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Electronic Supporting Information

Fundamental Curiosity of Multivicinal Inter-Halide Stereocenters

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I. Experimental section

General methods

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry dichloromethane (CH_2Cl_2) was obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns using a Vacuum Atmospheres Inc. Solvent Purification System. Yields refer to chromatographically and spectroscopically (^{1}H 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 $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g K_2CO_3, and 1.25 mL 10 % NaOH in 200 mL of water), a phenol solution (3 g of phenol in 95 mL of EtOH and 5 mL of sulfuric acid), or a phenol/Ac_2O solution (3 g of phenol in 95 mL of Ac_2O and 5 mL of sulfuric acid) followed by heating with a heatgun as developing agents. SiliaFlash® P60 (particle size 40–63 mm, 230– 400 mesh) was used for flash column chromatography. NMR spectra were recorded on an Agilent DD2 spectrometer (at 500 MHz for ^{1}H, 470 MHz for ^{19}F, and 126 MHz for ^{13}C) and calibrated using residual undeuterated solvent peaks ($CDCl_3$ ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm; acetone-d_6: ^{1}H δ = 2.05 ppm, ^{13}C δ = 29.84 ppm) as an internal reference. ^{19}F NMR spectra were calibrated using hexafluorobenzene, which gives a signal at ^{19}F δ = -162.29 ppm with respect to that of the reference compound $CFCl_3$. 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, and ^{19}F gc2HSQC) two-dimensional correlation spectroscopy. Infrared (IR) spectra were recorded using an ABB MB3000 Spectrometer with a diamond crystal plate, or Bomem MB100 Arid zone with a NaCl disk. 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 (ESI). Either protonated molecular ions $[M + nH]^{n+}$, sodium adducts $[M + Na]^+$, ammonium adducts $[M + NH_4]^+$ or deprotonated molecular ions $[M - nH]^{n-}$ were used for empirical formula

confirmation. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter at 589 nm and are reported in units of 10^{-1} (deg cm^2 g^{-1}). Melting points were measured on a Stanford Research System OptiMelt MPA100 151 automated melting point apparatus.

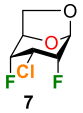
General procedures

General procedure I: Hydrolysis of 1,6-anhydro-difluorohalogenohexopyranose analogues

To a stirred solution of the starting 1,6-anhydro-difluorohalohexopyranose in a specified volume of CH_2Cl_2 at 0 °C, was added dropwise a specified volume of a 1 M solution of BCl_3 in CH_2Cl_2. The mixture was stirred, under an argon atmosphere, at room temperature for 2 h. The reaction mixture was cooled at 0 °C, a specified volume of H_2O was added, and the organic solvent was removed under reduced pressure. The resulting mixture was stirred at room temperature for 1 h, and the remaining water was evaporated under a gentle stream of air.

General procedure II: Reduction of difluorohalogenohexopyranose analogues

A specified amount of $NaBH_4$ was added to a stirred solution of the starting difluorohalogenohexopyranose in anhydrous EtOH. The resulting mixture was stirred at room temperature for 1 h and was neutralized to pH ≈ 7 with acidic resin. The mixture was filtered and concentrated under reduced pressure.



7

1,6-Anhydro-2,3,4-trideoxy-3-chloro-2,4-difluoro-β-D-allopyranose (7). To a solution of 1,6-anhydro-2,4-difluoro-2,4-difluoro-β-D-glucopyranose **4**[1] (390.6 mg, 2.351 mmol, 1.0 equiv.) in CH_2Cl_2 (11.8 mL, 0.2 M) at 0 °C under an argon atmosphere was added pyridine (0.76 mL, 9.404 mmol, 4.0 equiv.) and Tf_2O (0.79 mL, 4.702 mmol, 2.0 equiv.). The mixture was stirred at room temperature for 30 min and then quenched with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 and the combined organic phases were successively washed with aqueous 1 M HCl solution and brine. The

organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate **5** was used for the next step without further purification and dissolved in MeCN (1.1 mL, 0.2 M) in a sealed tube. Me_4NCl (236 mg, 2.151 mmol, 10 equiv.) was added, and the tube was sealed and stirred at 100 °C for 7 days. After cooling down to room temperature, the mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:3 → 1:1) to give **7** as a white amorphous solid (30.2 mg, 0.1636 mmol, 73 % yield over 2 steps): R_f = 0.38 (silica, EtOAc/hexanes 2:3); $[\alpha]_D^{25}$ = −73.1 (c 0.4, $CHCl_3$); IR (ATR, diamond crystal) *v* 2978, 2916, 1327, 1134, 1057, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.66 (dd, *J* = 1.9, 1.9 Hz, 1H, H1), 4.88 (ddd, *J* = 6.0, 5.9, 2.7 Hz, 1H, H5), 4.60 (ddd, *J* = 47.6, 3.2, 3.2 Hz, 1H, H4), 4.49 (ddd, *J* = 48.6, 3.4, 3.1 Hz, 1H, H2), 4.14 (dddd, *J* = 29.0, 27.2, 3.8, 3.8 Hz, 1H, H3), 3.86 (dddd, *J* = 8.2, 5.2, 5.2, 2.5 Hz, 1H, H6a), 3.78 (ddd, *J* = 8.6, 1.0, 1.0 Hz, 1H, H6b) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 99.0 (d, *J* = 24.8 Hz, 1C, C1), 86.9 (dd, *J* = 193.2, 1.0 Hz, 1C, C4), 85.9 (dd, *J* = 194.1, 1.0 Hz, 1C, C2), 74.6 (d, *J* = 19.6 Hz, 1C, C5), 64.1 (d, *J* = 6.1 Hz, 1C, C6), 51.2 (dd, *J* = 19.5, 19.1 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -194.93 (dddddd, *J* = 47.0, 29.0, 6.4, 6.3, 6.2, 1.0 Hz, 1F, F4), -198.04 (dddd, *J* = 48.8, 27.0, 8.4, 2.3 Hz, 1F, F2) ppm; the compound does not ionize.

8

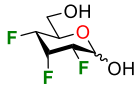
1,6-Anhydro-2,3,4-trideoxy-3-bromo-2,4-difluoro-β-D-allopyranose (8). To a solution of 1,6-anhydro-2,4-difluoro-2,4-difluoro-β-D-glucopyranose **4** (101.8 mg, 0.6128 mmol, 1.0 equiv.) in CH_2Cl_2 (3.0 mL, 0.2 M) at 0 °C under an argon atmosphere was added pyridine (0.20 mL, 2.452 mmol, 4.0 equiv.) and Tf_2O (0.21 mL, 1.226 mmol, 2.0 equiv.). The mixture was stirred at room temperature for 30 min and then quenched with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 and the combined organic phases were successively washed with aqueous 1 M HCl solution and brine. The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude triflate **5** was used for the next step without further purification and dissolved in DMF (2.6 mL, 0.22 M) in a sealed tube. Bu_4NBr (1.882 g, 5.840 mmol, 10 equiv.) was added, and the tube was sealed and stirred at 120 °C for 16 h. After cooling down to room temperature, the mixture was quenched with H_2O, and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:2 → 2:3) to give **8** as a pale yellow amorphous solid (124.0 mg, 0.5414 mmol, 88 % yield over 2 steps): R_f = 0.40 (silica, EtOAc/hexanes 2:3); $[\alpha]_D^{25}$ = −58.1 (c 0.3, $CHCl_3$); IR (ATR, diamond crystal) *v* 2970, 2916, 2854, 1335, 1126, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.65 (dd, *J* = 2.6, 1.2 Hz, 1H, H1), 4.89 (dddd, *J* = 6.0, 5.6, 2.9, 0.6 Hz, 1H, H5), 4.57 (ddd, *J* = 47.2, 3.1, 3.1 Hz, 1H, H4), 4.46 (ddd, *J* = 48.4, 3.2, 2.9 Hz, 1H, H2), 4.21 (dddd, *J* = 30.6, 28.7, 3.8, 3.8 Hz, 1H, H3), 3.87 (dddd, *J* = 10.8, 5.2, 3.1, 2.4 Hz, 1H, H6b), 3.81 (ddd, *J* = 8.5, 1.1, 1.1 Hz, 1H, H6a) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 99.2 (d, *J* = 25.8 Hz, 1C, C1), 86.9 (dd, *J* = 192.4, 1.0 Hz, 1C, C4), 86.0 (dd, *J* = 193.0, 1.2 Hz, 1C, C2), 74.8 (d, *J* = 20.3 Hz, 1C, C5), 64.2 (d, *J* = 5.9 Hz, 1C, C6), 41.3 (dd, *J* = 20.0, 20.0 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -188.82 (ddddd, *J* = 46.9, 30.6, 6.2, 6.0, 6.0 Hz, 1F, F4), -192.43 (dddd, *J* = 48.2, 28.6, 7.4, 2.5 Hz, 1F, F2) ppm; the compound does not ionize.

9

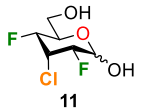
1,6-Anhydro-2,3,4-trideoxy-2,4-difluoro-3-iodo-β-D-allopyranose (9). To a solution of 1,6-anhydro-2,4-difluoro-2,4-difluoro-β-D-glucopyranose **4** (390.7 mg, 2.352 mmol, 1.0 equiv.) in CH_2Cl_2 (11.8 mL, 0.2 M) at 0 °C under an argon atmosphere was added pyridine (0.76 mL, 9.408 mmol, 4.0 equiv.) and Tf_2O (0.79 mL, 4.704 mmol, 2.0 equiv.). The mixture was stirred at room temperature for 30 min and then quenched with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 and the combined organic phases were successively washed with aqueous 1 M HCl solution and brine. The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate **5** was used for the next step without further purification and dissolved in

DMF (11 mL, 0.2 M) in a sealed tube. Bu_4NI (8.881 g, 22.41 mmol, 10 equiv.) was added, and the tube was sealed and stirred at 120 °C for 16 h. After cooling down to room temperature, the mixture was quenched with H_2O, and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:3 → 1:1) to give **9** as a pale yellow amorphous solid (558.0 mg, 2.022 mmol, 86 % yield over 2 steps): R_f = 0.46 (silica, EtOAc/hexanes 2:3); $[\alpha]_D^{25}$ = −56.6 (c 0.5, $CHCl_3$); IR (ATR, diamond crystal) *ν* 2978, 2916, 1327, 1126, 1041, 987 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.59 (dd, *J* = 2.3, 0.7 Hz, 1H, H1), 4.83 (dddd, *J* = 6.3, 5.0, 2.5, 0.8 Hz, 1H, H5), 4.46 (ddd, *J* = 46.8, 3.3, 3.3 Hz, 1H, H4), 4.40 (dddd, *J* = 33.0, 31.3, 3.9, 3.5 Hz, 1H, H3), 4.35 (dddd, *J* = 47.5, 3.2, 3.2, 0.7 Hz, 1H, H2), 3.88 (dddd, *J* = 8.3, 7.5, 5.0, 2.5 Hz, 1H, H6b), 3.85 (ddd, *J* = 8.1, 0.6, 0.6 Hz, 1H, H6a) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 98.9 (d, *J* = 27.1 Hz, 1C, C1), 87.5 (dd, *J* = 190.5, 1.3 Hz, 1C, C4), 86.6 (dd, *J* = 191.0, 0.8 Hz, 1C, C2), 74.7 (d, *J* = 20.9 Hz, 1C, C5), 64.4 (d, *J* = 6.3 Hz, 1C, C6), 17.4 (dd, *J* = 21.2, 21.2 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -178.25 (dddddd, *J* = 46.4, 33.2, 5.7, 5.0, 5.0, 0.9 Hz, 1F, F4), -182.60 (dddd, *J* = 47.5, 31.3, 5.7, 2.3 Hz, 1F, F2) ppm; the compound does not ionize.



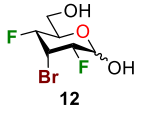
10

2,3,4-Trideoxy-2,3,4-trifluoro-α/β-D-allopyranose (10). The known 1,6-anhydro-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranose **6**[1] (218.3 mg, 1.299 mmol, 1.0 equiv.) was hydrolysed with BCl_3 (1 M in CH_2Cl_2, 6.5 mL, 6.495 mmol, 5.0 equiv.) in CH_2Cl_2 (13 mL, 0.1 M) and water (46 mL, 2.554 mmol, 2.0 equiv.) following the general procedure I. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 4:1) to give an anomeric mixture of **10** (α/β 1:13) as a white amorphous solid (232.1 mg, 1.247 mmol, 96 % yield). The spectroscopic data derived from compound **10** match those reported in the literature.[1]



11

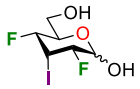
2,3,4-Trideoxy-3-chloro-2,4-difluoro-α/β-D-allopyranose (11). 1,6-Anhydro-2,3,4-trideoxy-3-chloro-2,4-difluoro-β-D-allopyranose **7** (78.0 mg, 0.4226 mmol, 1.0 equiv.) was hydrolysed with BCl_3 (1 M in CH_2Cl_2, 2.2 mL, 2.113 mmol, 5.0 equiv.) in CH_2Cl_2 (4.2 mL, 0.1 M) and water (15 mL, 0.8304 mmol, 2.0 equiv.) following the general procedure I. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 3:2 → 4:1) to give an anomeric mixture of **11** (α/β 1:19) as a white amorphous solid (60.0 mg, 0.2962 mmol, 70 % yield): R_f = 0.39 (silica, EtOAc/hexanes 4:1); $[\alpha]_D^{25}$ = −9.34 (c 0.4, MeOH); IR (ATR, diamond crystal) *v* 3340, 3117, 2901, 1342, 1142, 1018, 656 cm^{-1}; only the β anomer has been attributed in ^1H NMR, ^{13}C NMR, and ^{19}F NMR; ^1H NMR (500 MHz, Acetone-d_6) δ 6.37 (d, *J* = 6.3 Hz, 1H, O*H*1), 5.16 (ddd, *J* = 7.2, 6.3, 1.3 Hz, 1H, H1), 5.09 (dddd, *J* = 7.3, 7.3, 3.5, 3.5 Hz, 1H, H3), 4.92 (dddd, *J* = 46.2, 8.7, 3.5, 1.4 Hz, 1H, H4), 4.48 (dddd, *J* = 46.9, 7.2, 3.5, 1.5 Hz, 1H, H2), 3.98 (ddd, *J* = 7.4, 4.6, 4.4, 2.5 Hz, 1H, H5), 3.96 (dd, *J* = 6.5, 6.5 Hz, 1H, O*H*6), 3.83 (dddd, *J* = 12.3, 5.6, 2.3, 2.3 Hz, 1H, H6b), 3.67 (dddd, *J* = 12.2, 7.1, 4.3, 2.2 Hz, 1H, H6a) ppm; ^{13}C {^1H} NMR (126 MHz, Acetone-d_6) δ 92.0 (d, *J* = 22.9 Hz, 1C, C1), 87.3 (dd, *J* = 194.4, 3.9 Hz, 1C, C2), 83.7 (dd, *J* = 190.8, 3.7 Hz, 1C, C4), 72.6 (d, *J* = 23.1 Hz, 1C, C5), 60.4 (d, *J* = 1.1 Hz, 1C, C6), 59.9 (dd, *J* = 17.4, 17.4 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -194.85 (dddd, *J* = 47.0, 7.5, 3.9, 1.2 Hz, 1F, F1), -196.25 (ddddd, *J* = 46.0, 7.3, 4.6, 2.3, 2.2 Hz, 1F, F4) ppm; HRMS calcd for $C_6H_8ClF_2O_3^-$ $[M - H]^-$ 201.0136 found 201.0140.



12

2,3,4-Trideoxy-3-bromo-2,4-difluoro-α/β-D-allopyranose (12). 1,6-Anhydro-2,3,4-trideoxy-3-bromo-2,4-difluoro-β-D-allopyranose **8** (165.00 mg, 0.7205 mmol, 1.0 equiv.) was hydrolysed with BCl_3 (1 M in CH_2Cl_2, 3.6 mL, 3.602 mmol, 5.0 equiv.) in CH_2Cl_2 (7.2 mL, 0.1 M) and water (25.5 mL, 1.416 mmol, 2.0 equiv.) following the general procedure I. The obtained crude was purified by flash column chromatography (silica gel,

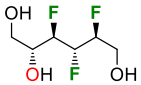
EtOAc/hexanes 3:2 → 4:1) to give an anomeric mixture of **12** (α/β 1:17) as a white amorphous solid (160.0 mg, 0.6477 mmol, 90 % yield): R_f = 0.42 (silica, EtOAc/hexanes 4:1); $[\alpha]_D^{25}$ = −10.5 (c 0.5, MeOH); IR (ATR, diamond crystal) *v* 3340, 2932, 1443, 1080, 1030, 1011 cm^{-1}; only the β anomer has been attributed in ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR; ^{1}H NMR (500 MHz, Acetone-d_6) δ 6.38 (d, *J* = 6.5 Hz, 1H, O*H*1), 5.18 (ddd, J_2 = 6.8, 6.7, 1.4 Hz, 1H, H1), 5.14 (dddd, *J* = 7.4, 7.4, 3.6, 3.6 Hz, 1H, H3), 4.78 (dddd, *J* = 46.5, 8.6, 3.5, 1.2 Hz, 1H, H4), 4.37 (dddd, *J* = 47.4, 6.9, 3.5, 1.5 Hz, 1H, H2), 3.99 (ddd, *J* = 8.6, 3.8, 3.3 Hz, 1H, H5), 3.98 (dd, *J* = 6.7, 5.5 Hz, 1H, O*H*6), 3.82 (dddd, *J* = 12.2, 5.1, 5.0, 2.3 Hz, 1H, H6a), 3.68 (dddd, *J* = 12.2, 6.5, 4.3, 2.2 Hz, 1H, H6b) ppm; ^{13}C {^{1}H} NMR (126 MHz, Acetone-d_6) δ 93.7 (d, *J* = 22.6 Hz, 1C, C1), 87.7 (dd, *J* = 193.6, 4.2 Hz, 1C, C2), 84.2 (dd, *J* = 190.0, 3.6 Hz, 1C, C4), 74.7 (d, *J* = 22.5 Hz, 1C, C5), 61.3 (s, 1C, C6), 53.9 (dd, *J* = 17.5, 17.5 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -189.77 (dddd, *J* = 47.4, 7.6, 3.9, 1.4 Hz, 1F, F2), -190.73 (dddd, *J* = 46.6, 7.4, 2.3, 2.2 Hz, 1F, F4) ppm; HRMS calcd for $C_6H_8BrF_2O_3^-$ $[M - H]^-$ 244.9630 found 244.9636.



13

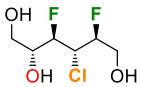
2,3,4-Trideoxy-2,4-difluoro-3-iodo-α/β-D-allopyranose (13). 1,6-Anhydro-2,3,4-trideoxy-2,4-difluoro-3-iodo-β-D-allopyranose **9** (100.5 mg, 0.3641 mmol, 1.0 equiv.) was hydrolysed with BCl_3 (1 M in CH_2Cl_2, 2.9 mL, 2.113 mmol, 8.0 equiv.) in CH_2Cl_2 (3.6 mL, 0.1 M) and water (12.9 mL, 0.7155 mmol, 2.0 equiv.) following the general procedure I. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 3:2 → 4:1) to give an anomeric mixture of **13** (α/β 1:16) as a white amorphous solid (85.4 mg, 0.2904 mmol, 80 % yield): R_f = 0.46 (silica, EtOAc/hexanes 4:1); $[\alpha]_D^{25}$ = −13.5 (c 0.5, MeOH); IR (ATR, diamond crystal) *v* 3340, 2925, 1327, 1095, 1080, 1026 cm^{-1}; only the β anomer has been attributed in ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR; ^{1}H NMR (500 MHz, Acetone-d_6) δ 6.38 (d, *J* = 6.4 Hz, 1H, O*H*1), 5.17 (dddd, *J* = 9.4, 9.4, 3.8, 3.8 Hz, 1H, H3), 5.14 (ddd, *J* = 6.4, 6.3, 2.3 Hz, 1H, H1), 4.26 (dddd, *J* = 47.2, 7.6, 3.8, 1.1 Hz, 1H, H4), 4.01 (dd, *J* = 6.7, 5.5 Hz, 1H, O*H*6), 3.94 (dddd, *J* = 7.8, 4.6, 4.3, 3.2 Hz, 1H, H5), 3.92 (dddd, *J* = 48.0, 6.3, 3.9, 1.1 Hz, 1H, H2), 3.82 (dddd, *J* = 12.2, 5.5, 3.5,

1.7 Hz, 1H, H6a), 3.69 (dddd, *J* = 12.2, 6.8, 4.4, 2.3 Hz, 1H, H6a) ppm; ^{13}C {^{1}H} NMR (126 MHz, Acetone-d_6) δ 94.9 (d, *J* = 23.2 Hz, 1C, C1), 87.7 (dd, *J* = 191.4, 4.0 Hz, 1C, C2), 84.6 (dd, *J* = 188.5, 3.9 Hz, 1C, C4), 76.6 (d, *J* = 21.9 Hz, 1C, C5), 61.5 (s, 1C, C6), 33.2 (dd, *J* = 18.1, 18.1 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -181.06 (dddddd, *J* = 47.3, 9.4, 4.6, 4.4, 2.3, 1.7 Hz, 1F, F4), -181.31 (dddd, *J* = 48.4, 9.3, 4.4, 2.0 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_8F_2IO_3^-$ [M - H]$^-$ 292.9492 found 292.9495.



14

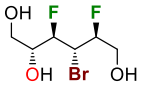
2,3,4-Trideoxy-2,3,4-trifluoro-D-allitol (14). 2,3,4-Trideoxy-2,3,4-trifluoro-α/β-D-allopyranose **10** (192 mg, 1.032 mmol, 1.0 equiv.) was reduced with $NaBH_4$ (68.3 mg, 1.805 mmol, 1.75 equiv.) in anhydrous EtOH (10 mL, 0.1 M) following the general procedure II. The obtained crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:9) to give **14** as a colorless oil (180.5 mg, 0.9593 mmol, 93 % yield). The spectroscopic data derived from compound **14** match those reported in the literature.[2]



15

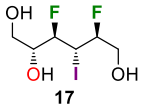
2,3,4-Trideoxy-3-chloro-2,4-difluoro-D-allitol (15). 2,3,4-Trideoxy-3-chloro-2,4-difluoro-α/β-D-allopyranose **11** (21.5 mg, 0.1061 mmol, 1.0 equiv.) was reduced with $NaBH_4$ (20.0 mg, 0.5306 mmol, 5.0 equiv.) in anhydrous EtOH (1.0 mL, 0.1 M) following the general procedure II. The obtained crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:9) to give **15** as a colorless oil (20.0 mg, 0.0978 mmol, 92 % yield): R_f = 0.49 (silica, MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{25}$ = −2.63 (c 0.8, MeOH); IR (ATR, diamond crystal) *v* 3323, 2926, 2854, 1456, 1242, 1030, 885 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 4.97 (dddd, *J* = 46.4, 8.0, 4.4, 2.4, 1H, H2), 4.86 (ddd, *J* = 45.8, 8.4, 2.5 Hz, 1H, H4), 4.76 (dddd, *J* = 22.0, 8.0, 6.9, 2.5 Hz, 1H, H3), 4.34 (d, *J* = 6.4 Hz, 1H, O*H*5), 4.24 (dd, *J* = 6.0, 6.0 Hz, 1H, O*H*1), 4.01 (ddddd, *J* = 8.4, 7.4, 5.3, 4.0, 3.0 Hz, 1H, H5), 3.97 – 3.92 (m, 1H, O*H*6), 3.92 (dddd, *J* = 26.0, 13.0, 6.0, 2.4 Hz, 1H, H1b), 3.90 (dddd, *J* = 29.7, 13.0, 6.0, 4.7 Hz, 1H, H1a), 3.76 (dddd, *J* = 11.5, 5.3, 3.1, 3.1 Hz, 1H, H6a), 3.67

(dddd, *J* = 11.2, 7.0, 4.3, 2.6 Hz, 1H, H6b) ppm; ^{13}C {^{1}H} NMR (126 MHz, Acetone-d_6) δ 93.4 (dd, *J* = 175.6, 5.6 Hz, 1C, C2), 93.0 (dd, *J* = 178.7, 3.4 Hz, 1C, C4), 71.2 (dd, *J* = 25.5, 3.2 Hz, 1C, C5), 63.3 (d, *J* = 3.1 Hz, 1C, C6), 62.1 (dd, *J* = 20.9, 2.2 Hz, 1C, C1), 58.4 (dd, *J* = 25.1, 21.6 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -187.73 (dddd, *J* = 46.3, 29.8, 26.5, 6.9 Hz, 1F, F2), -198.57 (ddddd, *J* = 45.1, 21.8, 6.5, 2.5, 2.0 Hz, 1F, F4) ppm; HRMS calcd for $C_6H_{10}ClF_2O_3^-$ [M - H]$^-$ 203.0292 found 203.0295.



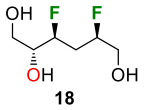
16

2,3,4-Trideoxy-3-bromo-2,4-difluoro-D-allitol (16). 2,3,4-Trideoxy-3-bromo-2,4-difluoro-α/β-D-allopyranose **12** (217.3 mg, 0.8796 mmol, 1.0 equiv.) was reduced with $NaBH_4$ (58.2 mg, 1.539 mmol, 1.75 equiv.) in anhydrous EtOH (8.8 mL, 0.1 M) following the general procedure II. The obtained crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:9) to give **16** as a colorless oil (214.3 mg, 0.8605 mmol, 98 % yield): R_f = 0.49 (silica, MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{25}$ = −1.69 (c 0.9, MeOH); IR (ATR, diamond crystal) *v* 3371, 2924, 2854, 1373, 1273, 1072 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 5.00 (dddd, *J* = 46.5, 8.0, 4.5, 2.3 Hz, 1H, H2), 4.86 (ddd, *J* = 45.7, 8.3, 2.5 Hz, 1H, H4), 4.82 (dddd, *J* = 23.0, 8.0, 7.3, 2.5 Hz, 1H, H3), 4.35 (d, *J* = 3.8 Hz, 1H, O*H*5), 4.24 (dd, *J* = 6.1, 6.1 Hz, 1H, O*H*1), 4.06 – 3.87 (m, 4H, H1a, H1b, H5, O*H*6), 3.76 (dd, *J* = 11.5, 3.0 Hz, 1H, H6b), 3.67 (dd, *J* = 11.2, 1.5 Hz, 1H, H6a) ppm; ^{13}C {^{1}H} NMR (126 MHz, Acetone-d_6) δ 93.4 (dd, *J* = 176.7, 4.7 Hz, 1C, C2), 93.2 (dd, *J* = 178.6, 4.0 Hz, 1C, C4), 72.2 (dd, *J* = 25.6, 3.0 Hz, 1C, C5), 63.3 (d, *J* = 2.8 Hz, 1C, C6), 63.1 (dd, *J* = 20.9, 2.1 Hz, 1C, C1), 50.5 (dd, *J* = 23.3, 21.4 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -183.16 (dddd, *J* = 46.7, 28.4, 28.3, 7.1 Hz, 1F, F2), -196.03 (ddd, *J* = 45.2, 22.1, 3.5 Hz, 1F, F4) ppm; HRMS calcd for $C_6H_{10}BrF_2O_3^-$ [M - H]$^-$ 246.9787 found 246.9792.



17

2,3,4-Trideoxy-3-iodo-2,4-difluoro-D-allitol (17). 2,3,4-Trideoxy-2,4-difluoro-3-iodo-α/β-D-allopyranose **13** (10.8 mg, 0.03673 mmol, 1.0 equiv.) was reduced with $NaBH_4$ (2.4 mg, 0.06344 mmol, 1.73 equiv.) in anhydrous EtOH (0.37 mL, 0.1 M) following the general procedure II. The obtained crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:9) to give **17** as a colorless oil (9.8 mg, 0.03310 mmol, 90 % yield): R_f = 0.50 (silica, MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{25}$ = 3.86 (c 0.7, MeOH); IR (ATR, diamond crystal) *v* 3337, 2930, 2881, 1452, 1234, 1022, 878 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 4.89 (dddd, *J* = 24.3, 8.2, 8.2, 2.8 Hz, 1H, H3), 4.83 (dddd, *J* = 46.4, 8.1, 4.9, 2.1 Hz, 1H, H2), 4.65 (ddd, *J* = 45.1, 8.2, 2.4 Hz, 1H, H4), 4.32 (d, *J* = 6.5 Hz, 1H, O*H*5), 4.21 (dd, *J* = 6.0, 6.0 Hz, 1H, O*H*1), 4.04 (dddd, *J* = 28.0, 13.0, 5.7, 2.1 Hz, 1H, H1b), 3.98 (ddddd, *J* = 8.2, 6.6, 6.4, 4.6, 3.1 Hz, 1H, H5), 3.97 (dddd, *J* = 28.2, 13.0, 6.0, 4.9 Hz, 1H, H1a), 3.94 (dd, *J* = 6.0, 5.8 Hz, 1H, O*H*6), 3.75 (dddd, *J* = 11.5, 5.8, 3.1, 3.1 Hz, 1H, H6b), 3.67 (dddd, *J* = 11.2, 6.0, 4.6, Hz, 1H, H6a). ^{13}C {^1H} NMR (126 MHz, Acetone-d_6) δ 94.0 (dd, *J* = 177.9, 5.2 Hz, 1C, C4), 93.8 (dd, *J* = 177.0, 4.3 Hz, 1C, C2), 73.7 (dd, *J* = 25.8, 2.5 Hz, 1C, C5), 64.9 (dd, *J* = 20.9, 2.3 Hz, 1C, C1), 63.3 (d, *J* = 2.9 Hz, 1C, C6), 29.9 (dd, *J* = 20.7, 20.7 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -177.62 (dddd, *J* = 47.3, 28.2, 28.0, 8.1 Hz, 1F, F2), -190.63 (ddd, *J* = 45.3, 23.6, 6.6 Hz, 1F, F4) ppm; HRMS calcd for $C_6H_{15}F_2IO_3^+$ $[M + NH_4]^+$ 314.0059 found 314.0052.

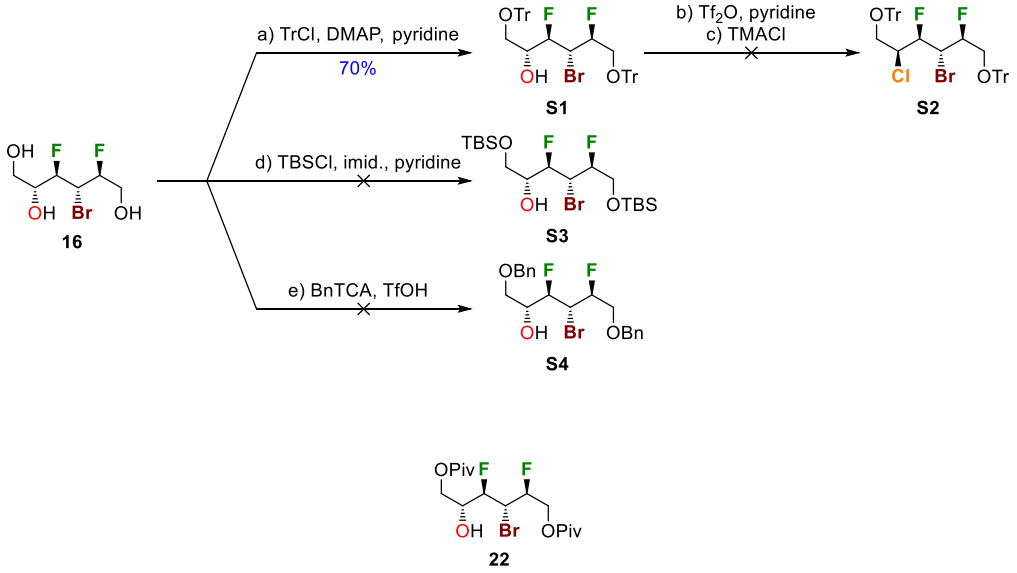


18

2,3,4-Trideoxy-2,4-difluoro-D-allitol (18). To a stirred solution of 2,3,4-trideoxy-2,4-difluoro-3-iodo-α/β-D-allopyranose **13** (12.5 mg, 0.04251 mmol, 1.0 equiv.) in anhydrous EtOH (0.43 mL, 0.1 M) was added $NaBH_4$ (12.9 mg, 0.3401 mmol, 8.0 equiv.). The mixture was stirred at 50 °C for 1 h. After the mixture was cooled down to room temperature, 1 mL of MeOH was added, and the mixture was neutralized to pH ≈ 7 with acidic resin. The mixture was filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:9) to give **18** as a

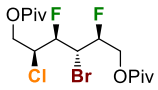
colorless oil (4.8 mg, 0.02821 mmol, 66 % yield): R_f = 0.52 (silica, MeOH/CH_2Cl_2 3:17); $[\alpha]_D^{25}$ = −6.91 (c 0.5, MeOH); IR (ATR, diamond crystal) *v* 3350, 2926, 2856, 1441, 1230, 1051, 860 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 4.75 (ddddd, *J* = 48.8, 6.0, 6.0, 6.0, 3.4 Hz, 1H, H2), 4.65 (dddd, *J* = 48.1, 9.0, 6.0, 3.4 Hz, 1H, H4), 4.14 (d, *J* = 5.5 Hz, 1H, O*H*5), 4.05 (dd, *J* = 6.0, 6.0 Hz, 1H, O*H*1), 3.79 (dd, *J* = 5.9, 5.1 Hz, 1H, O*H*6), 3.76 – 3.63 (m, 4H, H1a, H1b, H5, H6b), 3.59 (ddd, *J* = 11.2, 5.2, 5.1 Hz, 1H, H6a), 2.21 (ddddd, *J* = 34.2, 21.9, 15.2, 6.1, 3.5 Hz, 1H, H3b), 2.07 (ddddd, *J* = 18.6, 18.5, 15.0, 8.5, 6.3 Hz, 1H, H3a) ppm; ^{13}C {^1H} NMR (126 MHz, Acetone-d_6) δ 93.1 (dd, *J* = 169.3, 2.9 Hz, 1C, C2), 91.6 (dd, *J* = 169.6, 5.9 Hz, 1C, C4), 73.8 (d, *J* = 23.6 Hz, 1C, C5), 64.5 (dd, *J* = 22.8, 1.1 Hz, 1C, C1), 63.3 (d, *J* = 5.9 Hz. 1C, C6), 33.5 (dd, *J* = 21.1, 21.1 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -188.01 (dddddd, *J* = 48.8, 25.0, 24.0, 21.9, 18.4, 3.5 Hz, 1F, F2), -189.96 (ddddd, *J* = 48.1, 34.2, 19.0, 11.2, 1.8 Hz, 1F, F4) ppm; the compound does not ionize.

Selective protection of primary hydroxyl groups of 16



1,6-Bis-*O*-pivaloyl-2,3,4-trideoxy-3-bromo-2,4-difluoro-D-allitol (22) 2,3,4-Trideoxy-3-bromo-2,4-difluoro-D-allitol **16** (32.9 mg, 0.1321 mmol, 1.0 equiv.) was diluted in pyridine (1.3 mL, 0.1 M), and PivCl (32.4 µL, 0.2642 mmol, 2.0 equiv.) was added. The reaction mixture was heated at 60 °C for 18 h. The mixture was then cooled down to room temperature, quenched with a saturated solution of $NaHCO_3$, and extracted with CH_2Cl_2.

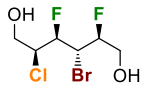
The combined organic phase was washed with 1 M HCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:9) to give **22** as a white amorphous solid (30.4 mg, 0.07285 mmol, 55 % yield): R_f = 0.47 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = −1.70 (c 0.9, MeOH); IR (ATR, diamond crystal) *v* 3485, 2974, 2876, 1732, 1396, 1283, 1149 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.17 (dddd, *J* = 46.1, 8.9, 4.6, 2.1 Hz, 1H, H2), 4.77 (ddd, *J* = 45.2, 8.4, 2.6 Hz, 1H, H4), 4.60 (dddd, *J* = 20.6, 9.1, 6.5, 2.6 Hz, 1H, H3), 4.54 (dddd, *J* = 24.3, 13.0, 1.9, 0.9 Hz, 1H, H1b), 4.45 (ddd, *J* = 29.7, 13.0, 4.6 Hz, 1H, H1a), 4.44 (ddd, *J* = 12.1, 2.1, 2.1 Hz, 1H, H6b), 4.27 (dddd, *J* = 8.4, 5.5, 4.8, 2.1 Hz, 1H, H5), 4.25 (ddd, *J* = 12.1, 4.8, 2.1 Hz, 1H, H6a), 2.85 (sbr, 1H, O*H*5), 1.24 – 1.23 (m, 18H, 2×COC(C*H*$_3$)$_3$) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 179.8 (s, 1C, *C*OC(CH$_3$)$_3$), 178.1 (s, 1C, *C*OC(CH$_3$)$_3$), 90.8 (dd, *J* = 180.9, 3.0 Hz, 1C, C4), 89.5 (dd, *J* = 179.9, 6.0 Hz, 1C, C2), 70.4 (dd, *J* = 26.6, 3.4 Hz, 1C, C5), 65.5 (d, *J* = 2.6 Hz, 1C, C6), 64.0 (dd, *J* = 20.9, 1.8 Hz, 1C, C1), 47.7 (dd, *J* = 23.1, 21.7 Hz, 1C, C3), 39.2 (s, 1C, CO*C*(CH$_3$)$_3$), 39.1 (s, 1C, CO*C*(CH$_3$)$_3$), 27.3 (s, 3C, COC(*C*H$_3$)$_3$), 27.2 (s, 3C, COC(*C*H$_3$)$_3$) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -181.72 (dddd, *J* = 46.1, 30.2, 24.1, 6.5 Hz, 1F, F2), -194.70 (ddd, *J* = 44.1, 20.6, 5.5 Hz, 1F, F4) ppm; HRMS calcd for $C_{16}H_{28}BrF_2O_5^+$ $[M + H]^+$ 417.1083 found 417.1097.



23

1,6-Bis-*O*-pivaloyl-2,3,4,5-tetradeoxy-3-bromo-5-chloro-2,4-difluoro-L-talitol (23). To a stirred solution of 1,6-bis-*O*-pivaloyl-2,3,4-trideoxy-3-bromo-2,4-difluoro-D-allitol **22** (59.3 mg, 0.1421 mmol, 1.0 equiv.) in pyridine (1.4 mL, 0.1 M) at 0 °C was added PPh_3 (372.7 mg, 1.421 mmol, 10.0 equiv.) and CCl_4 (0.14 mL, 1.421 mmol, 10.0 equiv.). The reaction mixture was stirred at room temperature for 18 h. The mixture was diluted with CH_2Cl_2 and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$, and brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:4) to give **23** as a white amorphous solid (61.1 mg, 0.1402 mmol, 99 % yield): R_f = 0.54

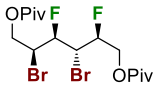
(silica, EtOAc/hexanes 1:4); $[\alpha]_D^{25}$ = 2.61 (c 1.0, $CHCl_3$); IR (ATR, diamond crystal) *v* 1972, 2874, 1718, 1283, 1157, 638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.06 (dddd, *J* = 46.3, 6.7, 3.7, 3.0 Hz, 1H, H2), 4.96 (ddd, *J* = 46.3, 9.7, 1.7 Hz, 1H, H4), 4.62 (dddd, *J* = 27.0, 7.8, 6.3, 1.7 Hz, 1H, H5), 4.54 (dddd, *J* = 17.2, 9.7, 5.3, 3.0 Hz, 1H, H3), 4.46 (ddd, *J* = 11.4, 6.4, 1.3 Hz, 1H, H6b), 4.44 (dddd, *J* = 17.4, 12.6, 6.7, 1.9 Hz, 1H, H1b), 4.36 (dddd, *J* = 26.1, 12.6, 3.7, 0.5 Hz, 1H, H1a), 4.27 (dd, *J* = 11.5, 7.7 Hz, 1H, H5), 1.23 (s, 9H, $COC(CH_3)_3$), 1.22 (s, 9H, $COC(CH_3)_3$) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 178.1 (s, 1C, $COC(CH_3)_3$), 177.7 (s, 1C, $COC(CH_3)_3$), 90.7 (dd, *J* = 182.1, 2.4 Hz, 1C, C2), 89.0 (dd, *J* = 188.2, 5.5 Hz, 1C, C4), 64.0 (dd, *J* = 25.5, 6.0 Hz, 1C, C1), 63.5 (d, *J* = 5.2 Hz, 1C, C6), 57.1 (d, *J* = 19.6 Hz, 1C, C5), 47.2 (dd, *J* = 22.6, 22.6 Hz, 1C, C3), 38.99 (s, 1C, $COC(CH_3)_3$), 38.95 (s, 1C, $COC(CH_3)_3$), 27.22 (s, 3C, $COC(CH_3)_3$), 27.21 (s, 3C, $COC(CH_3)_3$) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -189.87 (ddddd, *J* = 46.5, = 27.0, 5.3, 3.5, 1.3 Hz, 1F, F4), -192.02 (dddddd, *J* = 46.3, 27.0, 17.4, 17.4, 3.5, 2.1 Hz, 1F, F2) ppm; HRMS calcd for $C_{16}H_{30}BrClF_2NO_4^+$ $[M + NH_4]^+$ 452.1009 found 452.1026.



24

2,3,4,5-Tetradeoxy-3-bromo-5-chloro-2,4-difluoro-L-talitol (24). To a stirred solution of 1,6-bis-*O*-pivaloyl-2,3,4,5-tetradeoxy-3-bromo-5-chloro-2,4-difluoro-L-talitol **23** (57.0 mg, 0.1308 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (1.3 mL, 0.1 M) at -78 °C under an argon atmosphere was added DIBAL (0.57 M in THF, 1.8 mL, 1.046 mmol, 8.0 equiv.). The reaction mixture was stirred between -60 and -40 °C for 8 h. The mixture was quenched with EtOAc, warmed to room temperature, and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$, and brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:9 → 3:2). The resulting product was recrystallized from acetone to give **24** as a colorless crystal (22.8 mg, 0.08524 mmol, 65 % yield): R_f = 0.31 (silica, EtOAc/hexanes 1:1); $[\alpha]_D^{25}$ = 26.4 (c 0.6, MeOH); IR (ATR, diamond crystal) *v* 3350, 2951, 2885, 1462, 1248, 1047, 849 cm^{-1}; H NMR (500 MHz, Acetone-d_6) δ 5.30 (ddd, *J* = 45.7, 9.3, 2.1 Hz, 1H, H4), 4.96 (dddd, *J* = 46.4, 5.9, 4.4, 3.5 Hz,

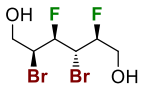
1H, H2), 4.67 (dddd, *J* = 15.8, 9.4, 7.8, 3.4 Hz, 1H, H3), 4.63 (dd, *J* = 6.1, 6.1 Hz, 1H, O*H*6), 4.53 (dddd, *J* = 26.9, 8.0, 6.0, 2.1 Hz, 1H, H5), 4.37 (dd, *J* = 6.1, 6.1 Hz, 1H, O*H*6), 4.00 – 3.80 (m, 4H, H1a, H1b, H6a, H6b) ppm; ^{13}C {^{1}H} NMR (126 MHz, Acetone-d_6) δ 94.5 (dd, *J* = 178.7, 2.0 Hz, 1C, C2), 90.0 (dd, *J* = 184.4, 5.7 Hz, 1C, C4), 63.1 (d, *J* = 5.2 Hz, 1C, C6), 62.9 (dd, *J* = 24.2, 4.2 Hz, 1C, C1), 62.1 (dd, *J* = 19.4, 1.2 Hz, 1C, C5), 49.3 (dd, *J* = 23.5, 22.3 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -191.75 (dddddd, *J* = 46.5, 23.7, 18.9, 15.8, 4.7, 4.3 Hz, 1F, F2), -193.11 (dddd, *J* = 45.6, 26.9, 7.8, 4.3 Hz, 1F, F4) ppm; HRMS calcd for $C_6H_9BrClF_2O_2^-$ [M - H]$^-$ 264.9448 found 264.9458.



25

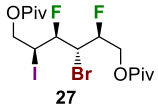
1,6-Bis-*O*-pivaloyl-2,3,4,5-tetradeoxy-3,5-dibromo-2,4-difluoro-L-talitol (25). To a stirred solution of 1,6-bis-*O*-pivaloyl-2,3,4-trideoxy-3-bromo-2,4-difluoro-D-allitol **22** (24.5 mg, 0.05871 mmol, 1.0 equiv.) in pyridine (0.6 mL, 0.1 M) at 0 °C was added PPh_3 (153.9 mg, 0.5871 mmol, 10.0 equiv.) and CBr_4 (195 mg, 0.5871 mmol, 10.0 equiv.). The reaction mixture was stirred at room temperature for 4 days. The mixture was diluted with CH_2Cl_2 and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$, and brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:4) to give **25** as a white amorphous solid (23.3 mg, 0.04852 mmol, 83 % yield): R_f = 0.66 (silica, EtOAc/hexanes 1:9); $[\alpha]_D^{25}$ = 7.05 (c 0.5, $CHCl_3$); IR (ATR, diamond crystal) *v* 2974, 1732, 1481, 1281, 1215, 1148 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (dddd, *J* = 46.3, 6.7, 3.7, 2.9 Hz, 1H, H2), 4.81 (ddd, *J* = 46.6, 9.7, 1.6 Hz, 1H, H4), 4.65 (dddd, *J* = 28.3, 8.0, 6.1, 1.6 Hz, 1H, H5), 4.54 (ddd, *J* = 11.3, 5.9, 1.1 Hz, 1H, H6b), 4.52 (dddd, *J* = 17.4, 9.7, 5.1, 3.0 Hz, 1H, H3), 4.44 (dddd, *J* = 17.4, 12.6, 6.8, 2.0 Hz, 1H, H1b), 4.36 (ddd, *J* = 26.3, 12.6, 3.7 Hz, 1H, H1a), 4.30 (dd, *J* = 11.5, 8.3 Hz, 1H, H6a), 1.23 (s, 9H, COC(C*H*$_3$)$_3$), 1.22 (s, 9H, COC(C*H*$_3$)$_3$) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.1 (s, 1C, *C*OC(CH$_3$)$_3$), 177.6 (s, 1C, *C*OC(CH$_3$)$_3$), 90.7 (dd, *J* = 182.1, 2.5 Hz, 1C, C2), 88.5 (dd, *J* = 187.6, 5.5 Hz, 1C, C4), 64.0 (dd, *J* = 25.6, 6.0 Hz, 1C, C1), 63.8 (d, *J* = 4.1 Hz, 1C, C6), 49.1 (d, *J* = 19.7 Hz, 1C C5), 48.8 (dd, *J* = 22.4, 22.4 Hz, 1C, C3), 39.00 (s, 1C,

CO*C*(CH_3)$_3$), 38.95 (s, 1C, CO*C*(CH_3)$_3$), 27.23 (s, 3C, COC(*C*H_3)$_3$), 27.22 (s, 3C, COC(*C*H_3)$_3$) ppm; 19F NMR (470 MHz, $CDCl_3$) δ -185.64 (dddd, *J* = 46.7, 28.3, 5.1, 3.5 Hz, 1F, F4), -191.86 (ddddd, *J* = 46.3, 26.0, 17.4, 17.4, 3.5 Hz, 1F, F2) ppm; HRMS calcd for $C_{16}H_{30}Br_2F_2NO_4^+$ $[M + NH_4]^+$ 496.0504 found 496.0519.



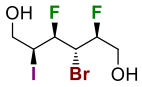
26

2,3,4,5-Tetradeoxy-3,5-dibromo-2,4-difluoro-L-talitol (26). To a stirred solution of 1,6-bis-*O*-pivaloyl-2,3,4,5-tetradeoxy-3,5-dibromo-2,4-difluoro-L-talitol **25** (23.3 mg, 0.04852 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (0.5 mL, 0.1 M) at -78 °C under an argon atmosphere was added DIBAL (0.57 M in THF, 0.68 mL, 0.3882 mmol, 8.0 equiv.). The reaction mixture was stirred between -60 and -40 °C for 6 h. The mixture was quenched with EtOAc, warmed to room temperature, and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$, and brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:9 → 3:2) to give **26** as a white amorphous solid (9.5 mg, 0.03045 mmol, 63 % yield): R_f = 0.47 (silica, EtOAc/hexanes 3:2); $[\alpha]_D^{25}$ = 28.4 (c 0.5, MeOH); IR (ATR, diamond crystal) *v* 3352, 2941, 2853, 1456, 1379, 1067, 856 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 5.18 (ddd, *J* = 45.9, 9.4, 2.0 Hz, 1H, H4), 4.96 (dddd, *J* = 46.4, 6.2, 4.3, 3.3 Hz, 1H, H2), 4.69 (ddd, *J* = 6.7, 5.6, 0.8 Hz, 1H, O*H*6), 4.64 (dddd, *J* = 16.0, 9.4, 7.5, 3.4 Hz, 1H, H3), 4.61 (dddd, *J* = 28.3, 8.7, 5.8, 2.0 Hz, 1H, H5), 4.37 (ddd, *J* = 6.0, 5.9, 1.2 Hz, 1H, O*H*1), 3.99 – 3.84 (m, 4H, H1a, H1b, H6a, H6b) ppm; ^{13}C {^{1}H} NMR (126 MHz, Acetone-d_6) δ 94.4 (dd, *J* = 178.8, 2.3 Hz, 1C, C2), 89.4 (dd, *J* = 183.9, 5.7 Hz, 1C, C4), 63.6 (d, *J* = 4.3 Hz, 1C, C6), 63.0 (dd, *J* = 24.3, 4.3 Hz, 1C, C1), 55.4 (dd, *J* = 19.6, 1.1 Hz, 1C, C5), 50.9 (dd, *J* = 22.7, 22.7 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -188.91 (dddd, *J* = 45.9, 28.3, 7.5, 4.8 Hz, 1F, F4), -191.63 (ddddd, *J* = 46.4, 24.0, 19.5 16.0, 4.9 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_9Br_2F_2O_2^-$ $[M - H]^-$ 308.8943 found 308.8942.



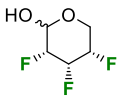
27

1,6-Bis-*O*-pivaloyl-2,3,4,5-tetradeoxy-3-bromo-2,4-difluoro-5-iodo-L-talitol (27). To a stirred solution of 1,6-bis-*O*-pivaloyl-2,3,4-trideoxy-3-bromo-2,4-difluoro-D-allitol **22** (24.2 mg, 0.05799 mmol, 1.0 equiv.) in pyridine (0.6 mL, 0.1 M) at 0 °C was added PPh_3 (136.7 mg, 0.5799 mmol, 10.0 equiv.) and I_2 (152.0 mg, 0.5799 mmol, 10.0 equiv.). The reaction mixture was stirred at room temperature for 5 days. The mixture was diluted with CH_2Cl_2 and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$, and brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:19) and repurified by flash column chromatography (silica gel, Et2O/pentane 1:25 → 1:9) to give **27** as a white amorphous solid (16.8 mg, 0.03187 mmol, 55 % yield): R_f = 0.56 (silica, EtOAc/hexanes 1:9); $[\alpha]_D^{25}$ = 5.19 (c 0.1, $CHCl_3$); IR (ATR, diamond crystal) *v* 2972, 2934, 1732, 1479, 1279, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.04 (dddd, *J* = 46.3, 6.7, 3.3, 3.3 Hz, 1H, H2), 4.75 (dddd, *J* = 30.9, 9.3, 5.8, 1.6 Hz, 1H, H5), 4.59 (ddd, *J* = 11.5, 5.8, 1.0 Hz, 1H, H6b), 4.44 (dddd, *J* = 17.5, 12.5, 6.8, 2.0 Hz, 1H, H1b), 4.40 (dddd, *J* = 17.2, 9.8, 4.6, 3.4 Hz, 1H, H3), 4.36 (ddd, *J* = 25.9, 12.5, 3.7 Hz, 1H, H1a), 4.27 (dd, *J* = 11.5, 9.2 Hz, 1H, H6a), 4.22 (ddd, *J* = 47.4, 9.7, 1.6 Hz, 1H, H4), 1.23 (s, 9H, $COC(CH_3)_3$), 1.23 (s, 9H, $COC(CH_3)_3$) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 178.1 (s, 1C, $COC(CH_3)_3$), 177.5 (s, 1C, $COC(CH_3)_3$), 90.6 (dd, *J* = 182.2, 2.4 Hz, 1C, C2), 88.5 (dd, *J* = 186.4, 5.6 Hz, 1C, C4), 65.6 (d, *J* = 2.6 Hz, 1C, C6), 64.1 (dd, *J* = 25.5, 6.0 Hz, 1C, C1), 51.8 (dd, *J* = 21.6, 21.6 Hz, 1C, C3), 39.01 (s, 1C, $COC(CH_3)_3$), 38.96 (s, 1C, $COC(CH_3)_3$), 29.3 (d, *J* = 20.1 Hz, 1C, C5), 27.26 (s, 3C, $COC(CH_3)_3$), 27.24 (s, 3C, $COC(CH_3)_3$) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -177.77 (dddd, *J* = 47.6, 30.9, 4.6, 2.9 Hz, 1F, F4), -191.38 (ddddd, *J* = 46.4, 25.9, 17.2, 17.2, 2.9 Hz, 1F, F2) ppm. HRMS calcd for $C_{16}H_{30}BrF_2INO_4^+$ $[M + NH_4]^+$ 544.0365 found 544.0369.



28

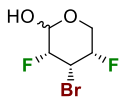
2,3,4,5-Tetradeoxy-3-bromo-2,4-difluoro-5-iodo-L-talitol (28). To a stirred solution of 1,6-bis-*O*-pivaloyl-2,3,4,5-tetradeoxy-3-bromo-2,4-difluoro-5-iodo-L-talitol **27** (15.8 mg, 0.02997 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (0.3 mL, 0.1 M) at -78 °C under an argon atmosphere was added DIBAL (0.57 M in THF, 0.42 mL, 0.2398 mmol, 8.0 equiv.). The reaction mixture was stirred between -60 and -40 °C for 6 h. The mixture was quenched with EtOAc, warmed to room temperature, and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$, and brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:9 → 3:2) to give **28** as a white amorphous solid (7.1 mg, 0.01978 mmol, 66 % yield): R_f = 0.56 (silica, EtOAc/hexanes 3:2); $[\alpha]_D^{25}$ = 19.1 (c 0.3, MeOH); IR (ATR, diamond crystal) *v* 3360, 2920, 2851, 1462, 1379, 1063, 856 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 4.95 (dddd, *J* = 46.5, 6.3, 4.4, 3.1 Hz, 1H, H2), 4.75 (ddd, *J* = 6.8, 5.4, 1.0 Hz, 1H, O*H*6), 4.70 (dddd, *J* = 31.0, 9.7, 5.5, 2.0 Hz, 1H, H5), 4.64 (ddd, *J* = 46.0, 9.5, 1.9 Hz, 1H, H4), 4.54 (dddd, *J* = 15.8, 9.5, 7.5, 3.2 Hz, 1H, H3), 4.36 (ddd, *J* = 5.7, 5.7, 1.1 Hz, 1H, O*H*1), 3.98 (ddd, *J* = 11.3, 5.4, 5.2 Hz, 1H, H6b), 4.00 – 3.86 (m, 2H, H1a, H1b), 3.86 (ddd, *J* = 11.4, 9.6, 7.0 Hz, 1H, H6a) ppm; ^{13}C {^1H} NMR (126 MHz, Acetone-d_6) δ 94.4 (dd, *J* = 178.9, 2.0 Hz, 1C, C2), 89.1 (dd, *J* = 182.5, 5.9 Hz, 1C ,C4), 65.5 (d, *J* = 3.0 Hz, 1C, C6), 63.1 (dd, *J* = 24.6, 4.3 Hz, 1C, C1), 53.8 (dd, *J* = 22.1, 22.1 Hz, 1C, C3), 37.0 (dd, *J* = 20.0, 0.6 Hz, 1C, C5) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -181.43 (dddd, *J* = 46.0, 31.4, 7.5, 5.5 Hz, 1F, F4), -191.32 (dddddd, *J* = 46.5, 23.5, 19.0, 15.8, 4.4, 1.5 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_9BrF_2IO_2^-$ $[M - H]^-$ 356.8804 found 356.8791.



