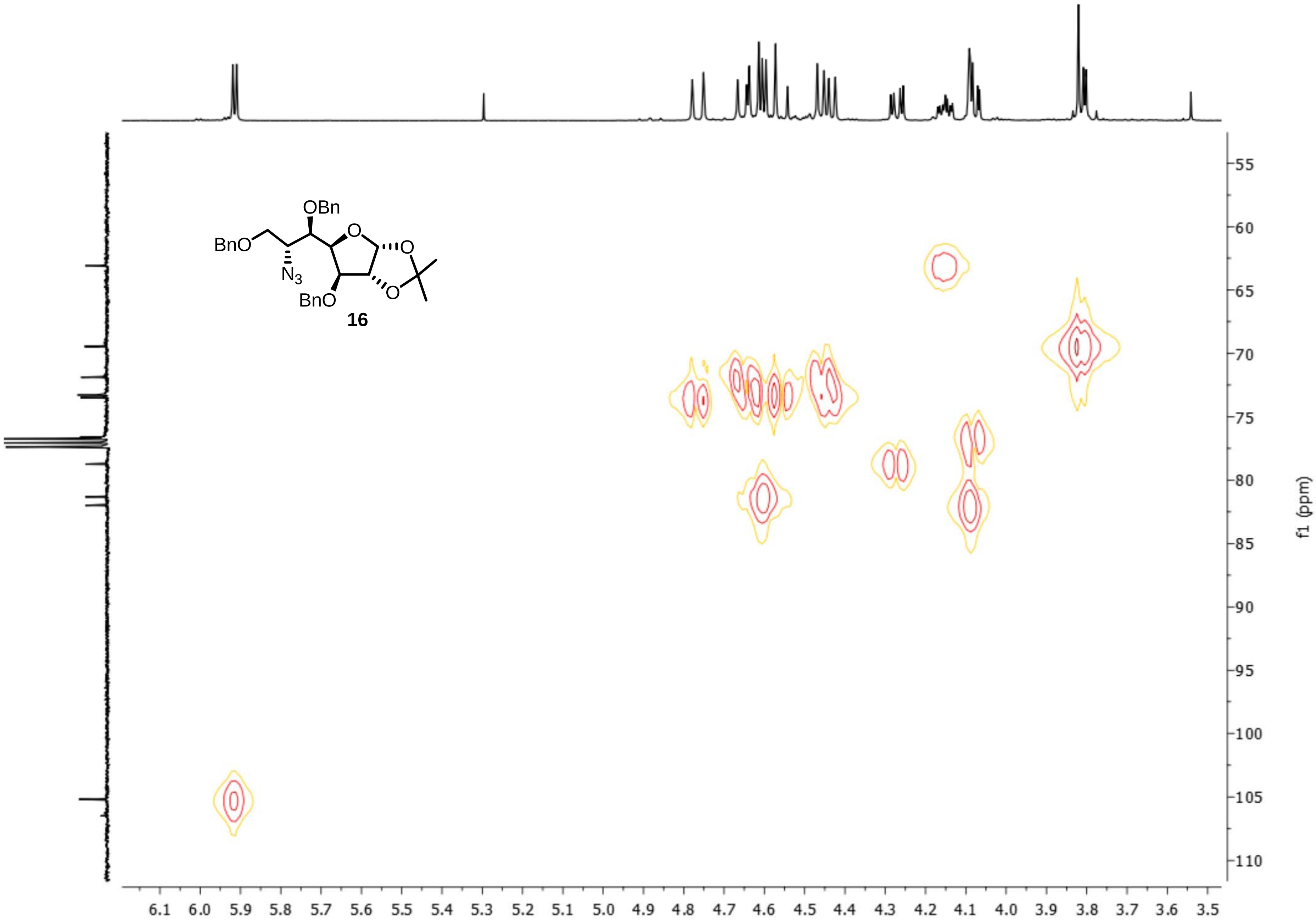


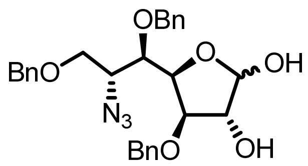
^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



[1]H-RMN ($CDCl_3$, 400 MHz, δ ppm)

HMQC

[13]C-RMN ($CDCl_3$, 100 MHz, δ ppm)



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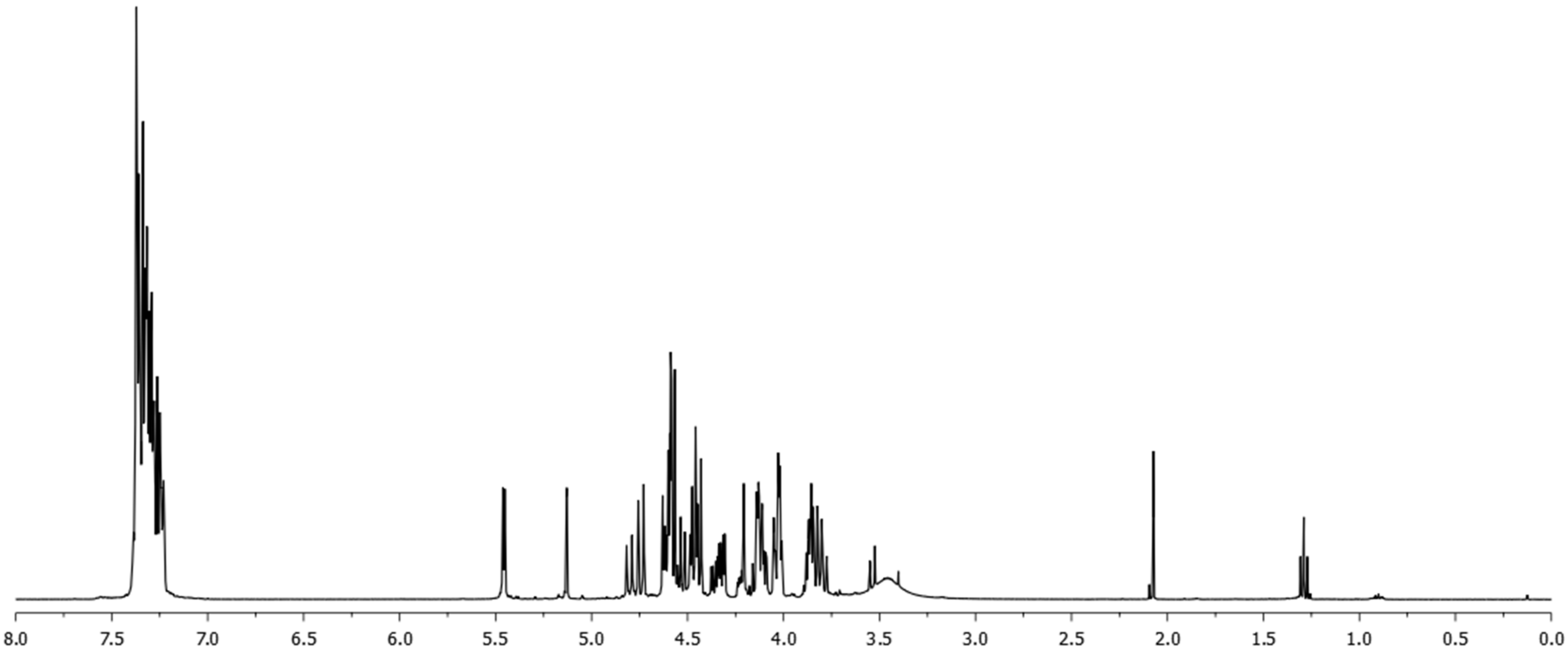
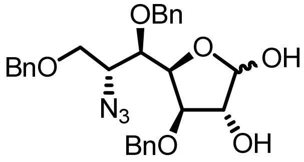


^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



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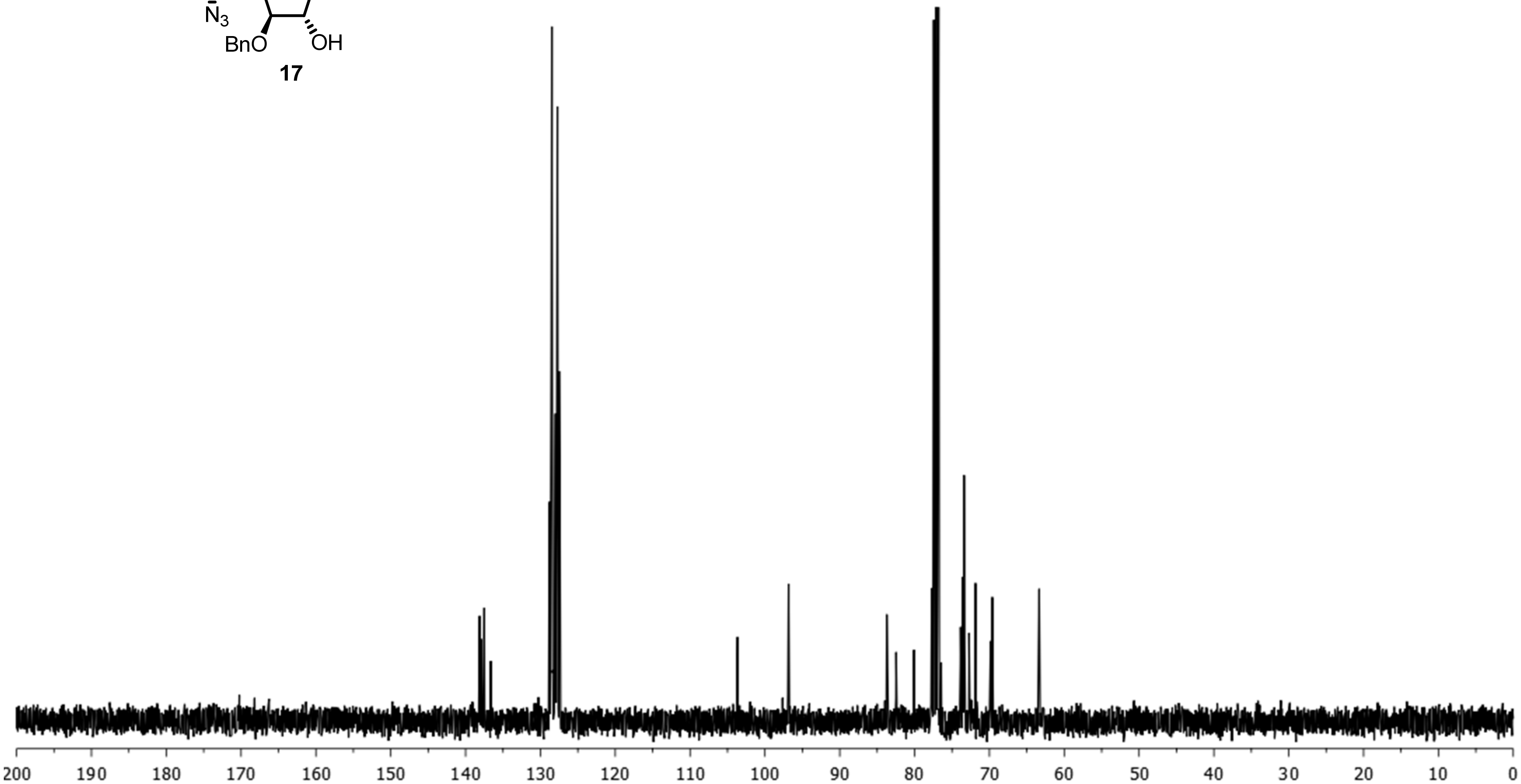
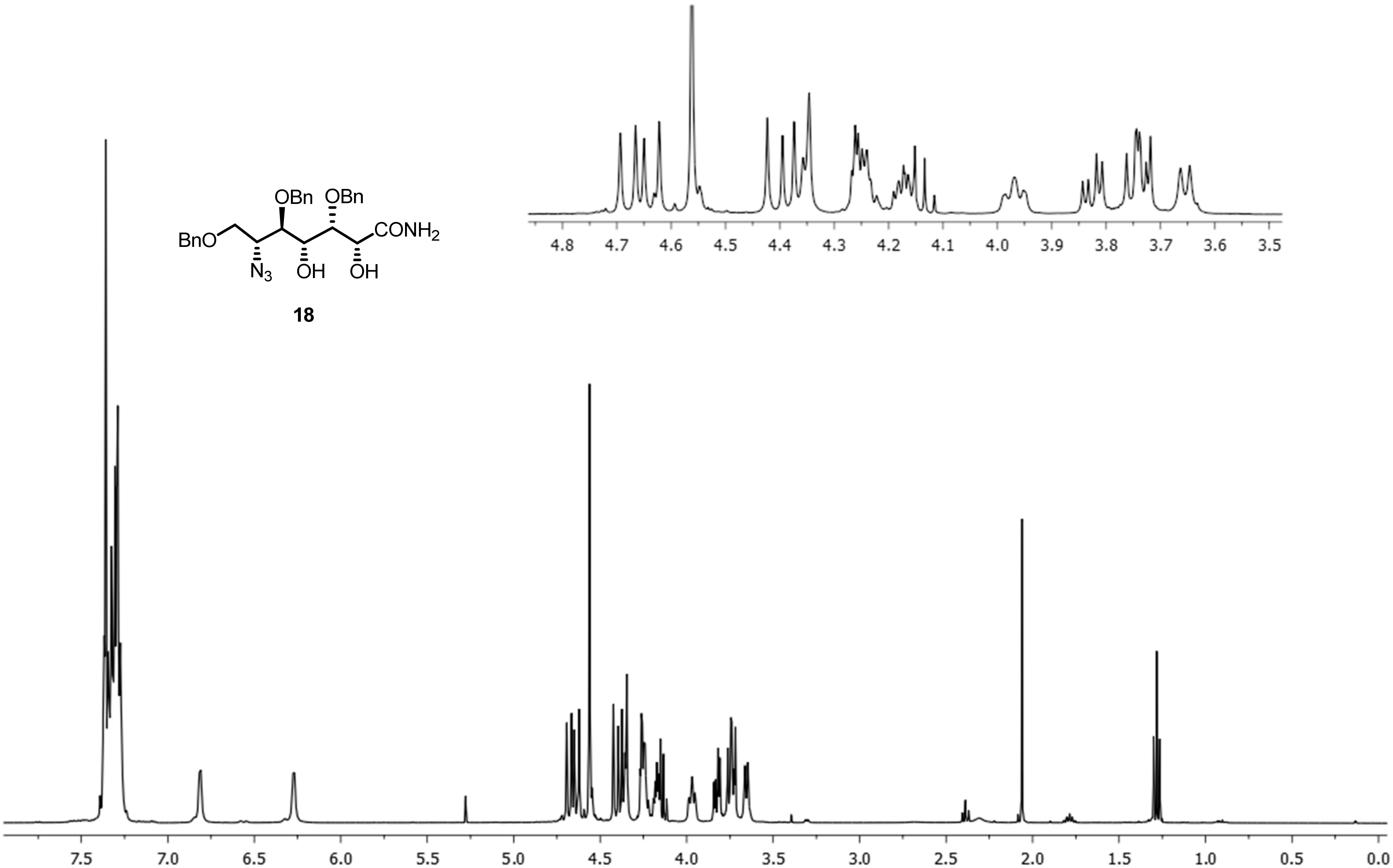


[13]C-RMN ($CDCl_3$, 100 MHz, δ ppm)



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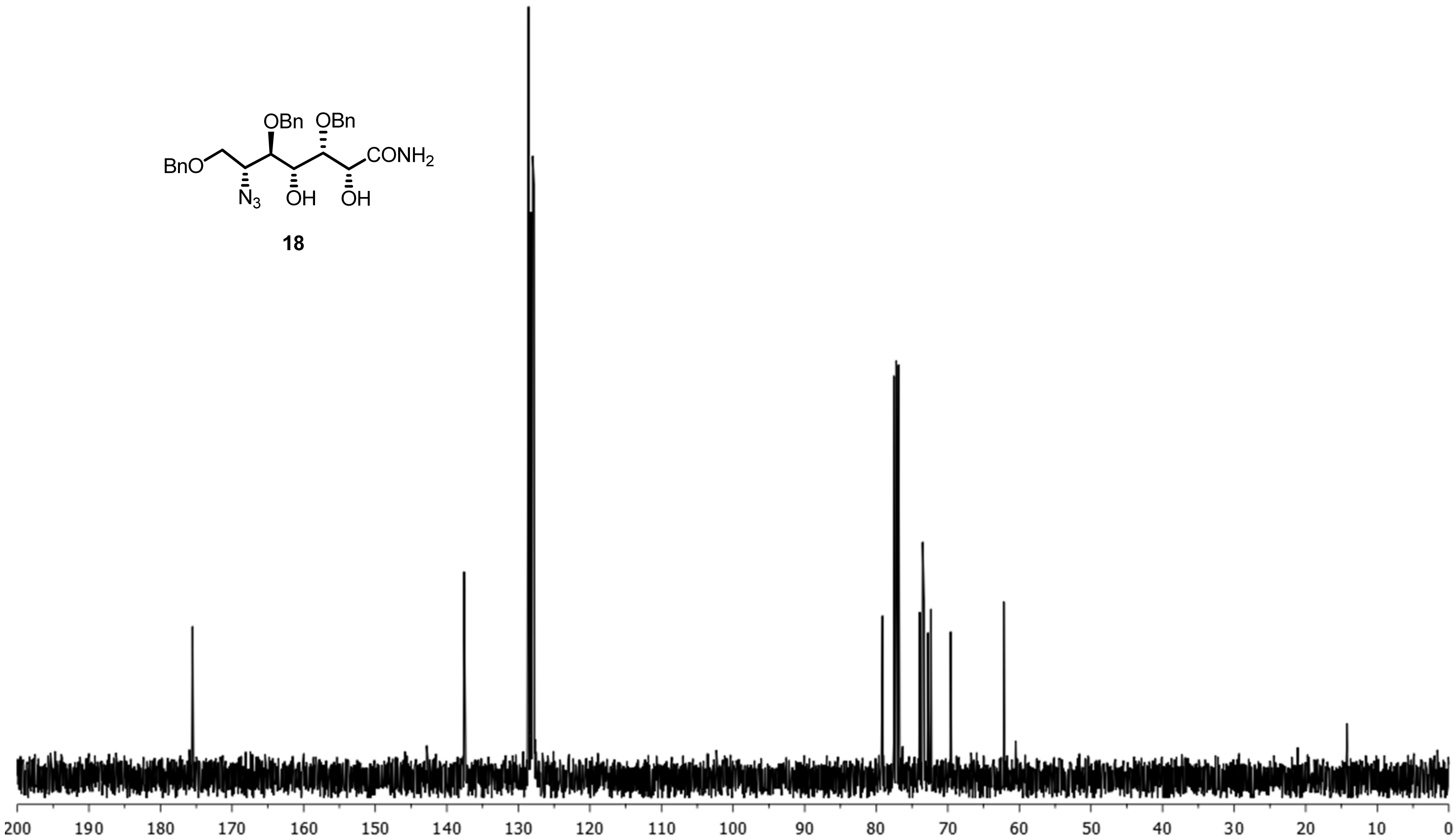
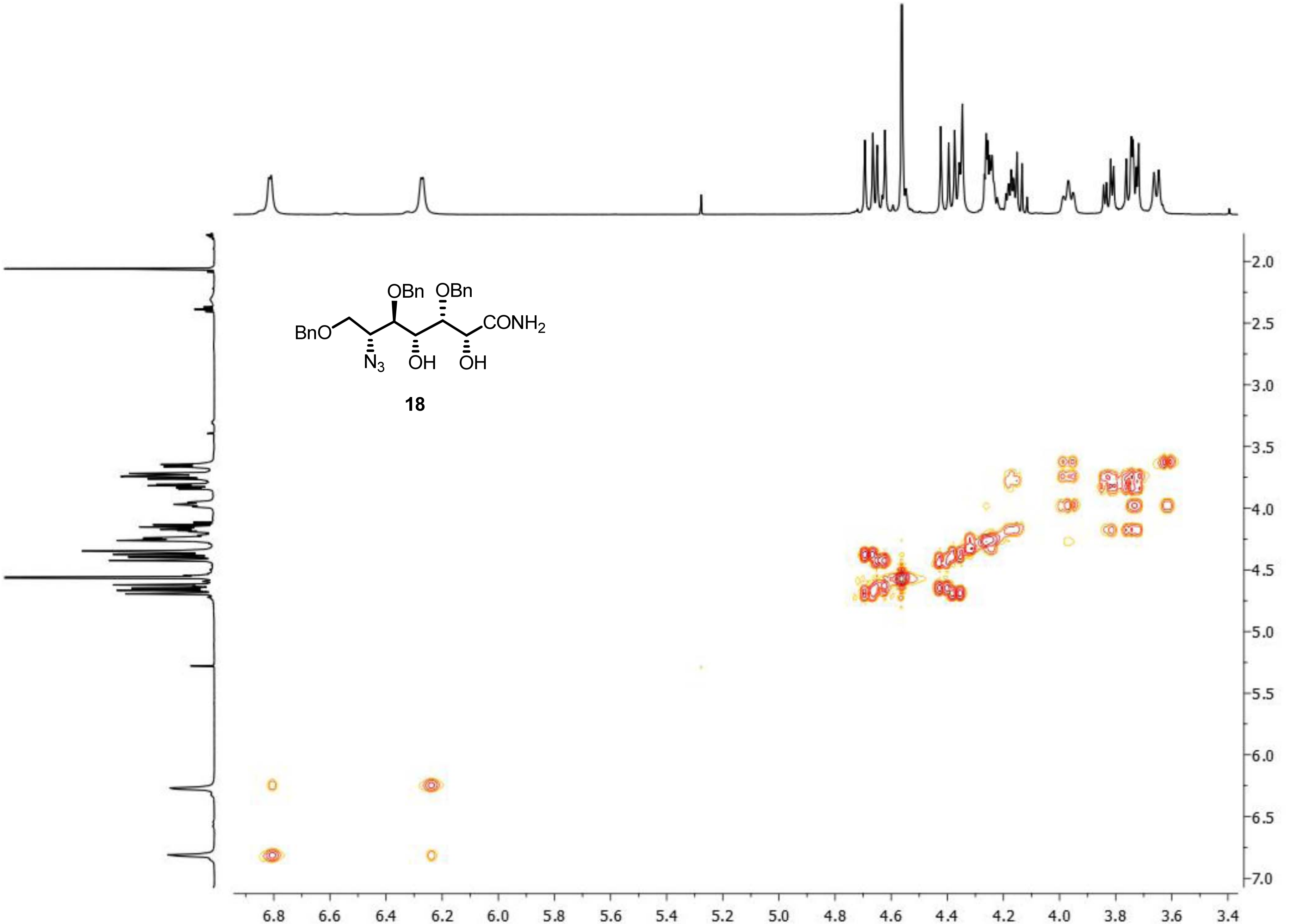
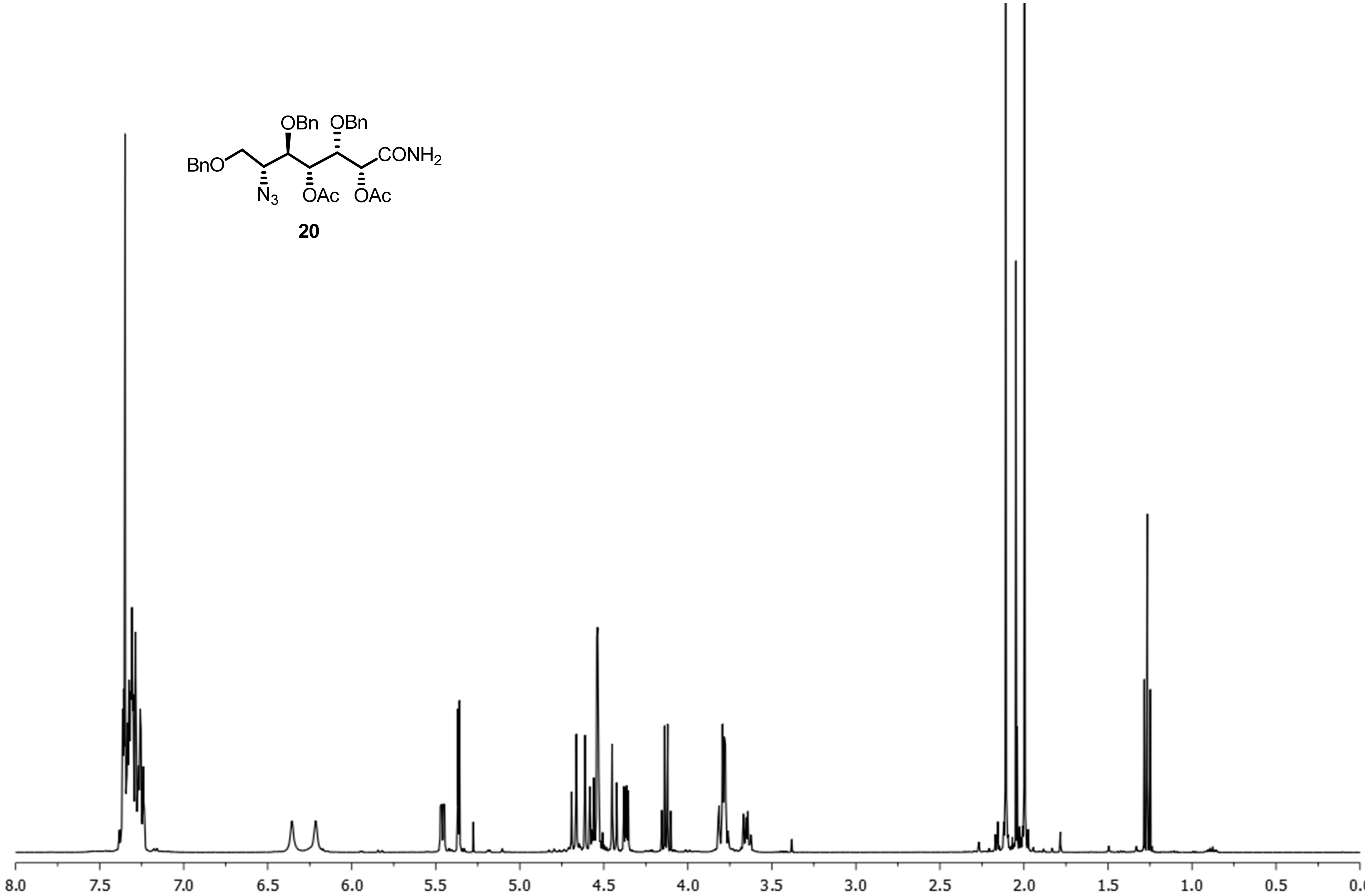
^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



