BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Supporting Information

for

Fluorine effect in nucleophilic fluorination at C4 of 1,6-anhydro-2,3-dideoxy-2,3-difluoro-β-D-hexopyranose

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Detailed experimental procedures, characterization data, copies of ^{1}H, ^{13}C, ^{19}F, COSY, and HSQC NMR spectra of all new compounds, and optimization of the deoxyfluorination

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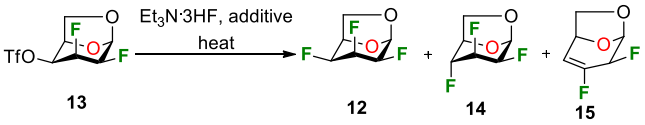
I. Experimental section

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 1.5 g of $KMnO_4$, 10 g K_2CO_3, and 1.25 mL 10% NaOH in 200 mL of water, 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 Bomem MB-Series Arid Zone FTIR MB-155 Spectrometer, with a ZnSe crystal plate. 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 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}).

Optimization of the fluorodeoxygenation using $Et_3N{\cdot}3HF$

Table S1. Optimization of the selective synthesis of trifluorotalose analogue **12** and trifluoromannose analogue **14** using $Et_3N{\cdot}3HF$.



Entry[a]	Additive (equiv)	Temperature (°C)	Conversion (%)[b]	Yields (%)[b]		
				12	**14**	**15**
1	Et_3N (50)	80	100	21	44	20
2	DIPEA (50)	80	98	23	36	15
3[c]	Et_3N (50)	80	77	21	11	4
4[c]	Et_3N (50)	80	87	25	12	3
5[d]	Et_3N (50)	80	30	6	15	7
6[d]	Et_3N (50)	90	50	12	24	10
7[d]	Et_3N (50)	100	99	29	38	22
8	Et_3N (15)	80	98	29	32	11
9	Et_3N (23)	80	97	33	34	12
10	**Et_3N (30)**	**80**	**100**	**22**	**48**	**15**
11	Et_3N (30)	70	79	7	19	7
12	Et_3N (30)	90	100	14	23	11
13	Et_3N (30)	100	100	18	30	19
14[e]	Et_3N (30)	80	96	19	45	20
15[f]	Et_3N (30)	80	100	24	48	21
16	quinuclidine (30)	80	100	6	18	22
17	pyridine (30)	80	92	29	6	4
18	(−)-sparteine (30)	80	99	10	43	14
19	DBU (30)	80	100	0	25	67
20[g]	pyridine (120)	80	46	1	0	2
21	**–**	**80**	**98**	**70**	**3**	**0**

[a]Reactions were carried out in a glass seal tube with 15 equivalents of $Et_3N{\cdot}3HF$ for 24 h unless otherwise stated.
[b]Conversions and yields were determined with the ^{19}F NMR (470 MHz, $CDCl_3$) using 2-fluoro-4-nitrotoluene as internal standard.
[c]Reactions were carried out in a PTFE test tube instead of a glass seal tube for 24 h (entry 3), and 48 h (entry 4).
[d]Reactions were heated in a microwave reactor for 2 h.
[e]The reaction was stirred for 12 h.
[f]The reaction was stirred for 48 h.
[g]Pyridine·9HF was used instead of $Et_3N{\cdot}3HF$.

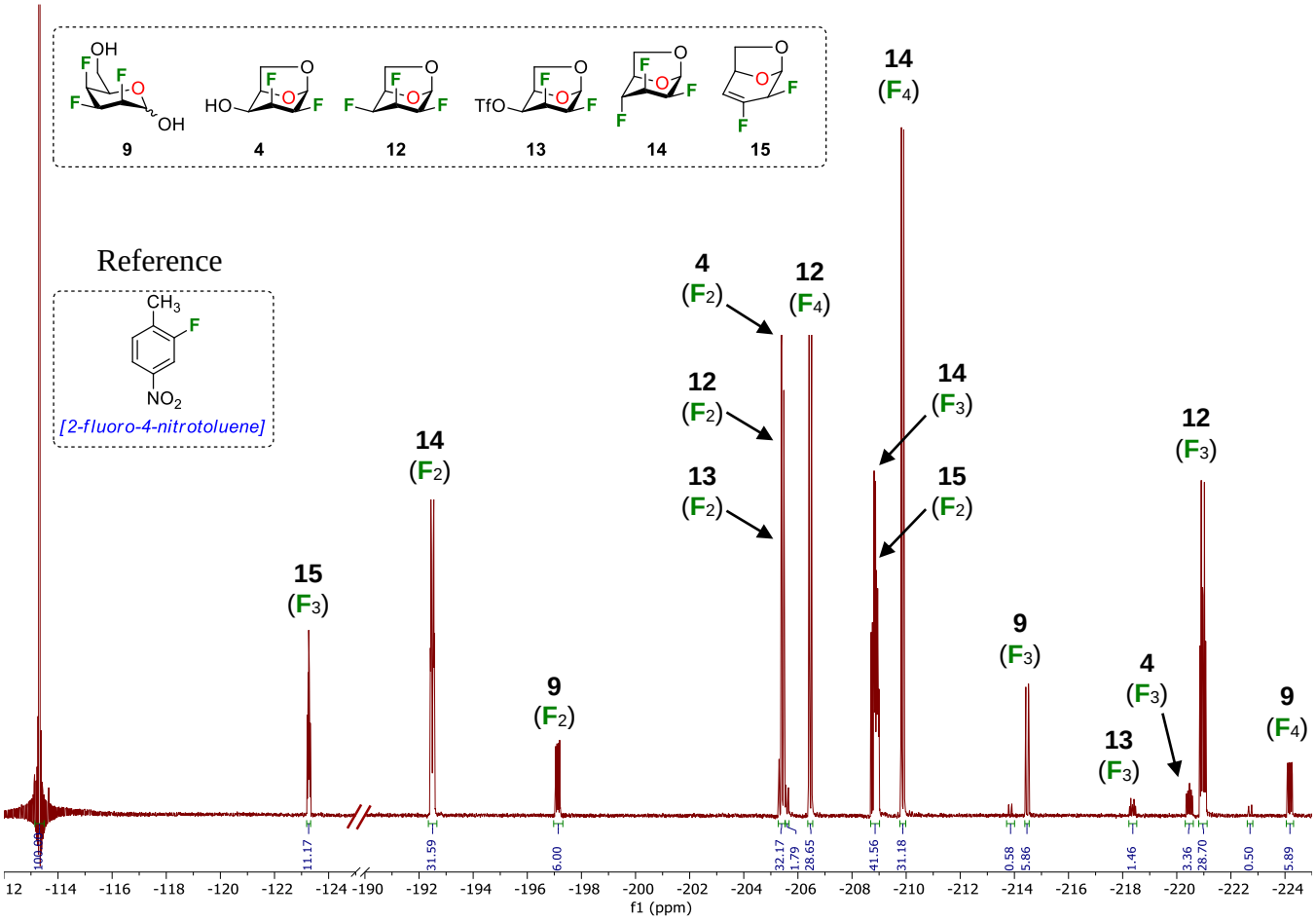


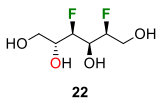
Figure S1. Typical ^{19}F NMR spectrum (470 MHz, $CDCl_3$) observed for the fluorodeoxygenation using $Et_3N{\cdot}3HF$ (entry 8 of Table S1).

General Procedures

General procedure I: C4 deoxyfluorination conditions using DAST (Table 1)

To a stirred solution of the starting 1,6-anhydro-2,3-dideoxy-2,3-difluoro-β-D-hexopyranoses **2–5** (1 equiv) in CH_2Cl_2 (0.1 M) was added DAST (1 equiv) and 2-fluoro-4-nitrotoluene (1 equiv). The resulting mixture was heated in a microwave reactor at 100 °C for 1 h. After this time, $CDCl_3$ (0.5 mL was added, and a ^{19}F NMR spectrum of the resulting mixture was taken to give an NMR yield of products **10–12**.

2,4-Dideoxy-2,4-difluoroglucitol (**22**). Reduction using $LiAlH_4$: To a stirred solution of difluoroglucose

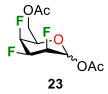


22

21[1] (51.0 mg, 0.1644 mmol, 1.0 equiv) in THF (1.6 mL) at 0 °C, was added 1 M $LiAlH_4$ in THF (0.67 mL, 0.6740 mmol, 5.0 equiv). The resulting mixture was stirred at 0 °C for 2 h then 2 mL of MeOH was added, and the mixture was neutralized to pH ≈ 7 with acidic resin (Amberlite IR-120). The mixture was filtered and concentrated under reduced pressure. The obtained crude product was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:9) to give **22** as a white amorphous solid (17.8 mg, 0.0954 mmol, 58% yield). Reduction using $NaBH_4$: To a stirred solution of difluoroglucose **21** (15.4 mg, 0.0836 mmol, 1.0 equiv) in ethanol (1.0 mL) at room temperature was added $NaBH_4$ (16.0 mg, 0.4182 mmol, 5.0 equiv). The resulting mixture was stirred at room temperature for 1.5 h then 1 mL of methanol was added, and the mixture was neutralized to pH ≈ 7 with acidic resin (Amberlite IR-120). The mixture was filtered and concentrated under reduced pressure. The obtained crude product was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:9) to give **22** as a white amorphous solid (11.0 mg, 0.0591 mmol, 71% yield): R_f = 0.18 (silica, MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{25} = -7.08$ (c 0.5, MeOH); IR (ATR, diamond crystal) *ν* 3308, 2935, 2841, 1425, 1231, 1032, 865 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 4.63 (dtd, *J* = 48.3, 5.6, 3.3 Hz, 1H, H2), 4.59 (ddd, *J* = 46.8, 7.9, 2.0 Hz, 1H, H4), 4.37 (d, *J* = 6.5 Hz, 1H, O*H*3), 4.20 (ddtd, *J* = 29.6, 17.3, 6.0, 1.9 Hz, 1H, H3), 4.21 – 4.14 (m, 1H, O*H*5), 4.10 (t, *J* = 5.8 Hz, 1H, O*H*1), 4.01 – 3.96 (m, 1H, H5), 3.94 – 3.71 (m, 4H, O*H*6, H1a, H1b, H6a), 3.67 – 3.60 (m, 1H, H6b) ppm; ^{13}C {^1H} NMR (126 MHz, Acetone-d_6) δ 96.1 (dd, *J* = 173.4, 3.3 Hz, 1C, C2), 92.4 (dd, *J* = 175.7, 5.5 Hz, 1C, C4), 70.3 (d, *J* = 25.4 Hz, 1C, C5), 69.3 (dd, *J* = 21.1, 18.0 Hz, 1C, C3), 63.4 (d, *J* = 3.8 Hz, 1C, C6), 62.1 (dd, *J* = 22.7, 2.0 Hz, 1C, C1) ppm; ^{19}F NMR (470 MHz, Acetone-

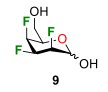
d_6) δ -200.01 (dtdd, J = 48.3, 25.2, 17.1, 2.9 Hz, 1F, F2), -209.38 (ddd, J = 46.5, 29.5, 7.3 Hz, 1F, F4) ppm; HRMS calcd for $C_6H_{16}O_4NF_2^+$ $[M + NH_4]^+$ 204.1042 found 204.1046.

1,6-Di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α/β-D-talopyranose (**23**). This compound was prepared in a similar manner as described previously.[2] To a stirred solution of difluorotalose **4**[3] (142.9 mg, 0.8602 mmol, 1.0 equiv) in CH_2Cl_2 (8.6 mL) at room temperature was added pyridine (0.21 mL, 2.580 mmol, 3.0 equiv) and 1 M Tf_2O solution in CH_2Cl_2 (1.3 mL, 1.290 mmol, 1.5 equiv). The resulting mixture was stirred for 1 h then quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were washed with a saturated aqueous NaCl solution (40 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude triflate **13** was used in the next step without further purification. Following the optimized condition for retention of configuration (Table S1, entry 21), fluorodeoxygenation of triflate **13** was carried with $Et_3N{\cdot}3HF$ (2.1 mL, 12.903 mmol, 15.0 equiv) allowing formation of intermediate **12**. After 24 h, the mixture was cooled down to 0 °C, Ac_2O (16 mL, 172.0 mmol, 200 equiv) and H_2SO_4 (3.7 mL, 68.82 mmol, 80 equiv) were added. The resulting mixture was stirred at room temperature for 16 h then a saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture was stirred for 0.5 h. The mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (2 × 50 mL), an aqueous 1 M HCl solution (50 mL) and a saturated aqueous NaCl solution (50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes 2:3) to give an anomeric mixture (α/β, 23:1) of **23** as a colourless thick oil (125.5 mg, 0.4645 mmol, 54% yield). The spectroscopic data derived of **23** match those reported in the literature.[3]



23

2,3,4-Trideoxy-2,3,4-trifluoro-α/β-D-talopyranose (**9**). This compound was prepared in a similar manner as described previously.[2] To a stirred solution of compound **23** (47.6 mg, 0.1762 mmol, 1.0 equiv) in water (1.7 mL) at room temperature, was added an aqueous 12 M HCl solution (3.5 mL). The mixture was stirred room temperature for 1 h and then evaporated with a gentle air flow. The obtained yellow crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 4:1) to give pure product **9** (α/β, 10:1) as a colorless thick oil (32.4 mg, 0.1741 mmol, 99% yield). The spectroscopic data derived of **9** match those reported in the literature.[3]