29

(3*R*,4*S*,5*S*)-3,4,5-Trifluorotetrahydro-2*H*-pyran-2-ol (29). To a stirred solution of 2,3,4-trideoxy-2,3,4-trifluoro-D-allitol **14** (185.7 mg, 0.9589 mmol, 1.0 equiv.) in water (15 mL, 0.064 M) room temperature was added $NaIO_4$ (316.3 mg, 1.479 mmol, 1.5 equiv.). The

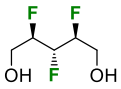
reaction mixture was stirred at room temperature for 3 h. The water was evaporated under reduced pressure, and the crude was dissolved in acetone and CH_2Cl_2, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:1) to give an anomeric mixture of **29** (α/β 1:15) as a white amorphous solid (138.3 mg, 0.8859 mmol, 90 % yield): R_f = 0.41 (silica, EtOAc/hexanes 3:2); $[\alpha]_D^{25}$ = 67.54 (c 0.4, $CHCl_3$); IR (ATR, diamond crystal) *v* 3381, 2957, 1690, 1636, 1258, 1101, 1068 cm^{-1}; only the β anomer has been attributed in ^1H NMR, ^{13}C NMR, and ^{19}F NMR; ^1H NMR (500 MHz, Acetone-d_6) δ 6.20 (dd, *J* = 5.0, 1.6 Hz, 1H, O*H*), 5.29 (dddd, *J* = 6.5, 6.0, 5.0, 3.9 Hz, 1H, H1), 5.03 (ddddd, *J* = 45.7, 25.5, 24.5, 2.8, 2.8 Hz, 1H, H3), 4.93 (dddddd, *J* = 49.1, 11.2, 4.2, 2.7, 2.7, 1.2 Hz, 1H, H4), 4.66 (ddddd, *J* = 49.4, 11.9, 3.9, 3.0, 1.2 Hz, 1H, H2), 4.10 (ddd, *J* = 29.1, 13.0, 2.2 Hz, 1H, H5a), 3.89 (dddd, *J* = 13.0, 11.1, 6.5, 4.3 Hz, 1H, H5b) ppm; ^{13}C {^1H} NMR (126 MHz, Acetone-d_6) δ 93.4 (dd, *J* = 27.5, 6.5 Hz, 1C, C1), 87.6 (ddd, *J* = 185.4, 16.2, 1.7 Hz, 1C, C2), 86.6 (ddd, *J* = 186.2, 17.0, 1.0 Hz, 1C, C4), 85.9 (ddd, *J* = 187.9, 16.4, 16.4 Hz, 1C, C3), 61.2 (dd, *J* = 22.2, 5.4 Hz, 1C, C5) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -204.60 (ddddd, *J* = 49.4, 25.5, 20.1, 13.8, 6.1 Hz, 1F, F2), -206.54 (dddddd, *J* = 49.0, 29.2, 24.0, 20.3, 12.6, 11.4 Hz, 1F, F4), -211.64 (ddddd, *J* = 45.7, 20.3, 20.3, 11.9, 11.2 Hz) ppm; HRMS calcd for $C_5H_7F_3O_2Na^+$ $[M + Na]^+$ 179.0294 found 179.0296.



30

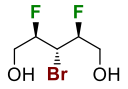
(3*R*,4*S*,5*S*)-4-Bromo-3,5-difluorotetrahydro-2*H*-pyran-2-ol (30). To a stirred solution of 2,3,4-trideoxy-3-bromo-2,4-difluoro-D-allitol **16** (337.2 mg, 1.354 mmol, 1.0 equiv.) in water (21 mL, 0.064 M) room temperature was added $NaIO_4$ (434.4 mg, 2.031 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 3 h. The water was evaporated under reduced pressure, and the crude was dissolved in acetone and CH_2Cl_2, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 2:3 → 1:1) to give an anomeric mixture of **30** (α/β 1:10) as a white amorphous solid (252.7 mg, 1.164 mmol, 85 % yield): R_f = 0.36 (silica, EtOAc/hexanes 1:1); $[\alpha]_D^{25}$ = 7.44 (c 0.3, MeOH); IR (ATR, diamond

crystal) *v* 3221, 2949, 2837, 1653, 1410, 1113, 1014 cm^{-1}; only the β anomer has been attributed in ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (dd, *J* = 6.7, 2.2 Hz, 1H, H1), 4.68 (ddddd, *J* = 46.4, 2.6, 2.4, 1.5, 1.2 Hz, 1H, H4), 4.59 (dddd, *J* = 46.6, 2.5, 2.4, 1.2 Hz, 1H, H2), 4.43 (dddd, *J* = 31.5, 29.9, 2.8, 2.8 Hz, 1H, H3), 4.20 (ddd, *J* = 37.0, 13.3, 1.5 HZ, 1H, H5a), 4.08 (ddd, *J* = 13.0, 13.0, 2.4 Hz, 1H, H5b) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 92.0 (d, *J* = 31.8 Hz, 1C, C1), 87.2 (d, *J* = 185.5 Hz, 1C, C2), 86.7 (d, *J* = 189.0 Hz, 1C, C4), 61.9 (d, *J* = 21.5 Hz, 1C, C5), 43.0 (dd, *J* = 18.6, 18.6 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -192.28 (ddddd, *J* = 46.9, 36.7, 30.0, 22.6, 12.4 Hz, 1F, F4), -193.17 (dddd, *J* = 47.1, 31.9, 22.6, 6.6 Hz, 1F, F2) ppm; HRMS calcd for $C_5H_{11}BrF_2NO^+$ $[M + NH_4]^+$ 233.9936 found 233.9941.



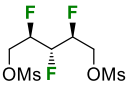
31

(2*R*,3*s*,4*S*)-2,3,4-Trifluoropentane-1,5-diol (31). (3*R*,4*S*,5*S*)-3,4,5-Trifluorotetrahydro-2*H*-pyran-2-ol **29** (126.2 mg, 0.8084 mmol, 1.0 equiv.) was reduced with $NaBH_4$ (53.5 mg, 1.415 mmol, 1.75 equiv.) in anhydrous EtOH (8 mL, 0.1 M) following the general procedure II. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 3:2) to give **31** as a colorless oil (116.9 mg, 0..7343 mmol, 91 % yield): R_f = 0.36 (silica, EtOAc/hexanes 3:2); IR (ATR, diamond crystal) *v* 3344, 2953, 1691, 1456, 1259, 1043, 868 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 5.01 (dtt, *J* = 45.8, 14.7, 14.7, 4.8, 4.8 Hz, 1H, H3), 4.85 (dddddd, *J* = 47.5, 15.9, 5.6, 4.7, 3.5, 0.8 Hz, 2H, H2, H4), 4.28 (dd, *J* = 5.9, 5.9 Hz, 2H, O*H*1, O*H*5), 3.89 (dddddd, *J* = 26.4, 12.8, 5.9, 3.3, 1.6, 0.9 Hz, 2H, H1a, H5a), 3.83 (dddddd, *J* = 30.5, 12.7, 5.8, 5.8, 2.3, 0.9 Hz, 2H, H1b, H5b) ppm; ^{13}C {^{1}H} NMR (126 MHz, Acetone-d_6) δ 92.6 (ddd, *J* = 173.7, 24.4, 4.3 Hz, 2C, C2, C4), 89.4 (dt, *J* = 174.1, 25.1, 25.1 Hz, 1C, C3), 60.9 (ddd, *J* = 22.4, 6.8 Hz, 2.7 Hz, 2C, C1, C5) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -201.42 (dddddd, *J* = 48.2, 27.0, 25.6, 14.6, 12.1, 1.4 Hz, 2F, F2, F4), -206.16 (dtttt, *J* = 45.8, 15.9, 15.9, 12.1, 12.1, 2.0, 2.0, 1.9, 1.9 Hz, 1F, F3) ppm; HRMS calcd for $C_5H_8F_3O_2^-$ $[M - H]^-$ 157.0482 found 157.0480.



32

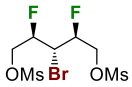
(2*R*,3*s*,4*S*)-3-Bromo-2,4-difluoropentane-1,5-diol (32). (3*R*,4*S*,5*S*)-4-Bromo-3,5-difluorotetrahydro-2*H*-pyran-2-ol **30** (252.7 mg, 1.164 mmol, 1.0 equiv.) was reduced with $NaBH_4$ (77 mg, 2.038 mmol, 1.75 equiv.) in anhydrous EtOH (12 mL, 0.1 M) following the general procedure II. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 3:7 → 1:1) to give **32** as a colorless oil (198.9 mg, 0.9081 mmol, 78 % yield): R_f = 0.46 (silica, EtOAc/hexanes 3:2); IR (ATR, diamond crystal) *v* 3325, 2943, 1636, 1425, 1234, 1030, 862 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 4.88 (dddd, *J* = 46.9, 6.0, 4.2, 4.2 Hz, 2H, H2, H4), 4.65 (tt, *J* = 11.9, 11.9, 6.0, 6.0 Hz, 1H, H3), 4.31 (dd, *J* = 5.9, 5.9 Hz, 2H, O*H*1, O*H*5), 3.94 (ddd, *J* = 26.1, 5.9, 4.2 Hz, 2H, H1b, H5b), 3.94 (ddd, *J* = 25.0, 5.9, 4.2 Hz, 2H, H1a, H5a) ppm; ^{13}C {^1H} NMR (126 MHz, Acetone-d_6) δ 94.0 (dd, *J* = 117.4, 4.8 Hz, 2C, C2, C4), 62.8 (dd, *J* = 22.4, 2.4 Hz, 2C ,C1, C5), 49.0 (t, *J* = 22.7, 22.7 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -188.09 (ddddd, *J* = 46.9, 26.1, 25.0, 11.9, 1.1 Hz, 2F, F2, F4) ppm; HRMS calcd for $C_5H_{13}BrF_2NO_2^+$ $[M + NH_4]^+$ 236.0092 found 236.0094.



33

(2*R*,3*s*,4*S*)-2,3,4-Trifluoropentane-1,5-diyl dimethanesulfonate (33). To a solution of (2*R*,3*s*,4*S*)-2,3,4-trifluoropentane-1,5-diol **31** (28.8 mg, 0.1821 mmol, 1.0 equiv.) in CH_2Cl_2 (1.8 mL, 0.1 M) at 0 °C was added Et_3N (0.13 mL, 0.9105 mmol, 5.0 equiv.). MsCl (70.4 µL, 0.9105 mmol, 5.0 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 5.5 h. The precipitate was filtered out and the organic phase was concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 2:3) to give **33** as a colorless oil (49.2 mg, 0.1565 mmol, 86 % yield): R_f = 0.45 (silica, EtOAc/hexanes 3:2); IR (NaCl) *v* 2925, 2854, 1462, 1377, 1176, 961, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.08 (ddddd, *J* = 46.9, 12.6, 5.4, 5.4, 2.9 Hz, 2H, H2, H4), 4.92 (dtt, *J* = 44.7, 13.2, 13.2, 5.3, 5.3 Hz, 1H, H3), 4.55 (dddd, *J* = 24.3, 12.4, 3.0, 1.1 Hz, 2H, H1a, H5a),

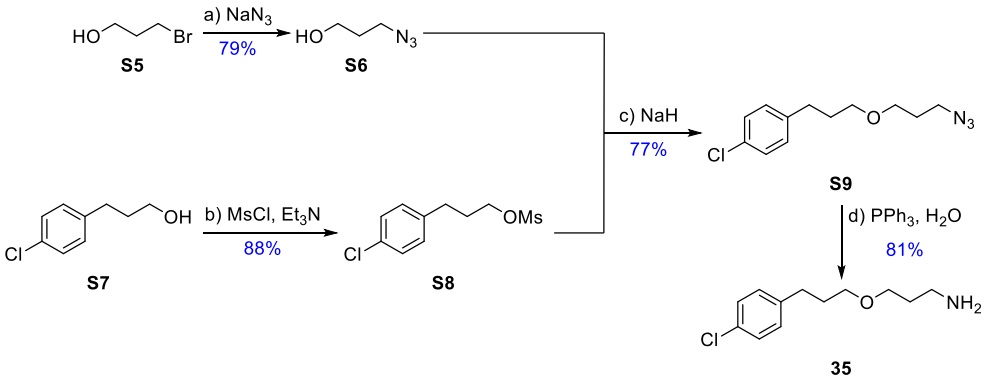
4.49 (dddd, J = 24.8, 12.4, 5.5, 1.9 Hz, 2H, H1b, H5b), 3.10 (s, 6H, 2×SO_2CH_3) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 87.7 (ddd, J = 181.3, 26.0, 4.1 Hz, 2C, C2, C4), 86.6 (dt, J = 180.2, 25.8, 25.8 Hz, 1C, C3), 66.2 (ddd, J = 23.7, 6.7, 3.5 Hz, 2C, C1, C5), 38.0 (s, 2C, 2×SO_2CH_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -201.05 (dddddd, J = 46.9, 24.8, 24.2, 13.2, 13.2, 1.9 Hz, 2F, F2, F4), -203.39 (dtttt, J = 44.8, 13.2, 13.2, 12.6, 12.6, 1.9, 1.9, 1.1, 1.1 Hz, 1F, F3) ppm; HRMS calcd for $C_7H_{17}F_3NO_6S_2^+$ $[M + NH_4]^+$ 332.0444 found 332.0451.

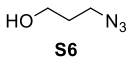


34

(2*R*,3*s*,4*S*)-3-Bromo-2,4-difluoropentane-1,5-diyl dimethanesulfonate (34). To a solution of (2*R*,3*s*,4*S*)-3-bromo-2,4-difluoropentane-1,5-diol **32** (28.1 mg, 0.1283 mmol, 1.0 equiv.) in CH_2Cl_2 (1.3 mL, 0.1 M) at 0 °C was added Et_3N (89.4 μL, 0.6415 mmol, 5.0 equiv.). MsCl (49.6 μL, 0.6415 mmol, 5.0 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 5.5 h. The precipitate was filtered out and the organic phase was concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 2:3) to give **34** as a colorless oil (47.0 mg, 0.1253 mmol, 98 % yield): R_f = 0.51 (silica, EtOAc/hexanes 3:2); IR (ATR, diamond crystal) ν 2958, 2924, 2854, 1462, 1356, 1174, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.09 (dddd, J = 46.1, 6.2, 5.0, 2.9 Hz, 2H, H2, H4), 4.62 (dddd, J = 23.9, 12.3, 5.0, 1.1 Hz, 2H, H1a, H5a), 4.58 (ddd, J = 23.3, 12.3, 3.0 Hz, 2H, H1b, H5b), 4.40 (tt, J = 12.2, 12.2, 6.3, 6.3 Hz, 1H, H3), 3.10 (s, 6H, 2×SO_2CH3) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 89.7 (dd, J = 184.4, 3.9 Hz, 2C, C2, C4), 68.1 (dd, J = 23.8, 3.8 Hz, 2C, C1, C5), 44.2 (t, J = 22.9, 22.9 Hz, 1C, C3), 38.0 (s, 2C, 2×SO_2CH3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -186.49 (dddd, J = 46.6, 23.9, 23.7, 12.1 Hz, 2F, F2, F4) ppm; HRMS calcd for $C_7H_{17}BrF_2NO_6S_2^+$ $[M + NH_4]^+$ 391.9643 found 391.9651.

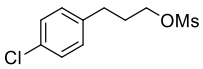
Synthesis of amine 35





S6

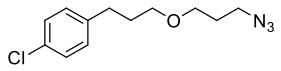
3-Azidopropan-1-ol (S6). To a solution of 3-bromopropan-1-ol **S5** (1.0099 g, 7.266 mmol, 1.0 equiv.) in water (7.2 mL, 1.0 M) was added NaN_3 (945 mg, 14.54 mmol, 2.0 equiv.). The mixture was stirred at 60 °C for 3 days. After cooling down to room temperature extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, Et_2O/pentane 1:1) to give **S2** as a colorless oil (578.4 mg, 5.723 mmol, 79 % yield). The spectroscopic data derived from compound **S2** match those reported in the literature.[3]



S8

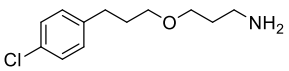
3-(4-Chlorophenyl)propyl methanesulfonate (S8). To a solution of 3-(4-chlorophenyl)propan-1-ol **S7** (250 mg, 1.465 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (4.4 mL, 0.33 M) at 0 °C was added Et_3N (0.27 mL, 1.949 mmol, 1.33 equiv.) and MsCl (0.14 mL, 1.758 mmol, 1.2 equiv.). The mixture was stirred at 0 °C for 30 min and room temperature for 3 h. The reaction mixture was then diluted with CH_2Cl_2, and the organic phase was washed with water, 1 M HCl, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:5 → 3:7) to give **S4** as a colorless oil

(320.3 mg, 1.288 mmol, 88 % yield). The spectroscopic data derived from compound **S4** match those reported in the literature.[4]



S9

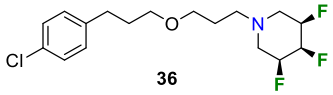
1-(3-(3-Azidopropoxy)propyl)-4-chlorobenzene (S9). To a solution of 3-azidopropan-1-ol **S6** (106.2 mg, 1.051 mmol, 1.0 equiv.) in *N*,*N*-dimethylacetamide (3.5 mL, 0.3 M) was added 60 % NaH in mineral oil (126 mg, 3.153 mmol, 3 equiv.). The mixture was heated at 50 °C for 1 h. The reaction mixture was cooled to room temperature and a solution of 3-(4-chlorophenyl)propyl methanesulfonate **S8** (300 mg, 1.206 mmol, 1.15 equiv.) in *N*,*N*-dimethylacetamide (1.8 mL) was added. The mixture was stirred at room temperature for 5 h, quenched with a mixture of water/brine (1:1), then extracted with toluene. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash chromatography (silica gel, Et_2O/pentane 0:1 → 3:17) to give **S5** as a colorless oil (205.5 mg, 0.8099 mmol, 77 % yield): R_f = 0.53 (silica, Et_2O/pentane 1:9); IR (NaCl) ν 3027, 2945, 2865, 2097, 1492, 1119, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.3 Hz, 2H, $H_{o\text{-}Cl}$), 7.11 (d, J = 8.5 Hz, 2H, $H_{m\text{-}Cl}$), 3.48 (t, J = 6.0, 6.0 Hz, 2H, -O-CH_2-CH_2-CH_2-N_3), 3.41 (t, J = 6.4, 6.4 Hz, 2H, Ar-CH_2-CH_2-CH_2-O-), 3.40 (t, J = 6.5, 6.5 Hz, 2H, -O-CH_2-CH_2-CH_2-N_3), 2.66 (t, J = 7.5, 7.5 Hz, 2H, Ar-CH_2-CH_2-CH_2-O-), 1.86 (tt, J = 7.5, 7.5, 6.4, 6.4 Hz, 2H, Ar-CH_2-CH_2-CH_2-O-), 1.85 (tt, J = 6.5, 6.5, 6.0, 6.0 Hz, 2H, -O-CH_2-CH_2-CH_2-N_3) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 140.5 (s, 1C, $C_{p\text{-}Cl}$), 131.6 (s, 1C, *C*-Cl), 129.9 (s, 2C, $C_{m\text{-}Cl}$), 128.6 (s, 2C, $C_{o\text{-}Cl}$), 70.0 (s, 1C, Ar-CH_2-CH_2-*C*H_2-O-), 67.5 (s, 1C, -O-*C*H_2-CH_2-CH_2-N_3), 48.7 (s, 1C, -O-CH_2-CH_2-*C*H_2-N_3), 31.8 (s, 1C, Ar-*C*H_2-CH_2-CH_2-O-), 31.3 (s, 1C, Ar-CH_2-*C*H_2-CH_2-O-), 29.4 (s, 1C, -O-CH_2-*C*H_2-CH_2-N_3) ppm; HRMS calcd for $C_{12}H_{17}ClN_3O^+$ $[M + H]^+$ 254.1055 found 254.1058.



35

3-(3-(4-Chlorophenyl)propoxy)propan-1-amine (35). To a solution of 1-(3-(3-azidopropoxy)propyl)-4-chlorobenzene **S5** (145.3 mg, 0.5727 mmol, 1.0 equiv.) in dry THF

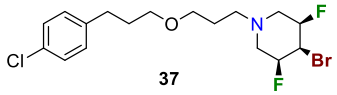
(5.7 mL, 0.1 M) was added PPh_3 (225.3 mg, 0.8590 mmol, 1.5 equiv.). After stirring at room temperature for 2 h, water (0.27 mL, 14.60 mmol, 25.5 equiv.) was added, and the mixture was stirred for 68 h at room temperature. The reaction mixture was evaporated to dryness and the obtained crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:19 → 1:4) to give **35** as a colorless oil (105.1 mg, 0.4615 mmol, 81 % yield): R_f = 0.40 (silica, MeOH/CH_2Cl_2 1:5); IR (NaCl) *v* 3406, 2927, 2866, 1492, 1112, 1015, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H, $H_{o\text{-}Cl}$), 7.11 (d, *J* = 8.5 Hz, 2H, $H_{m\text{-}Cl}$), 3.49 (t, *J* = 6.1, 6.1 Hz, 2H, -O-C*H*$_2$-CH_2-CH_2-NH_2), 3.40 (t, *J* = 6.4, 6.4 Hz, 2H, Ar-CH_2-CH_2-C*H*$_2$-O-), 3.15 – 2.94 (m, 2H, N*H*$_2$), 2.89 (t, *J* = 6.8, 6.7 Hz, 2H, -O-CH_2-CH_2-C*H*$_2$-NH_2), 2.64 (t, *J* = 7.9, 7.5 Hz, 2H, Ar-C*H*$_2$-CH_2-CH_2-O-), 1.89 – 1.82 (m, 2H, Ar-CH_2-C*H*$_2$-CH_2-O-), 1.81 – 1.76 (m, 2H, -O-CH_2-C*H*$_2$-CH_2-NH_2) ppm; ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 140.5 (s, 1C, $C_{p\text{-}Cl}$), 131.6 (s, 1C, *C*-Cl), 129.9 (s, 2C, $C_{m\text{-}Cl}$), 128.5 (s, 2C, $C_{o\text{-}Cl}$), 70.1 (s, 1C, Ar-CH_2-CH_2-*C*H_2-O-), 69.1 (s, 1C, -O-*C*H_2-CH_2-CH_2-NH_2), 39.6 (s, 1C, -O-CH_2-CH_2-*C*H_2-NH_2), 32.1 (s, 1C, -O-CH_2-*C*H_2-CH_2-NH_2), 31.8 (s, 1C, Ar-*C*H_2-CH_2-CH_2-O-), 31.3 (s, 1C, Ar-CH_2-*C*H_2-CH_2-O-) ppm; HRMS calcd for $C_{12}H_{19}ClNO^+$ $[M + H]^+$ 228.1150 found 228.1155.



36

(3*R*, 4*s*, 5*S*)-1-(3-(3-(4-Chlorophenyl)propoxy)propyl)-3,4,5-trifluoropiperidine (36). To a solution of (2*R*,3*s*,4*S*)-2,3,4-trifluoropentane-1,5-diyl dimethanesulfonate **33** (23.5 mg, 0.07477 mmol, 1.0 equiv.) in anhydrous EtOH (0.75 mL, 0.1 M) in a sealed tube was added 3-(3-(4-chlorophenyl)propoxy)propan-1-amine **35** (39.6 mg, 0.1739 mmol, 2.3 equiv.). The reaction mixture was stirred at 90 °C for 17 h. After being cooled down to room temperature, the volatiles were evaporated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:9 → 1:1) which permitted to recover 11.5 mg of **33**. The unclean fraction containing the desired product was then purified by flash column chromatography (silica gel, acetone/toluene 1:99 → 1:49) to give **35** as a colorless oil (5.0 mg, 0.01429 mmol, 19 % yield, 37 % yield brsm): R_f = 0.38 (silica, EtOAc/hexanes 2:3); IR (NaCl) *v* 2927, 2851, 1743, 1491, 1460, 1118, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.1 Hz, 2H, $H_{o\text{-}Cl}$), 7.11 (d,

J = 8.0 Hz, 2H, $H_{m\text{-Cl}}$), 5.11 (dbr, *J* = 55.2 Hz, 1H, -CHF-C*H*F-CHF-), 4.63 (sbr, 2H, -N-CH_2-C*H*F-), 3.44 (t, *J* = 6.2, 6.2 Hz, 2H, -O-C*H*$_2$-CH_2-CH_2-N-), 3.39 (t, *J* = 6.3, 6.3 Hz, 2H, Ar-CH_2-CH_2-C*H*$_2$-O-), 3.09 – 2.85 (m, 2H, -O-CH_2-CH_2-C*H*$_2$-N-), 2.80 – 2.47 (m, 4H, 2×-N-C*H*$_2$-CHF-), 2.65 (t, *J* = 7.7, 7.7 Hz, 2H, Ar-C*H*$_2$-CH_2-CH_2-O-), 1.85 (tt, *J* = 6.8, 6.8, 6.8, 6.8 Hz, 2H, Ar-CH_2-C*H*$_2$-CH_2-O-), 1.95 – 1.70 (m, 2H, -O-CH_2-C*H*$_2$-CH_2-N-) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.4 (s, 1C, $C_{p\text{-Cl}}$), 131.7 (s, 1C, C-Cl), 129.9 (s, 2C, $C_{m\text{-Cl}}$), 128.6 (s, 2C, $C_{o\text{-Cl}}$), 87.8 (s, 1C, -CHF-*C*HF-CHF-), 86.4 (s, 2C, 2×-N-CH_2-*C*HF-), 70.1 (s, 1C, Ar-CH_2-CH_2-*C*H_2-O-), 68.5 (s, 1C, O-*C*H_2-CH_2-CH_2-N-), 54.3 (s, 1C, -N-*C*H_2-CHF-), 50.2 (s, 1C, -O-CH_2-CH_2-*C*H_2-N-), 31.9 (s, 1C, Ar-*C*H_2-CH_2-CH_2-O-), 31.2 (s, 1C, Ar-CH_2-*C*H_2-CH_2-O-), 27.0 (s, 1C, -O-CH_2-*C*H_2-CH_2-N-) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -199.48 – -200.77 (m, 3F) ppm; HRMS calcd for $C_{17}H_{24}ClF_3NO^+$ $[M + H]^+$ 350.1493 found 350.1508.



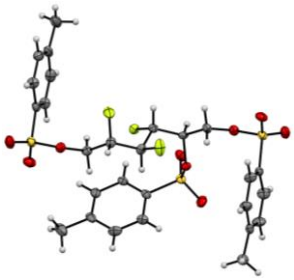
37

(3*R*, 4*s*, 5*S*)-4-Bromo-1-(3-(3-(4-chlorophenyl)propoxy)propyl)-3,5-difluoropiperidine (37). To a solution of (2*R*,3*s*,4*S*)-3-bromo-2,4-difluoropentane-1,5-diyl dimethanesulfonate **34** (25.5 mg, 0.06796 mmol, 1.0 equiv.) in anhydrous EtOH (0.7 mL, 0.1 M) in a sealed tube was added 3-(3-(4-chlorophenyl)propoxy)propan-1-amine **35** (38.7 mg, 0.1699 mmol, 2.5 equiv.). The reaction mixture was stirred at 90 °C for 24 h. After being cooled down to room temperature, the volatiles were evaporated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:9 → 1:1) which permitted to recover 10.7 mg of **34** and 5.0 mg of an elimination product. The unclean fraction containing the desired product was then purified by flash column chromatography (silica gel, acetone/toluene 1:99 → 1:49) to give **36** as a colorless oil (5.0 mg, 0.01217 mmol, 18 % yield, 31 % yield brsm, 78 % purity): R_f = 0.40 (silica, acetone/toluene 1:9); IR (NaCl) *v* 2925, 2854, 1744, 1492, 1463, 1116, 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H, $H_{o\text{-Cl}}$), 7.11 (d, *J* = 8.5 Hz, 2H, $H_{m\text{-Cl}}$), 4.84 – 4.51 (m, 3H, 2×C*H*F, C*H*Br), 3.44 (t, *J* = 6.2, 6.2 Hz, 2H, -O-C*H*$_2$-CH_2-CH_2-N-), 3.39 (t, *J* = 6.3, 6.3 Hz, 2H, Ar-CH_2-CH_2-C*H*$_2$-O-), 3.01 – 2.68 (m, 4H, 2×N-C*H*$_2$-CHF), 2.65 (dd, *J* = 8.5, 6.8 Hz, 2H, Ar-C*H*$_2$-CH_2-CH_2-O-), 1.89 – 1.81 (m, 2H Ar-CH_2-C*H*$_2$-

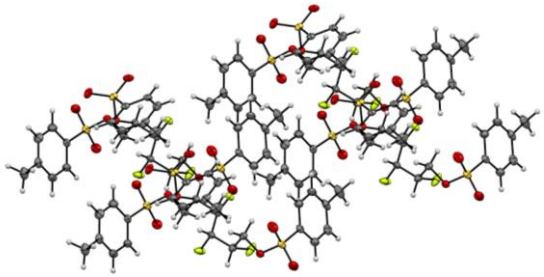
CH_2-O-), 1.81 – 1.74 (m, 2H, -O-CH_2-C*H*$_2$-CH_2-N-), 1.72 – 1.65 (m, 2H, -O-CH_2-CH_2-C*H*$_2$-N-) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.5 (s, 1C, $C_{p\text{-Cl}}$), 131.7 (s, 1C, C-Cl), 129.9 (s, 2C, $C_{m\text{-Cl}}$), 128.6 (s, 2C, $C_{o\text{-Cl}}$), 86.2 (s, 2C, 2×*C*HF), 84.9 (s, 1C, *C*HBr), 70.1 (s, 1C, Ar-CH_2-CH_2-*C*H_2-O-), 68.6 (s, 1C, O-*C*H_2-CH_2-CH_2-N-), 68.3 (s, 2C, N-*C*H_2), 54.4 (s, 1C, O-CH_2-*C*H_2-CH_2-N-), 52.6 (s, 1C, O-CH_2-CH_2-*C*H_2-N-), 31.8 (s, 1C, Ar-*C*H_2-CH_2-CH_2-O-), 31.2 (s, 1C, Ar-CH_2-*C*H_2-CH_2-O-) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -186.72 – -188.37 (m, 2F) ppm; HRMS calcd for $C_{17}H_{24}BrClF_2NO^+$ $[M + H]^+$ 410.0692 found 410.0697.

II. Crystal structure determination

Table S1. Crystal data and structure refinement for compound tritosyl-**14**



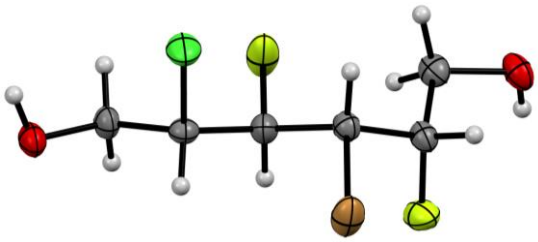
X-ray-derived ORTEP



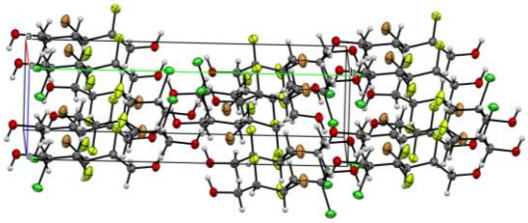
Extended packing arrangement

Empirical formula	$C_{27}H_{29}F_3O_9S_3$
Formula weight	650.38
Temperature [K]	100
Crystal system	monoclinic
Space group (number)	$P2_1$ (4)
a [Å]	11.1881(7)
b [Å]	9.6923(6)
c [Å]	27.0368(16)
α [°]	90
β [°]	94.553(3)
γ [°]	90
Volume [Å^3]	2922.6(3)
Z	4
ρ_{calc} [gcm^{-3}]	1.479
μ [mm^{-1}]	2.954
F(000)	1352
Crystal size [mm^3]	0.157×0.091×0.085
Crystal colour	clear light colourless
Crystal shape	Block
Radiation	Cu K_α (λ=1.54178 Å)
2Θ range [°]	3.28 to 140.57 (0.82 Å)
Index ranges	-13 ≤ h ≤ 13 -10 ≤ k ≤ 11 -32 ≤ l ≤ 32
Reflections collected	35261
Independent reflections	9642 R_{int} = 0.0351 R_{sigma} = 0.0329
Completeness to θ = 67.679°	99.3 %
Data / Restraints / Parameters	9642 / 1 / 763
Goodness-of-fit on F^2	1.039
Final *R* indexes	R_1 = 0.0494
[$I \geq 2\sigma(I)$]	wR_2 = 0.1288
Final *R* indexes	R_1 = 0.0517
[all data]	wR_2 = 0.1309
Largest peak/hole [eÅ^{-3}]	0.99/−0.37
Flack X parameter	0.000(13)

Table S2. Crystal data and structure refinement for compound **24**



X-ray-derived ORTEP



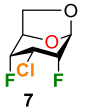
Extended packing arrangement

Empirical formula	$C_6H_{10}BrClF_2O_2$
Formula weight	267.50
Temperature [K]	150
Crystal system	orthorhombic
Space group (number)	$P2_12_12$ (18)
a [Å]	10.7019(6)
b [Å]	17.3028(10)
c [Å]	4.9473(3)
α [°]	90
β [°]	90
γ [°]	90
Volume [Å^3]	916.11(9)
Z	4
ρ_{calc} [gcm^{-3}]	1.939
μ [mm^{-1}]	5.839
F(000)	528
Crystal size [mm^3]	0.03×0.07×0.21
Crystal colour	clear light colourless
Crystal shape	plate
Radiation	Ga K_α (λ=1.34139 Å)
2Θ range [°]	8.45 to 112.92 (0.80 Å)
Index ranges	-12 ≤ h ≤ 13 -20 ≤ k ≤ 21 -5 ≤ l ≤ 5
Reflections collected	8226
Independent reflections	1770 R_{int} = 0.0504 R_{sigma} = 0.0391
Completeness to θ = 53.594°	100.0 %
Data / Restraints / Parameters	1770 / 0 / 112
Goodness-of-fit on F^2	1.093
Final *R* indexes	R_1 = 0.0299
[$I \geq 2\sigma(I)$]	wR_2 = 0.0676
Final *R* indexes	R_1 = 0.0367
[all data]	wR_2 = 0.0699
Largest peak/hole [eÅ^{-3}]	0.74/−0.40
Flack X parameter	0.09(5)

III. NMR spectra of compounds

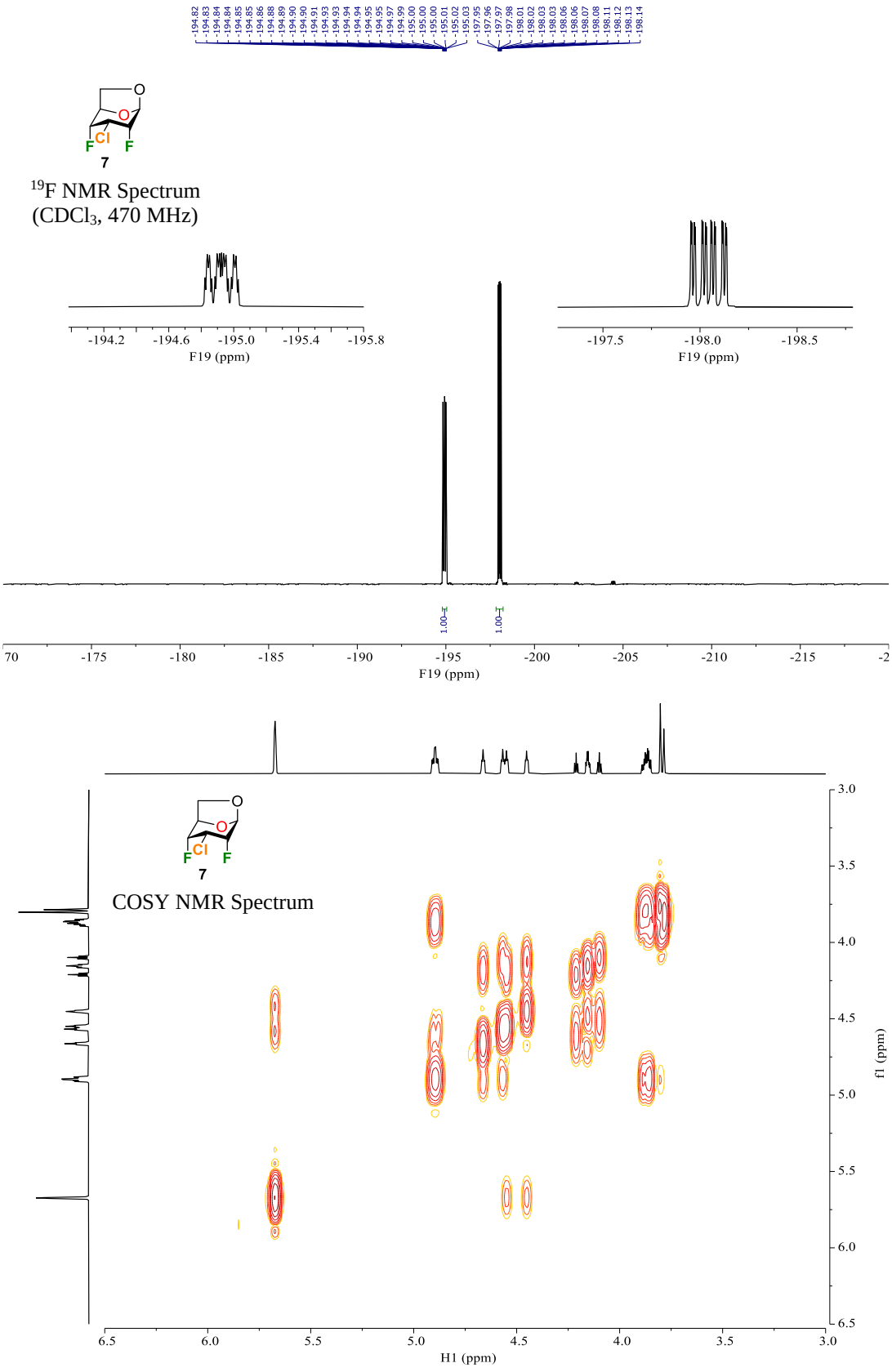
7

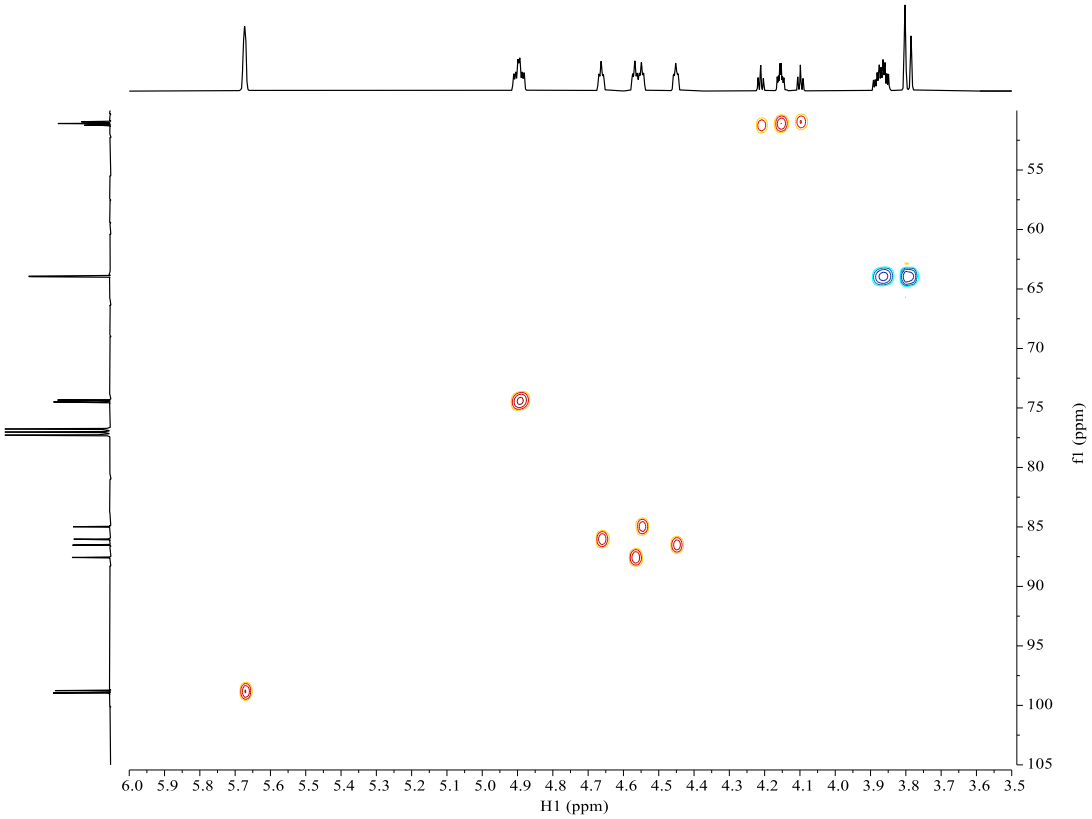
^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)

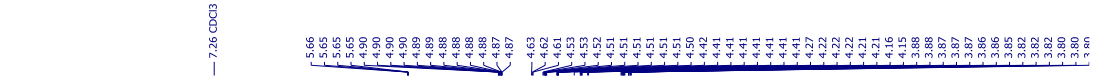


7

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

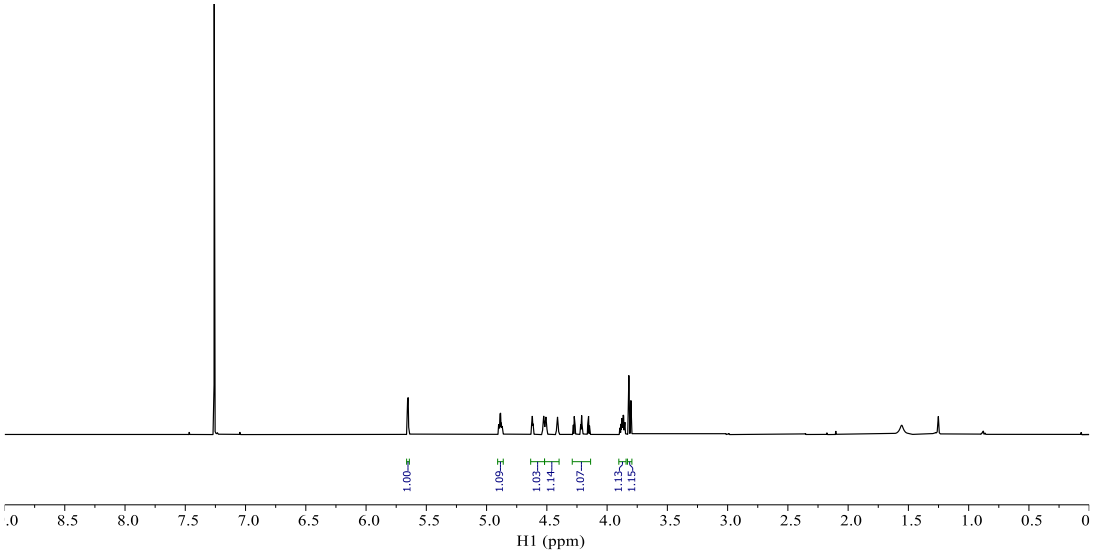

7
19F NMR Spectrum
(CDCl3, 470 MHz)
F19 (ppm)
7
COSY NMR Spectrum
H1 (ppm)
f1 (ppm)

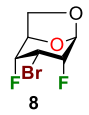




8

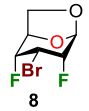
^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)





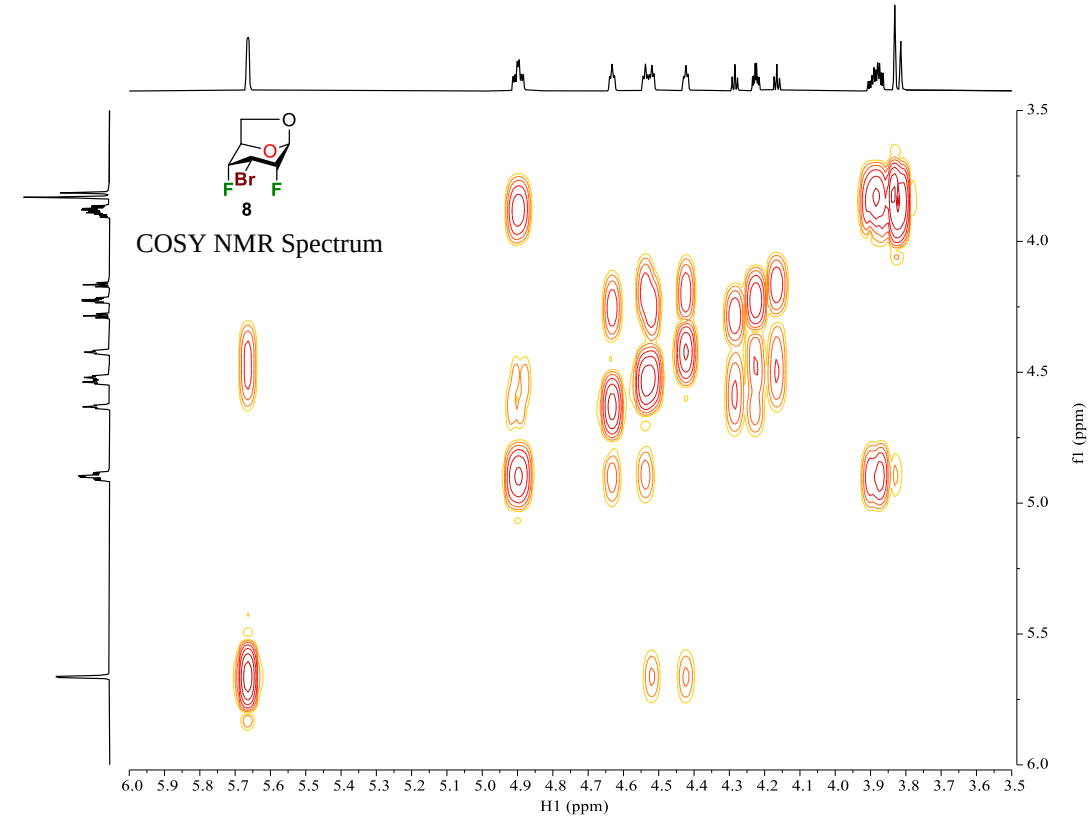
8

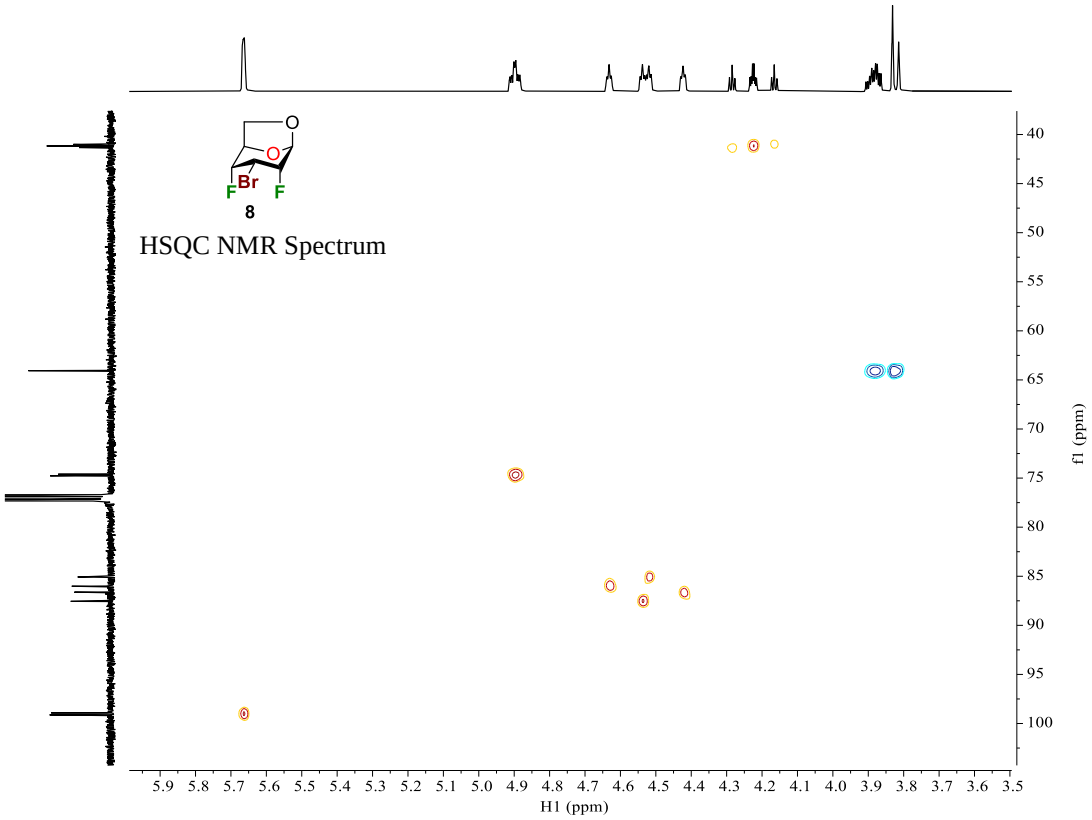
^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)

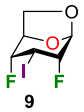


8

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

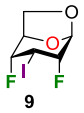

O
O
F
Br
F
8
COSY NMR Spectrum
3.5
4.0
4.5
5.0
5.5
6.0
f1 (ppm)
6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5
H1 (ppm)


O
O
F
Br
F
8
HSQC NMR Spectrum
40
45
50
55
60
65
70
75
80
85
90
95
100
f1 (ppm)
5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5
H1 (ppm)



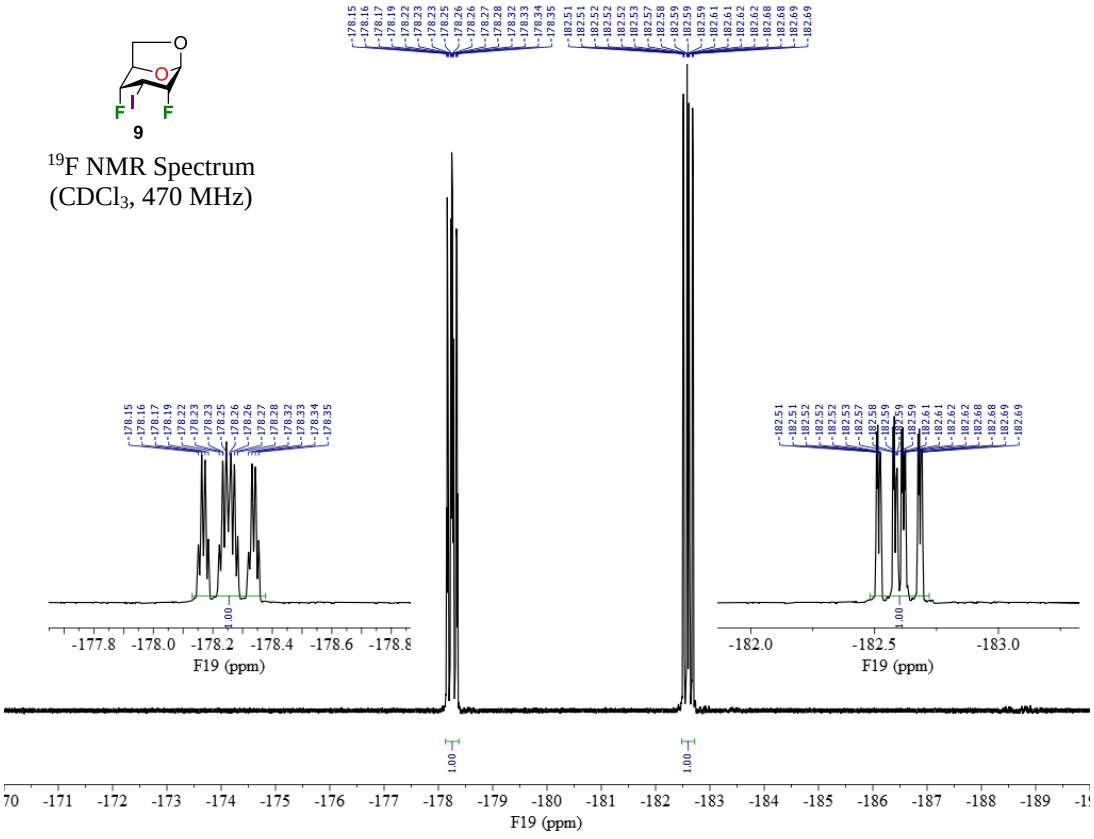
9

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

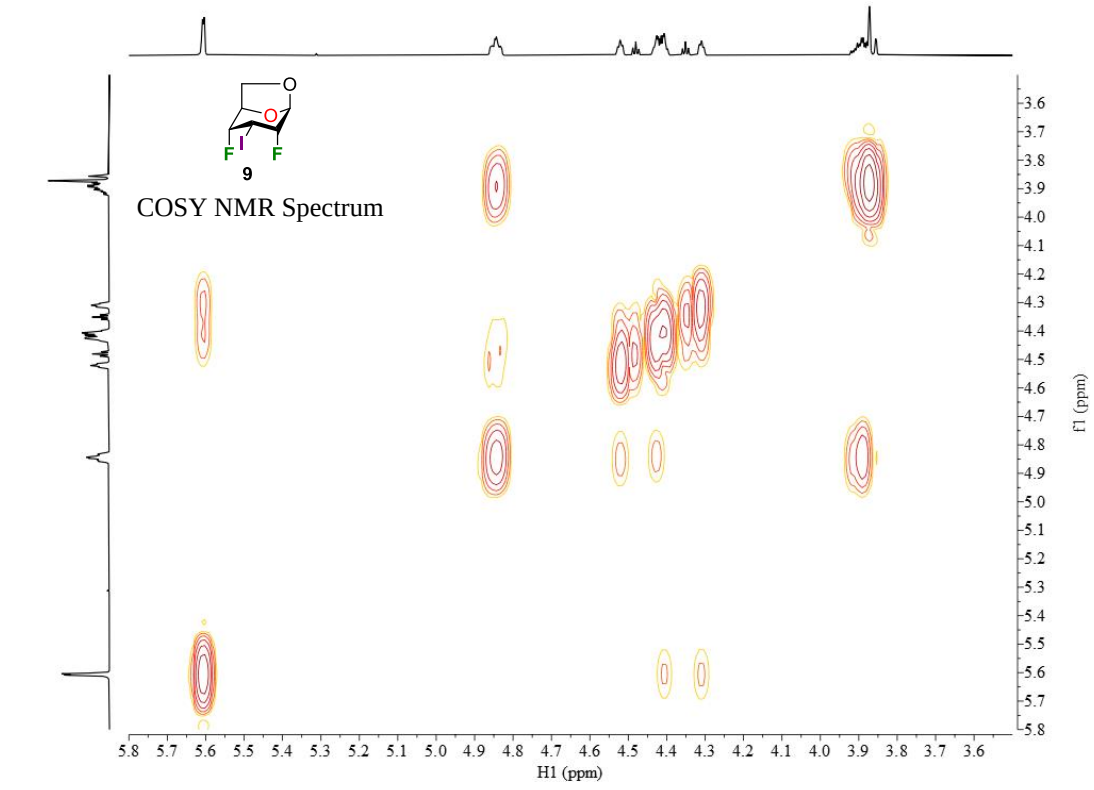


9

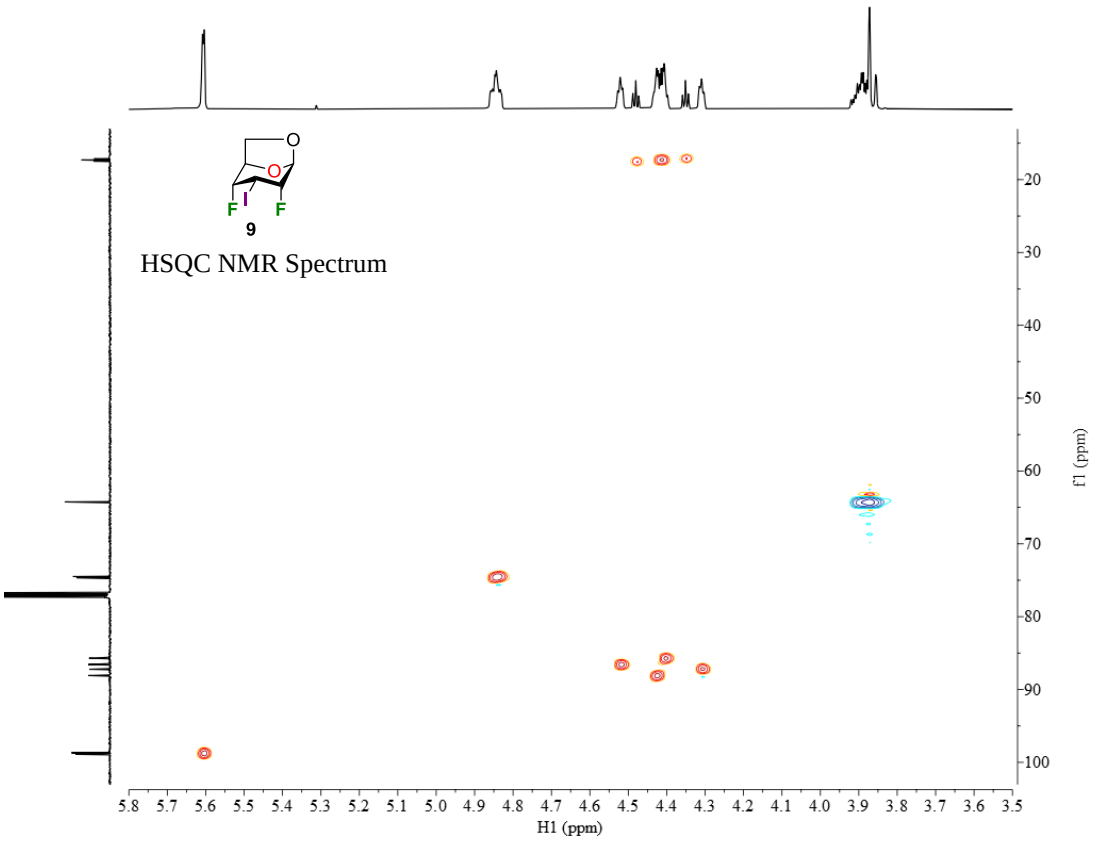
^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)



