

Efficient synthesis of a galectin inhibitor clinical candidate (TD139) using a Payne rearrangement/azidation reaction cascade

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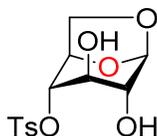
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I. Experimental Section.....	S2
II. Crystal data and structure refinement for compound 15.....	S9
III. NMR spectra of compounds.....	S10
IV. References.....	S20

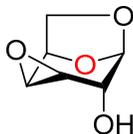
I. Experimental Section

General Methods

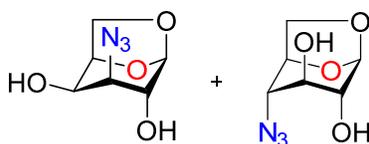
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Methylene chloride (CH_2Cl_2) and tetrahydrofuran (THF) were purified using a Vacuum Atmospheres Inc. Solvent Purification System. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality available and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and charring with a solution of 3 g of PhOH and 5 mL of H_2SO_4 in 100 mL of EtOH, followed by heating with a heatgun. SiliaFlash® P60 40-63 μm (230-400 mesh) was used for flash column chromatography. NMR spectra were recorded with an Agilent DD2 500 MHz spectrometer and calibrated using residual undeuterated solvent (Chloroform-*d*: ^1H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm) as an internal reference. Coupling constants (J) are reported in Hertz (Hz), and the following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad. Assignments of NMR signals were made by homonuclear (COSY) and heteronuclear (HSQC, HMBC, HOESY, 19F) two dimensional correlation spectroscopy. Infrared spectra were recorded using an ABB Bomem MB-Series Arid Zone FT-IR MB-155 Spectrometer. The absorptions are given in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were measured with an Agilent 6210 LC Time of Flight mass spectrometer in electrospray mode. Either protonated molecular ions $[\text{M} + n\text{H}]^{n+}$, sodium adducts $[\text{M} + \text{Na}]^+$ or ammonium adducts $[\text{M} + \text{NH}_4]^+$ were used for empirical formula confirmation. Optical rotations were measured with a JASCO DIP-360 digital polarimeter, and are reported in units of 10^{-1} ($\text{deg cm}^2 \text{g}^{-1}$).



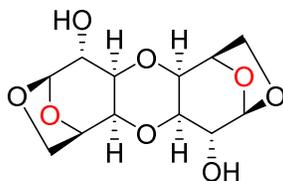
1,6-Anhydro-4-O-(4-toluenesulfonyl)-β-D-glucopyranose (10). To a solution of levoglucosan **9** (1.00 g, 6.2 mmol) in pyridine (20 mL) and toluene (15 mL) at 0 °C, was added a solution of tosyl chloride (1.24 g, 6.5 mmol, 1.05 equiv) in pyridine (7 mL) and toluene (20 mL) drop-wise over a period of 2 h. The reaction mixture was then stirred at 0 °C for 3 h and allowed to warm up to rt and stirred for 18 h. The reaction mixture was then quenched with MeOH (2 mL) and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give 1,6-anhydro-4-O-(4-toluenesulfonyl)-β-D-glucopyranose **10** (785 mg, 2.48 mmol, 40% yield) and 1,6-anhydro-2-O-(2-toluenesulfonyl)-β-D-glucopyranose **10a** (902 mg, 2.85 mmol, 46% yield) as amorphous white solids. The spectroscopic data derived from compound **10** and **10a** match those reported in the literature.¹



1,6;3,4-Dianhydro-β-D-glucopyranose (11). To a solution of **10** (153 mg, 0.485 mmol) in CH₂Cl₂/MeOH (5 mL, 4:1) was added dropwise at 0°C a methanolic 1 M NaOMe solution (485 μL, 0.485 mmol, 1 equiv). The mixture was stirred at room temperature for 2 h and then the reaction was neutralized to pH ≈ 7 with an acidic resin. The mixture was filtered and concentrated under reduced pressure. The crude was filtered through a silica gel plug (MeOH/CH₂Cl₂, 1:9) and was used for the next step without any further purification.

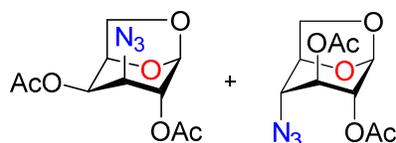


1,6-anhydro-3-azido-3-deoxy- β -D-galactopyranose (13) and 1,6-anhydro-4-azido-4-deoxy- β -D-glucopyranose (14). From 10: To a stirred solution of **10** (1.658 g, 5.241 mmol) was added an aqueous solution of sodium hydroxide 1 M (52 mL). The mixture was stirred at rt for 6 h and then neutralized to pH \approx 7 with an acidic resin. The mixture was filtered and rinse with methanol (30 mL) and concentrated under reduced pressure to remove methanol. Sodium azide (NaN_3) (1.703 g, 26.203 mmol, 5 equiv) and ammonium chloride (2.803 g, 52.406 mmol, 10 equiv) were then added and the reaction mixture was heated at reflux. After 2 days, more NaN_3 (681.4 mg, 10.481 mmol, 2 equiv) was added and the mixture was stirred for 2 additional days. The reaction was cooled down to rt and silica gel was added (10g). The solvent was removed under reduced pressure and the resulting dry-pack was purified by flash column chromatography (silica gel, $\text{MeOH}/\text{CH}_2\text{Cl}_2$, 0:100 to 3:17) to give an inseparable mixture of **13** and **14** (4:1) as a white amorphous solid (775 mg, 4.14 mmol, 79% yield). From 11: To a stirred solution of **11** (50 mg, 0.348 mmol) in dry DMF (7 mL) was added sodium hydride (60% dispersion in oil) (28 mg, 0.697 mmol, 2 equiv) under argon atmosphere. The reaction mixture was stirred 6 h prior addition of NaN_3 (113 mg, 1.742 mmol, 5 equiv) and NH_4Cl (186 mg, 3.483 mmol, 10 equiv) and then, the mixture was heated at 120°C for 18 h. After cooling to rt, silica gel was added (500 mg) and the solvent was removed under reduced pressure and the resulting dry-pack was purified by flash column chromatography (silica gel, $\text{MeOH}/\text{CH}_2\text{Cl}_2$, 0:100 to 3:17) to give an inseparable mixture of **13** and **14** (9:1) as a white amorphous solid (49 mg, 0.263 mmol, 75% yield).

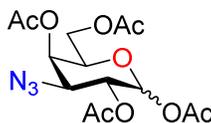


1,6-Anhydro-2,4-O-[1,6-Anhydro-2,4-deoxy- β -D-galactopyranos-2,4-yl]- β -D-galactopyranose (15). R_f = (silica, $\text{MeOH}/\text{CH}_2\text{Cl}_2$, 1:10); $[\alpha]_{\text{D}}^{25} = -65.5$ (c 0.5, MeOH); IR (ATR, diamond) ν 3450, 2943, 2924, 1148, 1030, 876, 852 cm^{-1} ; ^1H NMR (500 MHz, D_2O) δ 5.42 (d, $J = 2.0$ Hz, 1H), 4.67 (td, $J = 5.3, 4.3, 1.5$ Hz, 1H), 4.31 (dd, $J = 8.2, 1.5$ Hz, 1H), 4.29 (td, $J = 5.7, 1.2$ Hz, 1H), 3.86 (dd, $J = 5.9, 1.6$ Hz, 1H), 3.73 (t, $J = 1.8$ Hz, 2H), 3.72 (td, $J = 8.0, 5.2, 1.6$ Hz, 1H). ^{13}C NMR (126 MHz, D_2O) δ 100.7 (1C, C-1),

71.5 (1C, C-5), 71.0 (1C, C-3), 70.2 (1C, C-2), 69.7 (1C, C-4), 63.6 (1C, C-6). HRMS calcd for $C_{12}H_{15}O_8^-$ [M-H]⁻ 287.0772, found 287.0772.



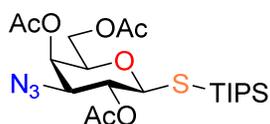
1,6-anhydro-2,4-di-O-acetyl-3-azido-3-deoxy- β -D-galactopyranose (8) and 1,6-anhydro-4-azido-4-deoxy- β -D-glucopyranose (18). To a stirred solution of **11** (21 mg, 0.1443 mmol) in dry DMF (2.8 mL) was added sodium hydride (60% dispersion in oil) (12 mg, 0.289 mmol, 2 equiv) under argon atmosphere. The reaction mixture was stirred 6 h prior addition of NaN_3 (47 mg, 0.722 mmol, 5 equiv) and NH_4Cl (76 mg, 1.429 mmol, 10 equiv). The mixture was heated at 120°C for 18 h and cooled to rt. Pyridine (690 μ L, 8.574 mmol, 60 equiv) was added followed by acetic anhydride (540 μ L, 5.711 mmol, 40 equiv). The mixture was stirred for 7 h at rt and quenched with water (10 mL). The mixture was extracted with CH_2Cl_2 (3 \times 10 mL) and the combined organic phase were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, EtOAc/Hexanes, 1:4 to 1:1) to give pure **8** as a pale yellow oil (29 mg, 0.105 mmol, 74% yield over 3 steps) and pure **18** as a pale yellow oil (3 mg, 0.096, 7% yield over 3 steps). *Analytical data for 8:* R_f = 0.6 (silica, EtOAc/hexanes, 1:1); IR (ATR, Diamond) ν 2966, 2907, 2106, 1736, 1219, 906, 727; 1H NMR (500 MHz, Chloroform-*d*) δ 5.40 (t, J = 1.5 Hz, 1H, H-1), 5.19 (ddt, J = 5.4, 4.2, 1.0, 0.5 Hz, 1H, H-4), 4.80 (t, J = 1.7 Hz, 1H, H-2), 4.49 (tdd, J = 4.2, 1.2, 0.6 Hz, 1H, H-5), 4.41 (dt, J = 7.7, 0.5 Hz, 1H, H-6_{endo}), 4.11 (dq, J = 5.8, 1.4 Hz, 1H, H-3), 3.72 (ddd, J = 7.6, 5.0, 0.7 Hz, 1H, H-6_{exo}), 2.17 (s, 3H, OAc), 2.14 (s, 3H, OAc); $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-*d*) δ 169.9 (1C, COCH₃), 169.7 (1C, COCH₃), 99.2 (1C, C-1), 72.2 (1C, C-5), 71.4 (1C, C-2), 67.0 (1C, C-4), 64.5 (1C, C-6), 58.4 (1C, C-3), 21.0 (1C, COCH₃), 20.6 (1C, COCH₃); HRMS calcd for $C_{10}H_{13}O_6N_3Na^+$ [M + Na]⁺ 294.0697, found 294.0663. *Analytical data for 18:* R_f = 0.52 (silica, EtOAc/hexanes, 1:1); IR (ATR, Diamond) ν 2965, 2907, 2107, 1735, 1220, 906, 727; 1H NMR (500 MHz, Chloroform-*d*) δ 5.50 (t, J = 1.5 Hz, 1H, H-1), 4.92 (p, J = 1.5 Hz, 1H, H-3), 4.69 (dq, J = 5.8, 1.3 Hz, 1H, H-5), 4.64 (q, J = 1.4 Hz, 1H, H-4), 4.06 (dd, J = 7.7, 1.0 Hz, 1H, H-6_{endo}), 3.86 (dd, J = 7.8, 5.6 Hz, 1H, H-6_{exo}), 3.22 (q, J = 2.1, 1.3 Hz, 1H, H-2), 2.16 (s, 3H, COCH₃), 2.13 (s, 3H, COCH₃); $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-*d*) δ 169.6 (1C, COCH₃), 169.2 (1C, COCH₃), 99.1 (1C, C-1), 74.5 (1C, C-5), 70.0 (1C, C-3), 68.1 (1C, C-4), 66.1 (1C, C-6), 59.0 (1C, C-2), 20.9 (1C, COCH₃), 20.8 (1C, COCH₃); HRMS calcd for $C_{10}H_{13}O_6N_3Na^+$ [M + Na]⁺ 294.0697, found 294.0666.