9

2,3,4-Trideoxy-2,3,4-trifluorotalitol (**24**). To a stirred solution of trifluorotalose **9** (24.3 mg, 0.1306 mmol, 1.0 equiv) in ethanol (1.3 mL) at room temperature was added $NaBH_4$ (24.7 mg, 0.6528 mmol, 5.0 equiv). The resulting mixture was stirred at room temperature for 1.5 h then 1 mL of methanol was added, and the mixture was neutralized to pH ≈ 7 with acidic resin (Amberlite IR-120). 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 **24** as a colorless oil (17.8 mg, 0.0980 mmol, 75% yield): R_f = 0.44 (silica, MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{25}$ = −11.8 (c 0.3, MeOH); IR (ATR, diamond crystal) *v* 3312, 2947, 2846, 1420, 1246, 1013, 891 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 5.09 (ddddd, *J* = 45.5, 18.6, 10.0, 7.5, 2.6 Hz, 1H, H3), 4.94 (dddddd, *J* = 47.9, 22.5, 6.0, 4.8, 2.6, 1.0 Hz, 1H, H2), 4.92 (dddd, *J* = 46.3, 8.1, 7.6, 2.0 Hz, 1H, H4), 4.32 (br s, 1H, O*H*5), 4.23 (t, *J* = 6.0 Hz, 1H, O*H*1), 4.01 (br s, 1H, O*H*6), 3.92 – 3.80 (m, 3H, H1a, H1b, H5), 3.67 (d, *J* = 6.7 Hz, 2H, H6a, H6b) ppm; ^{13}C {^1H} NMR (126 MHz, Acetone-d_6) δ 94.1 (dd, *J* = 174.3, 21.6, 1.2 Hz, C2), 89.8 (ddd, *J* = 175.6, 27.9, 6.9 Hz, C4), 89.1 (ddd, *J* = 173.3, 28.4, 23.1 Hz, C3), 70.3 (dd, *J* = 18.3, 3.4 Hz, C5), 62.6 (d, *J* = 6.2 Hz, C6), 60.7 (ddd, *J* = 23.5, 8.9, 5.1 Hz, C1) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ -200.41 (dddddd, *J* = 47.9, 26.0, 21.0, 18.6, 11.0, 1.5 Hz, 1F, F2), -205.41 (dddddd, *J* = 45.5, 22.5, 13.0, 11.0, 8.1, 2.6 Hz, 1F, F3), -216.67 (dddd, *J* = 46.3, 28.0, 13.0, 10.0 Hz, 1F, F4) ppm; HRMS calcd for $C_6H_{10}O_3F_3^-$ $[M - H]^-$ 187.0588 found 187.0597.

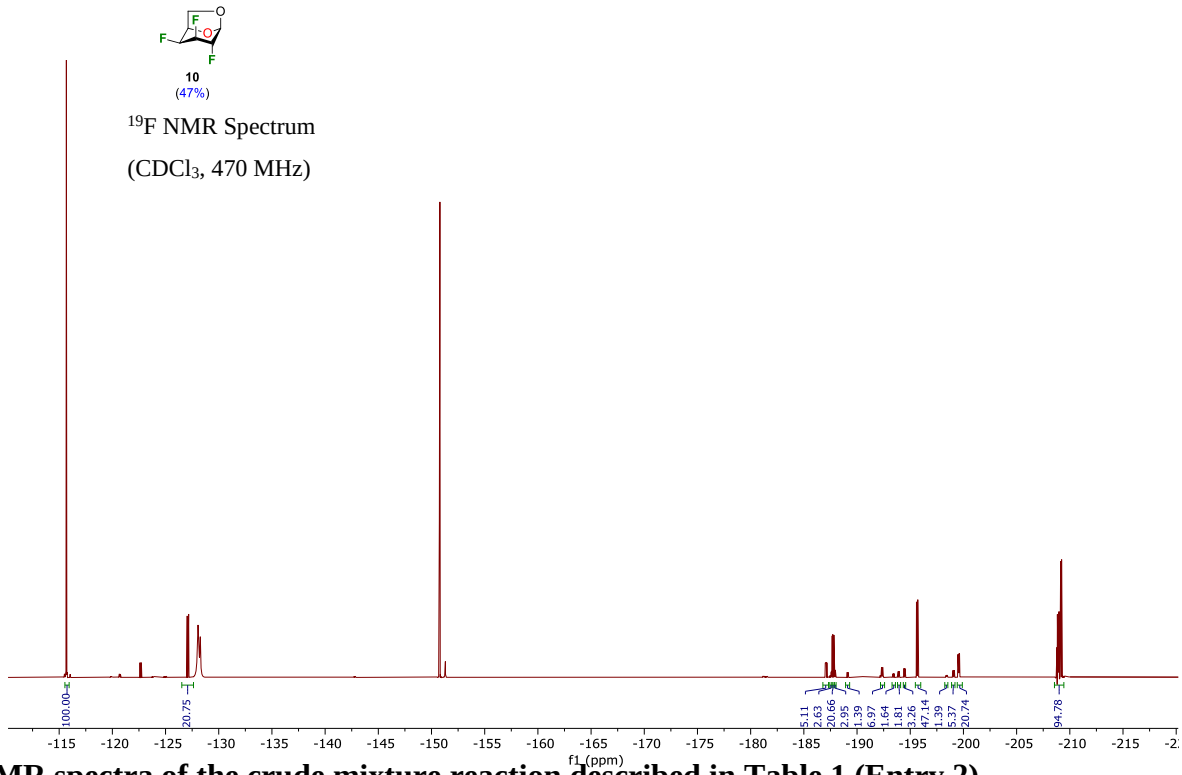
II. Density functional theory calculations

Table S2. Optimized cartesian coordinates of oxiranium cation intermediate **A** (CAM-B3LYP-D3/6-31+G(d,p)).

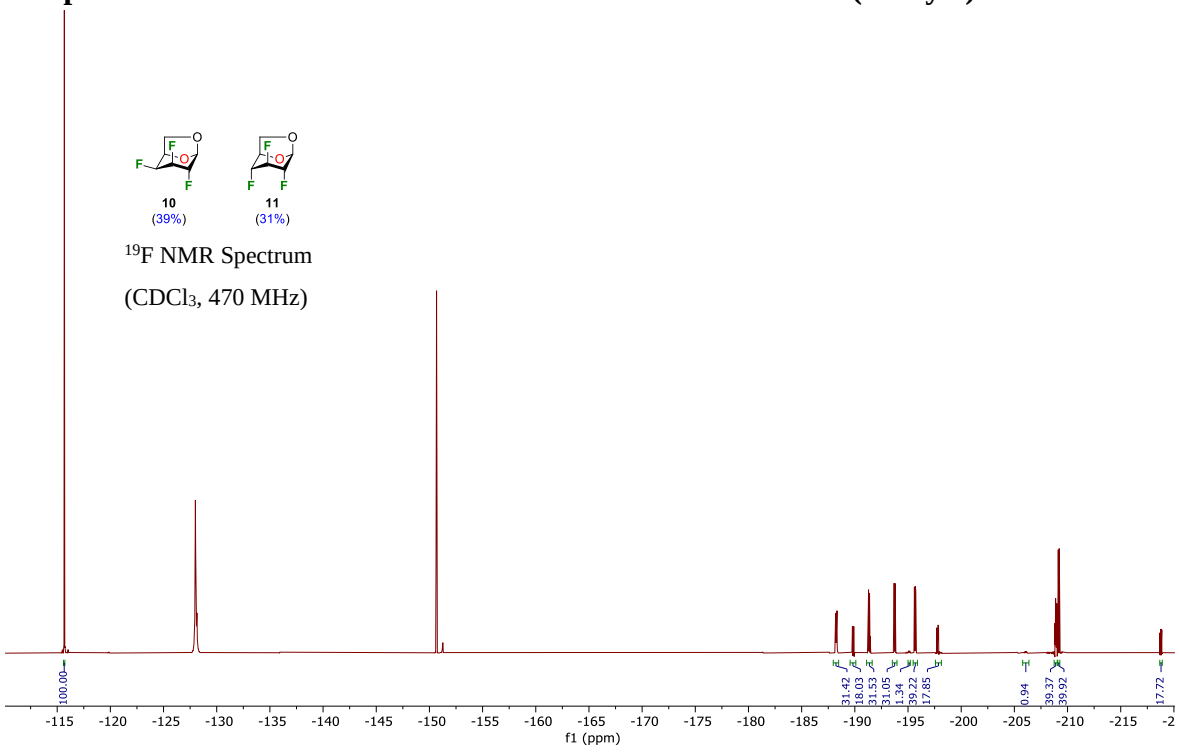
C	-0.899492000	1.097229000	-0.261771000
C	0.562676000	1.346740000	-0.577851000
C	1.596210000	0.638709000	0.186523000
O	1.163799000	0.062757000	-1.130289000
C	0.219976000	-1.094054000	-0.701890000
C	-1.140959000	-0.370839000	-0.686916000
H	-1.557904000	1.792612000	-0.784327000
H	2.617312000	1.004085000	0.133066000
H	0.329312000	-1.863953000	-1.464971000
H	-1.560094000	-0.392002000	-1.698373000
C	1.231873000	-0.404263000	1.244342000
O	0.729129000	-1.507618000	0.475525000
F	-1.107692000	1.257960000	1.087185000
F	-1.986656000	-0.997443000	0.170341000
H	0.487647000	-0.035669000	1.949906000
H	2.116537000	-0.761436000	1.768973000
H	0.851187000	2.189459000	-1.198514000

III. NMR spectra of compounds

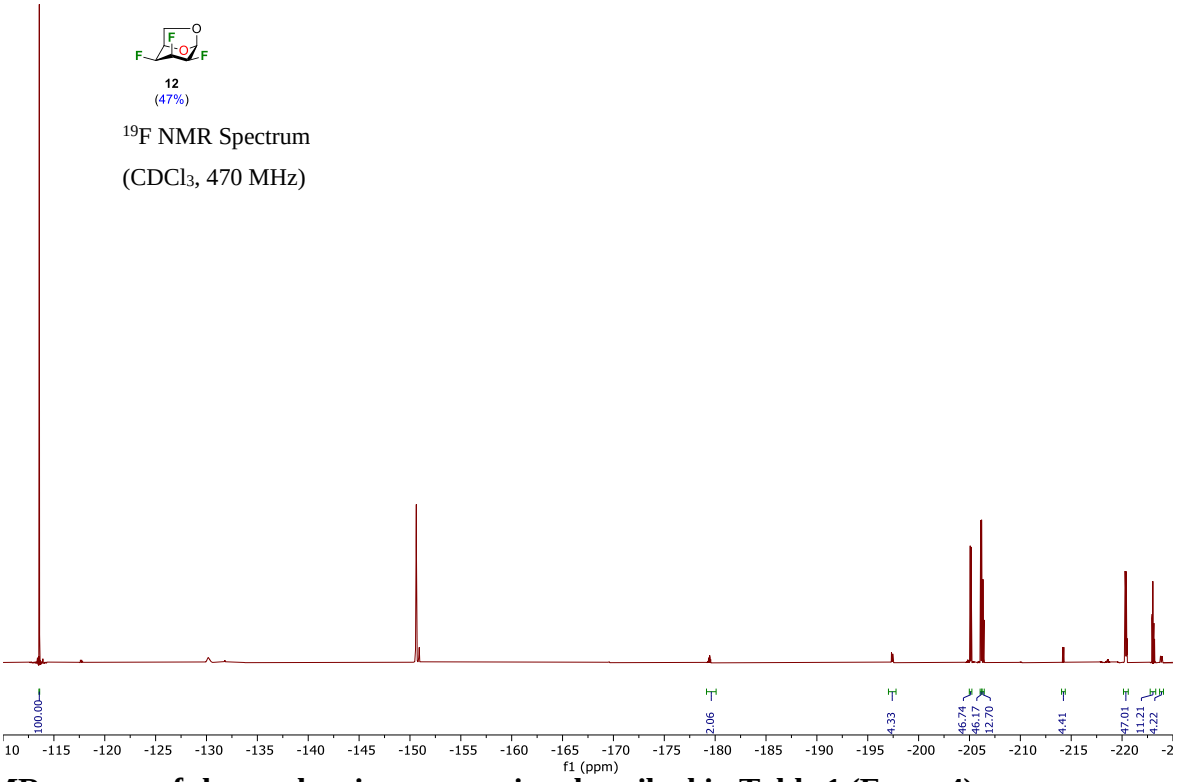
^{19}F NMR spectra of the crude mixture reaction described in Table 1 (Entry 1)



