



Supporting Information

for

Lipophilicity trends upon fluorination of isopropyl, cyclopropyl and 3-oxetanyl groups

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Beilstein J. Org. Chem. **2020**, *16*, 2141–2150. doi:10.3762/bjoc.16.182

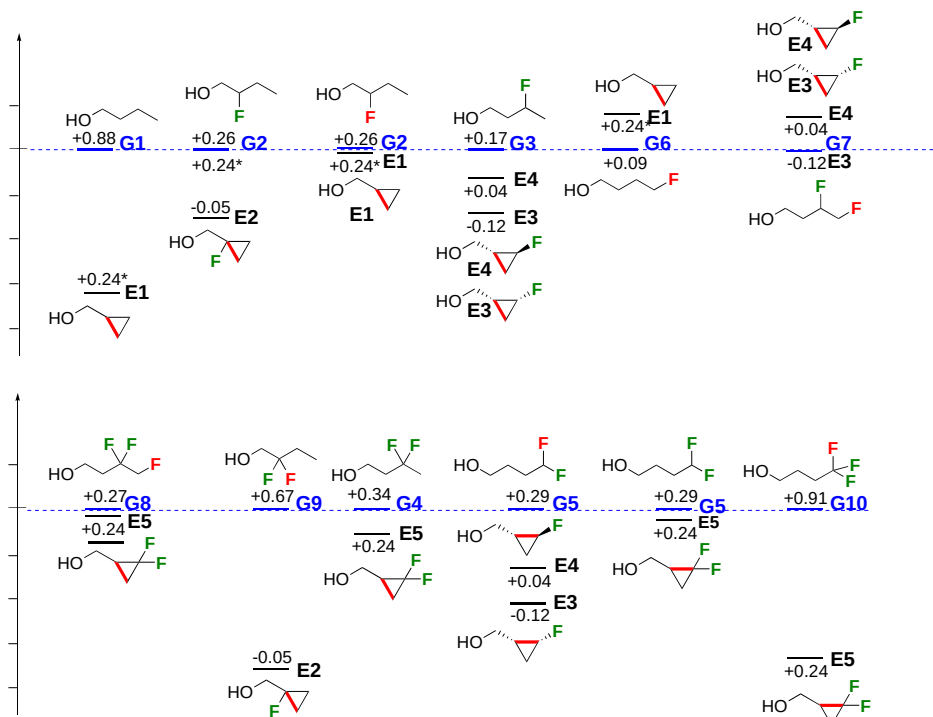
Synthesis, characterisation and copies of spectra of the novel compounds, details of the calculations, log*P* determinations of the nonfluorinated parents E1 and F1, and experimental measurements of the lipophilicities of the fluorinated derivatives

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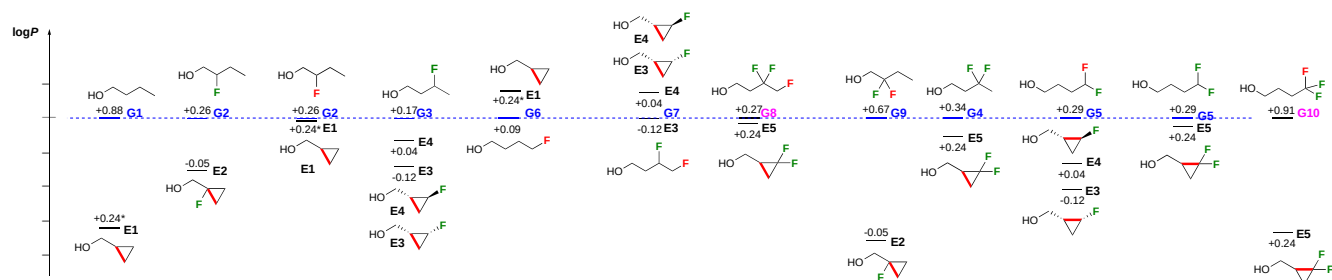
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1 Comparison between linear, isopropyl and cyclopropyl (Figure S1)

Full Figure:



2 Determination of the $\text{clog}P$ of the parent compounds cyclopropylmethanol E1 and (3-oxetanyl)methanol F1

No experimental $\log P$ values of these compounds are available in the literature. Instead, their values were estimated using the correlation between published experimental $\log P$ values for various alkanols, and their calculated values using various prediction tools. Experimental $\log P$ was plotted against $\text{clog}P$ for each predictor tool, and a linear regression performed. This provided an equation to obtain an estimated $\log P$ based on that calculator's $\text{clog}P$ value.

2.1 Experimental $\log P$ values^a for selected nonfluorinated alkanols (Table S1)

Compound	$\log P$	Compound	$\log P$
methanol	-0.77	3-hexanol	1.65
ethanol	-0.31	cyclohexanol	1.23
1,2-ethanediol	-1.36	1-heptanol	2.72
1-propanol	0.25	2-heptanol	2.31
2,2-dimethylpropan-1-ol	1.31	3-heptanol	2.24
2-propanol	0.05	4-heptanol	2.22
1,3-propanediol	-1.04	1-octanol	3.00
1-butanol	0.88	2-octanol	2.90
2-butanol	0.61	4-octanol	2.68
tert-butanol	0.35	3,3-dimethyl-2-butanol	1.48
1,4-butanediol	-0.83	3-methyl-1-butanol	1.16
1-pentanol	1.56	3-methyl-2-butanol	1.28
2-pentanol	1.19	2-methyl-2-butanol	0.89
3-pentanol	1.21	2,3-butanediol	-0.92
1-hexanol	2.03	2-methylpropan-1-ol	0.76
2-hexanol	1.76	1,2-propanediol	-0.92

^a C. Hansch, A. Leo, and D. Hoekman, *Exploring QSAR: Hydrophobic, Electronic, and Steric Constants*, American Chemical Society, 1995

2.2 ClogP values for selected nonfluorinated alkanols (Table S2)

Compound	Molinspiration ^a	Biobyte ^b	Marvin sketch ^c	ACD logP ^d	AZ logD _{7.4} ^e
methanol	-0.32	-0.76	-0.57	-0.72	-0.43
ethanol	0.06	-0.24	-0.22	-0.19	0.10
1,2-ethanediol	-0.95	-1.37	-1.31	-1.69	-0.62
1-propanol	0.56	0.29	0.25	0.34	0.64
2,2-dimethylpropan-1-ol	1.38	1.09	1.15	1.04	1.32
2-propanol	0.42	0.07	0.19	0.16	0.40
1,3-propanediol	-0.68	-1.04	-1.26	-1.04	-0.32
1-butanol	1.12	0.82	0.64	0.88	1.20
2-butanol	0.92	0.60	0.66	0.69	0.87
tert-butanol	0.87	0.47	0.27	0.51	0.57
1,4-butanediol	-0.41	-1.16	-0.81	-1.02	-0.20
1-pentanol	1.62	1.35	1.04	1.41	1.42
2-pentanol	1.48	1.13	1.06	1.22	1.35
3-pentanol	1.43	1.13	1.13	1.22	1.20
1-hexanol	2.13	1.88	1.43	1.94	1.70
2-hexanol	1.99	1.66	1.45	1.75	1.84
3-hexanol	1.98	1.66	1.52	1.75	1.69
cyclohexanol	1.59	1.27	1.02	1.34	1.32
1-heptanol	2.63	2.41	1.83	2.47	2.05
2-heptanol	2.49	2.19	1.85	2.29	2.23
3-heptanol	2.49	2.19	1.92	2.29	2.20
4-heptanol	2.54	2.19	1.92	2.29	2.18
1-octanol	3.14	2.94	2.23	3.00	2.43
2-octanol	3.00	2.72	2.24	2.82	2.63