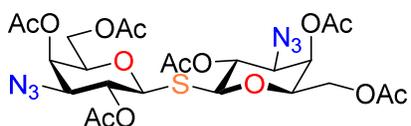
1,2,4,6-tetra-O-acetyl-3-azido- α/β -D-galactopyranose (16). To a stirred solution of a mixture of **13** and **14** (4:1) (728 mg, 3.887 mmol) in acetic anhydride (Ac_2O) (19 mL) at 0°C was added triethylsilyl trifluoromethanesulfonate ($\approx 40\text{-}60\ \mu\text{L}$, cat) under argon atmosphere. After 30 mins, a saturated aqueous NaHCO_3 solution (70 mL) was added and the mixture was stirred for 30 minutes. The reaction was extracted with CH_2Cl_2 ($3 \times 40\ \text{mL}$) and the combined organic phases were washed with a saturated aqueous NaHCO_3 solution ($2 \times 60\ \text{mL}$). The organic solution was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, EtOAc /Hexanes, 1:9 to 1:1) to give **16** as an anomeric mixture ($\alpha/\beta = 5.5:1$) as a white amorphous solid (1.114 g, 2.984 mmol, 77% yield) and **17** as an anomeric mixture ($\alpha/\beta = 5:1$) as a white amorphous solid (280.2 mg, 0.751 mmol, 19% yield). The spectroscopic data derived from compound **16** and **17** match those reported in the literature.²



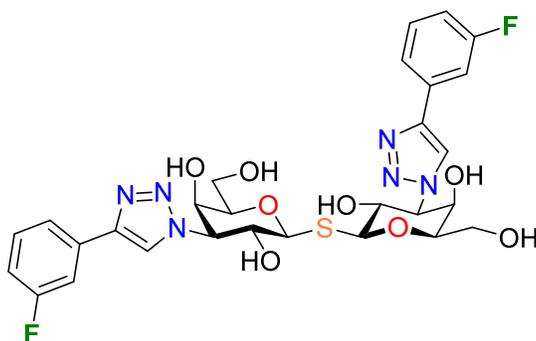
2,4,6-tri-O-acetyl-3-azido- α -D-galactopyranosyl bromide (3). From 16: To a stirred solution of **16** (41 mg, 0.111 mmol) in dry $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (10:1, 2.2 mL) was added TiBr_4 (82 mg, 0.222 mmol, 2 equiv) under argon atmosphere. The reaction mixture was stirred at rt for 36 h and quench with NaOAc (100 mg). Reaction mixture was diluted in CH_2Cl_2 and washed with H_2O ($3 \times 5\ \text{mL}$), the organic layer was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, EtOAc /Hexanes, 3:7 to 1:1) to give **3** as a clear oil (34 mg, 0.087 mmol, 74% yield). From 8: To a stirred solution of **8** (20 mg, 0.074 mmol) in dry CH_2Cl_2 (1 mL) was added acetic anhydride (226 μL , 2.212 mmol, 30 equiv) and TiBr_4 (271 mg, 0.737 mmol, 10 equiv). The reaction mixture was heated at 40°C for 20 h and then cooled to 0°C before addition of water. The organic phase was washed with water ($1 \times 5\ \text{mL}$) and a saturated aqueous NaHCO_3 solution ($1 \times 5\ \text{mL}$). The organic phase was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, EtOAc/Hexanes, 1:9 to 1:1) to give **3** as a clear oil (11 mg, 0.028 mmol, 38% yield) and **16** as a white amorphous solid (16 mg, 0.0434 mmol, 59% yield). The spectroscopic data derived from compound **3** match those reported in the literature.³



Tri-isopropylsilyl 2,4,6-tri-O-acetyl-3-azido-1-thio- β -D-galactopyranoside (19). Argon gas was purged for 10 min through a solution of **3** (344 mg, 0.866 mmol) in dry acetonitrile (17 mL). Then K_2CO_3 (363 mg, 2.625 mmol, 3 equiv) was added followed by TIPSSH (375.7 μ L, 1.750 mmol, 2 equiv), and the mixture was stirred for 3 h at rt. After this time, the solvent was evaporated under reduced pressure. Then, the residue was dissolved in CH_2Cl_2 (40 mL), washed with water (2 x 20 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude solid was purified by flash column chromatography (silica gel, EtOAc/Hexanes, 1:9 to 2:3) to give **19** as an amorphous yellowish solid (359 mg, 0.657 mmol, 76% yield). The spectroscopic data derived from compound **19** match those reported in the literature.⁴



Bis-(2,4,6-tri-O-acetyl-3-azido- β -D-galactopyranosyl)sulfane (2). To a solution of tri-isopropylsilyl **19** (209 mg, 0.383 mmol) in dry acetonitrile (4 mL) was added bromide **3** (166 mg, 0.421 mmol, 1.1 equiv) in dry acetonitrile (4 mL). Argon gas was purged for 10 min through the solution, and TBAF 1 M in THF (574 μ L, 0.574 mmol, 1.5 equiv) was added. After 15 min, the solvent was removed under reduced pressure and the crude solid was purified by flash column chromatography (silica gel, EtOAc/Hexanes, 3:7 to 1:1) to give **2** as an amorphous yellowish solid (187 mg, 0.283 mmol, 74% yield). The spectroscopic data derived from compound **2** match those reported in the literature.⁴

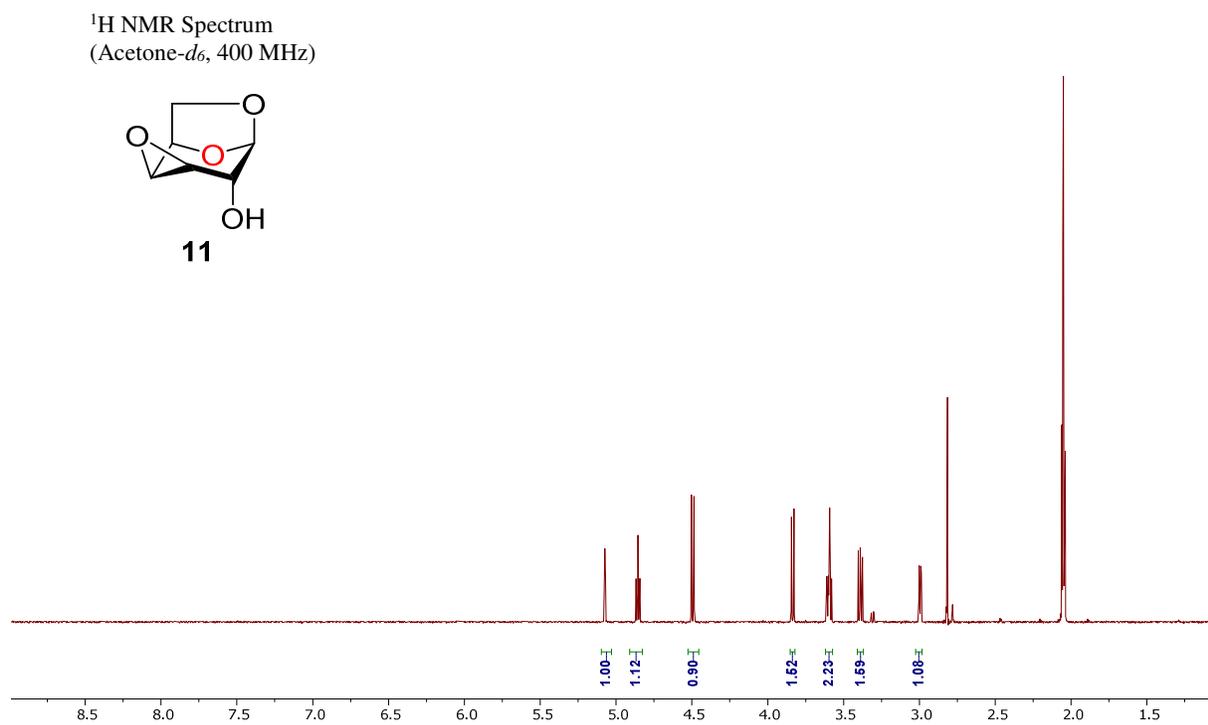
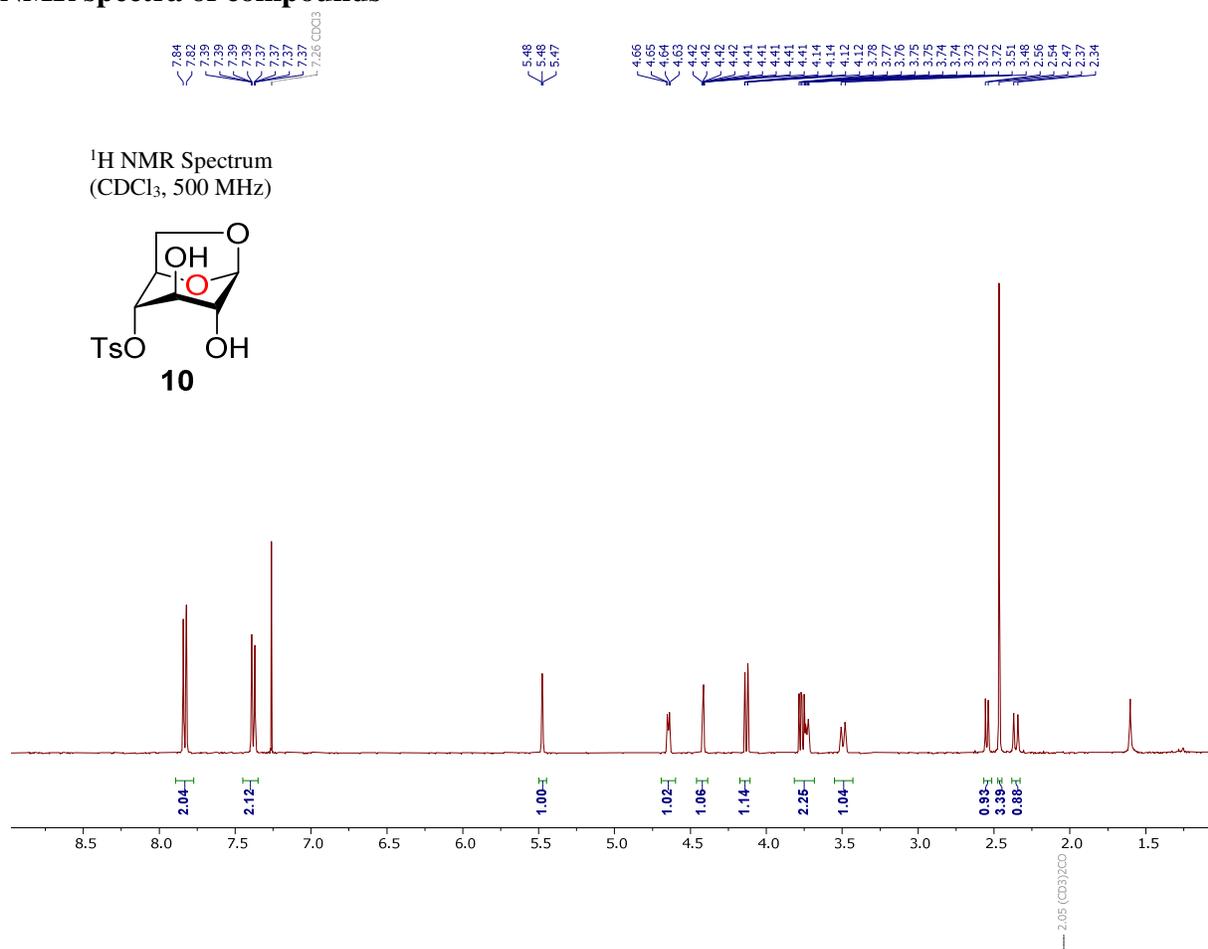