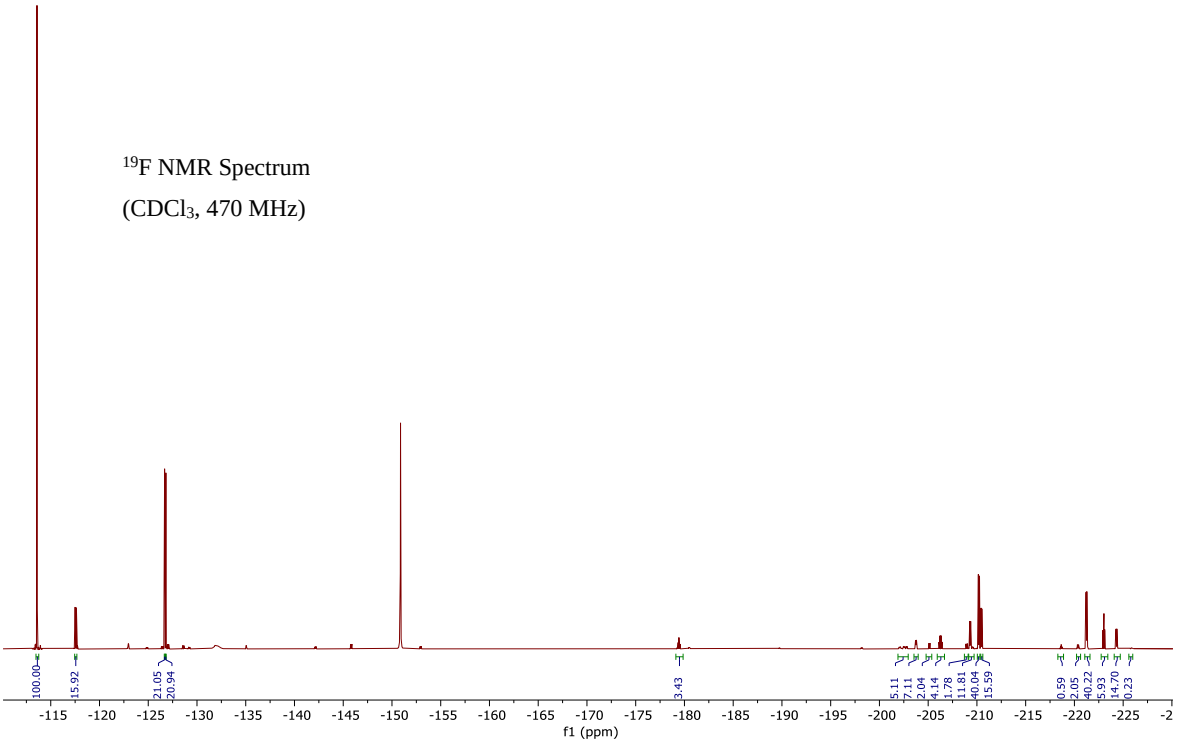
^{19}F NMR spectra of the crude mixture reaction described in Table 1 (Entry 2)



^{19}F NMR spectra of the crude mixture reaction described in Table 1 (Entry 3)



^{19}F NMR spectra of the crude mixture reaction described in Table 1 (Entry 4)



Compound 2

2

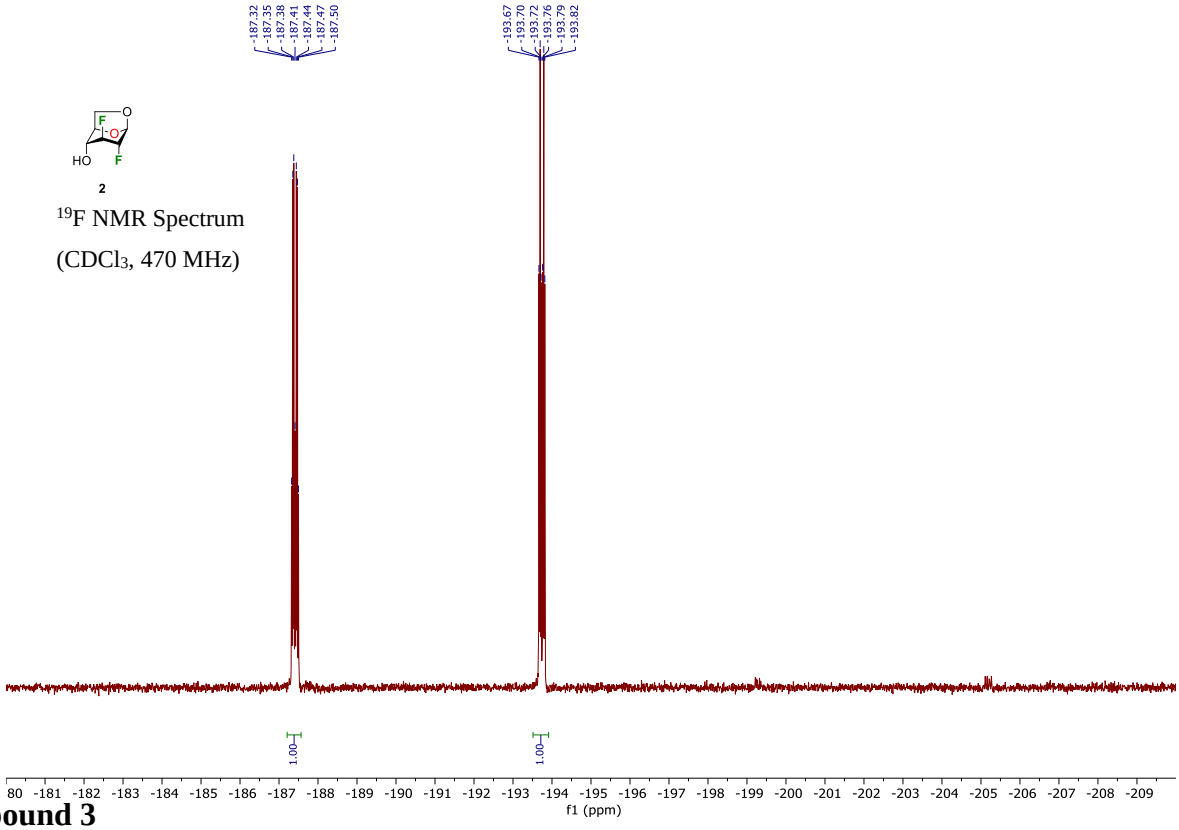
^{1}H NMR Spectrum

($CDCl_3$, 500 MHz)

2

^{13}C NMR Spectrum

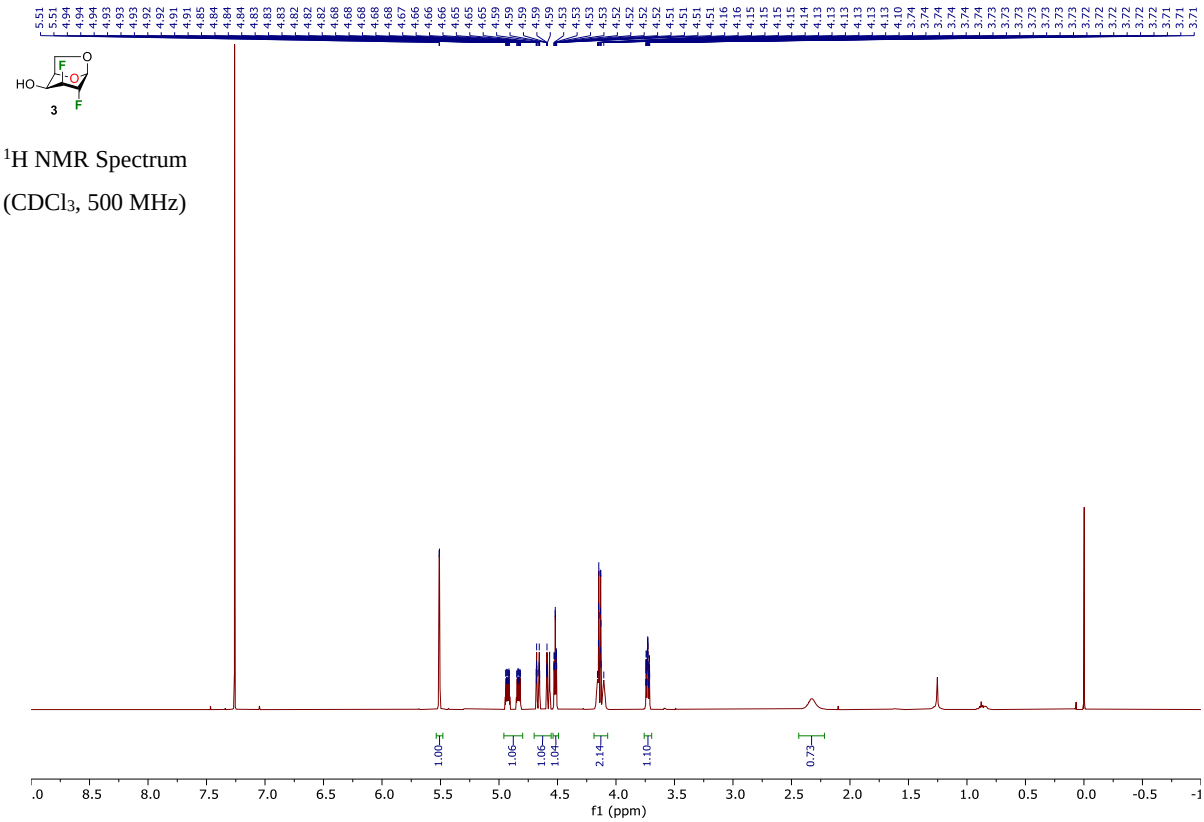
($CDCl_3$, 126 MHz)



^{19}F NMR Spectrum

($CDCl_3$, 470 MHz)

Compound 3



^{1}H NMR Spectrum

($CDCl_3$, 500 MHz)

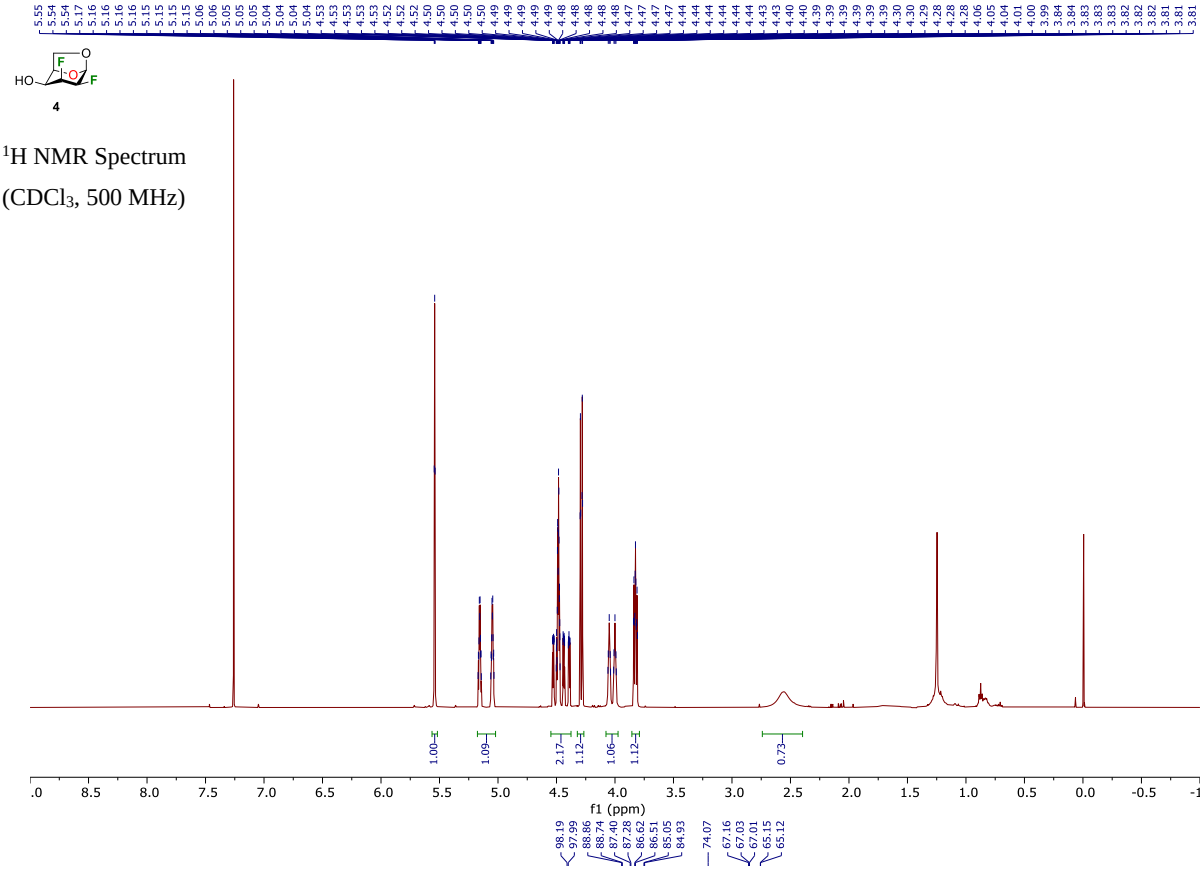
^{13}C NMR Spectrum

($CDCl_3$, 126 MHz)