^{1}H-RMN ($CDCl_3$ 400 MHz, δ ppm) COSY



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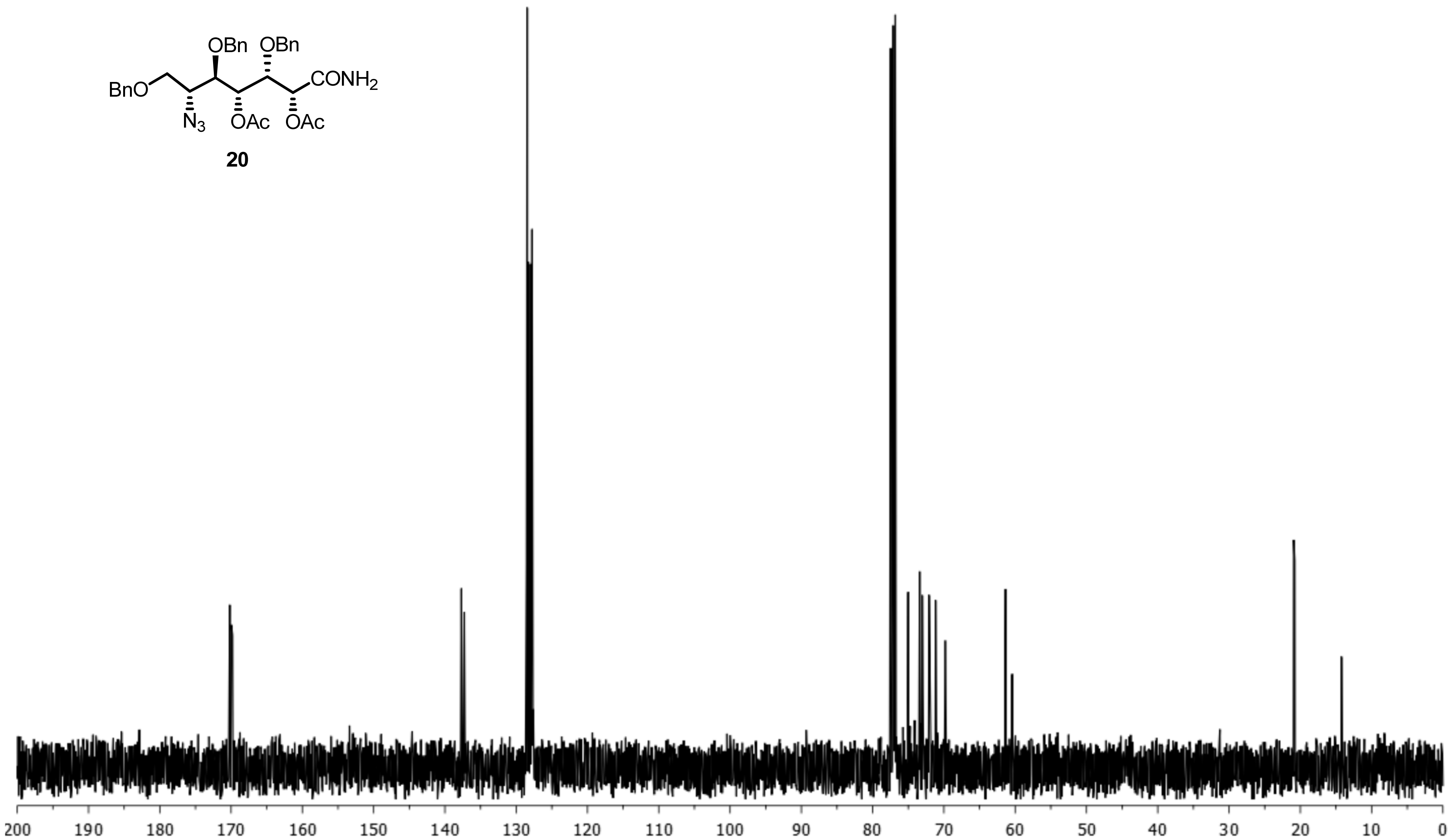
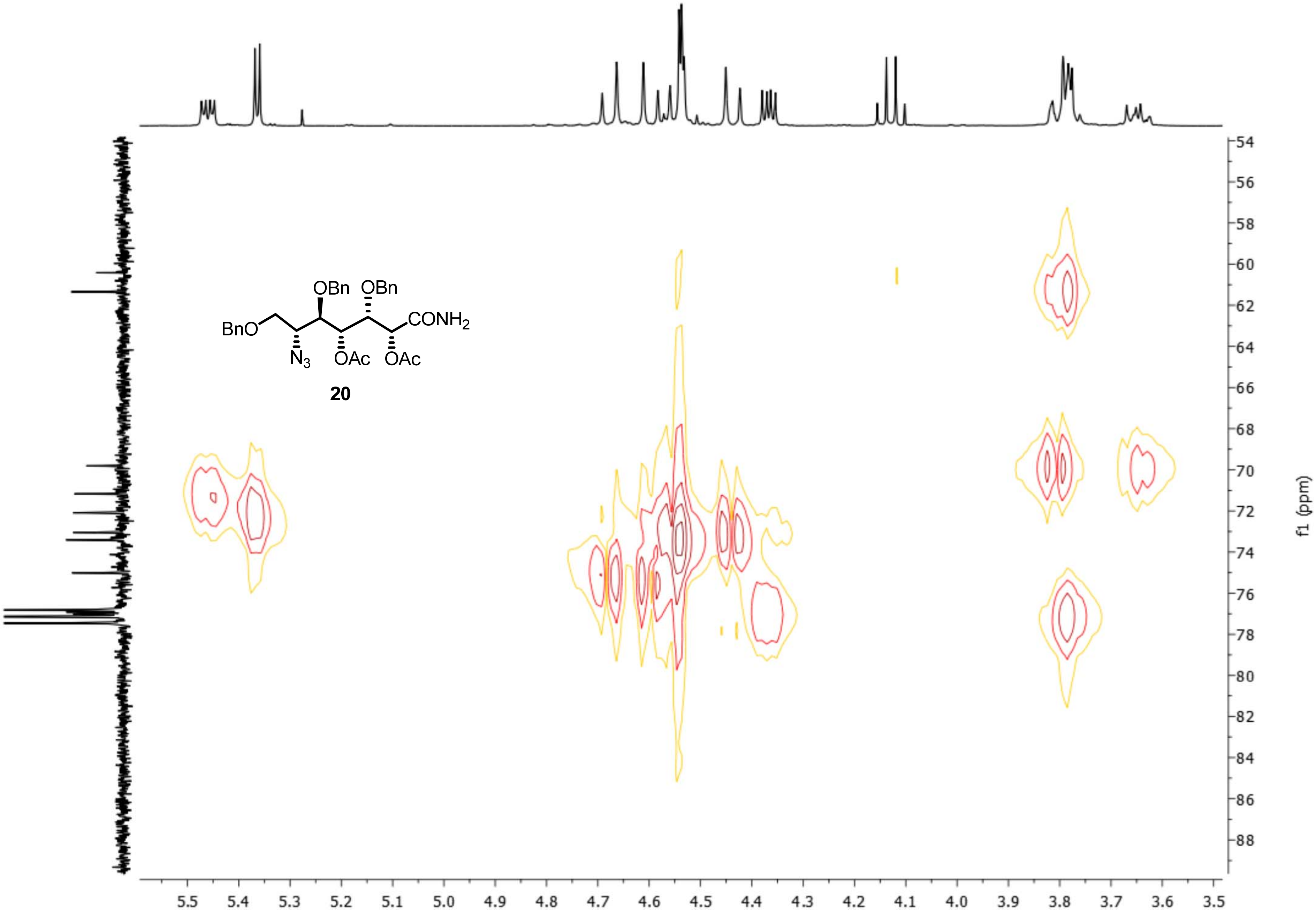
^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



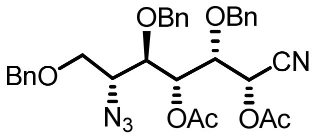
^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)

HMQC

^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



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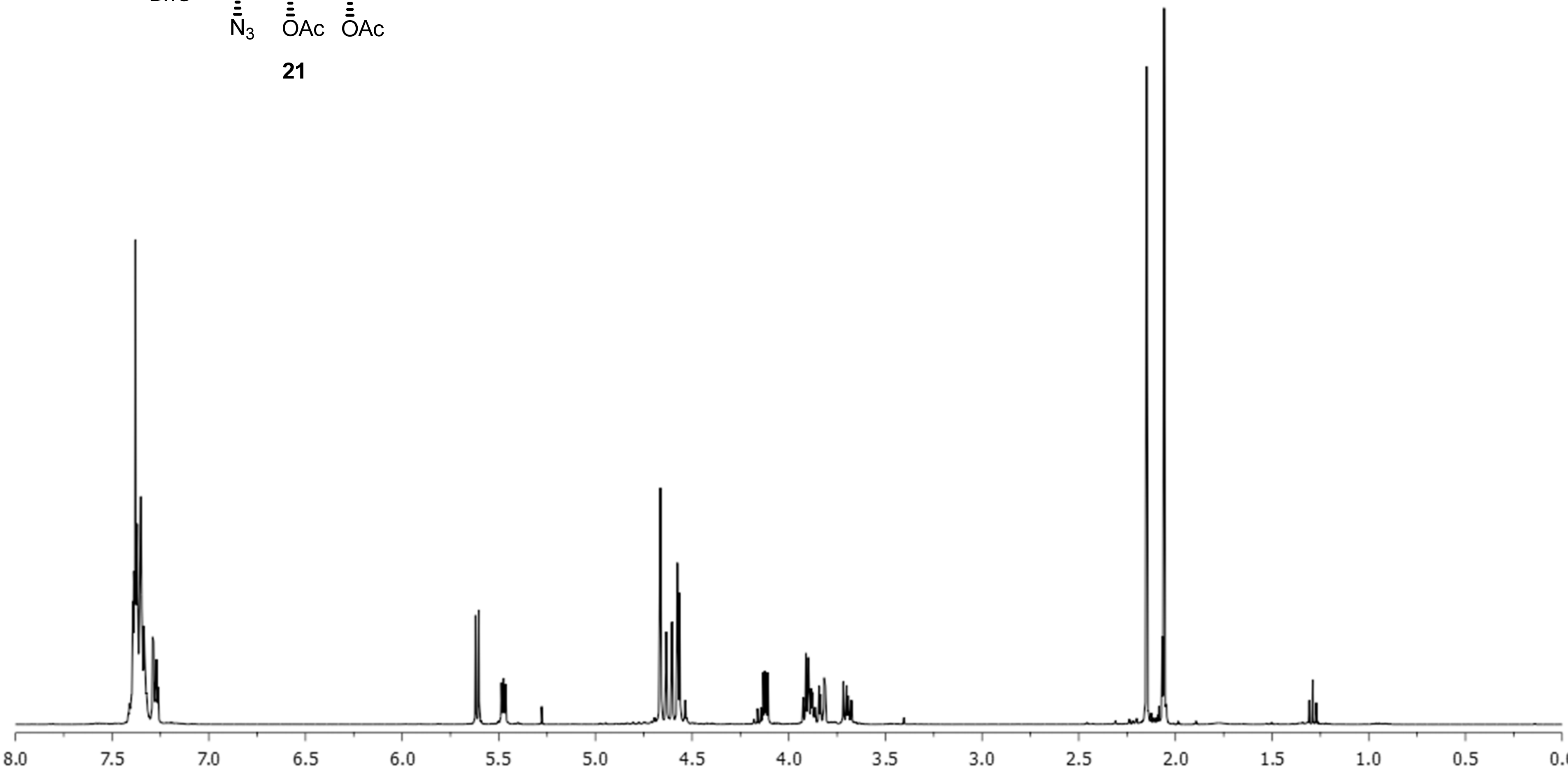
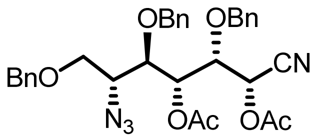


^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



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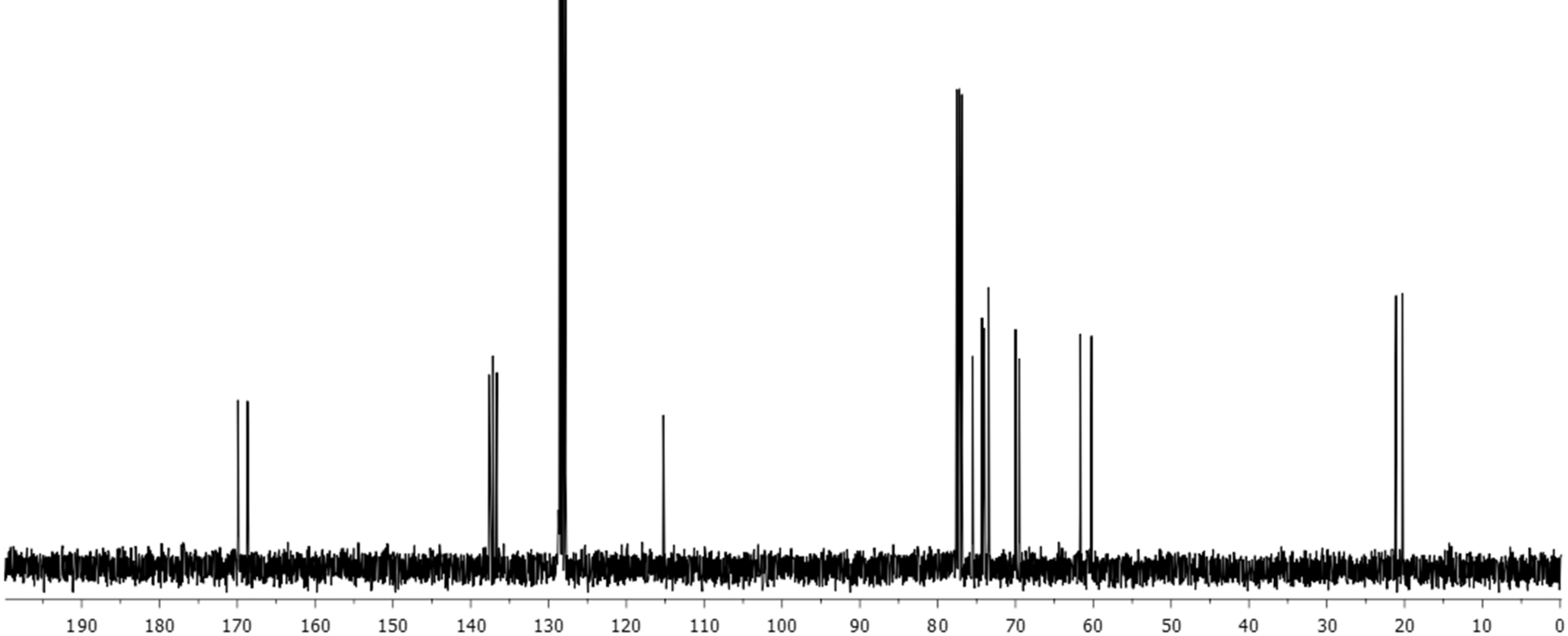
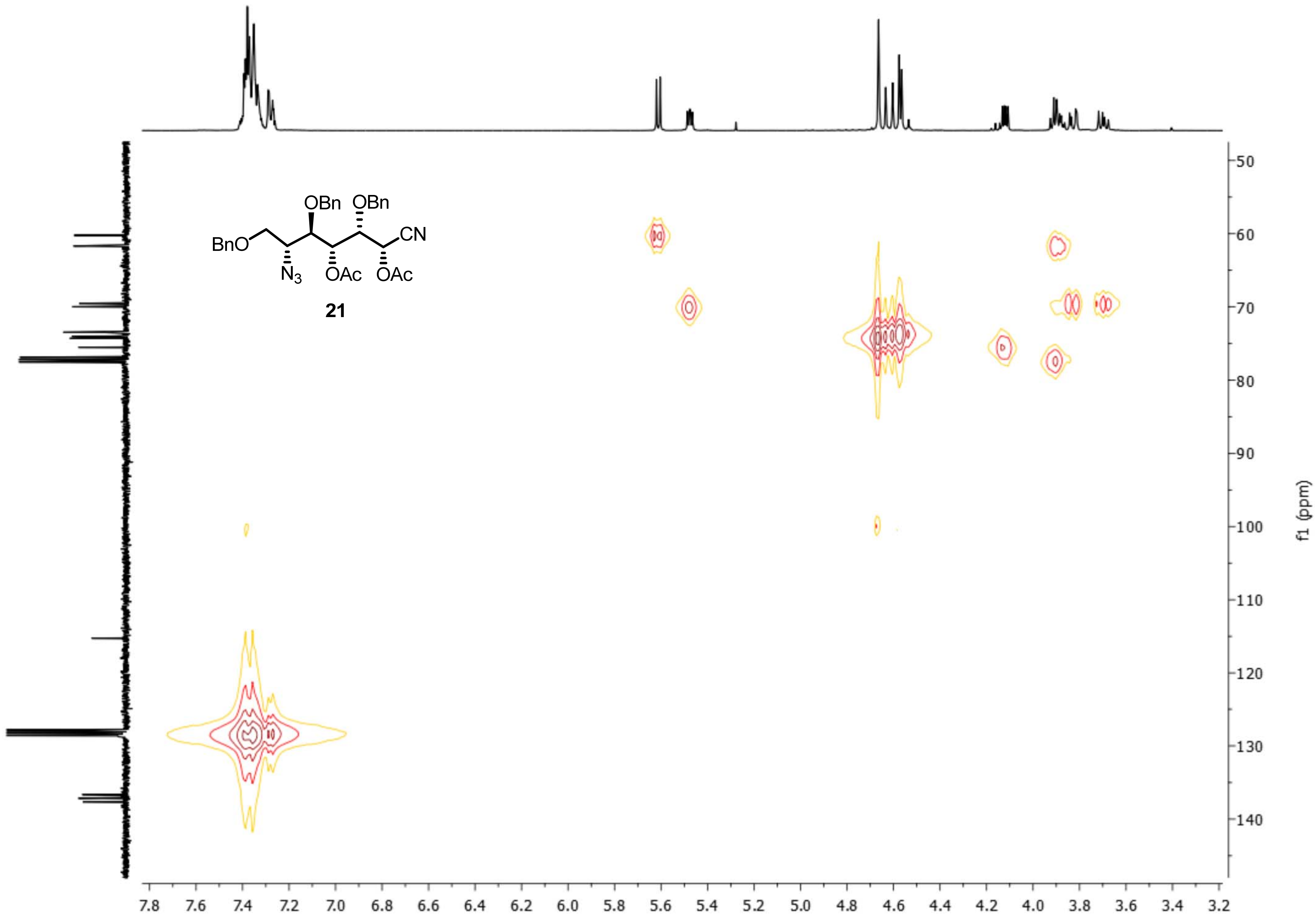