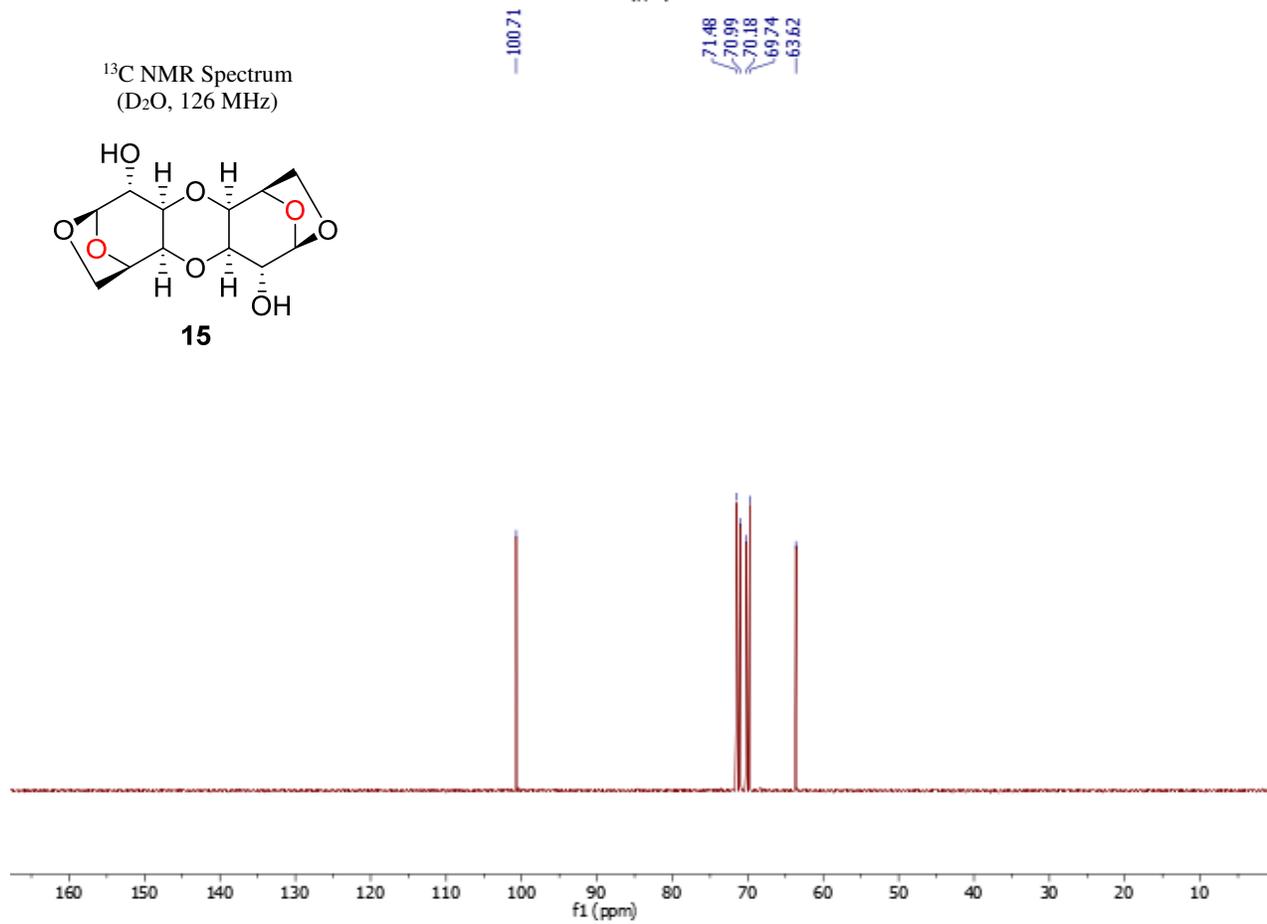
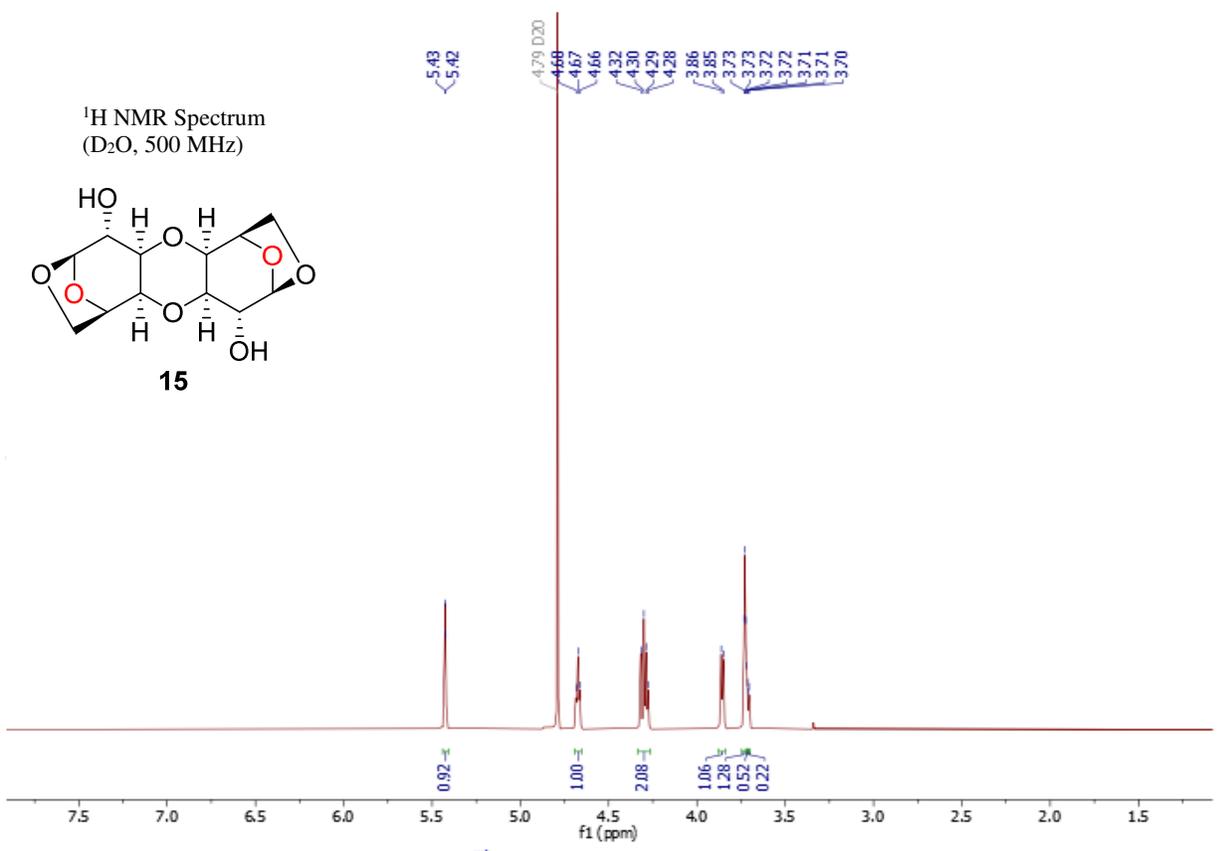
TD139 (1). To a solution of compound **2** (49 mg, 0.074 mmol) and CuI (7 mg, 0.037 mmol, 0.5 equiv) in DMF (3 mL) was added 1-ethynyl-3-fluorobenzene (34.2 μ L, 0.296 mmol, 4 equiv) and DIPEA (25.8 μ L, 0.148 mmol, 2 equiv). The mixture was stirred 24 h at 50 $^{\circ}$ C before addition of a saturated aqueous NH_4Cl solution (3 mL). Then, the organic solvent was evaporated under reduced pressure and the residue was diluted in water (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic solutions were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The obtained crude was dissolved in MeOH (3 mL) and DCM (1 mL) followed by addition of NaOMe (1 M in MeOH, 1 mL). The resulting solution was stirred 16 h and neutralized to $\text{pH} \approx 7$ with acidic resin. The mixture was filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (CH_2Cl_2 : MeOH 19:1 to 17:3) to give **TD139 (1)** as an amorphous white solid (31 mg, 0.048 mmol, 65% yield over 2 steps). The spectroscopic data derived from compound **1** match those reported in the literature.⁵