^{19}F NMR Spectrum

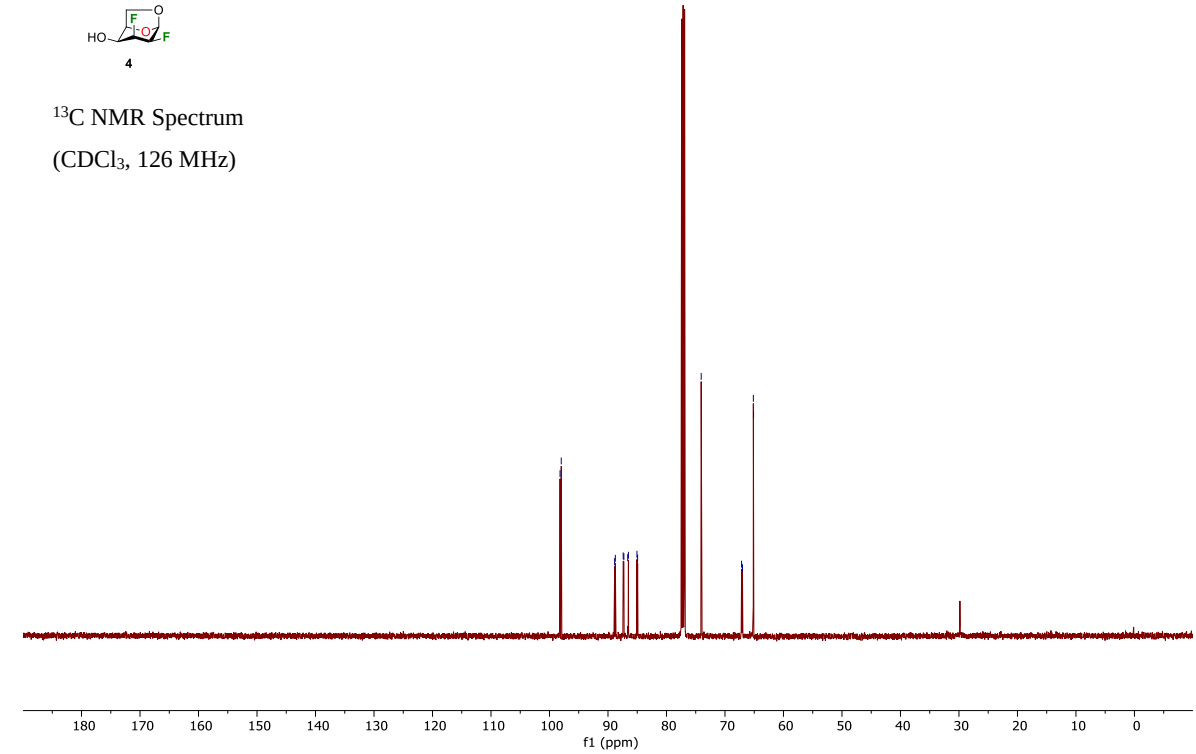
($CDCl_3$, 470 MHz)

Compound 4



^{1}H NMR Spectrum

($CDCl_3$, 500 MHz)



^{13}C NMR Spectrum

($CDCl_3$, 126 MHz)

4

^{19}F NMR Spectrum

($CDCl_3$, 470 MHz)

Compound 5

5

^{1}H NMR Spectrum

($CDCl_3$, 500 MHz)

5

^{13}C NMR Spectrum

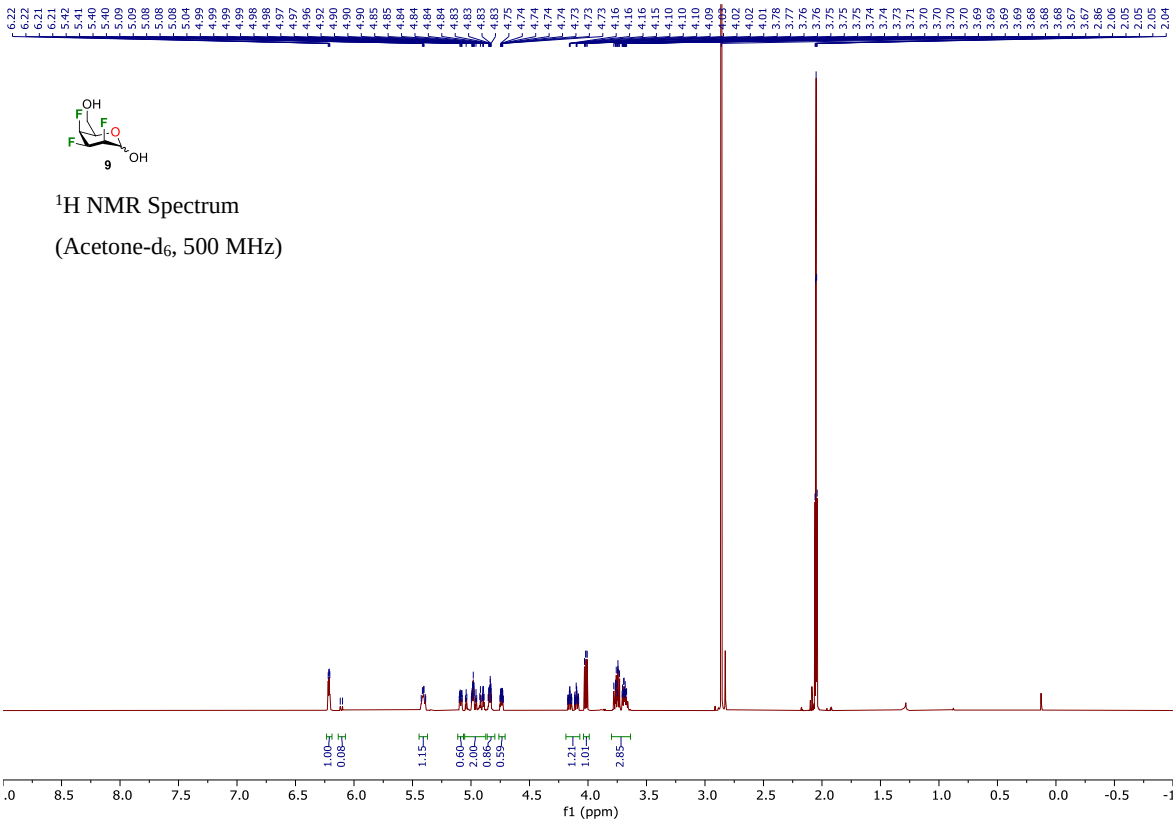
($CDCl_3$, 126 MHz)

5

^{19}F NMR Spectrum

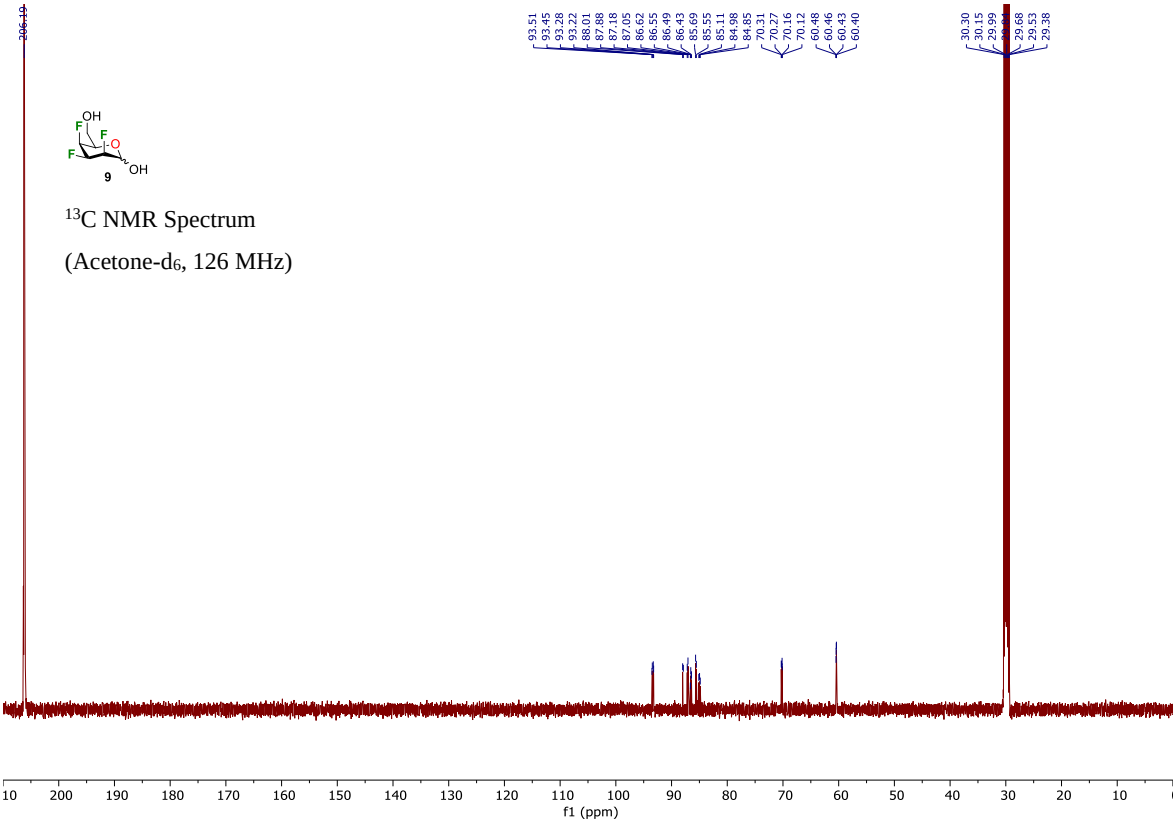
($CDCl_3$, 470 MHz)

Compound 9



^{1}H NMR Spectrum

(Acetone-d_6, 500 MHz)



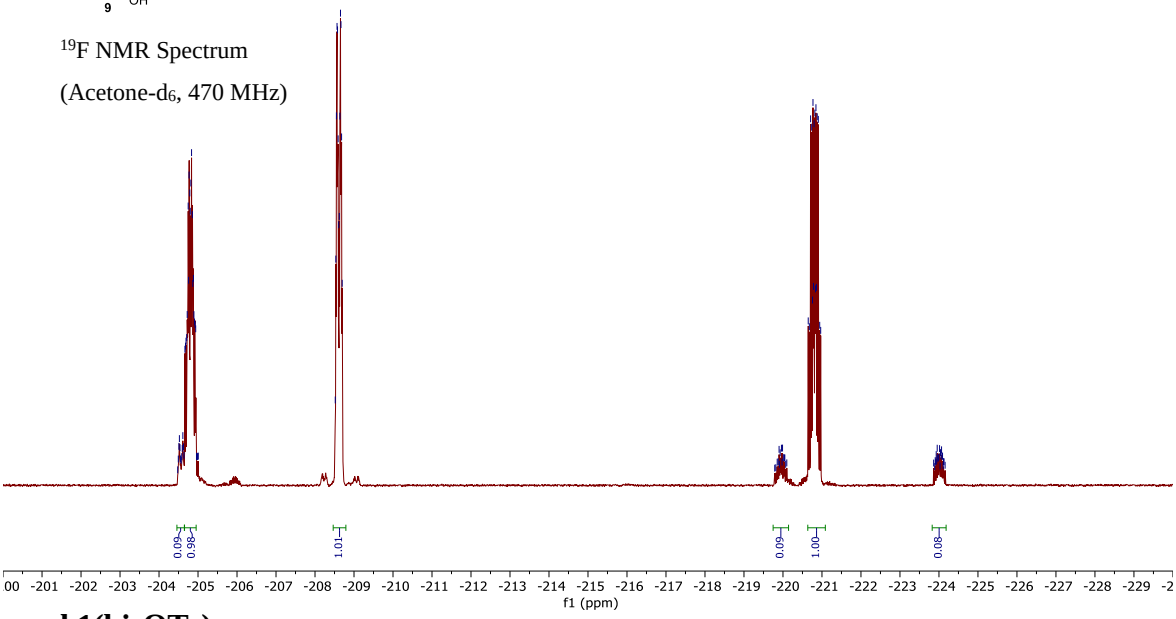
^{13}C NMR Spectrum

(Acetone-d_6, 126 MHz)

9

^{19}F NMR Spectrum

(Acetone-d_6, 470 MHz)



Compound 1(bisOTs)

^{1}H NMR Spectrum

($CDCl_3$, 400 MHz)