Compound	Molinspiration ^a	Biobyte ^b	Marvin sketch ^c	ACD logP ^d	AZ logD _{7.4} ^e
4-octanol	3.05	2.72	2.32	2.82	2.73
3,3-dimethyl-2-butanol	1.75	1.40	1.57	1.39	1.53
3-methyl-1-butanol	1.33	1.22	0.97	1.22	1.22
3-methyl-2-butanol	1.17	1.00	1.06	1.04	1.14
2-methyl-2-butanol	1.37	1.00	0.74	1.04	0.87
2,3-butanediol	-0.23	-0.75	-0.48	-0.99	0.10
2-methylpropan-1-ol	0.80	0.69	0.65	0.69	1.06
1,2-propanediol	-0.59	-1.06	-0.90	-1.34	-0.38

^a molinspector: <http://www.molinspiration.com/cgi-bin/properties>

^b Daylight/Biobyte ClogP Pomona College and BioByte, Inc., Claremont, CA (bio-loom version 1.6, program version 5: <http://www.biobyte.com/>)

^c MarvinSketch – ChemAxon: <https://docs.chemaxon.com/display/docs/logP+Plugin#logPPlugin-Method>.

^d **Version: 2018.1.1** ACDlogP was calculated using ACD/Labs software, version 2018 (see www.acdlabs.com).

^e AstraZeneca internal method.

2.3 Correlation of $\text{clog}P$ with experimental data for nonfluorinated alkanols (Figures S2–S6)

Each set of $\text{clog}P$ values from the individual calculators were plotted against the corresponding experimental values. The correlation was then determined for each data set.

2.3.1 Molinspiration (Figure S2)

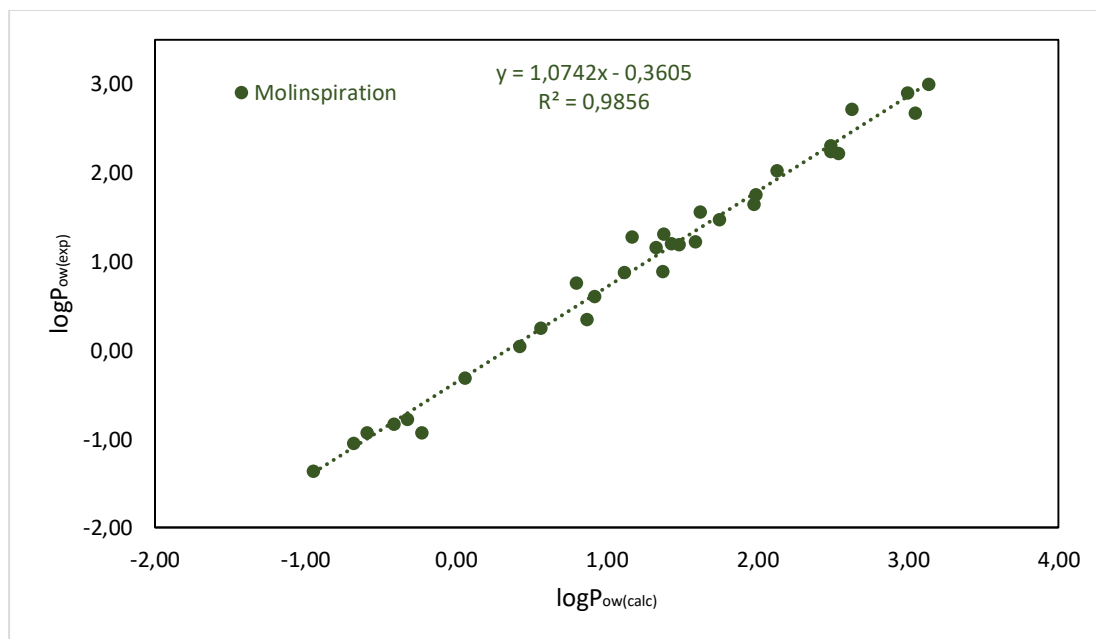


Figure S2: Correlation of the experimental data with $\text{clog}P$ values obtained with Molinspiration.