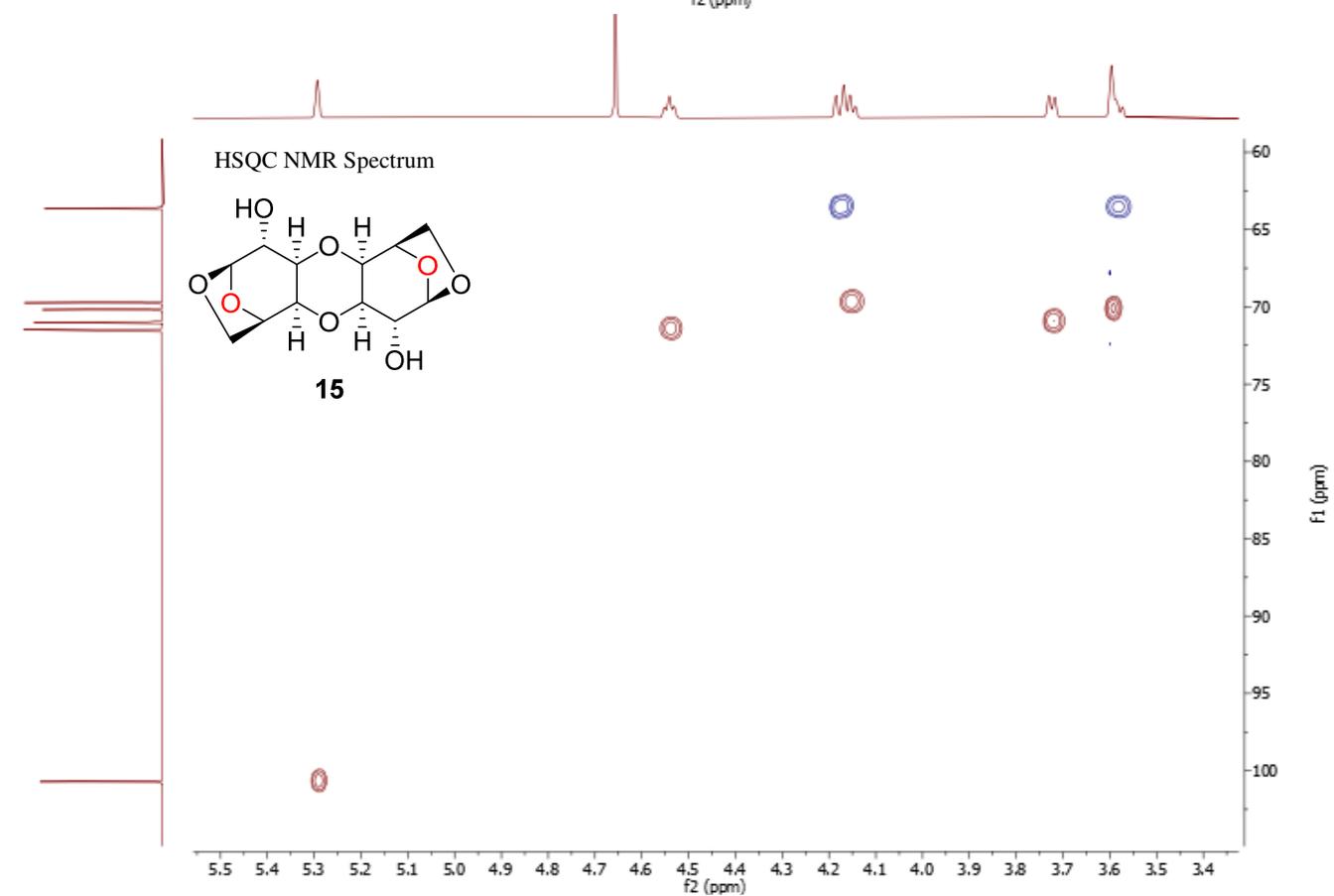
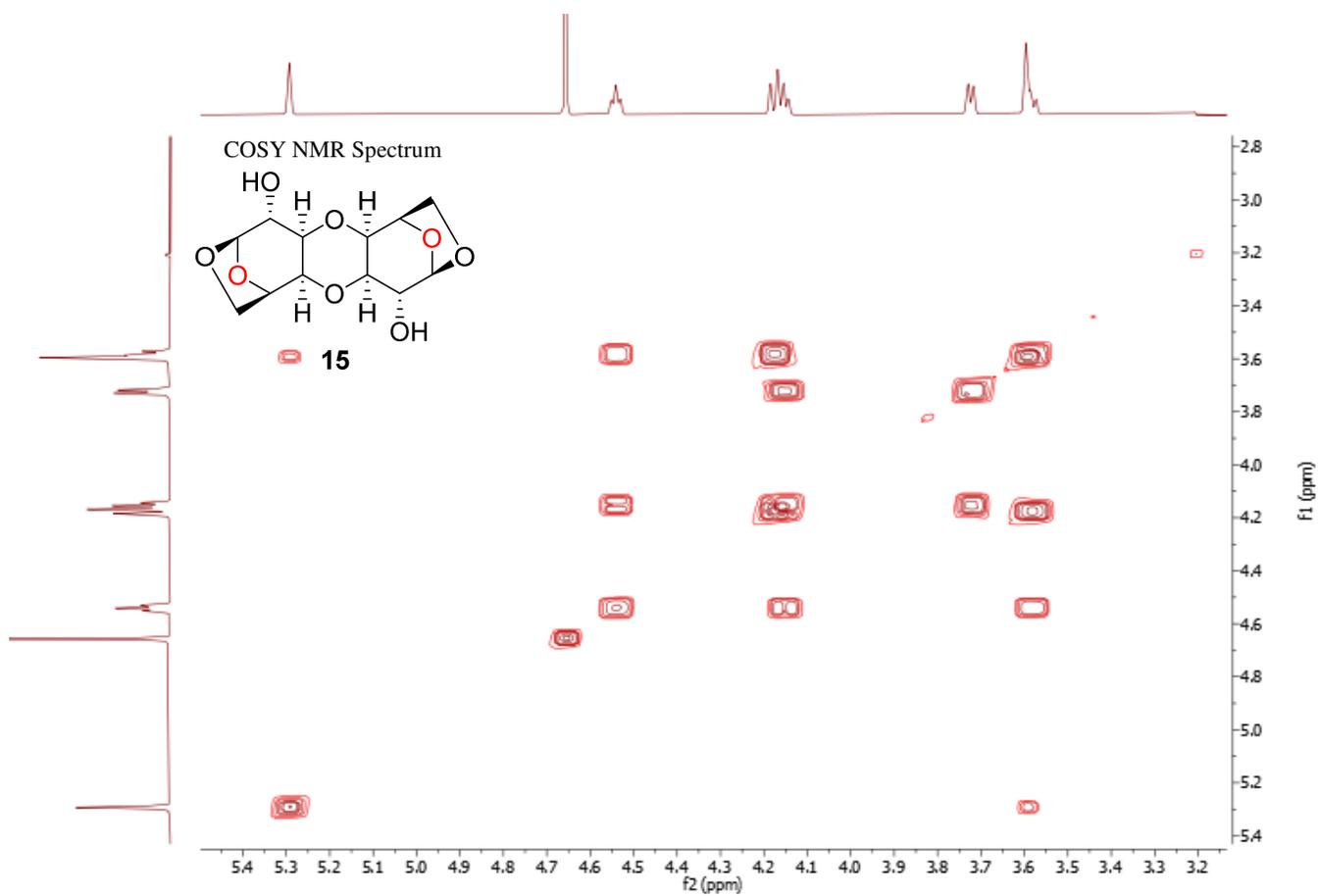
II. Crystal data and structure refinement for compound 15

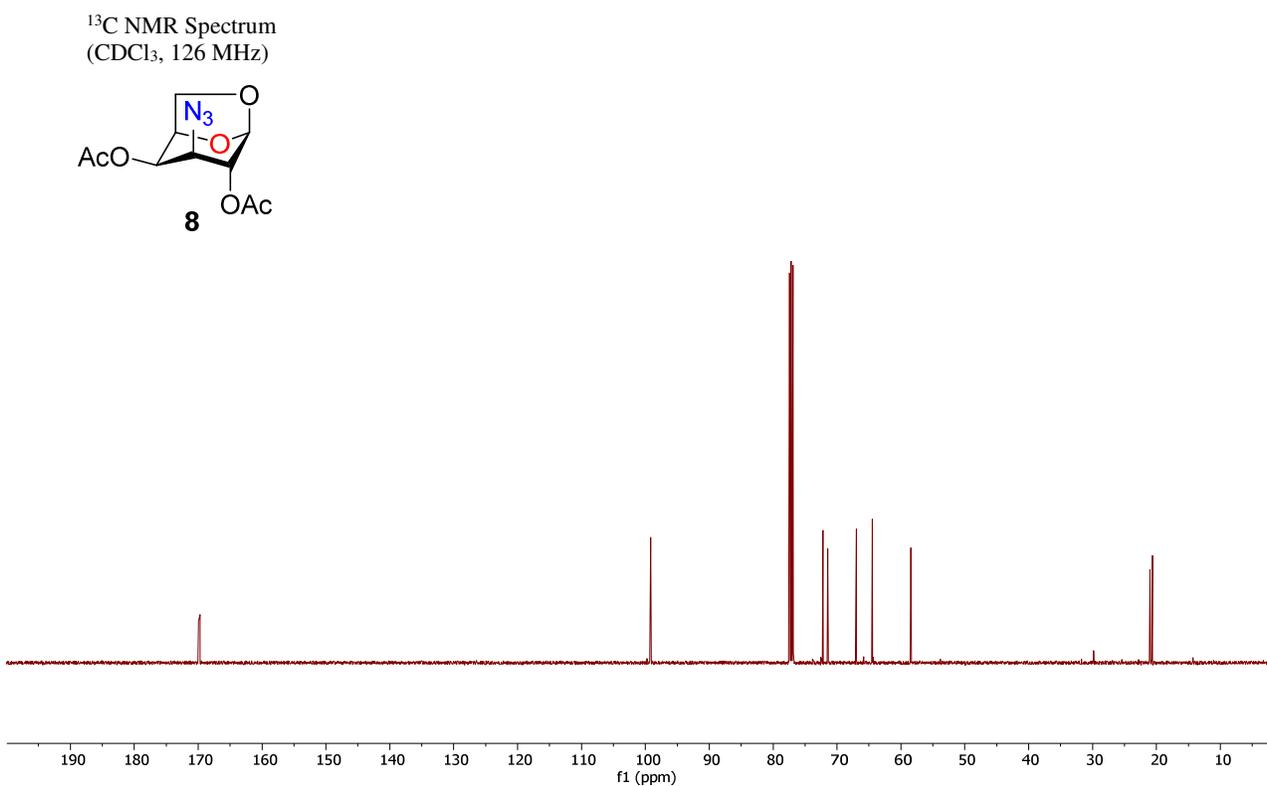
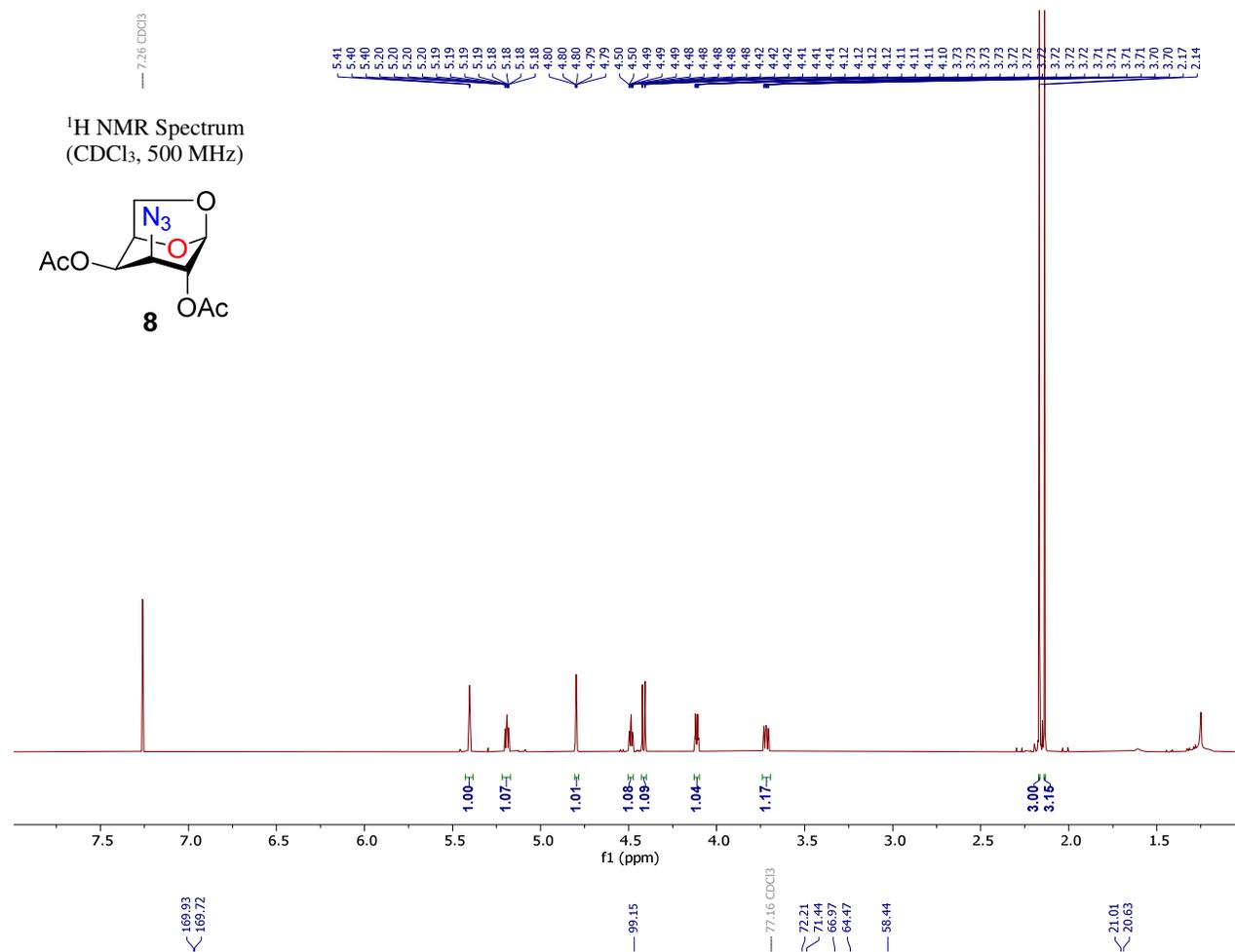
Empirical formula	C ₂₄ H _{34.5} O _{17.25}
Formula weight	599.01
Temperature/K	150
Crystal system	monoclinic
Space group	C2
a/Å	19.2032(9)
b/Å	6.1100(3)
c/Å	10.9617(5)
α/°	90
β/°	103.2710(10)
γ/°	90
Volume/Å ³	1251.81(10)
Z	2
ρ _{calc} /cm ³	1.589
μ/mm ⁻¹	0.755
F(000)	633.0
Crystal size/mm ³	0.25 × 0.2 × 0.16
Radiation	GaKα (λ = 1.34139)
2θ range for data collection/°	8.232 to 121.39
Index ranges	-24 ≤ h ≤ 24, -7 ≤ k ≤ 7, -14 ≤ l ≤ 14
Reflections collected	19903
Independent reflections	2861 [R _{int} = 0.0405, R _{sigma} = 0.0225]
Data/restraints/parameters	2861/7/202
Goodness-of-fit on F ²	1.147
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0507, wR ₂ = 0.1175
Final R indexes [all data]	R ₁ = 0.0507, wR ₂ = 0.1176
Largest diff. peak/hole / e Å ⁻³	0.41/-0.65
Flack parameter	0.0(2)