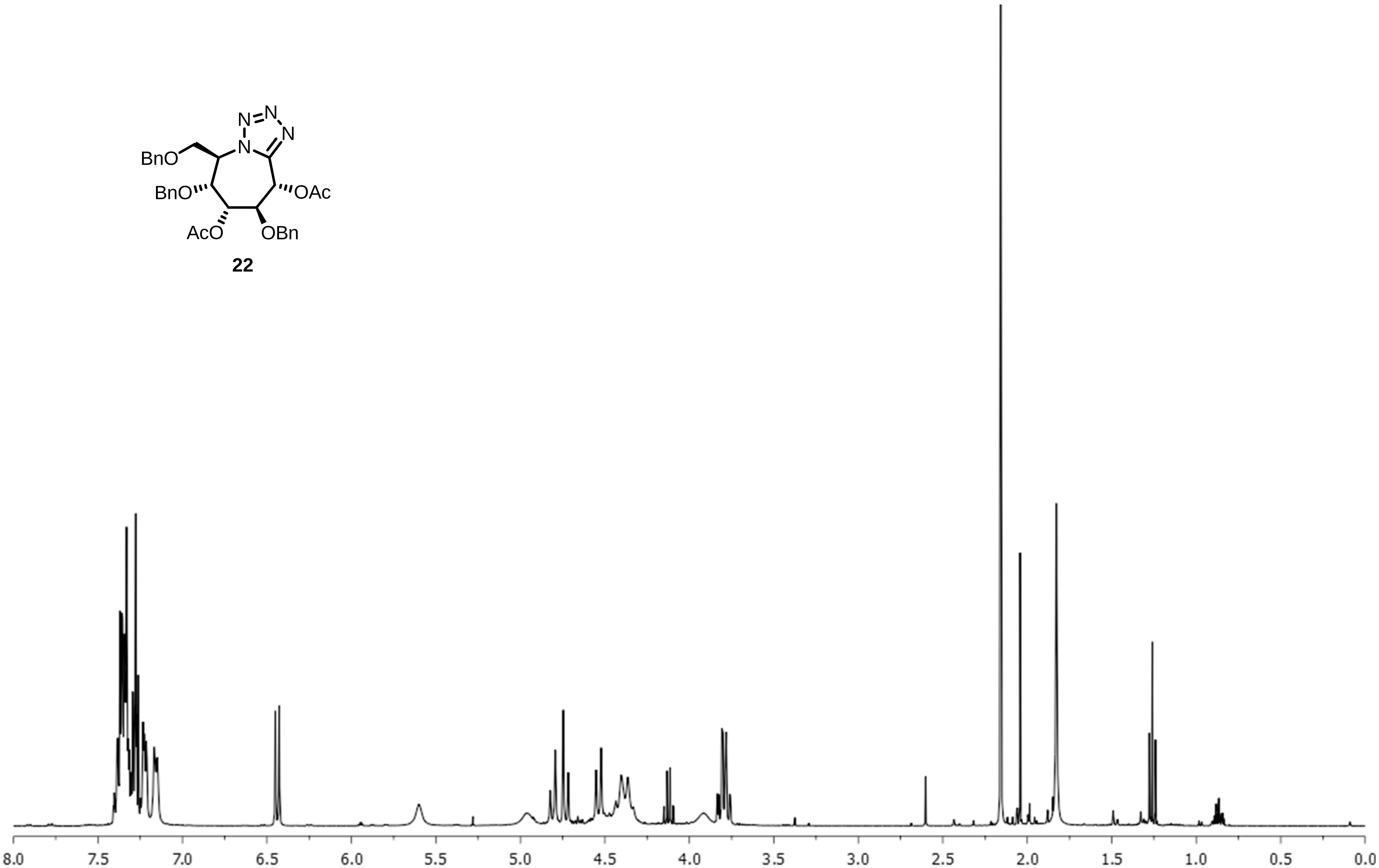
^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



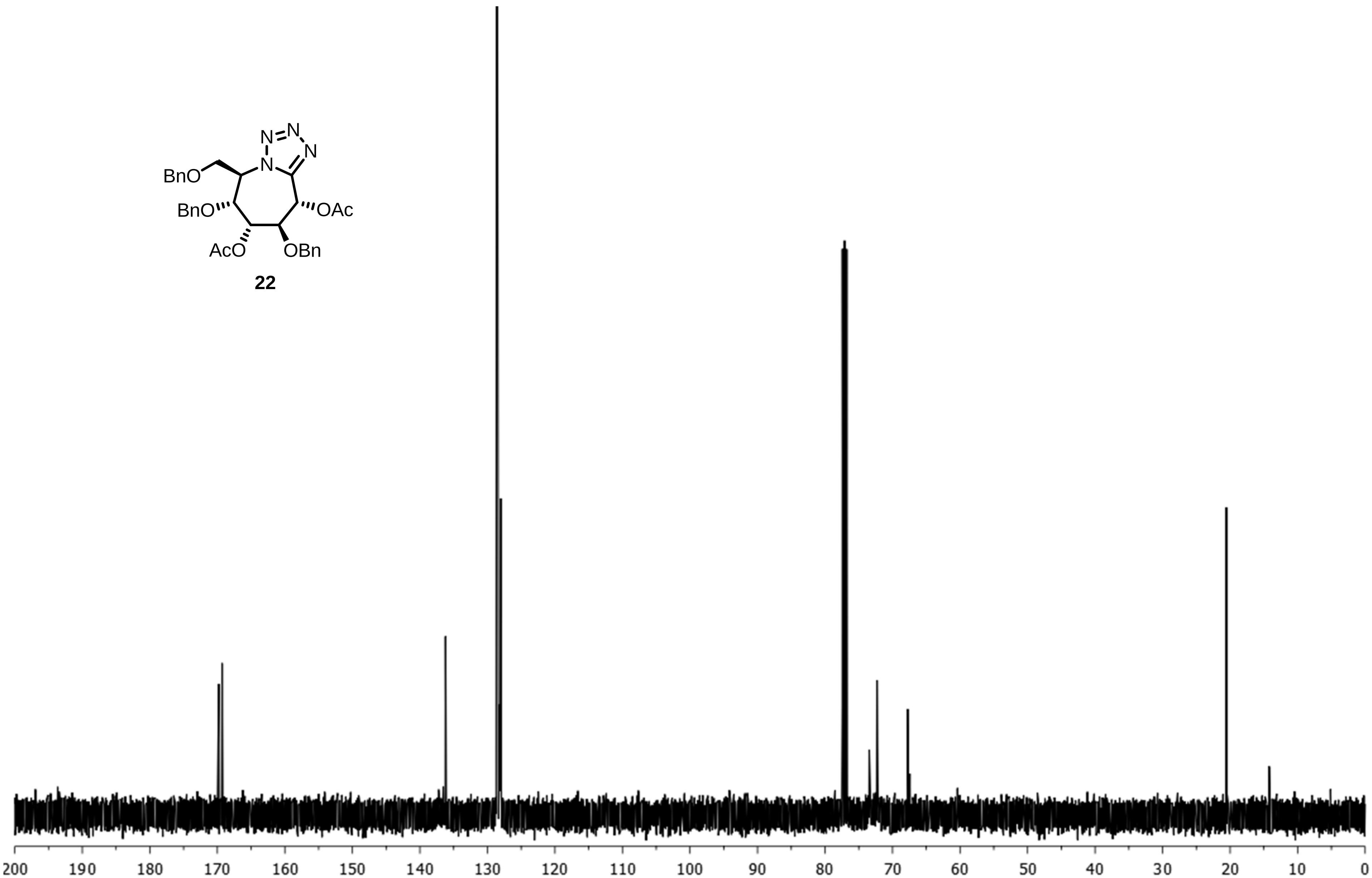
^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)

HMQC

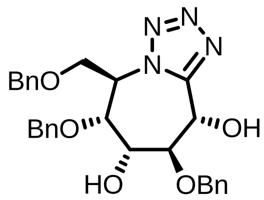
^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



^{1}H-RMN ($CDCl_3$, 400 Hz, δ ppm)



^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



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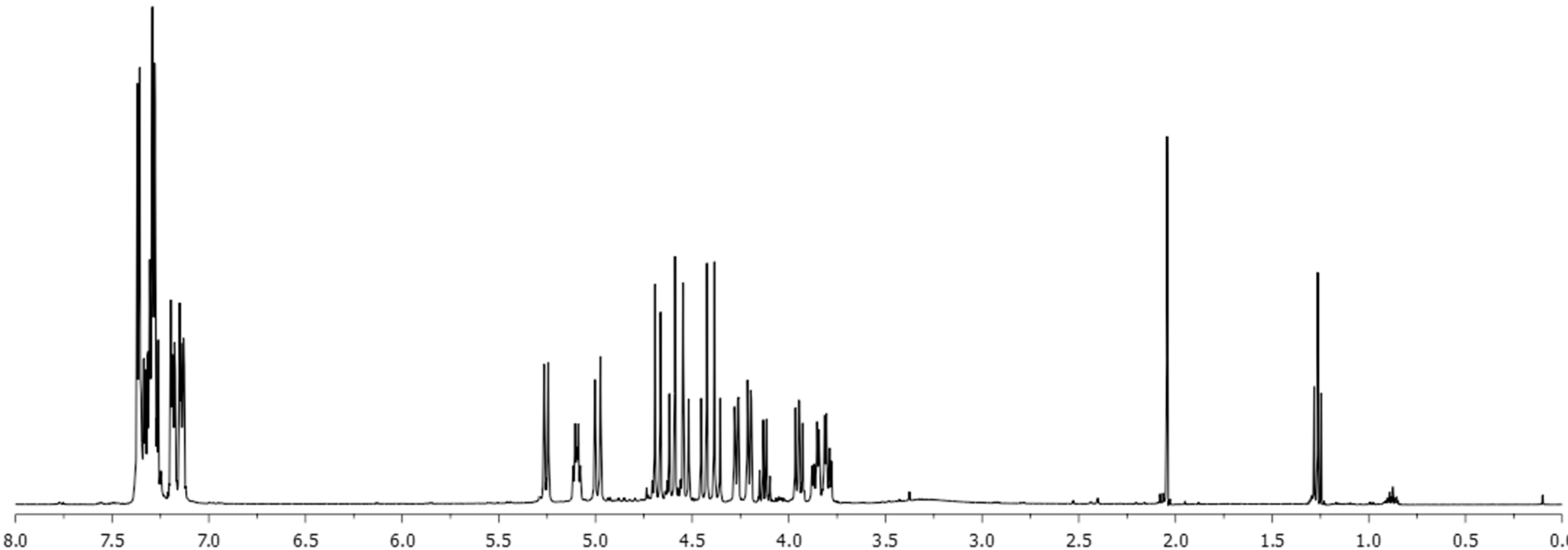
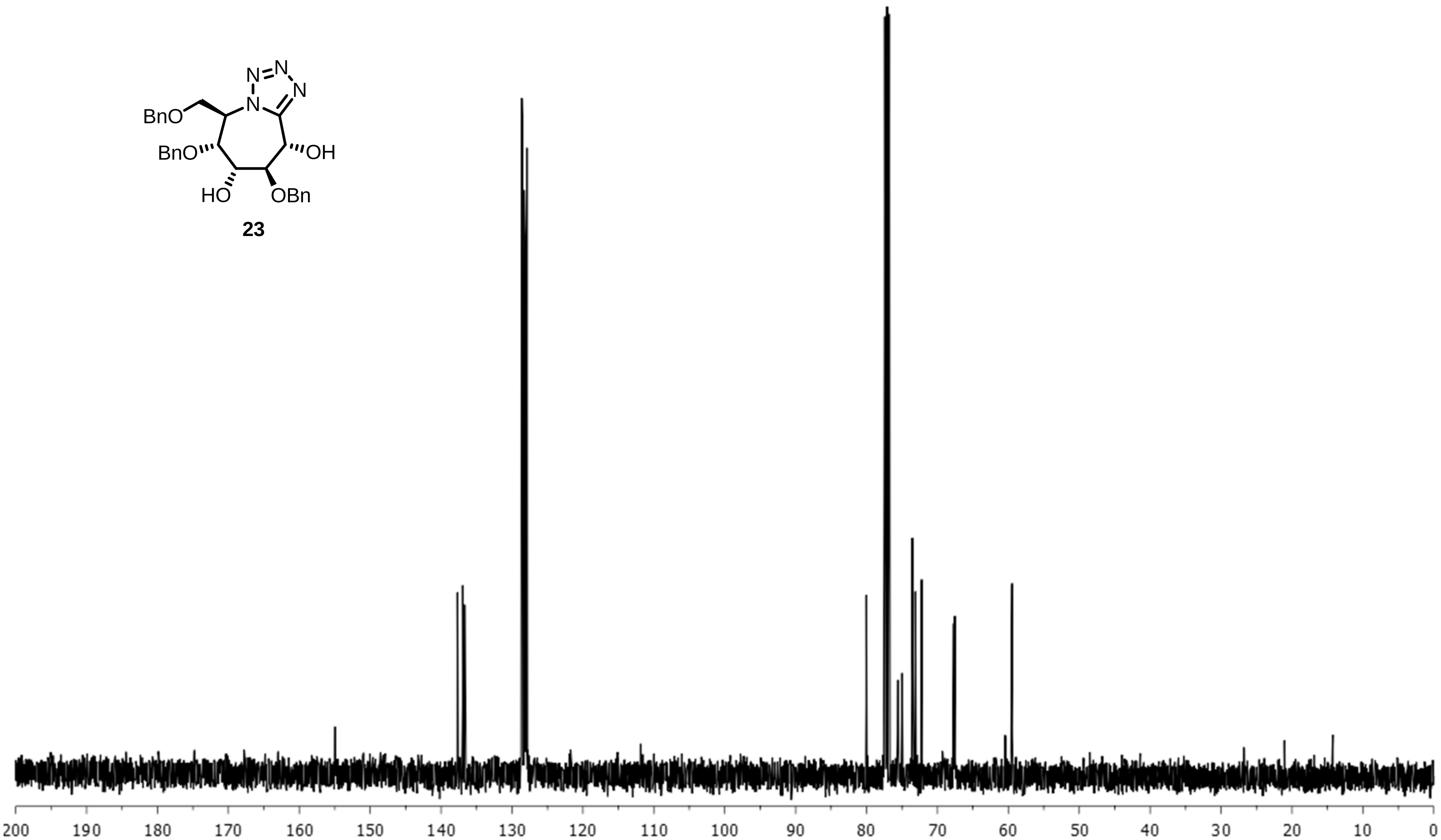
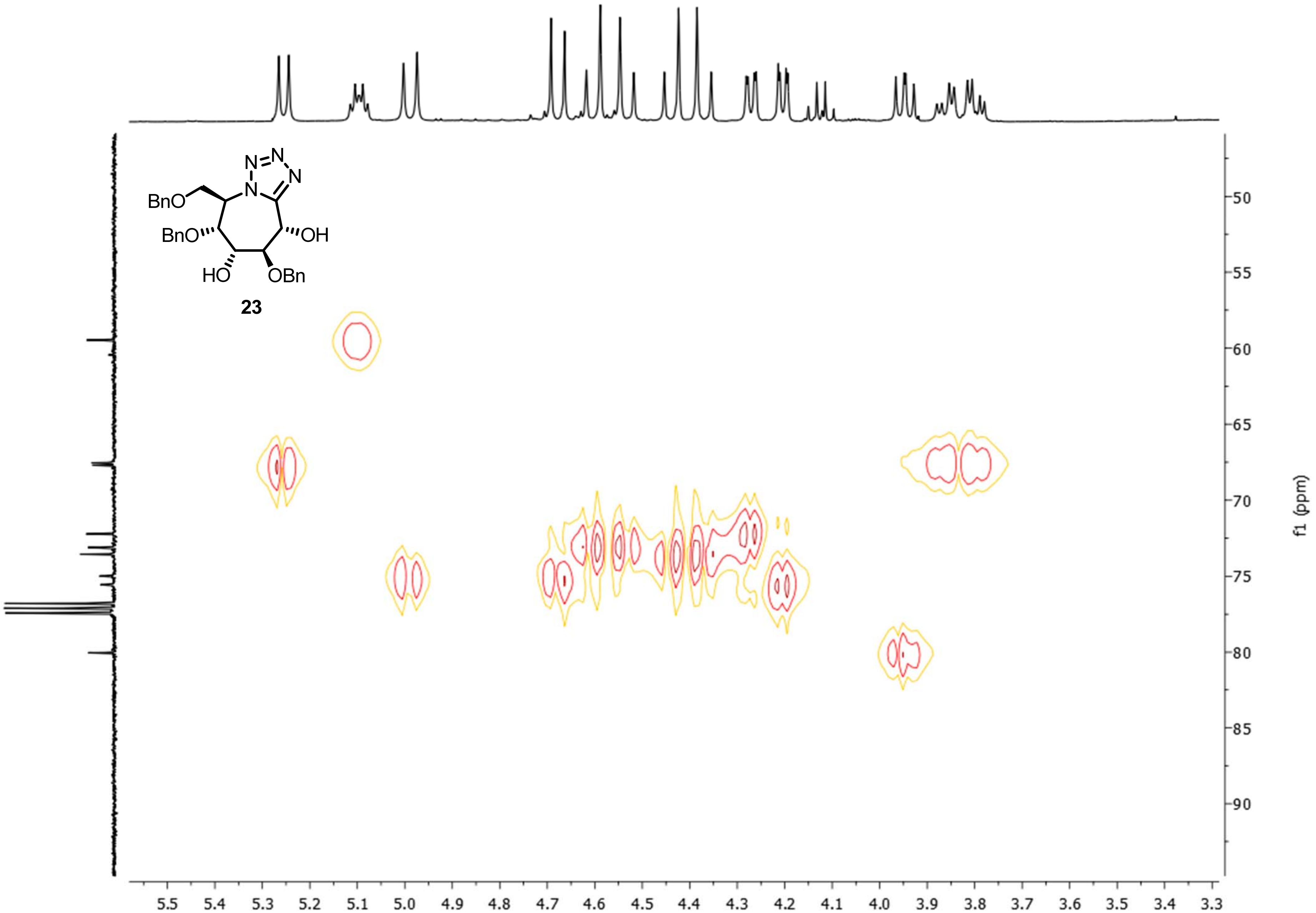


^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)