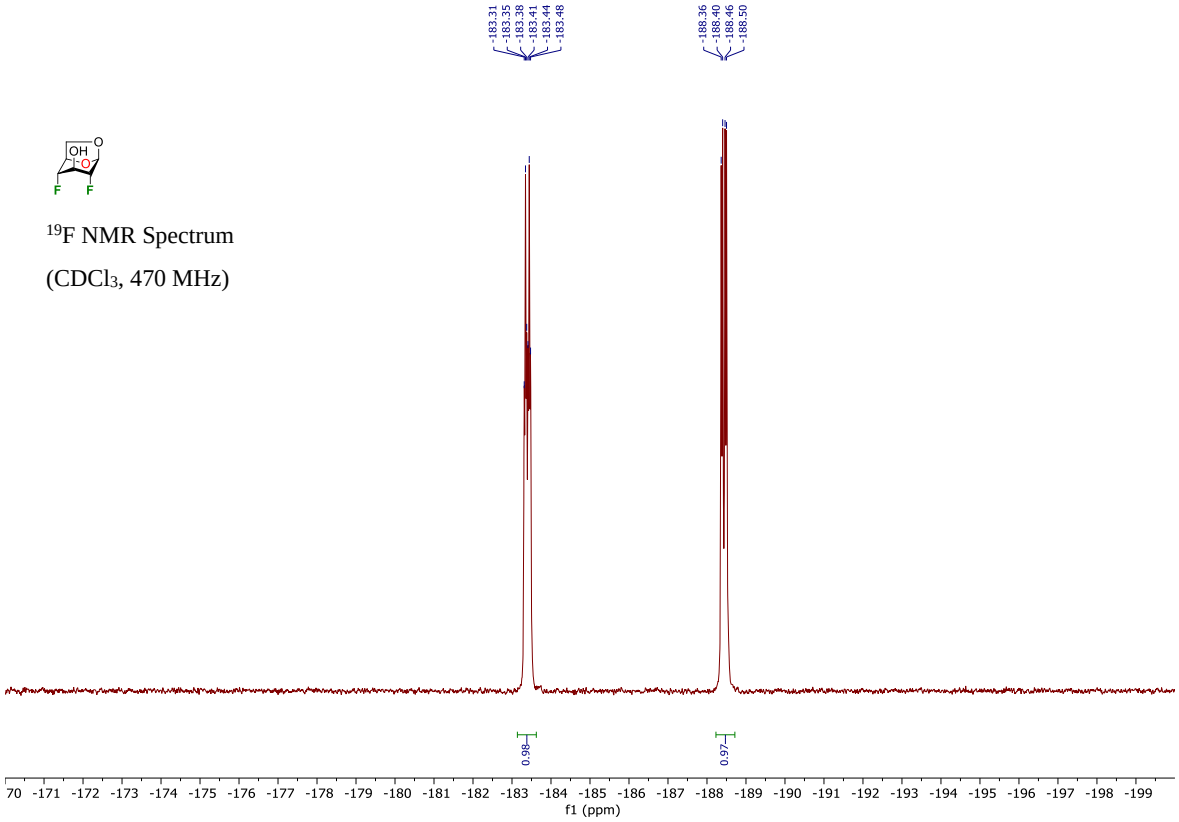
Compound 21(1,6-anhydro)

^{1}H NMR Spectrum

($CDCl_3$, 500 MHz)

^{13}C NMR Spectrum

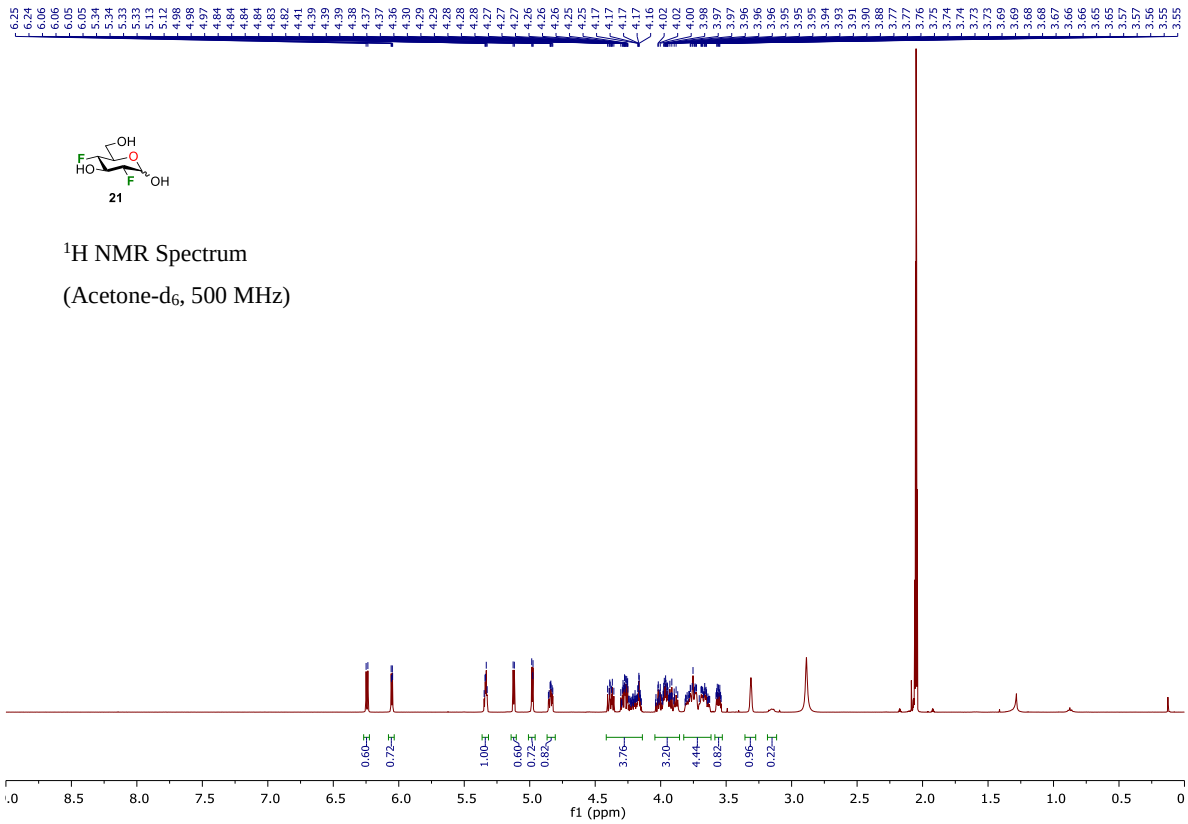
($CDCl_3$, 126 MHz)



^{19}F NMR Spectrum

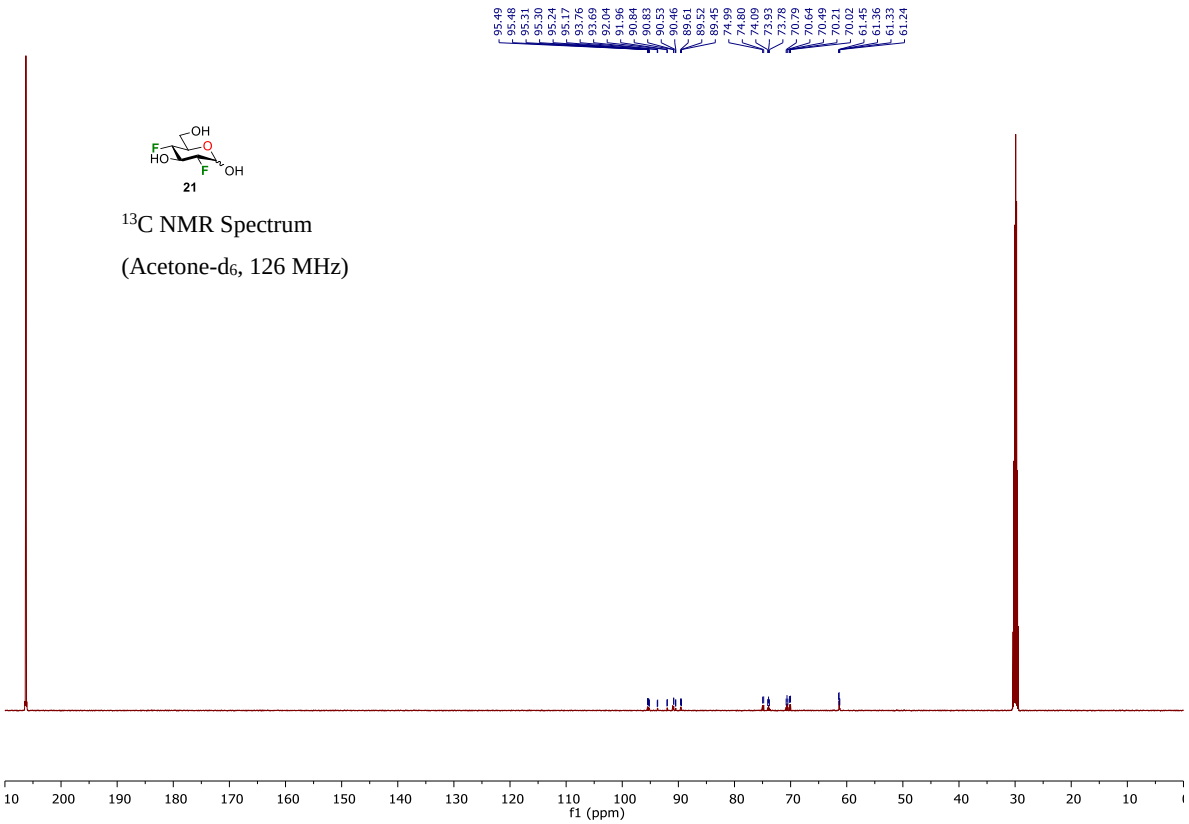
($CDCl_3$, 470 MHz)

Compound 21



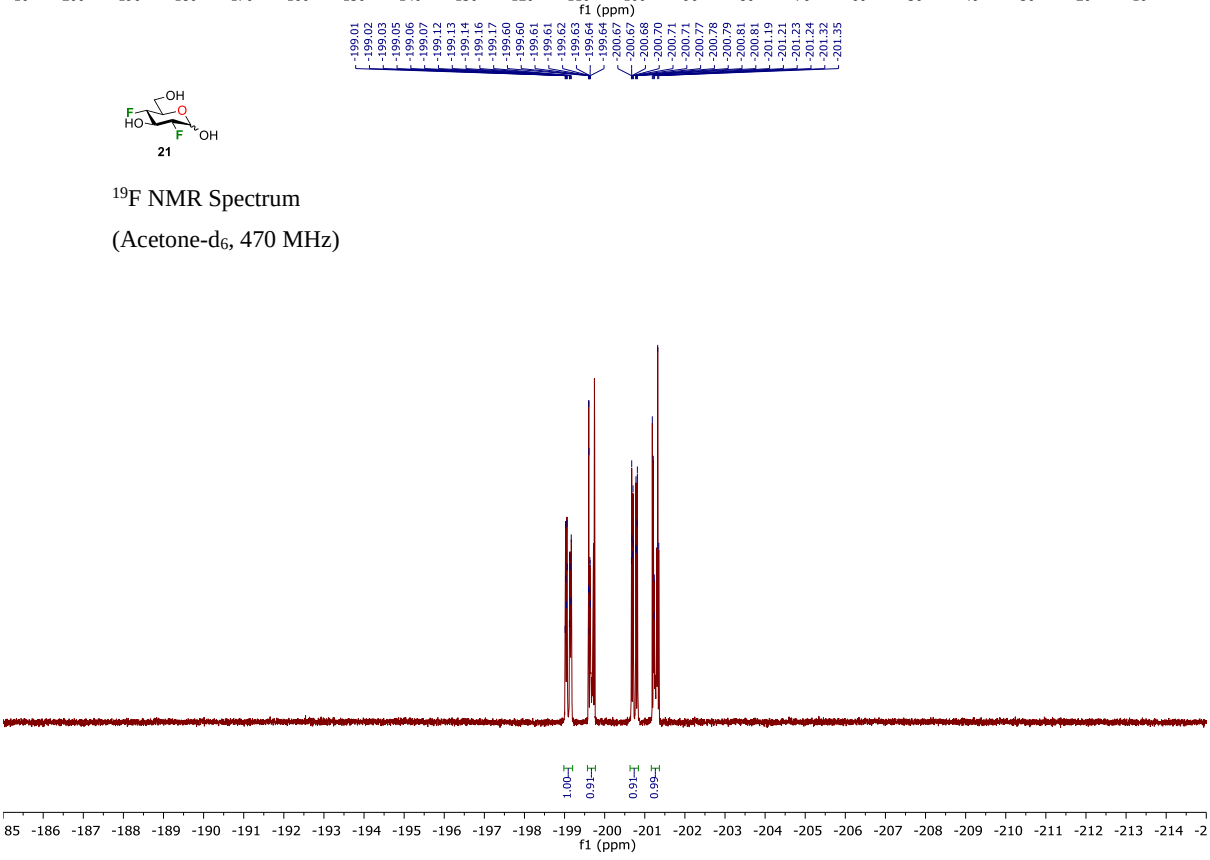
^{1}H NMR Spectrum

(Acetone-d_6, 500 MHz)