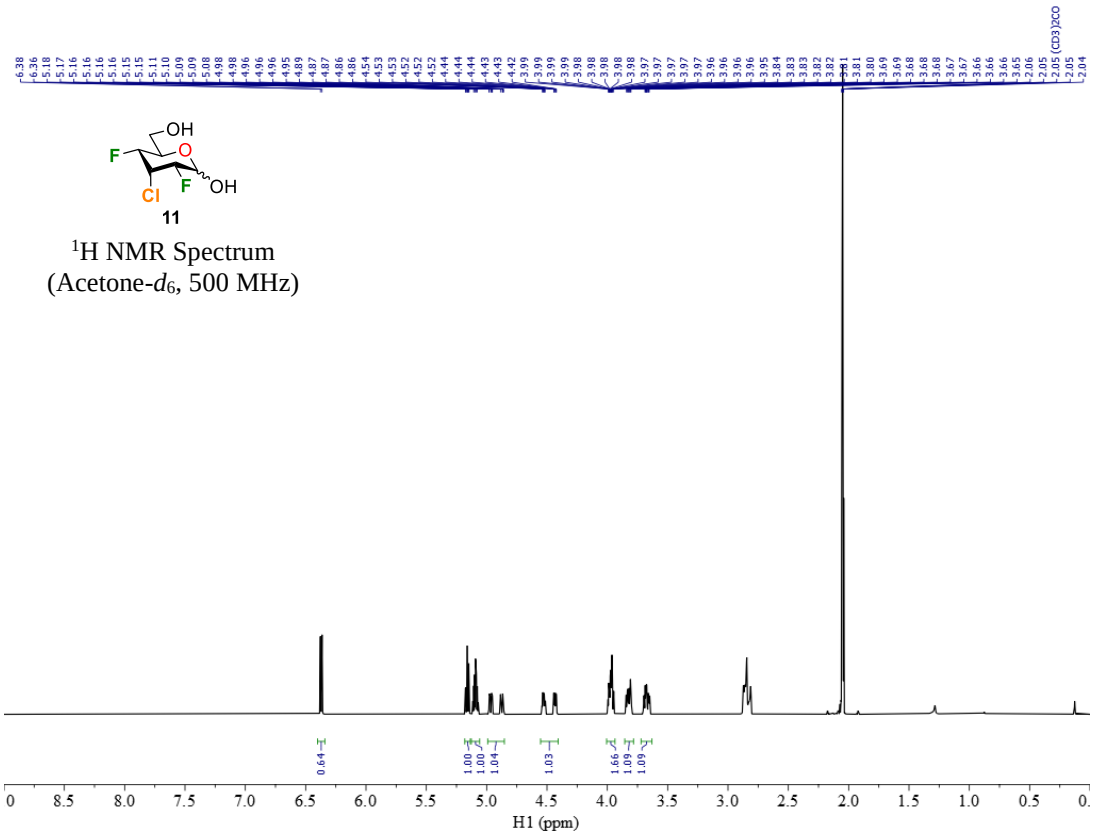
^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)



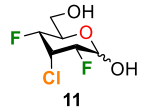
COSY NMR Spectrum



HSQC NMR Spectrum

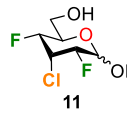


^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)



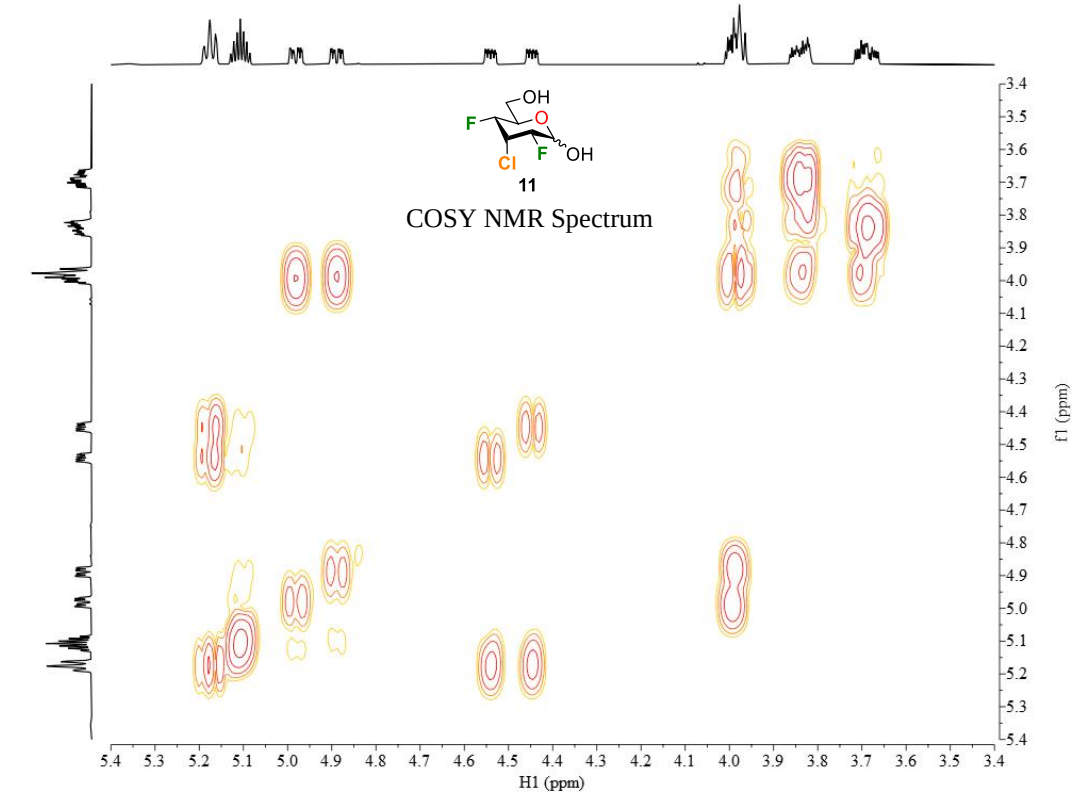
11

^{13}C NMR Spectrum
(Acetone-d_6, 500 MHz)

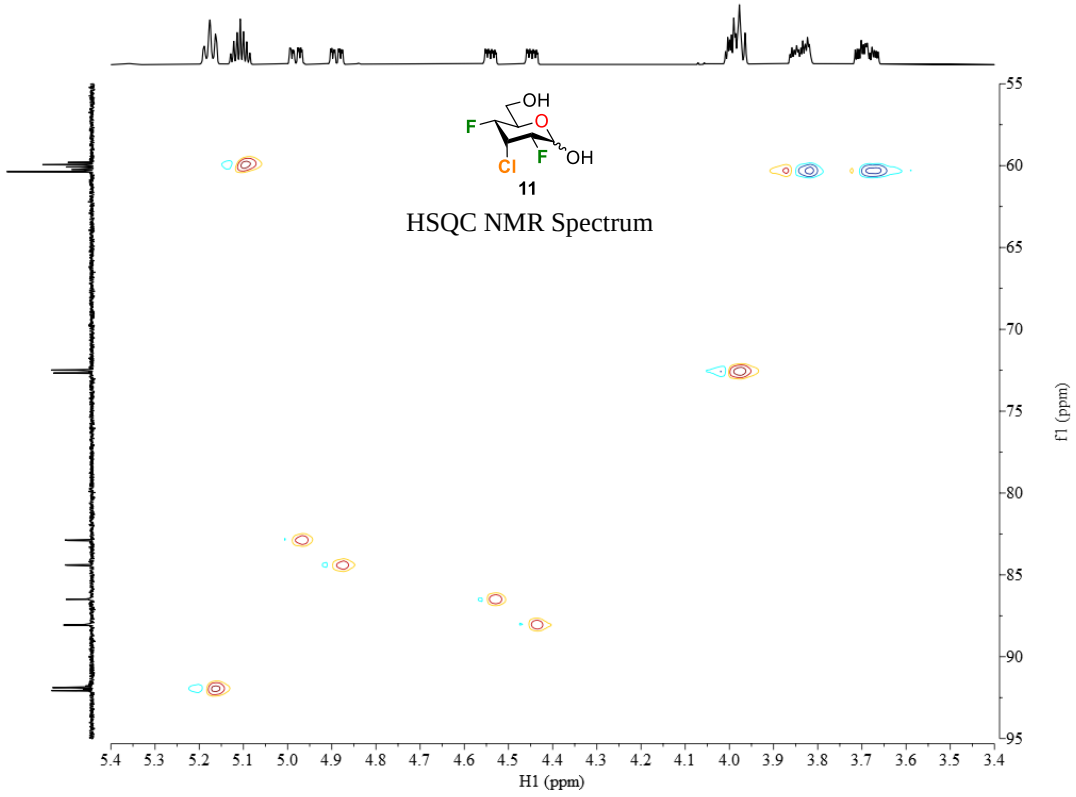


11

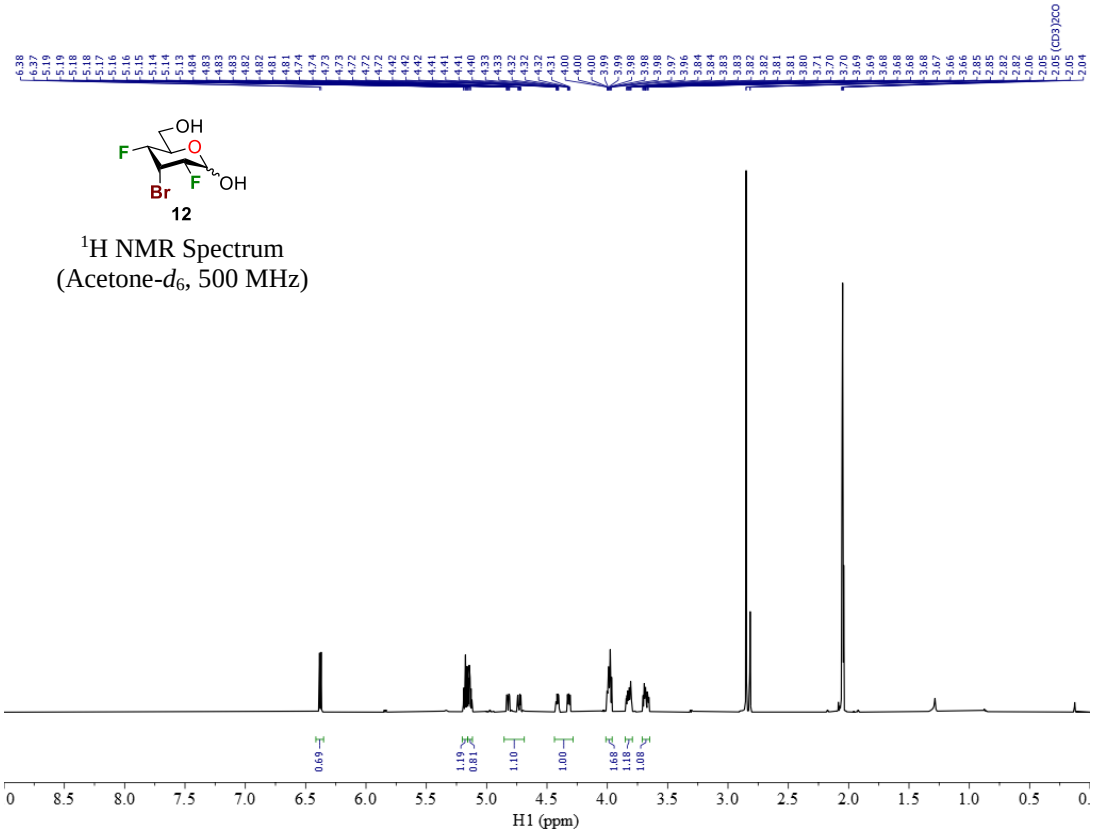
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



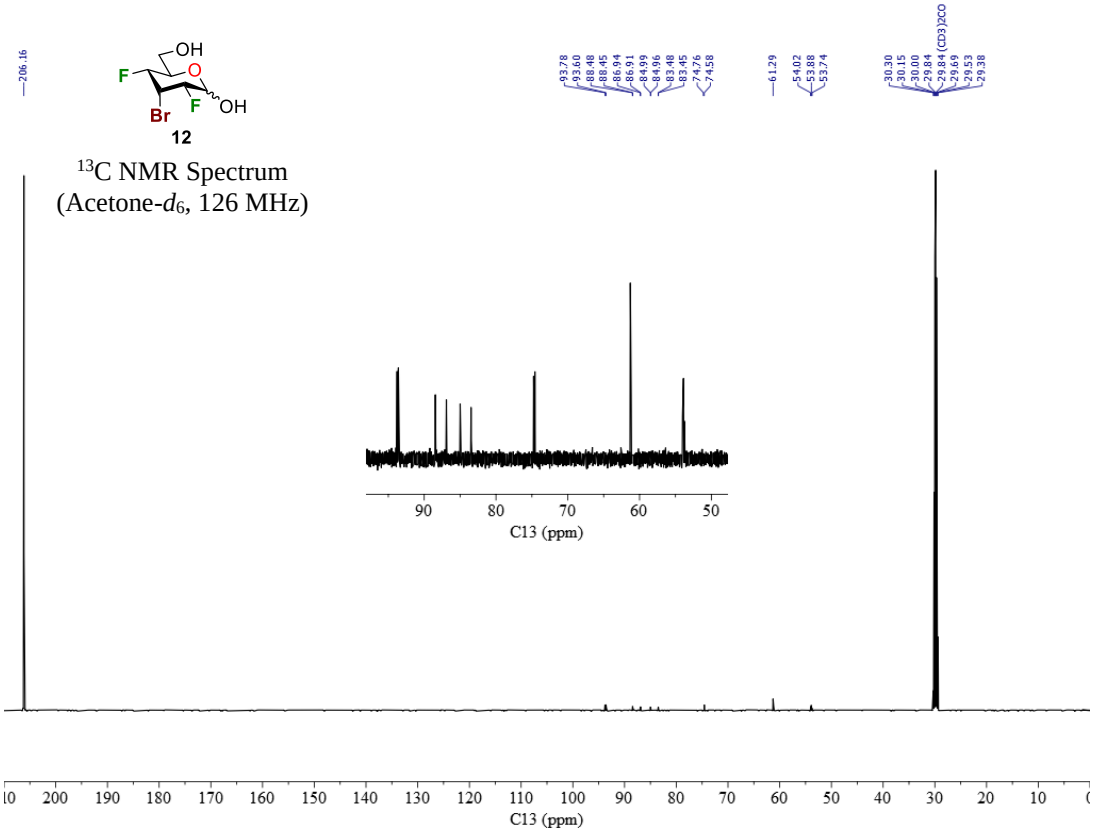
COSY NMR Spectrum



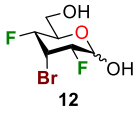
HSQC NMR Spectrum



^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)

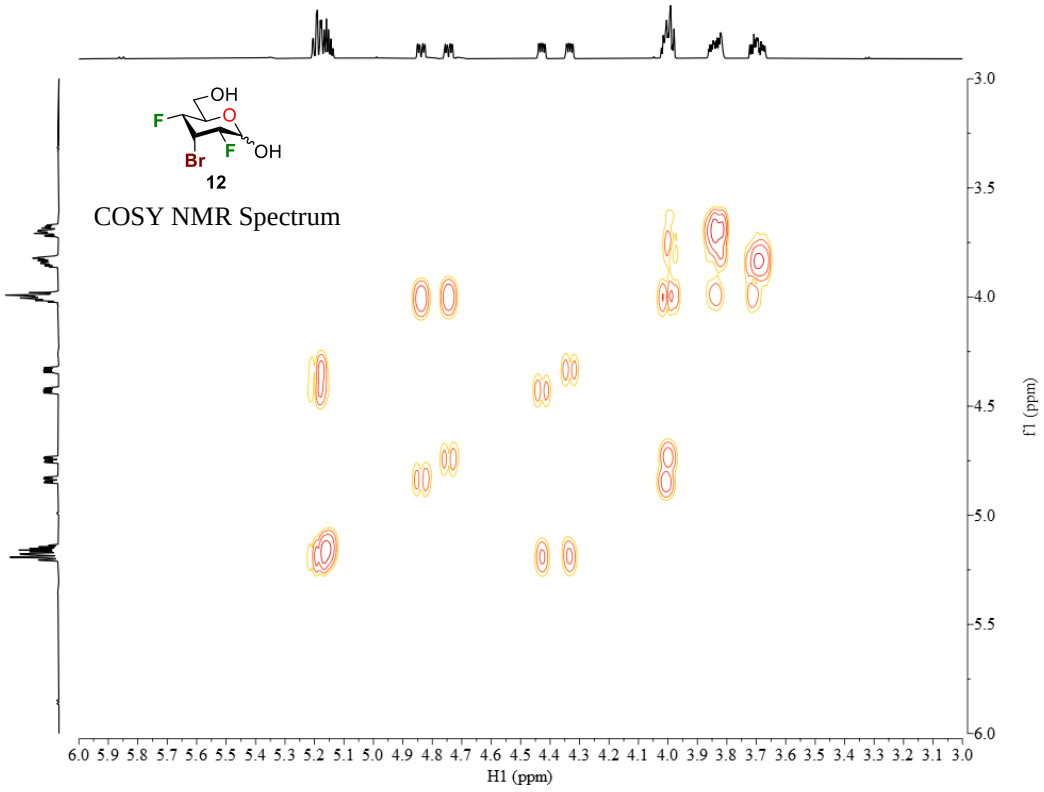


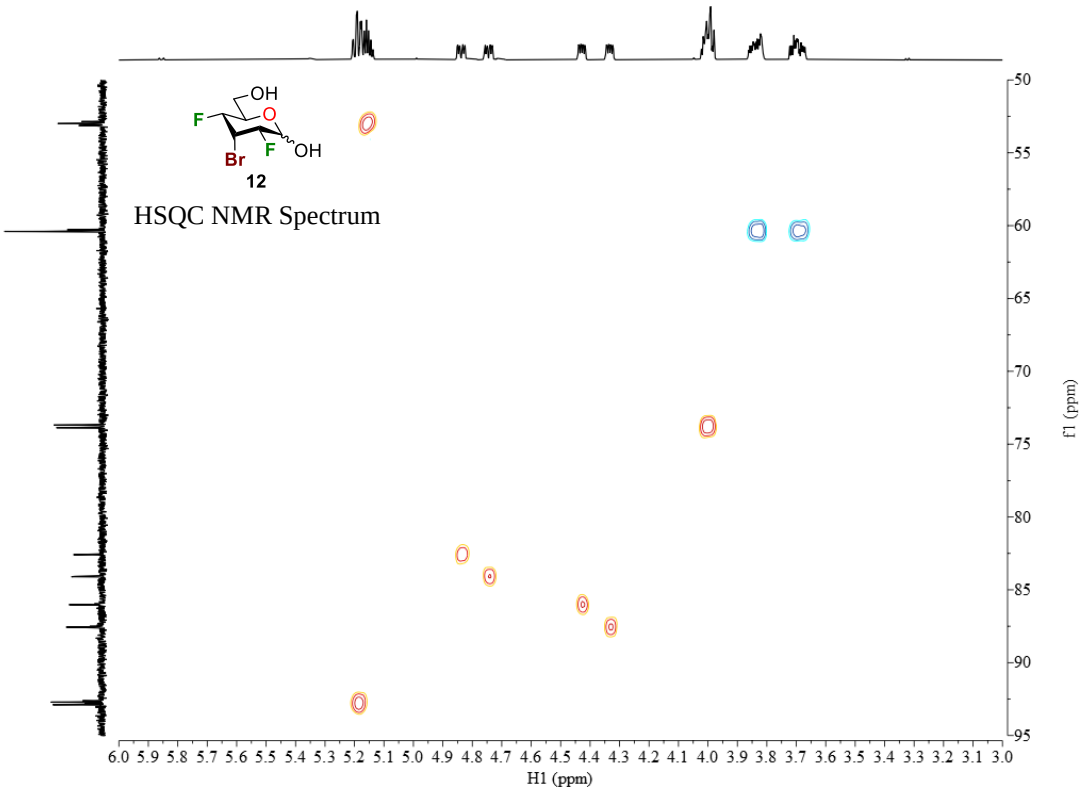
^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)

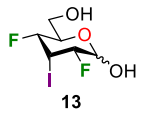


12

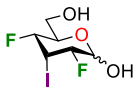
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)





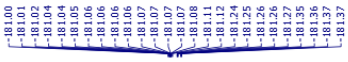


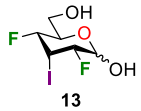
^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)



13

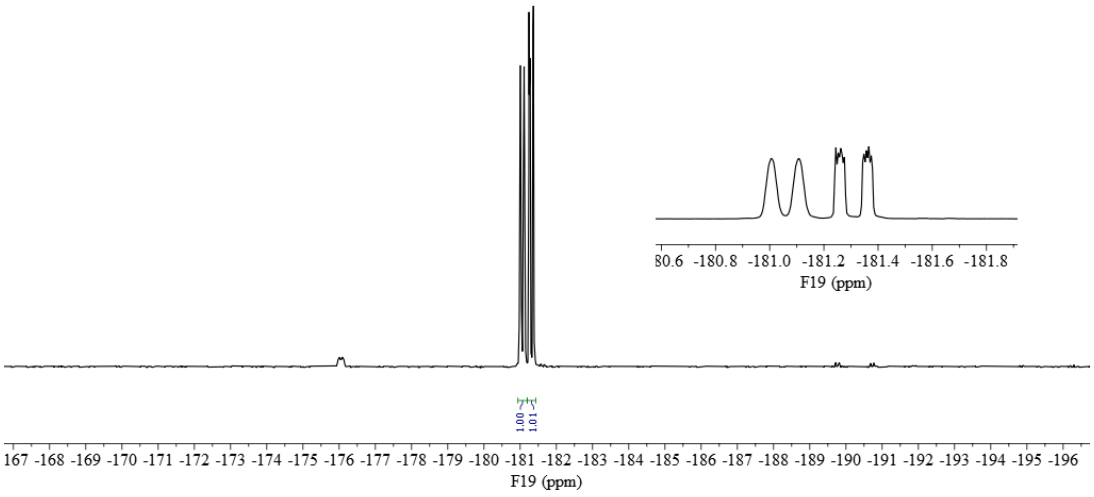
^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)

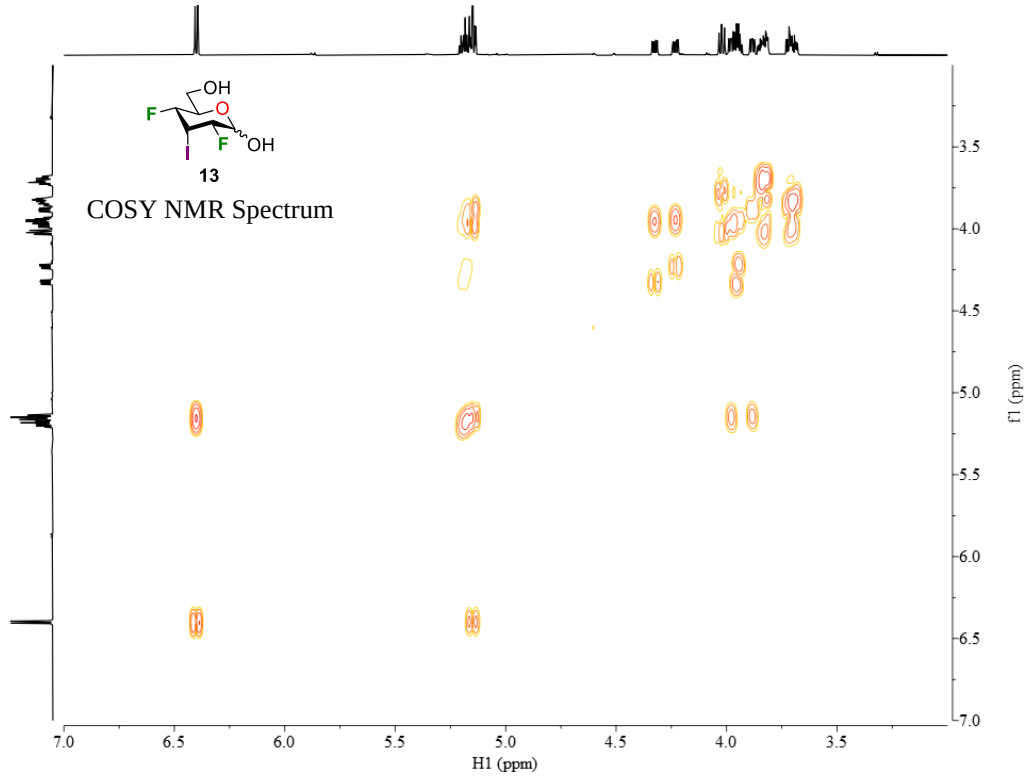


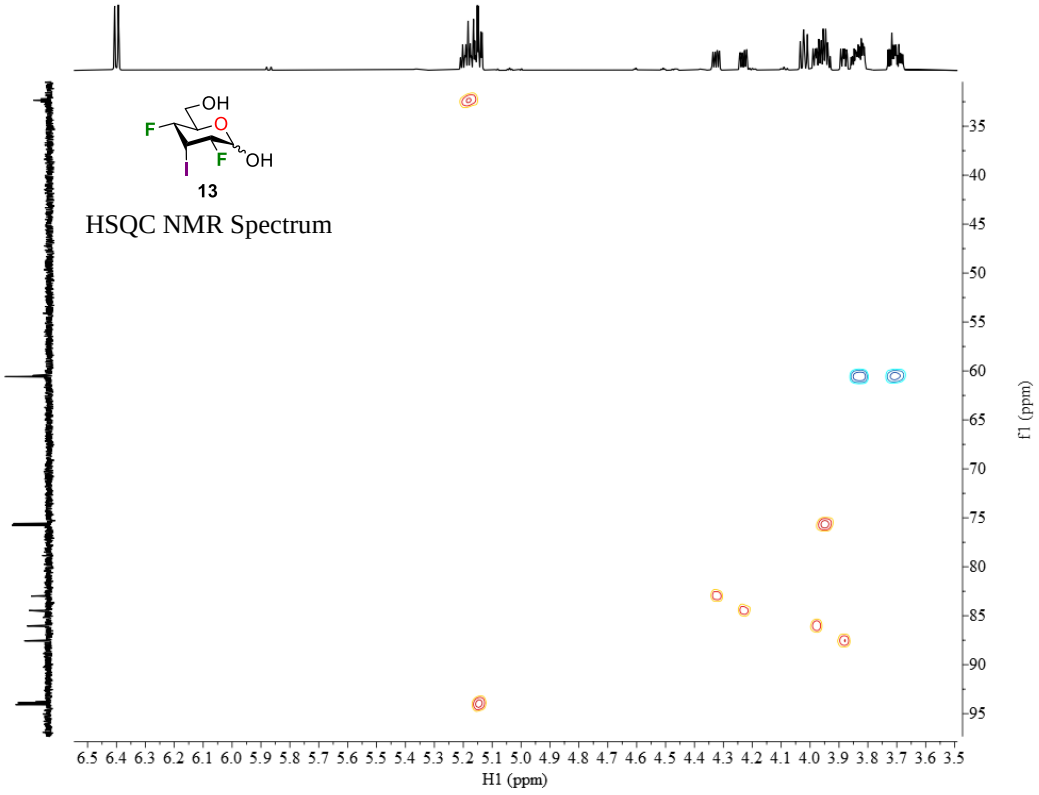


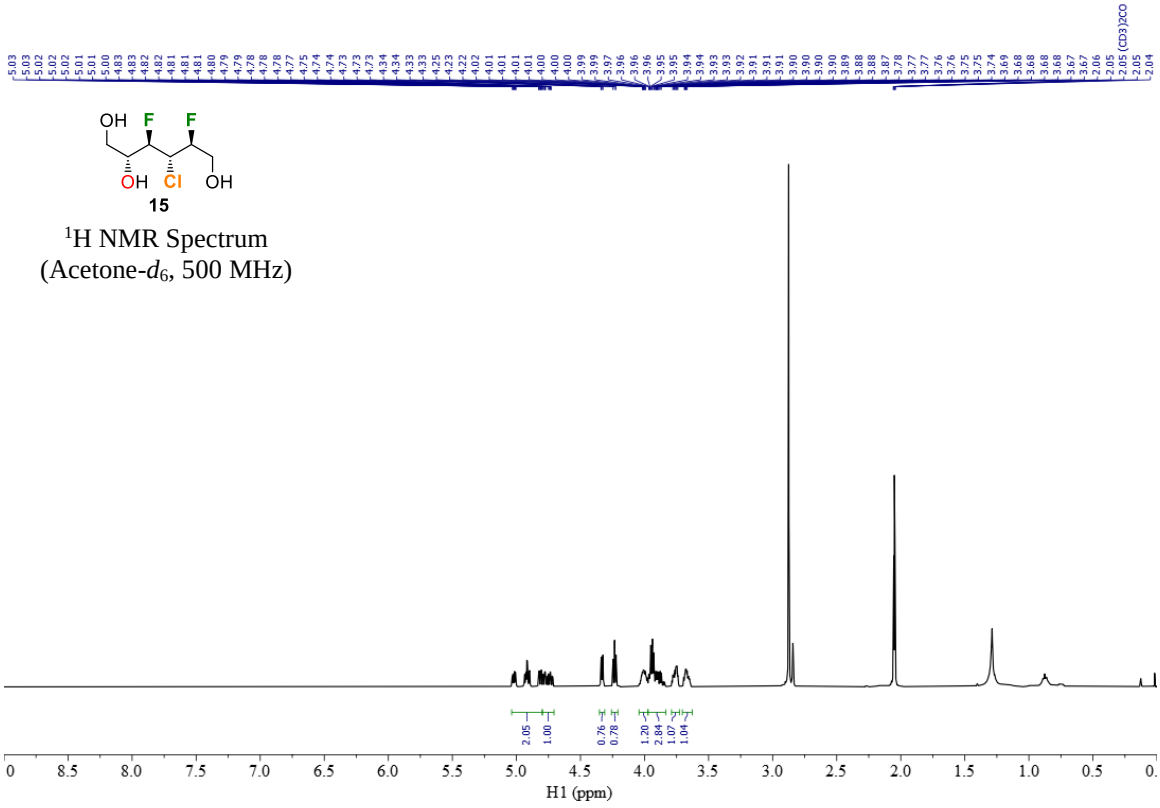
13

^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

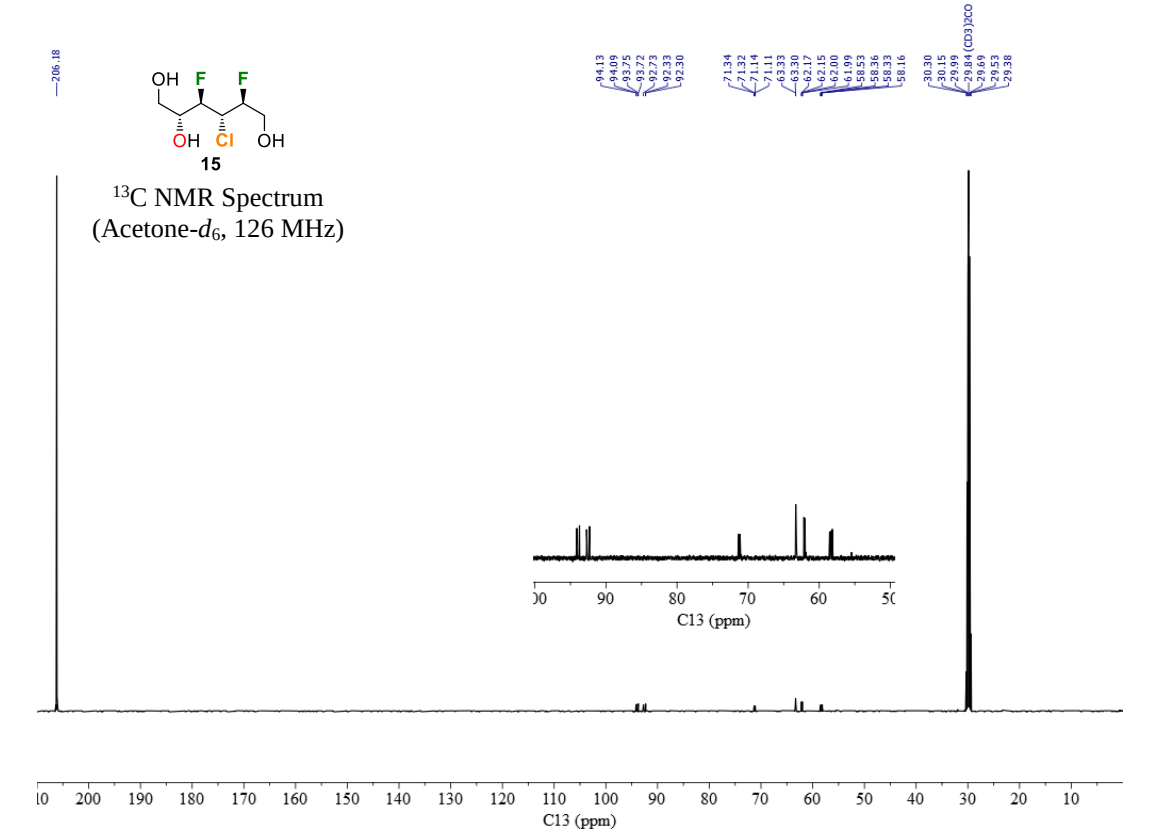



OH
O
F
F
OH
I
13
COSY NMR Spectrum
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
H1 (ppm)

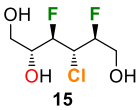

OH
O
F
F
OH
I
13
HSQC NMR Spectrum
35
40
45
50
55
60
65
70
75
80
85
90
95
f1 (ppm)
6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5
H1 (ppm)

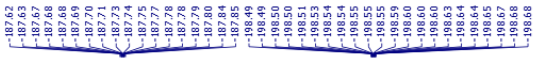


^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)

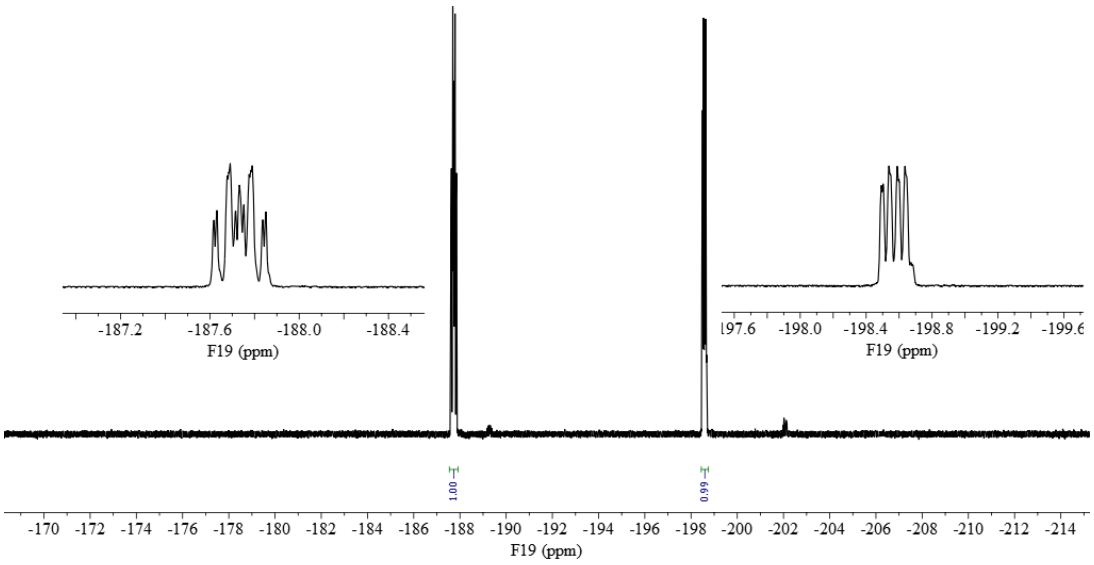


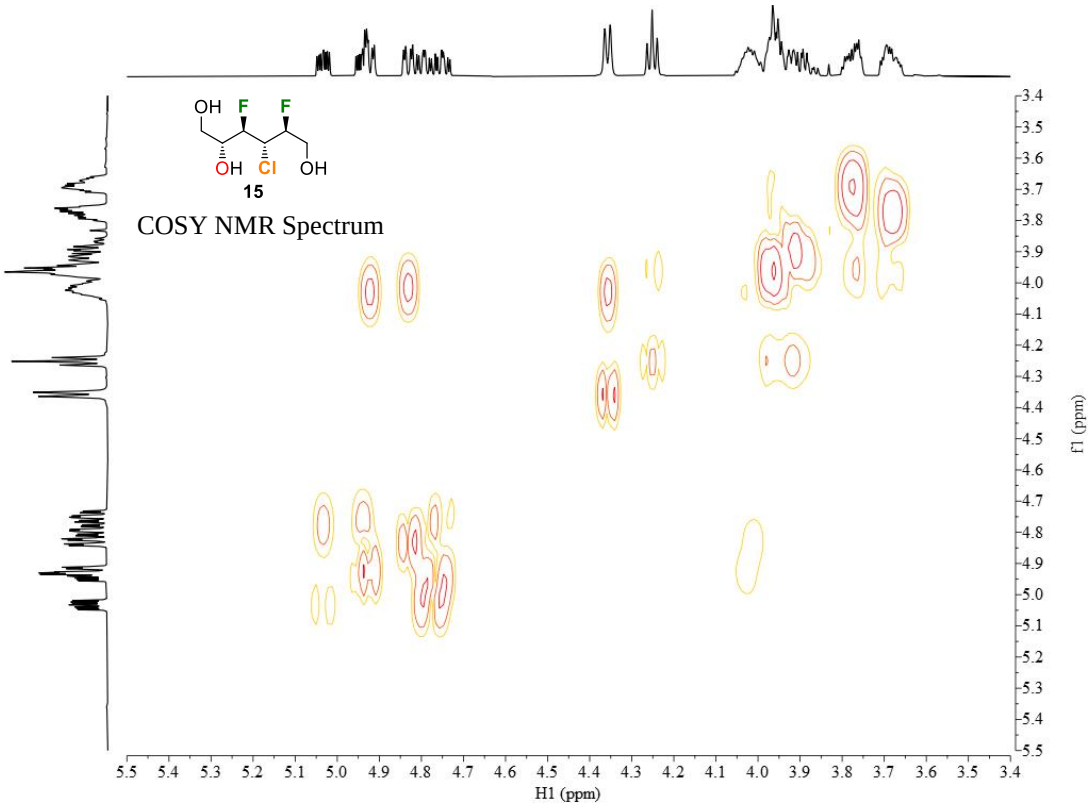
^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)



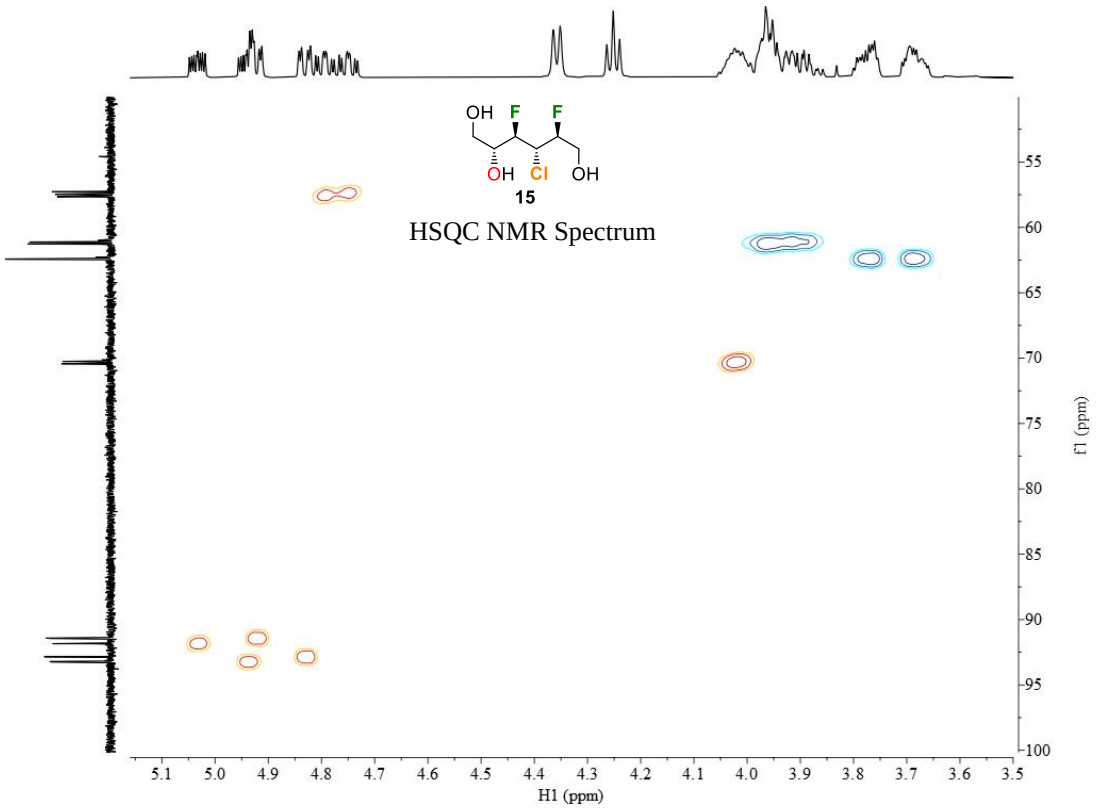


^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

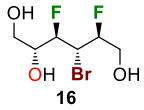




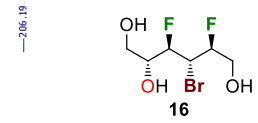
COSY NMR Spectrum



HSQC NMR Spectrum

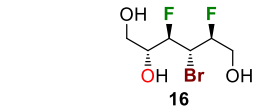


^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)



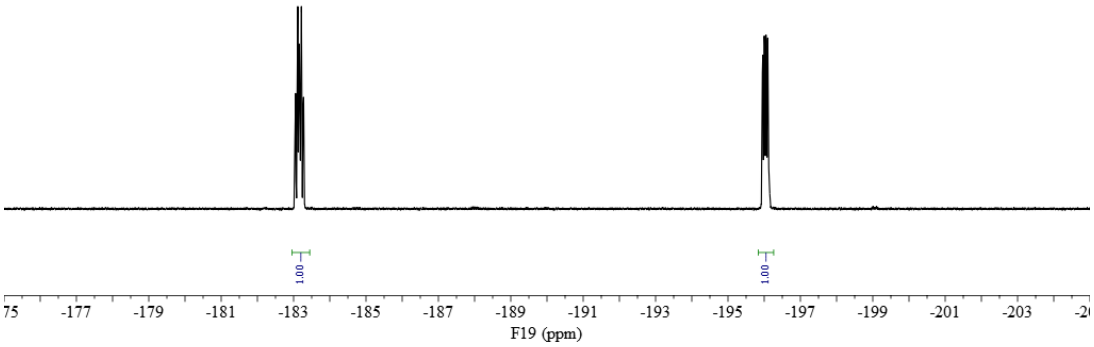
16

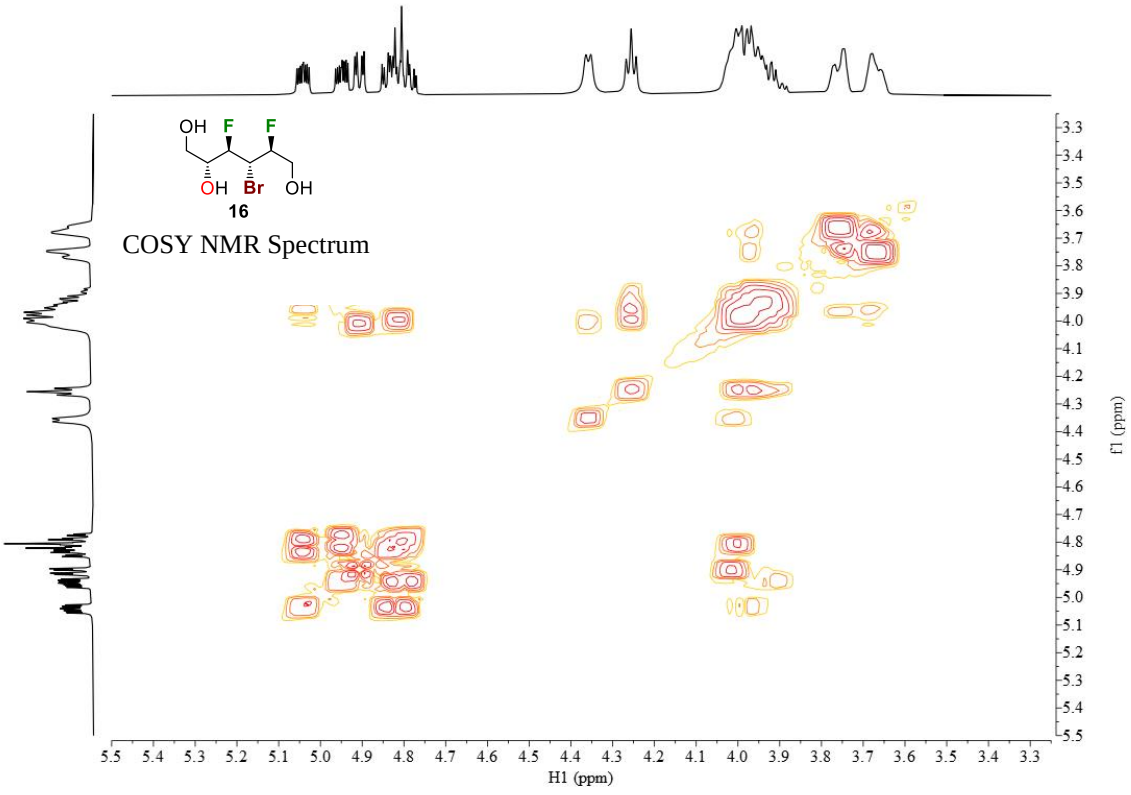
^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)

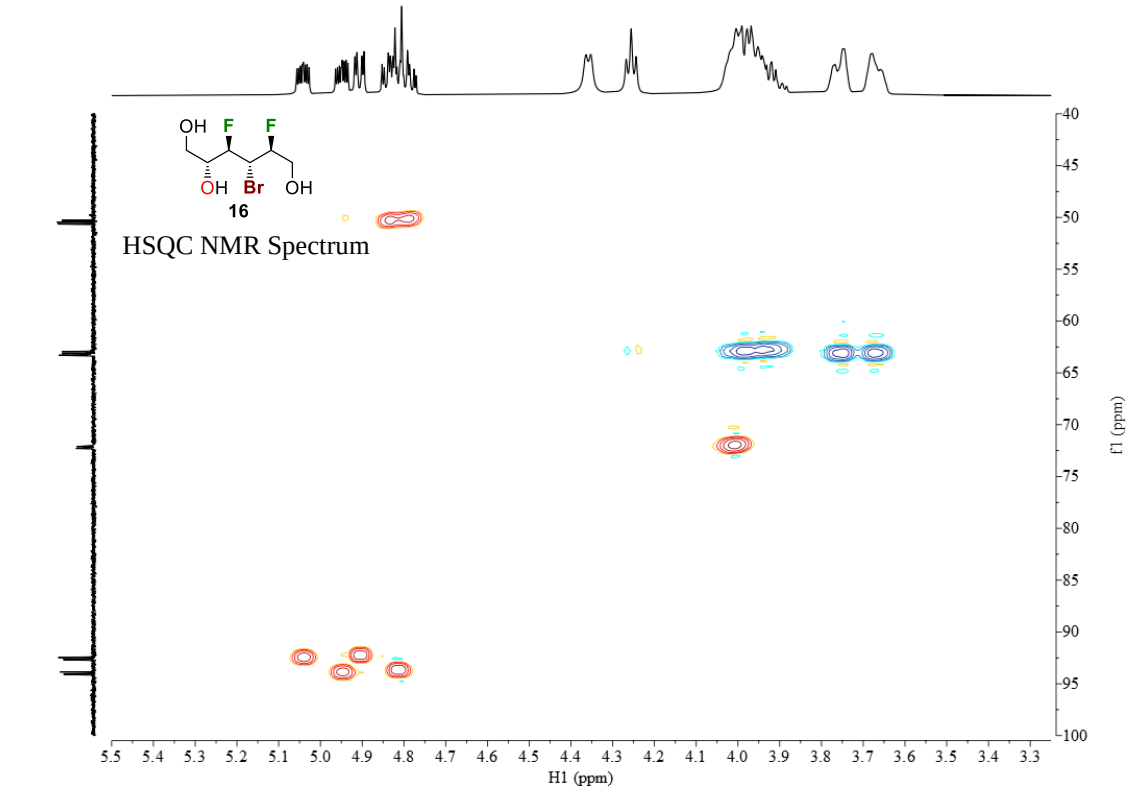


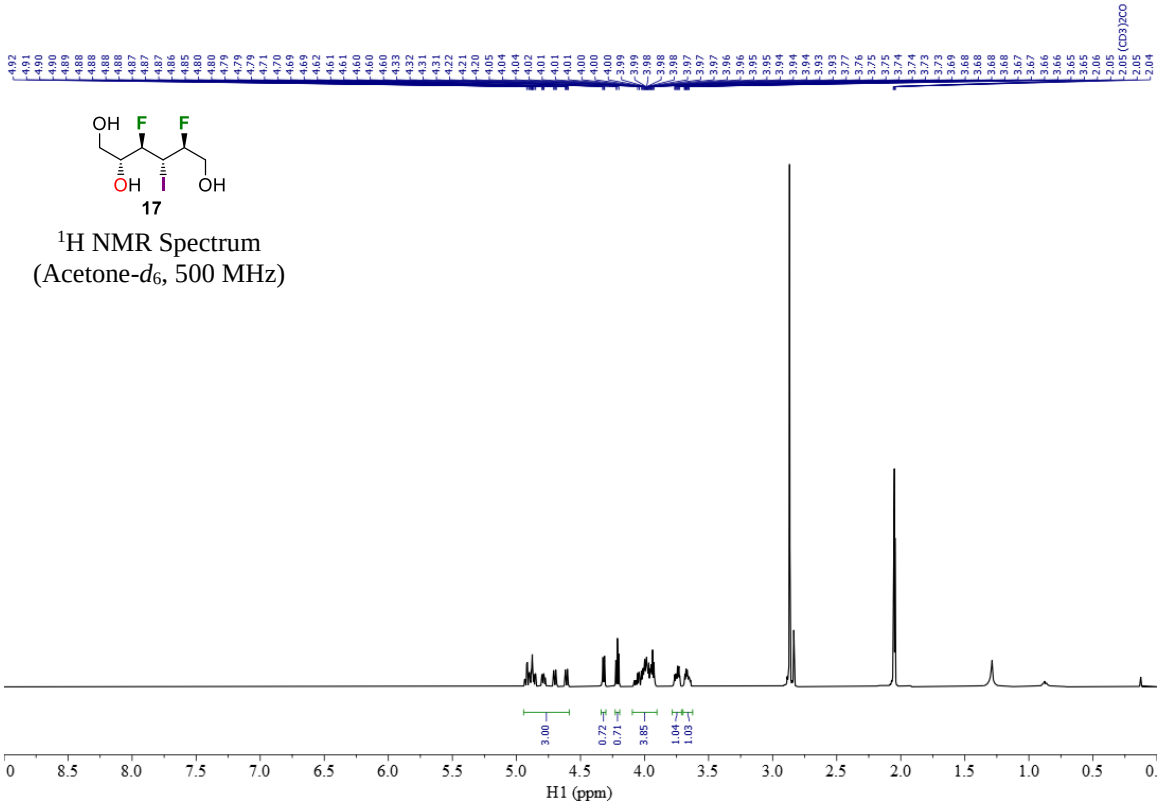
16

^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

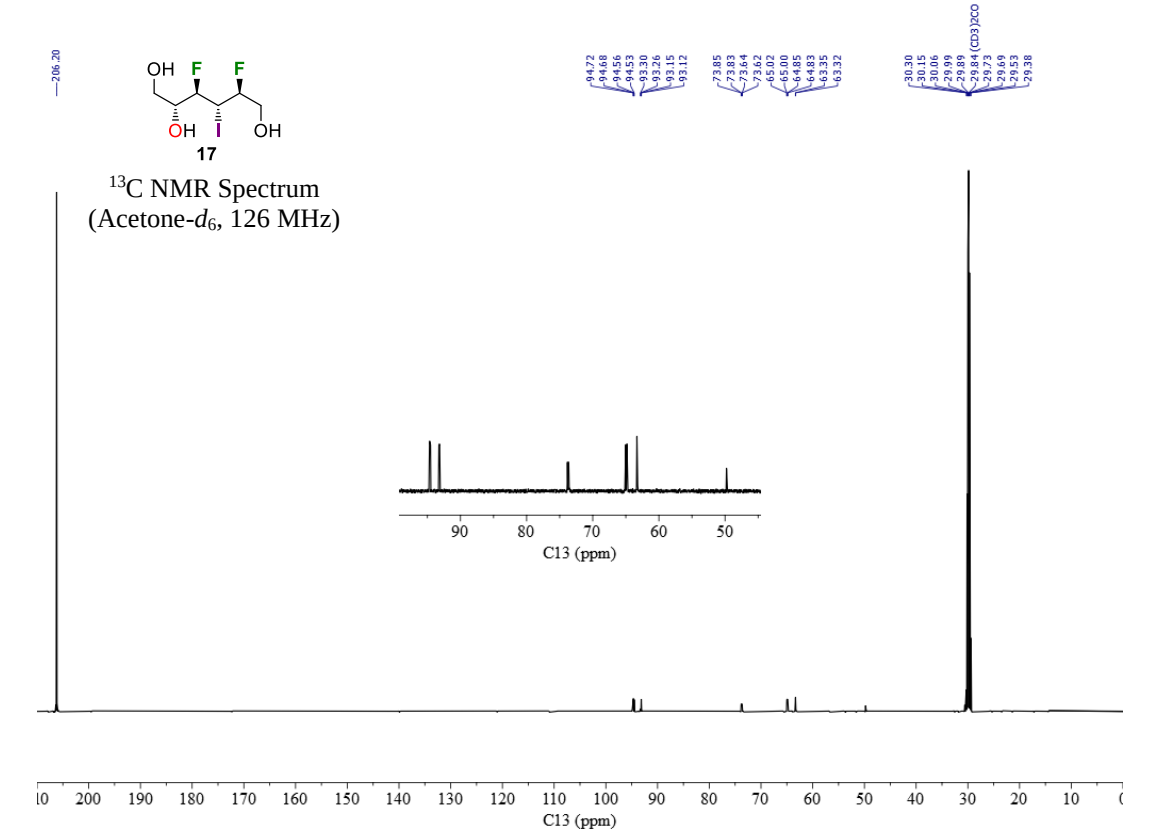



OH F F
OH Br OH
16
COSY NMR Spectrum
f1 (ppm)
H1 (ppm)