2.3.2 Biobyte (Figure S3)

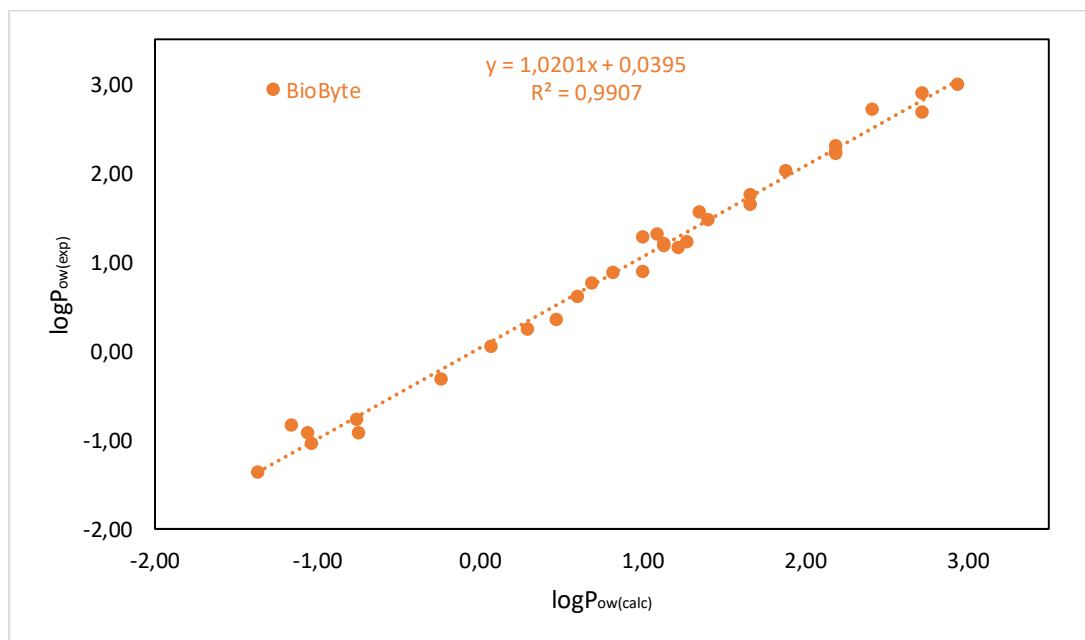
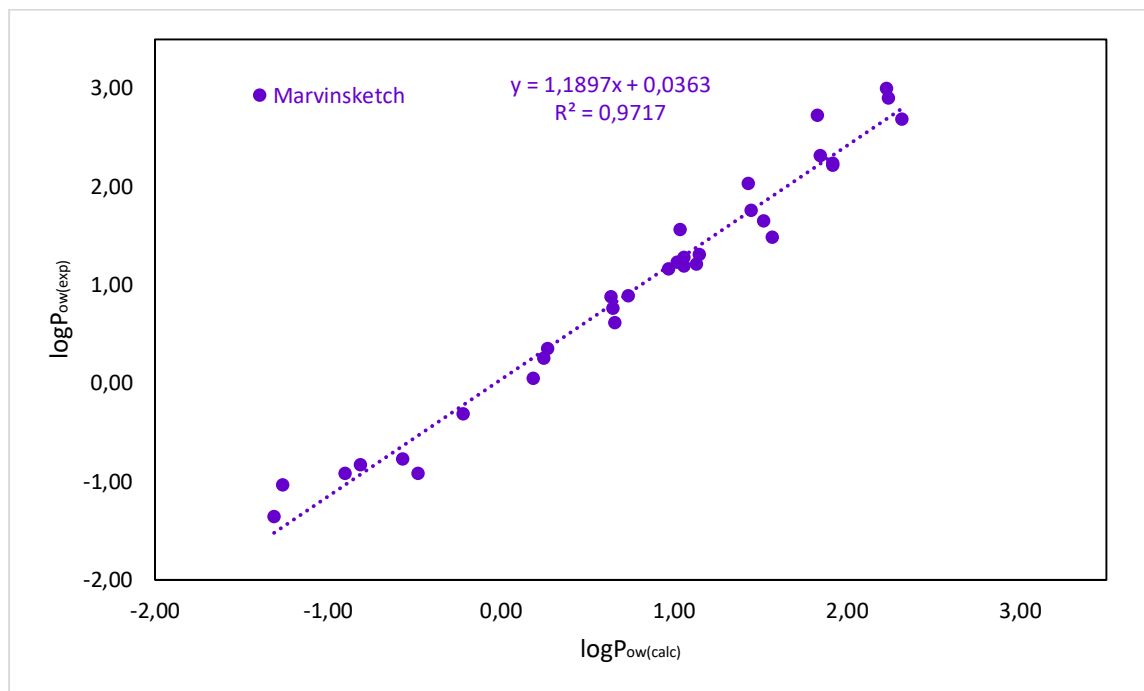
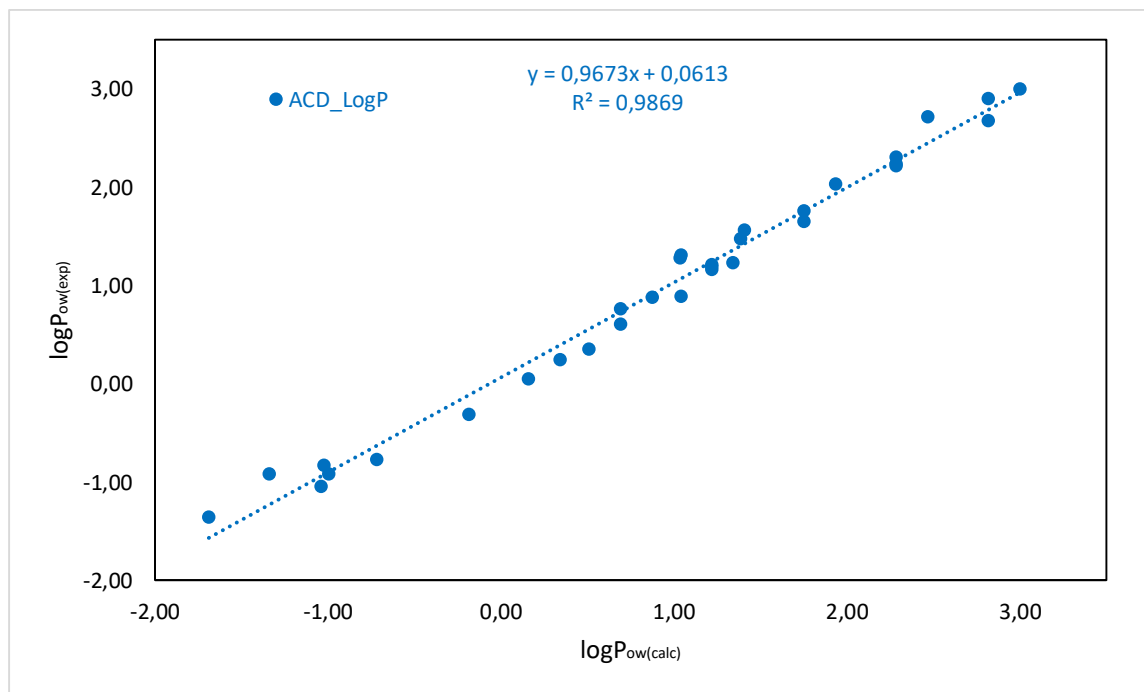


Figure S3: Correlation of the experimental data with $\text{clog}P$ values obtained with Biobyte.

2.3.3 MarvinSketch (Figure S4)

**Figure S4:** Correlation of the experimental data with $\text{clog}P$ values obtained with MarvinSketch.

2.3.4 ACDlogP (Figure S5)

**Figure S5:** Correlation of the experimental data with $\text{clog}P$ values obtained with ACDlogP.

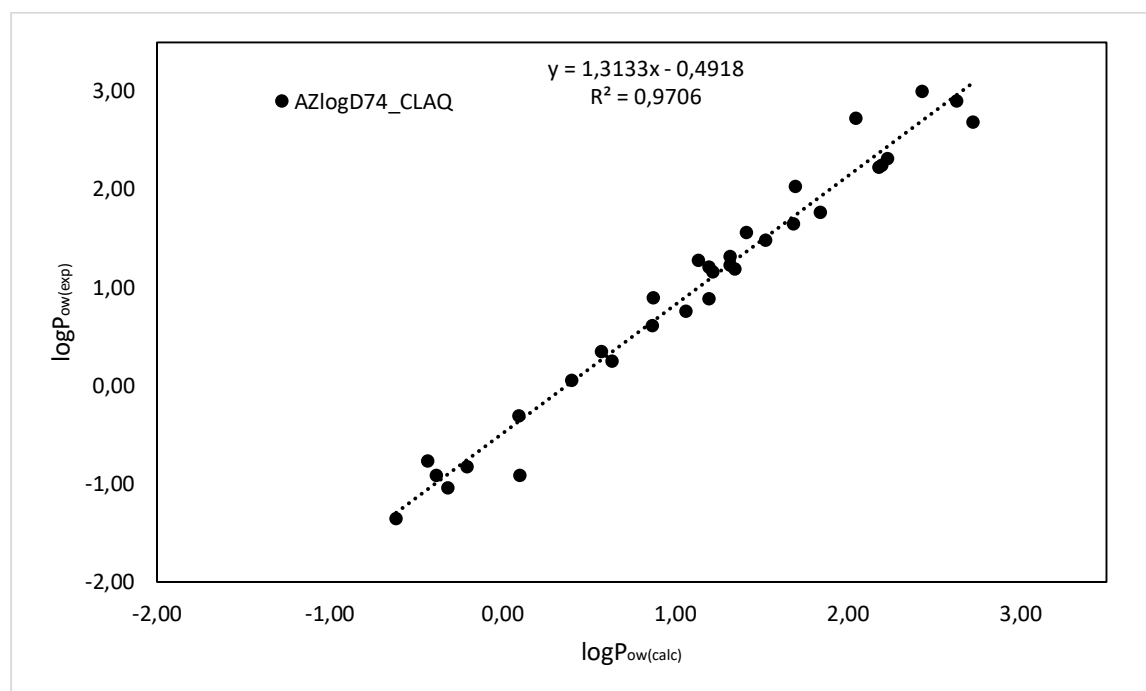
2.3.5 AZlogD_{7.4} (Figure S6)

Figure S6: Correlation of the experimental data with clogD values obtained with the internal AstraZeneca logD calculation programme.