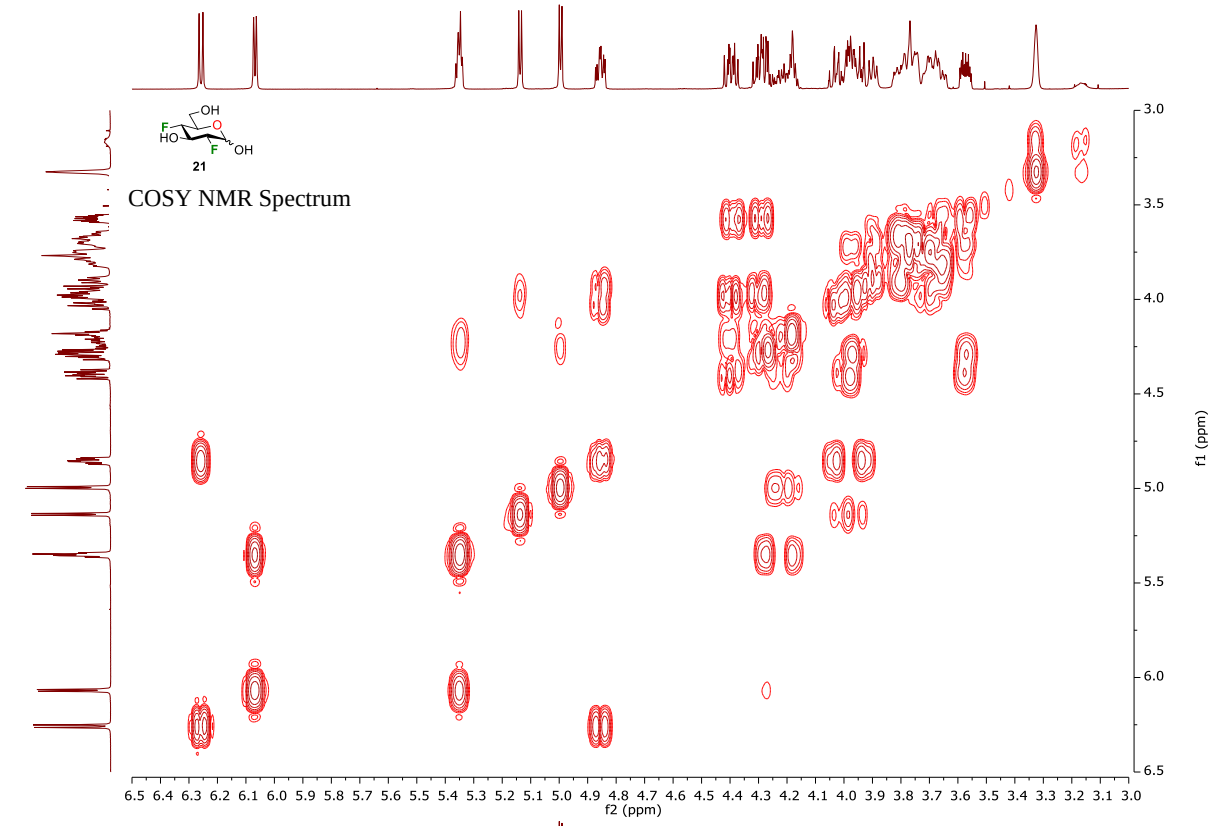
^{13}C NMR Spectrum

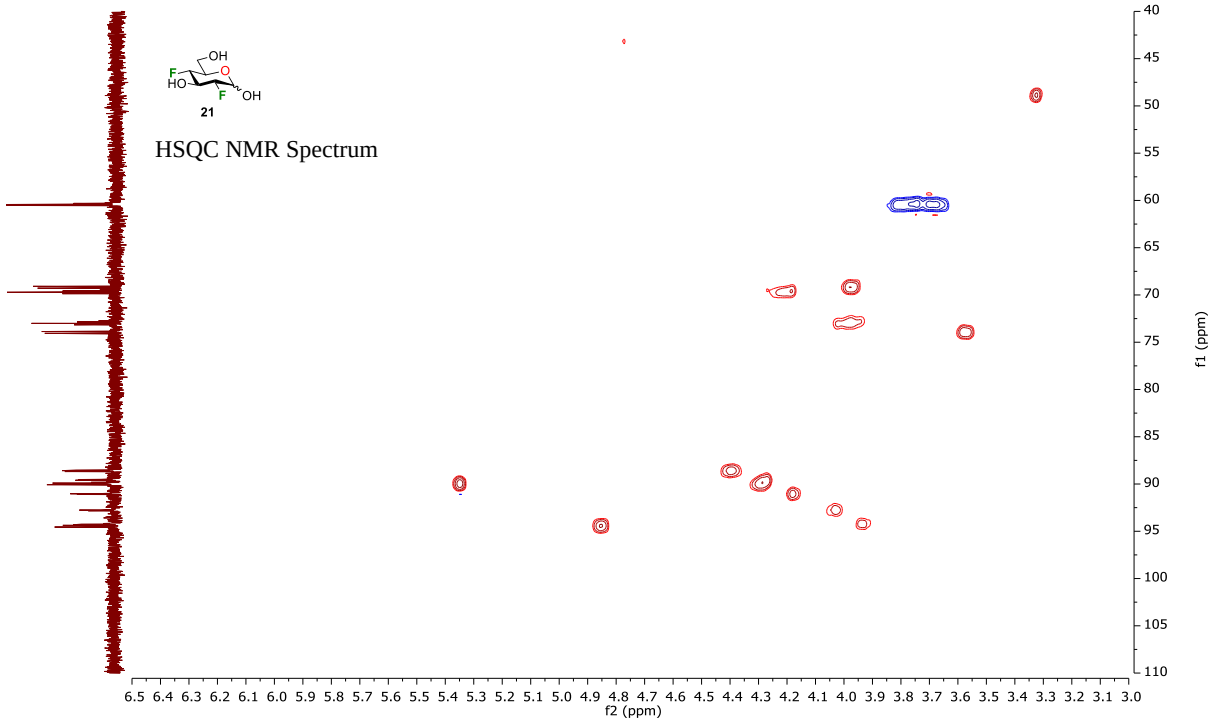
(Acetone-d_6, 126 MHz)



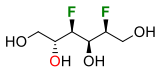
^{19}F NMR Spectrum

(Acetone-d_6, 470 MHz)


21
COSY NMR Spectrum
f2 (ppm)
f1 (ppm)


21
HSQC NMR Spectrum
f2 (ppm)
f1 (ppm)

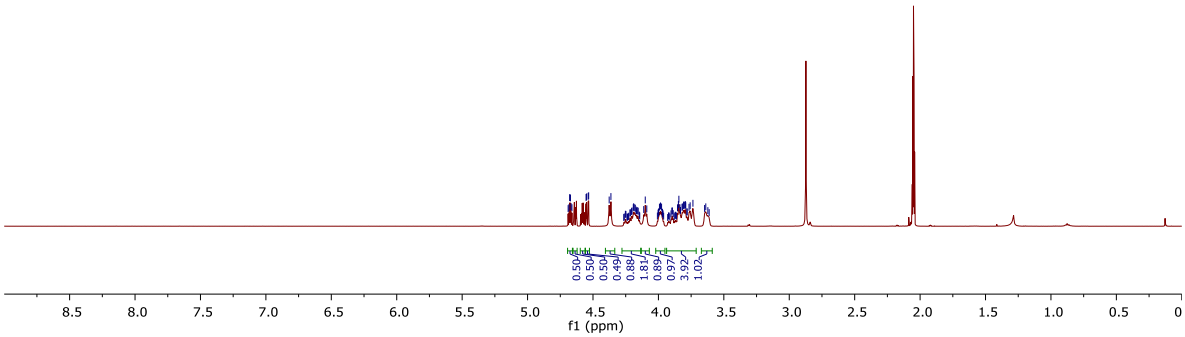
Compound 22

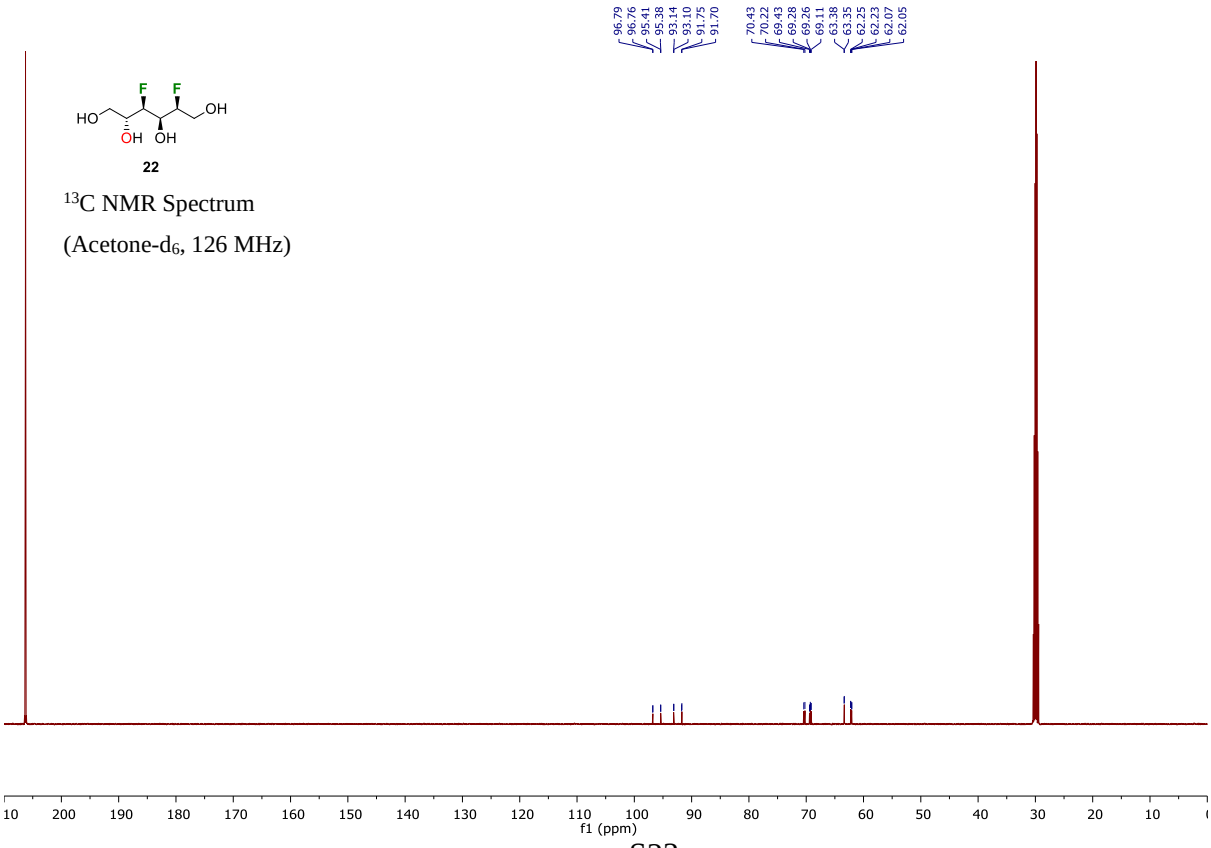


22

^{1}H NMR Spectrum

(Acetone-d_6, 500 MHz)

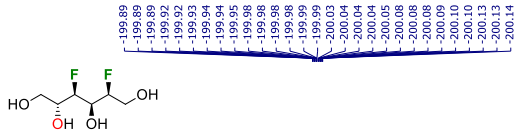




22

^{13}C NMR Spectrum

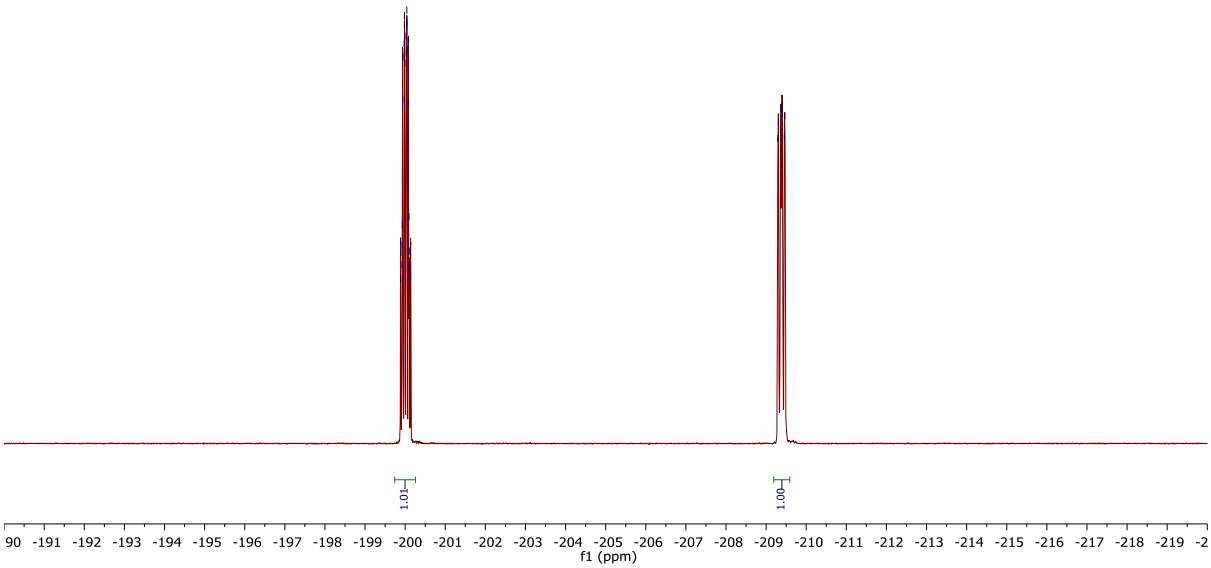
(Acetone-d_6, 126 MHz)