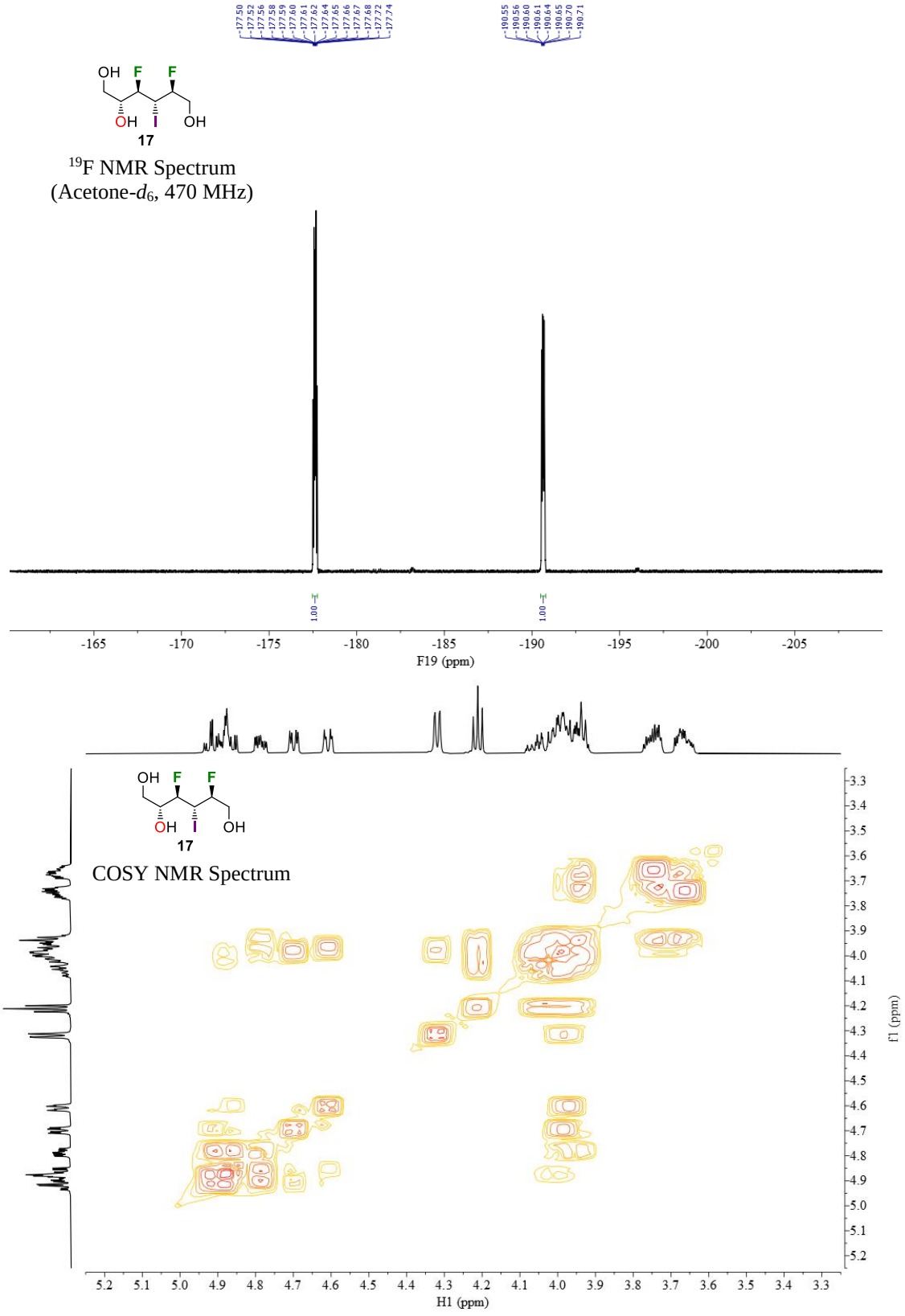

OH F F
OH Br OH
16
HSQC NMR Spectrum
f1 (ppm)
H1 (ppm)

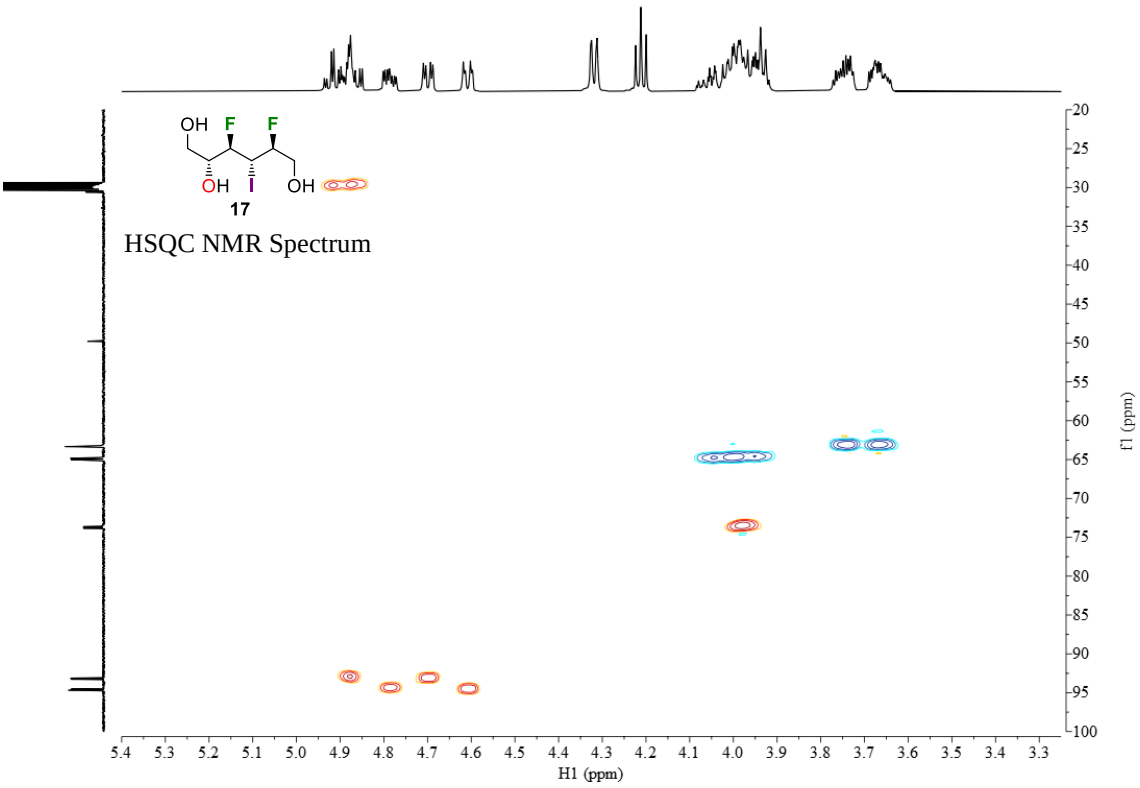


^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)

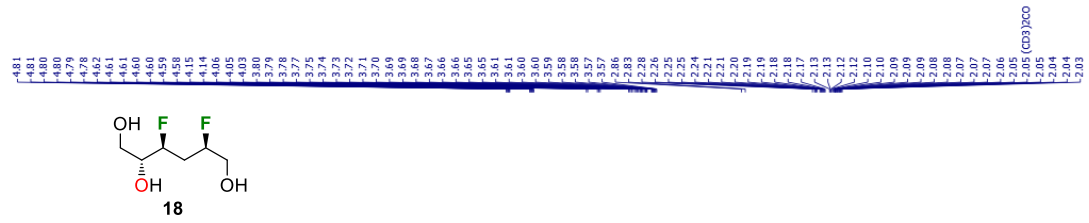


^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)

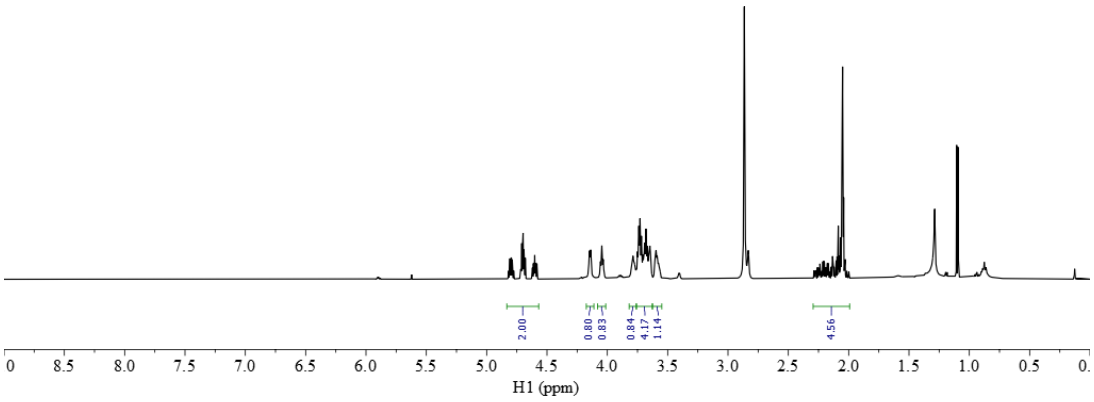

OH F F
OH I OH
17
19F NMR Spectrum
(Acetone-d6, 470 MHz)
F19 (ppm)
COSY NMR Spectrum
H1 (ppm)
f1 (ppm)

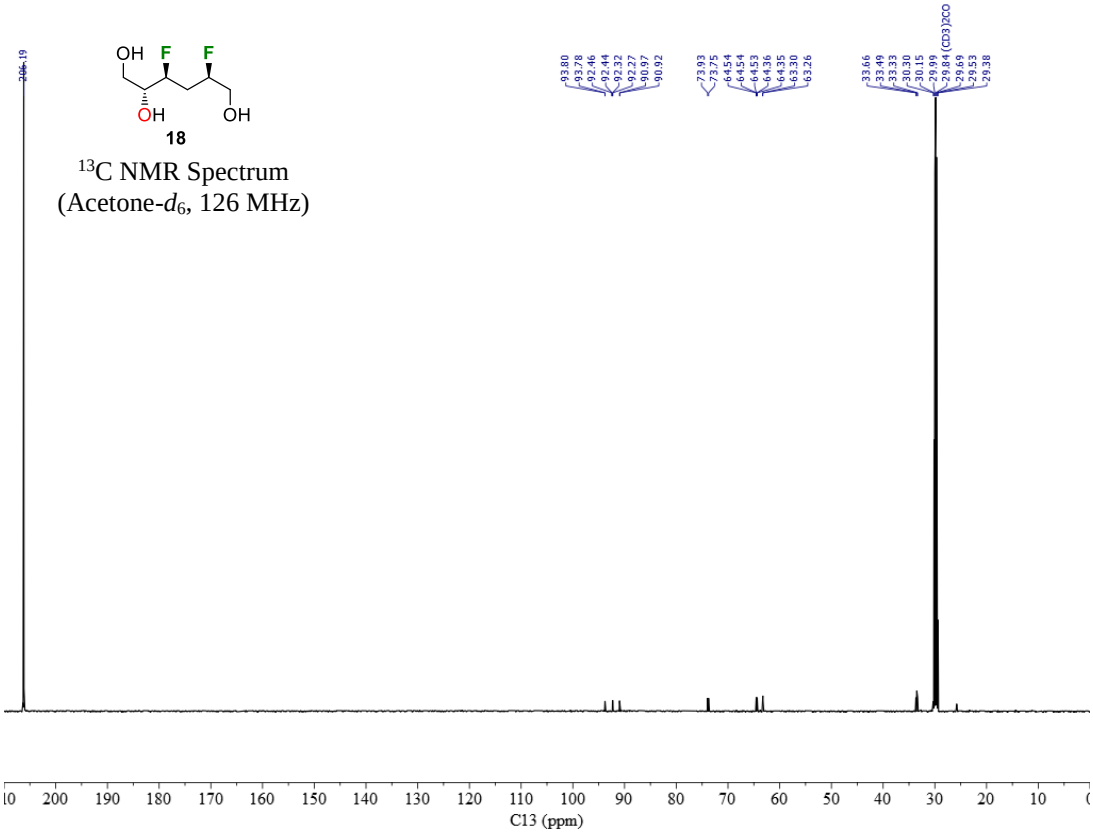


HSQC NMR Spectrum

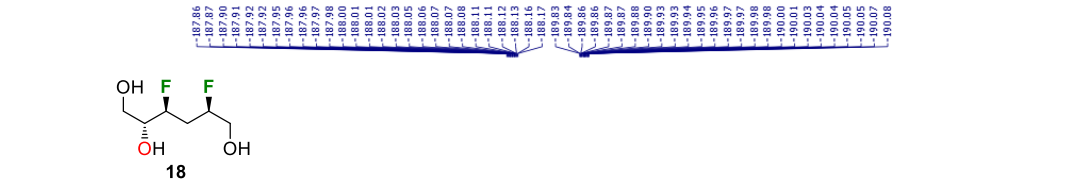


^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)

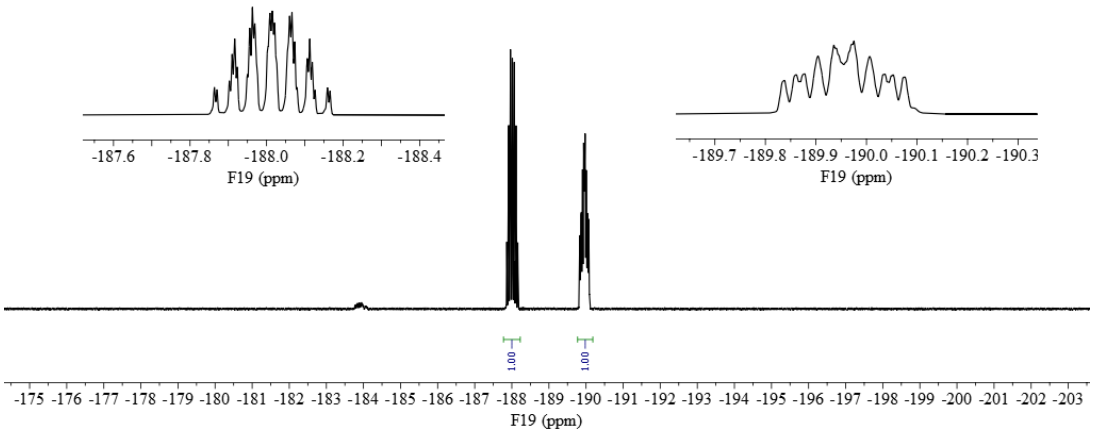


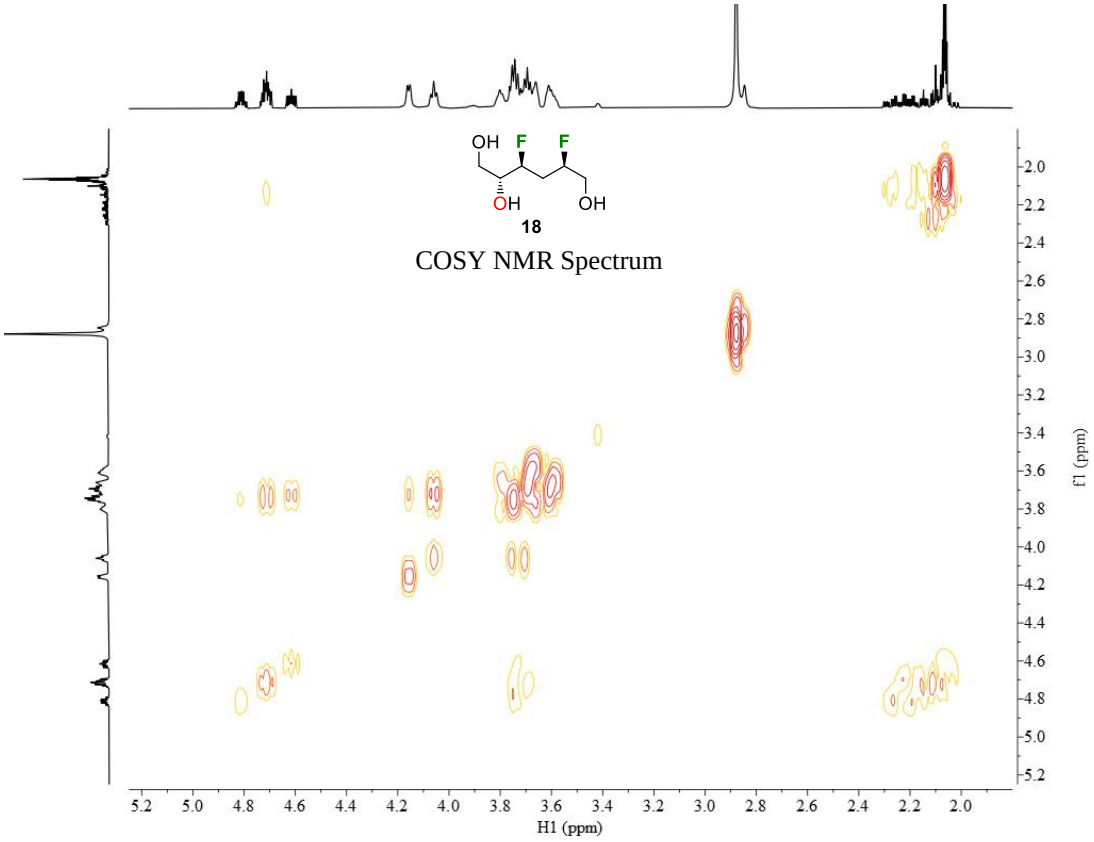


^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)

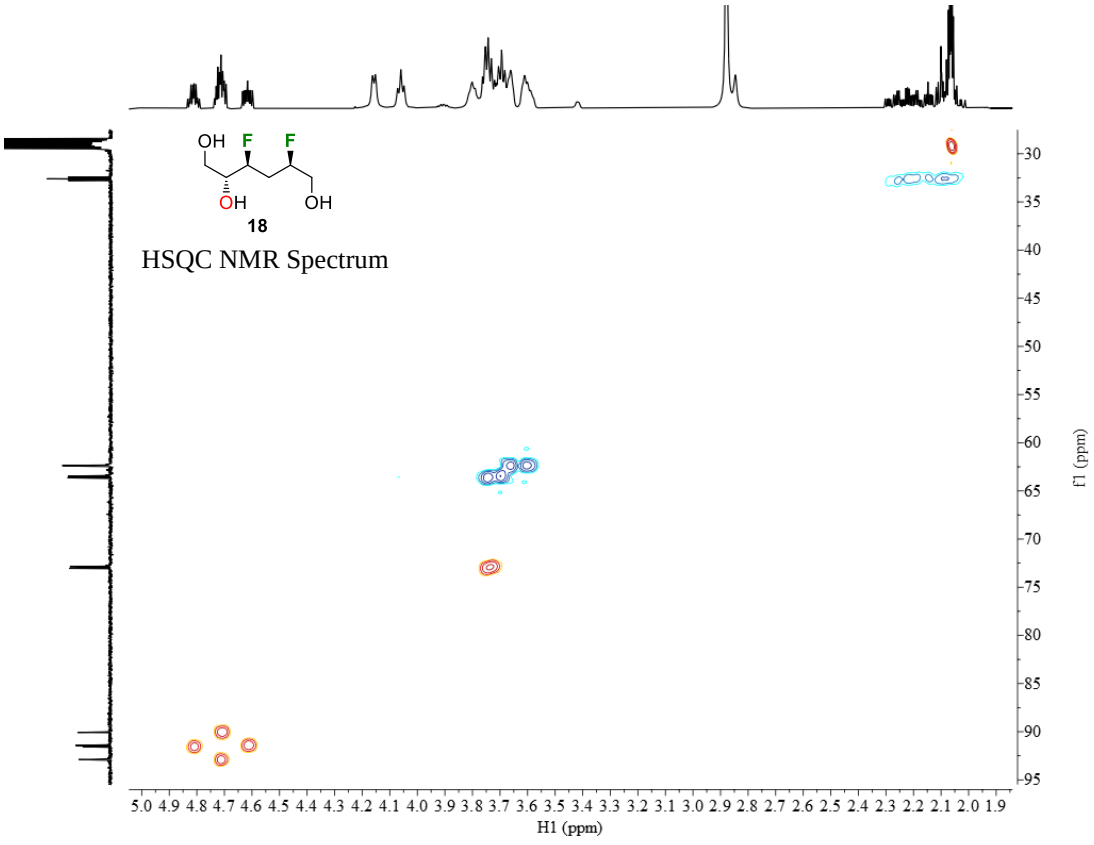


^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

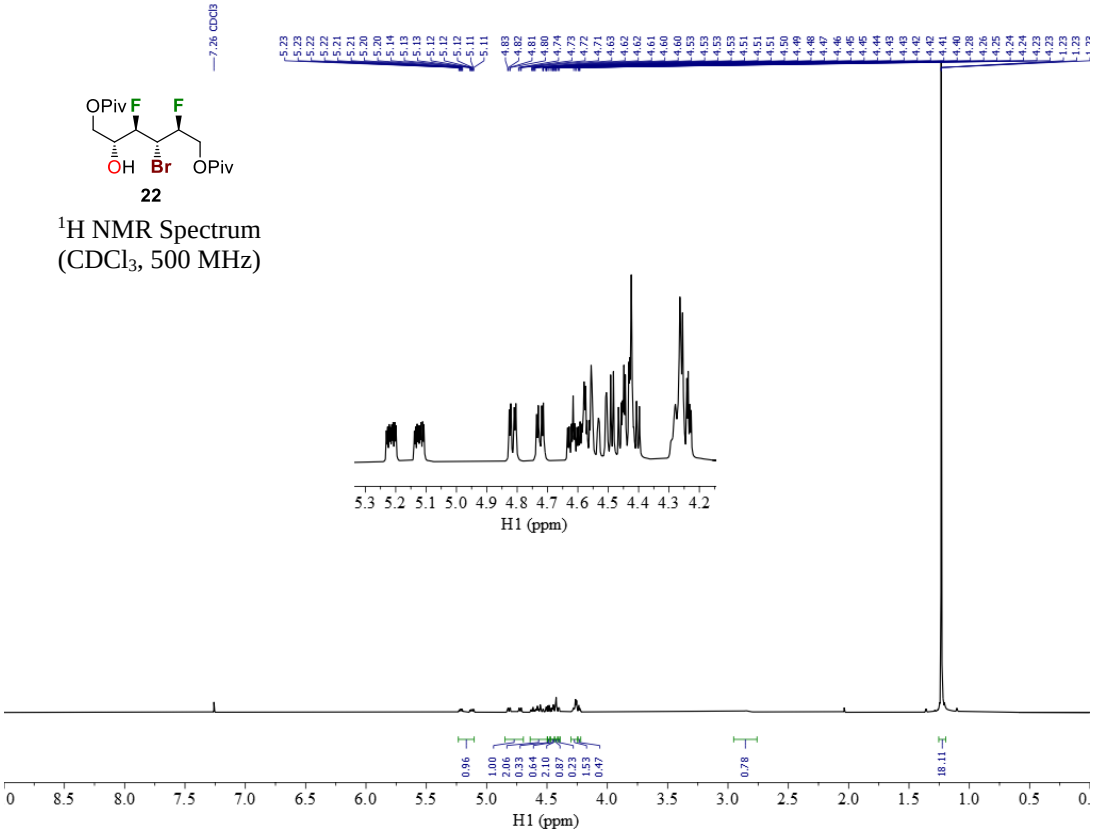




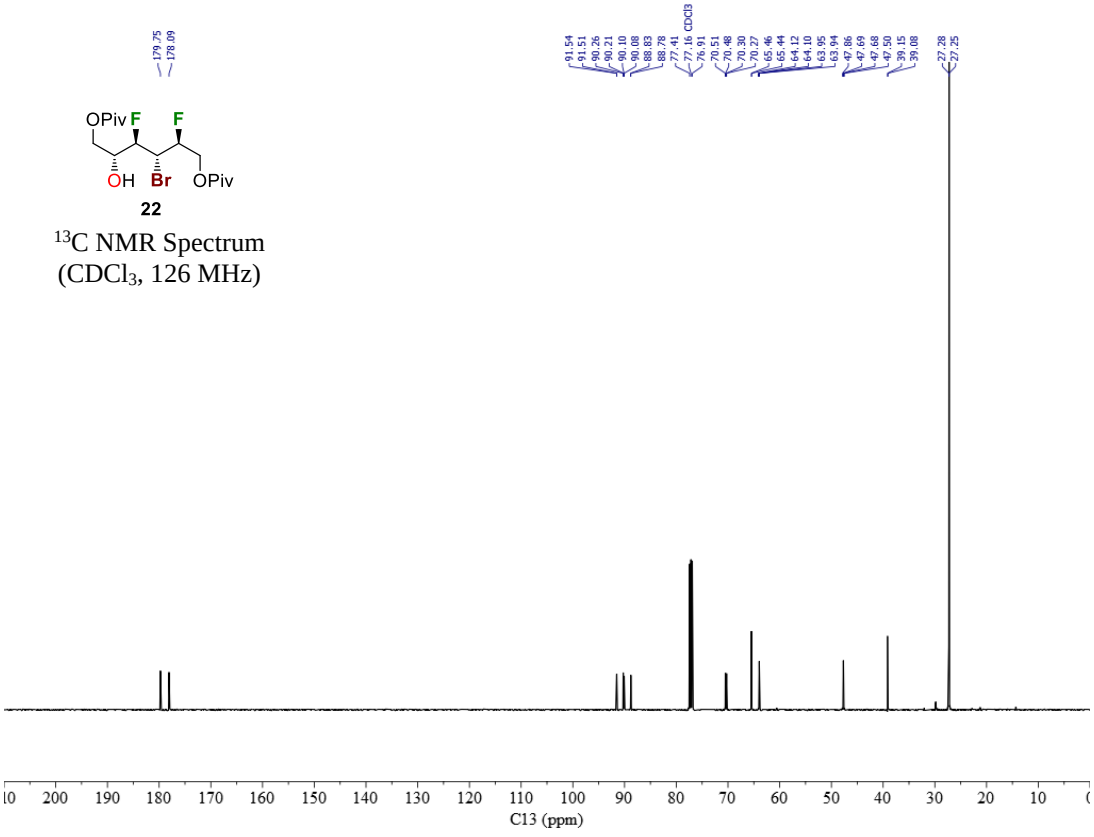
COSY NMR Spectrum



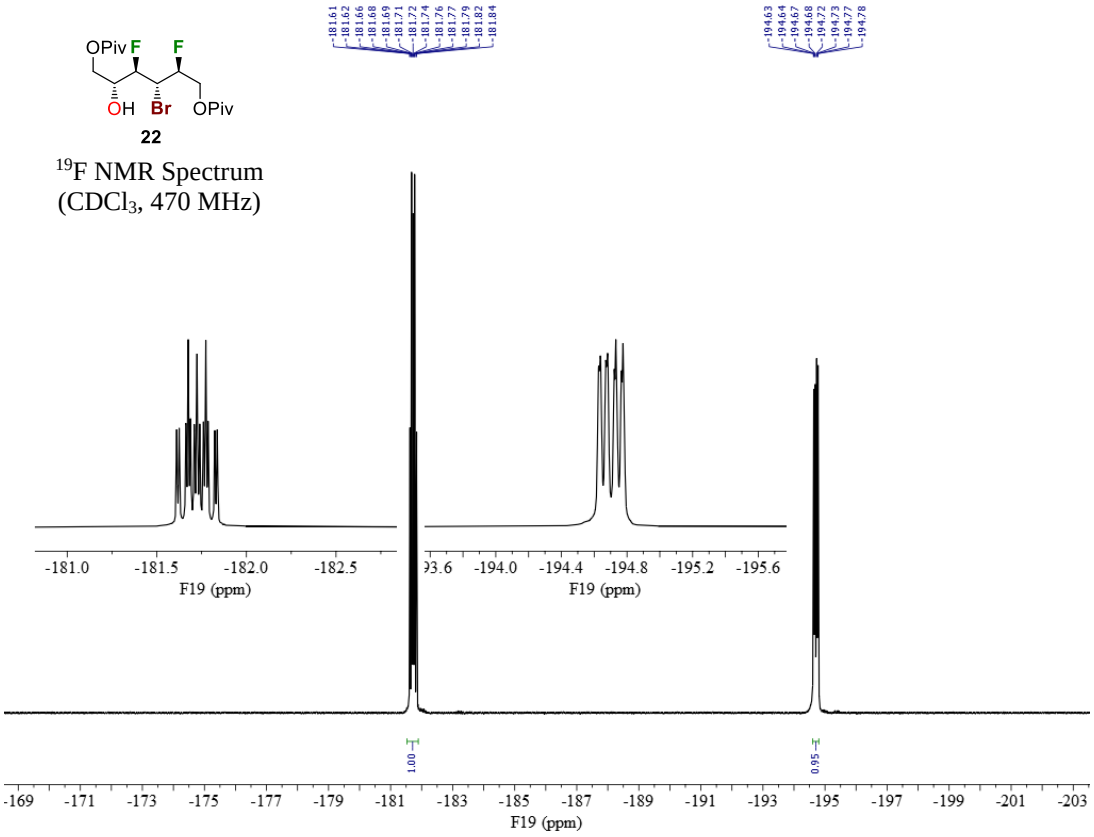
HSQC NMR Spectrum



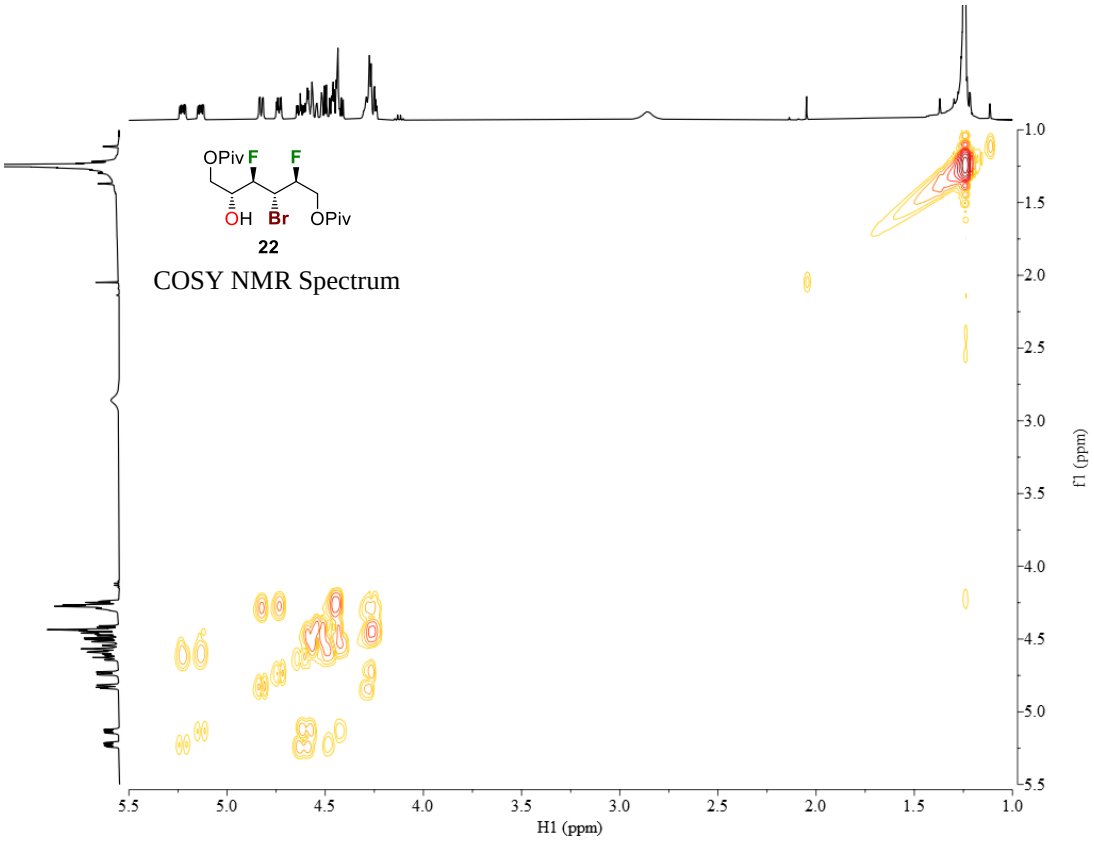
^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)



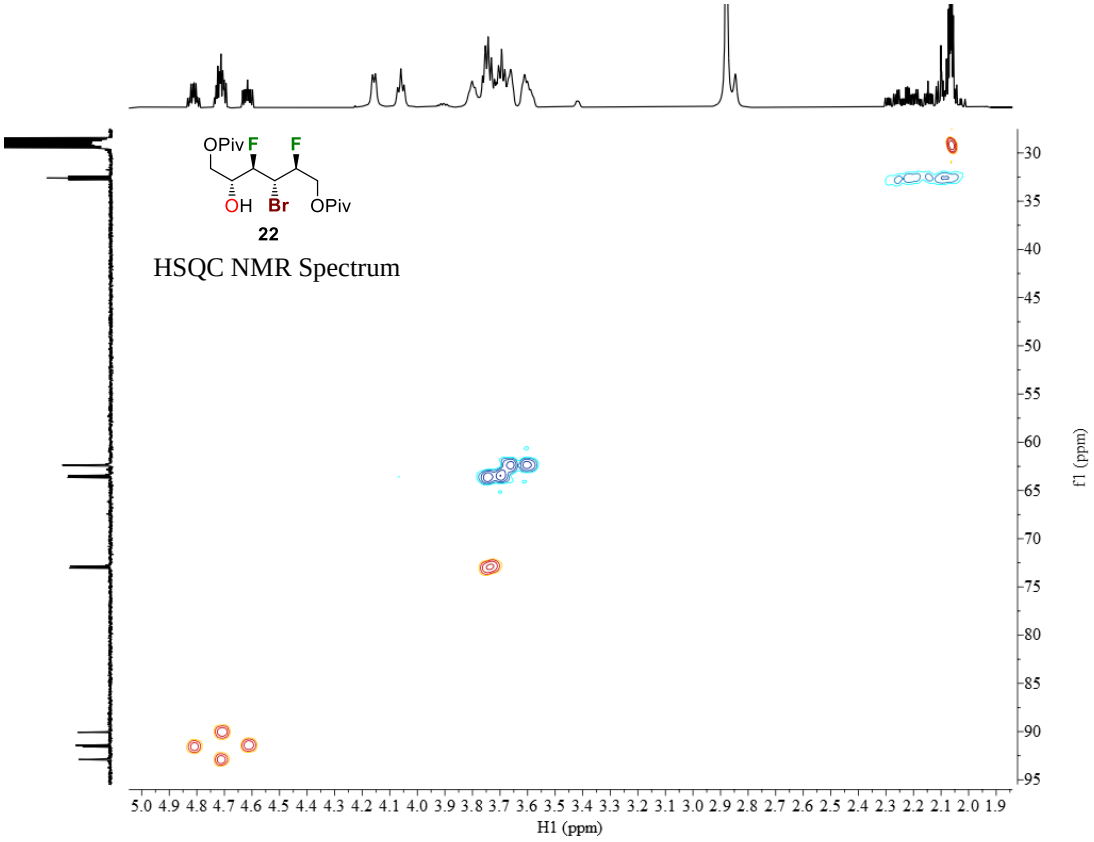
^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)



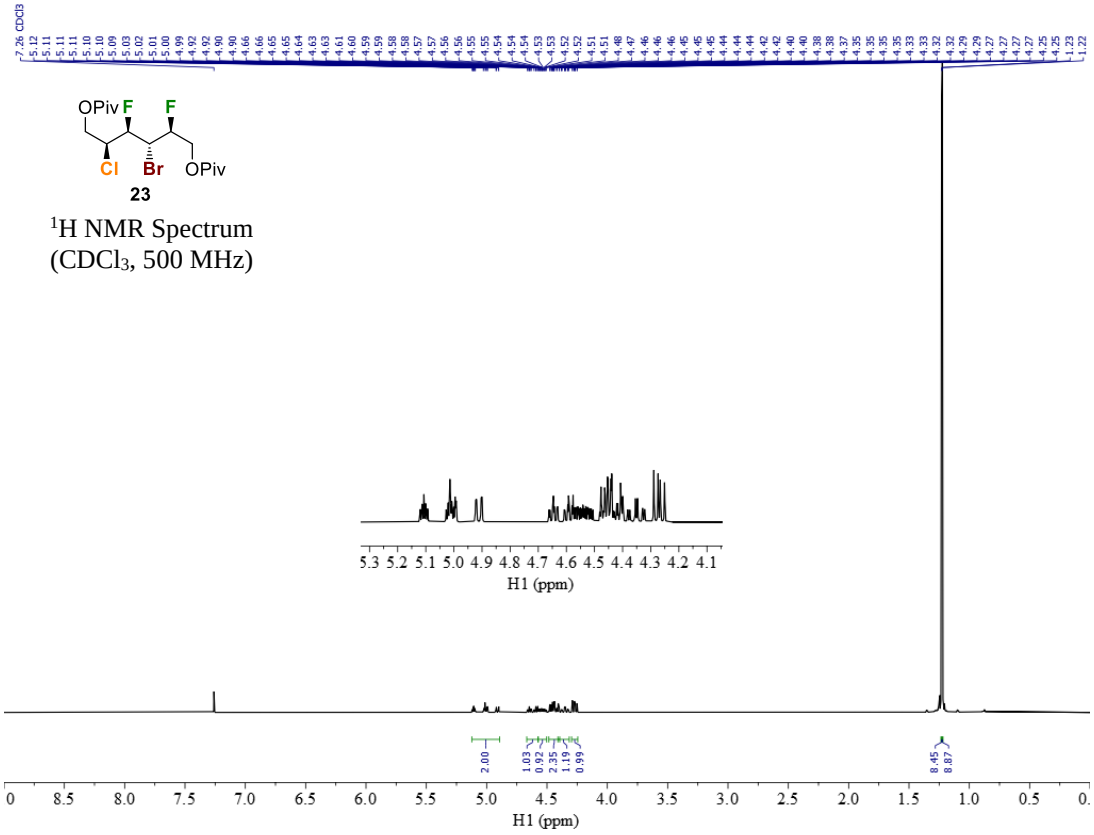
^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)



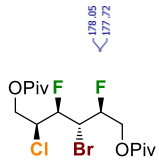
COSY NMR Spectrum



HSQC NMR Spectrum

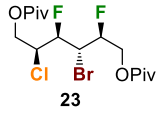


^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)



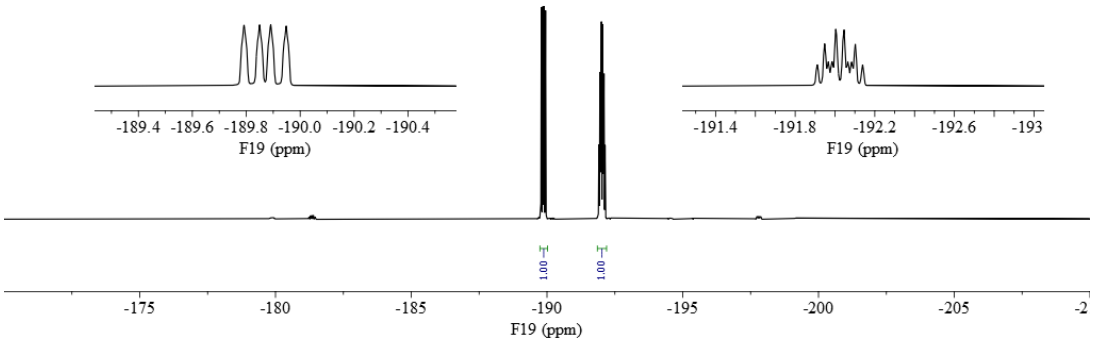
23

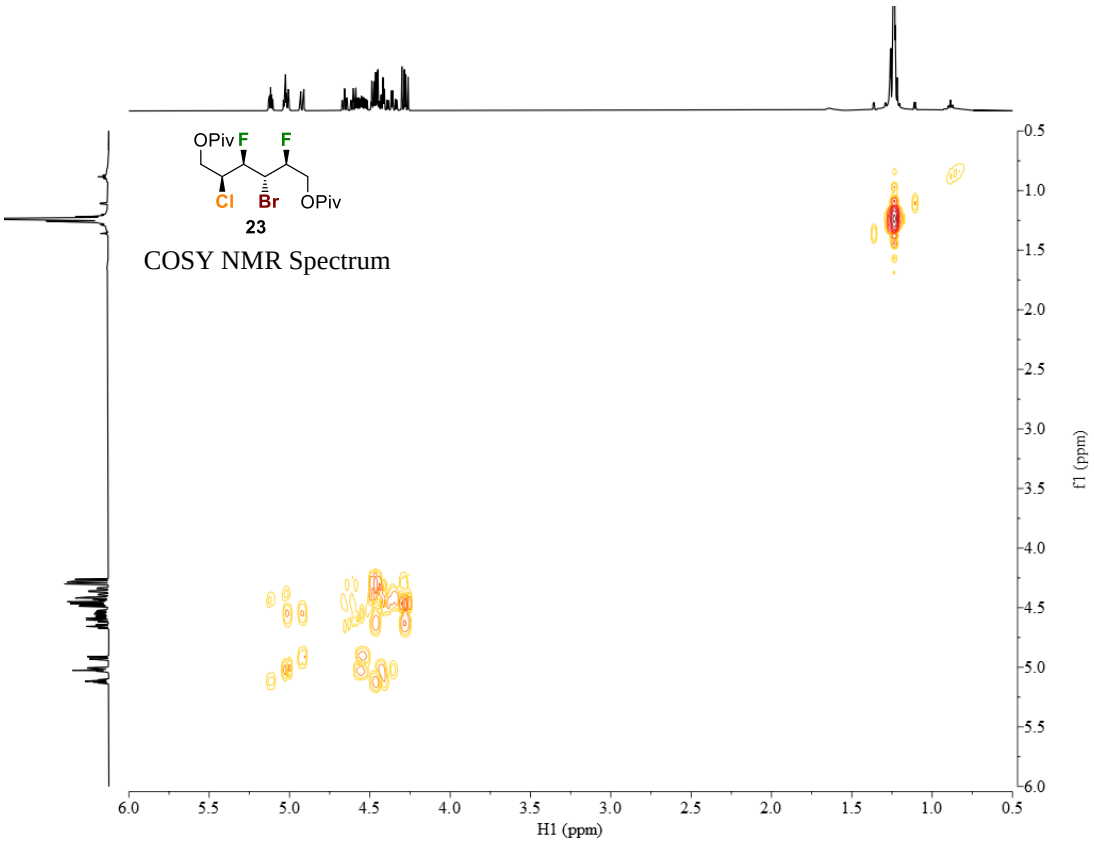
^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)

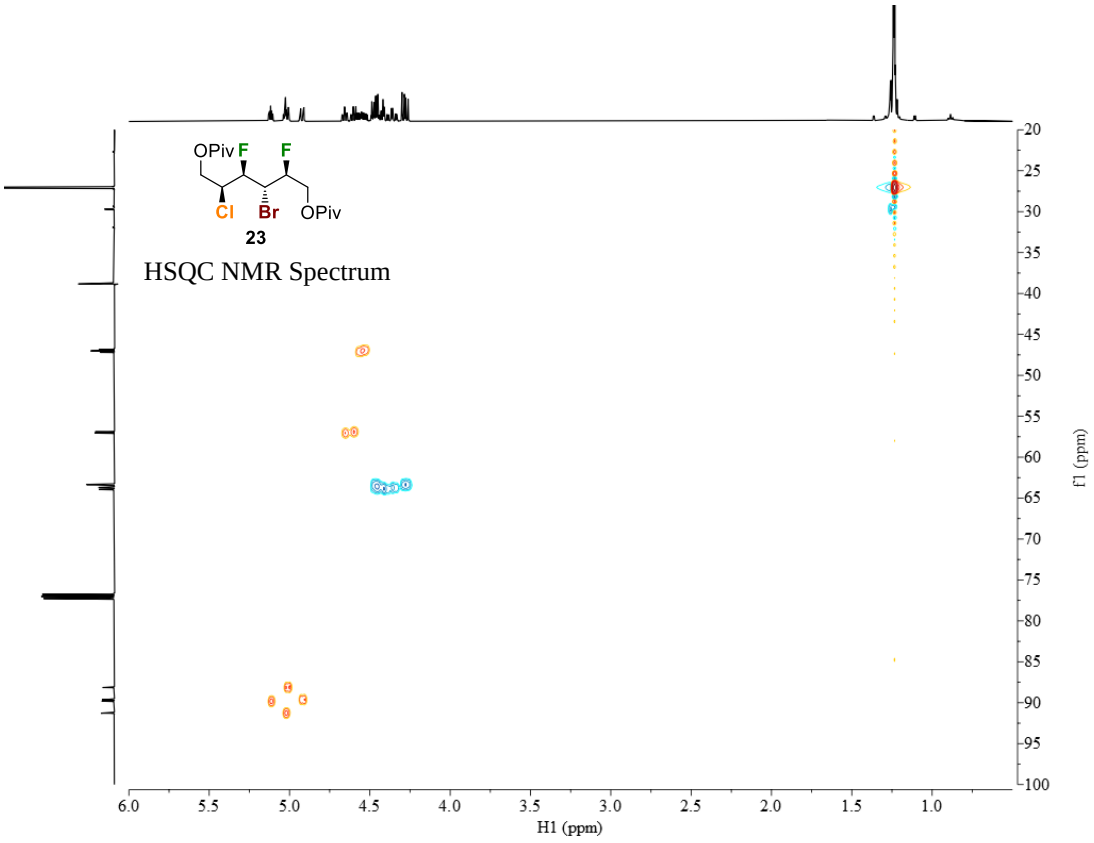


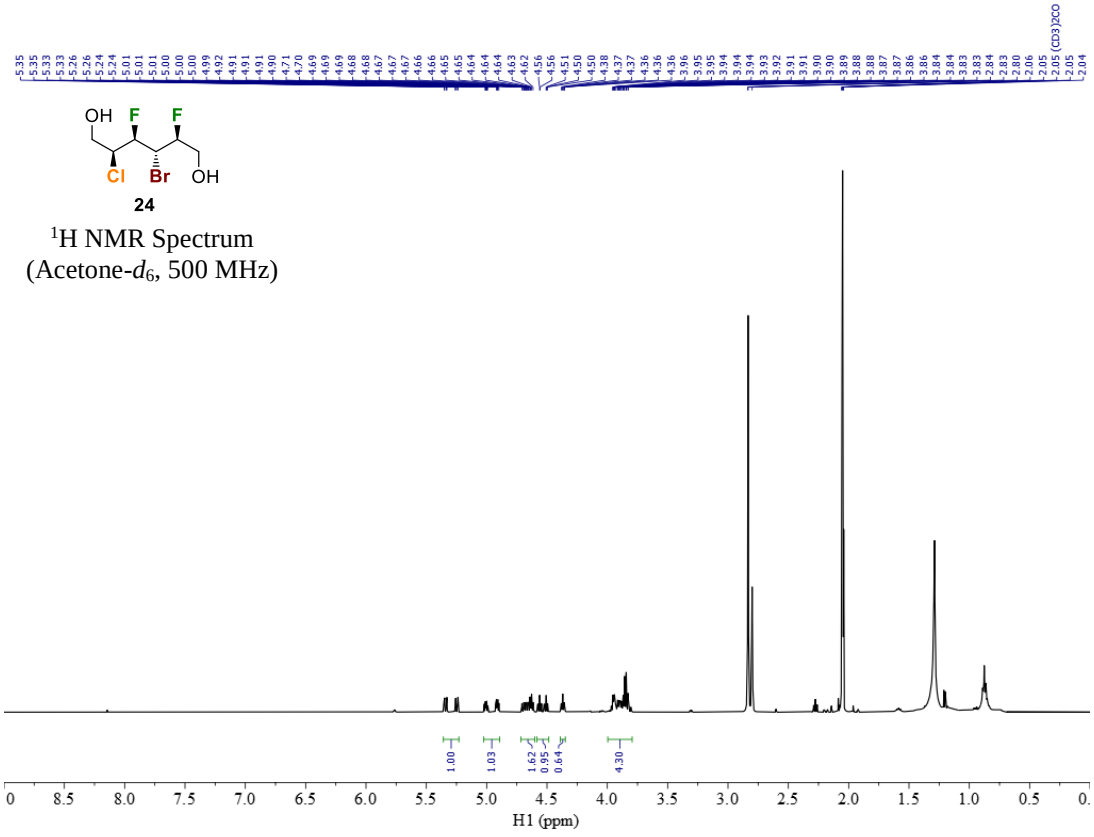
23

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

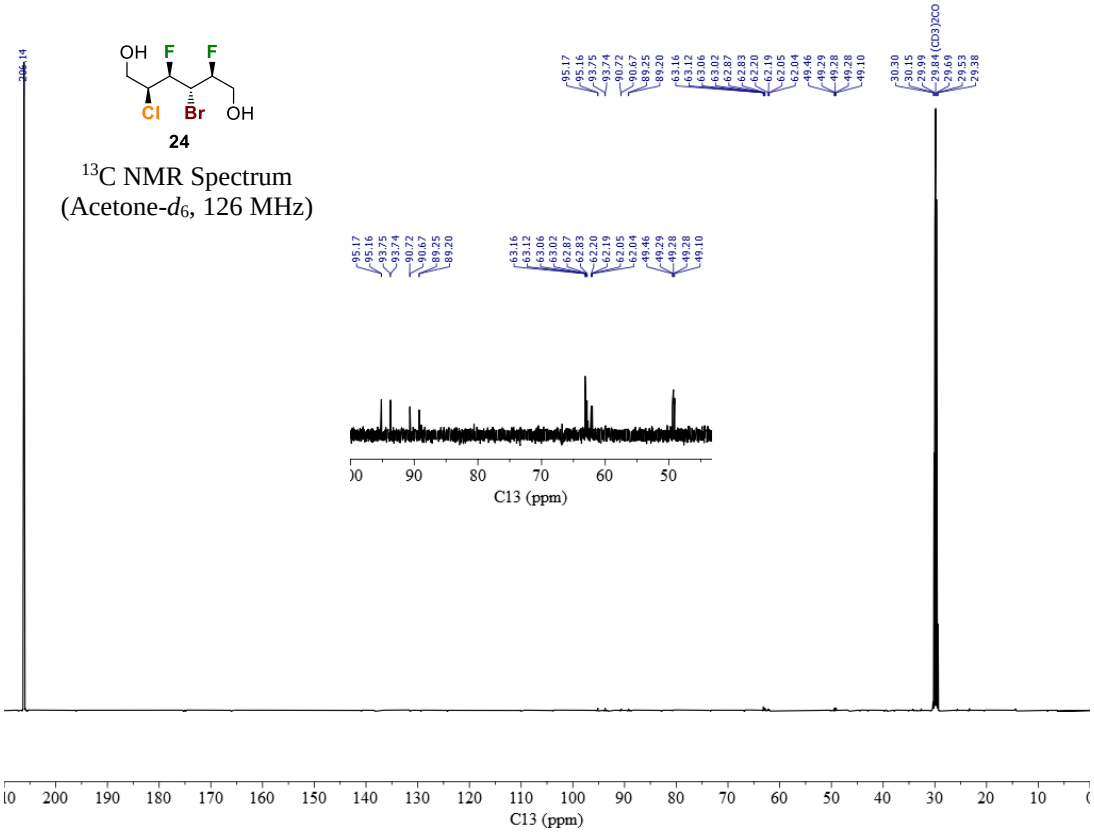



OPiv F F
Cl Br OPiv
23
COSY NMR Spectrum
f1 (ppm)
H1 (ppm)