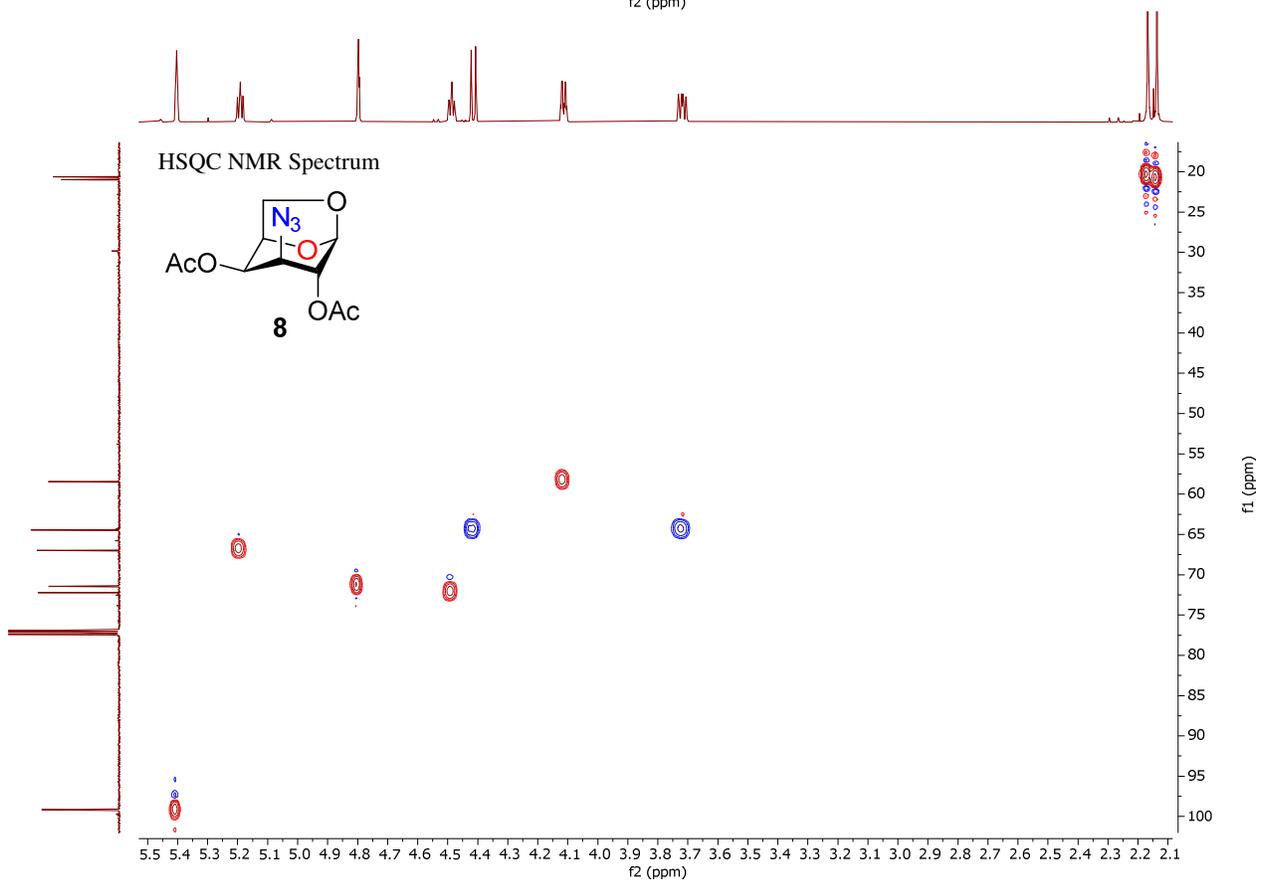
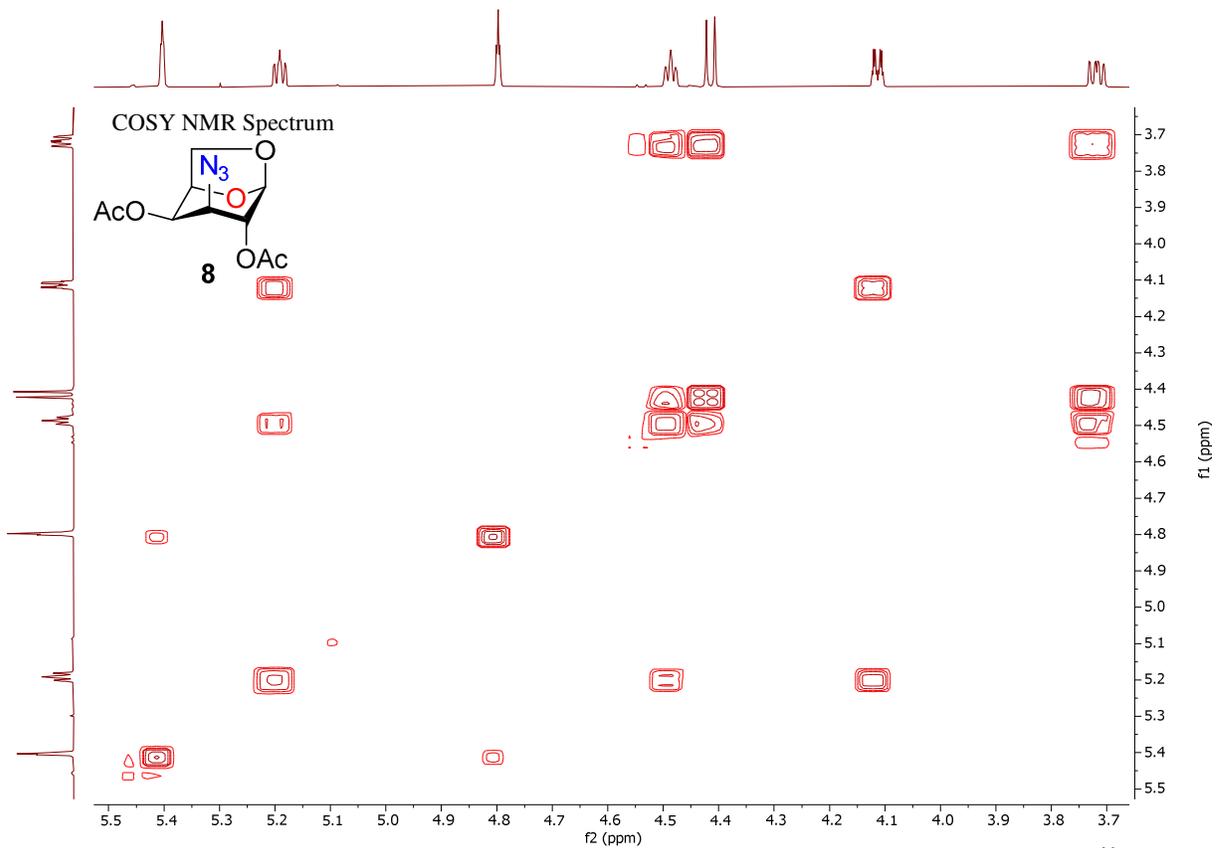
III. NMR spectra of compounds