2.3.6 Trendlines (Table S3)

Predictor	Trendline equation	R ² value
Molinspiration	$y = 1.0742x - 0.3605$	0.9856
Biobyte	$y = 1.0201x + 0.0395$	0.9907
Marvinsketch	$y = 1.1897x + 0.0363$	0.9717
ACDlogP	$y = 0.9673x + 0.0613$	0.9869
AZlogD _{7.4}	$y = 1.3133x - 0.4918$	0.9706

These trendline equations were used to estimate the logP value of each compound for each prediction tool. All methods showed high predictive power (from R² value), but there is considerable variation in the generated straight-line equations, and thus their estimated logP values. Therefore, the mean average across all methods was used as the final estimated value.

The standard deviation (σ) was calculated using the formula:

$$\sigma = \sqrt{\frac{1}{N} \sum_{i=1}^N (x_i - \bar{x})^2}$$

Where x_i are the individual estimated $\log P$ values and $\bar{x}$ is the mean average.

2.4 Estimated $\log P$ values: Cyclopropylmethanol (Table S4)

Predictor	Calculated $\log P$	Estimated $\log P$
Molinspiration	0.55	0.23
Biobyte	0.21	0.25
Marvinsketch	0.14	0.20
ACDlogP	0.18	0.24
AZlogD _{7.4}	0.60	0.30

The average of the estimated values was 0.24, and the standard deviation was 0.03.

The $\log P$ of cyclopropylmethanol was taken to be 0.24 ± 0.03 .

2.5 Estimated $\log P$ values: (3-oxetanyl)methanol (Table S5)

Predictor	Calculated $\log P$	Estimated $\log P$
Molinspiration	-0.10	-0.47
Biobyte	-0.61	-0.58
Marvinsketch	-0.82	-0.94
ACDlogP	-1.15	-1.05
AZlogD _{7.4}	-0.36	-0.96

The average of the estimated values was -0.80 , and the standard deviation was 0.23.

The $\log P$ of (3-oxetanyl)methanol was taken to be -0.80 ± 0.23 .

3 clogP values of the fluorinated derivatives and correlation with the experimental values

3.1 Table with the clogP values of five calculation methods (Table S6)

Compound (exp logP)	Molinspiration ^a	Biobyte ^b	Marvin sketch ^c	ACD logP ^d	AZ logD _{7.4} ^e
 D2 (0.10)	0.79	0.42	0.09	0.23	0.54
 D3 (0.29)	0.72	0.12	0.15	0.18	0.74
 D4 (0.58)	1.00	0.14	0.34	0.06	0.84
 D5 (0.98)	1.35	0.96	1.06	0.50	1.24
 E2 (-0.05)	0.41	0.05	-0.27	-0.26	0.40
 E3 (-0.12)	0.58	-0.02	-0.27	-0.41	0.25
 E4 (0.04)	0.58	-0.02	-0.27	-0.41	0.25
 E5 (0.24)	0.93	-0.11	0.23	-0.74	0.58
 F2 (-0.73)	-0.12	0.13	-0.94	-0.89	-0.04
 G2 (0.26)	0.84	0.55	0.48	0.41	0.62
 G3 (0.17)	0.61	0.25	0.06	0.18	0.41
 G4 (0.34)	0.97	0.27	0.55	0.06	0.62
 G5 (0.29)	0.79	-0.03	-0.01	-0.15	0.76
 G6 (0.09)	0.52	0.10	0.10	0.17	0.51
 G7 (-0.12)	0.53	0.08	-0.12	-0.29	0.27
 G8 (0.27)	0.89	0.38	0.67	-0.17	0.75
 G9 (0.67)	1.20	0.87	0.88	0.52	0.83
 G10 (0.91)	1.15	0.38	0.90	0.10	1.07

^a molinspector: <http://www.molinspiration.com/cgi-bin/properties>

^b Daylight/BioByte ClogP Pomona College and BioByte, Inc., Claremont, CA (bio-loom version 1.6, program version 5: <http://www.biobyte.com/>)

^c MarvinSketch – ChemAxon: <https://docs.chemaxon.com/display/docs/logP+Plugin#logPPlugin-Method>.

^d **Version: 2018.1.1** ACDlogP was calculated using ACD/Labs software, version 2018 (see www.acdlabs.com).

^e AstraZeneca internal method.

3.2 Correlation of $\text{clog}P$ with experimental data (Figures S7-S11)

3.2.1 Molinspiration (Figure S7)

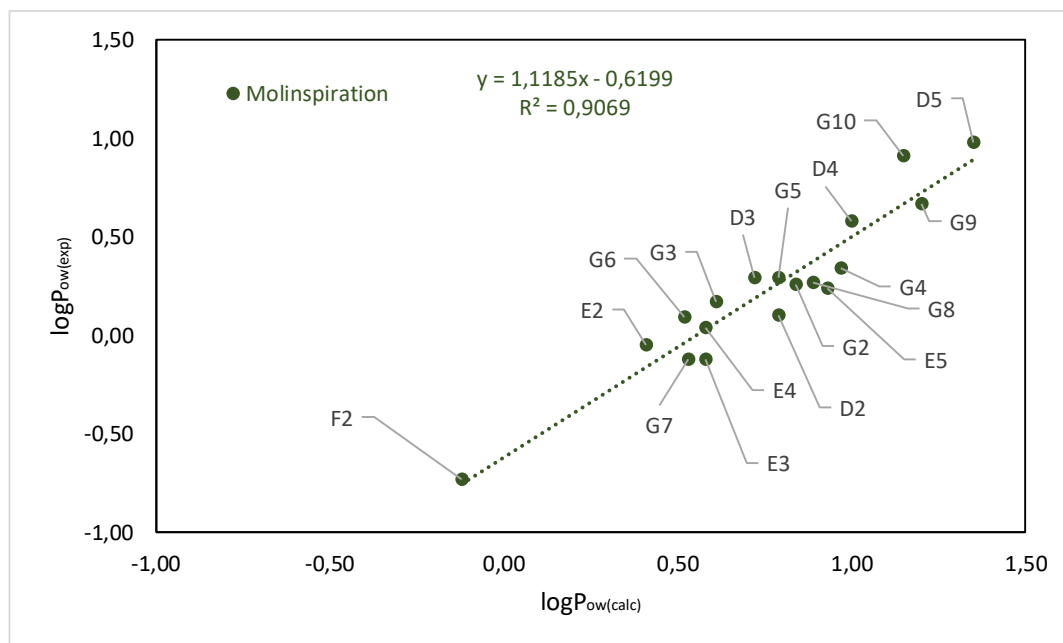


Figure S7. Correlation of the experimental data with $\text{clog}P$ values obtained with Molinspiration.