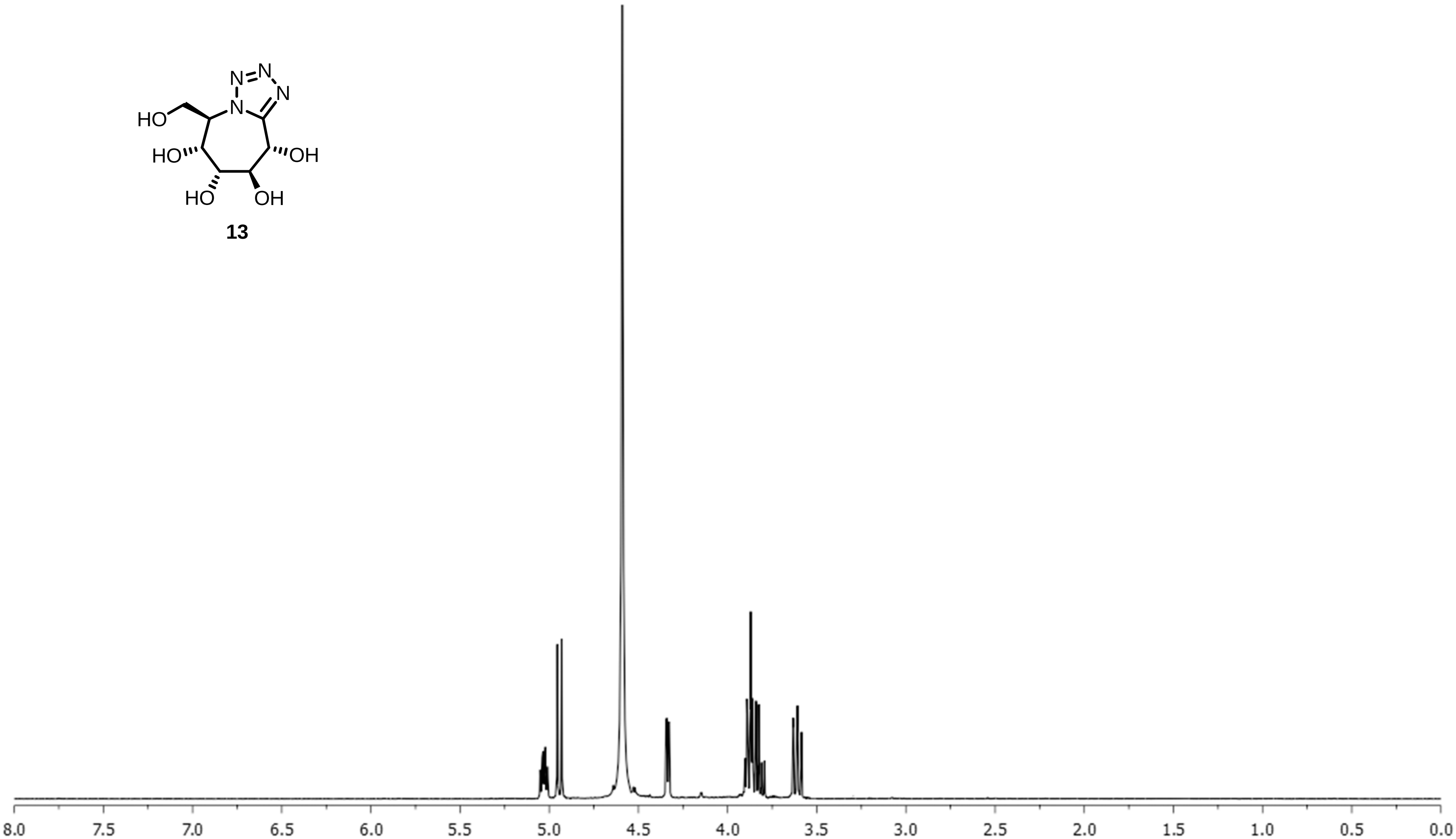


^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)

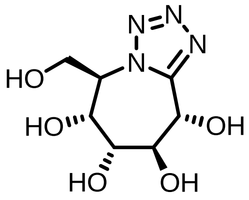


^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)
^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)

HMQC



^{1}H-RMN (D_2O, 400 MHz, δ ppm)



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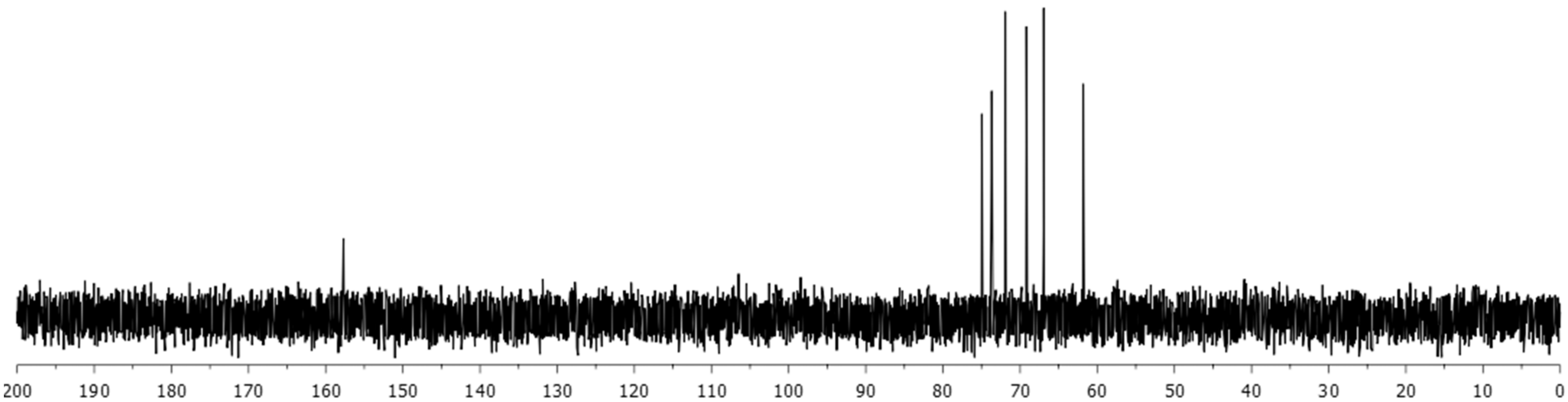
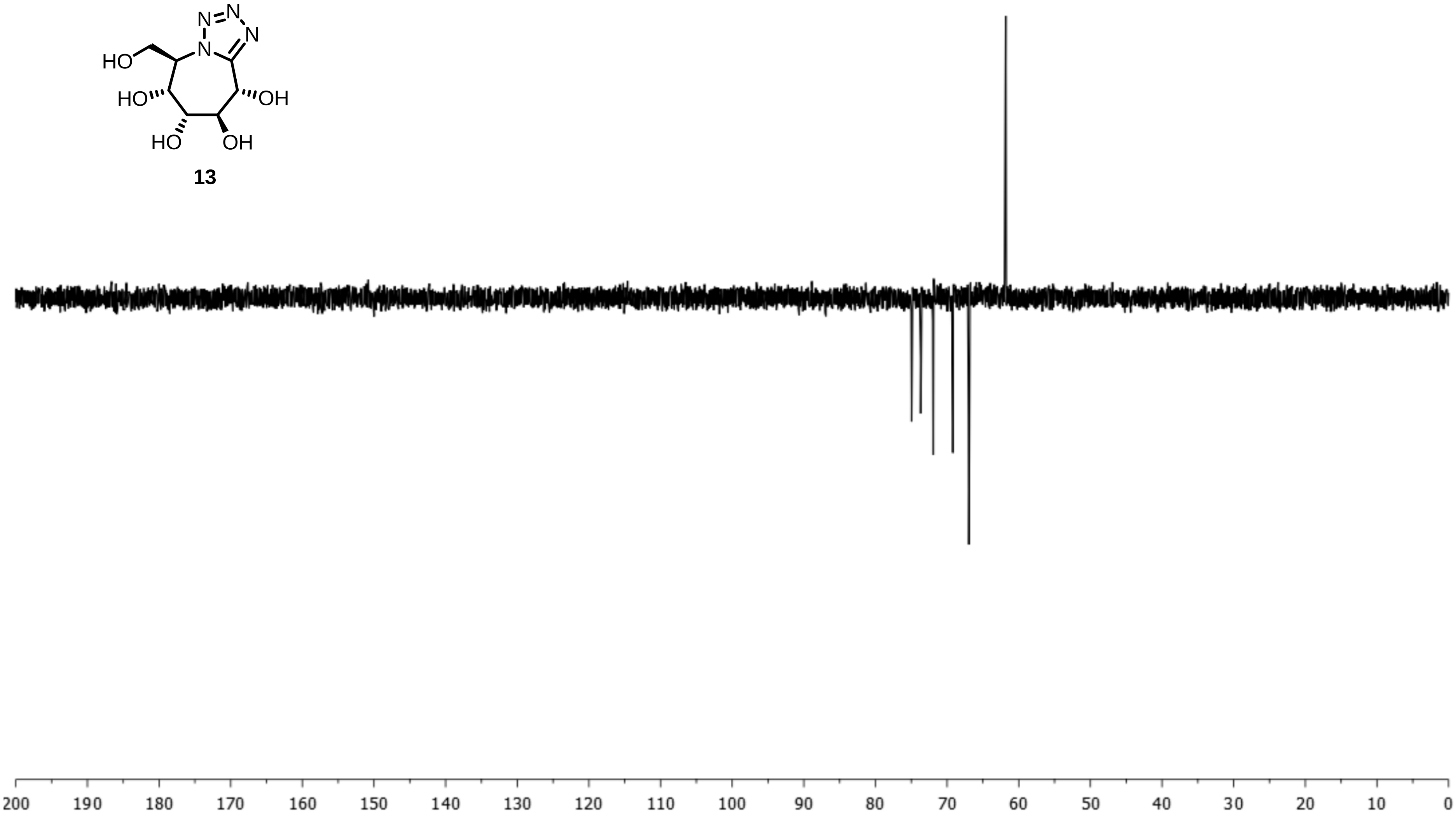
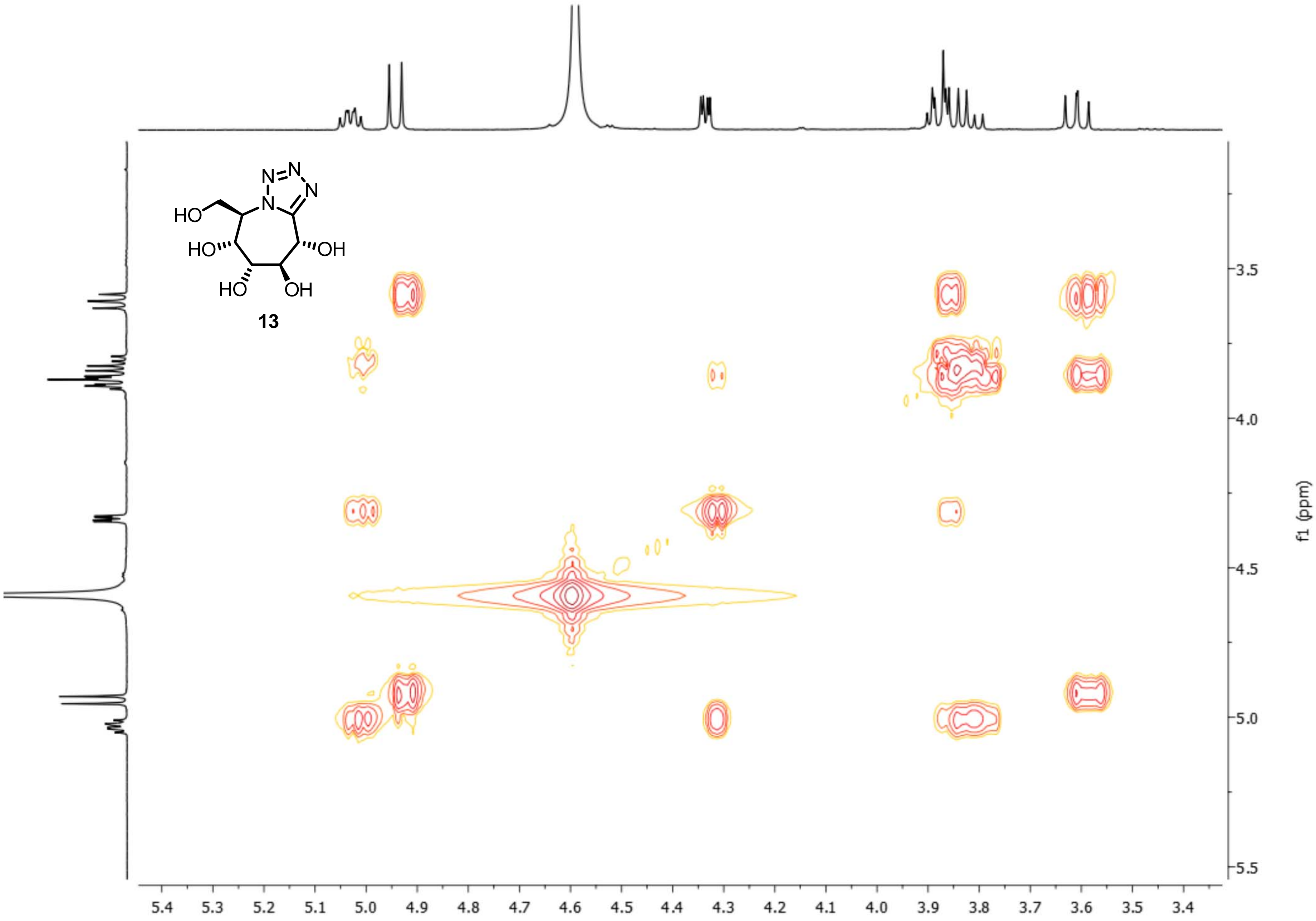


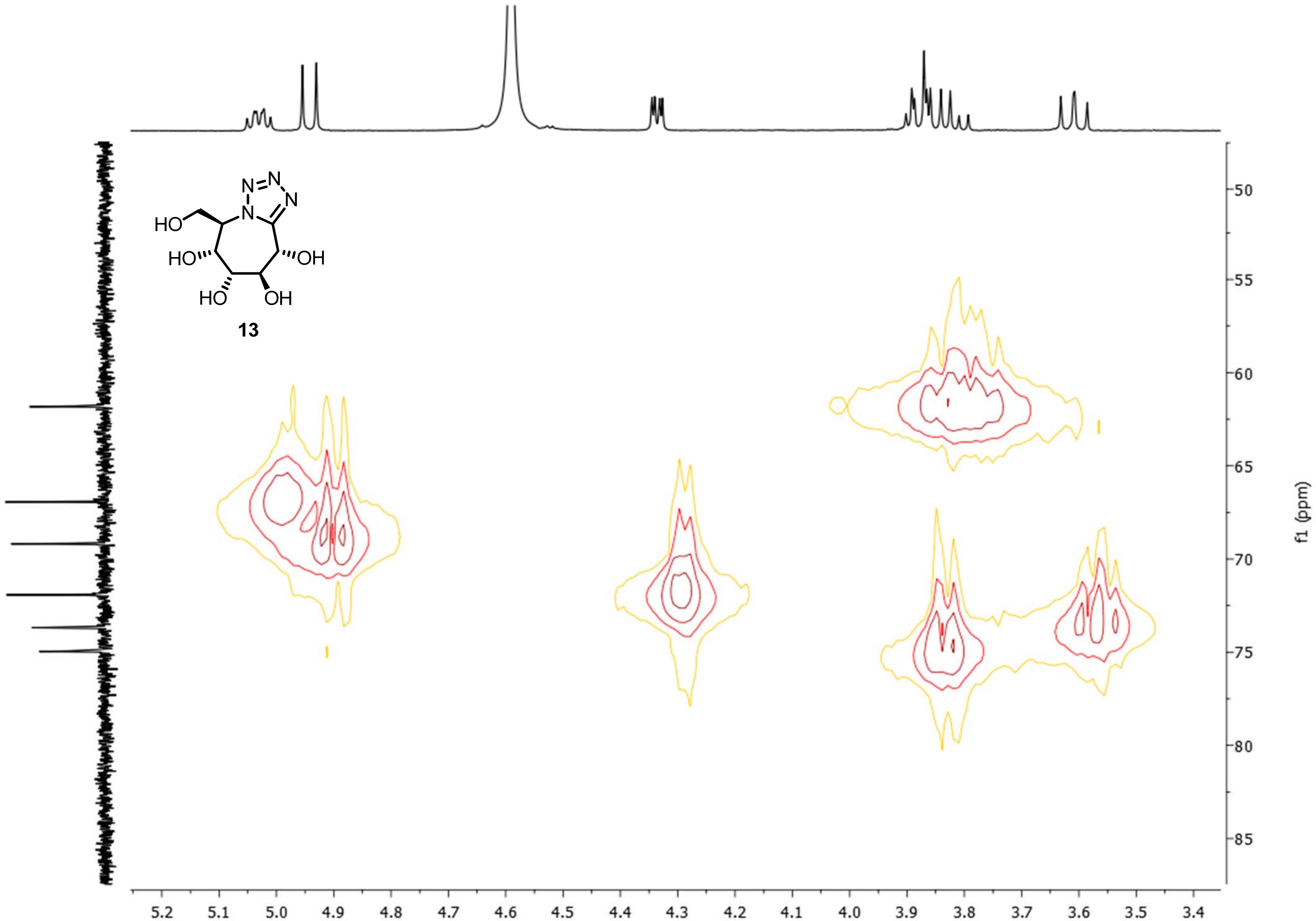
[13]C-RMN (D_2O, 100 MHz, δ pm)



^{13}C-RMN (D_2O, 100 MHz, δ ppm) DEPT



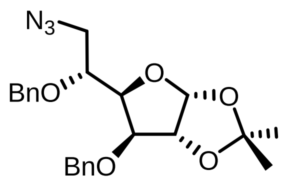
^{1}H-RMN (D_2O 400 MHz, δ ppm) COSY



^{1}H-RMN (D_2O, 400 MHz, δ ppm)

^{13}C-RMN (D_2O, 100 MHz, δ ppm)

HMQC



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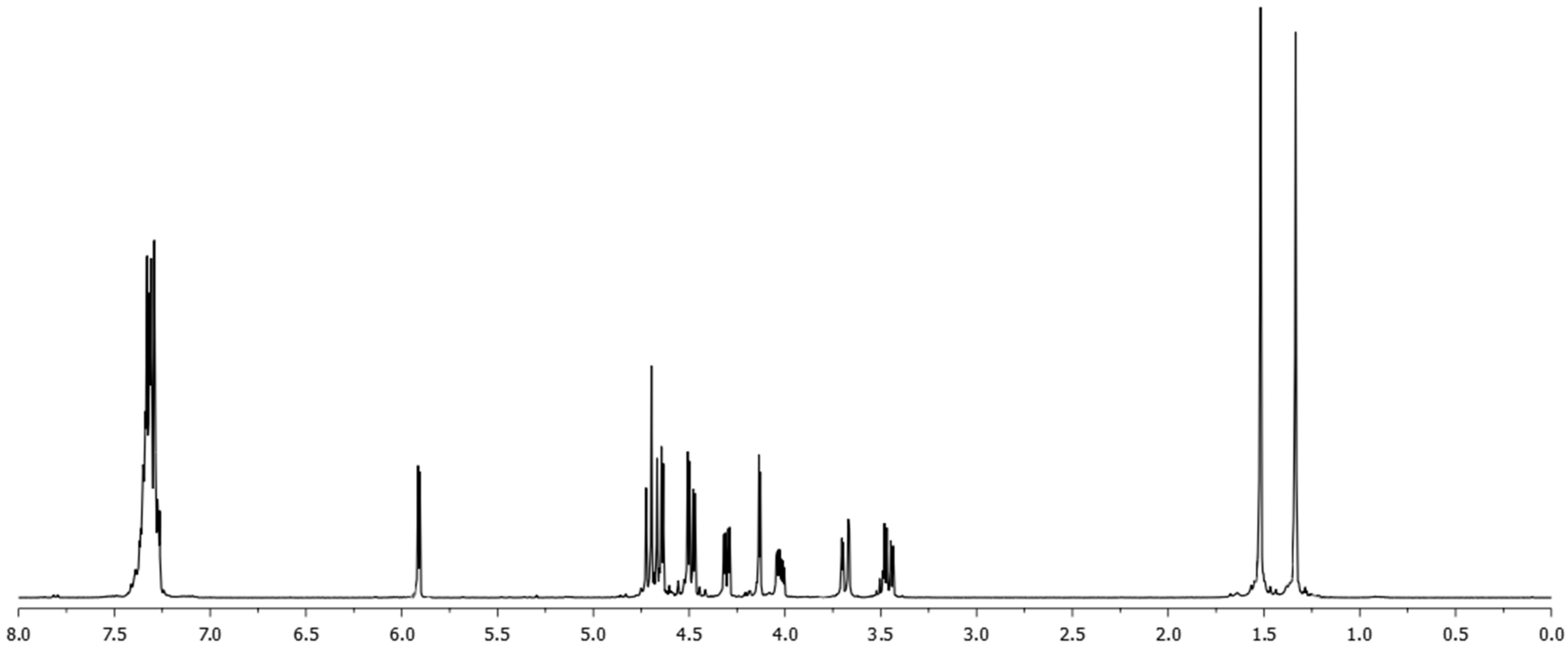
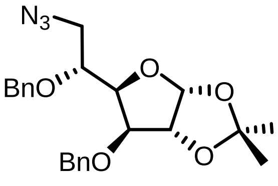


[1]H-RMN ($CDCl_3$, 400 MHz, δ ppm)