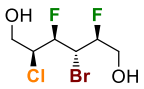

OPiv F F
Cl Br OPiv
23
HSQC NMR Spectrum
f1 (ppm)
H1 (ppm)



^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)

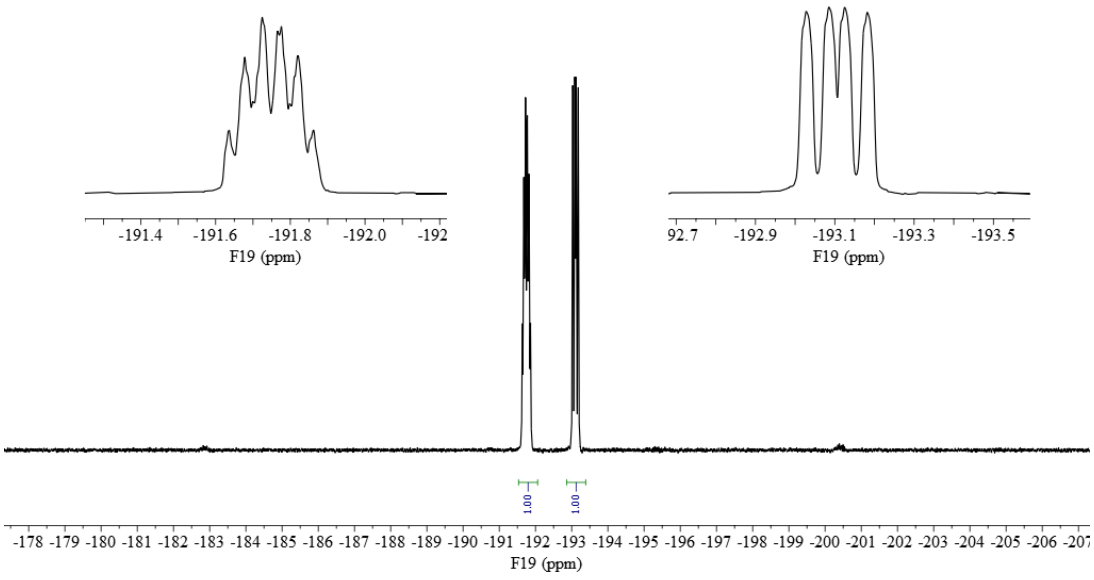


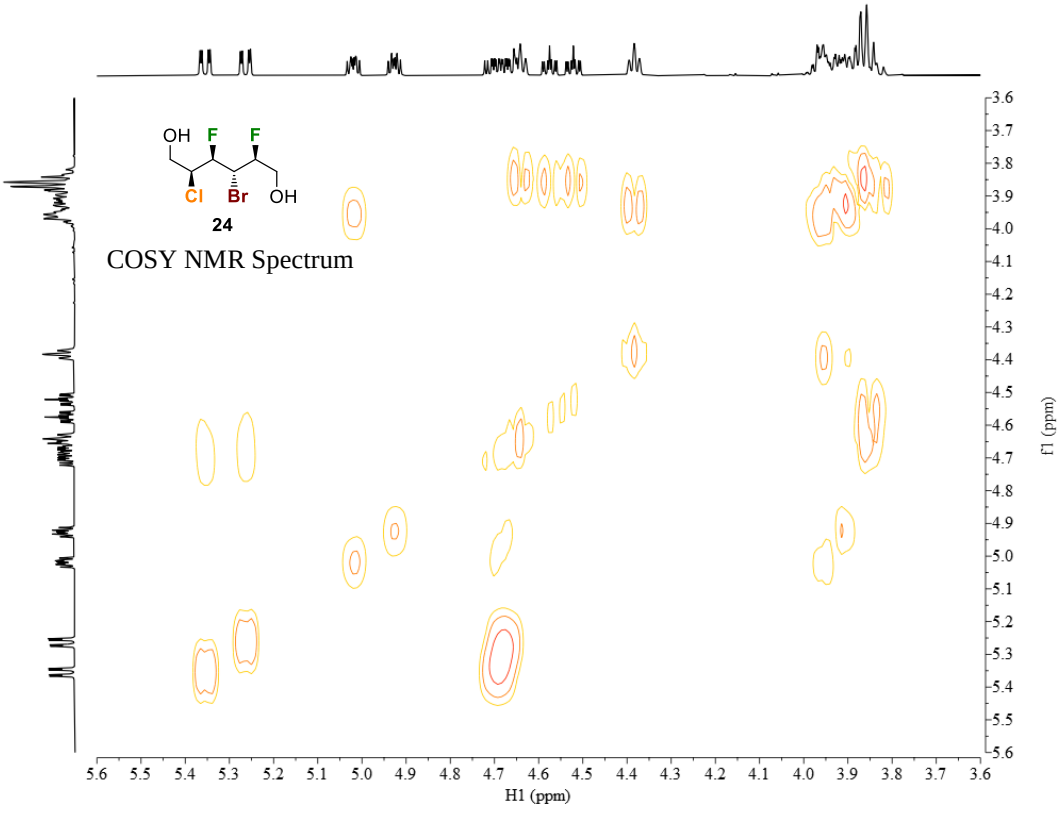
^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)

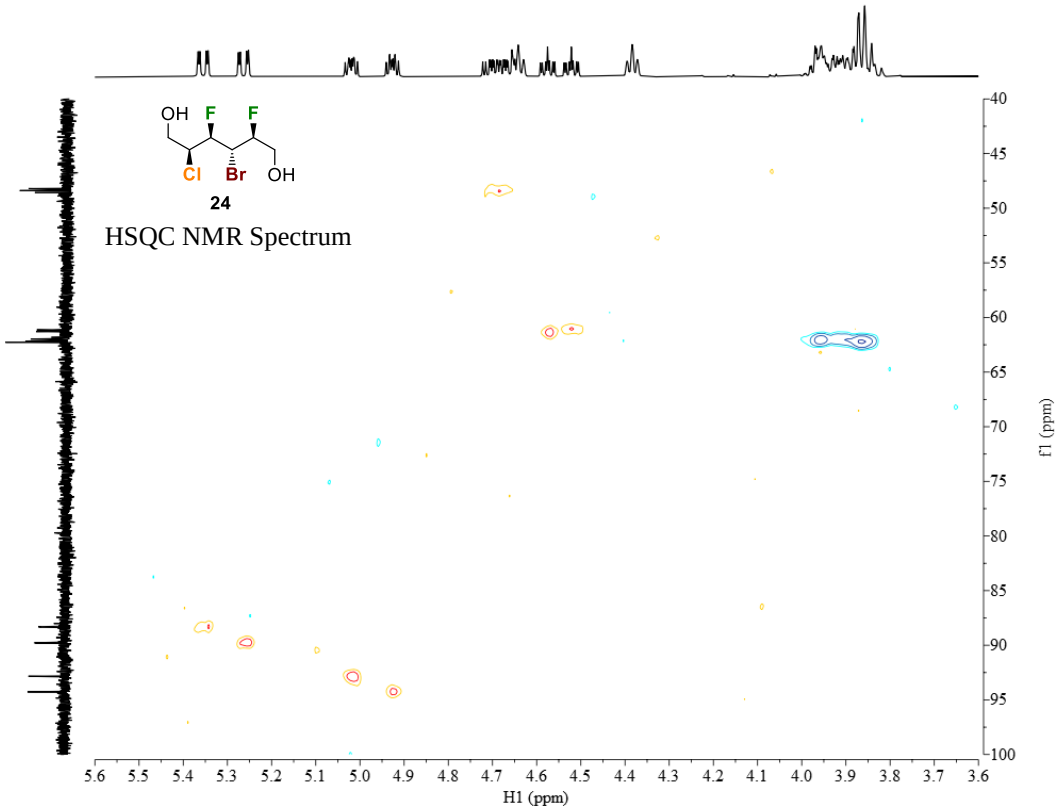


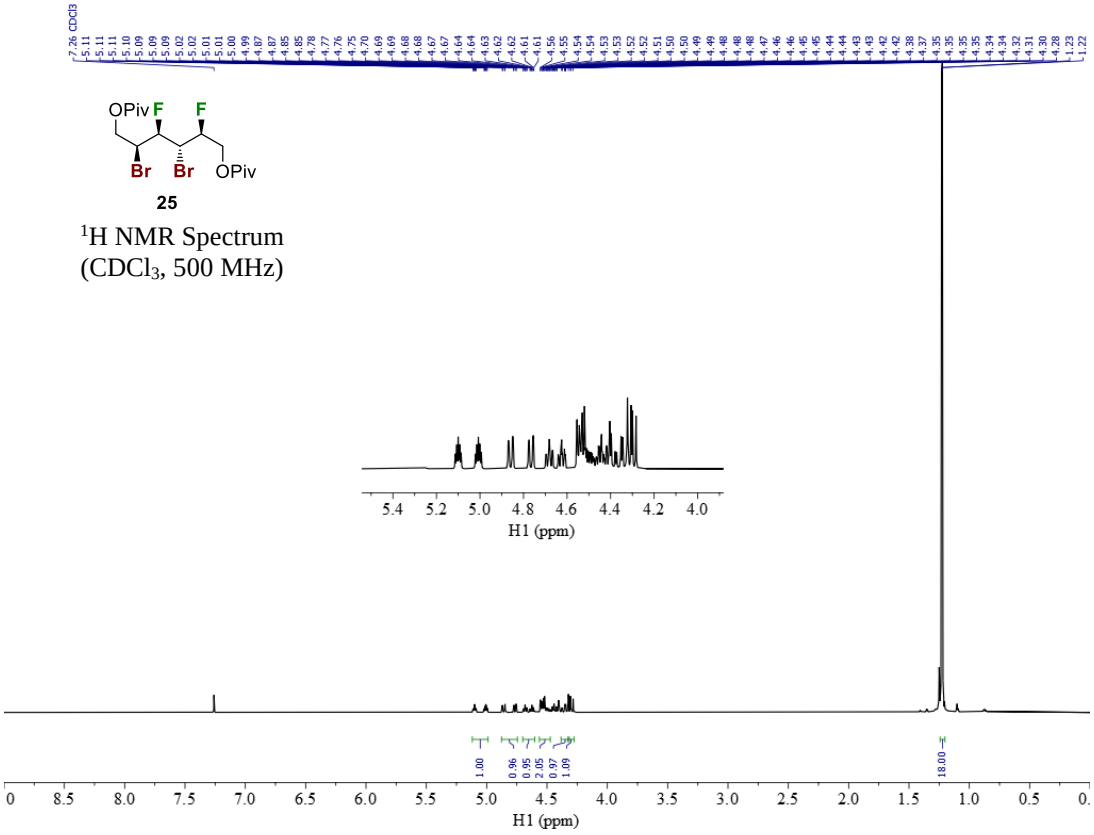
24

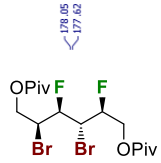
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)





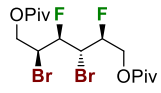

OH F F
Cl Br OH
24
HSQC NMR Spectrum
H1 (ppm)
f1 (ppm)


OPiv F F
Br Br OPiv
25
^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)
H1 (ppm)



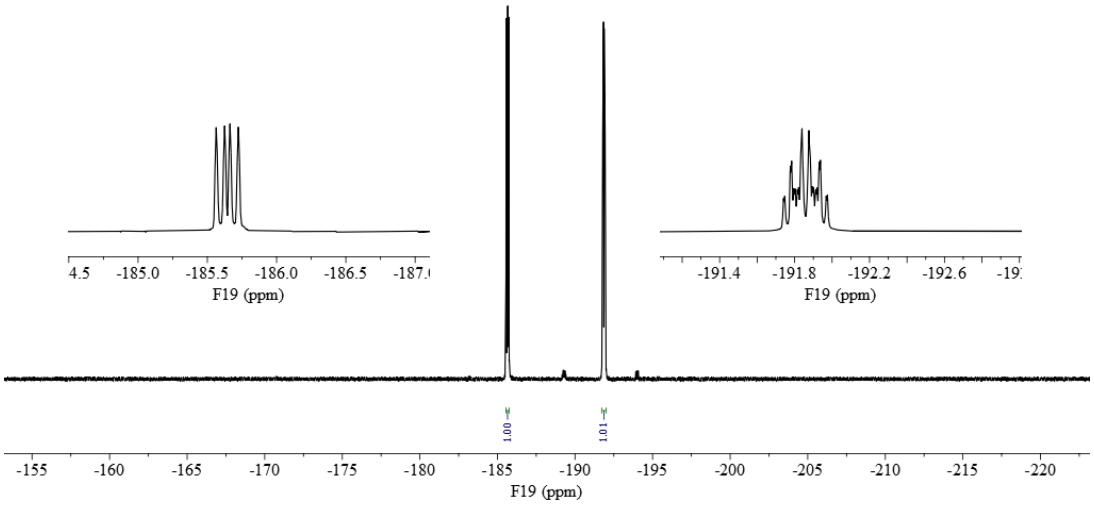
25

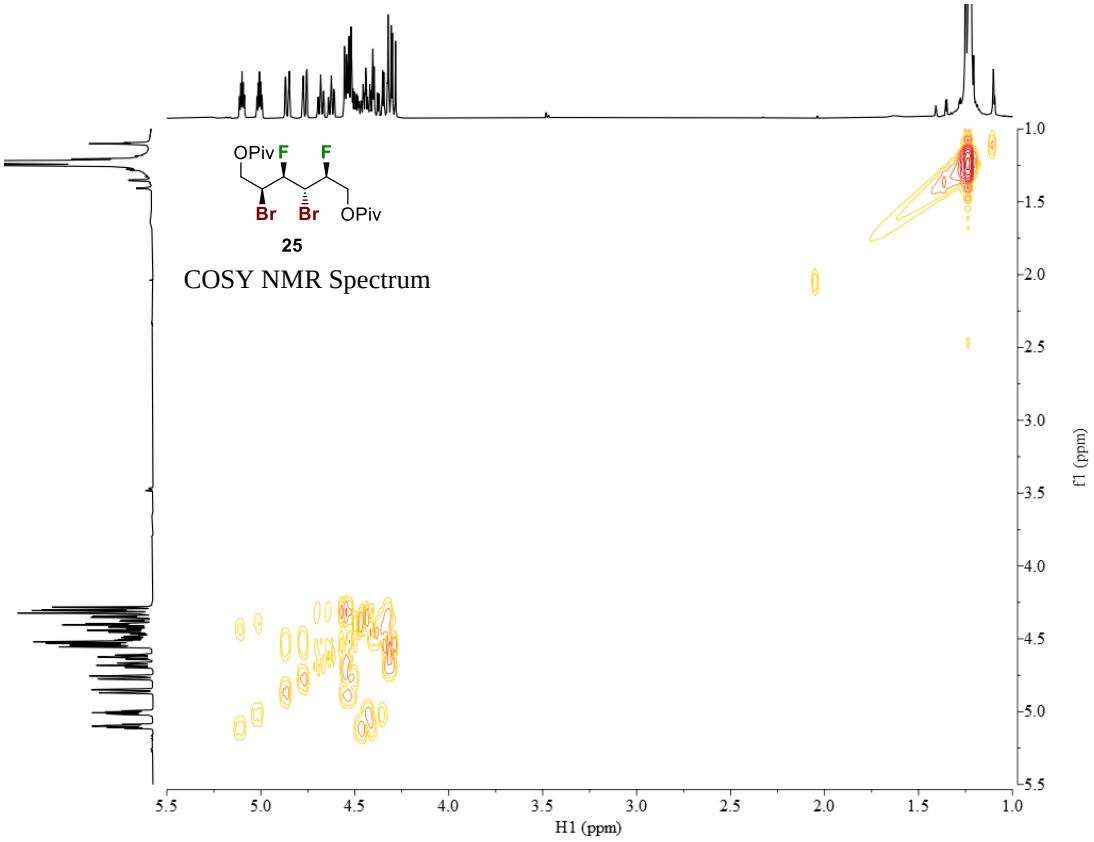
^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)



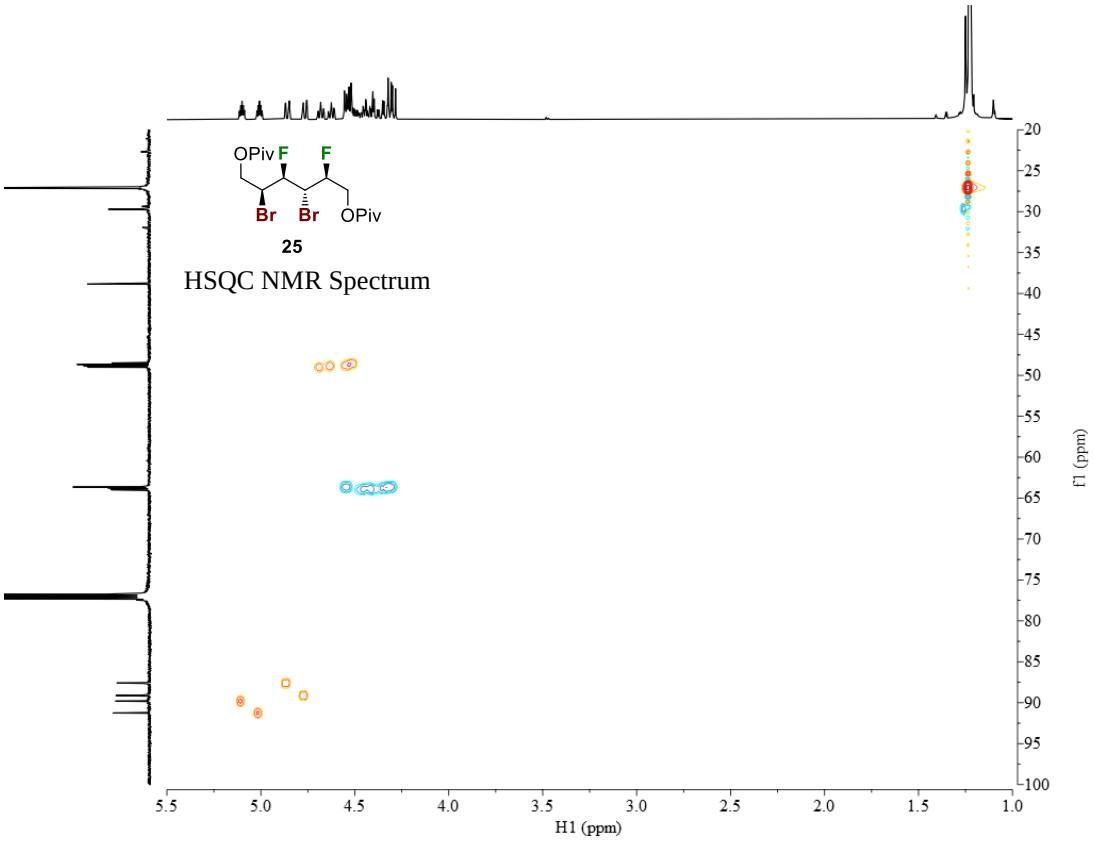
25

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

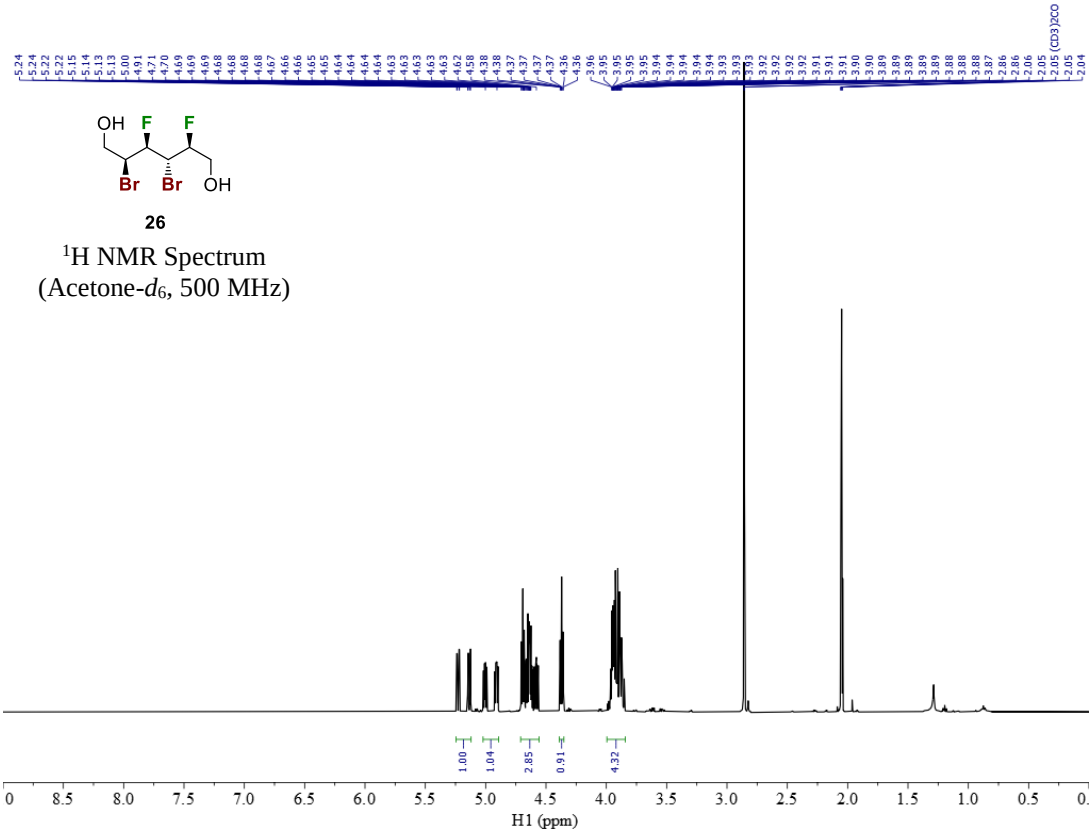




COSY NMR Spectrum

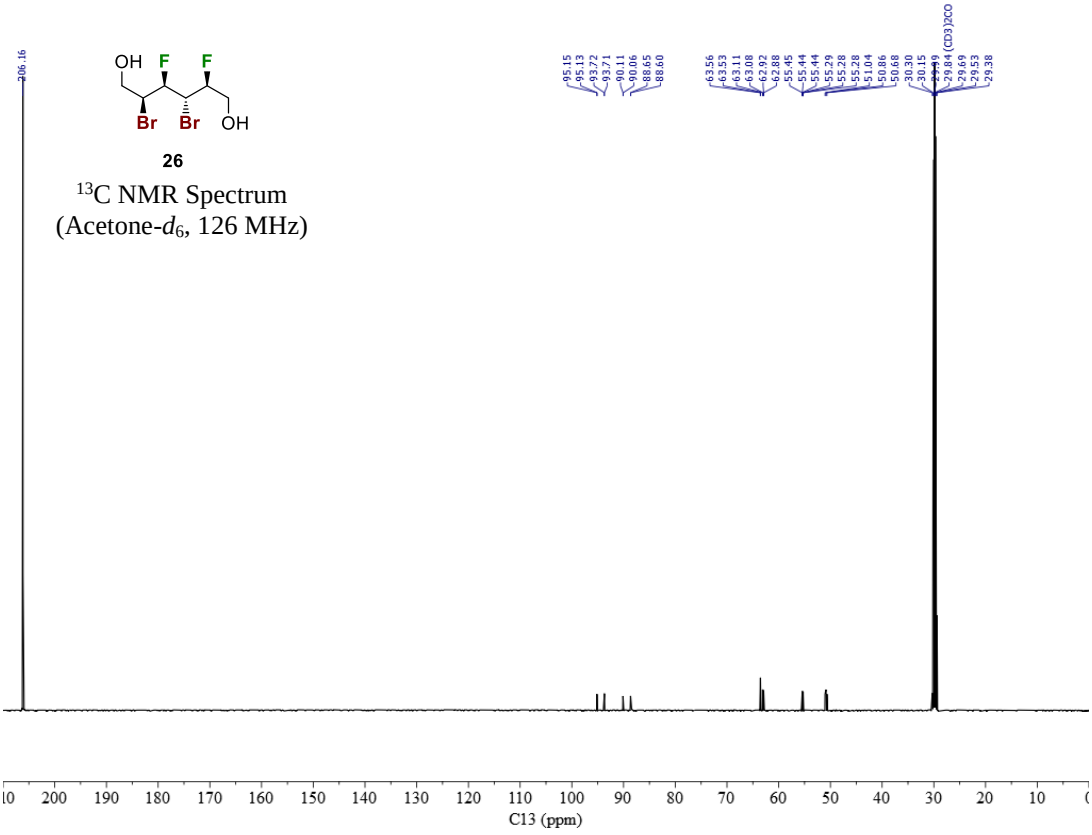


HSQC NMR Spectrum



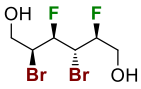
26

^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)



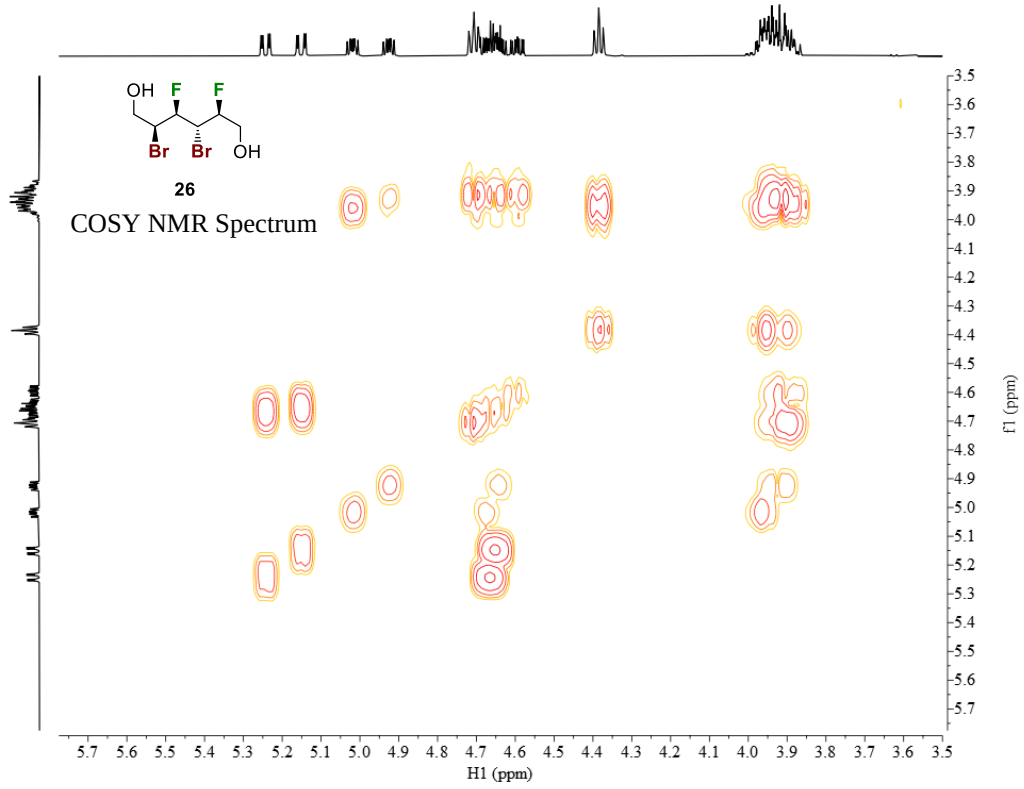
26

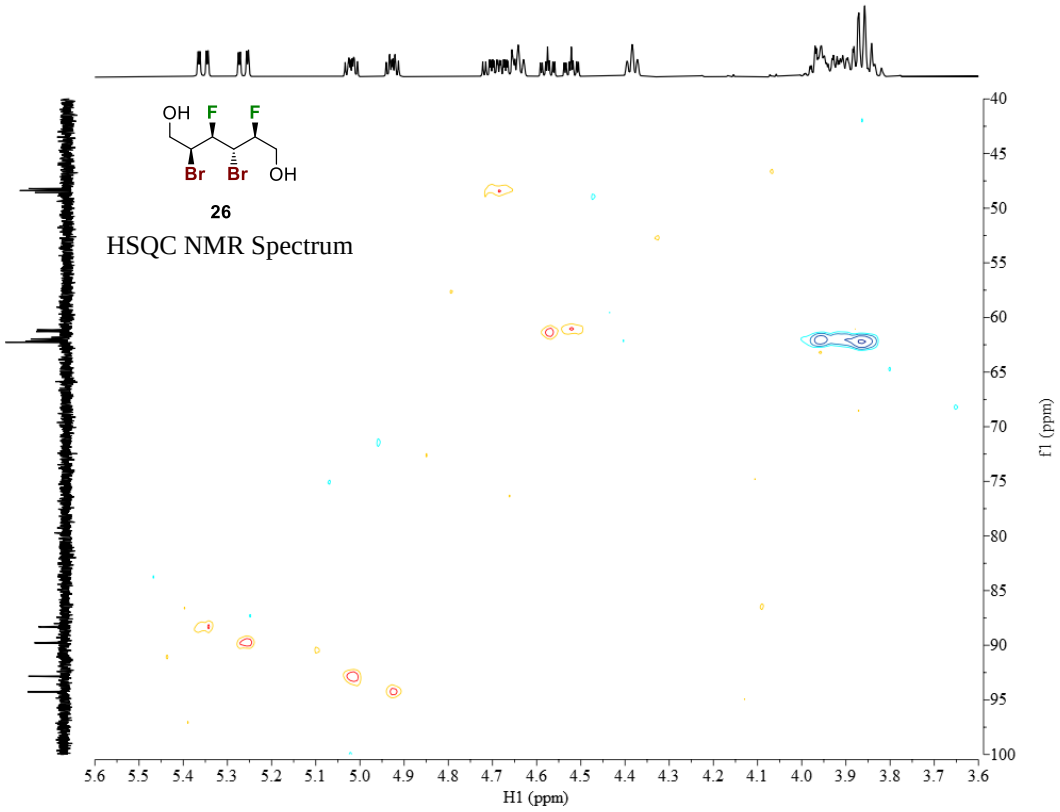
^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)

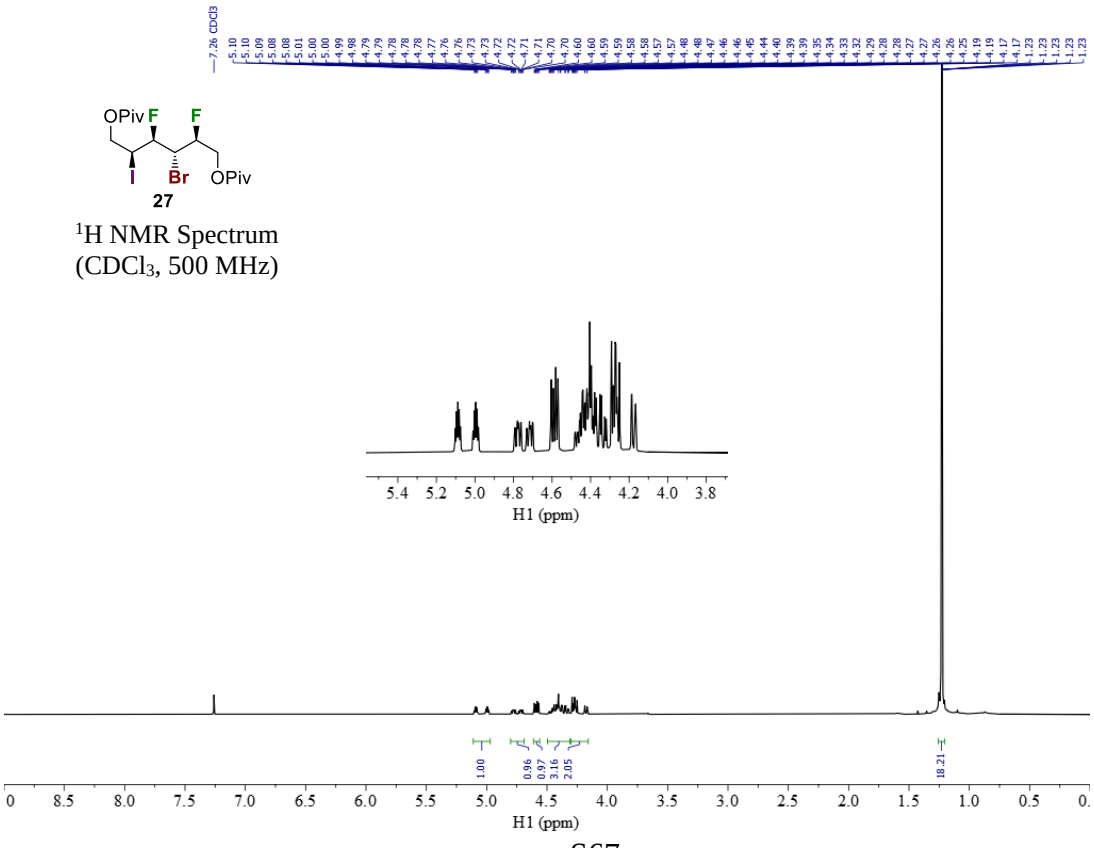


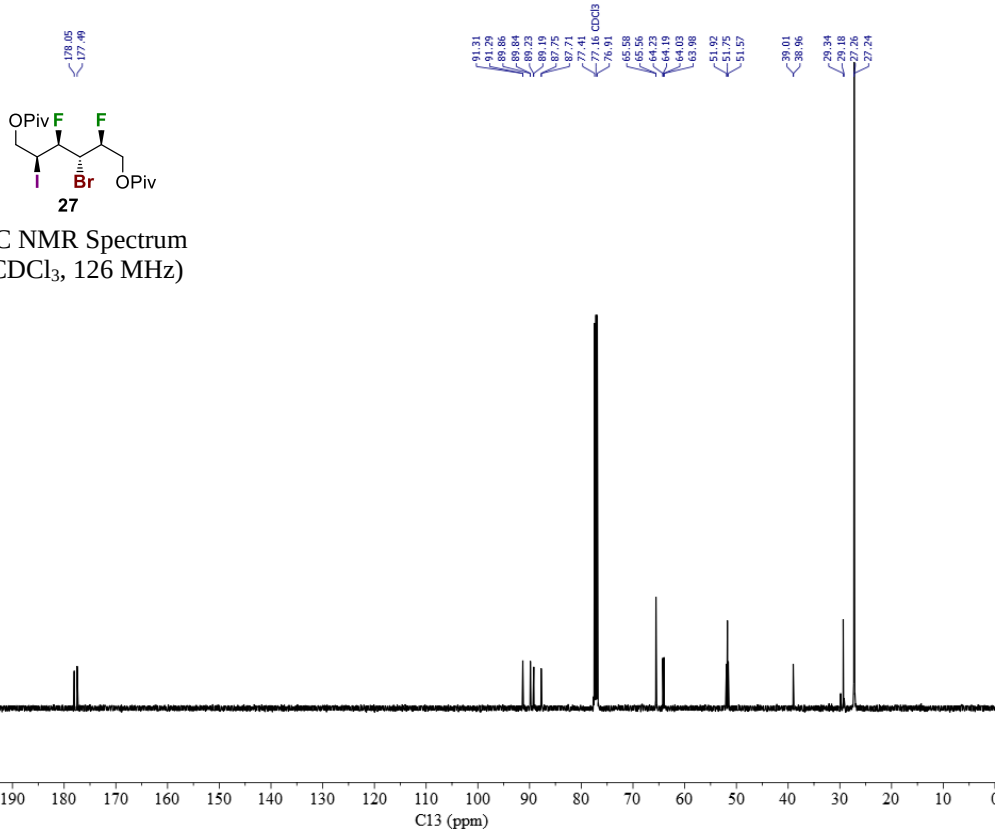
26

^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

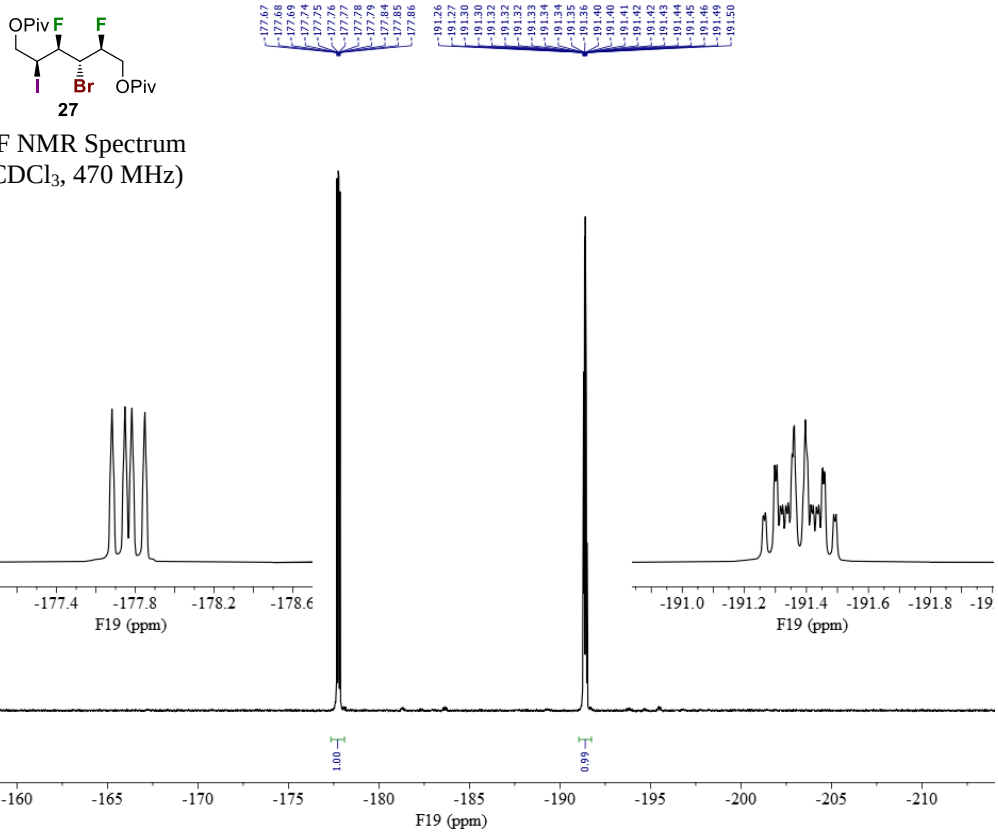



OH F F
Br Br OH
26
HSQC NMR Spectrum
f1 (ppm)
H1 (ppm)

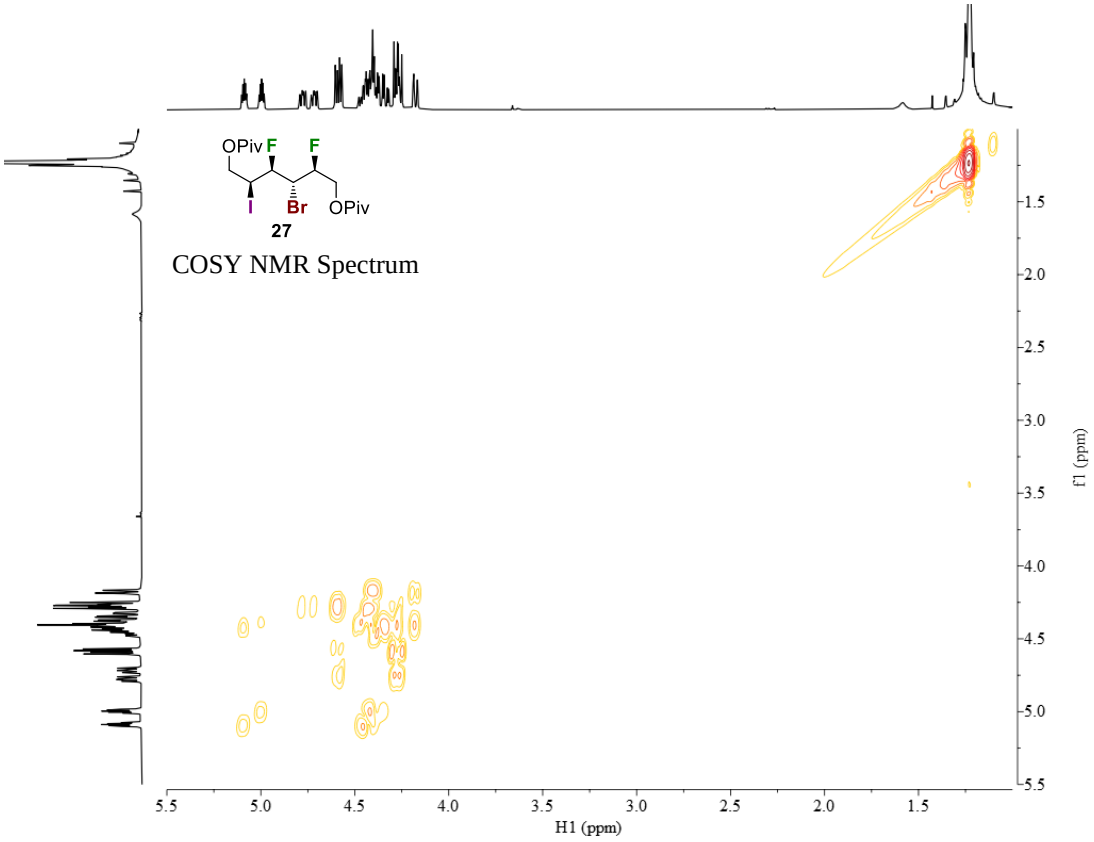

OPiv F F
I Br OPiv
27
1H NMR Spectrum
(CDCl3, 500 MHz)
H1 (ppm)

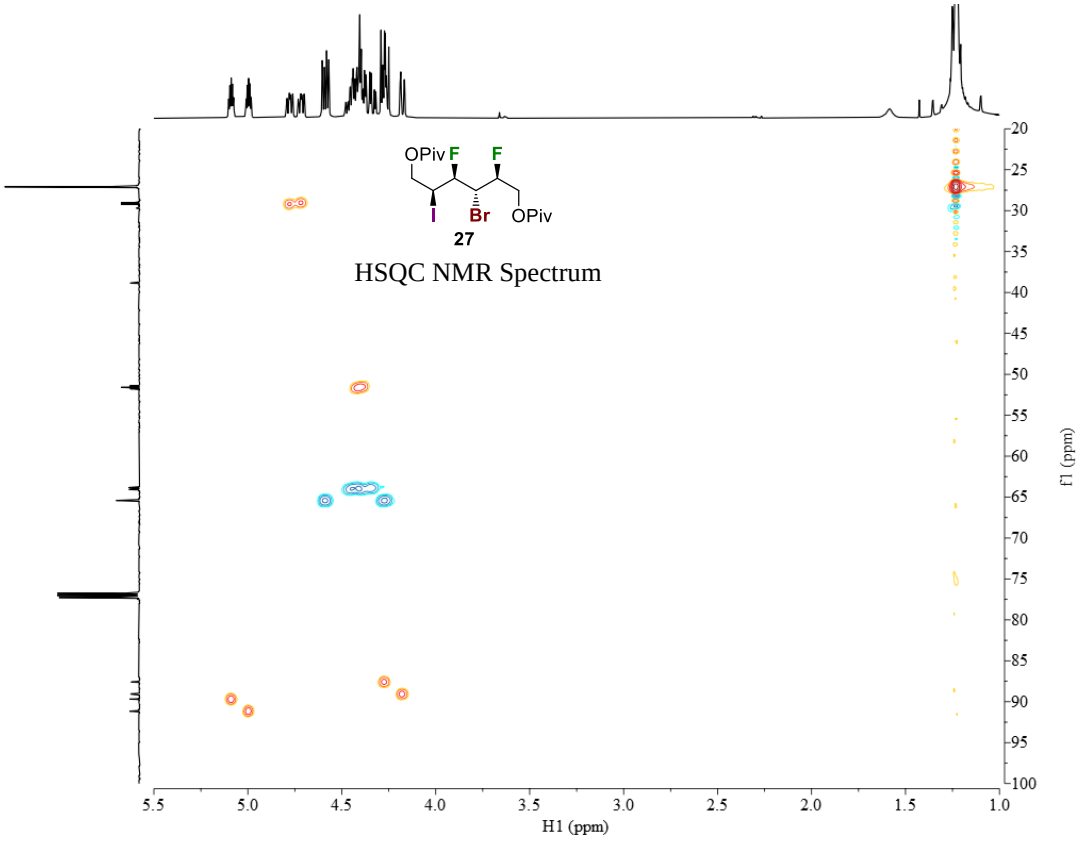


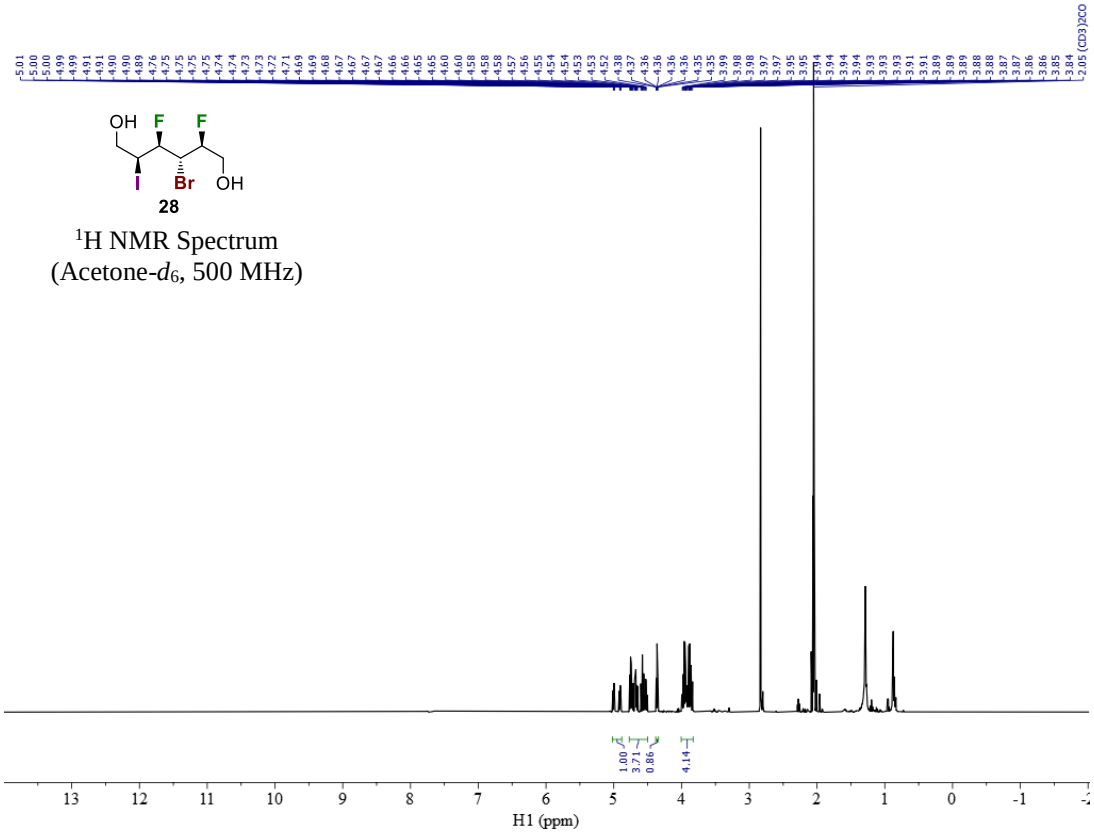
^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)



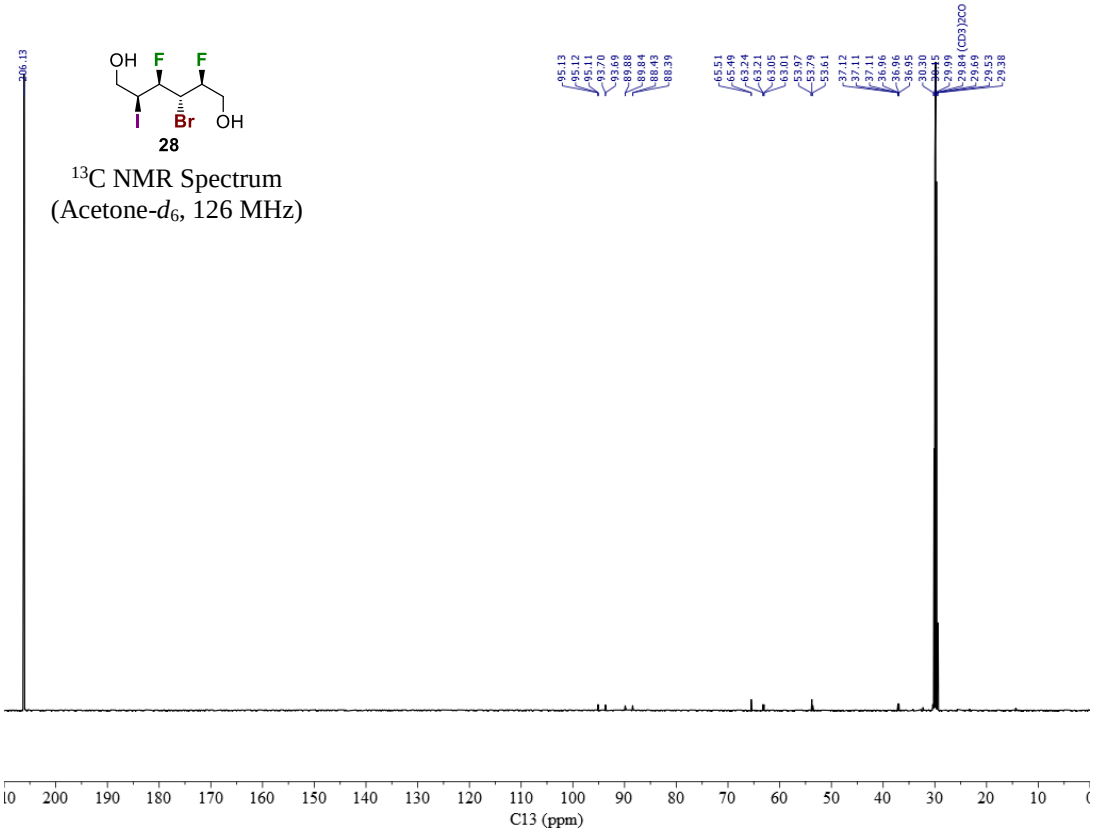
^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)


OPiv F F
I Br OPiv
27
COSY NMR Spectrum
H1 (ppm)
f1 (ppm)

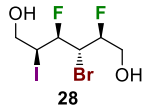

OPiv F F
I Br OPiv
27
HSQC NMR Spectrum
H1 (ppm)
f1 (ppm)



^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)

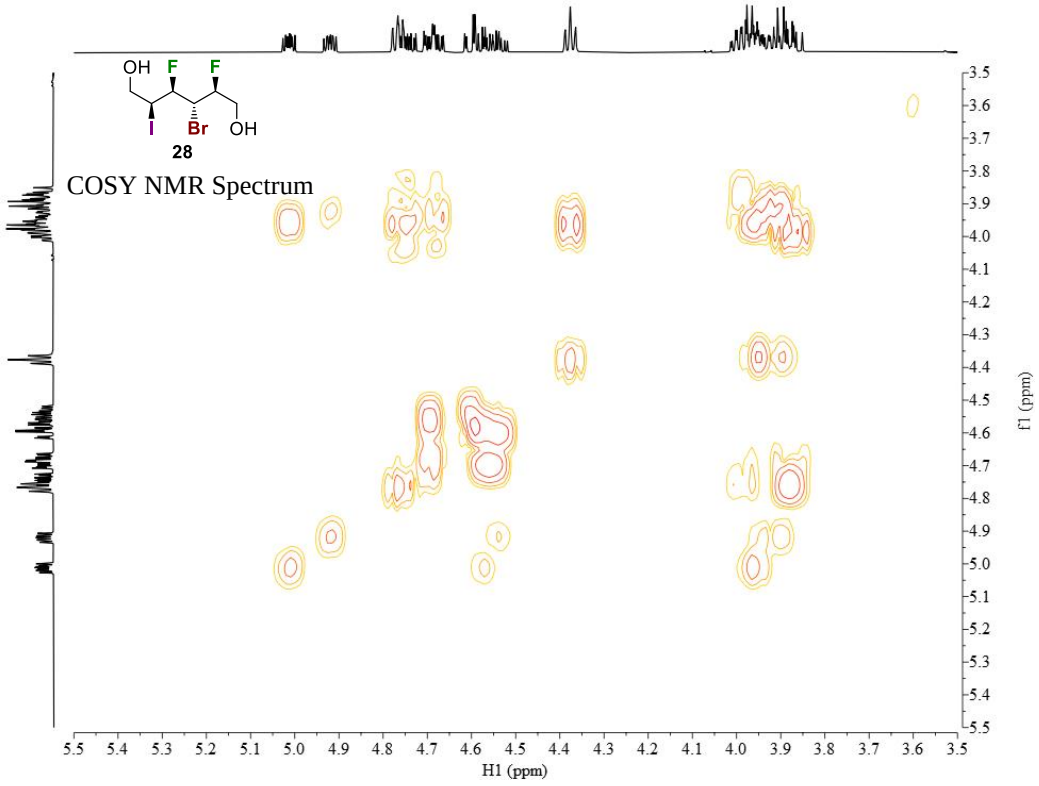


^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)