3.2.2 Biobyte (Figure S8)

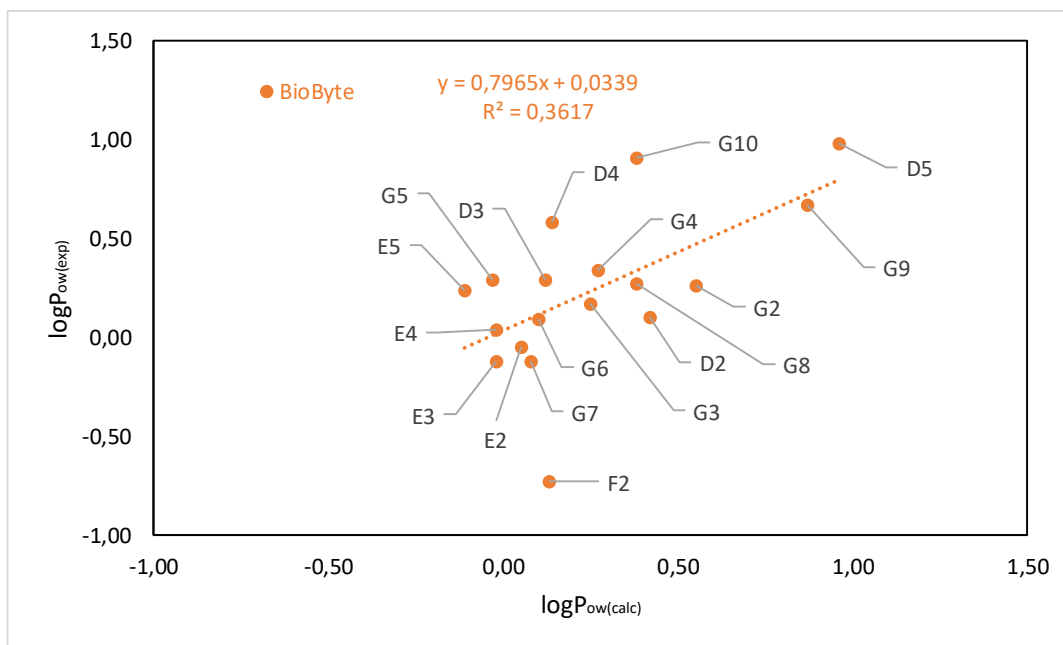
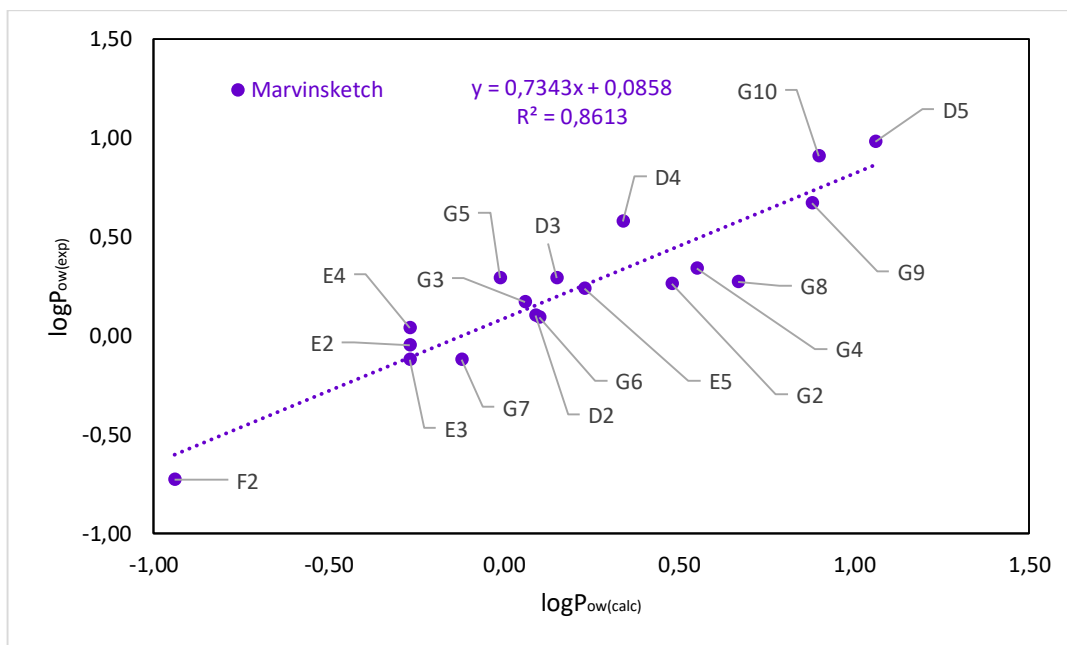
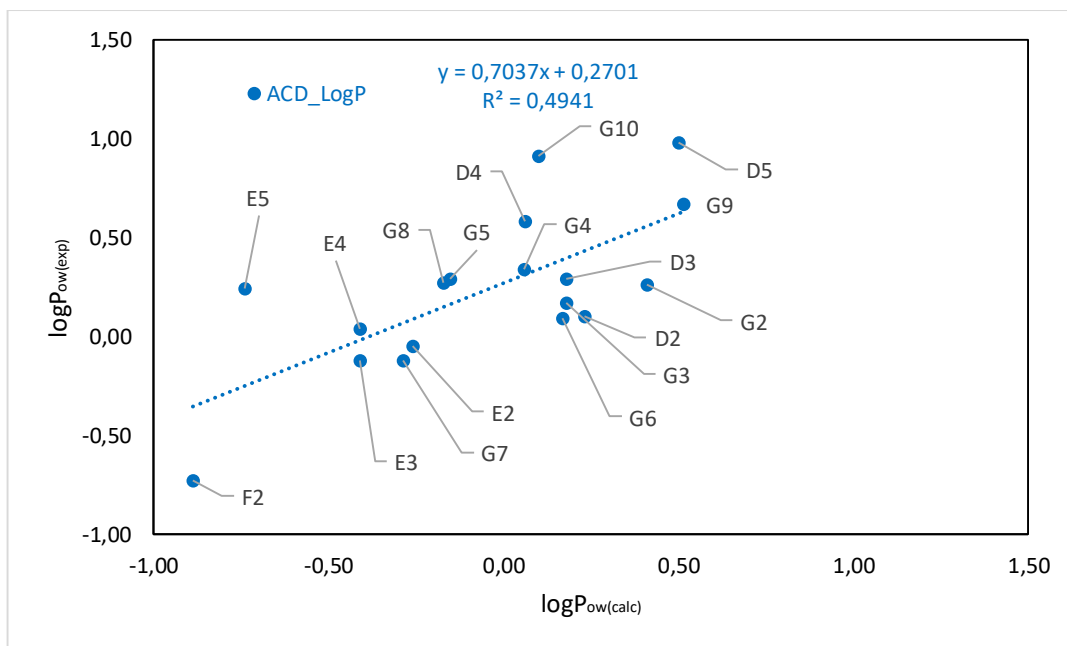


Figure S8. Correlation of the experimental data with $\text{clog}P$ values obtained with Biobyte.