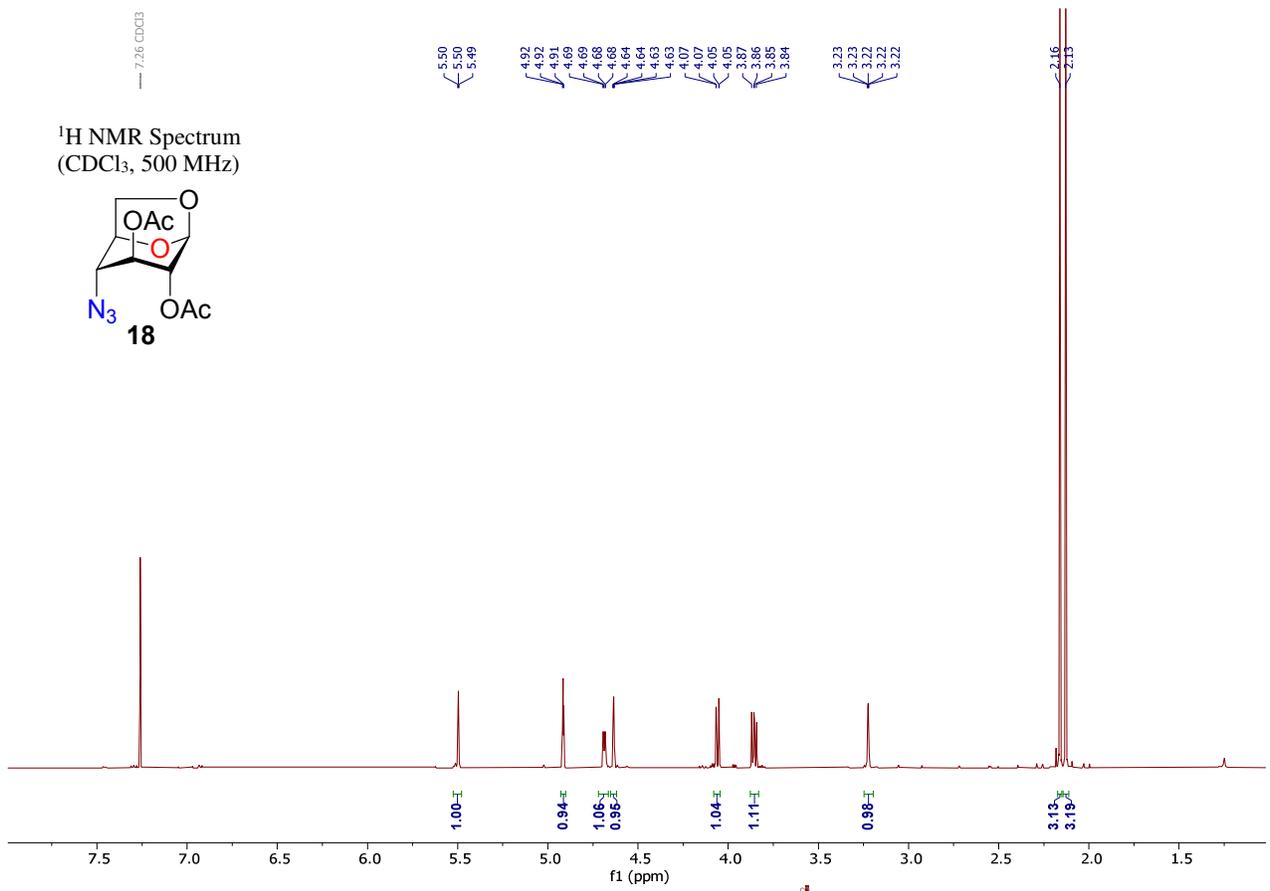
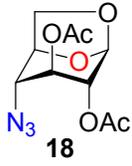




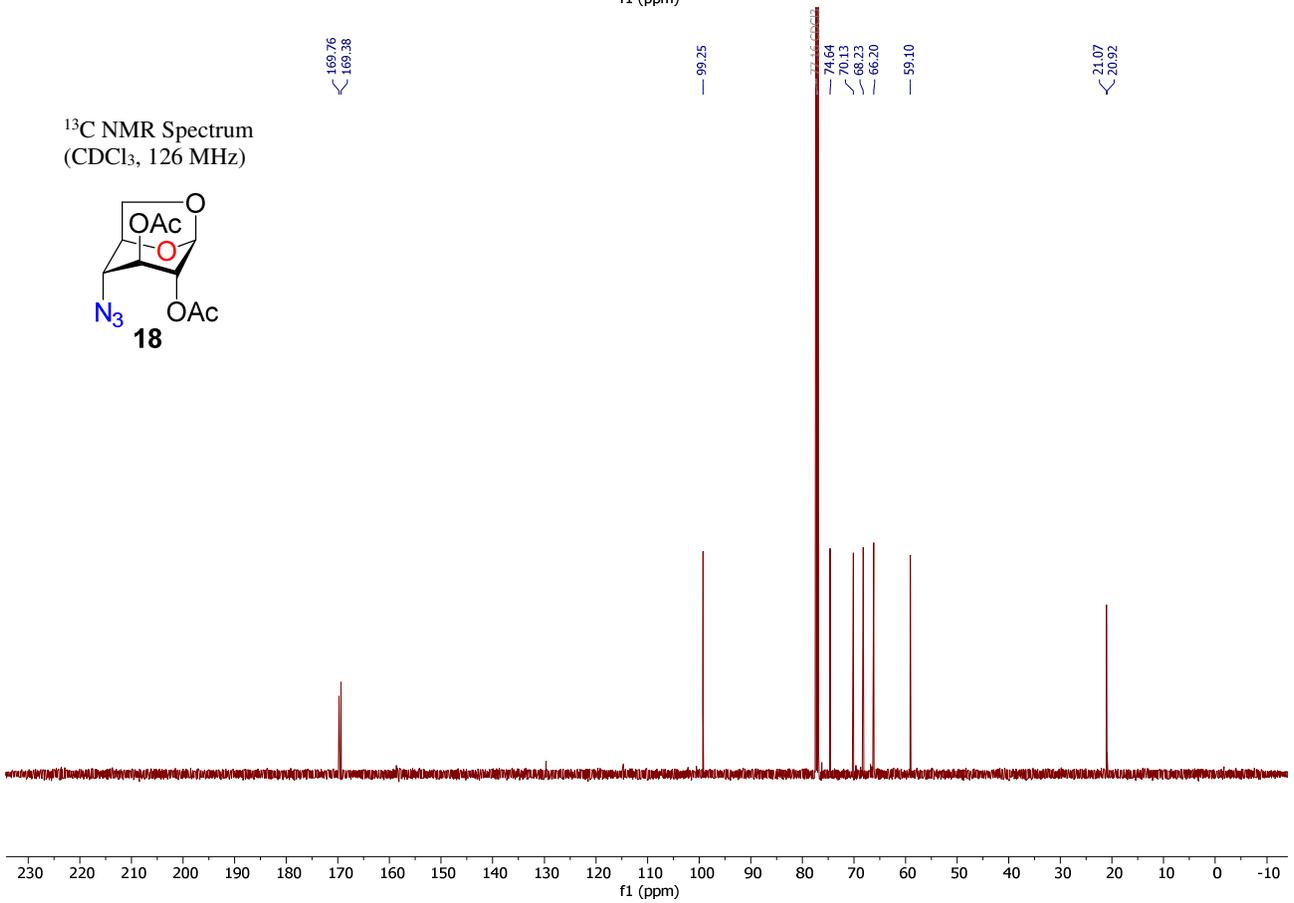


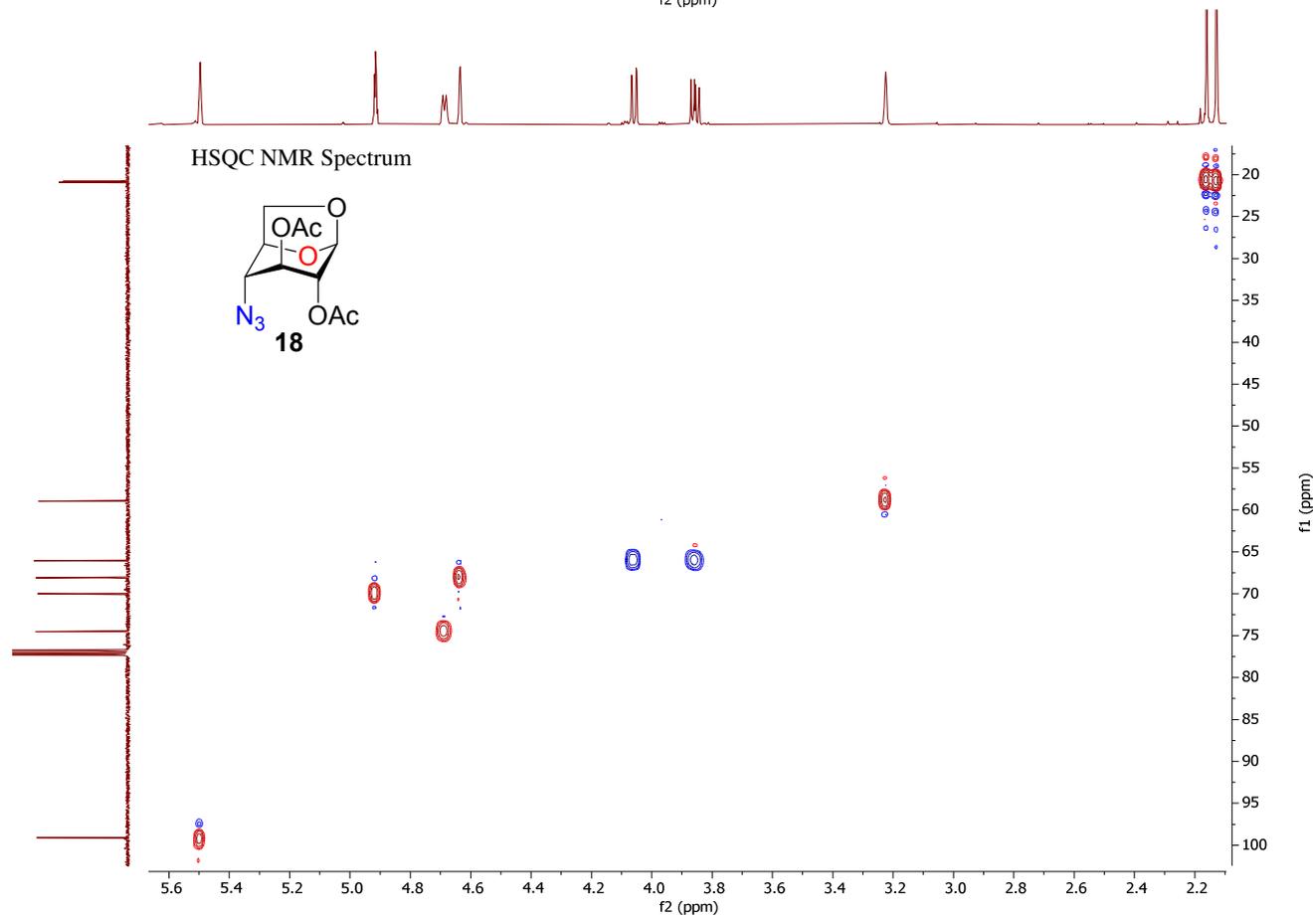
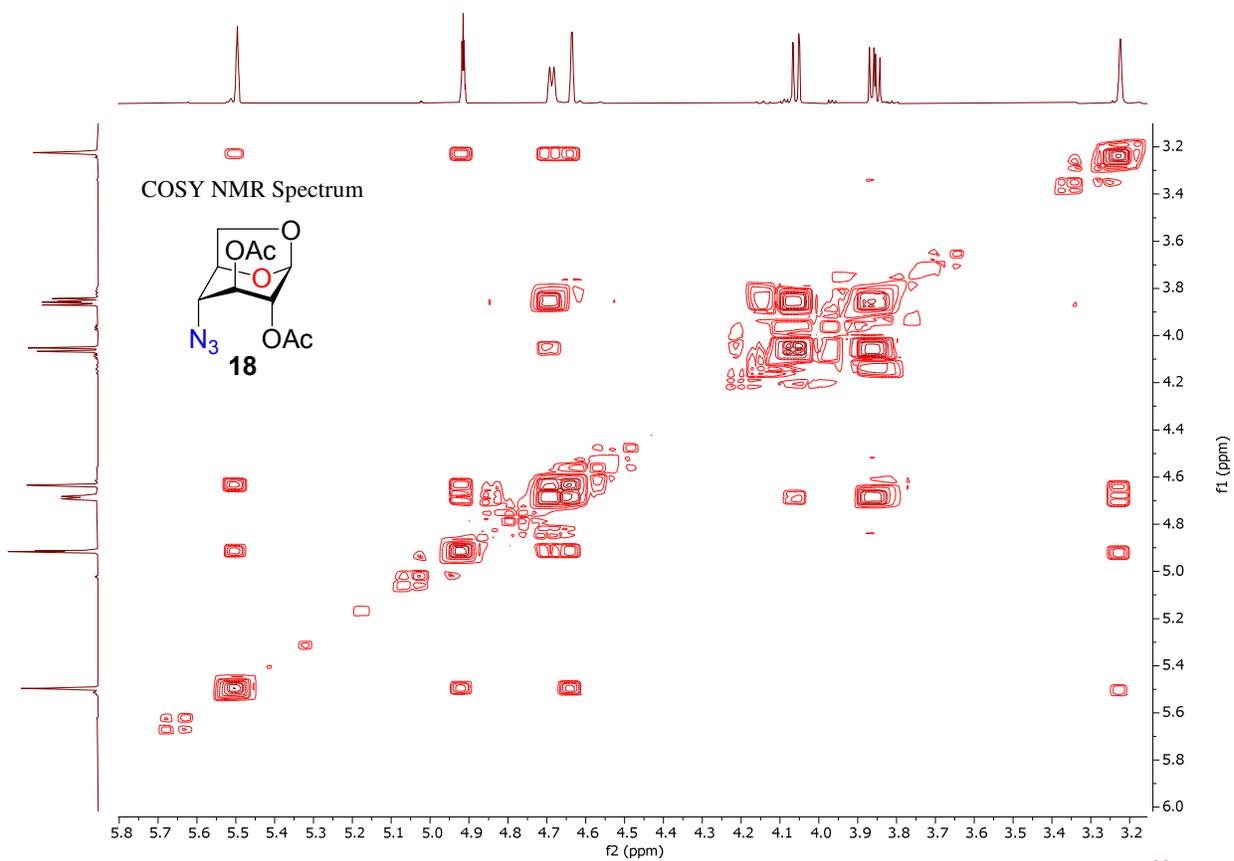