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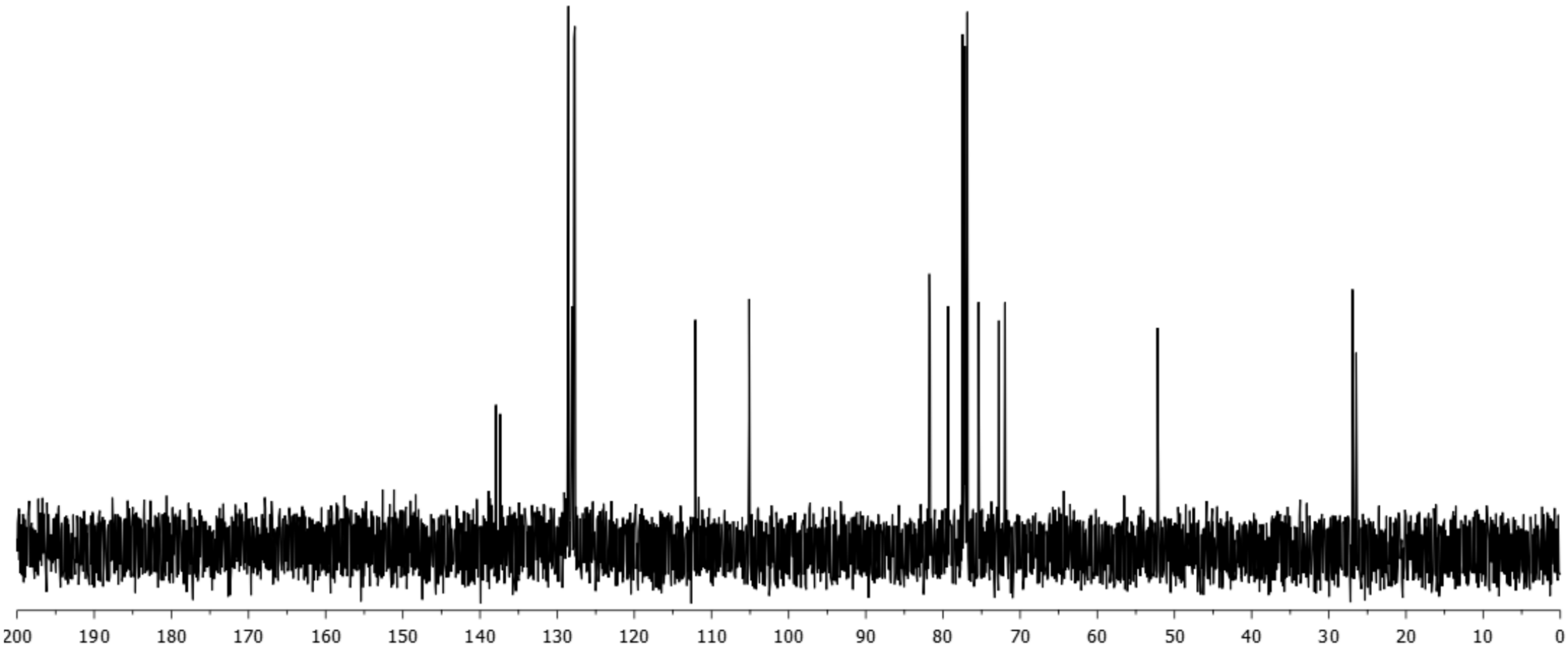
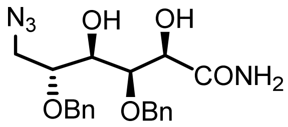


^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



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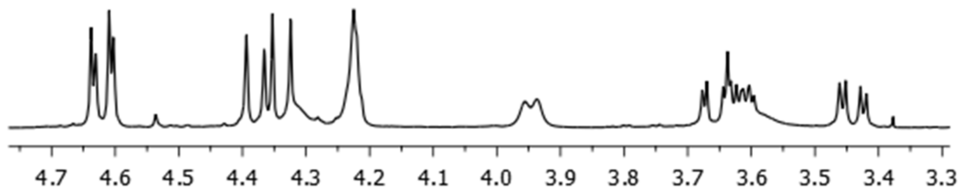
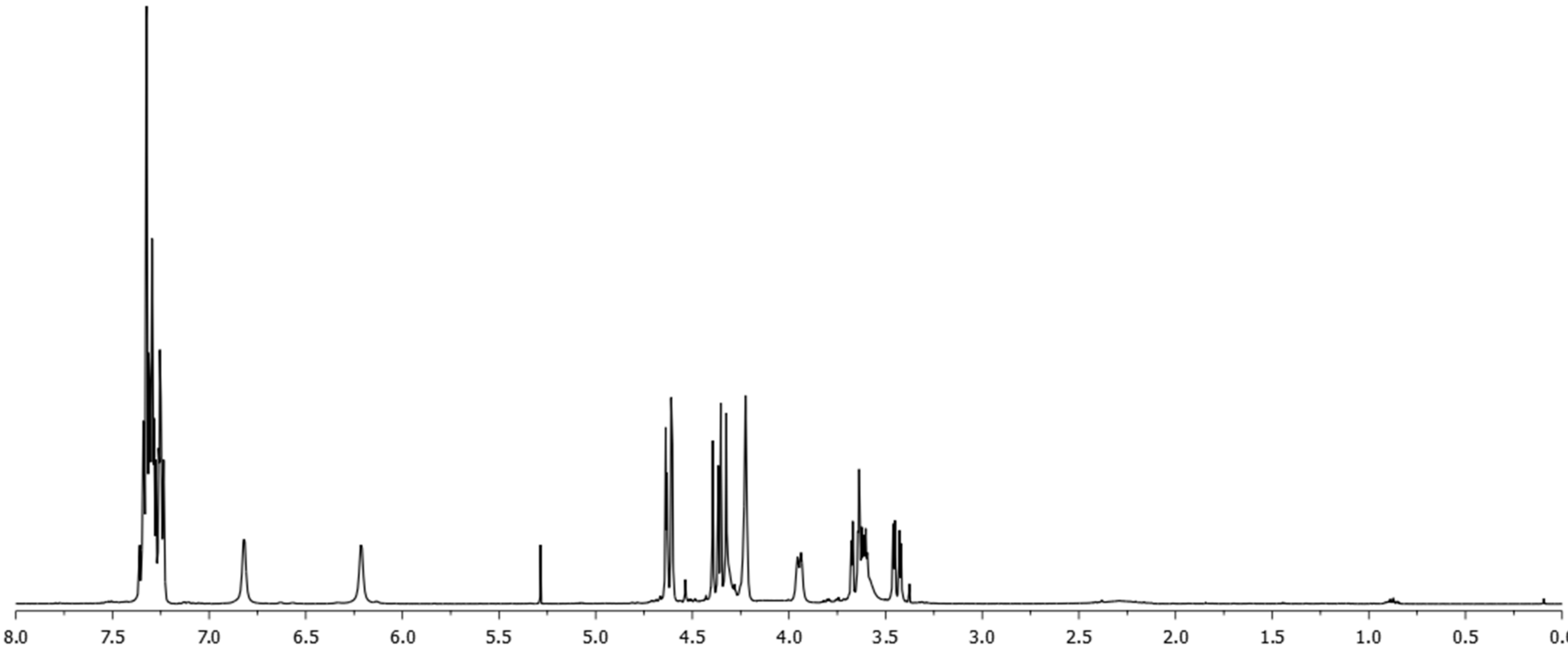
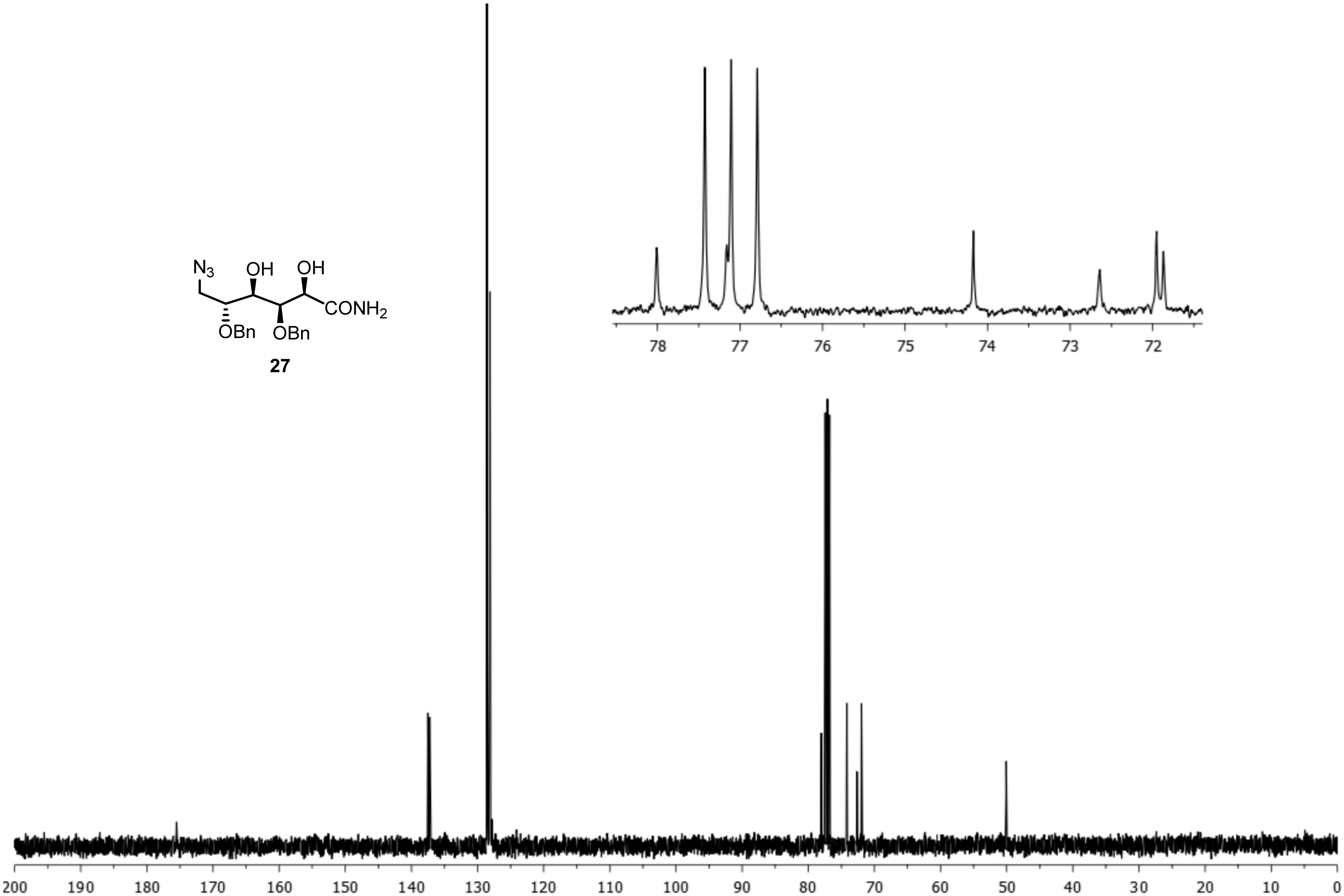
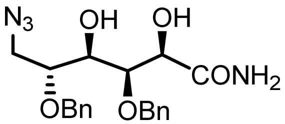




^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



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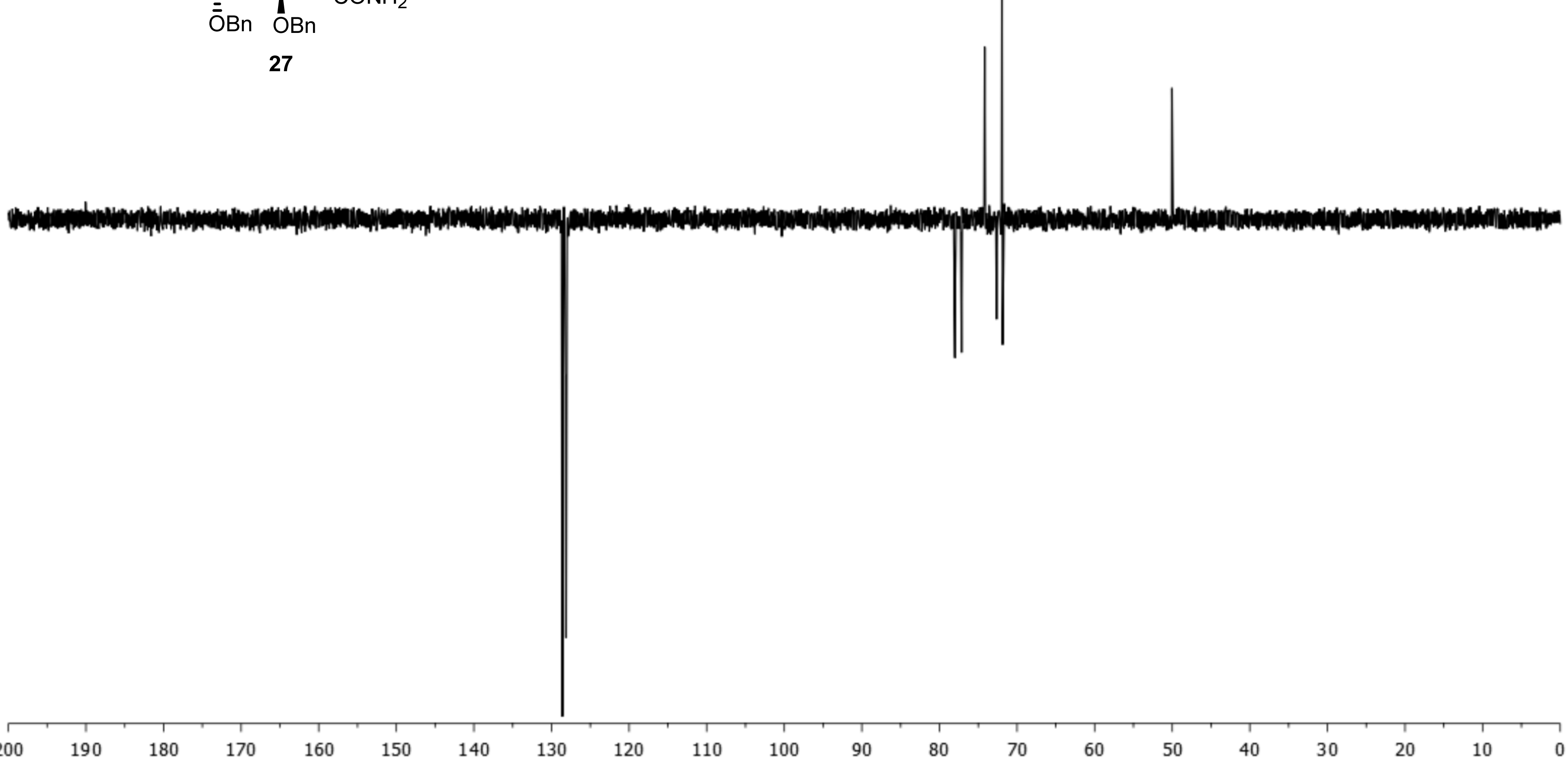
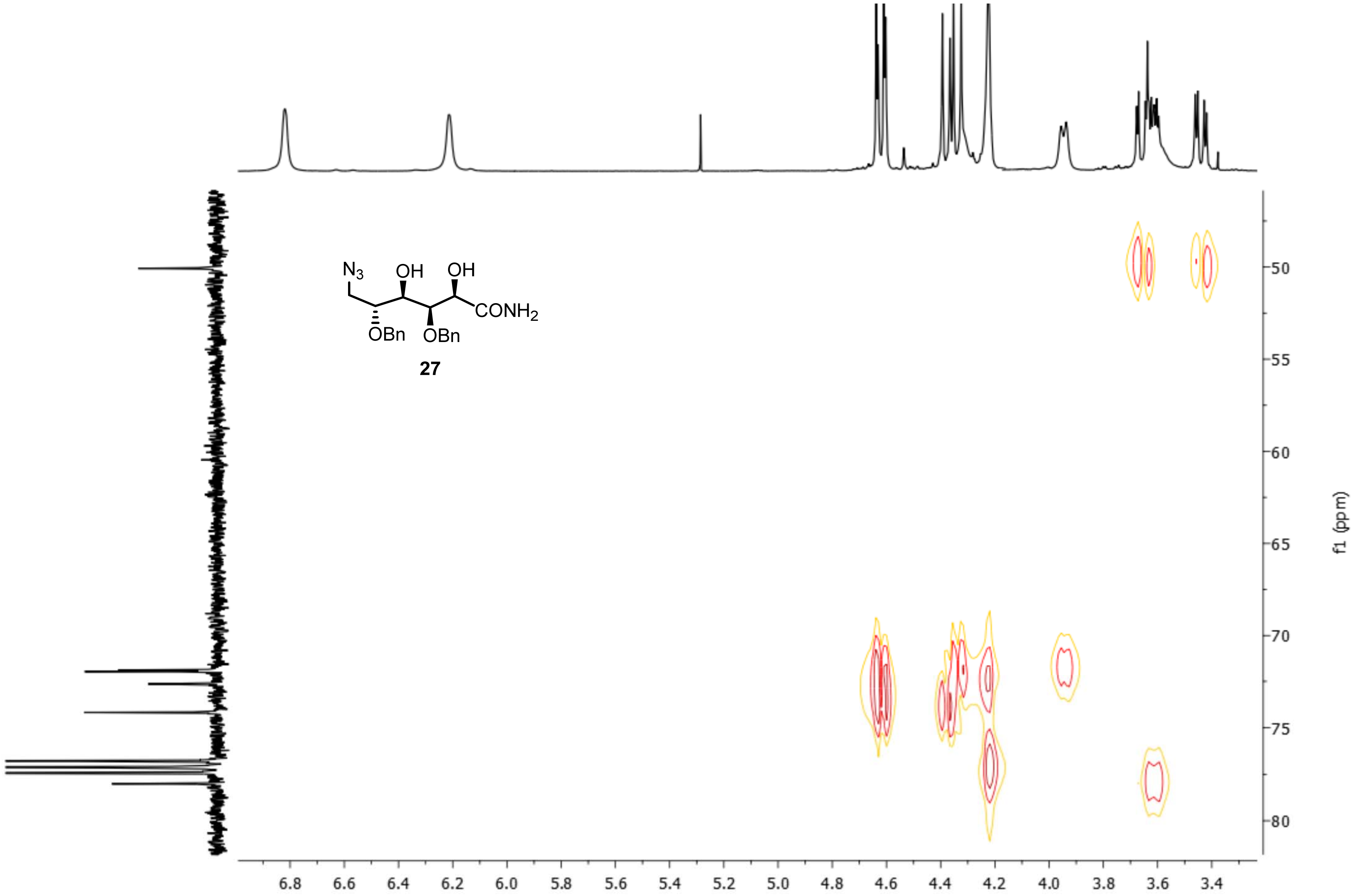


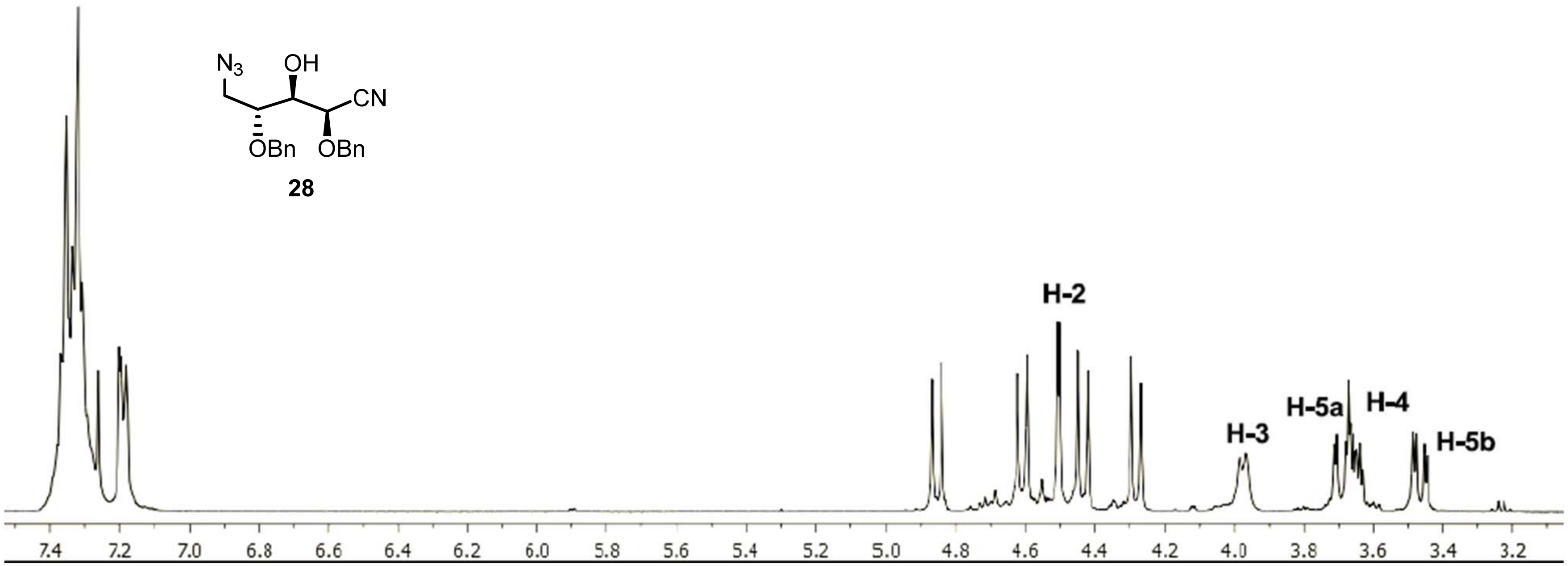
^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm) DEPT