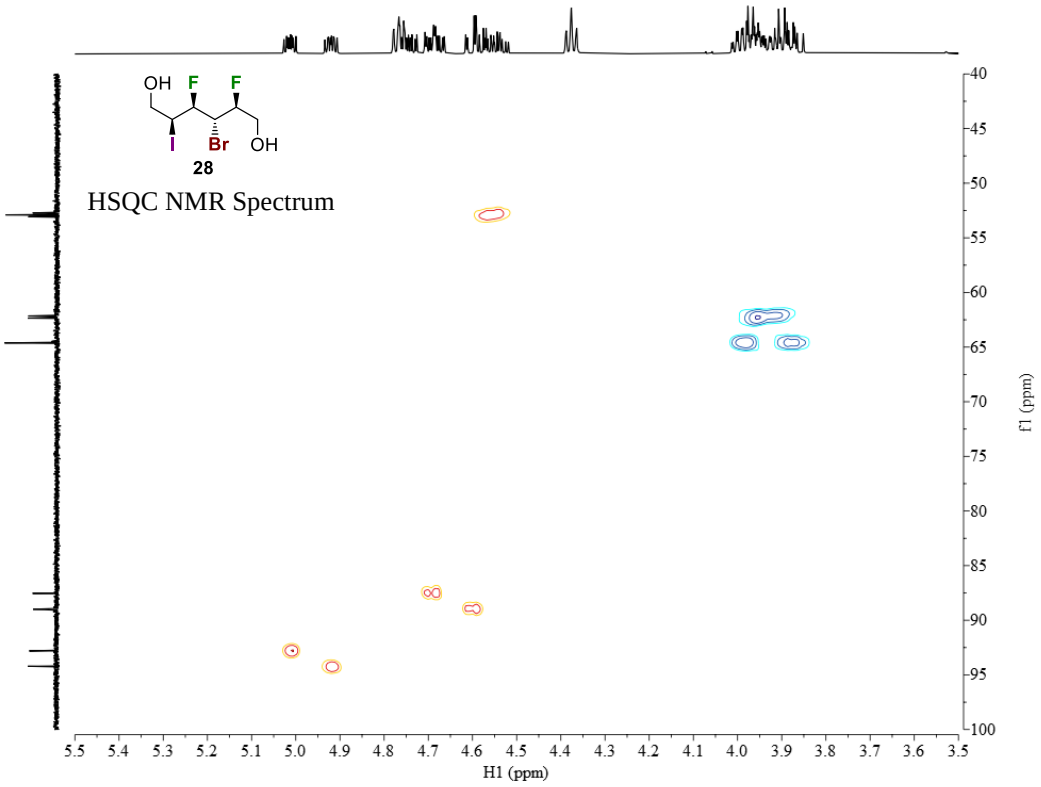


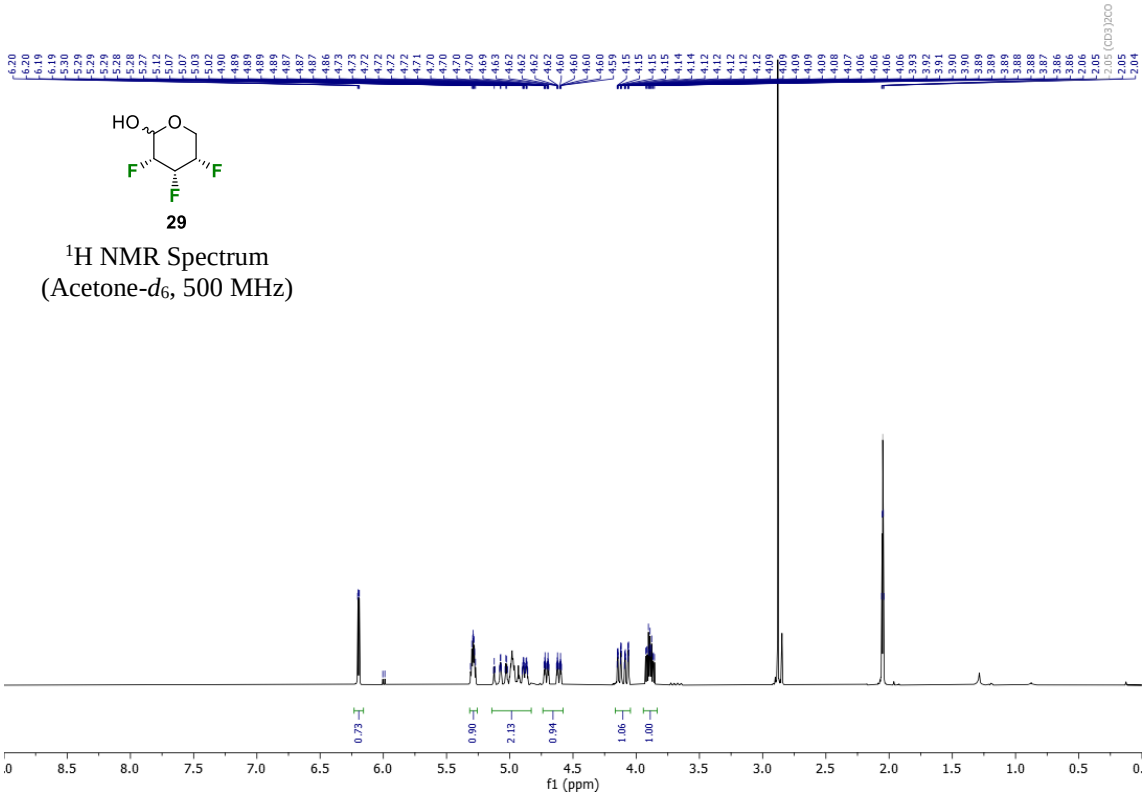
28

^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

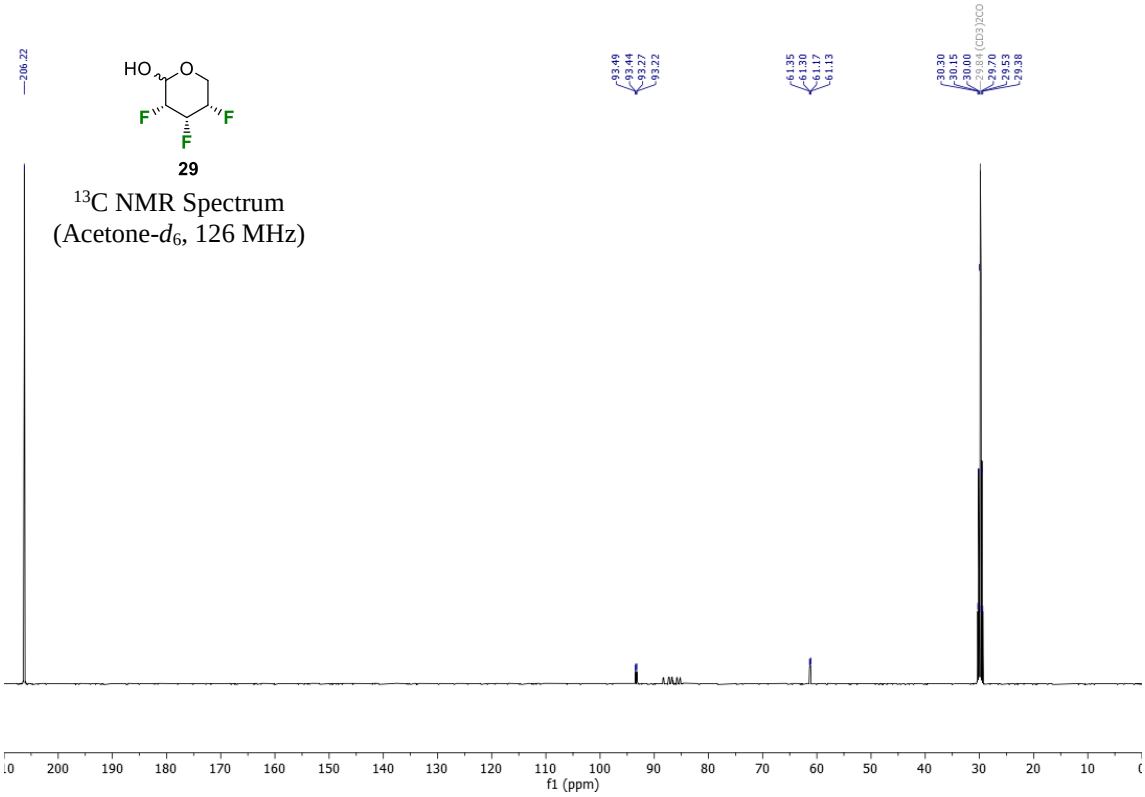


COSY NMR Spectrum



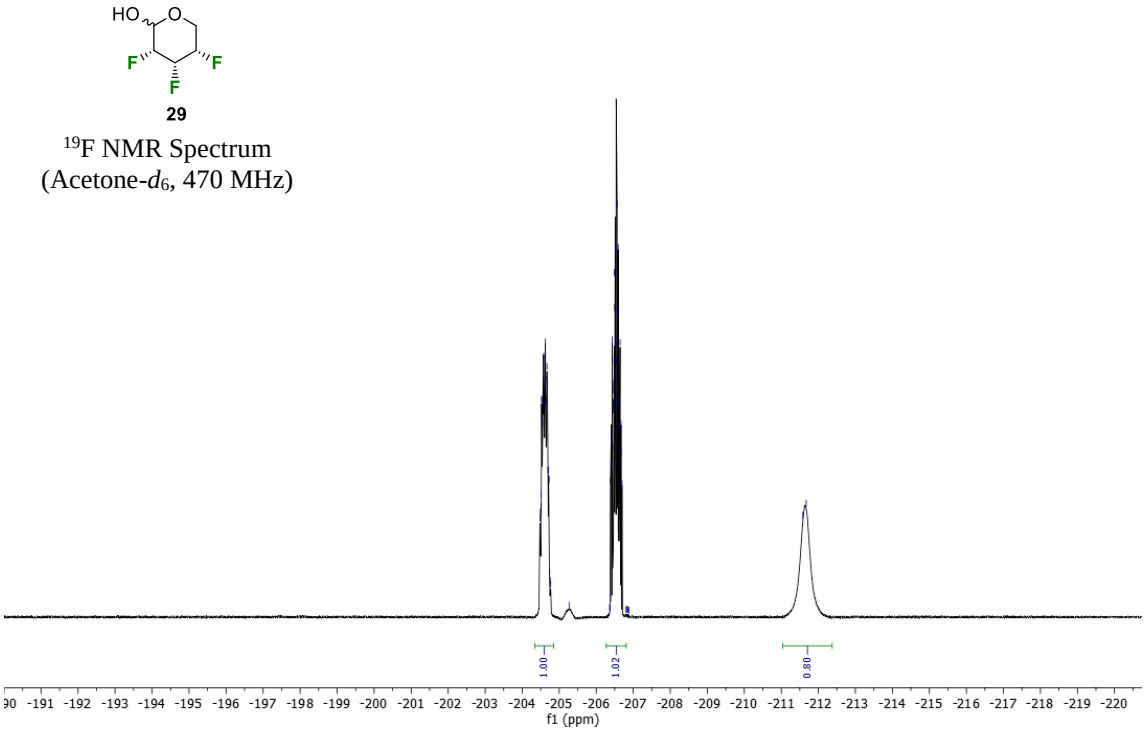


^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)



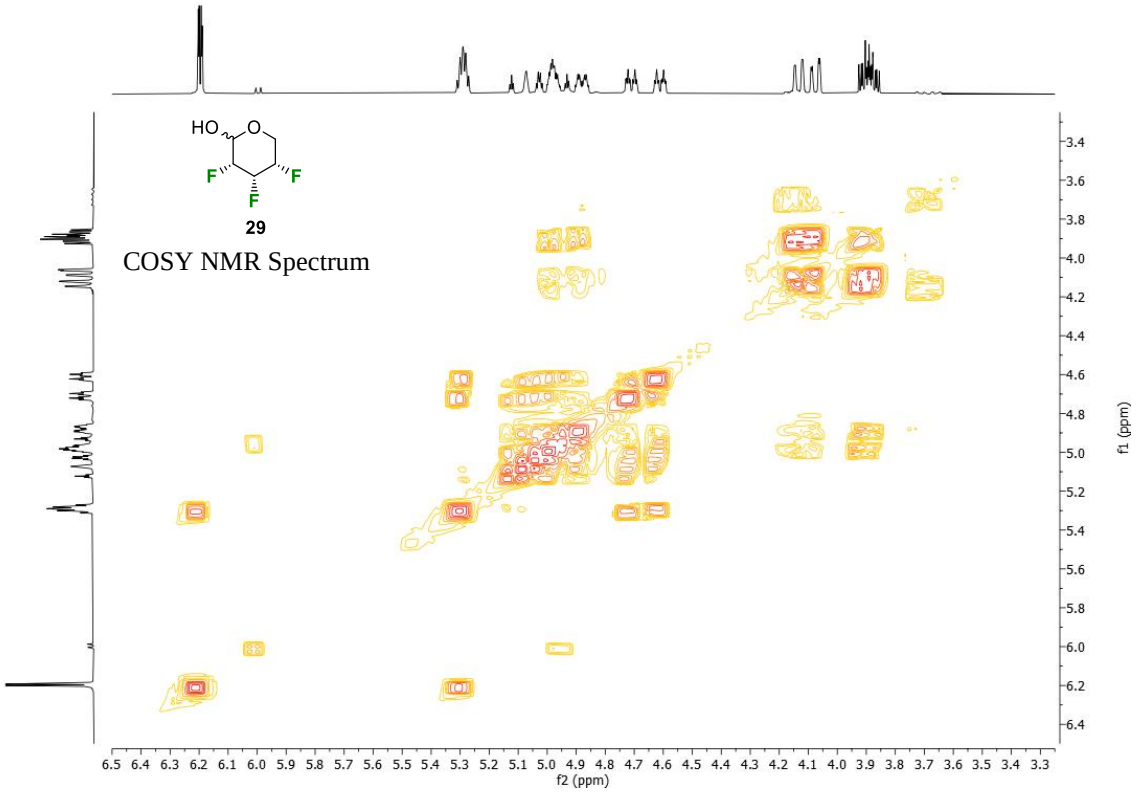
29

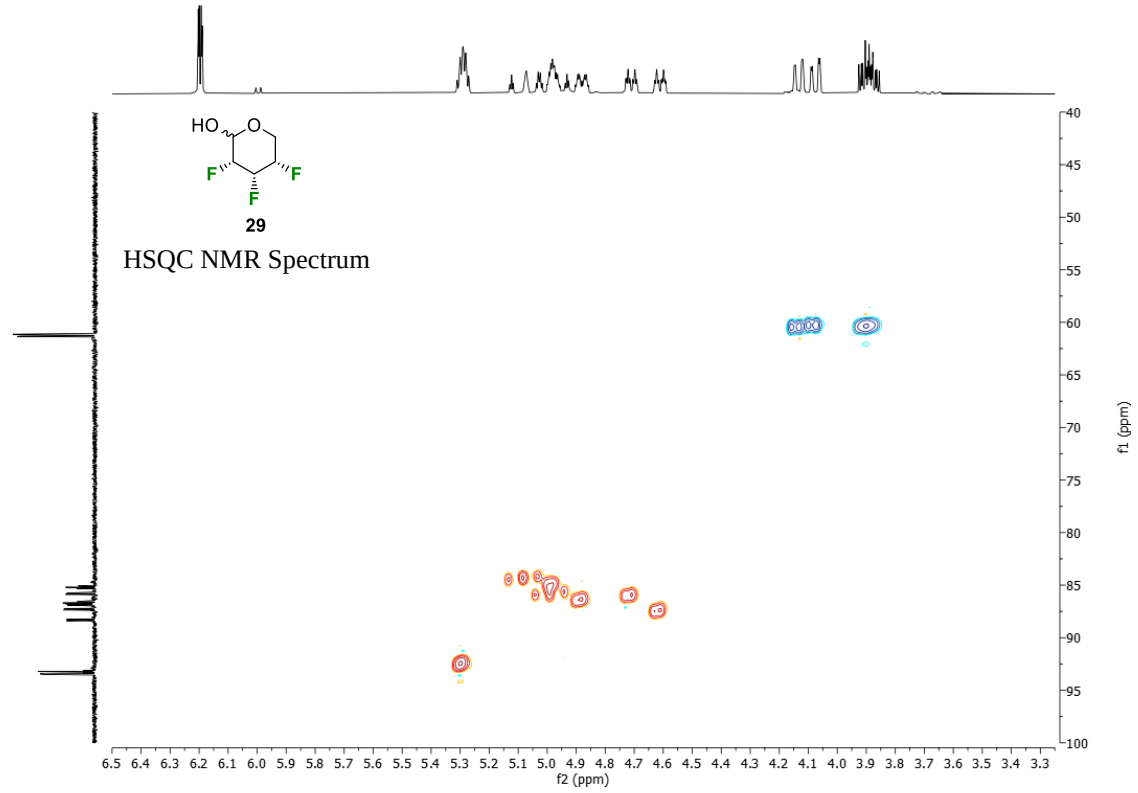
^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)

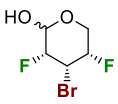


29

^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

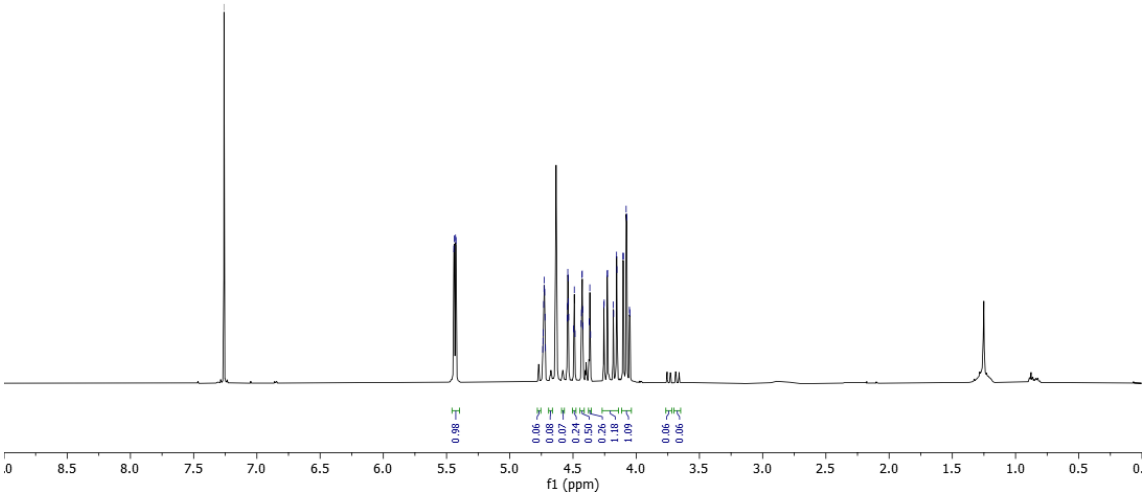

HO
O
F
F
F
29
COSY NMR Spectrum
f1 (ppm)
f2 (ppm)

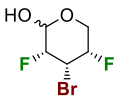

HO
O
F
F
F
29
HSQC NMR Spectrum
f1 (ppm)
f2 (ppm)



30

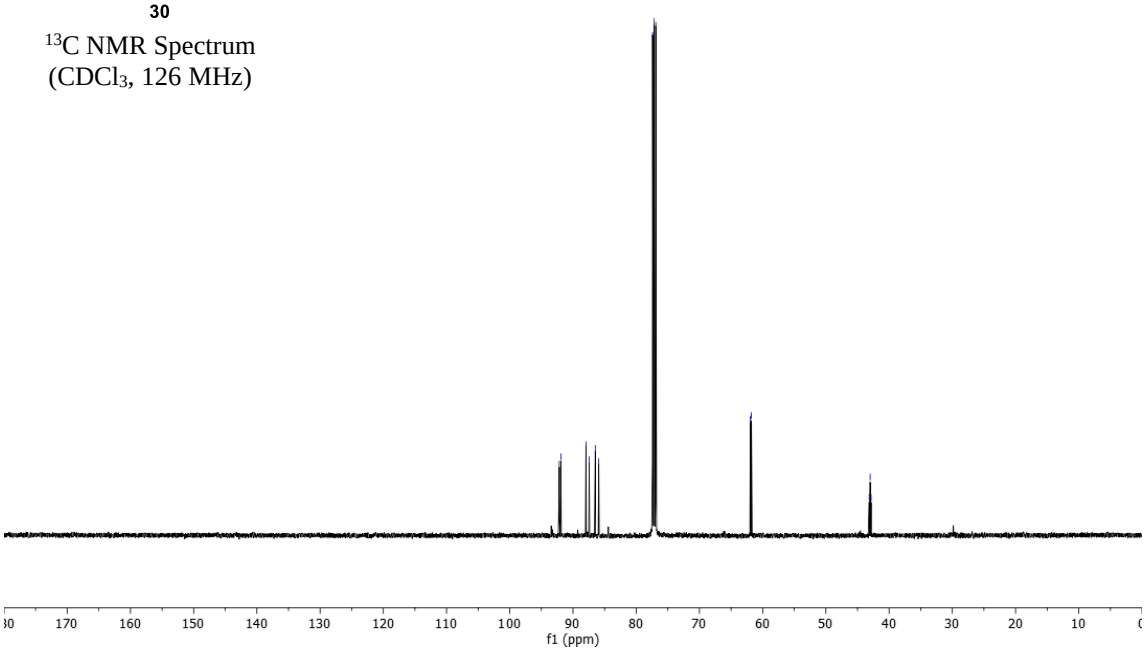
^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)

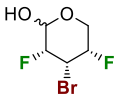




30

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



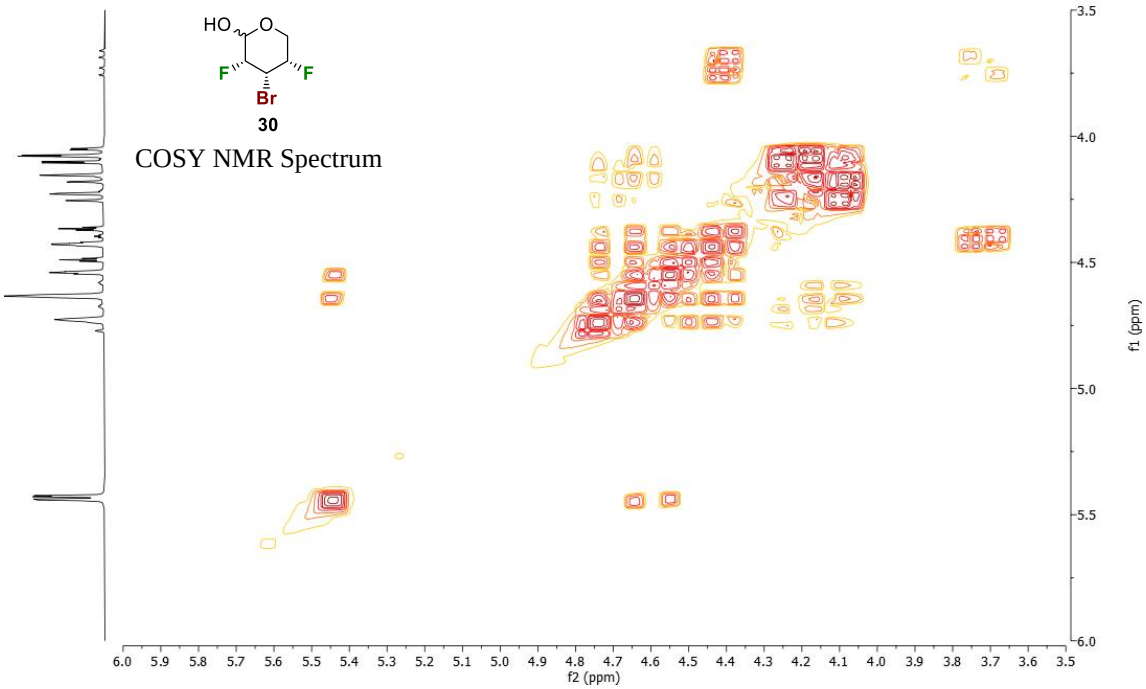


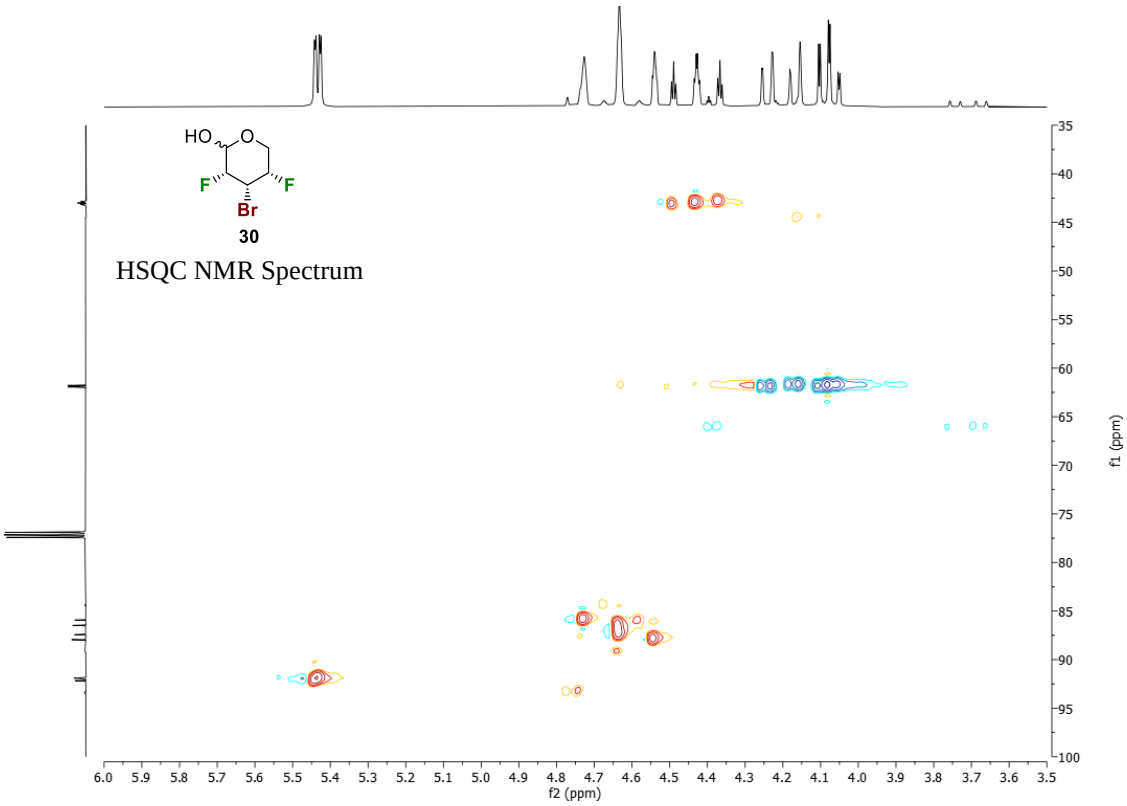
30

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

30

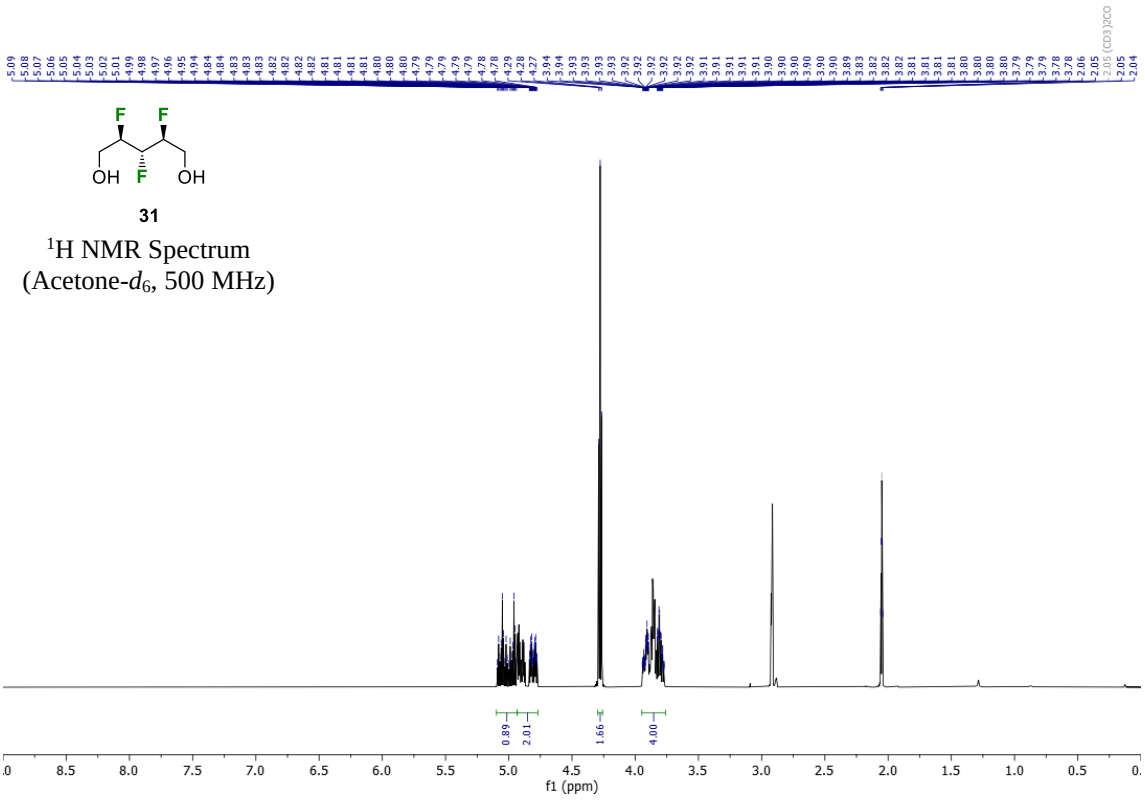
COSY NMR Spectrum





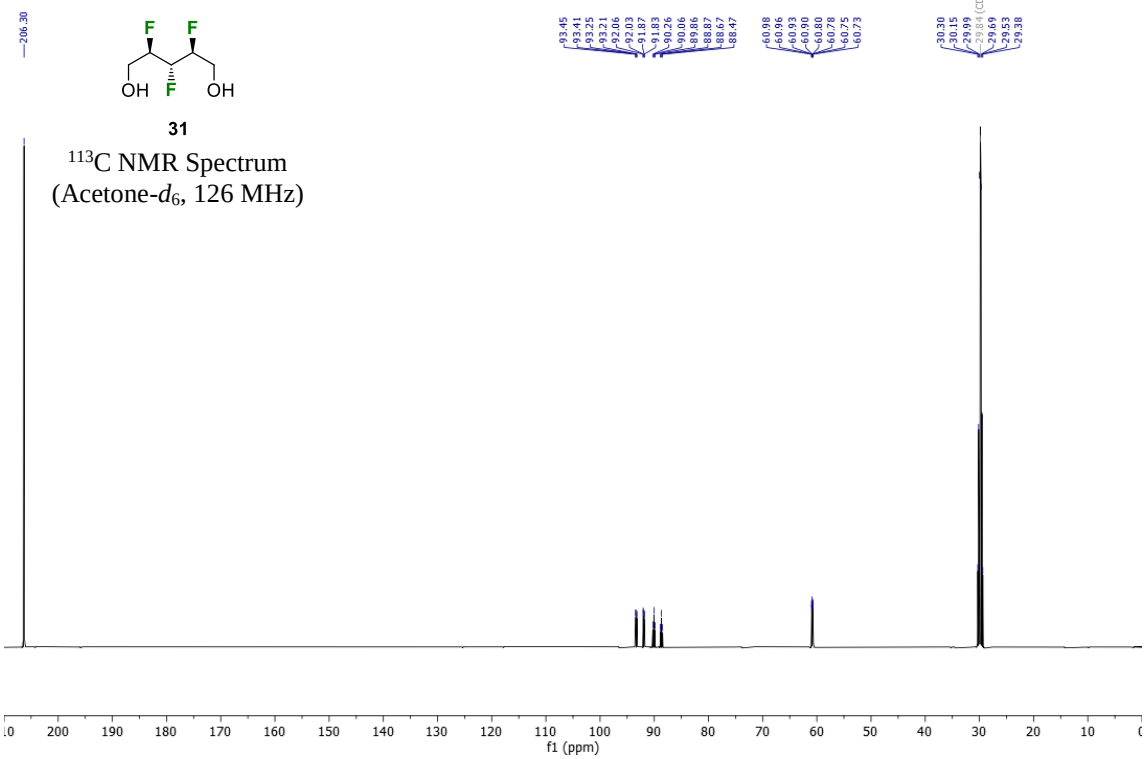
30

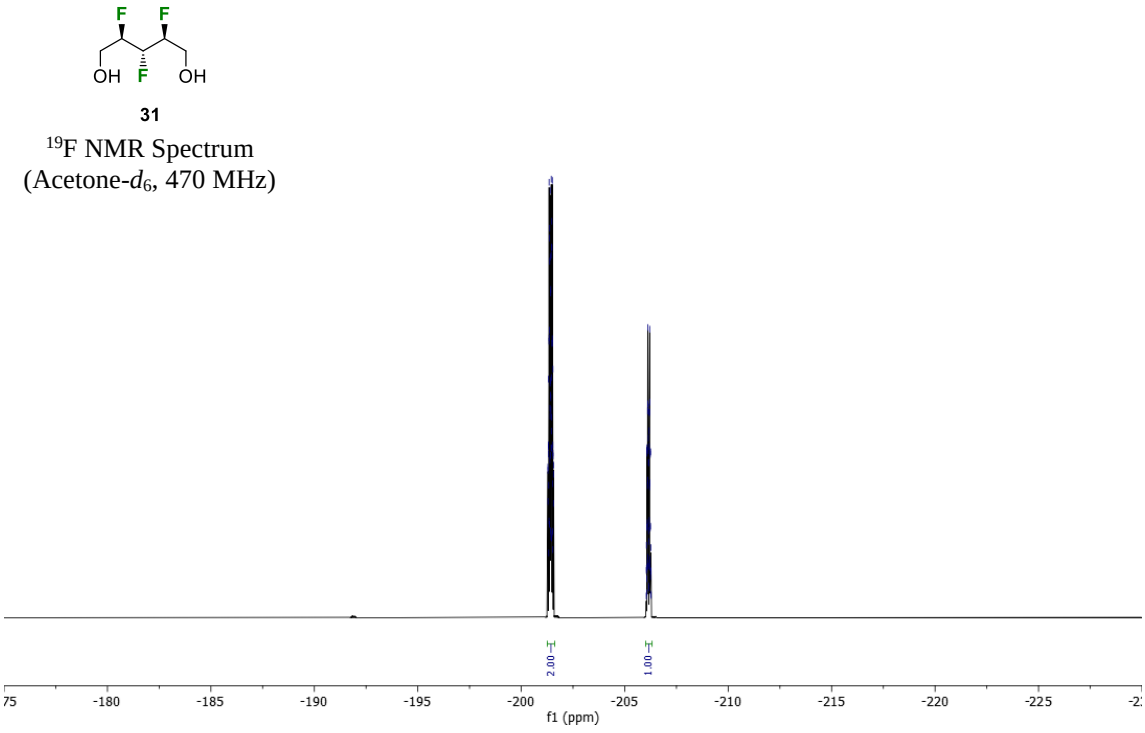
HSQC NMR Spectrum

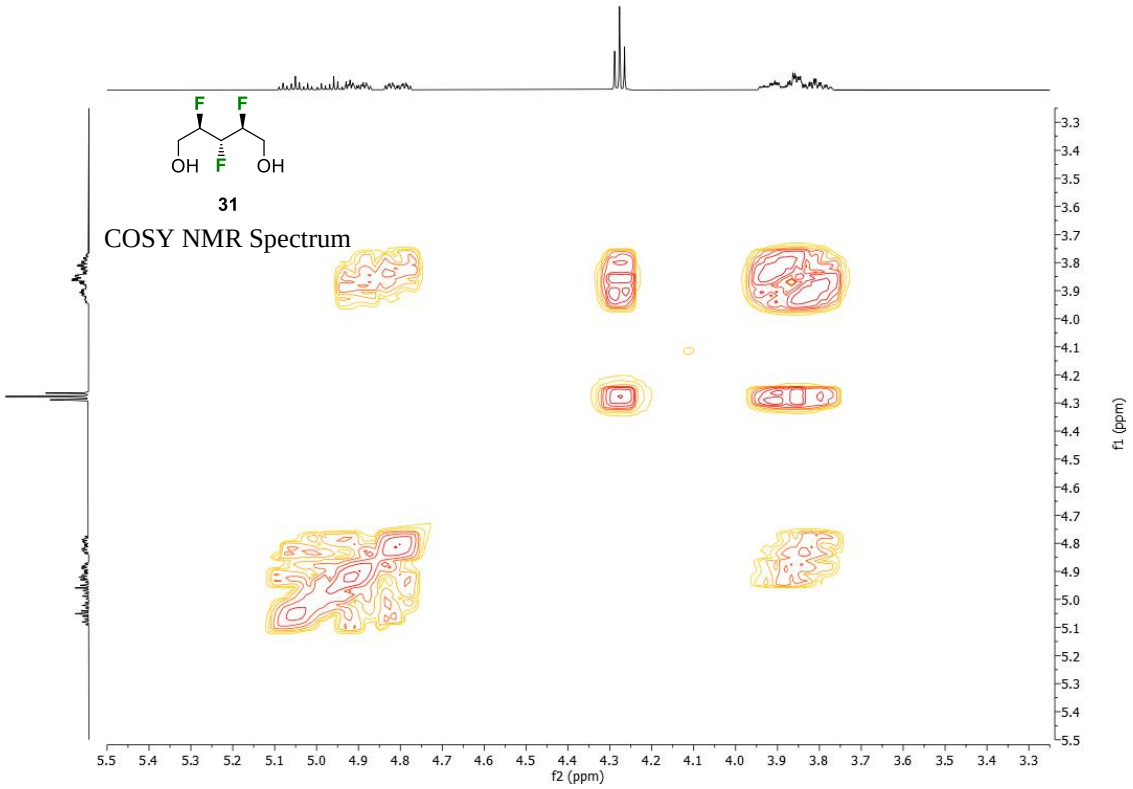


31

^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)

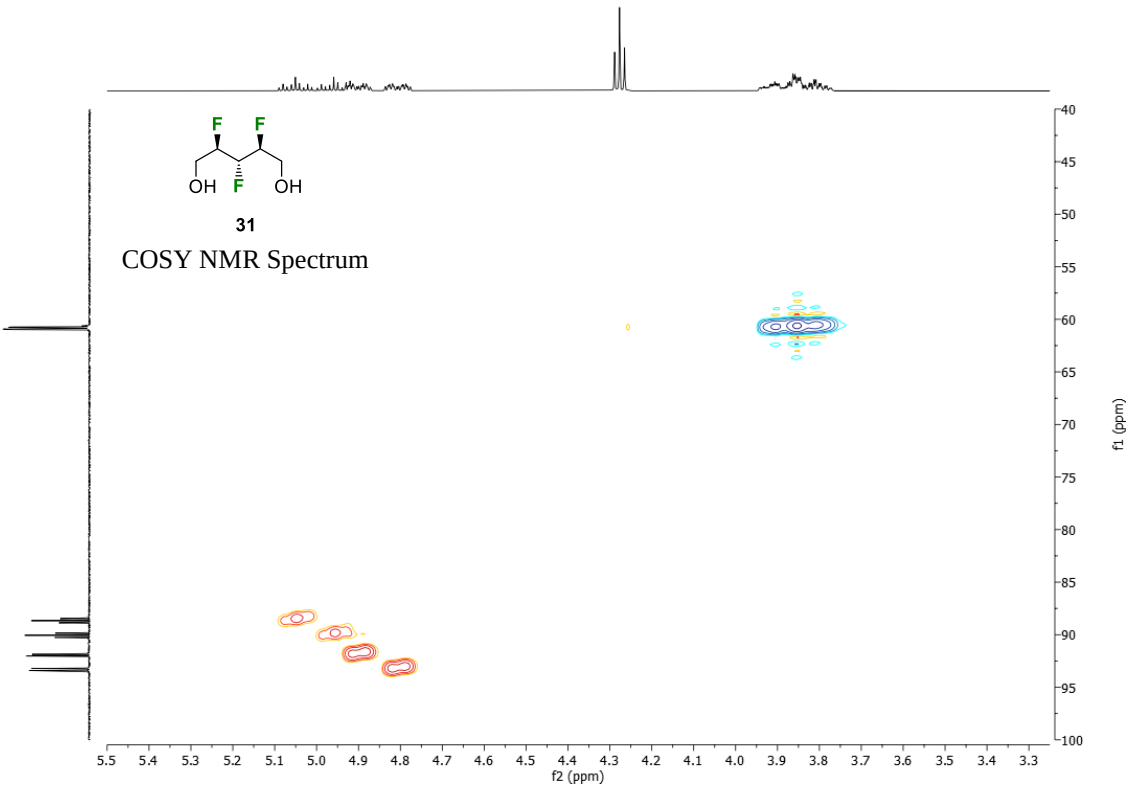

F F
OH F OH
31
^{113}C NMR Spectrum
(Acetone-d_6, 126 MHz)
f1 (ppm)


F F
OH F OH
31
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)
f1 (ppm)



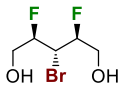
31

COSY NMR Spectrum



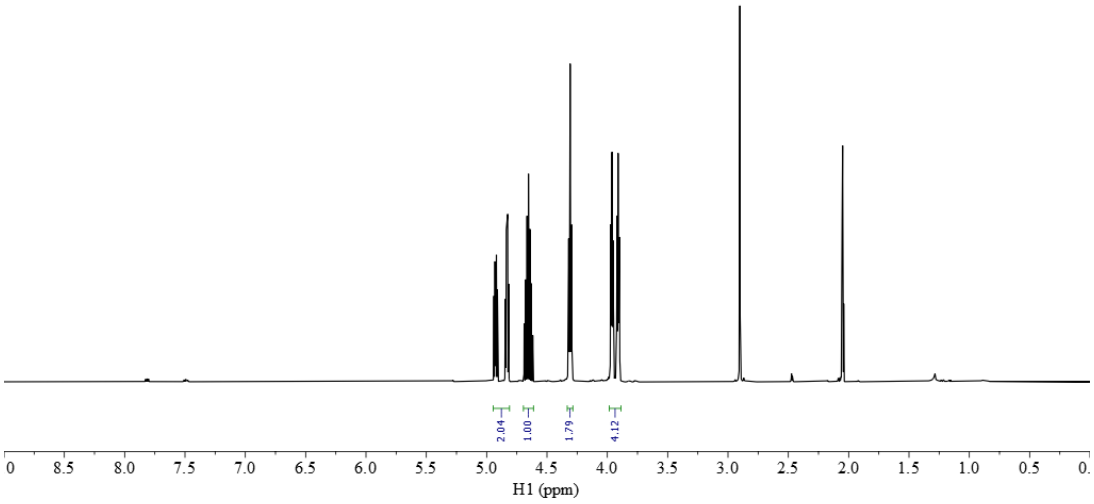
31

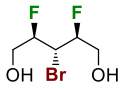
COSY NMR Spectrum



32

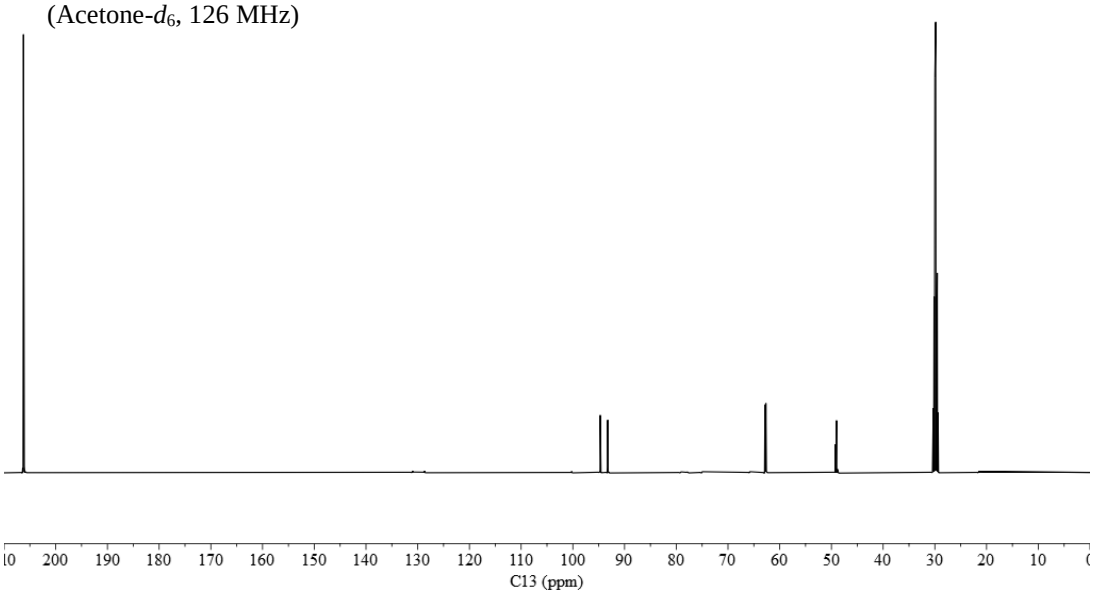
^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)

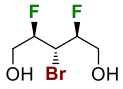




32

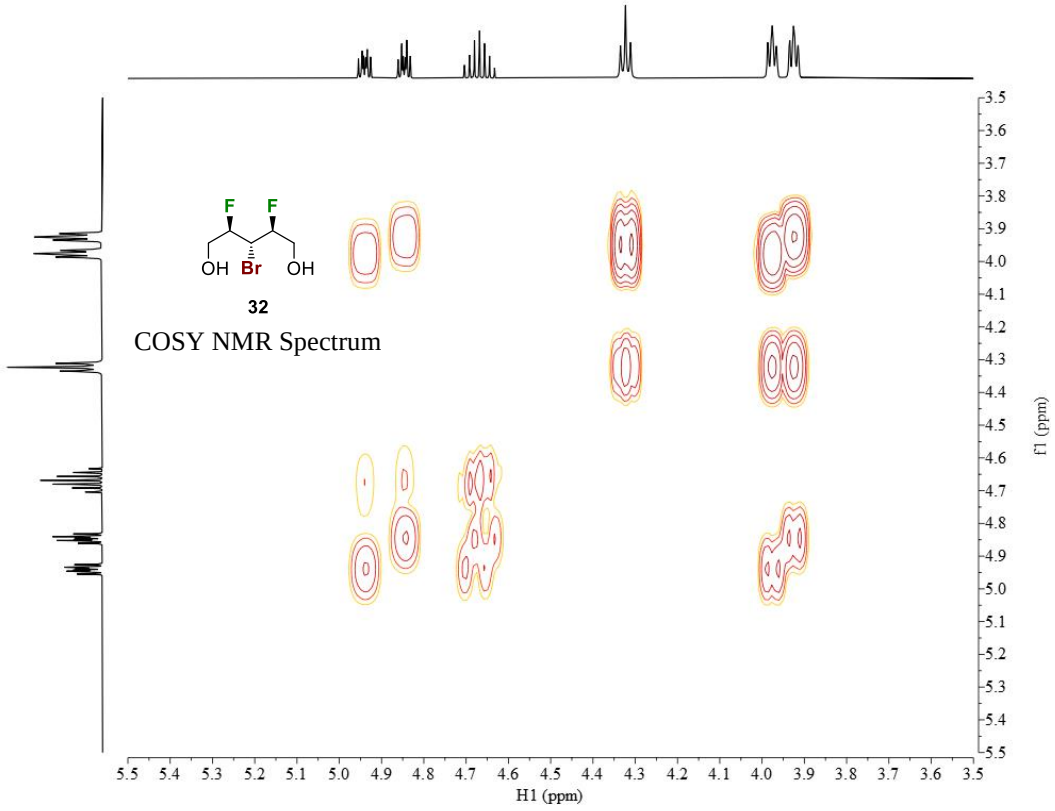
^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)





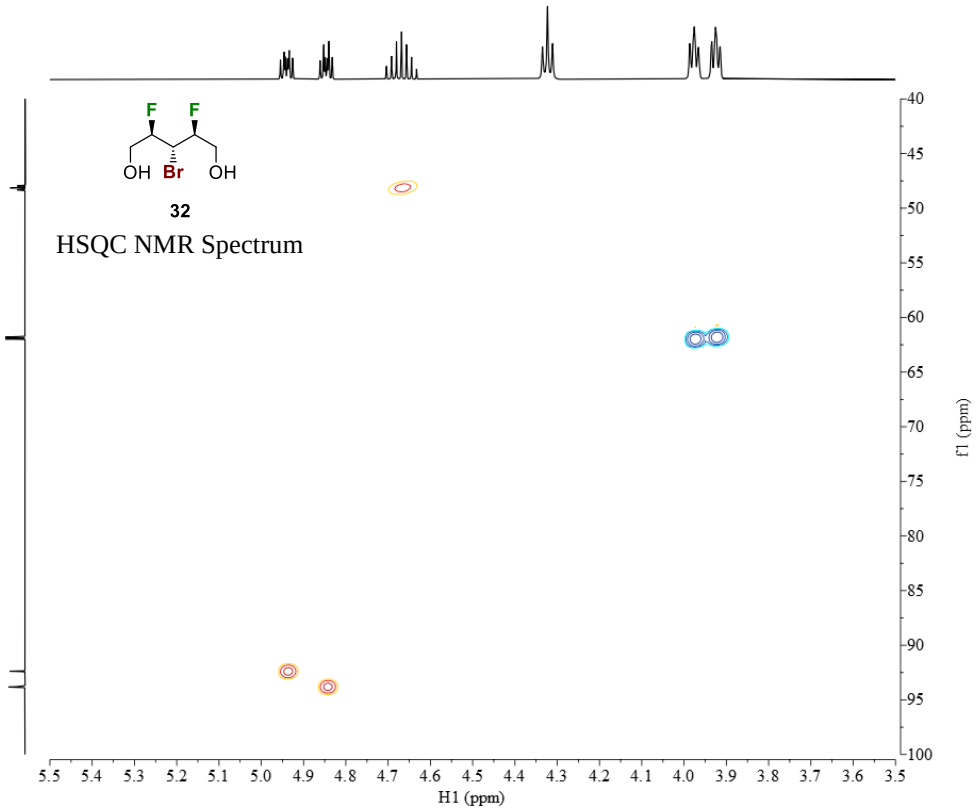
32

^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



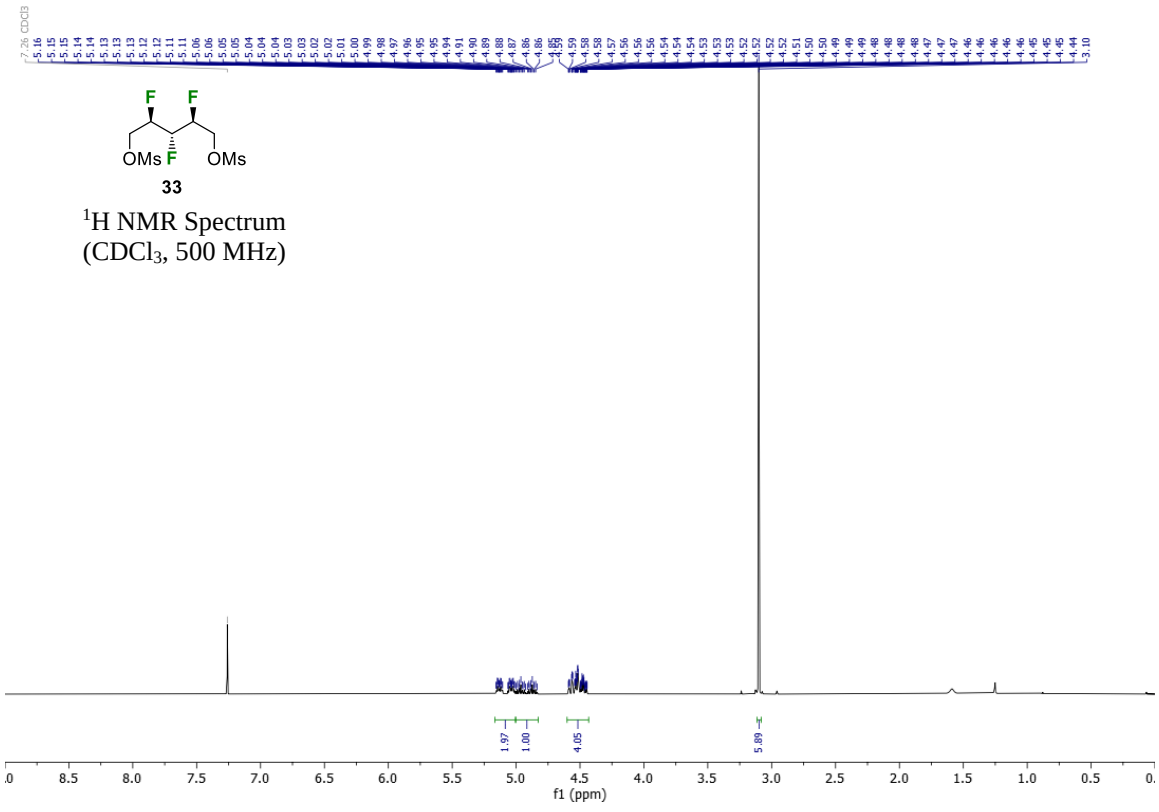
32

COSY NMR Spectrum



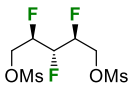
32

HSQC NMR Spectrum



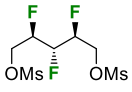
33

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



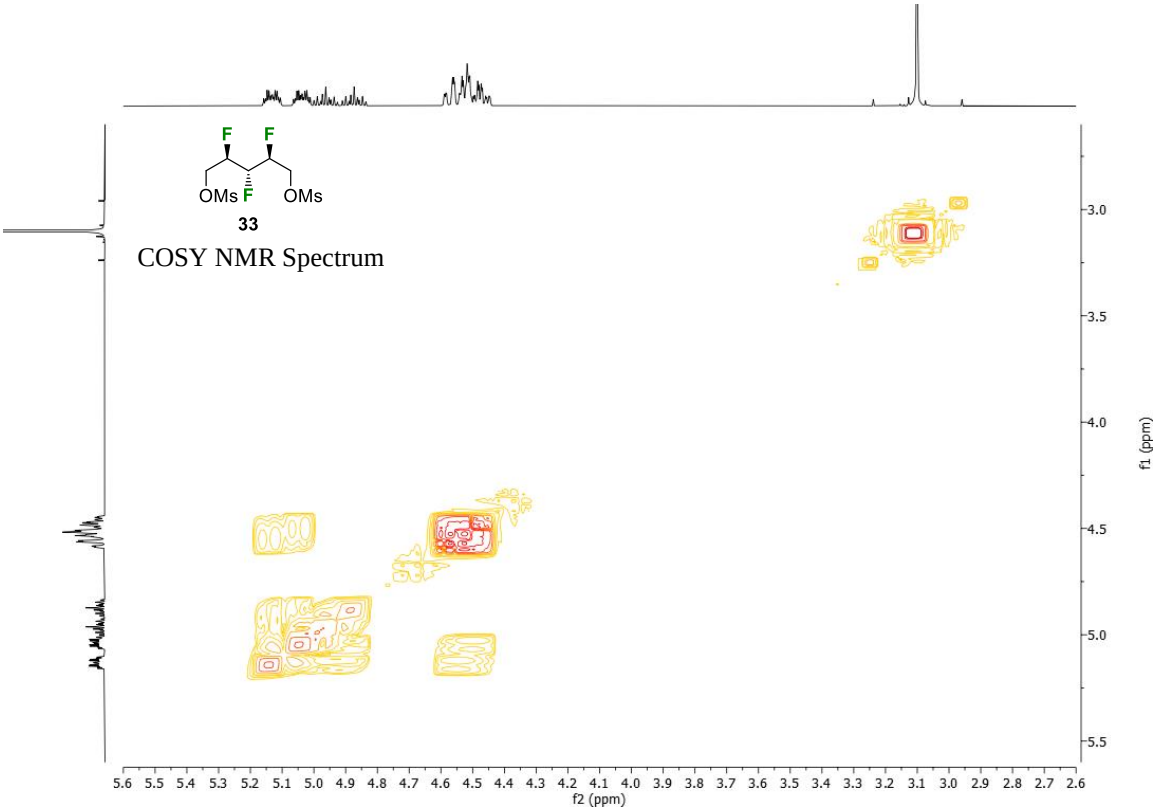
33

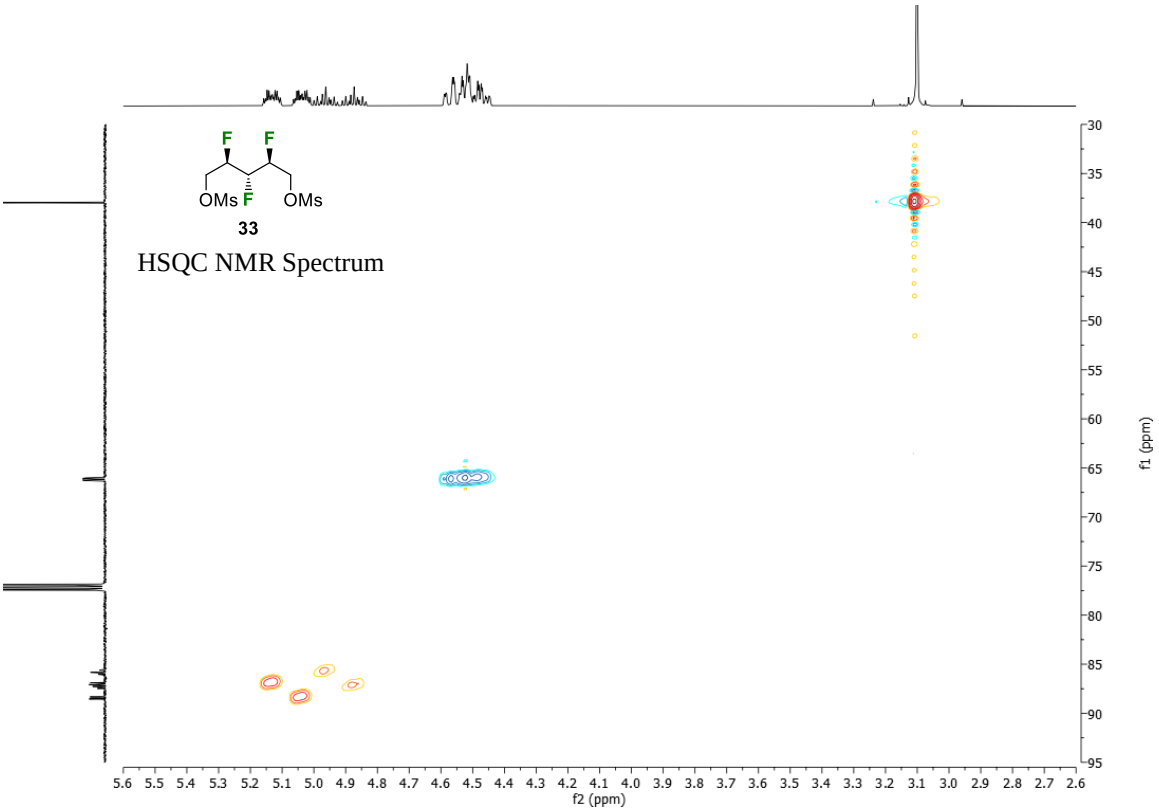
^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)