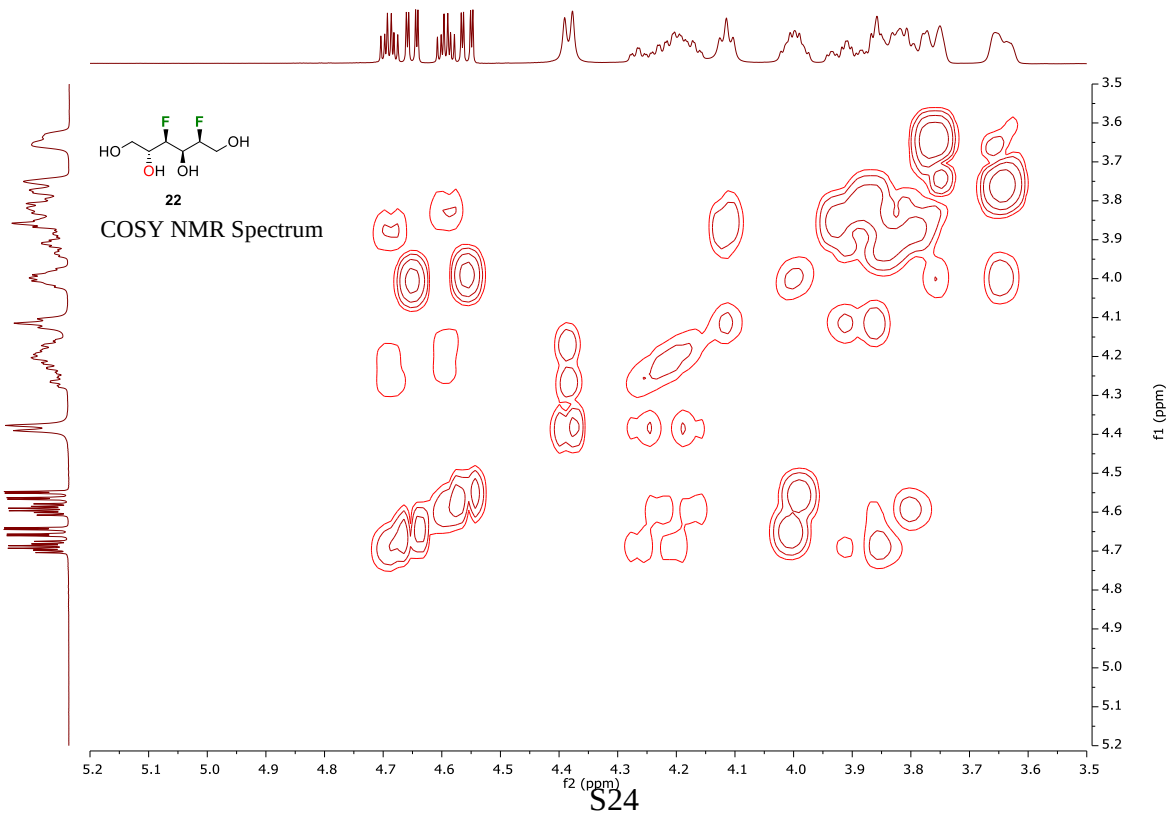


22

^{19}F NMR Spectrum

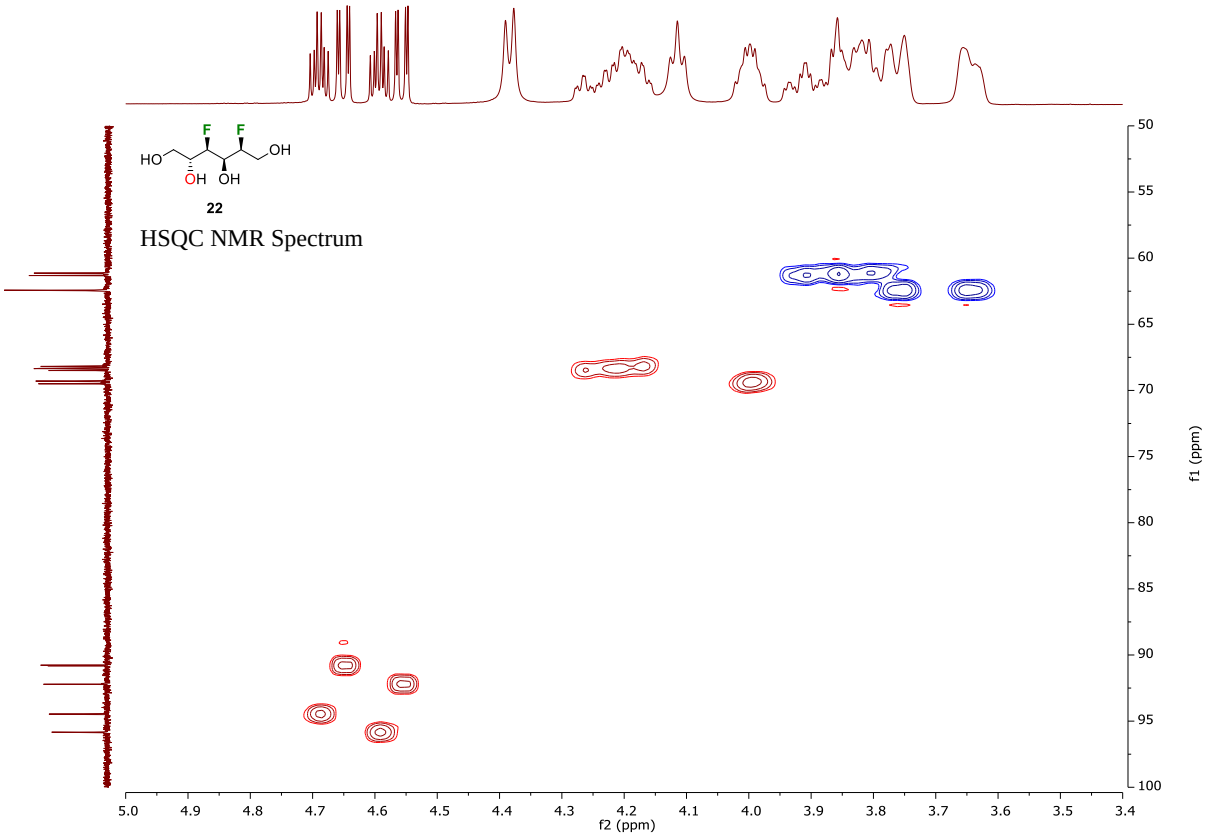
(Acetone-d_6, 470 MHz)



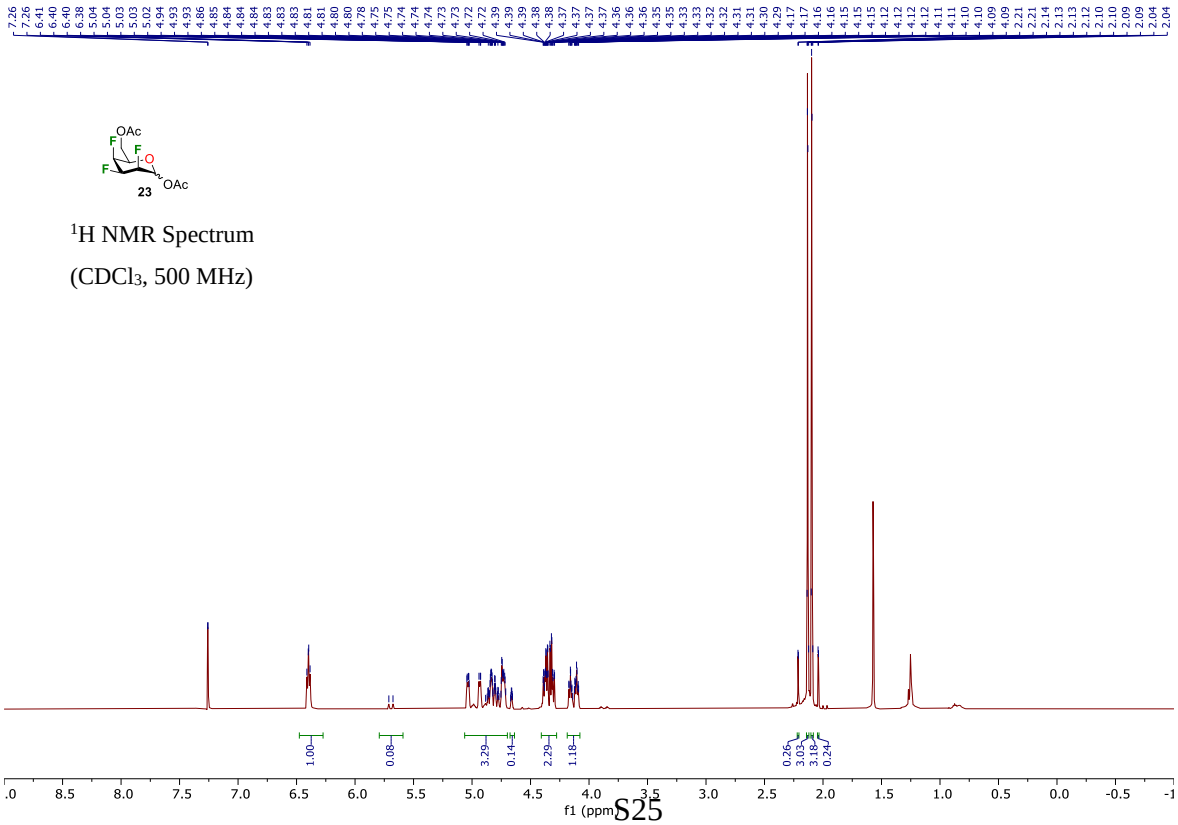


22

COSY NMR Spectrum

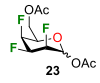


Compound 23



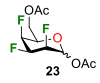
^{1}H NMR Spectrum

($CDCl_3$, 500 MHz)



^{13}C NMR Spectrum

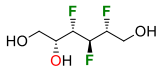
($CDCl_3$, 126 MHz)



^{19}F NMR Spectrum

($CDCl_3$, 470 MHz)

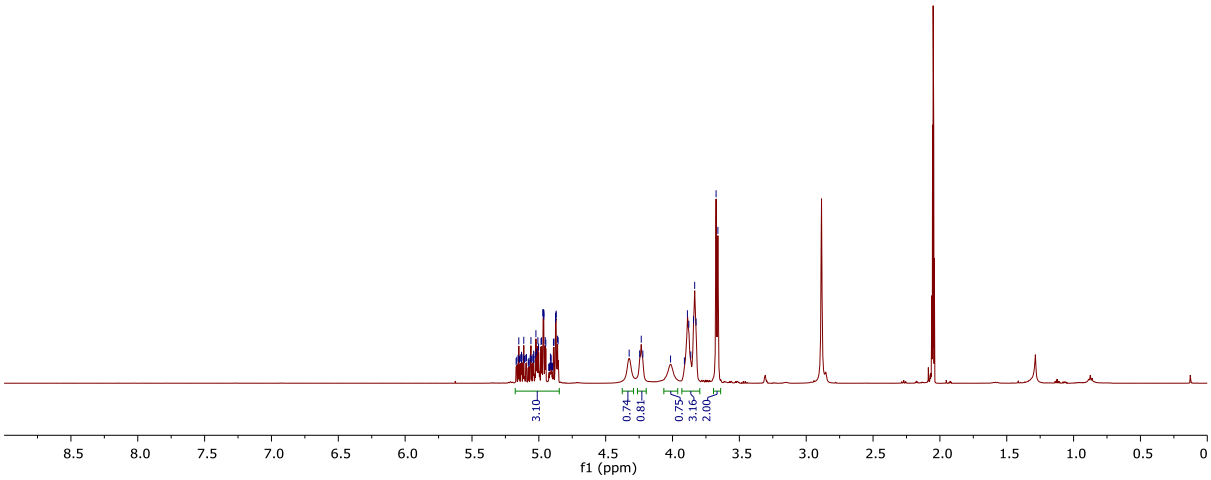
Compound 24



24

^{1}H NMR Spectrum

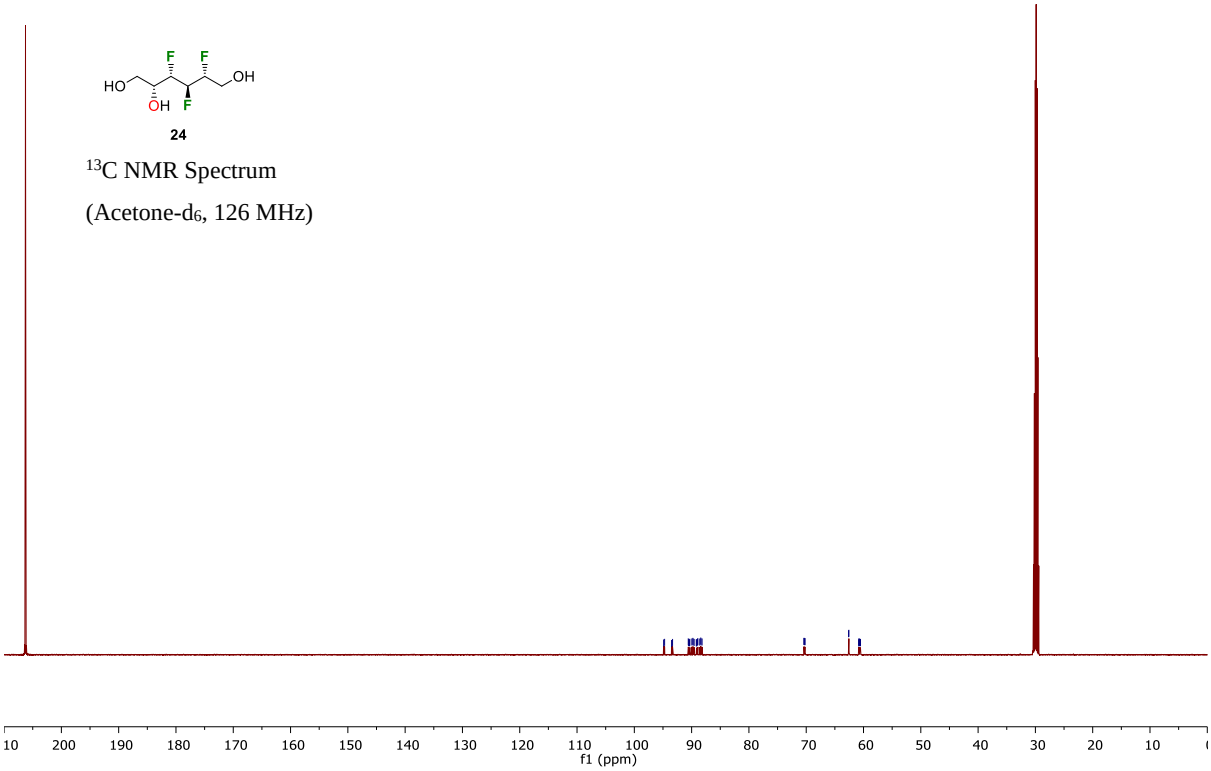
(Acetone-d_6, 500 MHz)