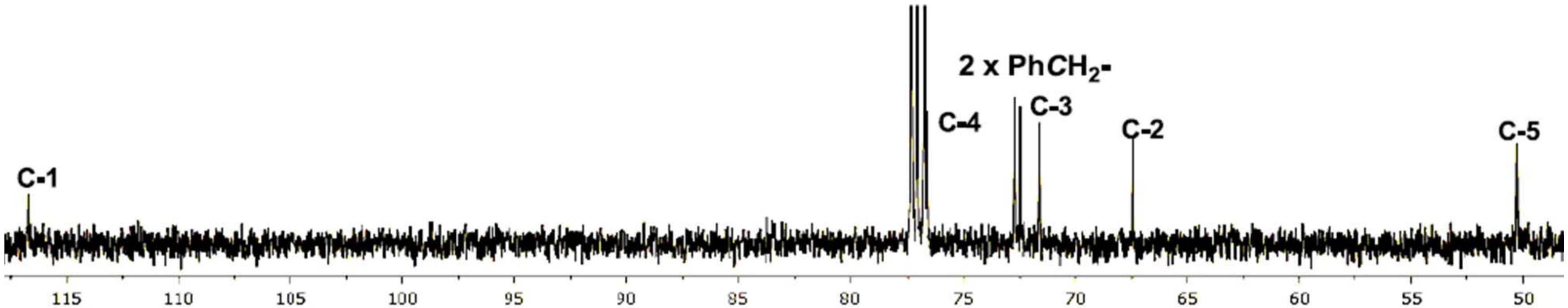
^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)

^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)

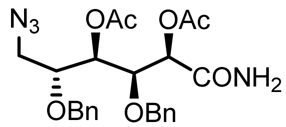
HMQC



^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



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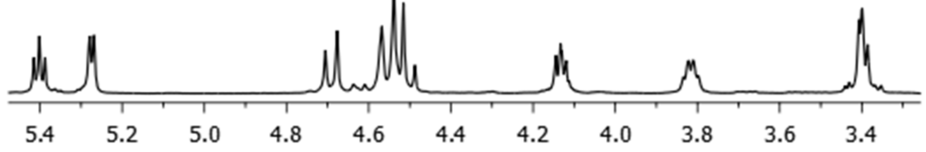
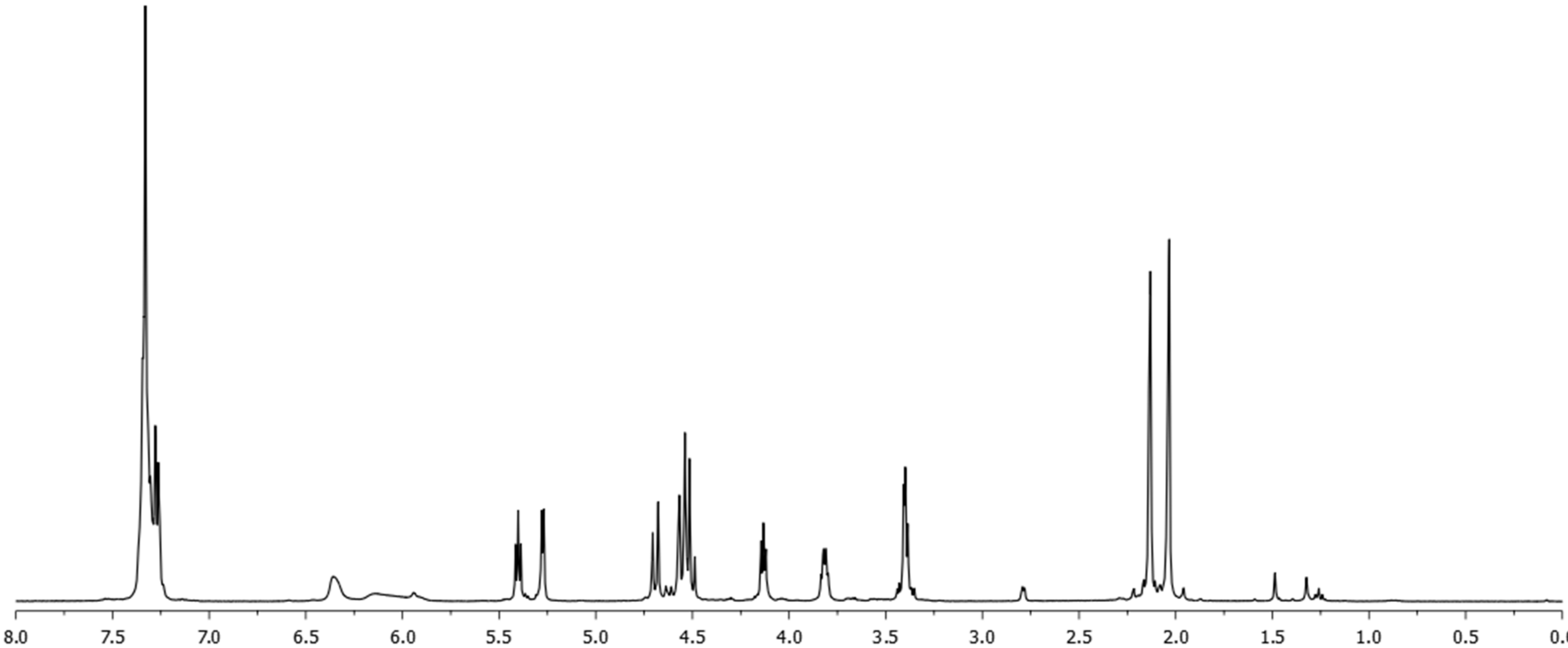
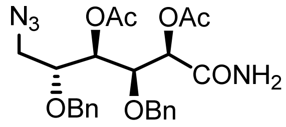




^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



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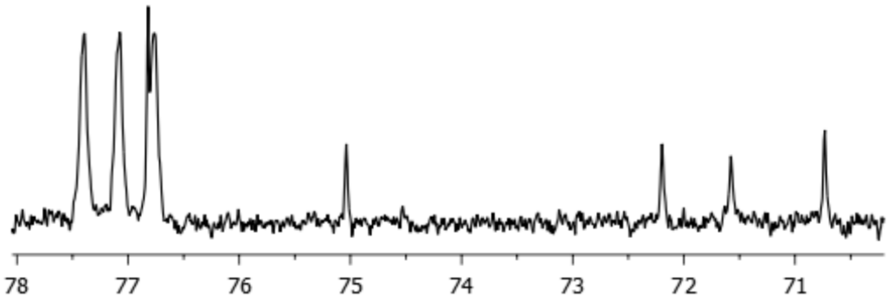
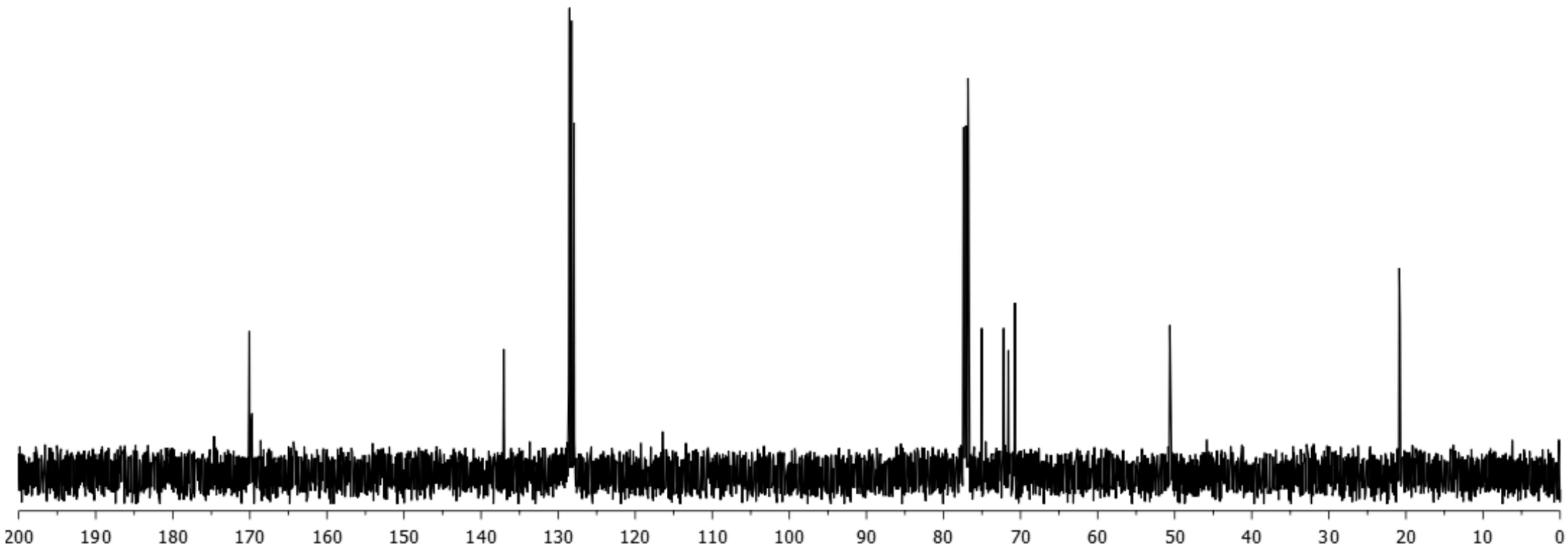
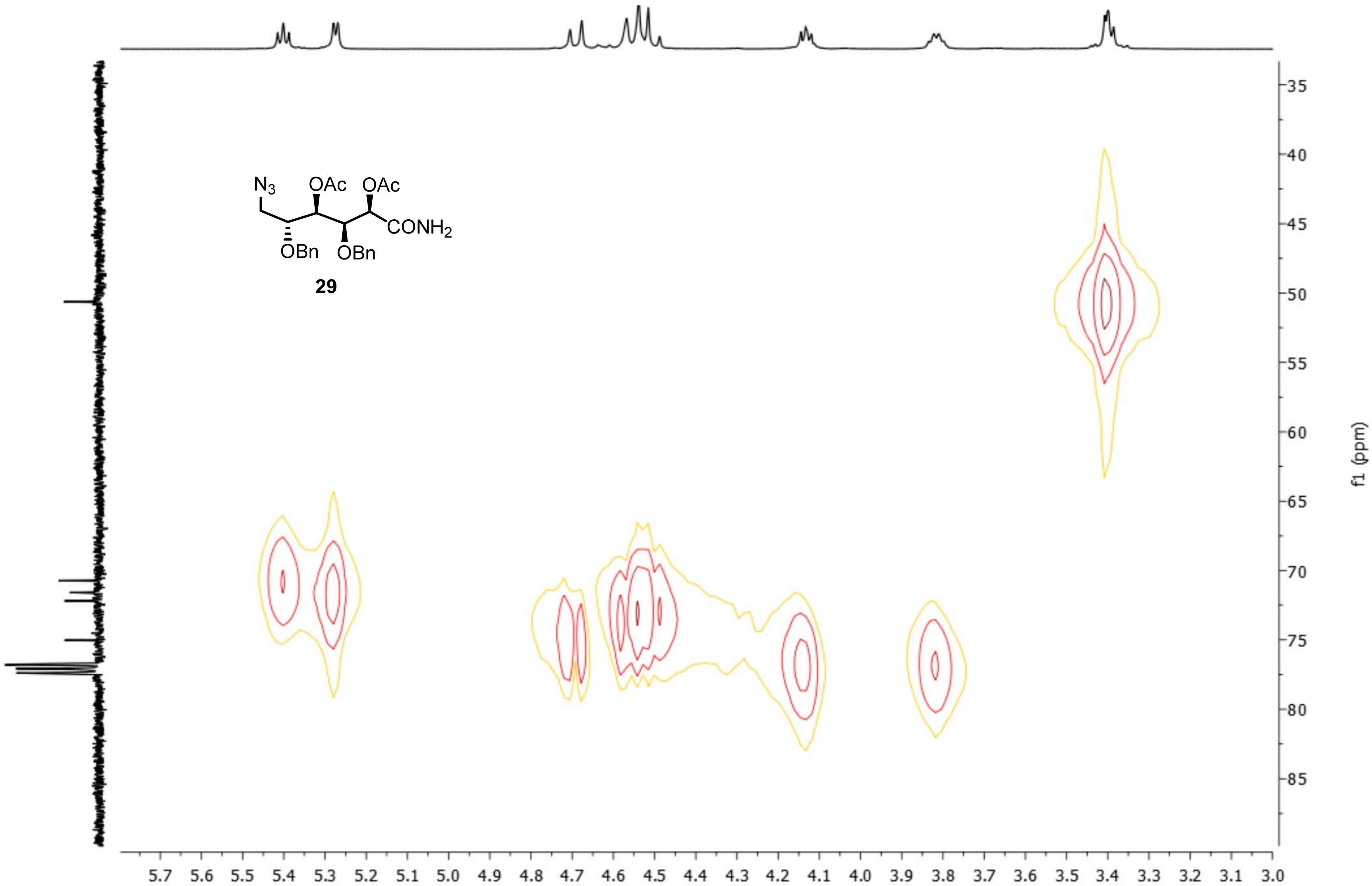




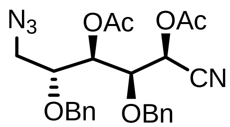
[13]C-RMN ($CDCl_3$, 100 MHz, δ ppm)



^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)

HMQC

^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



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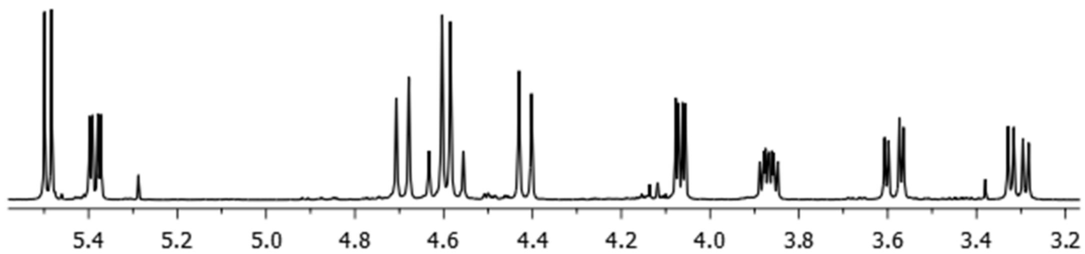
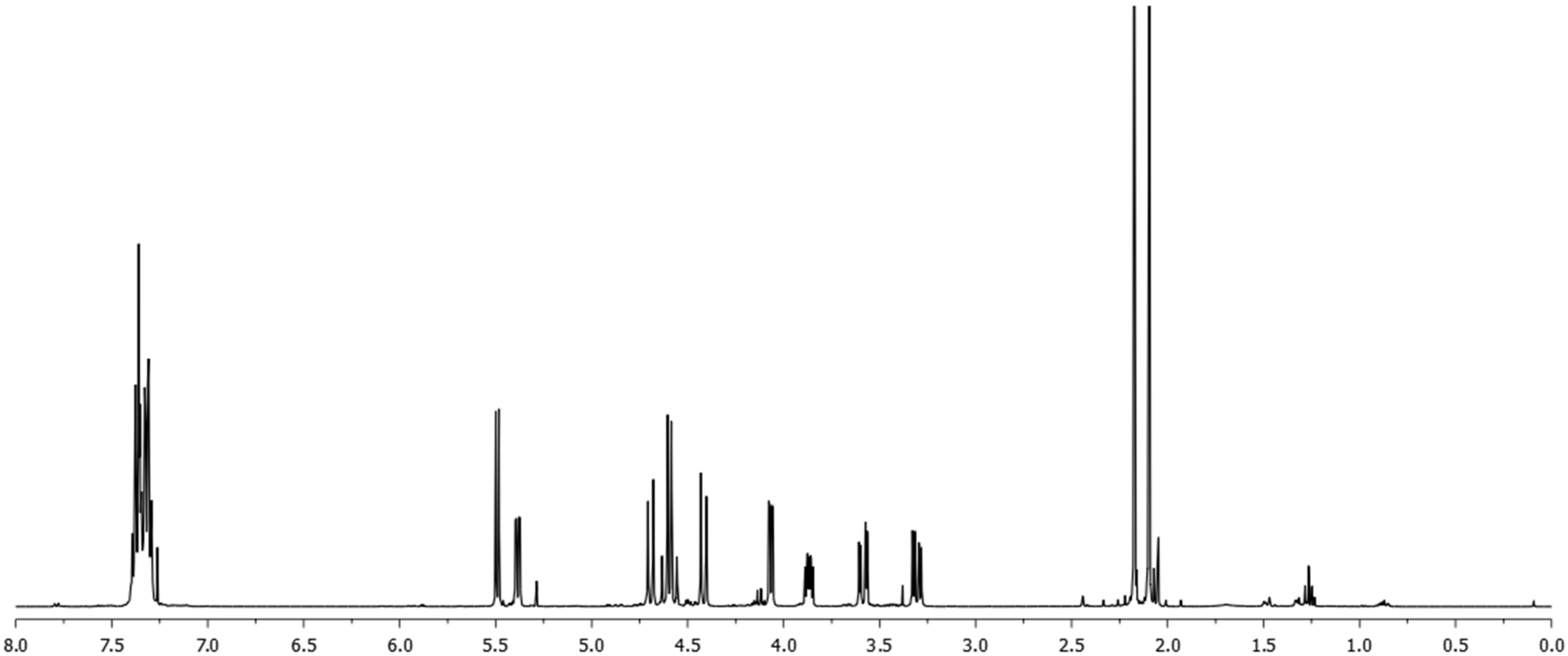
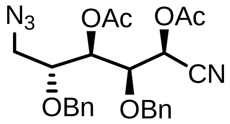
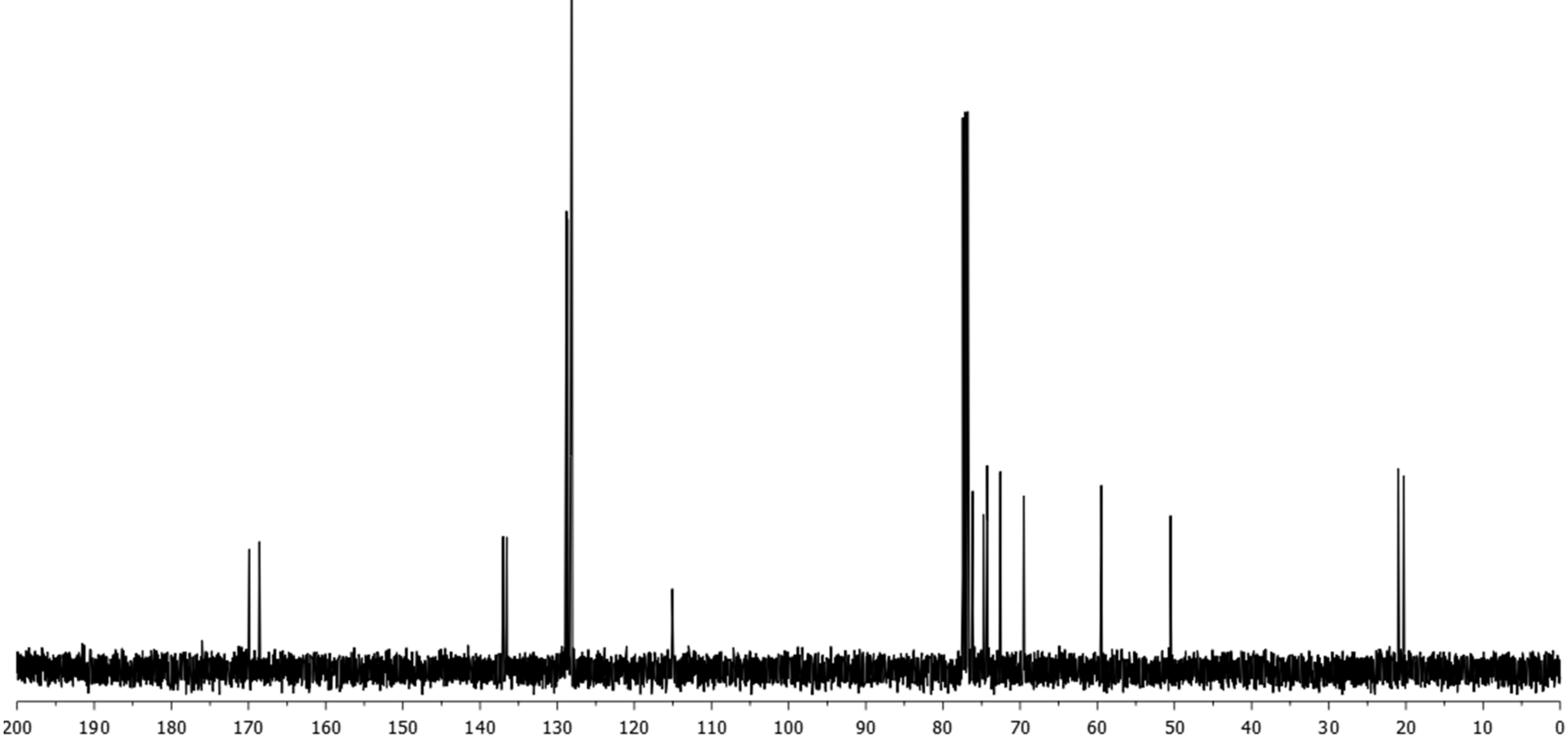