3.2.3 MarvinSketch (Figure S9)

**Figure S9.** Correlation of the experimental data with $\text{clog}P$ values obtained with MarvinSketch.

3.2.4 ACDlogP (Figure S10)

**Figure S10.** Correlation of the experimental data with $\text{clog}P$ values obtained with ACDlogP.

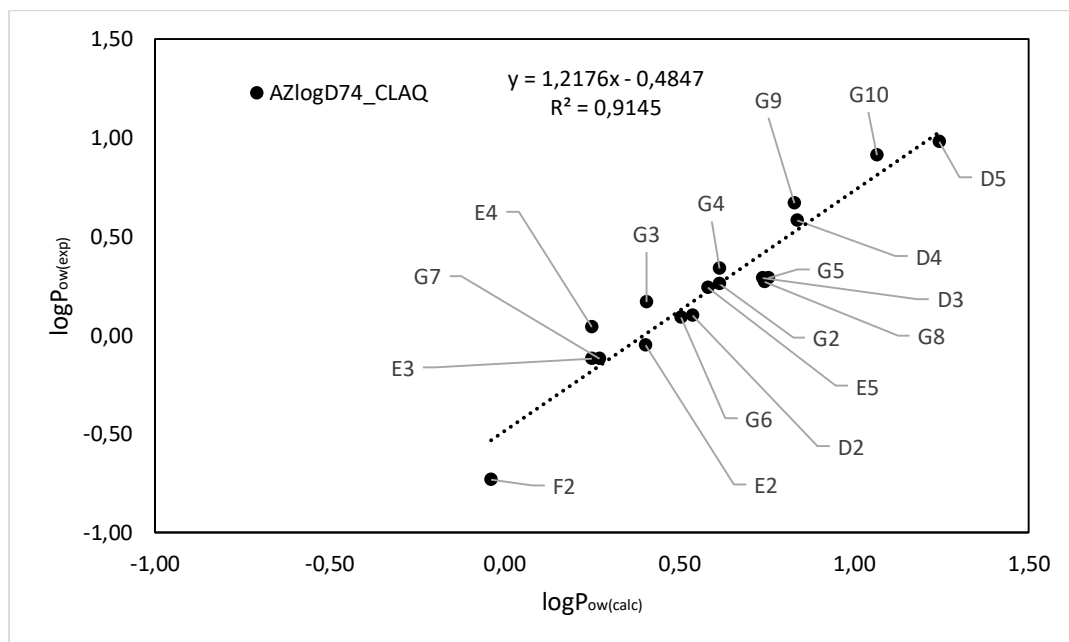
3.2.5 AZlogD_{7.4} (Figure S11)

Figure S11: Correlation of the experimental data with clogP values obtained with the internal AstraZeneca logP calculation programme.

3.2.6 Trendline (Table S7)

Predictor	Trendline equation	R^2 value
Molinspiration	$y = 1.1185x - 0.6199$	$R^2 = 0.9069$
Biobyte	$y = 0.7965x + 0.0339$	$R^2 = 0.3617$
Marvinsketch	$y = 0.7343x + 0.0858$	$R^2 = 0.8613$
ACDlogP	$y = 0.7037x + 0.2701$	$R^2 = 0.4941$
AZlogD _{7.4}	$y = 1.2176x - 0.4847$	$R^2 = 0.9145$

The AZlogD_{7.4} method gives the best predictive power (highest R^2 value), followed closely by Molinspiration.

4 Experimental log*P* data

4.1 Determination of log*P*

Lipophilicities of the fluorinated alkanols were determined using a previously published protocol:¹ to a 10 mL pear-shaped flask was added the compound (1.0–10 mg) for log*P* determination, the reference compound (1.0–10 mg, with known log*P* value, e.g., 2,2,2-trifluoroethanol, log*P*: +0.36), water (2 mL) and *n*-octanol (2 mL). The resulting biphasic mixture was stirred (at 600 rpm) for 2 h at 25 °C, and then left without stirring for 16 h at 25 °C to allow phase separation. An aliquot of 0.5 mL was taken from each phase using 1 mL syringes with long needles and added to two separate NMR tubes. A deuterated NMR solvent (0.1 mL, e.g., acetone-*d*₆), or a capillary tube containing deuterated NMR solvent, was added to the NMR tubes to enable signal locking. Because of the volatility of the used compounds, the NMR tubes were sealed using a blowtorch. For NMR samples with directly added deuterated solvent, the tubes were inverted 20 times for mixing. For ¹⁹F{¹H} NMR experiments, NMR parameters were set as follows: D1 30 s for the octanol sample, D1 60 s for the water sample; and O1P centered between two diagnostic fluorine peaks. If needed, an increased number of transients (NS) and/or narrower spectral window (SW) for a good S/N ratio (typically >300) was applied. After NMR data processing, integration ratios ρ_{oct} and ρ_{aq} (ρ_{oct} is defined as the integration ratio between the compound and the reference compound in the octanol sample; likewise, for ρ_{aq}) were obtained, and used in the equation ($\log P^{\text{x}} = \log P^{\text{ref}} + \log(\rho_{\text{oct}}/\rho_{\text{aq}})$) to obtain the log*P* value of the compound. The log*P* measurement of each compound was run in triplicate. Log*P* values of non-fluorinated compounds were taken from the literature.

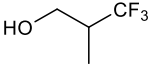
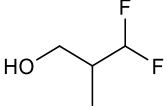
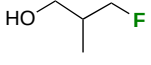
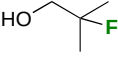
Calculation of standard deviation was carried out using the equation shown on p S11.

4.2 Standard NMR settings

Standard NMR parameter setting: SW, 300 ppm; centered O1P; NS 64; D1 30 sec (octanol sample), D1 60 sec (water sample). Any change from standard setting was described for each compound. Unless specified otherwise 2,2,2-trifluoroethanol (log*P*: +0.36) was used as the reference compound.

4.3 Tables S8-S10: data of all individual measurements

4.3.1 Isobutanol series (Table S8)

Compound	Nr	Experiments (octanol/water)	$\rho_{\text{oct}}/\rho_{\text{wat}}$	$\log P$	Average $\log P$	Error
	D5 *	se0419zw1/ se0419zw2	1.3020/ 0.3142	+0.977	+0.98	+0.978 (± 0.001)
		se0419zw4/ se0419zw5	1.3174/ 0.3175	+0.978		
		se0419zw6/ se0419zw7	1.2874/ 0.3095	+0.979		
	D4 **	se0319zw1/ se0319zw2	0.9798/ 0.5859	+0.583	+0.58	+0.583 (± 0.005)
		se0319zw3/ se0319zw4	0.9903/ 0.6016	+0.576		
		se0319zw5/ se0319zw6	0.9900/ 0.5845	+0.589		
	D3	au2616bj7/ au2616bj8	0.2390/ 0.2842	+0.28	+0.29	+0.289 (± 0.004)
		au2616bj9/ au2616bj10	0.3091/ 0.3649	+0.29		
		au2616bj11/ au2616bj12	0.1631/ 0.1898	+0.29		
	D2	au2416bj7/ au2416bj8	0.1647/ 0.2919	+0.11	+0.10	+0.104 (± 0.006)
		au2416bj9/ au2416bj10	0.1587/ 0.2902	+0.10		
		au2416bj12/ au2416bj11	0.4046/ 0.7306	+0.10		

*Change from standard in NMR parameter setting: SW (120 ppm); octanol sample, D1 (20 sec); water sample, D1 (40 sec).