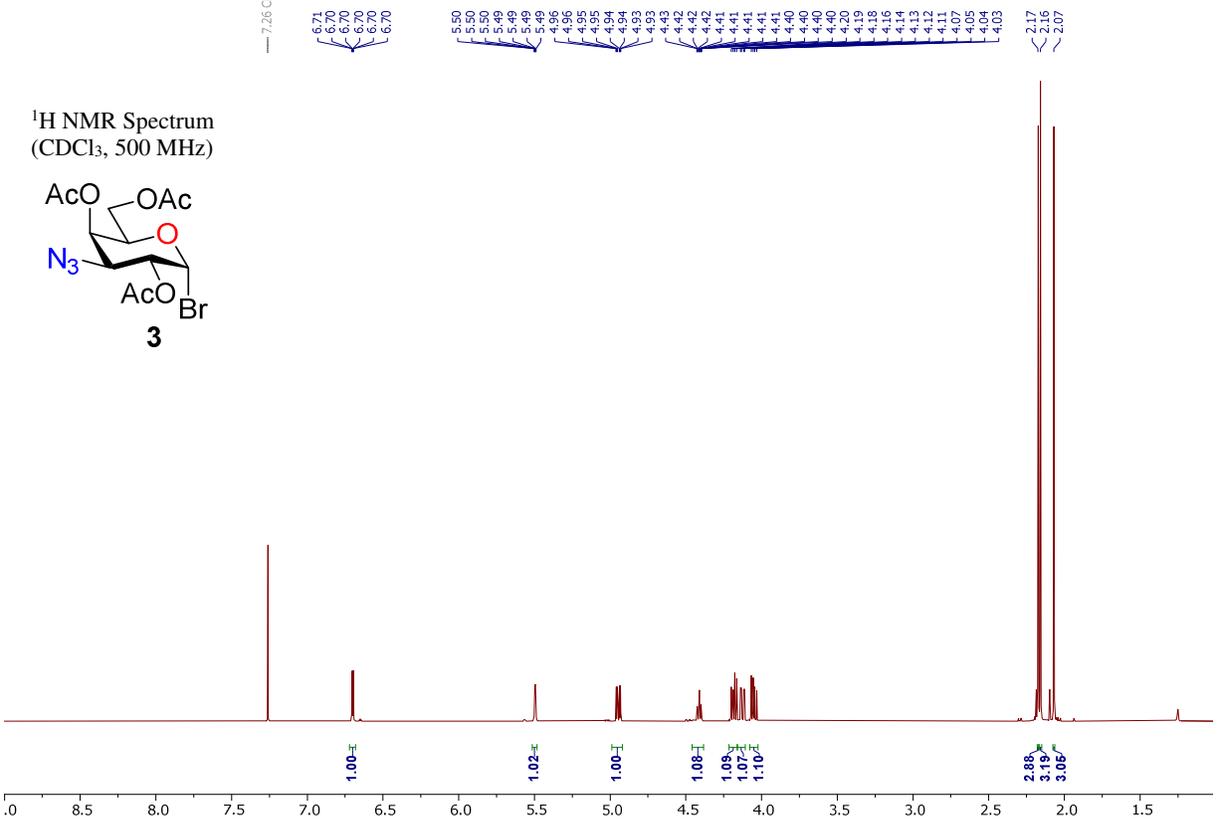
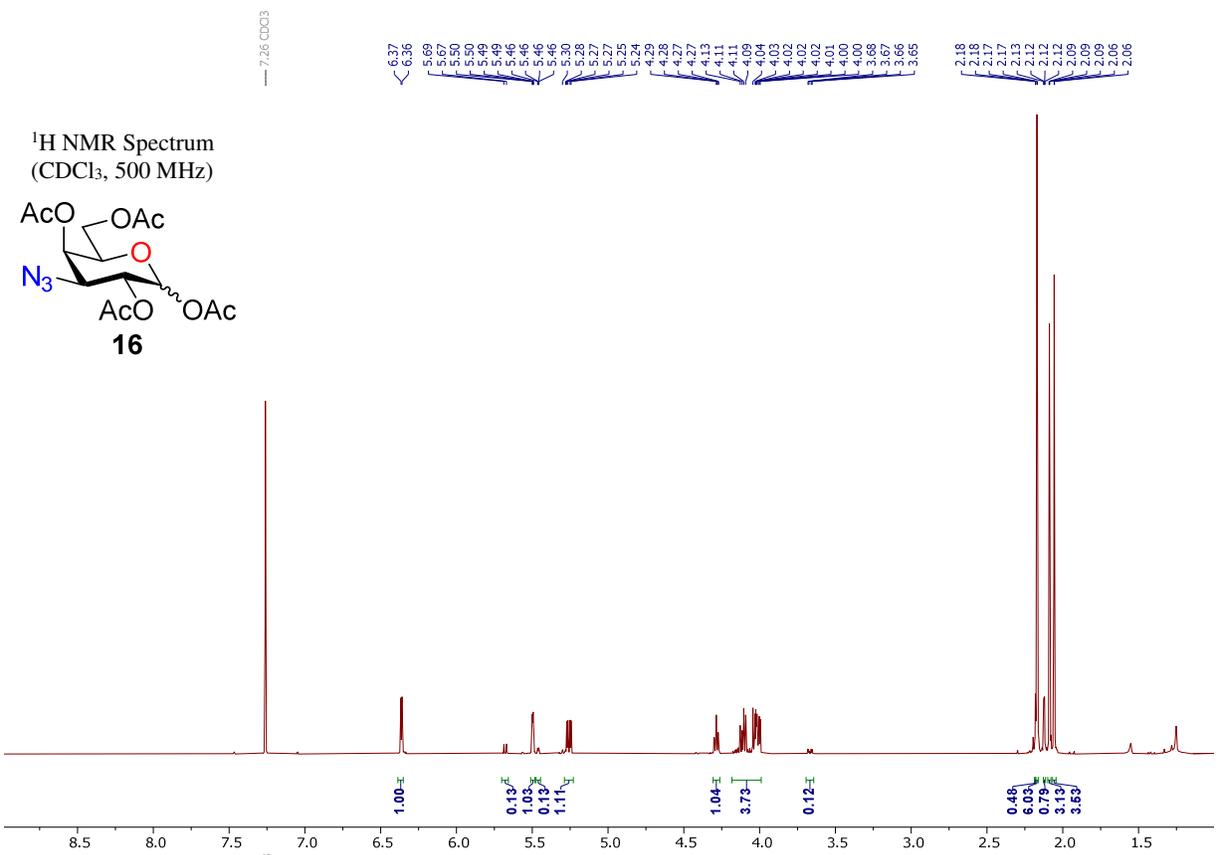
¹H NMR Spectrum
(CDCl₃, 500 MHz)