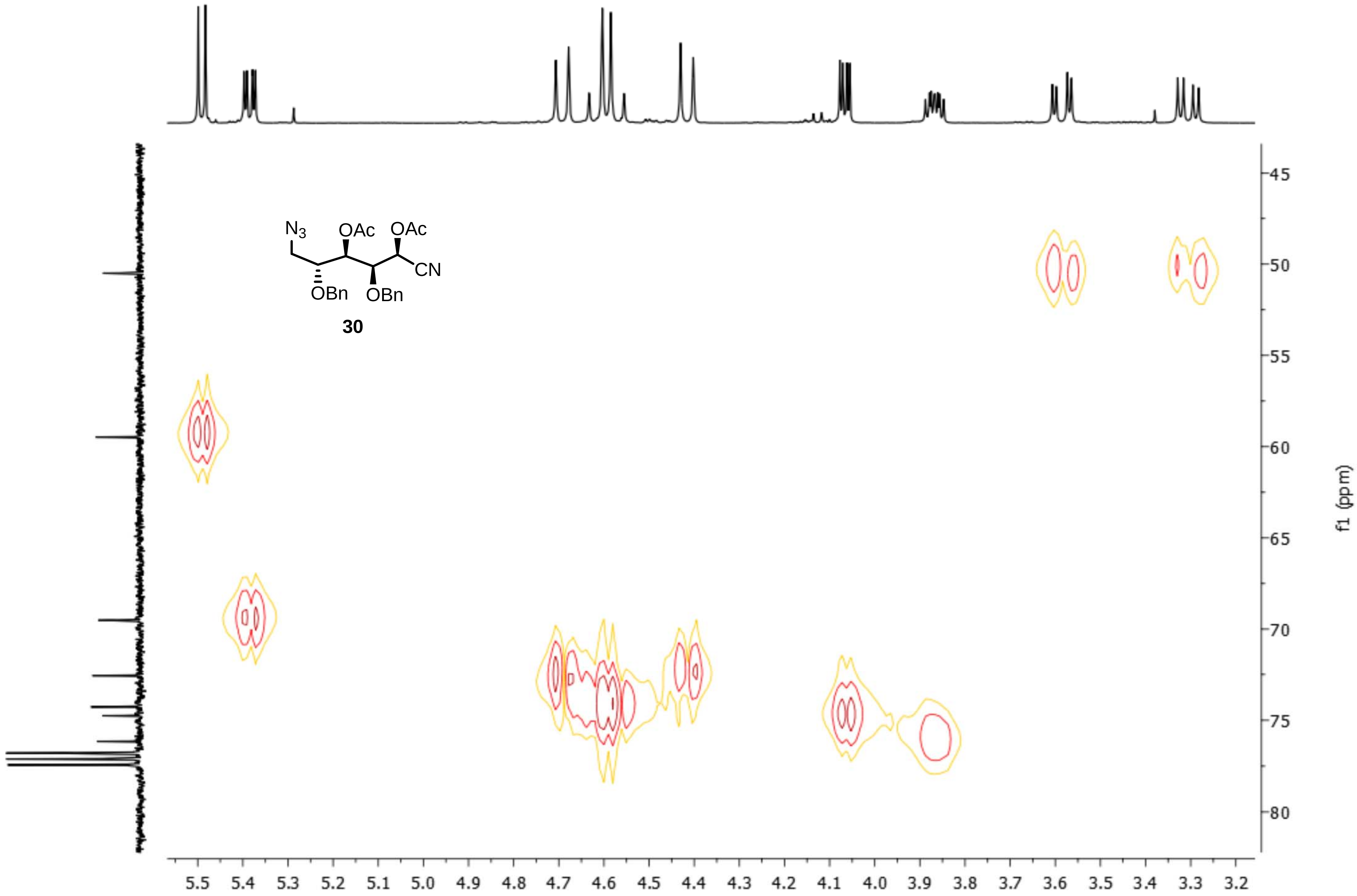
^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



30



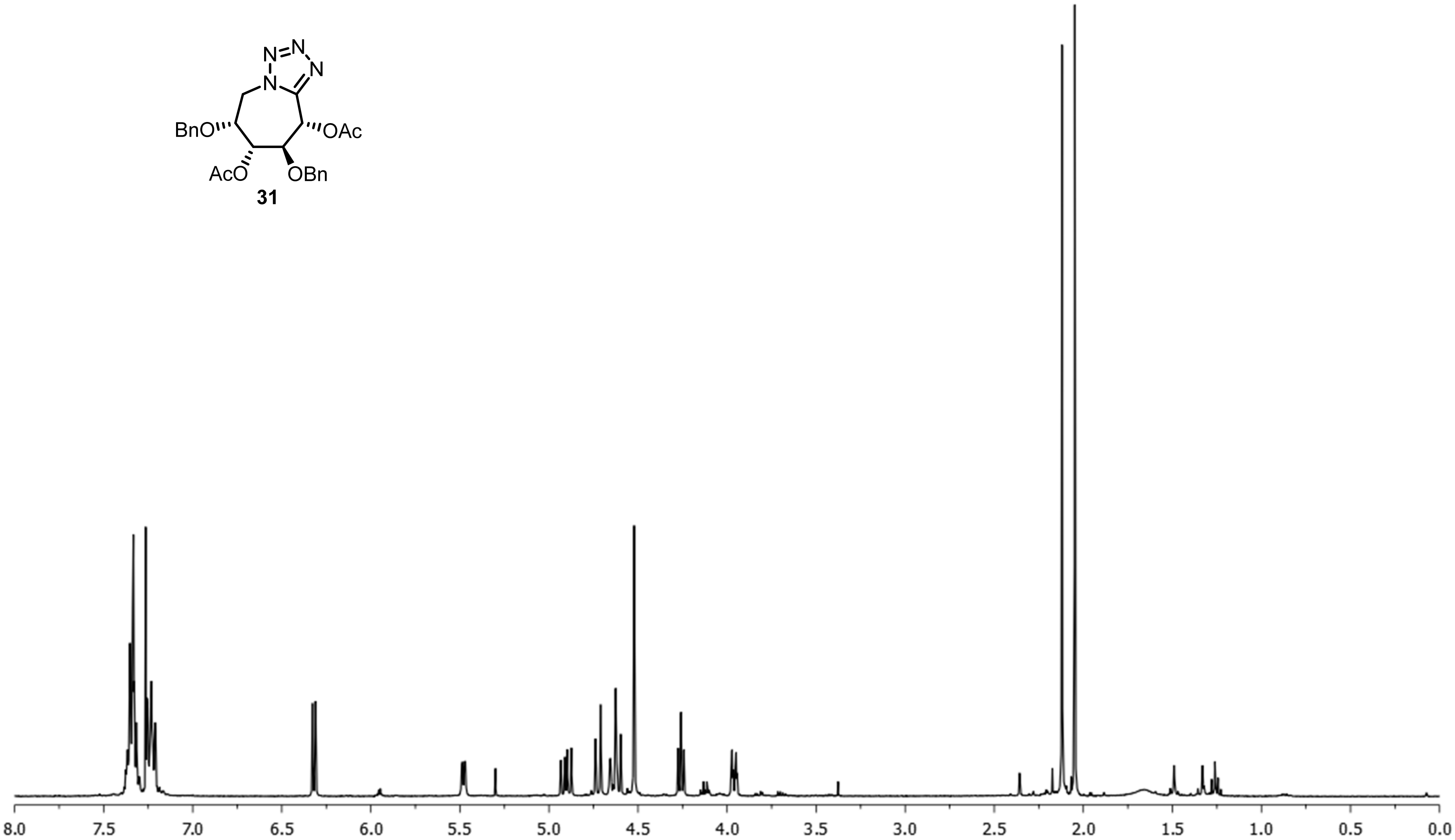
^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



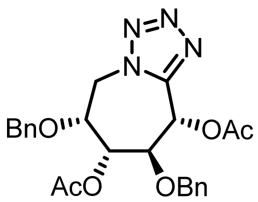
^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)

^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)

HMQC



^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



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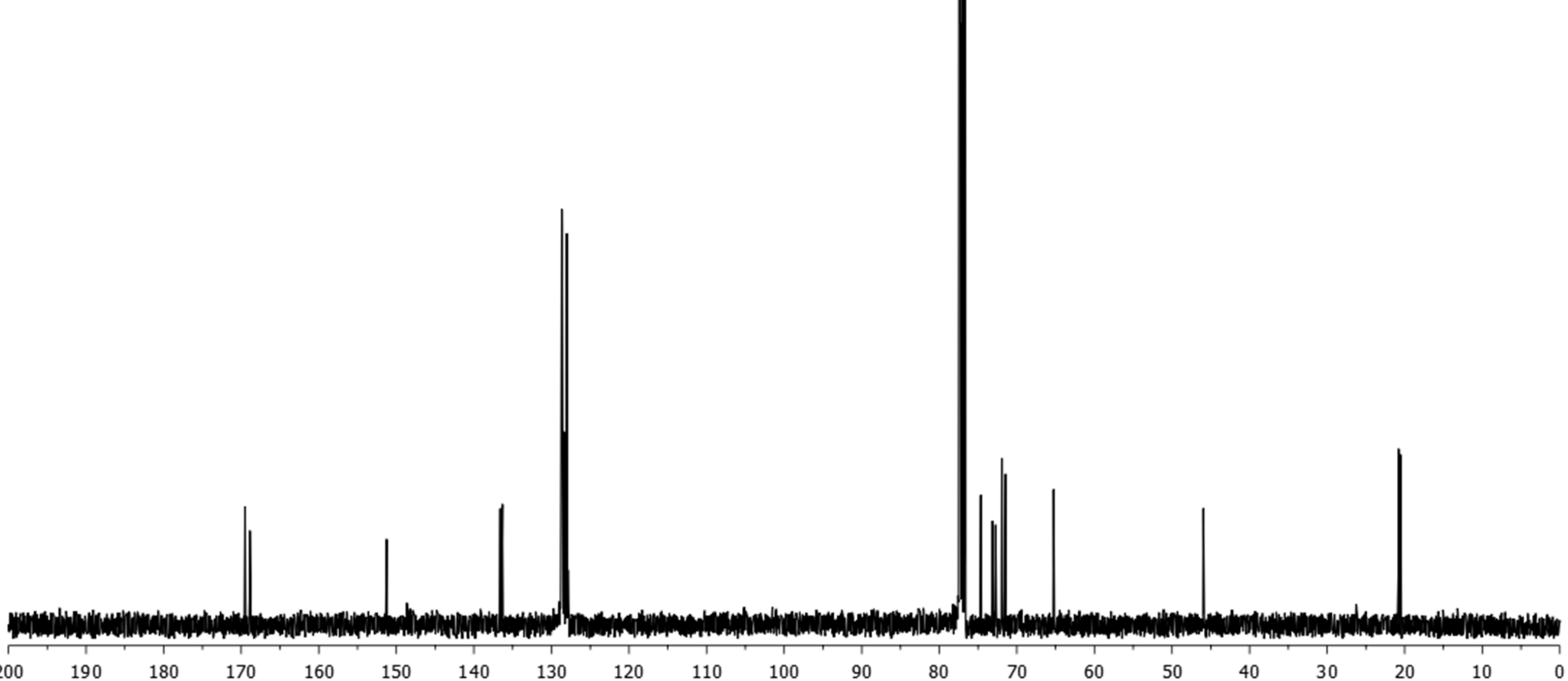
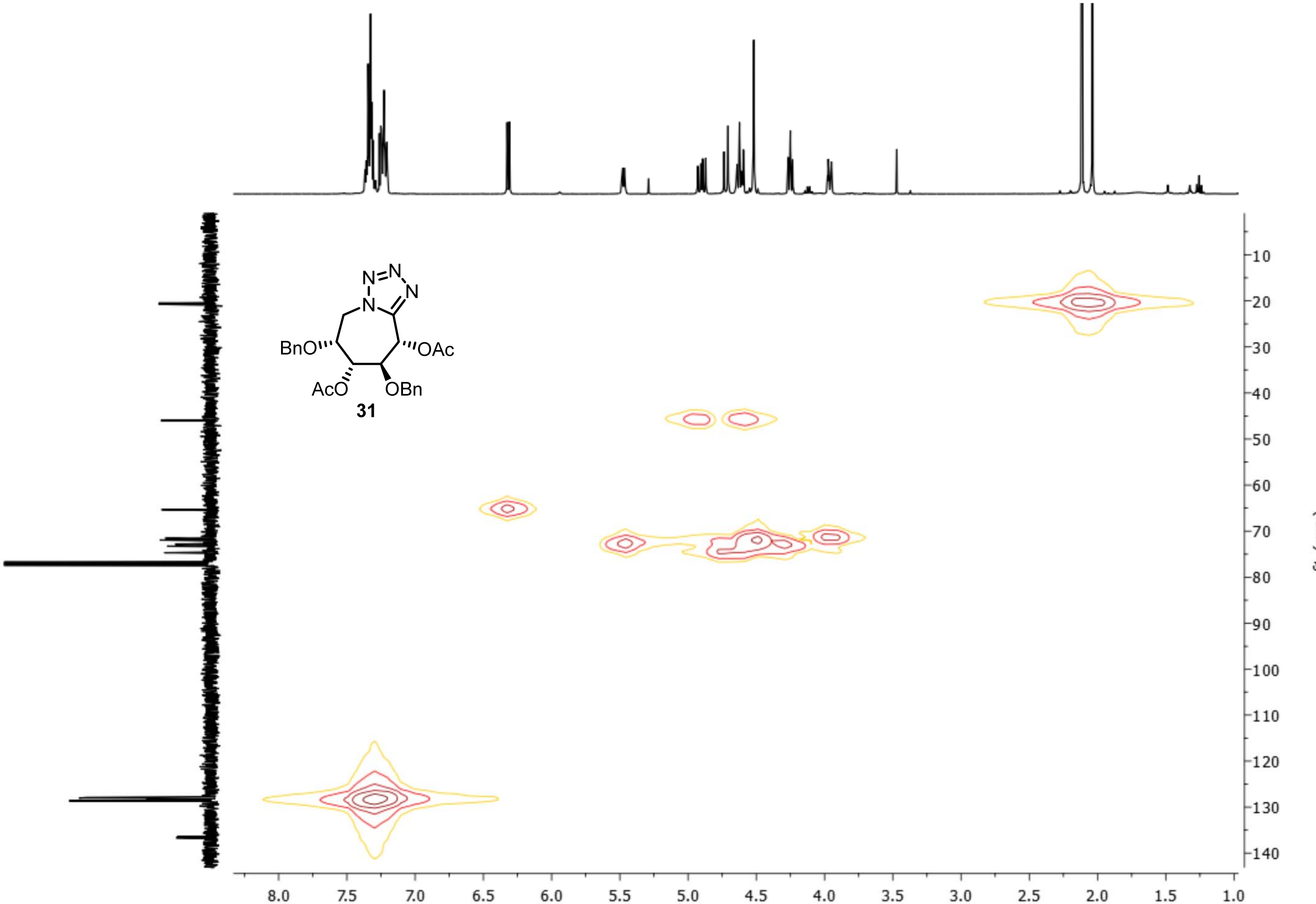
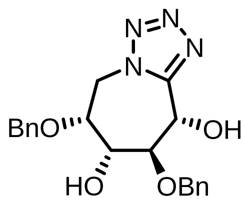


^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)

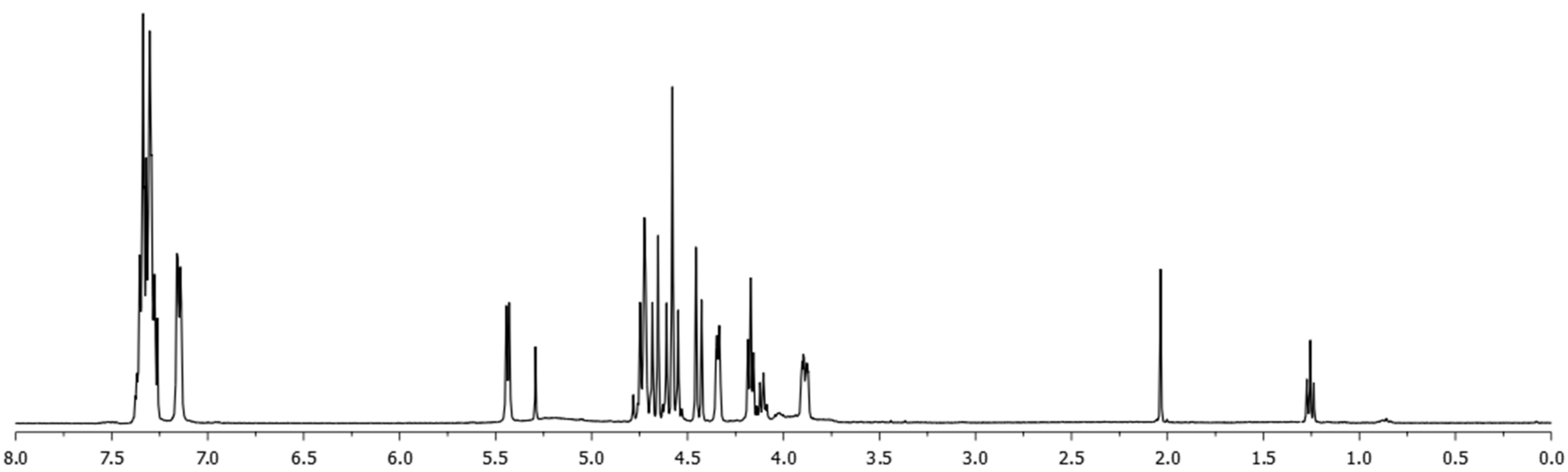


^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)
^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)