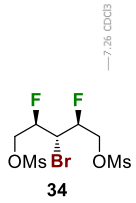


33

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

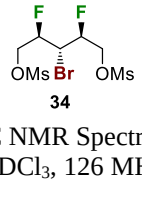

F F
OMs F OMs
33
COSY NMR Spectrum
f2 (ppm)
f1 (ppm)


F F
OMs F OMs
33
HSQC NMR Spectrum
f2 (ppm)
f1 (ppm)



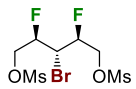
34

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



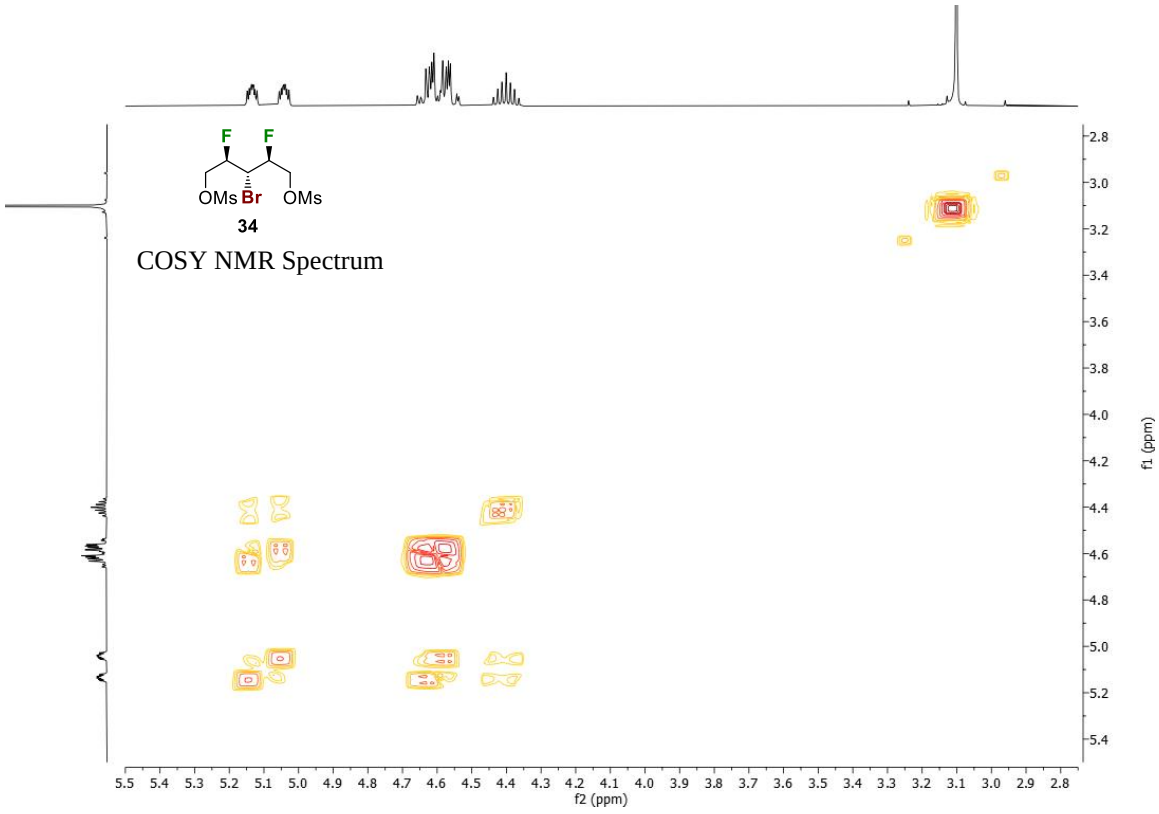
34

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

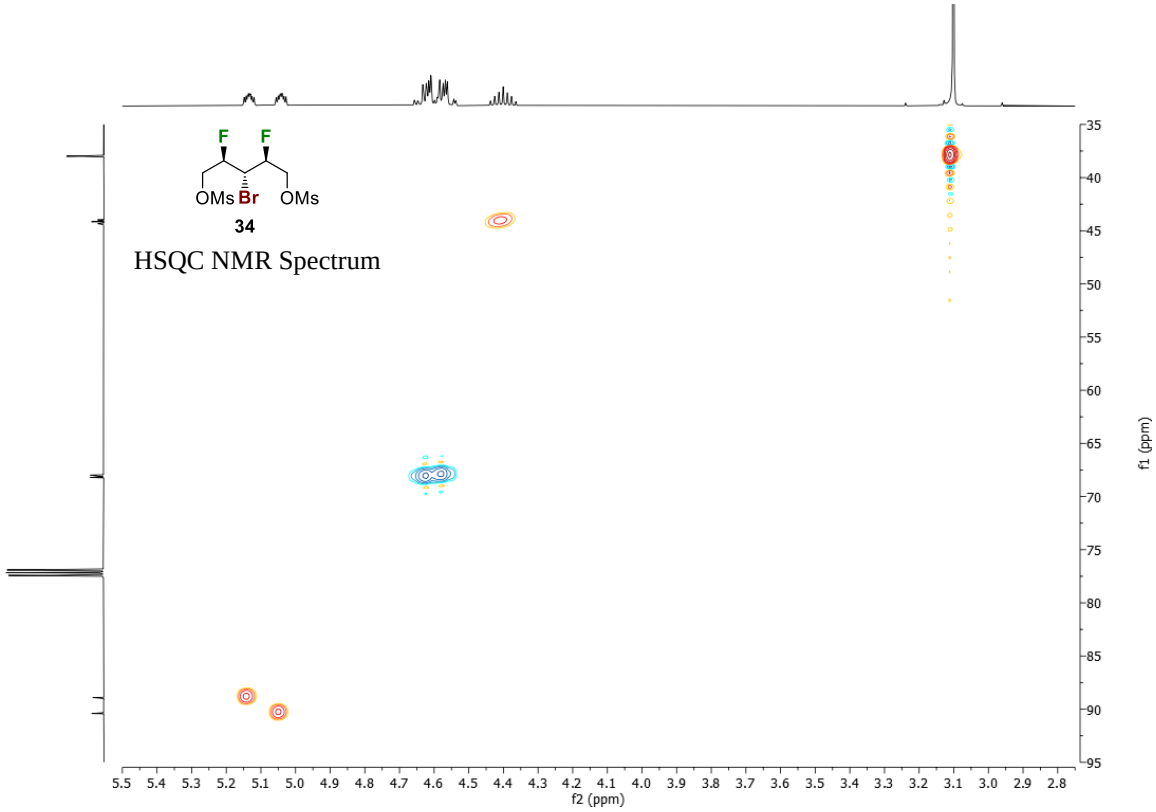


34

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

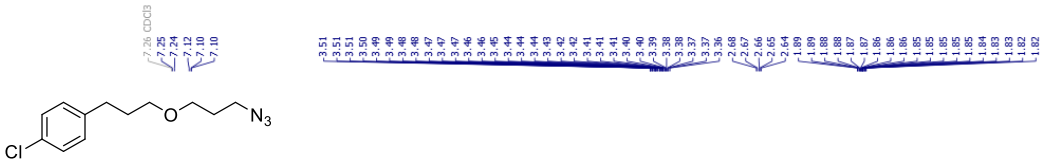


COSY NMR Spectrum



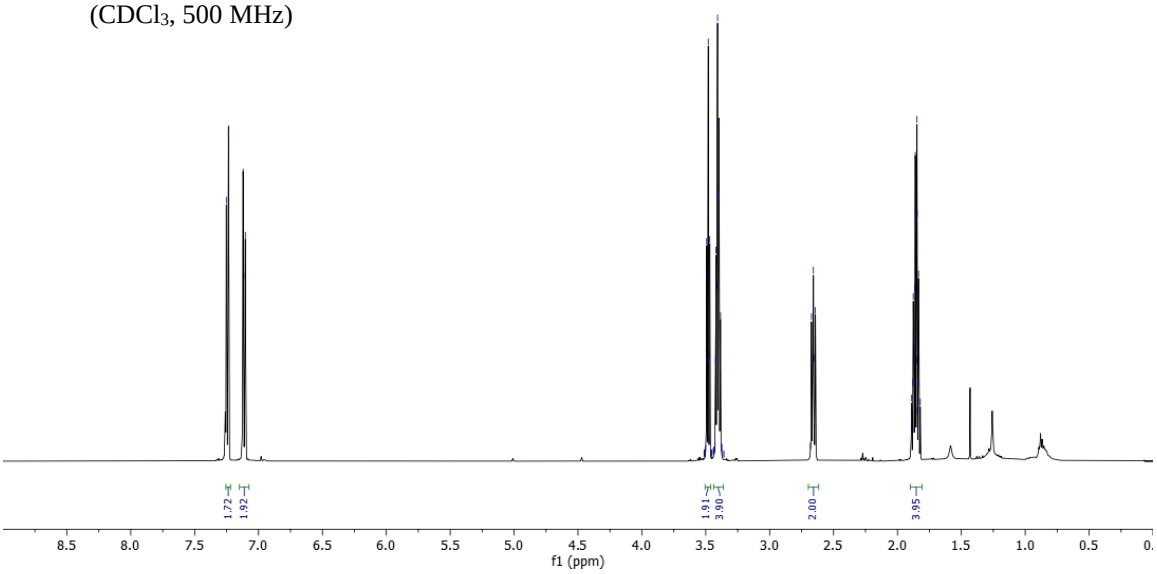
34

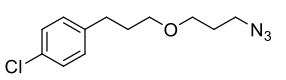
HSQC NMR Spectrum



S9

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



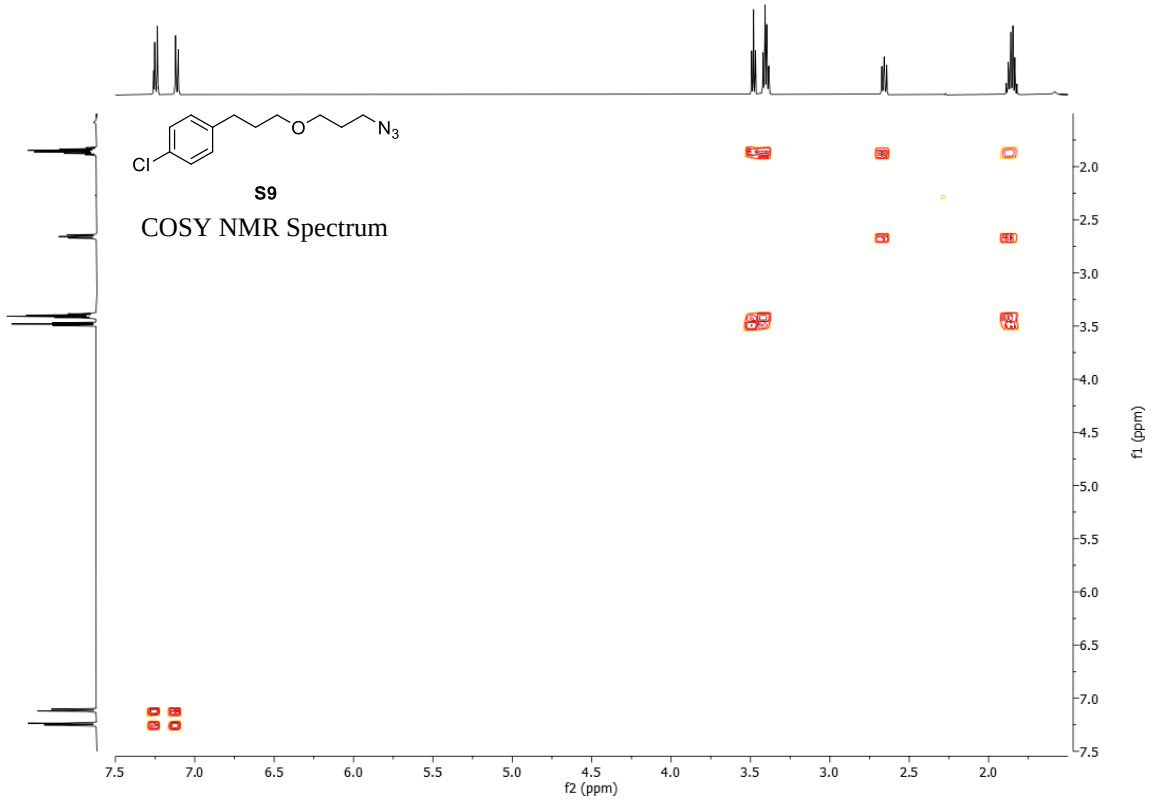


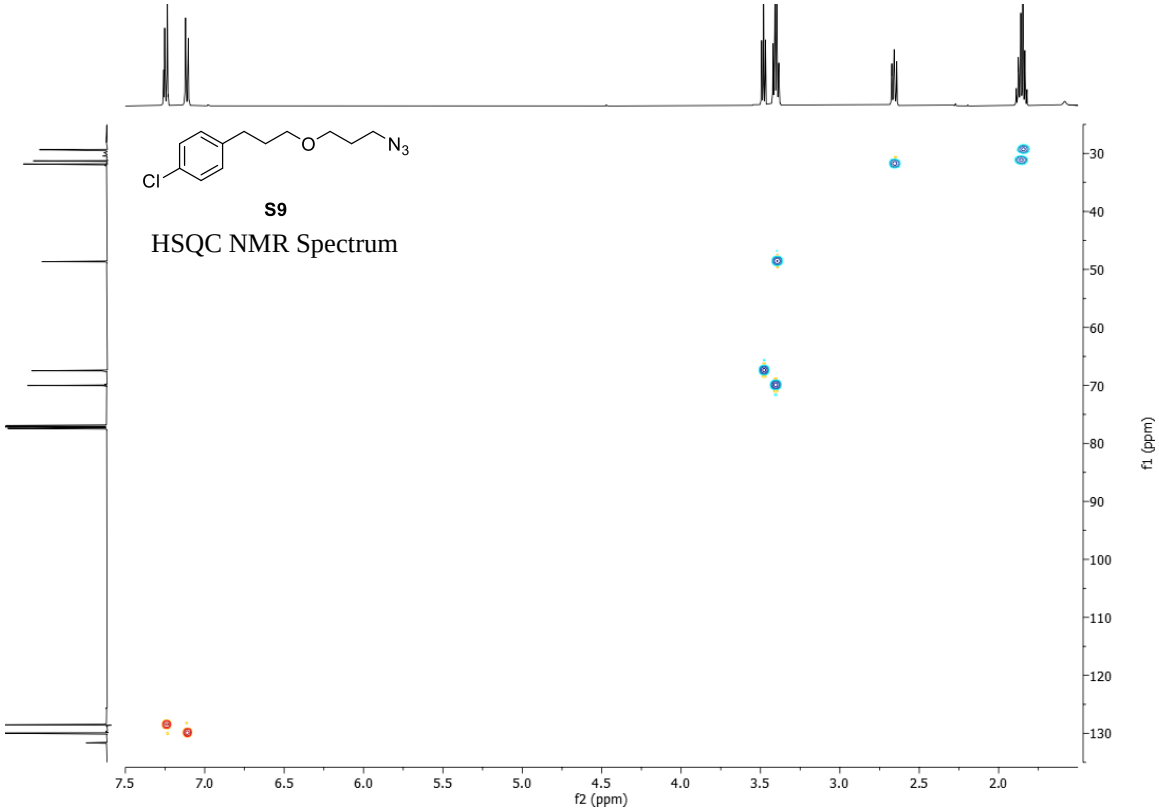
S9

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

S9

COSY NMR Spectrum



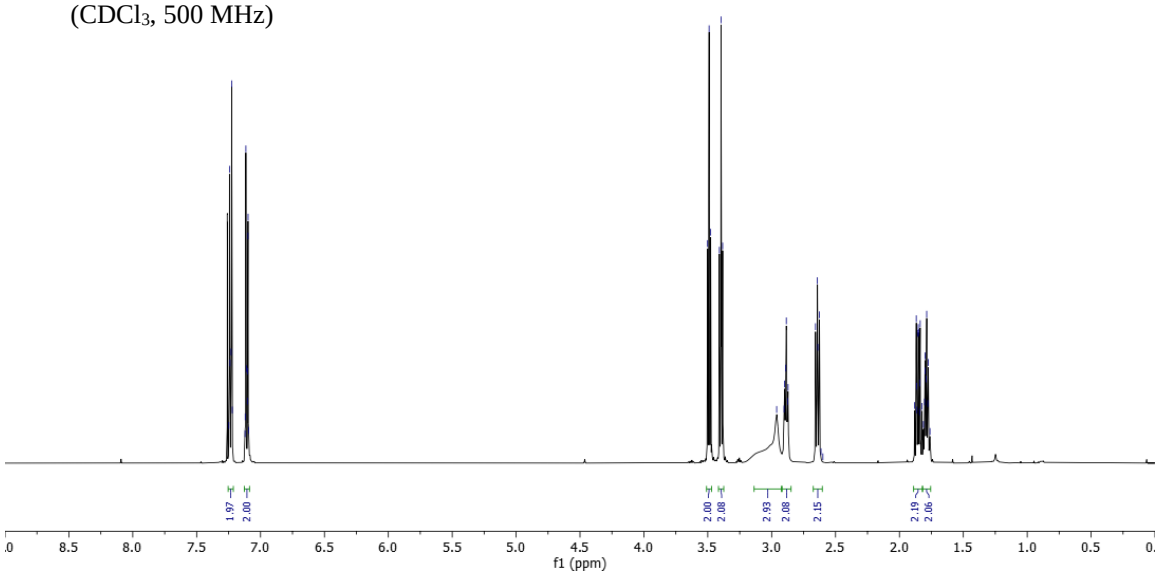


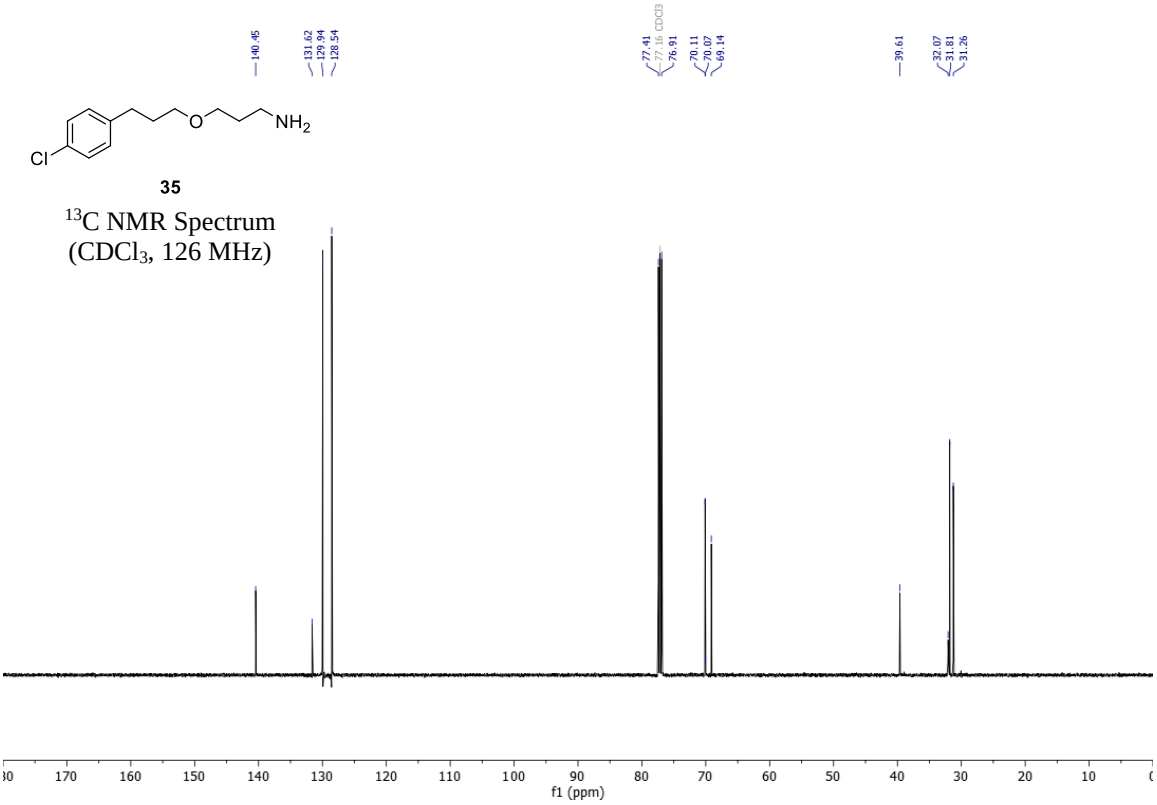
S9

HSQC NMR Spectrum

35

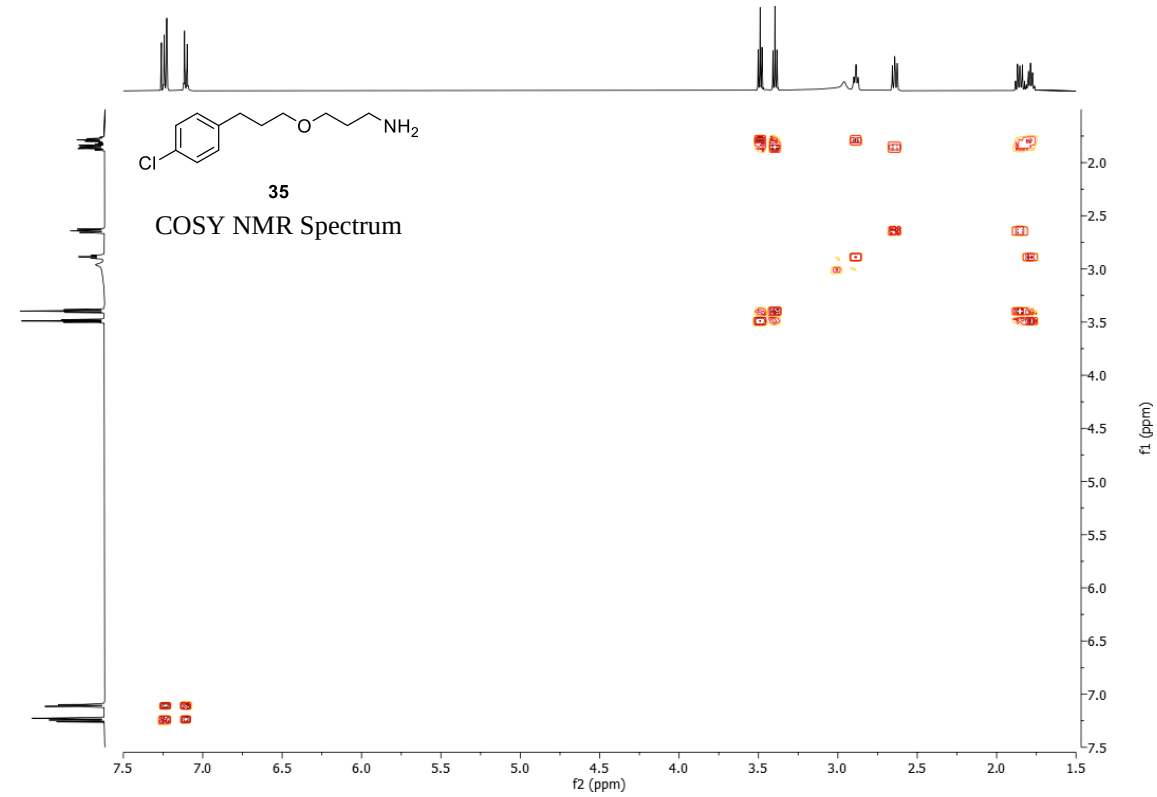
^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)





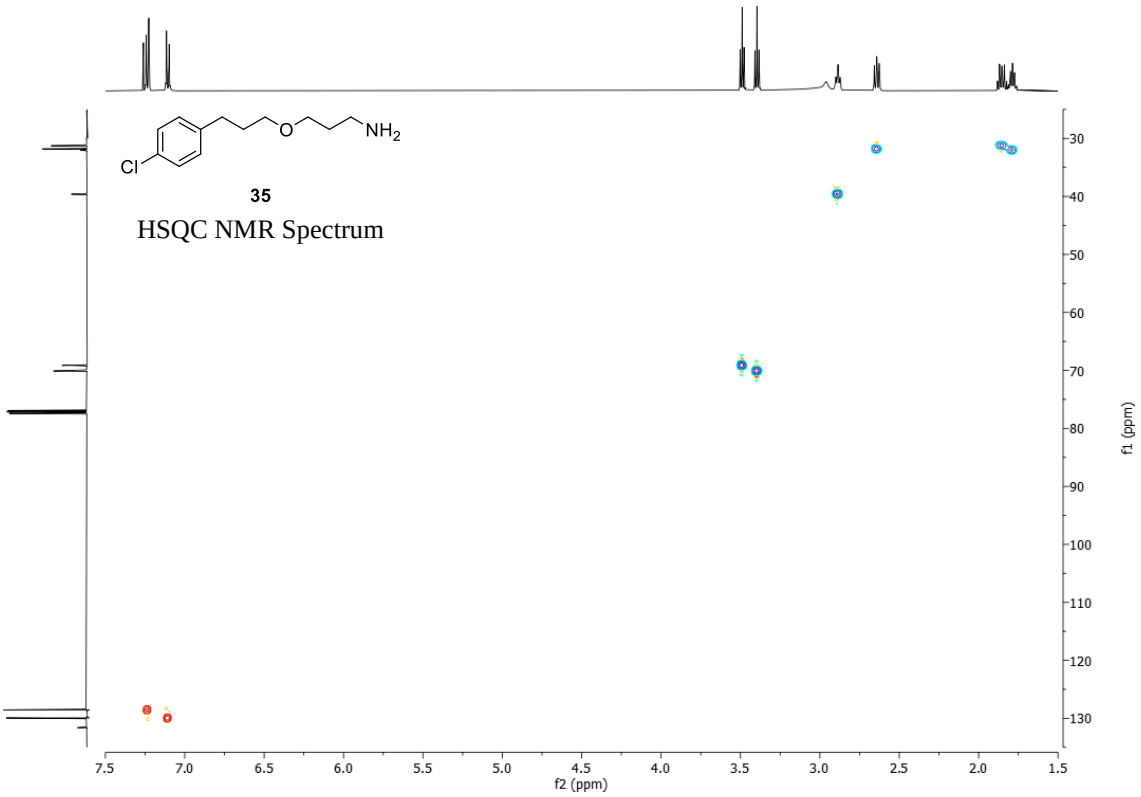
35

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



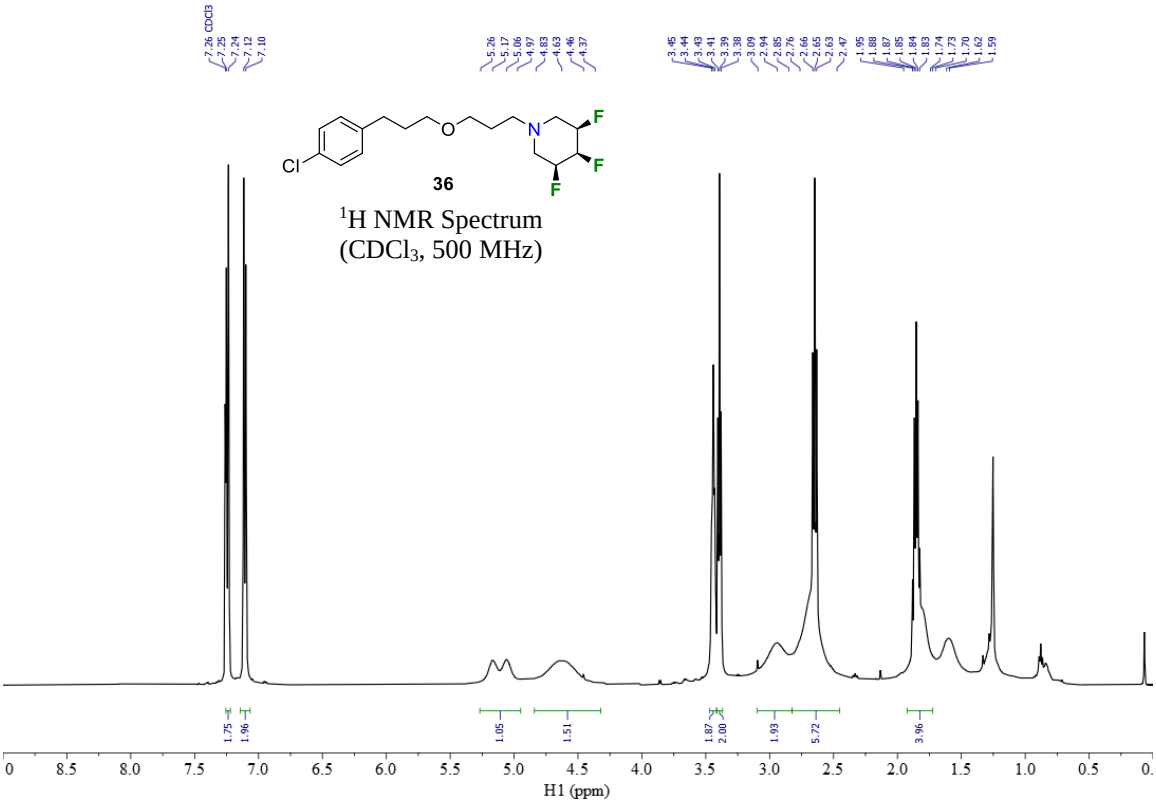
35

COSY NMR Spectrum



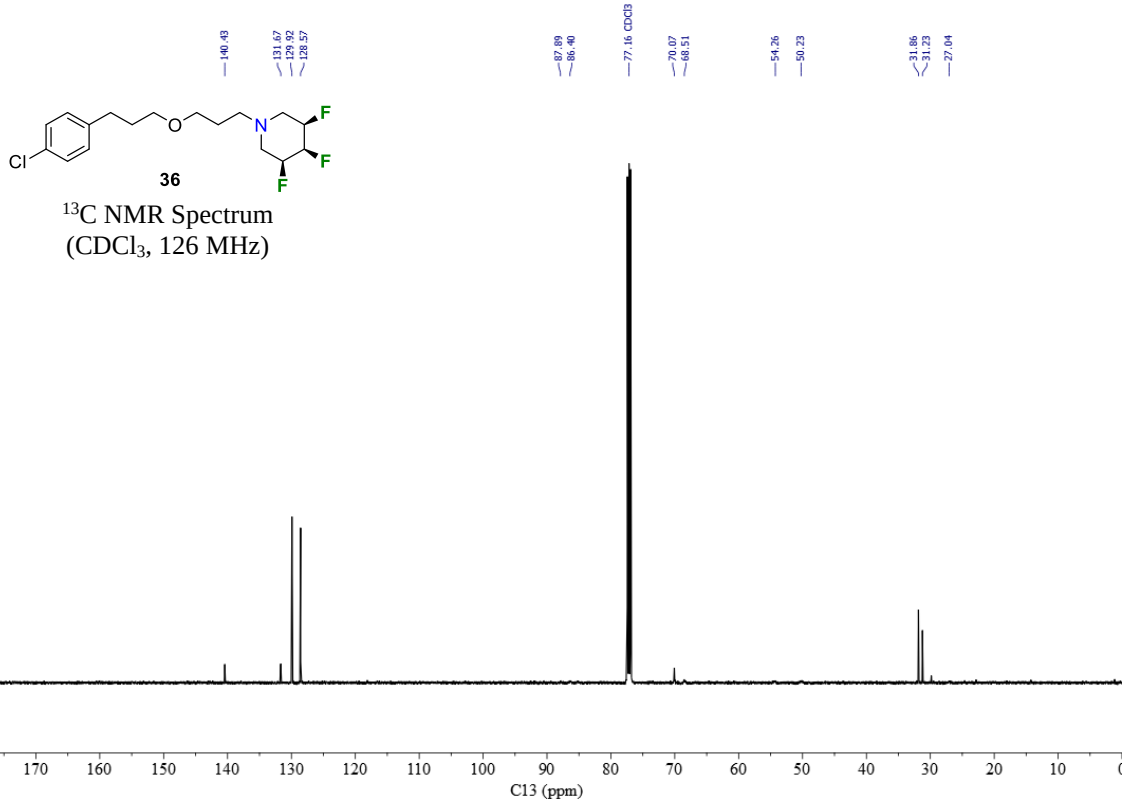
35

HSQC NMR Spectrum

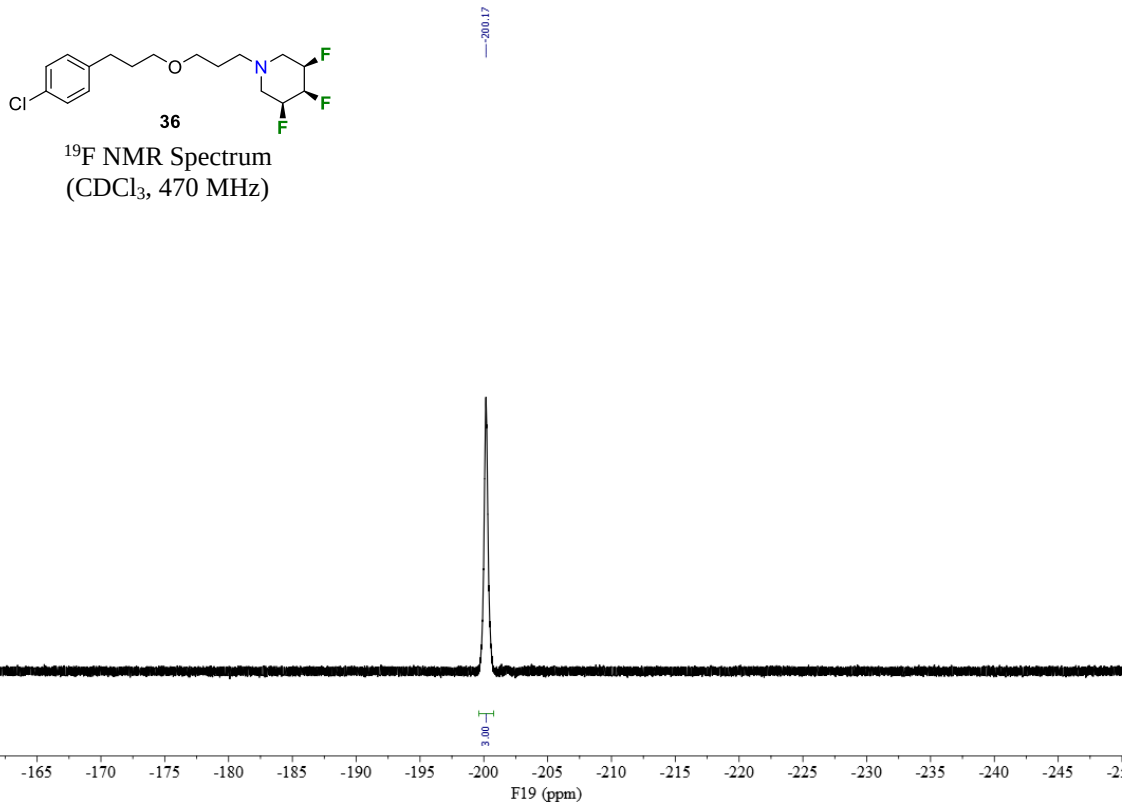


36

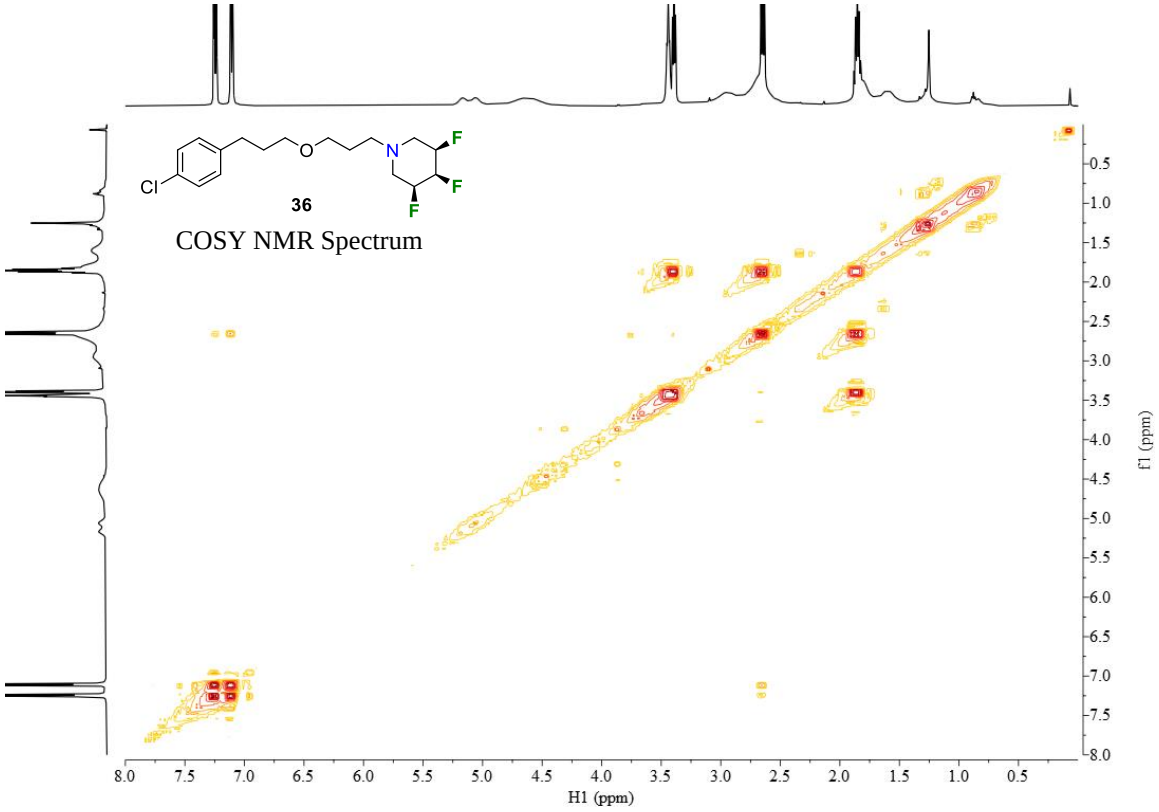
^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)

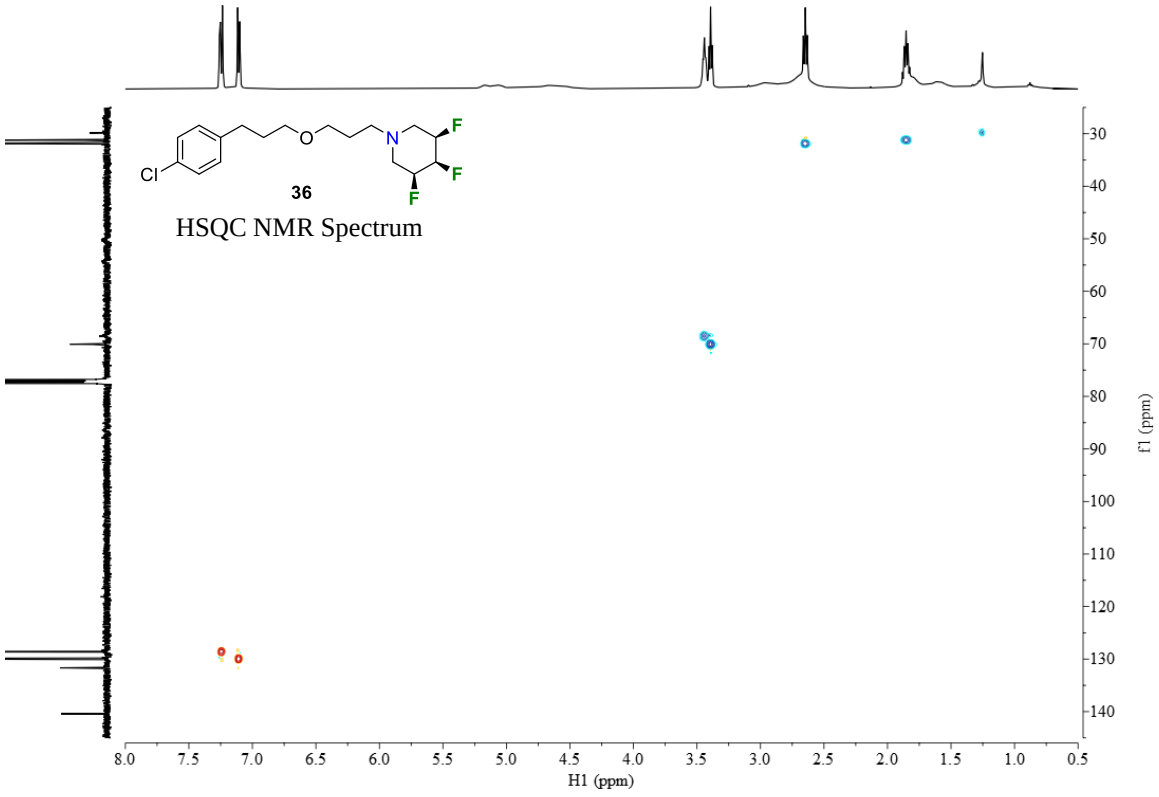


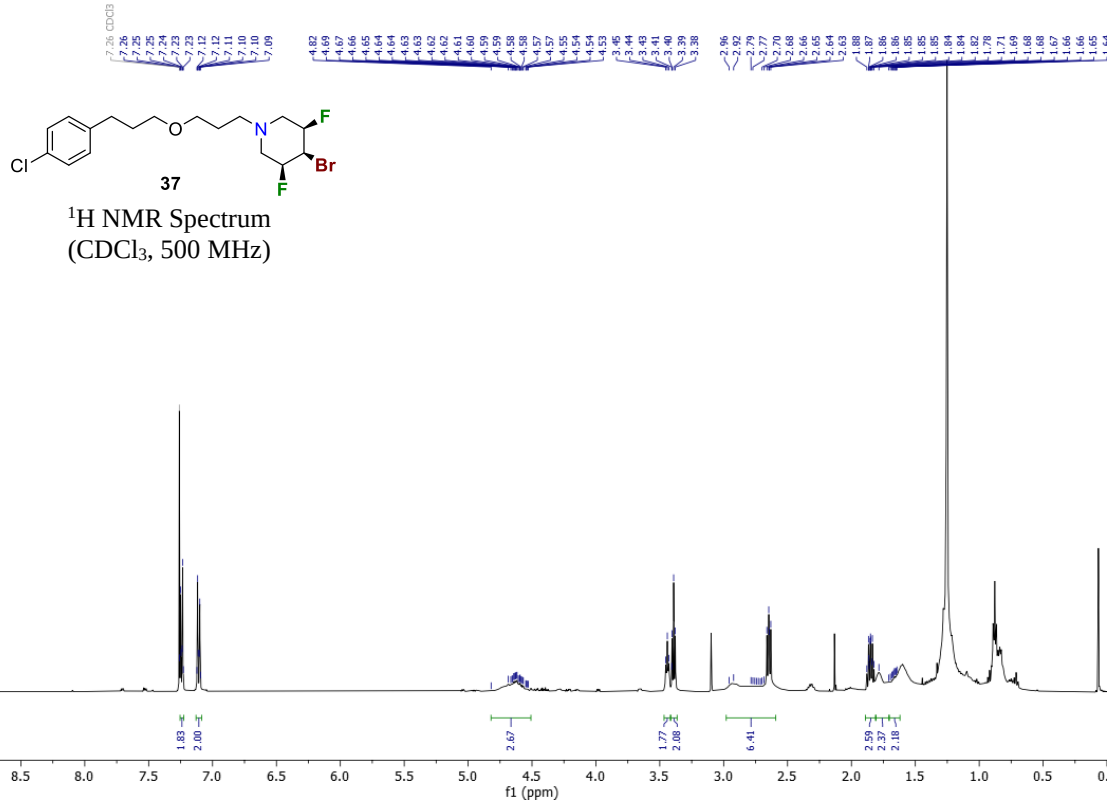
^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)



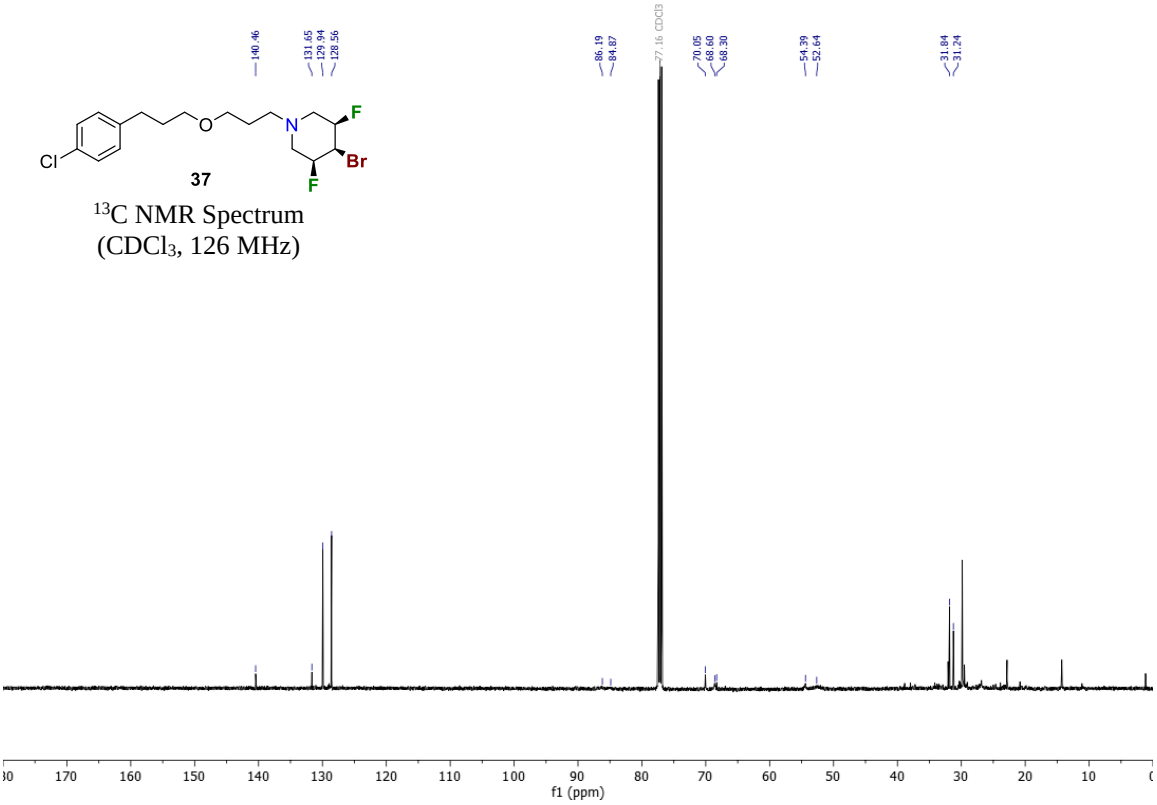
^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)


Cl
O
N
F
F
F
36
COSY NMR Spectrum
f1 (ppm)
H1 (ppm)

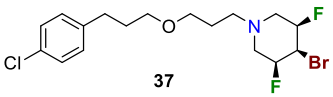

Cl
O
N
F
F
F
36
HSQC NMR Spectrum
f1 (ppm)
H1 (ppm)



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

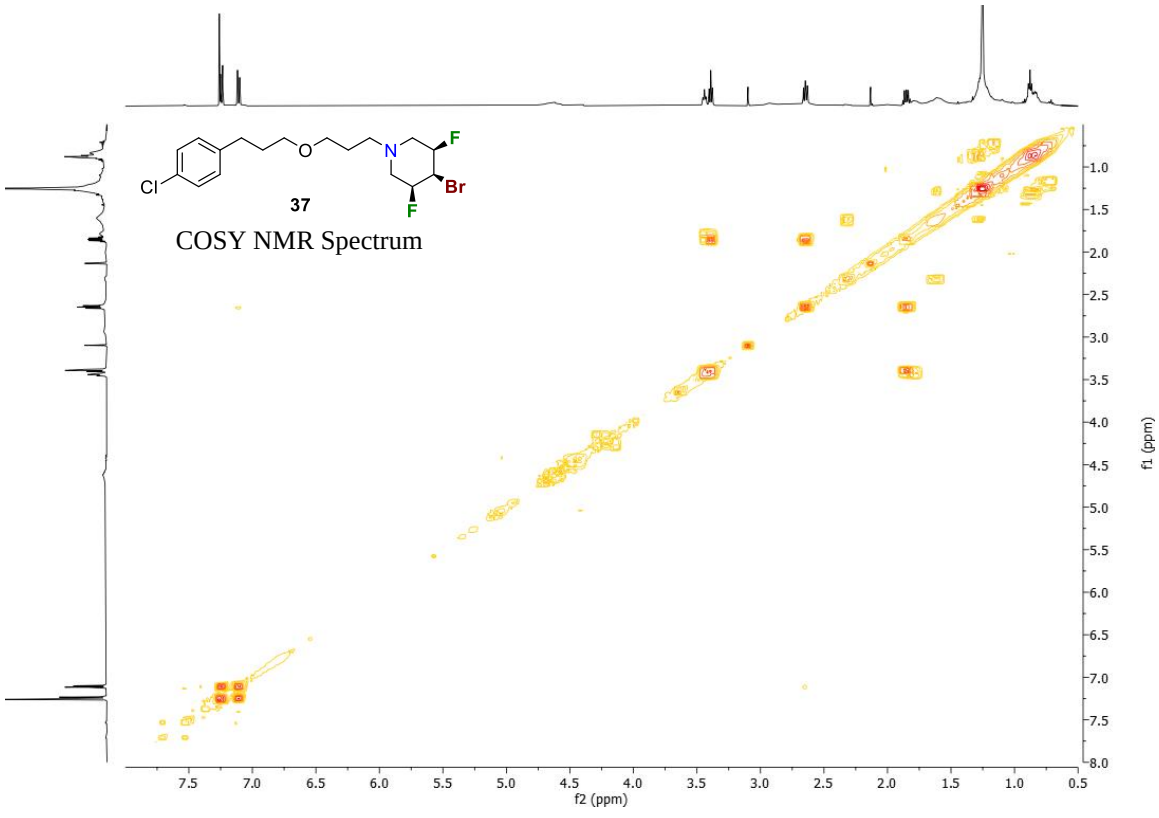


^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)



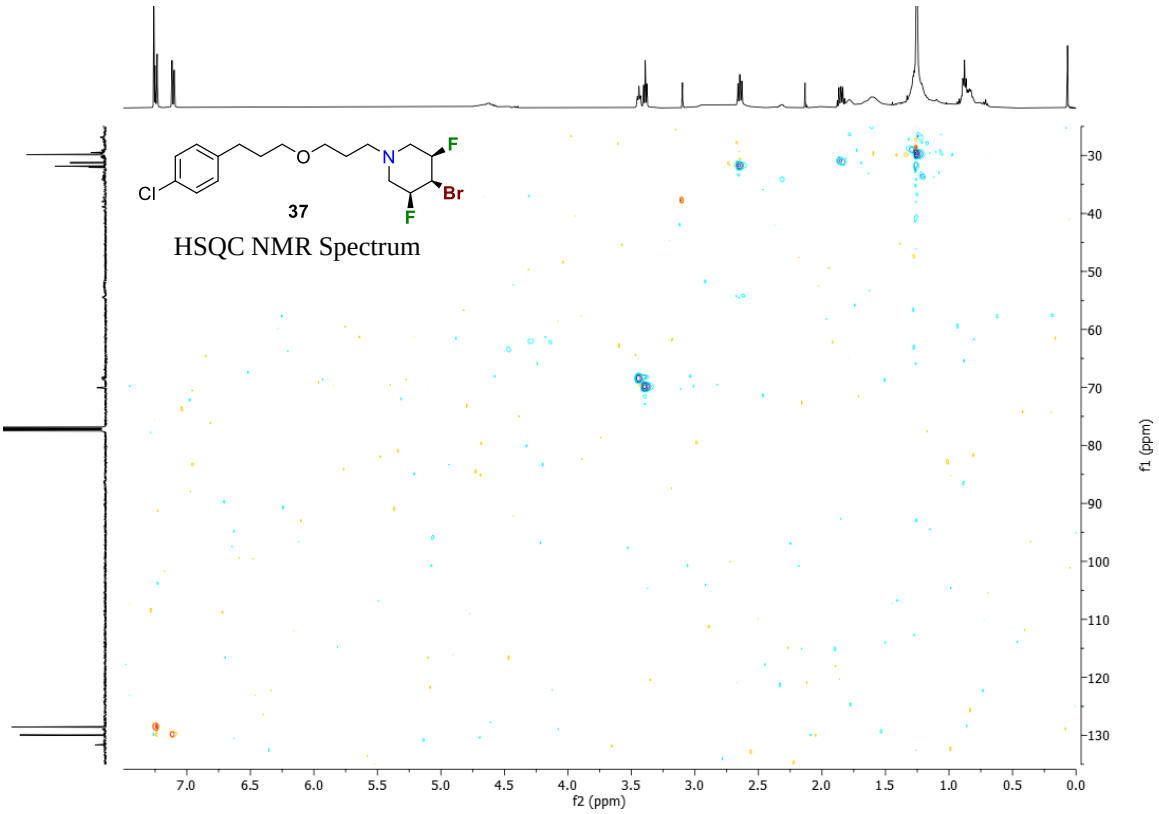
37

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)