**Change from standard in NMR parameter setting: SW (200 ppm); octanol sample, D1 (20 sec); water sample, D1 (40 sec).

4.3.2 Cyclopropylmethanol series (Table S9)

Compound	Nr	Experiment (octanol/water)	r_o/r_w	$\log P$	Average $\log P$	error
	E2	ma0818bj16/ ma0818bj17	0.3196/ 0.8280	-0.05	-0.05	-0.054 (± 0.004)
		ma0818bj18/ ma0818bj19	0.2721/ 0.7142	-0.06		
		ma0818bj20/ ma0818bj21	0.3051/ 0.7854	-0.05		
	E3	ma0918bj12/ ma0918bj13	0.1806/ 0.5405	-0.12	-0.12	-0.123 (± 0.005)
		ma0918bj14/ ma0918bj15	0.2152/ 0.6618	-0.13		
		ma0918bj16/ ma0918bj17	0.2742/ 0.8391	-0.13		
	E4	ma0918bj6/ ma0918bj7	2.8391/ 0.4521	+0.05	+0.04	+0.042 (± 0.004)
		ma0918bj8/ ma0918bj9	2.6565/ 0.4317	+0.04		
		ma0918bj10/ ma0918bj11	2.4055/ 0.3919	+0.04		
	E5	ma0818bj9/ ma0818bj10	0.6074/ 0.8029	+0.24	+0.24	+0.242 (± 0.004)
		ma0818bj11/ ma0818bj12	0.6010/ 0.7946	+0.24		
		ma0818bj13/ ma0818bj14	0.6163/ 0.7988	+0.25		

P2 and **P3** – Reference compound: 2-fluoroethan-1-ol ($\log P$: -0.75)

4.3.3 Oxetan-3-ylmethanol series (Table S10)

Compound	Nr	Experiment (octanol/water)	r_o/r_w	$\log P$	Average $\log P$	error
	F2	au2416bj13/ au2416bj14	0.2429/ 2.8355	- 0.70	-0.73	-0.729 (± 0.016)
		au2416bj15/ au2416bj16	0.1157/ 1.4632	- 0.74		
		au2416bj17/ au2416bj18	0.2416/ 3.0274	- 0.74		

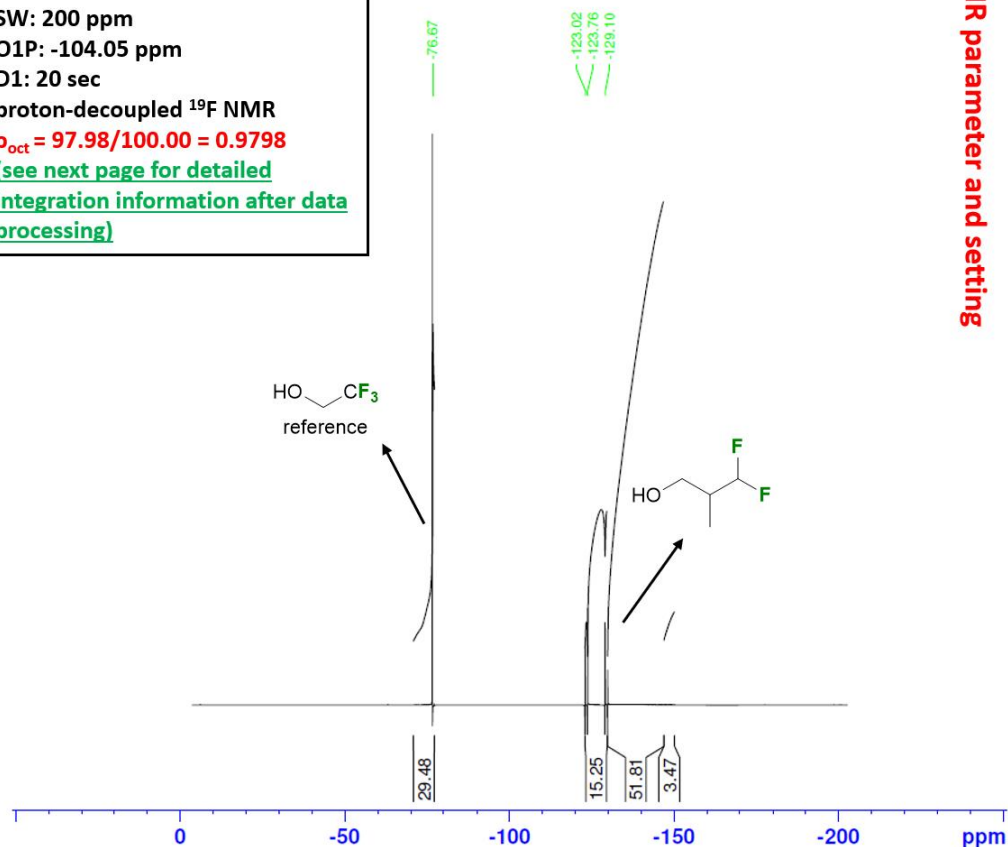
4.4 Example of NMR spectra for log*P* determination, with detailed NMR parameter information and integration details after reprocessing

The figures below show the initial and processed spectra of 3,3-difluoro-2-methylpropan-1-ol (**D4**)