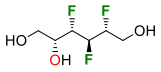


24

^{13}C NMR Spectrum

(Acetone-d_6, 126 MHz)

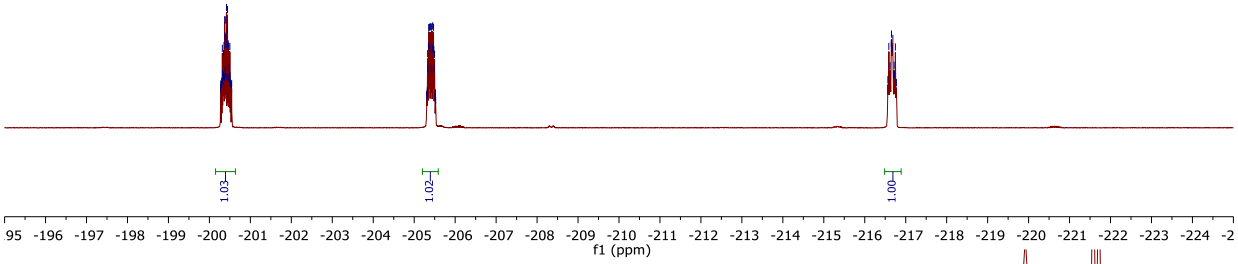


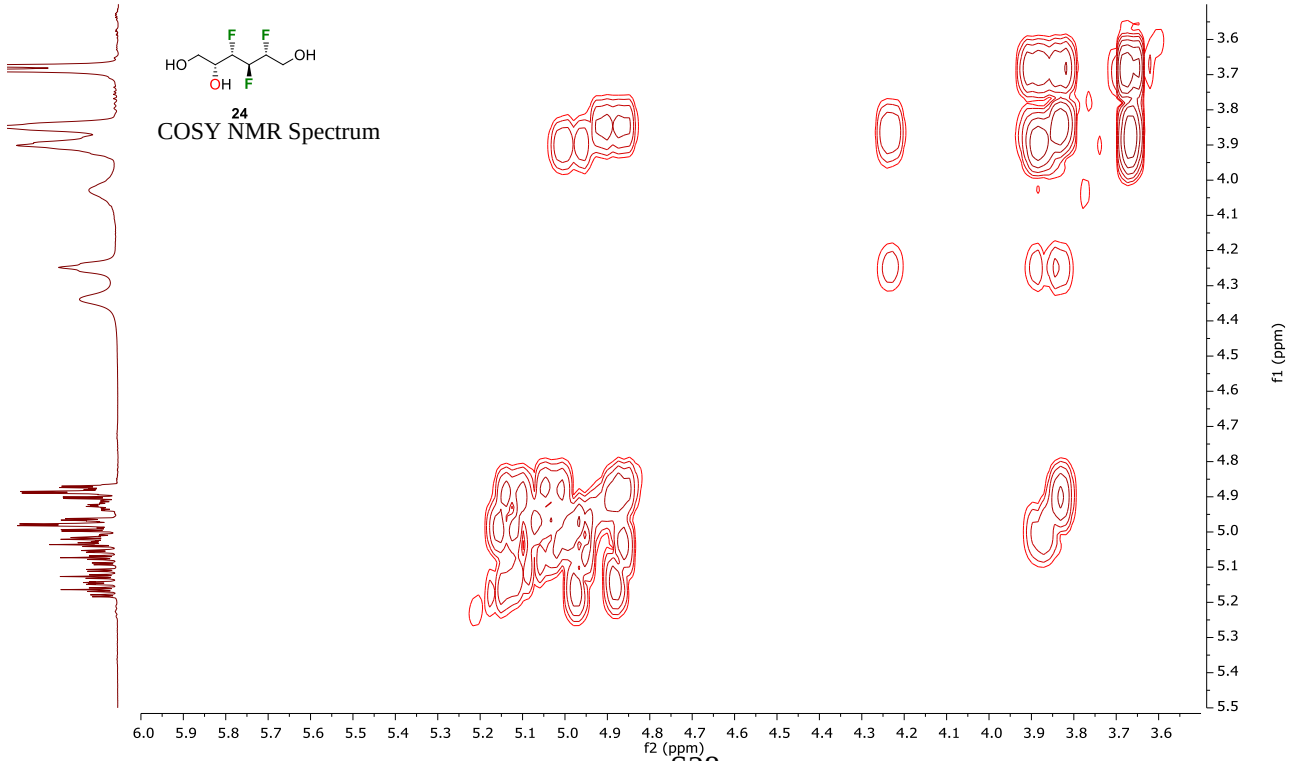


24

^{19}F NMR Spectrum

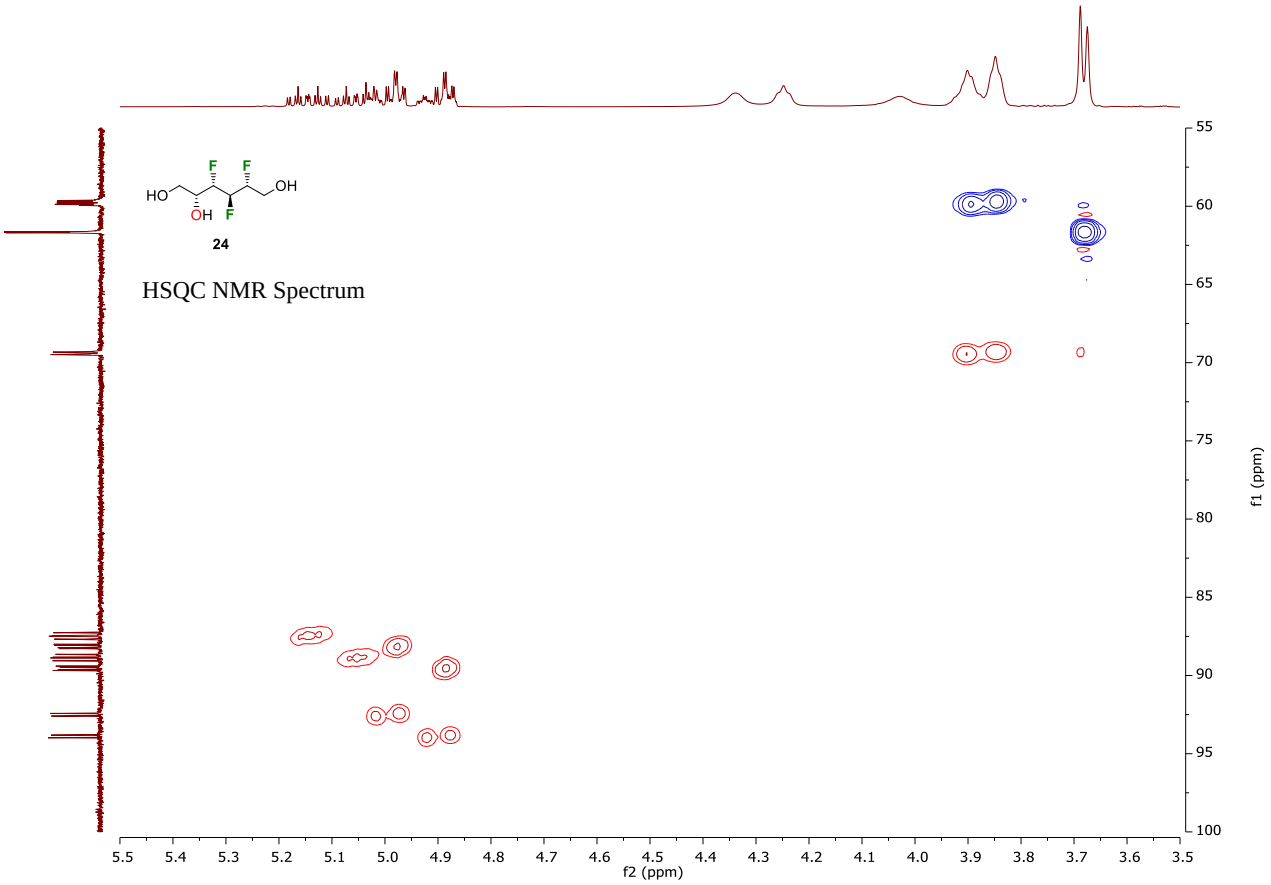
(Acetone-d_6, 470 MHz)

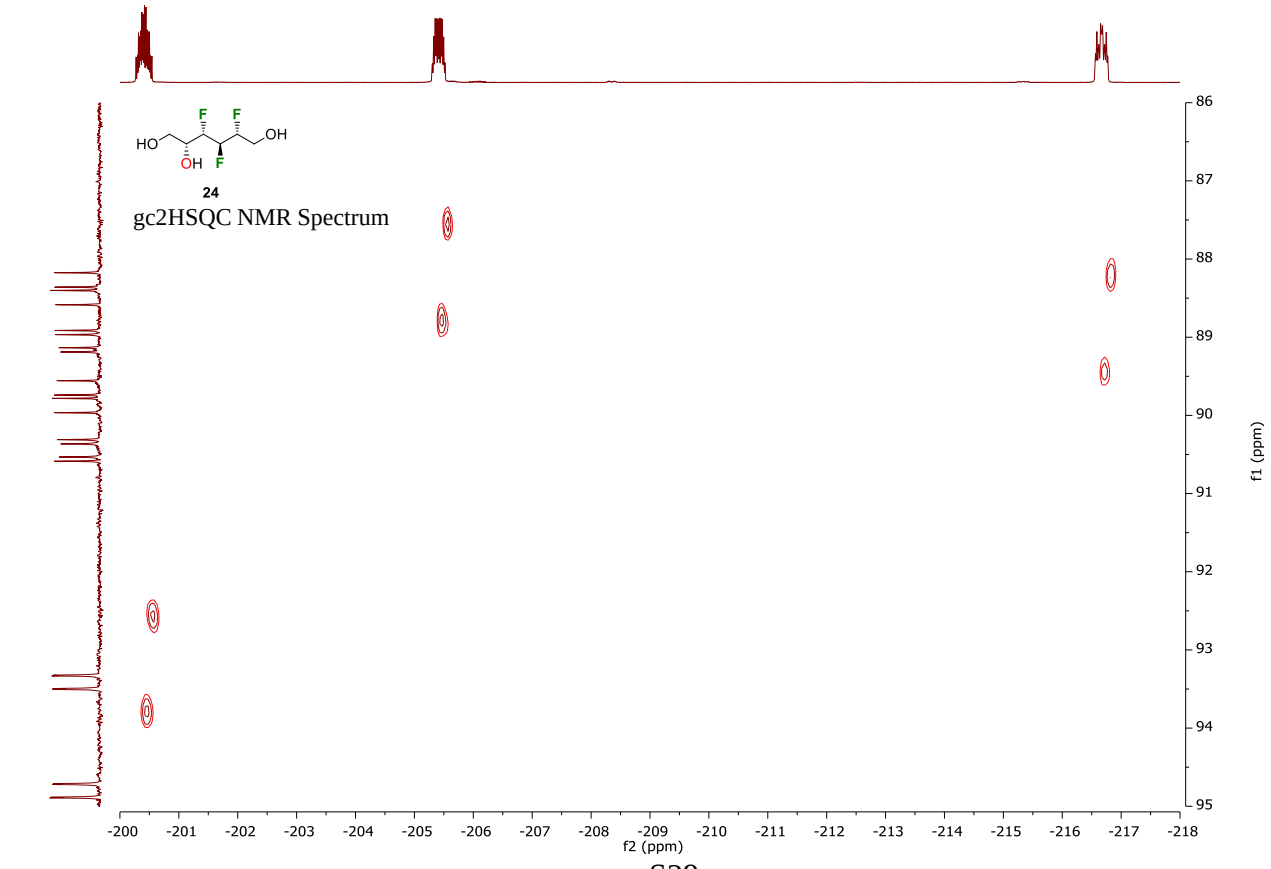




24

COSY NMR Spectrum


F
F
HO
OH
OH
F
24
HSQC NMR Spectrum
f2 (ppm)
f1 (ppm)


F
F
HO
OH
OH
F
24
gc2HSQC NMR Spectrum
f2 (ppm)
f1 (ppm)

IV. References

[1] St-Gelais, J.; Côté, É.; Lainé, D.; Johnson, P. A.; Giguère, D. *Chem. Eur. J.* **2020**, *26*, 13499–13506.

[2] St-Gelais, J.; Bouchard, M.; Denavit, V.; Giguère, D. *J. Org. Chem.* **2019**, *84*, 8509–8522.

[3] Denavit, V.; Lainé, D.; St-Gelais, J.; Johnson, P. A.; Giguère, D. *Nat. Commun.* **2018**, *9*, 4721.