37

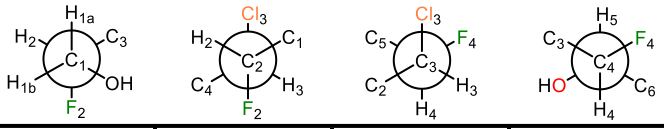
COSY NMR Spectrum



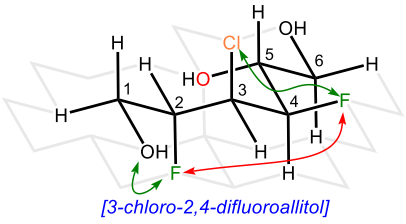
HSQC NMR Spectrum

IV. Solution-state conformation

Figure S1. Solution state conformation of compound **15** in acetone-d_6

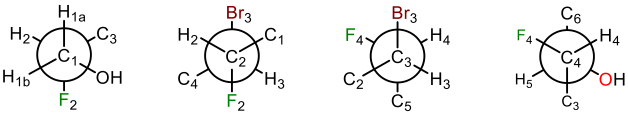


C1-C2 axis	C2-C3 axis	C3-C4 axis	C4-C5 axis
$^3JH_{1a}$-F_2 29.7 Hz $^3JH_{1b}$-F_2 26.0 Hz $^3JH_{1a}$-H_2 4.7 Hz $^3JH_{1b}$-H_2 2.4 Hz	$^3JF_2$-H_3 6.7 Hz $^3JH_2$-H_3 8.0 Hz	$^3JH_3$-H_4 2.5 Hz $^3JH_3$-F_4 22.0 Hz	$^3JF_4$-H_5 5.3 Hz $^3JH_4$-H_5 8.3 Hz

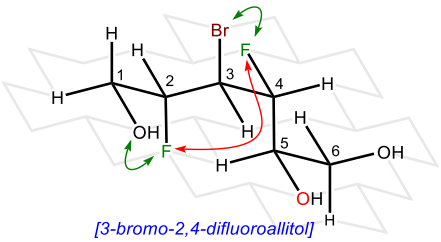


[3-chloro-2,4-difluoroallitol]

Figure S2. Solution state conformation of compound **16** in acetone-d_6

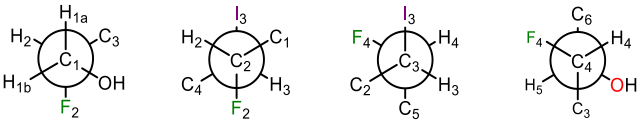


C1-C2 axis	C2-C3 axis	C3-C4 axis	C4-C5 axis
$^3JH_{1a}$-F_2 28.4 Hz $^3JH_{1b}$-F_2 28.4 Hz $^3JH_{1a}$-H_2 4.5 Hz $^3JH_{1b}$-H_2 2.3 Hz	$^3JF_2$-H_3 7.1 Hz $^3JH_2$-H_3 8.0 Hz	$^3JH_3$-H_4 2.5 Hz $^3JH_3$-F_4 22.0 Hz	$^3JF_4$-H_5 5.3 Hz $^3JH_4$-H_5 8.3 Hz

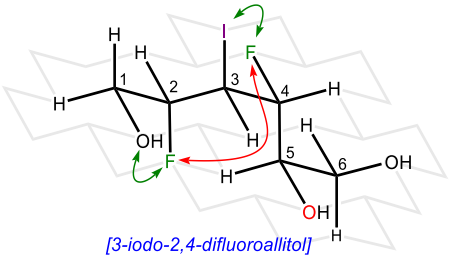


[3-bromo-2,4-difluoroallitol]

Figure S3. Solution state conformation of compound **17** in acetone-d_6

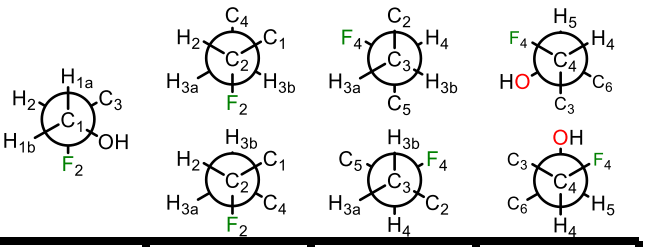


C1-C2 axis	C2-C3 axis	C3-C4 axis	C4-C5 axis
$^3JH_{1a}$-F_2 28.2 Hz $^3JH_{1b}$-F_2 28.0 Hz $^3JH_{1a}$-H_2 4.9 Hz $^3JH_{1b}$-H_2 2.1 Hz	$^3JF_2$-H_3 8.1 Hz $^3JH_2$-H_3 8.1 Hz	$^3JH_3$-H_4 2.8 Hz $^3JH_3$-F_4 24.3 Hz	$^3JF_4$-H_5 6.6 Hz $^3JH_4$-H_5 8.2 Hz

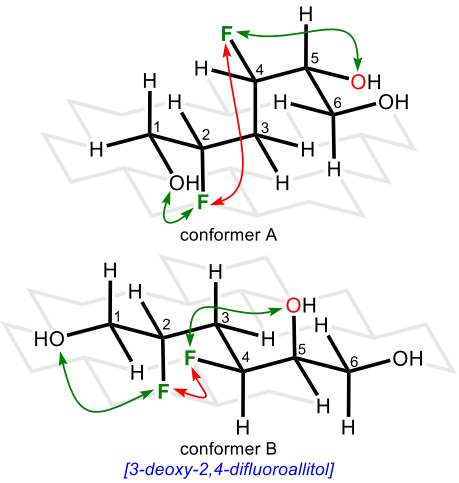


[3-iodo-2,4-difluoroallitol]

Figure S4. Solution state conformation of compound **18** in acetone-d_6



C1-C2 axis	C2-C3 axis	C3-C4 axis	C4-C5 axis
$^3JH_{1a}$-F_2 25.0 Hz $^3JH_{1b}$-F_2 24.0 Hz $^3JH_{1a}$-H_2 6.0 Hz $^3JH_{1b}$-H_2 6.0 Hz	$^3JF_2$-H_{3a} 18.4 Hz $^3JF_2$-H_{3b} 21.9 Hz $^3JH_2$-H_{3a} 6.0 Hz $^3JH_2$-H_{3b} 3.4 Hz	$^3JH_{3a}$-H_4 8.5 Hz $^3JH_{3b}$-H_4 6.1 Hz $^3JH_{3a}$-F_4 18.6 Hz $^3JH_{3b}$-F_4 34.2 Hz	$^3JF_4$-H_5 11.2 Hz $^3JH_4$-H_5 3.4 Hz



conformer A

conformer B

[3-deoxy-2,4-difluoroallitol]

Table S3. Thermochemistry for conformers of molecule **18** in vacuum (B3LYP/6-311+G*)

Conformer	Energy (Ha)	Enthalpy (Ha)	Gibbs' Free Energy (Ha)	Dipole moment (D)			
				X	Y	Z	Total
A	-661.185974	-661.185029	-661.238574	-0.898225	-1.11111	1.02895	1.76072
B	-661.181079	-661.180134	-661.233960	0.820353	1.20611	2.87256	3.19769

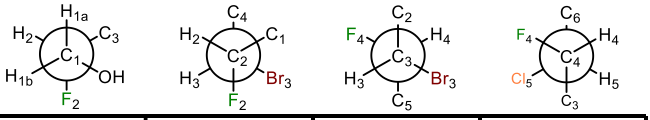
Table S4. Optimized geometry of conformer A in vacuum (B3LYP/6-311+G*)

Center Number	Atomic Number	Atomic Type	Coordinates (Å)		
			X	Y	Z
1	6	0	-2.739324000	-0.556899000	0.080528000
2	1	0	-2.485386000	-0.900462000	-0.920834000
3	1	0	-2.553508000	-1.388229000	0.774312000
4	6	0	-1.854185000	0.617749000	0.477744000
5	1	0	-2.261887000	1.082257000	1.384395000
6	6	0	-0.378090000	0.304442000	0.719134000
7	1	0	0.095557000	1.232021000	1.054503000
8	1	0	-0.276497000	-0.409589000	1.541262000
9	6	0	0.383988000	-0.206614000	-0.492493000
10	1	0	0.178749000	0.408501000	-1.372543000
11	6	0	1.893323000	-0.358928000	-0.311596000
12	1	0	2.285016000	-0.805233000	-1.234682000
13	6	0	2.645011000	0.945311000	-0.067485000
14	1	0	2.444690000	1.658246000	-0.869951000
15	1	0	2.319621000	1.392590000	0.880618000
16	8	0	-4.117589000	-0.219417000	0.036300000
17	1	0	-4.430396000	0.001750000	0.921969000
18	9	0	-1.932793000	1.610289000	-0.520346000
19	9	0	-0.096350000	-1.509817000	-0.810500000
20	8	0	2.207912000	-1.206740000	0.797030000
21	1	0	1.935037000	-2.109133000	0.592271000
22	8	0	4.044527000	0.729078000	-0.058558000
23	1	0	4.228136000	0.039305000	0.593135000

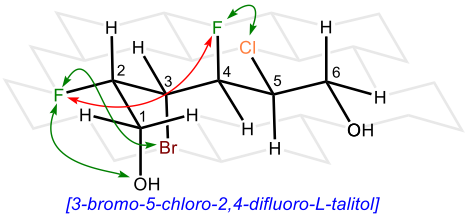
Table S5. Optimized geometry of conformer B in vacuum (B3LYP/6-311+G*)

Center Number	Atomic Number	Atomic Type	Coordinates (Å)		
			X	Y	Z
1	6	0	-2.739324000	-0.556899000	0.080528000
2	1	0	-2.485386000	-0.900462000	-0.920834000
3	1	0	-2.553508000	-1.388229000	0.774312000
4	6	0	-1.854185000	0.617749000	0.477744000
5	1	0	-2.261887000	1.082257000	1.384395000
6	6	0	-0.378090000	0.304442000	0.719134000
7	1	0	0.095557000	1.232021000	1.054503000
8	1	0	-0.276497000	-0.409589000	1.541262000
9	6	0	0.383988000	-0.206614000	-0.492493000
10	1	0	0.178749000	0.408501000	-1.372543000
11	6	0	1.893323000	-0.358928000	-0.311596000
12	1	0	2.285016000	-0.805233000	-1.234682000
13	6	0	2.645011000	0.945311000	-0.067485000
14	1	0	2.444690000	1.658246000	-0.869951000
15	1	0	2.319621000	1.392590000	0.880618000
16	8	0	-4.117589000	-0.219417000	0.036300000
17	1	0	-4.430396000	0.001750000	0.921969000
18	9	0	-1.932793000	1.610289000	-0.520346000
19	9	0	-0.096350000	-1.509817000	-0.810500000
20	8	0	2.207912000	-1.206740000	0.797030000
21	1	0	1.935037000	-2.109133000	0.592271000
22	8	0	4.044527000	0.729078000	-0.058558000
23	1	0	4.228136000	0.039305000	0.593135000

Figure S5. Solution state conformation of compound **24** in acetone-d_6

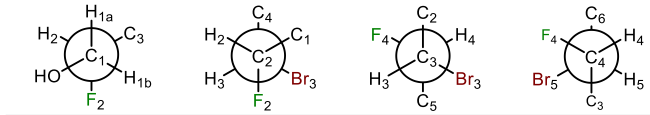


C1-C2 axis	C2-C3 axis	C3-C4 axis	C4-C5 axis
^3JH$_{1a}$-**F**$_2$ 23.7 Hz ^3JH$_{1b}$-**F**$_2$ 18.9 Hz ^3JH$_{1a}$-H$_2$ 5.9 Hz ^3JH$_{1b}$-H$_2$ 4.4 Hz	^3J**F**$_2$-H$_3$ 15.8 Hz ^3JH$_2$-H$_3$ 3.5 Hz	^3JH$_3$-H$_4$ 9.4 Hz ^3JH$_3$-**F**$_4$ 7.8 Hz	^3J**F**$_4$-H$_5$ 26.9 Hz ^3JH$_4$-H$_5$ 2.1 Hz

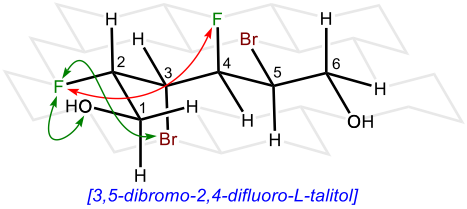


[3-bromo-5-chloro-2,4-difluoro-L-talitol]

Figure S6. Solution state conformation of compound **26** in acetone-d_6

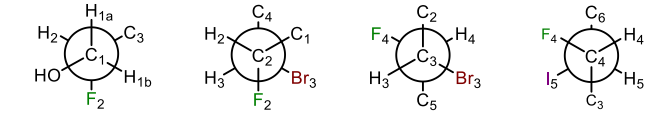


C1-C2 axis	C2-C3 axis	C3-C4 axis	C4-C5 axis
^3JH$_{1a}$-**F**$_2$ 24.0 Hz ^3JH$_{1b}$-**F**$_2$ 19.5 Hz ^3JH$_{1a}$-H$_2$ 4.4 Hz ^3JH$_{1b}$-H$_2$ 6.2 Hz	^3J**F**$_2$-H$_3$ 16.0 Hz ^3JH$_2$-H$_3$ 3.4 Hz	^3JH$_3$-H$_4$ 9.4 Hz ^3JH$_3$-**F**$_4$ 7.5 Hz	^3J**F**$_4$-H$_5$ 28.2 Hz ^3JH$_4$-H$_5$ 2.0 Hz

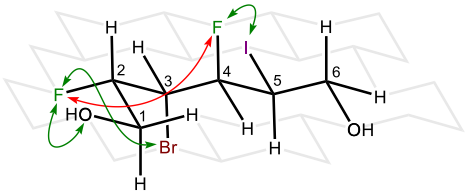


[3,5-dibromo-2,4-difluoro-L-talitol]

Figure S7. Solution state conformation of compound **28** in acetone-d_6



C1-C2 axis	C2-C3 axis	C3-C4 axis	C4-C5 axis
^3JH$_{1a}$-**F**$_2$ 23.5 Hz ^3JH$_{1b}$-**F**$_2$ 20.0 Hz ^3JH$_{1a}$-H$_2$ 4.4 Hz ^3JH$_{1b}$-H$_2$ 6.3 Hz	^3J**F**$_2$-H$_3$ 15.8 Hz ^3JH$_2$-H$_3$ 3.1 Hz	^3JH$_3$-H$_4$ 9.5 Hz ^3JH$_3$-**F**$_4$ 7.5 Hz	^3J**F**$_4$-H$_5$ 31.0 Hz ^3JH$_4$-H$_5$ 1.9 Hz



[3-bromo-5-iodo-2,4-difluoro-L-talitol]

V. Log *P* determination using ^{19}F NMR[5]

Equations:

Eq. 1)
$$\rho_{Oct} = \frac{I_{Oct}^{X}}{I_{Oct}^{ref}} \qquad \rho_{H_2O} = \frac{I_{H_2O}^{X}}{I_{H_2O}^{ref}}$$

Eq. 2)
$$\frac{\rho_{Oct}}{\rho_{H_2O}} = \frac{P^{X}}{P^{ref}}$$

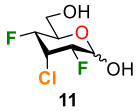
Eq. 3)
$$P^{X} = P^{ref}\left(\frac{\rho_{Oct}}{\rho_{H_2O}}\right)$$

Eq. 4)
$$\log P^{X} = \log P^{ref} + \log\left(\frac{\rho_{Oct}}{\rho_{H_2O}}\right)$$

ρ: Partition of compound X in the phase; I: Sum of all integration in the phase (ref = 100); *P*: *n*-octanol/H_2O partition; X: compound with unknown log *P*; ref: 2,2,2-trifluoroethanol (log *P* = 0.36)

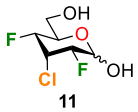
Compounds	I_{Oct}^{X}	ρ_{Oct}	$I_{H_2O}^{X}$	ρ_{H_2O}	$log\ P^{X}$
11	10.03	0.1103	22.76	0.2276	0.00
12	12.02	0.1202	18.83	0.1883	0.17
13	13.46	0.1346	12.42	0.1242	0.40
15	5.30	0.0530	37.70	0.3770	-0.49
16	2.04	0.0204	10.56	0.1056	-0.35
17	2.84	0.0284	8.79	0.0879	-0.13
18	0.71	0.0071	46.02	0.4602	-1.45
24	16.31	0.1631	3.96	0.0396	0.975
26	7.04	0.0704	1.10	0.0110	1.17
28	3.59	0.0359	0.19	0.0019	1.64

Log *P* ^{19}F NMR spectra
Compound 11



11

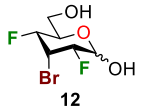
H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



11

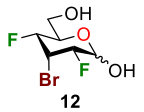
n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

Compound 12



12

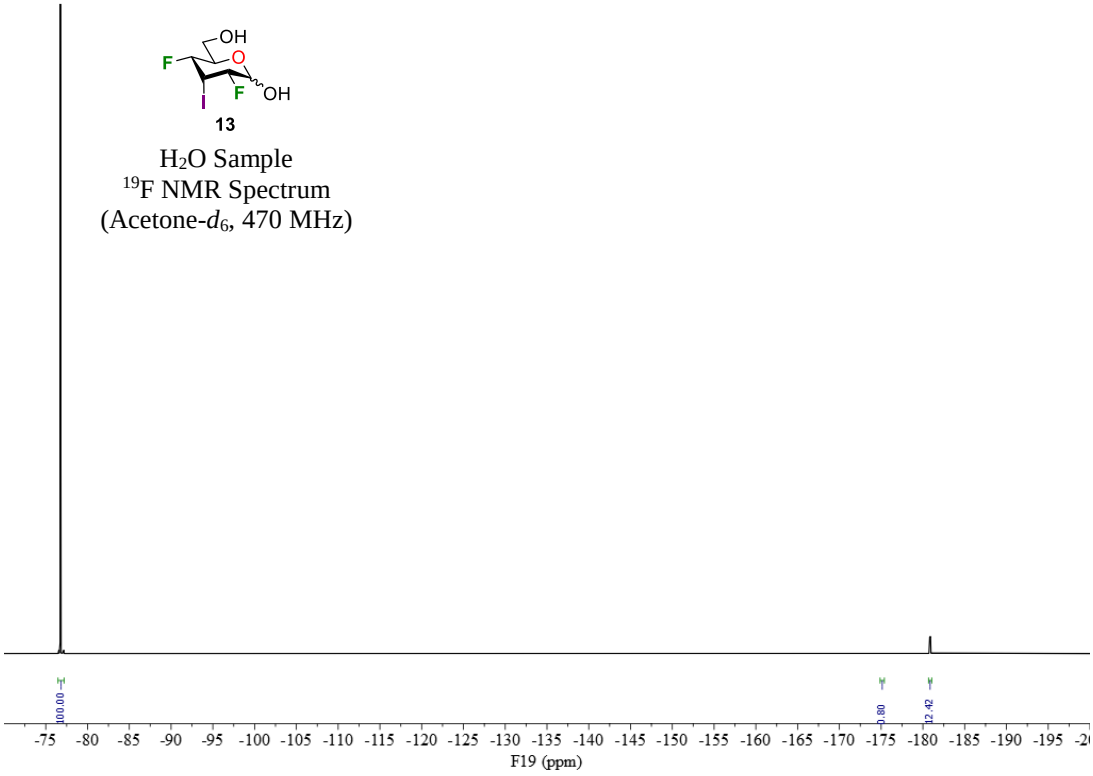
H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



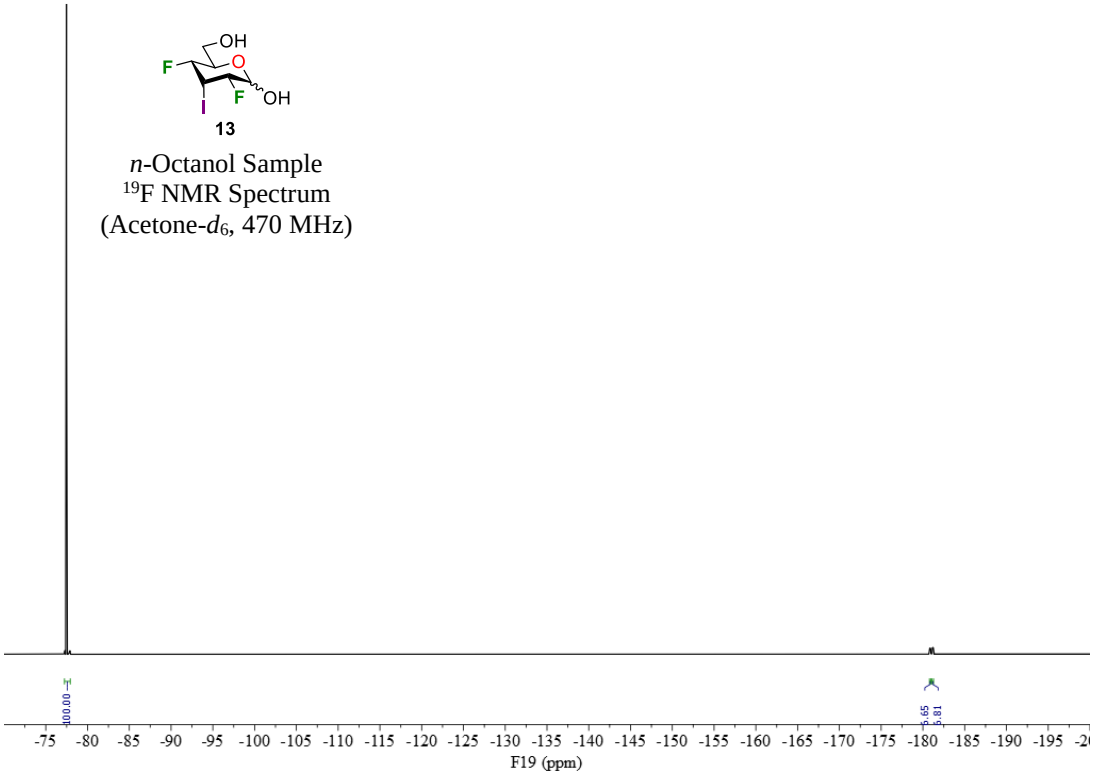
12

n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

Compound 13

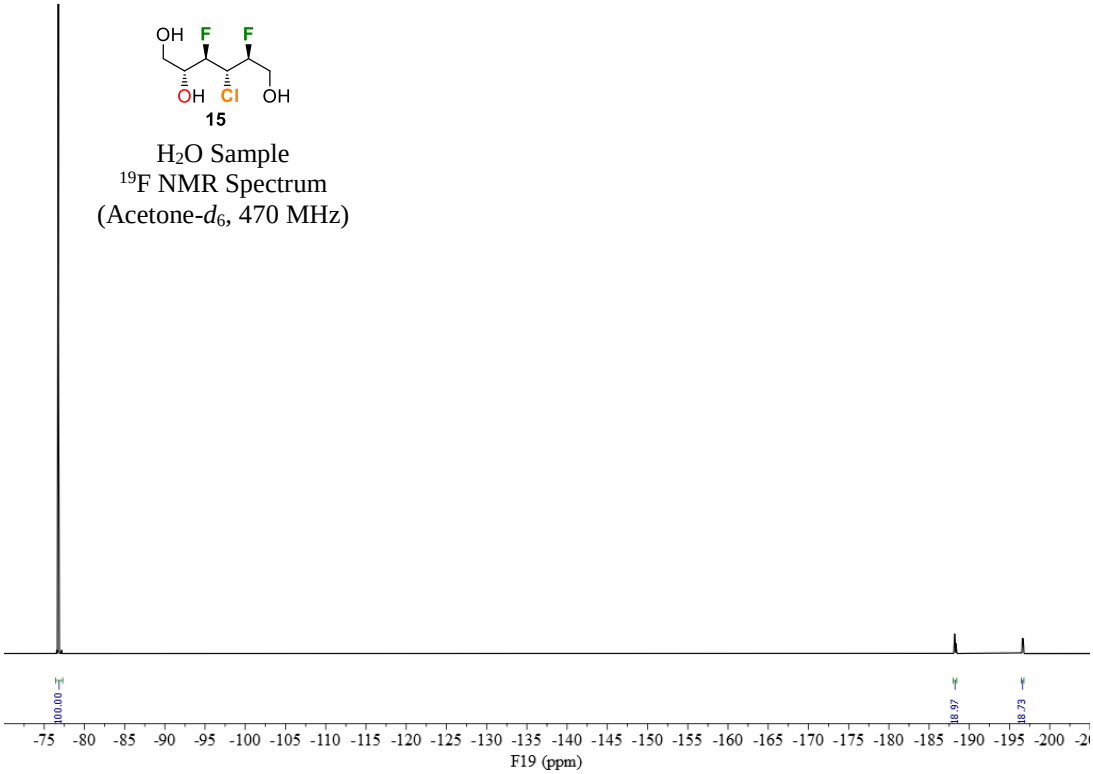


H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

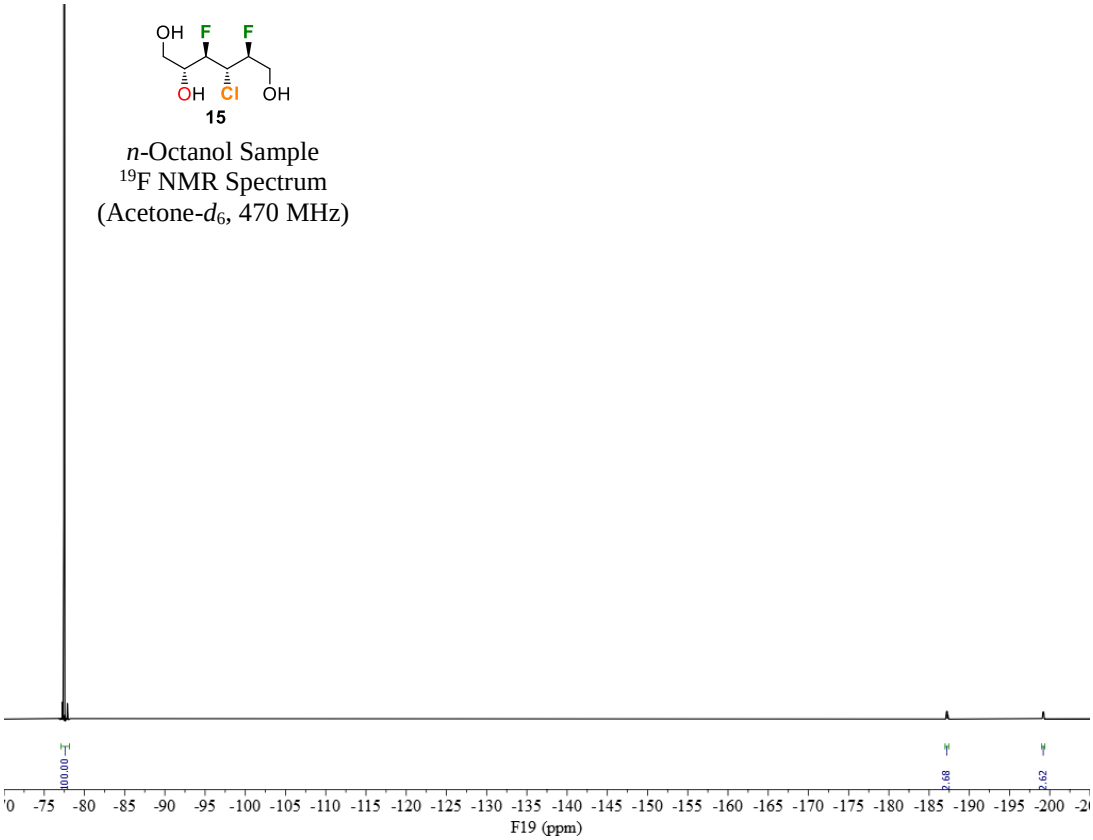


n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

Compound 15

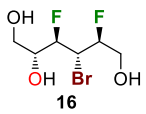


H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



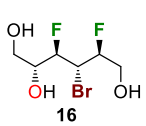
n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

Compound 16



16

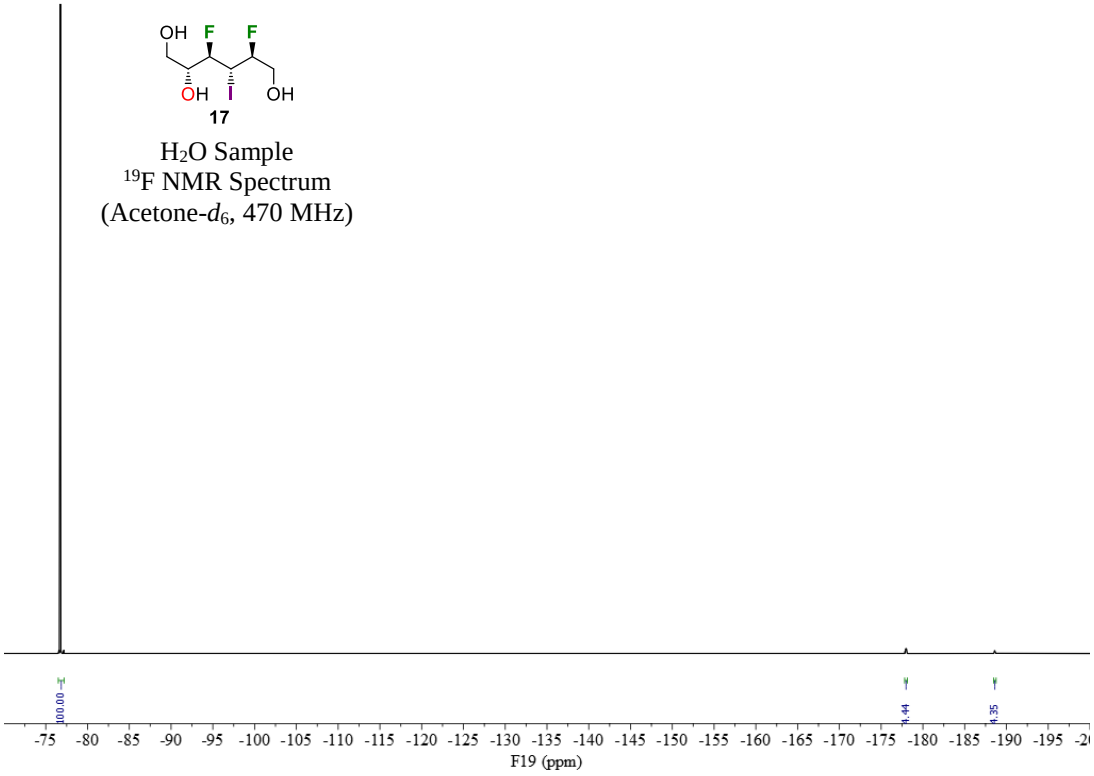
H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



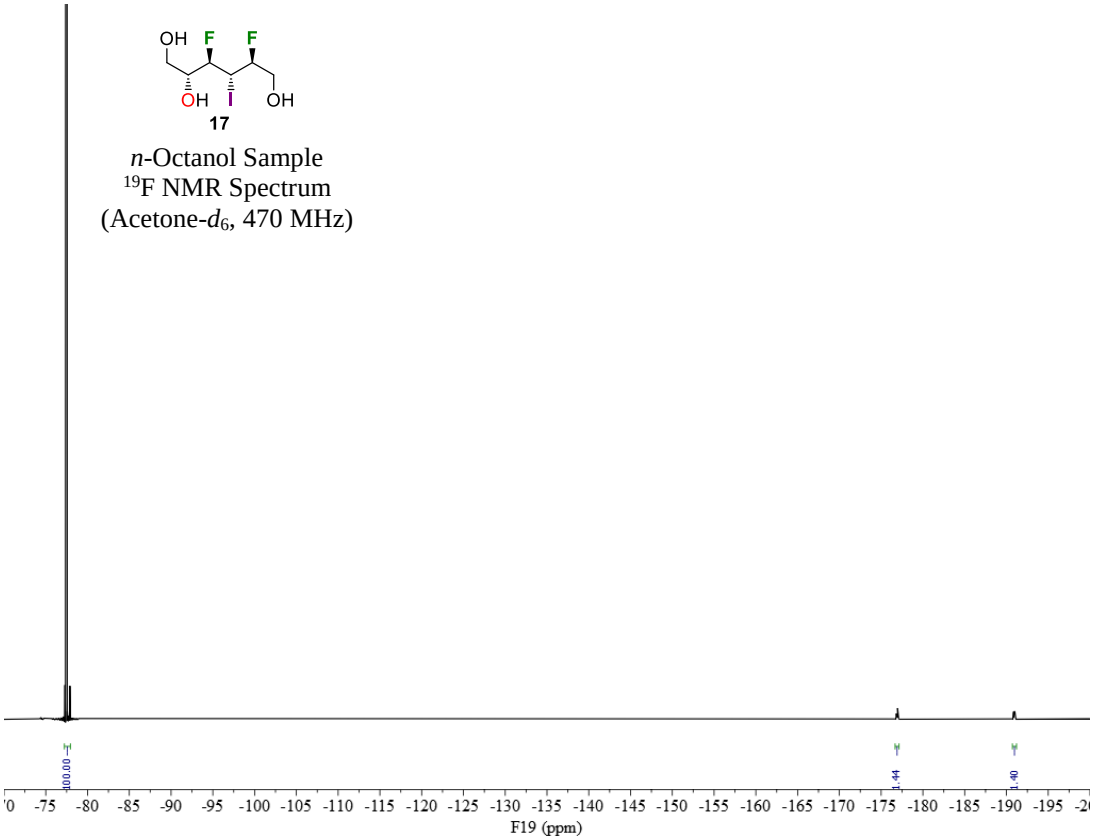
16

n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

Compound 17

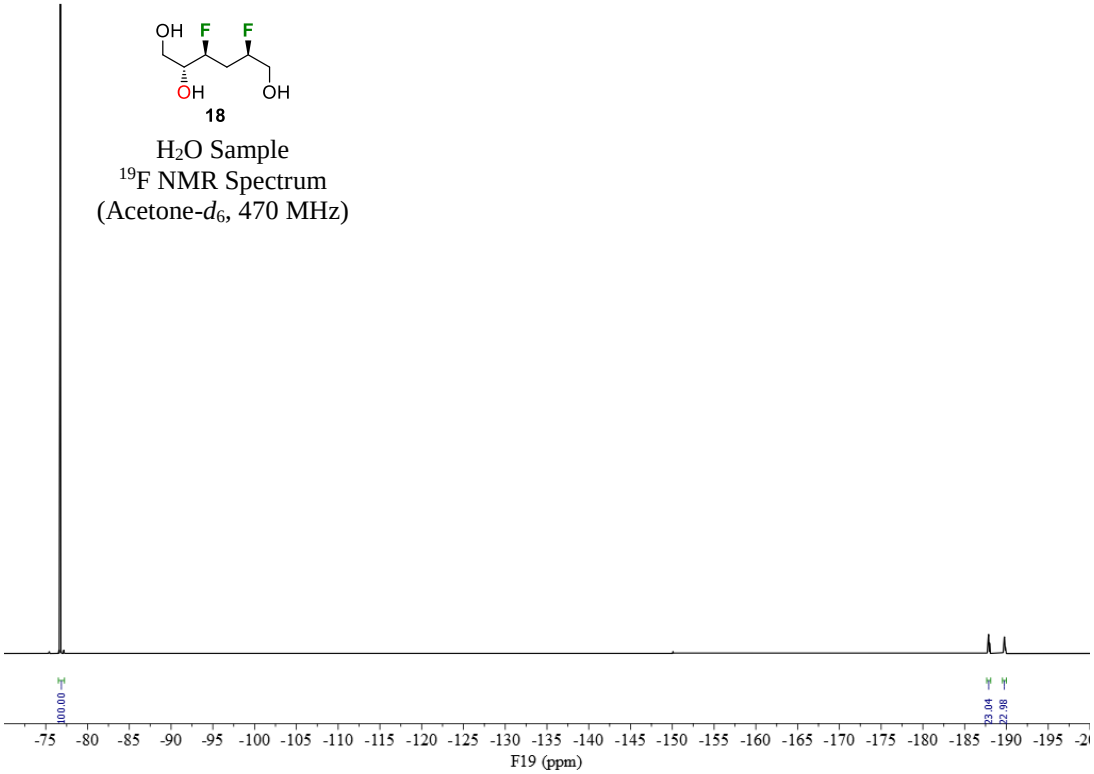


H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

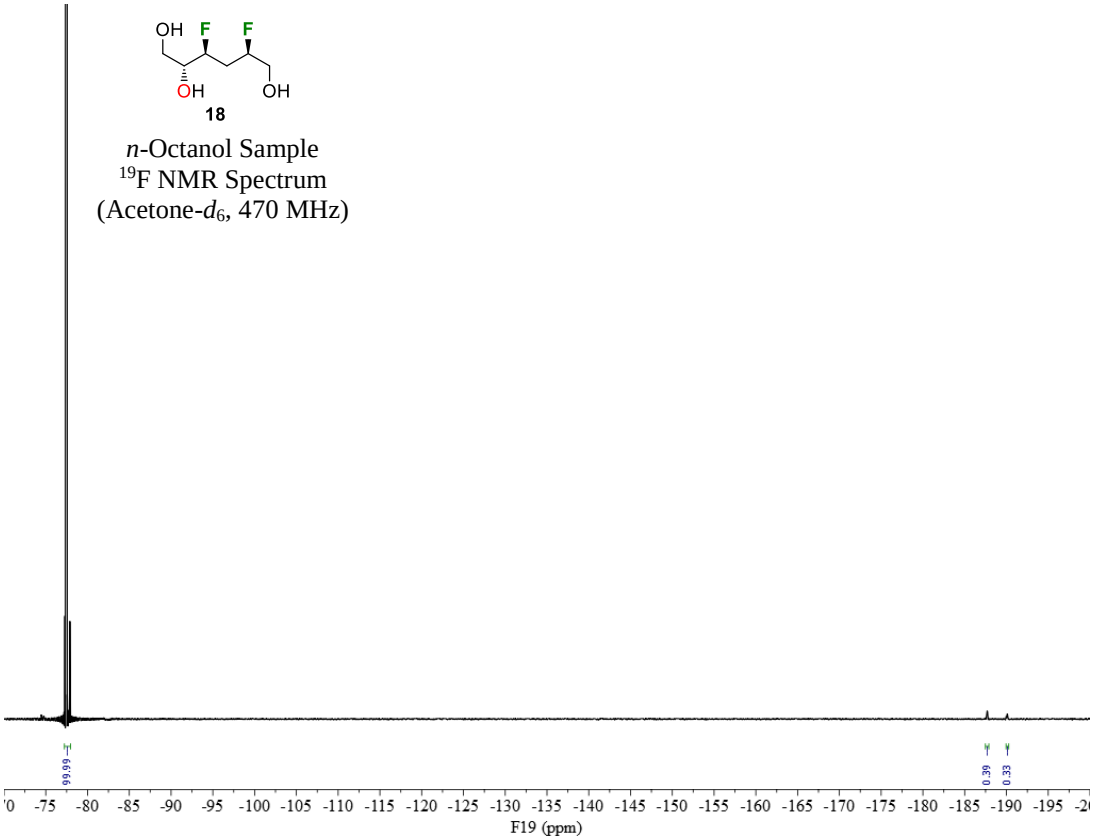


n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

Compound 18

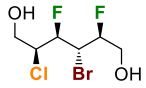


H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



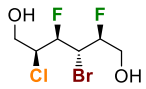
n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

Compound 24



24

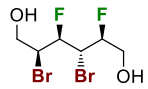
H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



24

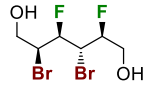
n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

Compound 26



26

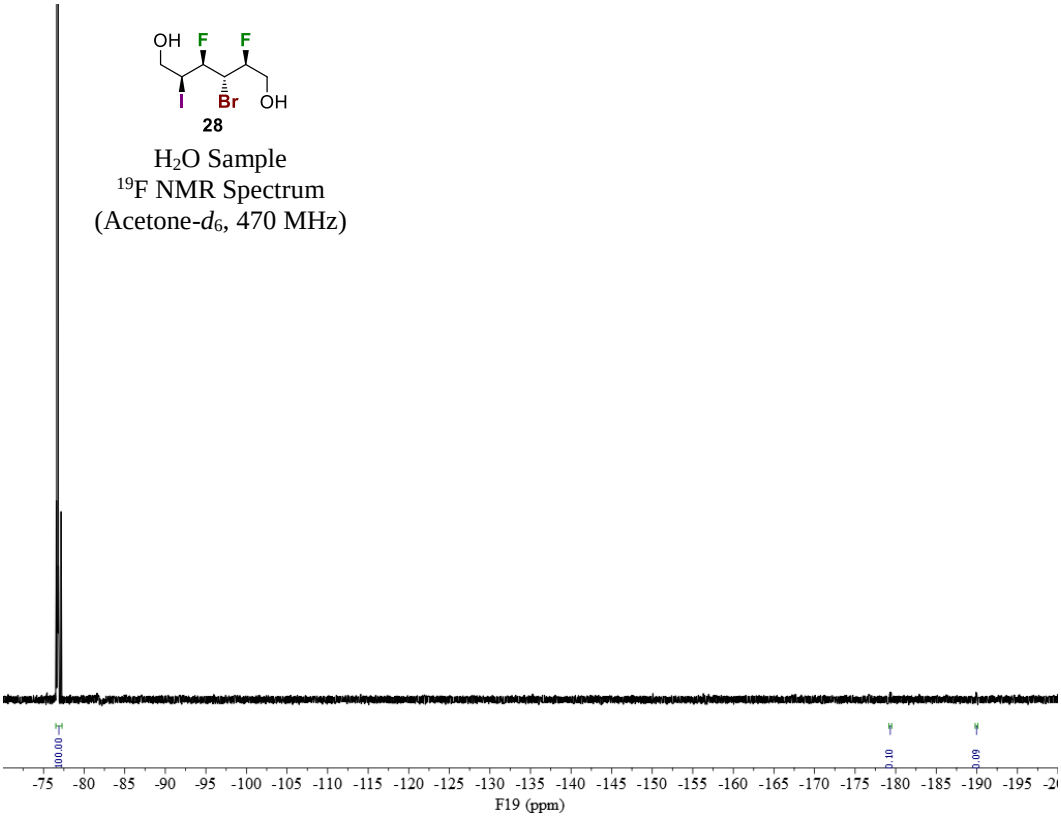
H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



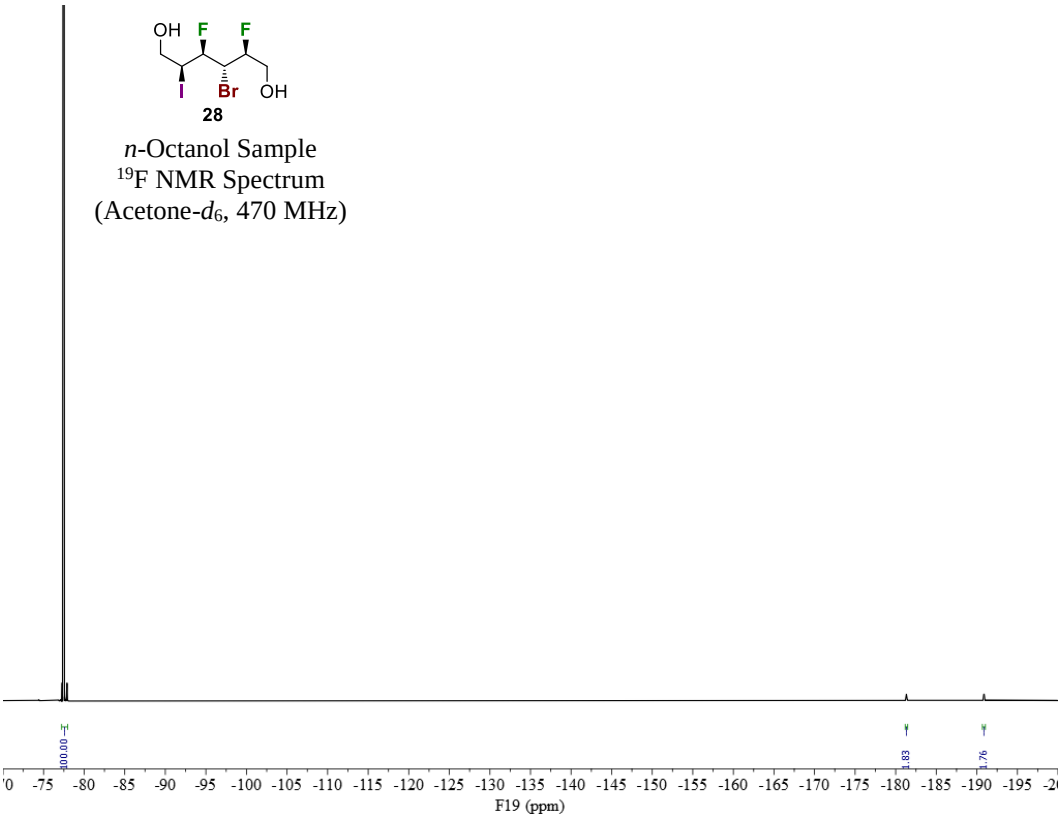
26

n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

Compound 28



H_2O Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



n-Octanol Sample
^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)

VI. Density functional theory calculations on Pitolisant and analogues

Table S6. Thermochemistry of Pitolisant analogues in vacuum (B3LYP/6-31+G*)

Compound	Dipole moment (D)			
	X	Y	Z	Total
Pitolisant	-1.54814	0.556954	1.96880	2.56576
36	-1.02685	-0.563209	-3.04759	3.26488
37	-1.19564	-0.503006	-2.86493	3.14452

Table S7. Optimized geometry of Pitolisant in vacuum (B3LYP/6-31+G*)

Center Number	Atomic Number	Atomic Type	Coordinates (Å)		
			X	Y	Z
1	6	0	-7.517217000	1.915124000	-0.000123000
2	6	0	-7.242639000	1.083479000	-1.261527000
3	6	0	-5.838300000	0.468788000	-1.214683000
4	7	0	-5.662949000	-0.327443000	0.000004000
5	6	0	-5.838367000	0.468873000	1.214628000
6	6	0	-7.242710000	1.083561000	1.261352000
7	1	0	-5.683788000	-0.188245000	-2.079949000
8	1	0	-5.088357000	1.283651000	-1.287810000
9	1	0	-5.683900000	-0.188101000	2.079947000
10	1	0	-5.088430000	1.283742000	1.287738000
11	6	0	-4.476808000	-1.182234000	0.000067000
12	1	0	-4.548381000	-1.836353000	0.880816000
13	1	0	-4.548339000	-1.836415000	-0.880639000
14	6	0	-3.098784000	-0.484468000	0.000073000
15	1	0	-2.992983000	0.159083000	-0.881858000
16	1	0	-2.993012000	0.159125000	0.881976000
17	6	0	-1.960587000	-1.496759000	0.000119000
18	1	0	-2.021828000	-2.148656000	0.889486000
19	1	0	-2.021793000	-2.148694000	-0.889221000
20	8	0	-0.720802000	-0.802052000	0.000127000
21	6	0	0.408293000	-1.660636000	0.000048000
22	1	0	0.383481000	-2.315052000	0.889534000
23	1	0	0.383442000	-2.314933000	-0.889522000
24	6	0	1.673102000	-0.809740000	0.000078000
25	1	0	1.662607000	-0.154829000	-0.880259000
26	1	0	1.662639000	-0.154939000	0.880496000
27	6	0	2.954368000	-1.668357000	-0.000003000

28	1	0	2.949514000	-2.325774000	0.880020000
29	1	0	2.949459000	-2.325695000	-0.880083000
30	6	0	5.965876000	0.364896000	1.213096000
31	6	0	6.531546000	0.756372000	-0.000025000
32	6	0	4.816788000	-0.428956000	1.201600000
33	1	0	4.380441000	-0.736831000	2.149721000
34	6	0	5.966090000	0.364567000	-1.213136000
35	6	0	4.220765000	-0.837928000	-0.000011000
36	1	0	6.418953000	0.670976000	-2.150830000
37	6	0	4.816998000	-0.429283000	-1.201626000
38	1	0	4.380816000	-0.737415000	-2.149740000
39	1	0	6.418576000	0.671559000	2.150785000
40	17	0	7.983080000	1.753323000	-0.000032000
41	1	0	-7.340085000	1.703684000	-2.162489000
42	1	0	-6.863343000	2.800802000	-0.000133000
43	1	0	-7.340212000	1.703827000	2.162268000
44	1	0	-7.980525000	0.273474000	-1.338551000
45	1	0	-8.550148000	2.286691000	-0.000164000
46	1	0	-7.980598000	0.273559000	1.338388000

Table S8. Optimized geometry of compound **36** in vacuum (B3LYP/6-31+G*)

Center Number	**Atomic Number**	**Atomic Type**	**Coordinates (Å)**		
			X	**Y**	**Z**
1	6	0	-6.512364000	1.570658000	0.003918000
2	6	0	-6.185147000	0.810506000	-1.276089000
3	6	0	-4.745031000	0.293278000	-1.213823000
4	7	0	-4.522979000	-0.475604000	-0.001394000
5	6	0	-4.747077000	0.284990000	1.215874000
6	6	0	-6.187318000	0.801739000	1.279232000
7	1	0	-5.890275000	2.477523000	0.007560000
8	1	0	-6.316621000	1.472616000	-2.140134000
9	9	0	-7.066409000	-0.255858000	-1.455851000
10	1	0	-4.573715000	-0.351370000	-2.082315000
11	1	0	-4.065839000	1.166954000	-1.312592000
12	1	0	-4.577197000	-0.365562000	2.080233000
13	1	0	-4.068094000	1.158001000	1.321758000
14	1	0	-6.320301000	1.457891000	2.147580000
15	9	0	-7.068843000	-0.265863000	1.450139000
16	6	0	-3.338684000	-1.329789000	-0.003345000

17	1	0	-3.411734000	-1.986527000	0.874167000
18	1	0	-3.410698000	-1.981112000	-0.884974000
19	6	0	-1.971440000	-0.615032000	-0.000394000
20	1	0	-1.874740000	0.033131000	-0.880746000
21	1	0	-1.875960000	0.028288000	0.883638000
22	6	0	-0.815186000	-1.607739000	-0.002394000
23	1	0	-0.865934000	-2.262394000	0.885379000
24	1	0	-0.865508000	-2.258288000	-0.893207000
25	8	0	0.407727000	-0.886993000	-0.000467000
26	6	0	1.557015000	-1.721213000	-0.001998000
27	1	0	1.545557000	-2.376793000	0.886460000
28	1	0	1.545455000	-2.373663000	-0.892755000
29	6	0	2.801940000	-0.841942000	-0.000562000
30	1	0	2.776811000	-0.186139000	-0.879936000
31	1	0	2.776884000	-0.189053000	0.880980000
32	6	0	4.102396000	-1.671287000	-0.001985000
33	1	0	4.112755000	-2.329837000	0.877099000
34	1	0	4.112463000	-2.327263000	-0.883000000
35	6	0	7.065573000	0.430084000	1.213680000
36	6	0	7.621108000	0.837433000	0.001045000
37	6	0	5.935716000	-0.390863000	1.201252000
38	1	0	5.507770000	-0.711332000	2.149041000
39	6	0	7.064584000	0.434366000	-1.212573000
40	6	0	5.349025000	-0.811333000	-0.000940000
41	1	0	7.509851000	0.752863000	-2.149863000
42	6	0	5.934741000	-0.386614000	-1.202124000
43	1	0	5.506026000	-0.703740000	-2.150691000
44	1	0	7.511596000	0.745276000	2.151727000
45	17	0	9.048037000	1.868595000	0.002278000
46	9	0	-7.840887000	1.993512000	0.004238000

Table S9. Optimized cartesian coordinates of compound **37** in vacuum (B3LYP/6-31+G*)

Center Number	**Atomic Number**	**Atomic Type**	**Coordinates (Å)**		
			X	**Y**	**Z**
1	6	0	5.522894000	0.944885000	-0.000184000
2	6	0	5.152138000	0.202565000	1.279030000
3	6	0	3.683090000	-0.230185000	1.212171000
4	7	0	3.416616000	-0.983104000	0.000161000
5	6	0	3.683170000	-0.230707000	-1.212156000

6	6	0	5.152222000	0.202013000	-1.279103000
7	35	0	7.397875000	1.530147000	-0.000250000
8	1	0	4.953616000	1.879555000	-0.000406000
9	1	0	5.311027000	0.855162000	2.144675000
10	9	0	5.961903000	-0.917189000	1.467932000
11	1	0	3.473437000	-0.863252000	2.081034000
12	1	0	3.059580000	0.684080000	1.309967000
13	1	0	3.473575000	-0.864147000	-2.080761000
14	1	0	3.059667000	0.683517000	-1.310388000
15	1	0	5.311173000	0.854237000	-2.145018000
16	9	0	5.961998000	-0.917825000	-1.467467000
17	6	0	2.181431000	-1.761977000	0.000289000
18	1	0	2.213171000	-2.419353000	-0.879194000
19	1	0	2.213131000	-2.419003000	0.880037000
20	6	0	0.862237000	-0.962483000	0.000101000
21	1	0	0.806865000	-0.311843000	0.882163000
22	1	0	0.806914000	-0.312171000	-0.882206000
23	6	0	-0.353481000	-1.881223000	0.000242000
24	1	0	-0.343240000	-2.535940000	-0.888902000
25	1	0	-0.343258000	-2.535644000	0.889604000
26	8	0	-1.529754000	-1.086916000	0.000099000
27	6	0	-2.727612000	-1.849848000	0.000206000
28	1	0	-2.755744000	-2.503486000	-0.889306000
29	1	0	-2.755744000	-2.503238000	0.889901000
30	6	0	-3.916856000	-0.896699000	0.000077000
31	1	0	-3.852125000	-0.244940000	0.880430000
32	1	0	-3.852161000	-0.245204000	-0.880474000
33	6	0	-5.265115000	-1.645774000	0.000208000
34	1	0	-5.315103000	-2.301348000	-0.879743000
35	1	0	-5.315064000	-2.301103000	0.880349000
36	6	0	-8.095840000	0.632058000	-1.213194000
37	6	0	-8.626024000	1.070672000	-0.000116000
38	6	0	-7.017519000	-0.255509000	-1.201651000
39	1	0	-6.609518000	-0.600071000	-2.149782000
40	6	0	-8.095023000	0.633335000	1.213073000
41	6	0	-6.457490000	-0.712060000	0.000096000
42	1	0	-8.520464000	0.976946000	2.150701000
43	6	0	-7.016715000	-0.254240000	1.201743000
44	1	0	-6.608081000	-0.597806000	2.149964000
45	1	0	-8.521906000	0.974681000	-2.150899000

46	17	0	-9.988340000	2.185793000	-0.000241000

VII. References

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