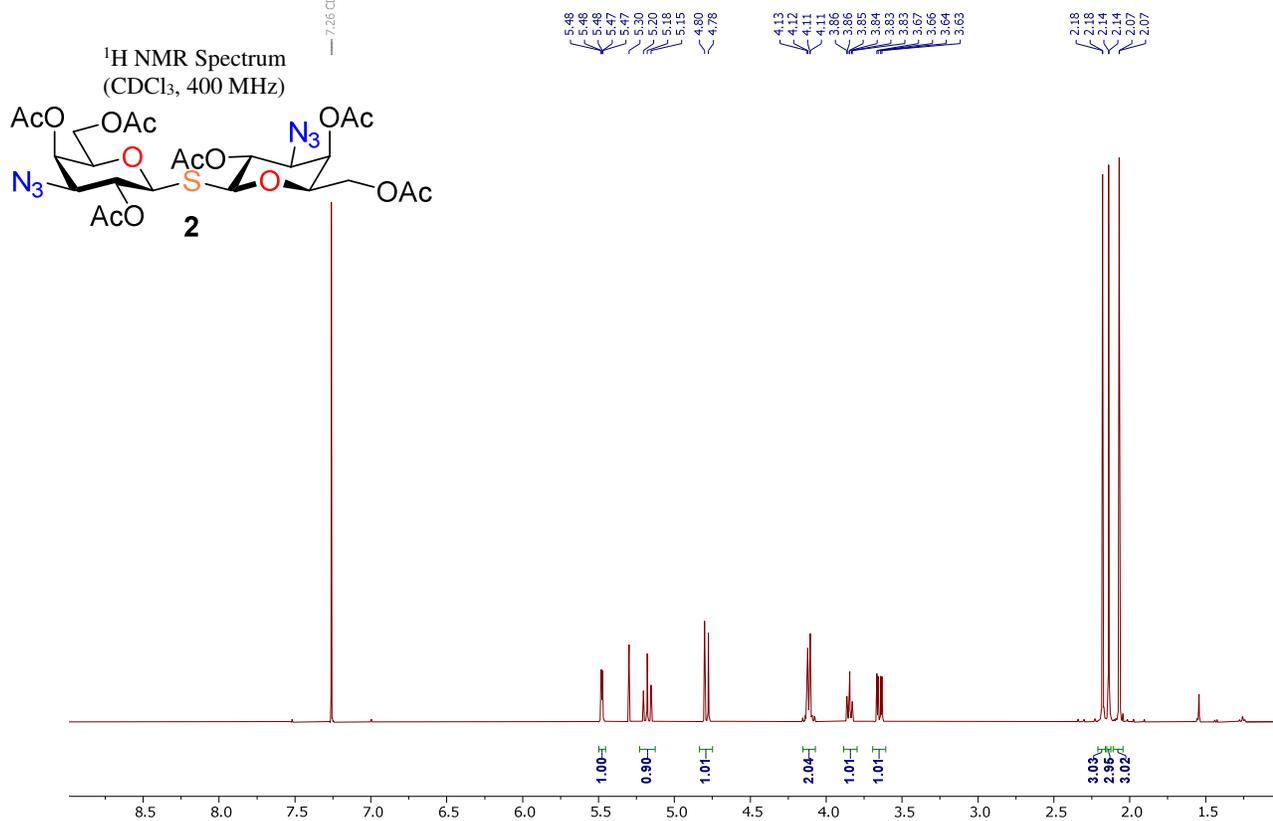
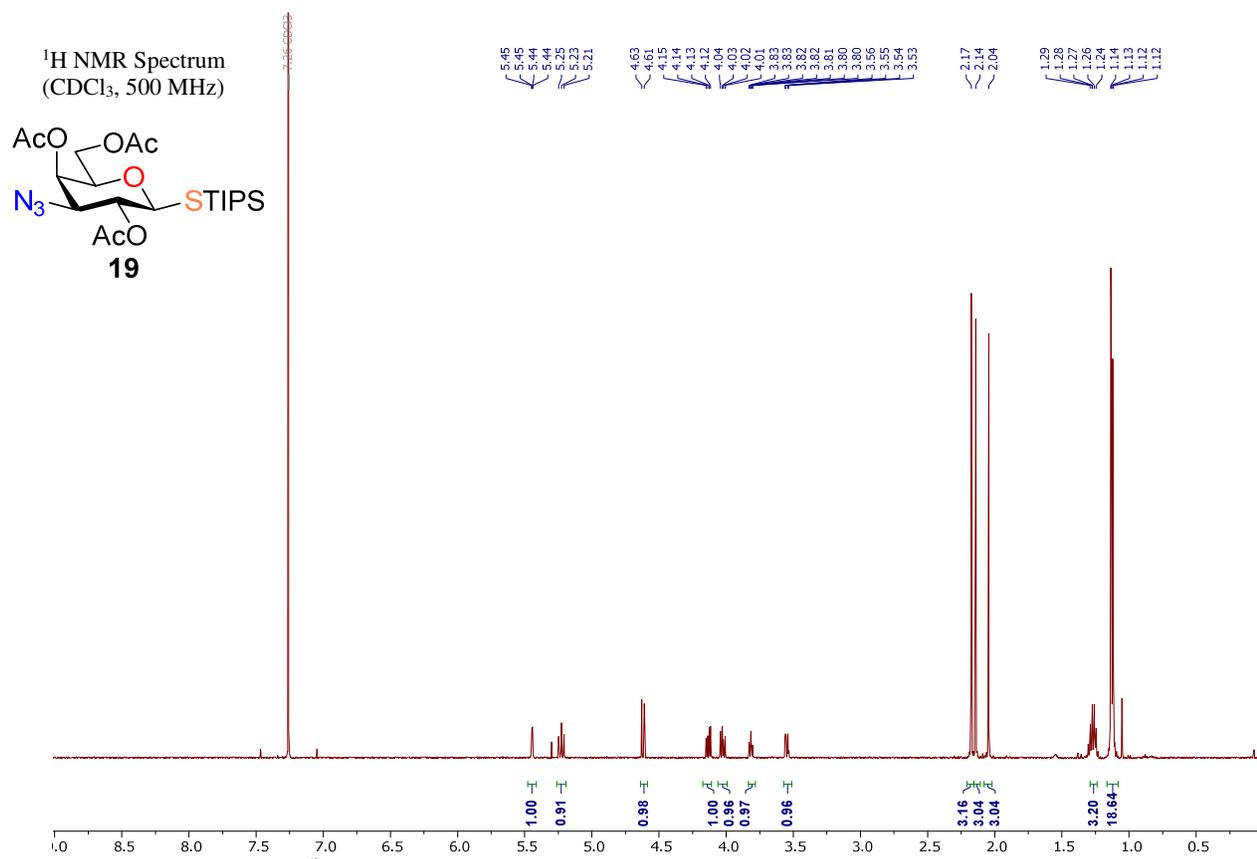


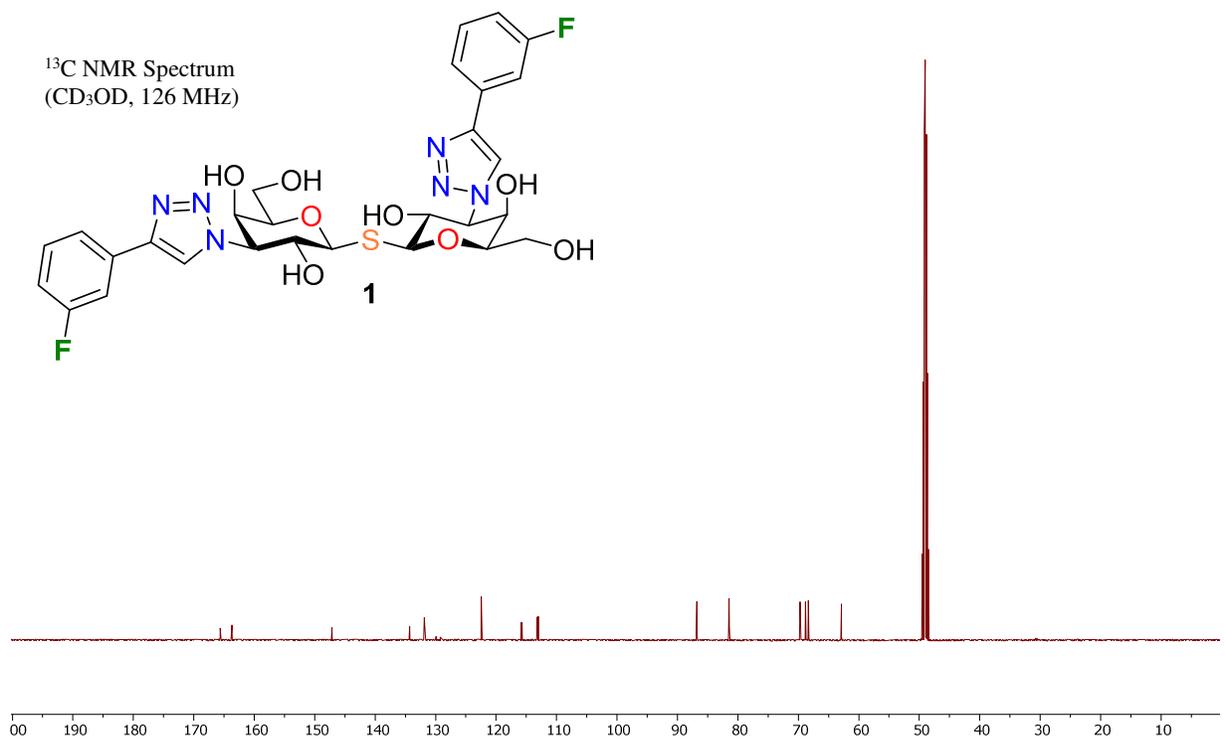
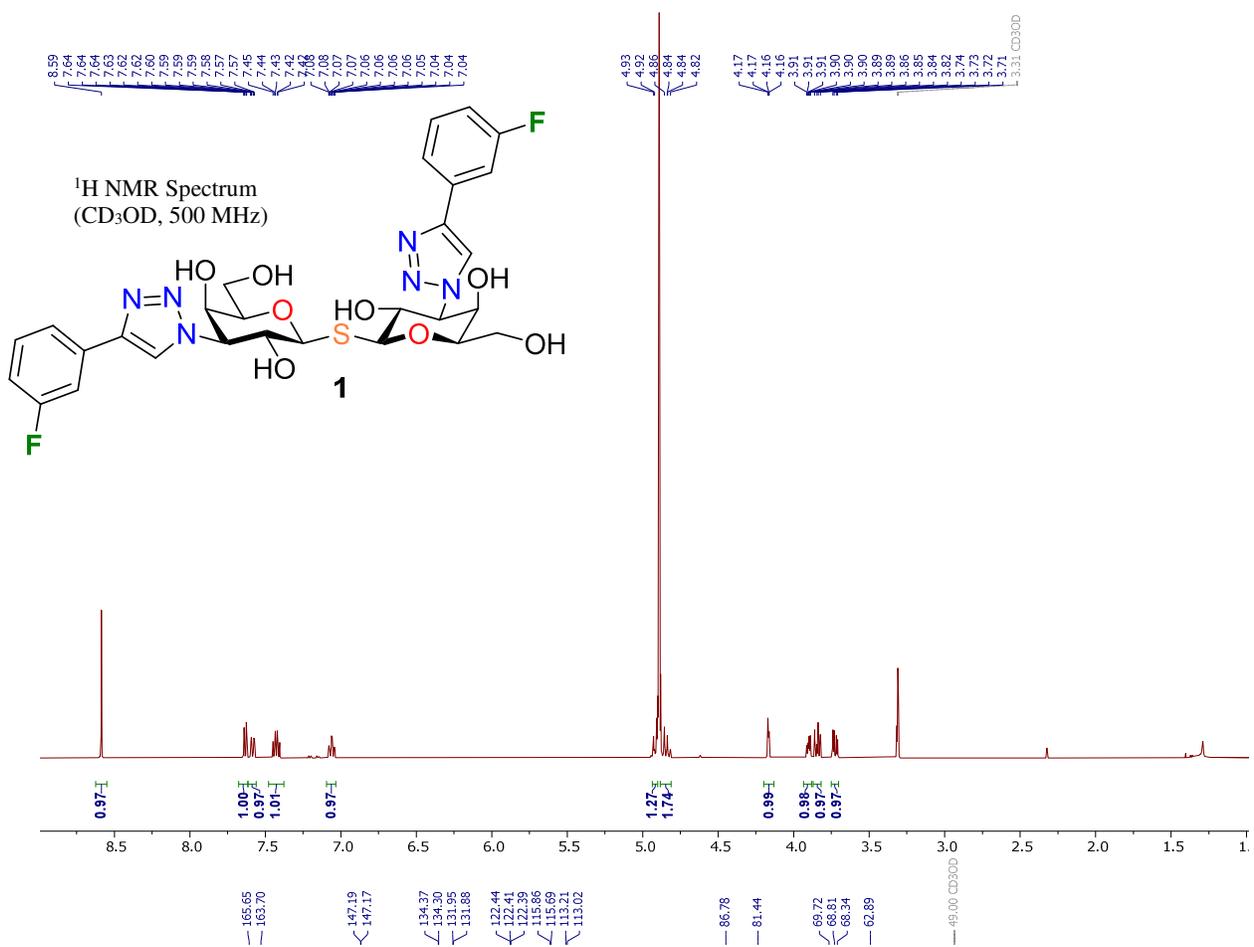
¹³C NMR Spectrum
(CDCl₃, 126 MHz)











IV. References

¹ T. B. Grindley, R. Thangarasa, *Carbohydr. Res.* 1988, **172**, 311–318.

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