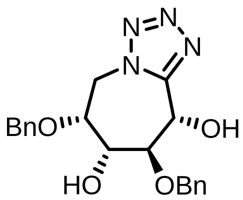
HMQC



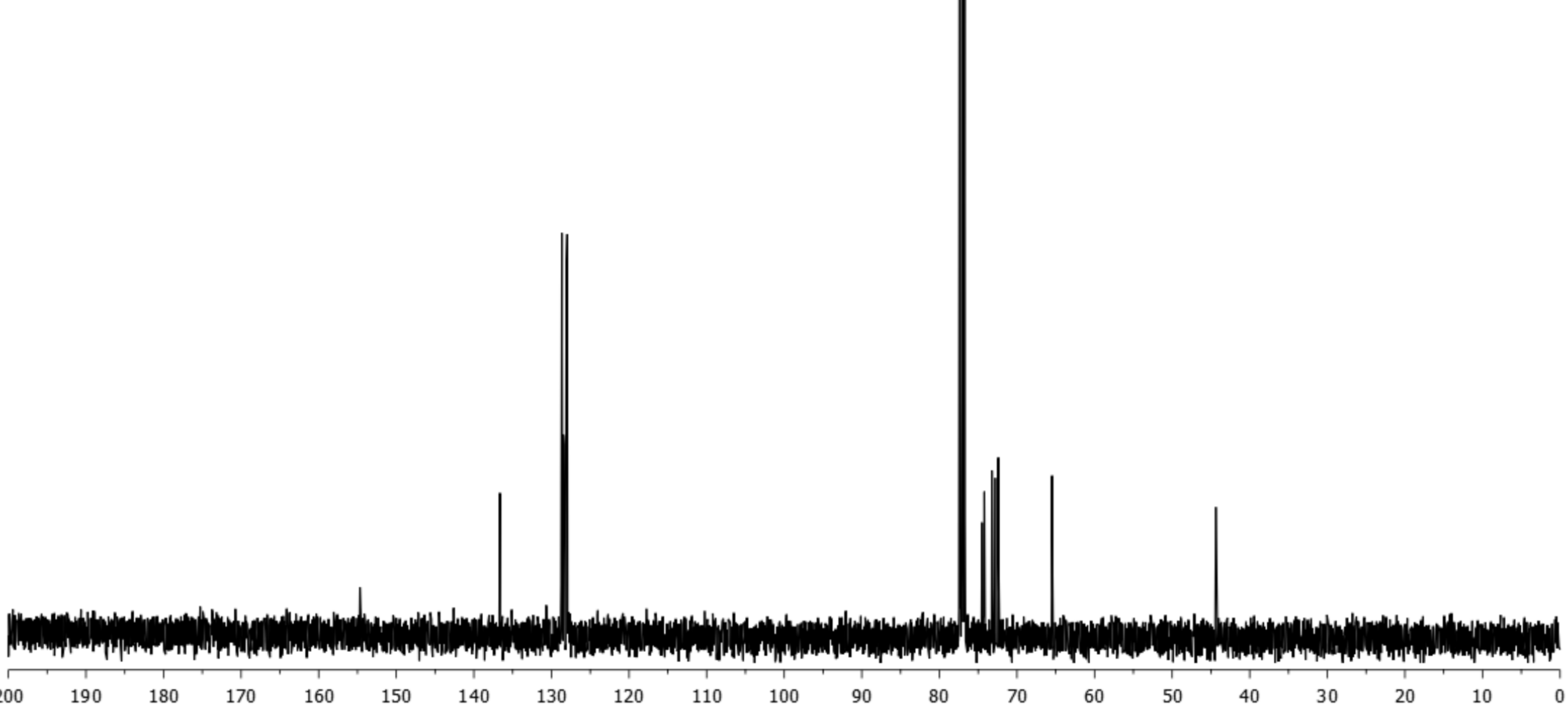
32



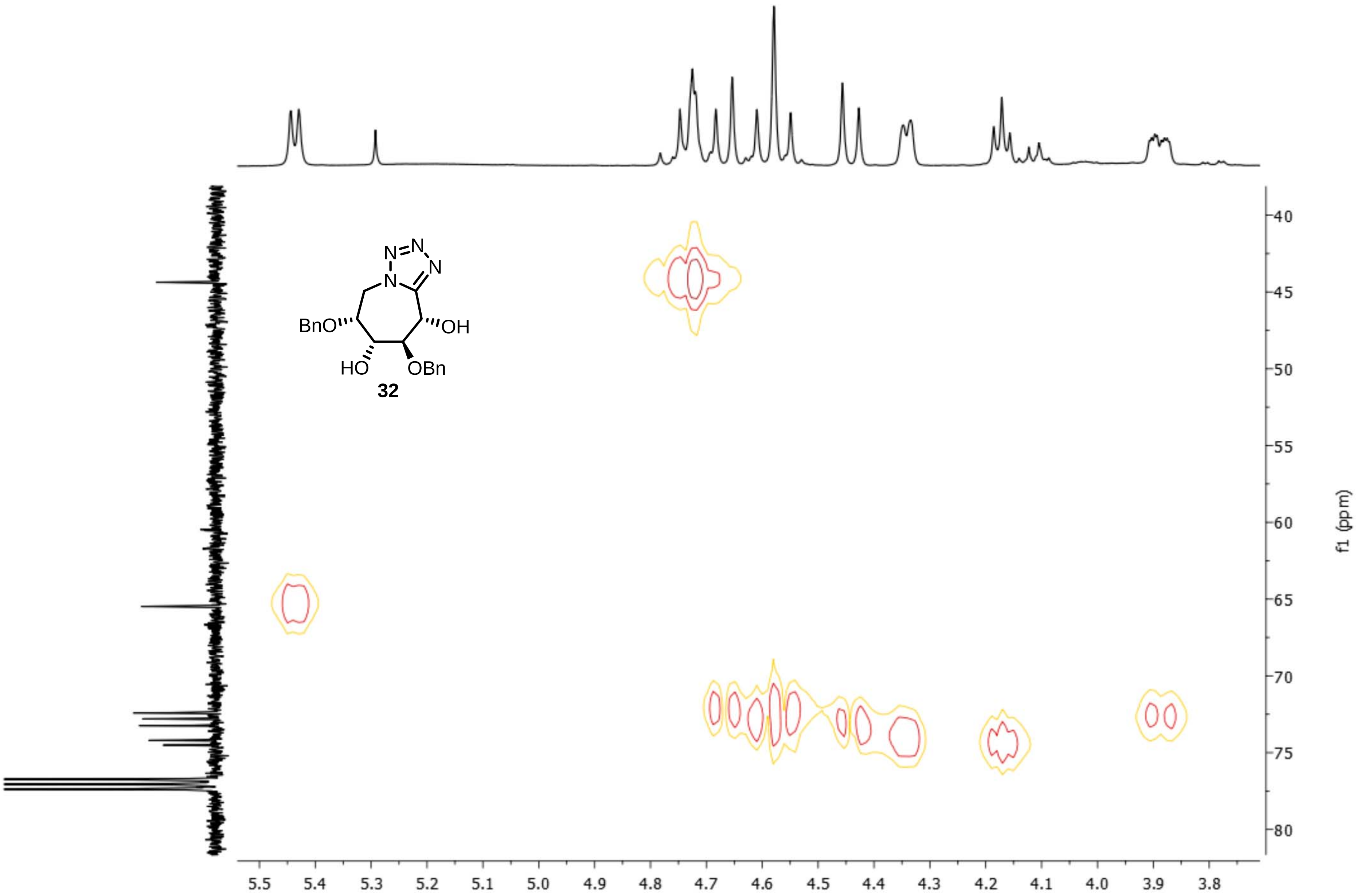
^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)



32



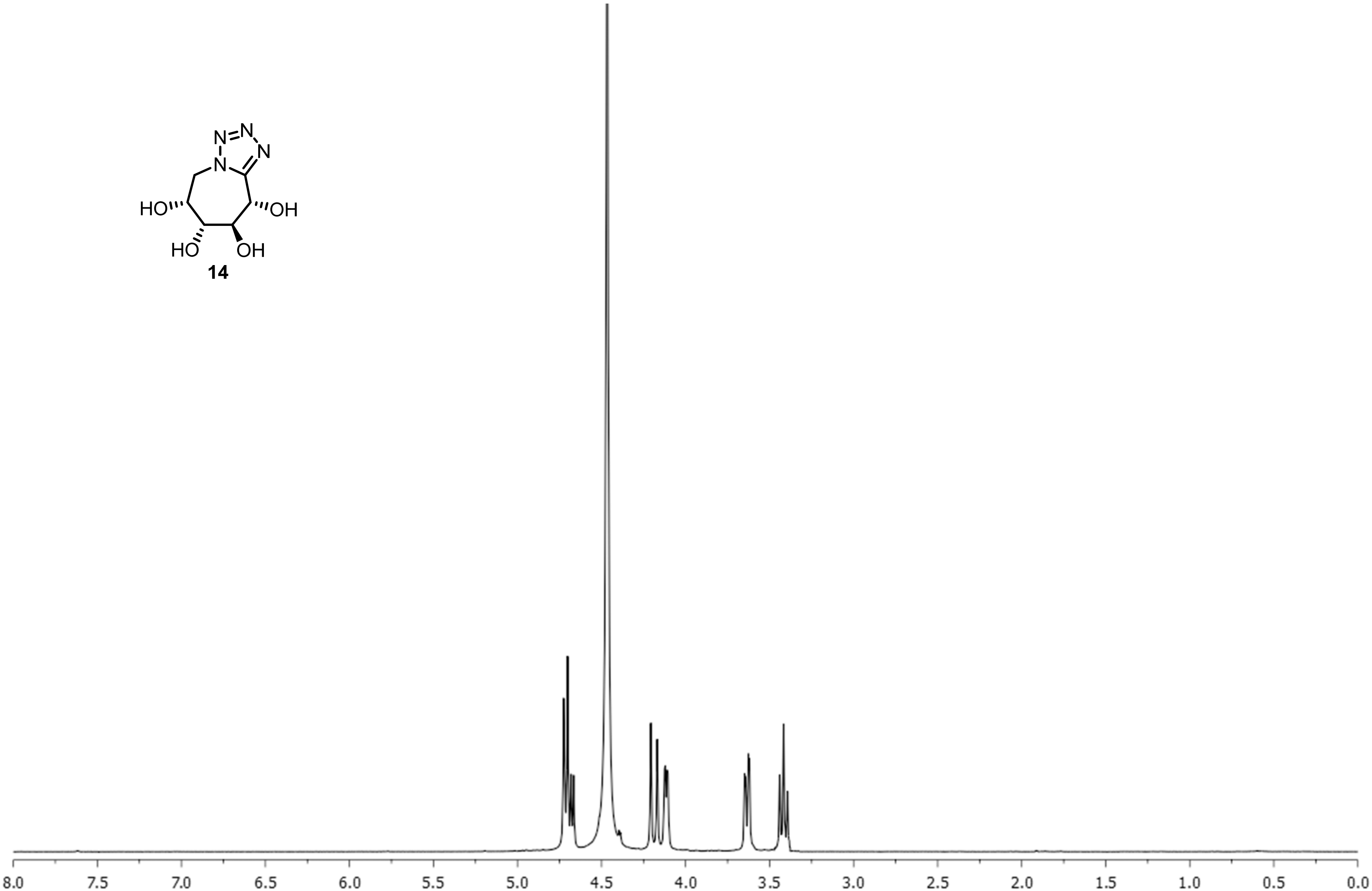
^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)



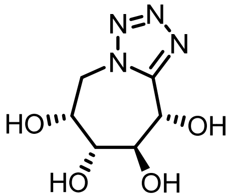
^{1}H-RMN ($CDCl_3$, 400 MHz, δ ppm)

^{13}C-RMN ($CDCl_3$, 100 MHz, δ ppm)

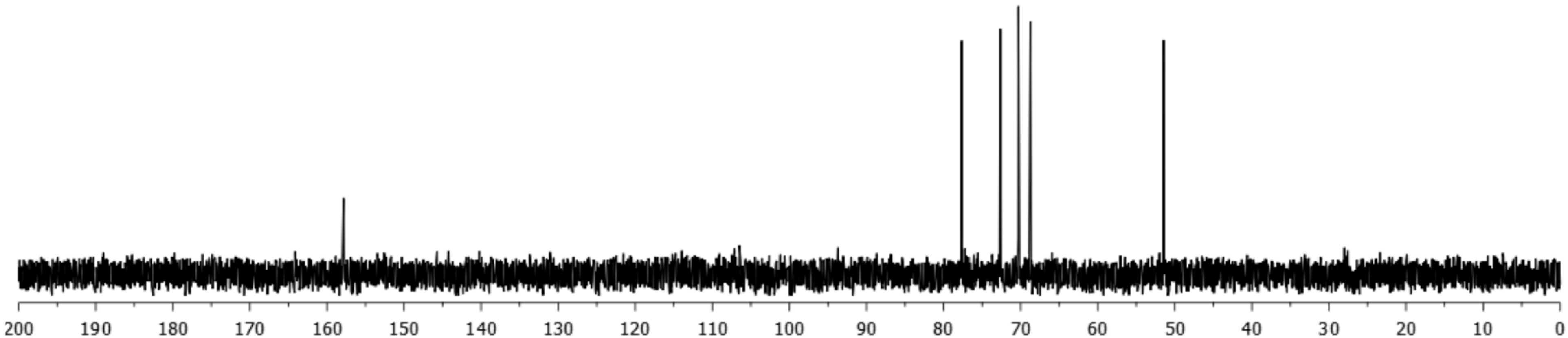
HMQC



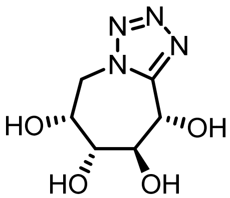
^{1}H-RMN (D_2O, 400 MHz, δ ppm)



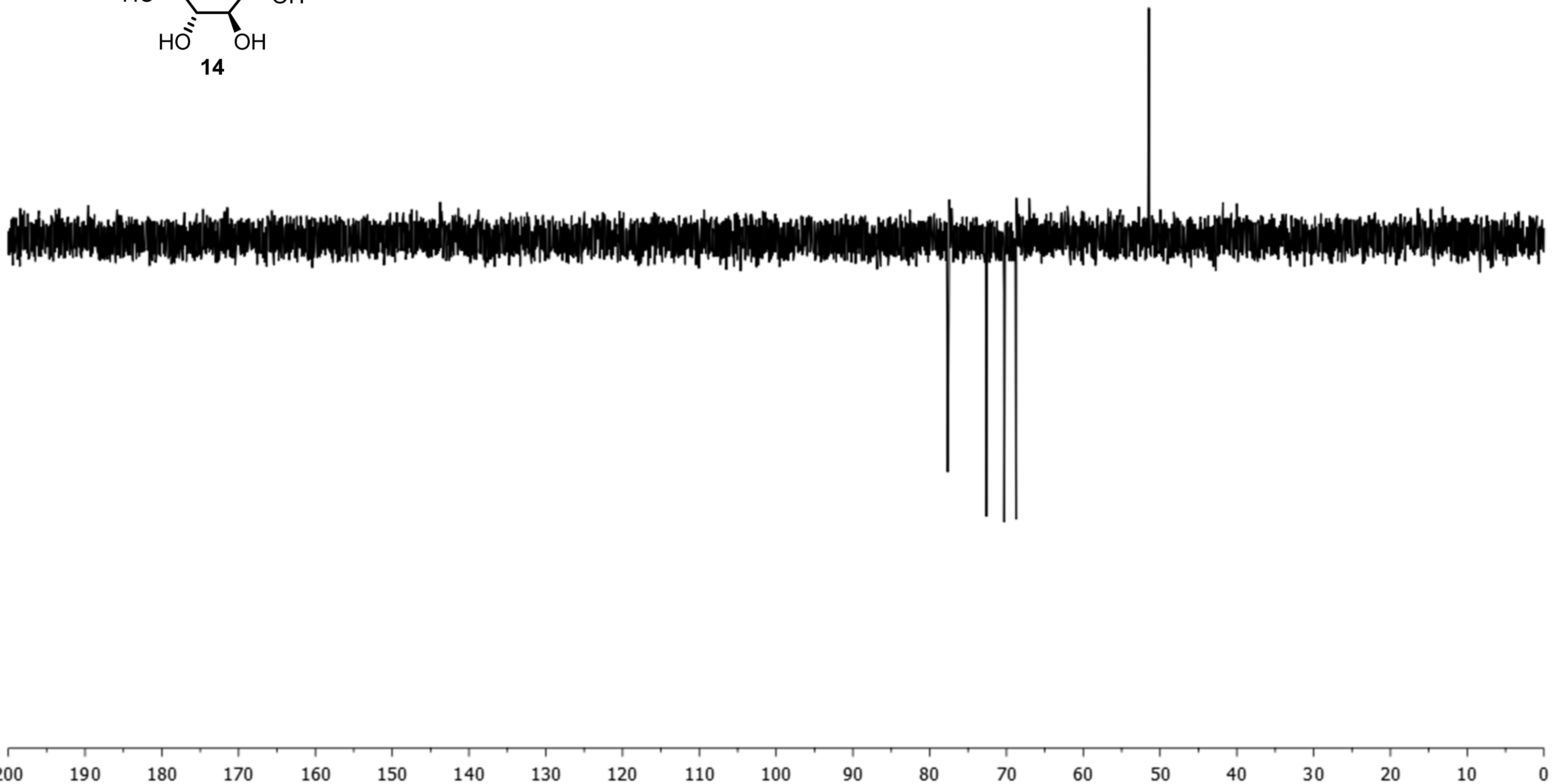
14



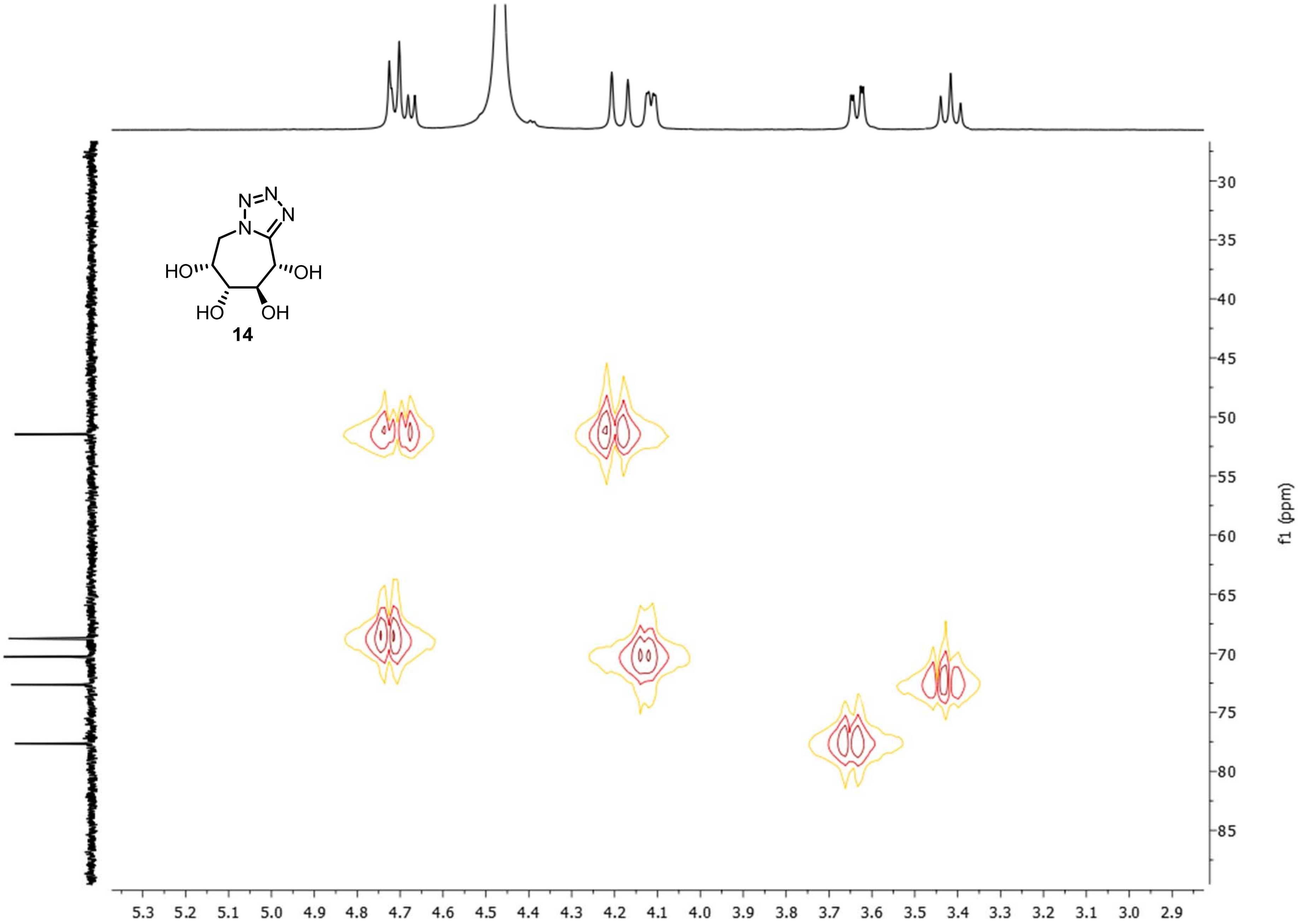
^{13}C-RMN (D_2O, 100 MHz, δ ppm)



14



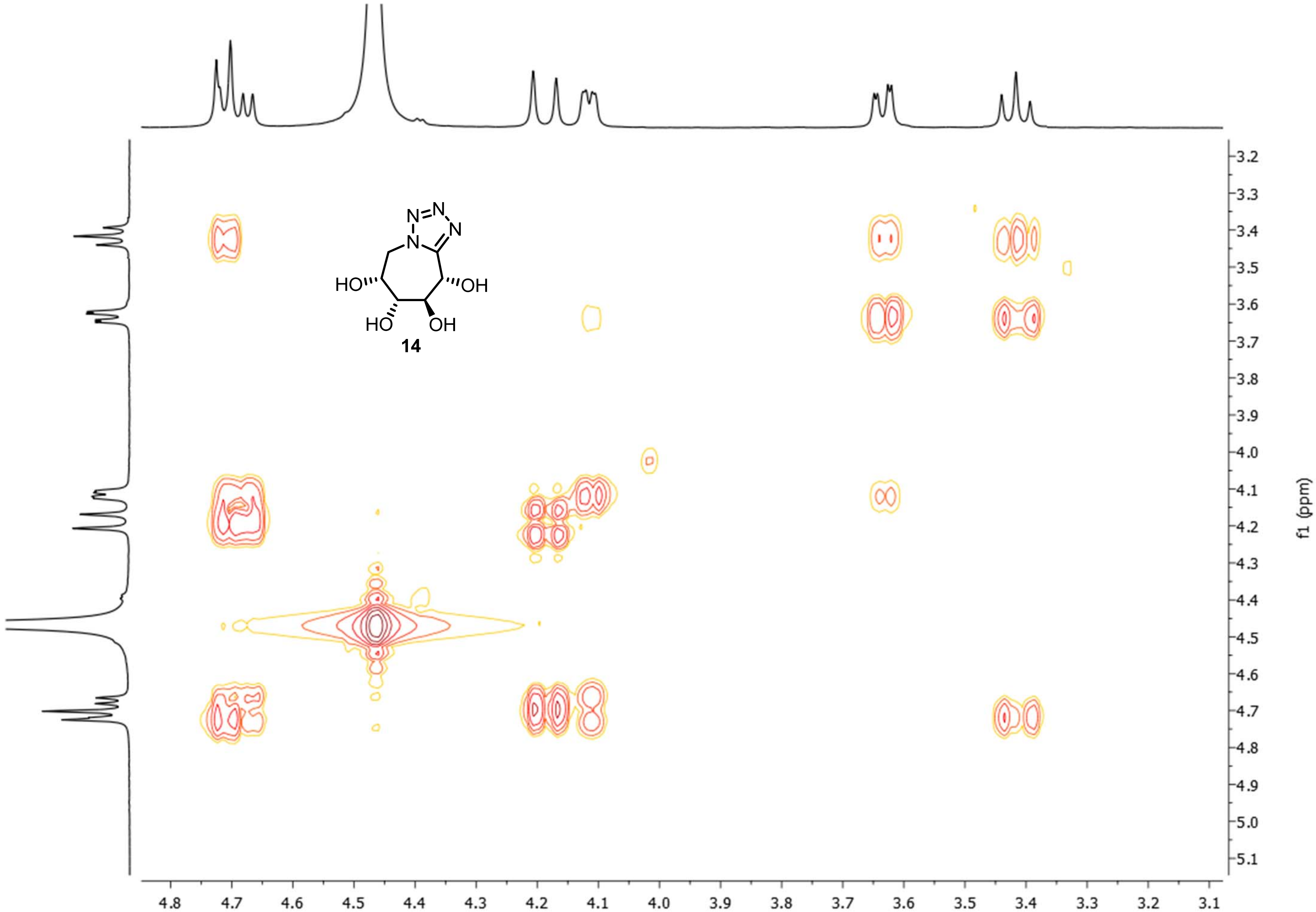
[13]C-RMN ($CDCl_3$, 100 MHz, δ ppm)   DEPT



^{1}H-RMN (D_2O, 400 MHz, δ ppm)

^{13}C-RMN (D_2O, 100 MHz, δ ppm)

HMQC



[1]H-RMN (D_2O 400 MHz, δ ppm) COSY