4.4.1 Octanol sample (Figure S12)

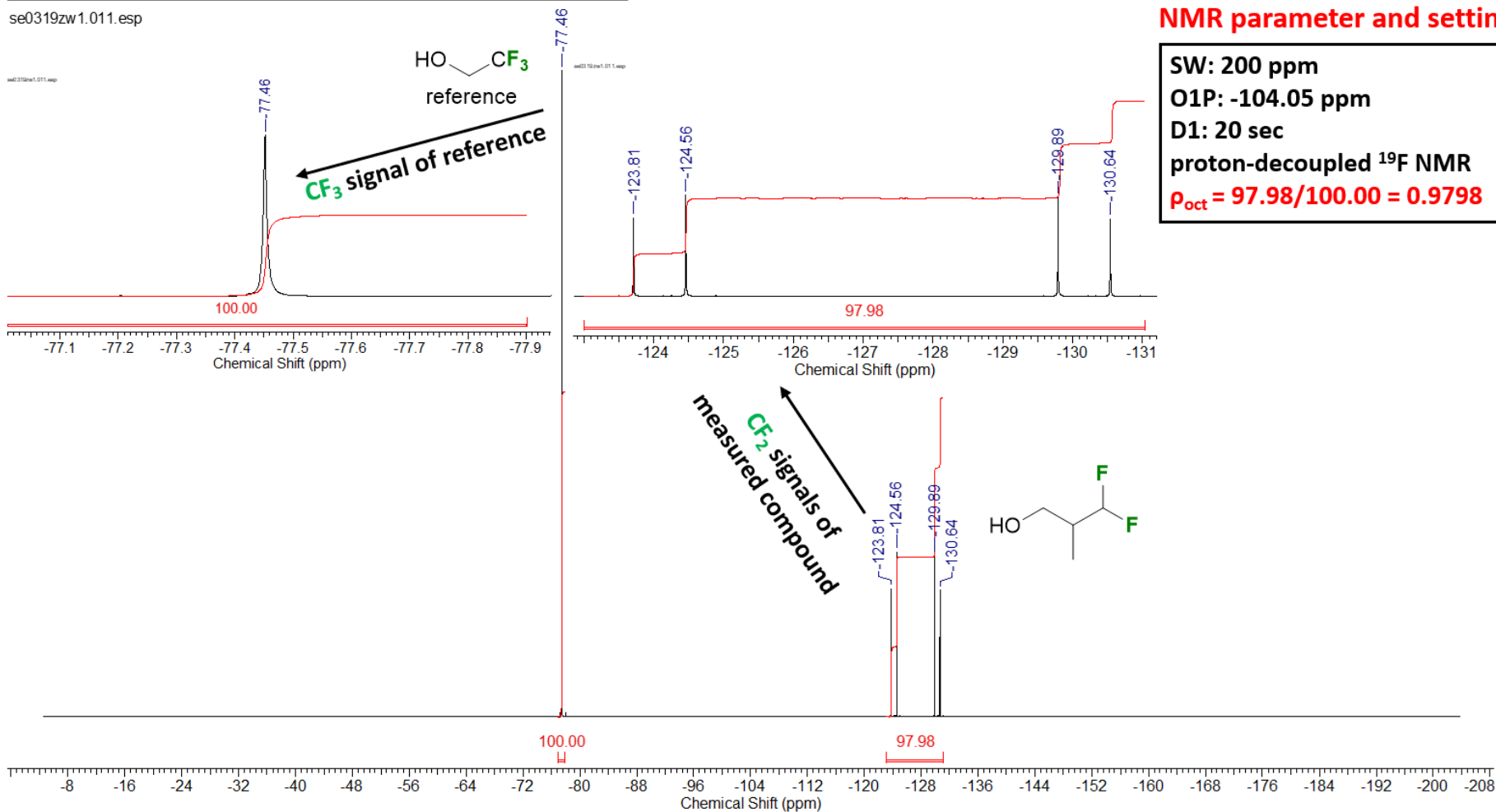
ZW8888-11-3 OCT

SW: 200 ppm
O1P: -104.05 ppm
D1: 20 sec
proton-decoupled ^{19}F NMR
 $p_{\text{oct}} = 97.98/100.00 = 0.9798$
(see next page for detailed
integration information after data
processing)



NMR parameter and setting

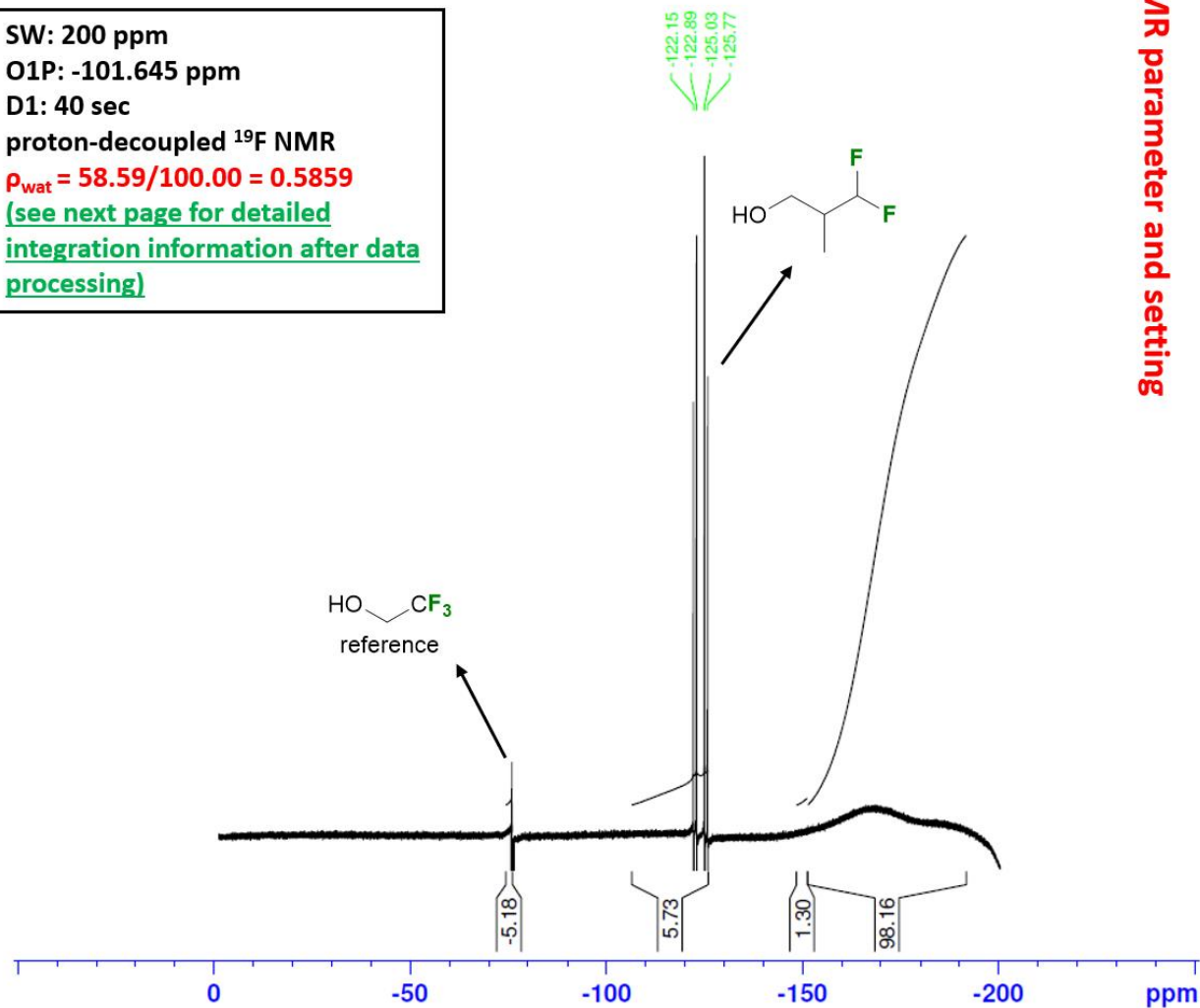
UNIVERSITY OF Southampton	
AVIIIHD400 [3]	
Current Data Parameters	
NAME	se0319zw1
EXPNO	11
PROCNO	1
F2 - Acquisition Parameters	
Date_	20190903
Time	15.57
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30q.2
TD	131072
SOLVENT	Acetone
NS	64
DS	4
SWH	75000.000 Hz
FIDRES	0.572205 Hz
AQ	0.8738133 sec
RG	212.69
DW	6.667 usec
DE	6.50 usec
TE	298.0 K
D1	20.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
===== CHANNEL f1 =====	
SFO1	376.4591914 MHz
NUC1	^{19}F
P1	14.00 usec
PLW1	25.11100006 W
===== CHANNEL f2 =====	
SFO2	400.1316005 MHz
NUC2	^1H
CPDPRG2	waltz16
PCPD2	90.00 usec
PLW2	16.05800056 W
PLW12	0.19825000 W
F2 - Processing parameters	
SI	65536
SF	376.4980709 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

se0319zw1.011.esp

4.4.2 Water sample (Figure S13)

ZW8888-11-3 WAT

SW: 200 ppm
 O1P: -101.645 ppm
 D1: 40 sec
 proton-decoupled ^{19}F NMR
 $\rho_{\text{wat}} = 58.59/100.00 = 0.5859$
 (see next page for detailed
 integration information after data
 processing)



NMR parameter and setting

UNIVERSITY OF
 Southampton

AVIIIHD400 [3]

Current Data Parameters

NAME se0319zw2
 EXPNO 11
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20190903
 Time_ 23.27
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zgfhigqn.2
 TD 131072
 SOLVENT Acetone
 NS 64
 DS 4
 SWH 75000.000 Hz
 FIDRES 0.572205 Hz
 AQ 0.8738133 sec
 RG 212.69
 DW 6.667 usec
 DE 6.50 usec
 TE 298.0 K
 D1 40.00000000 sec
 D11 0.03000000 sec
 D12 0.00002000 sec
 TD0 1

===== CHANNEL f1 =====

SFO1 376.4600969 MHz
 NUC1 ^{19}F
 P1 14.00 usec
 PLW1 25.11100006 W

===== CHANNEL f2 =====

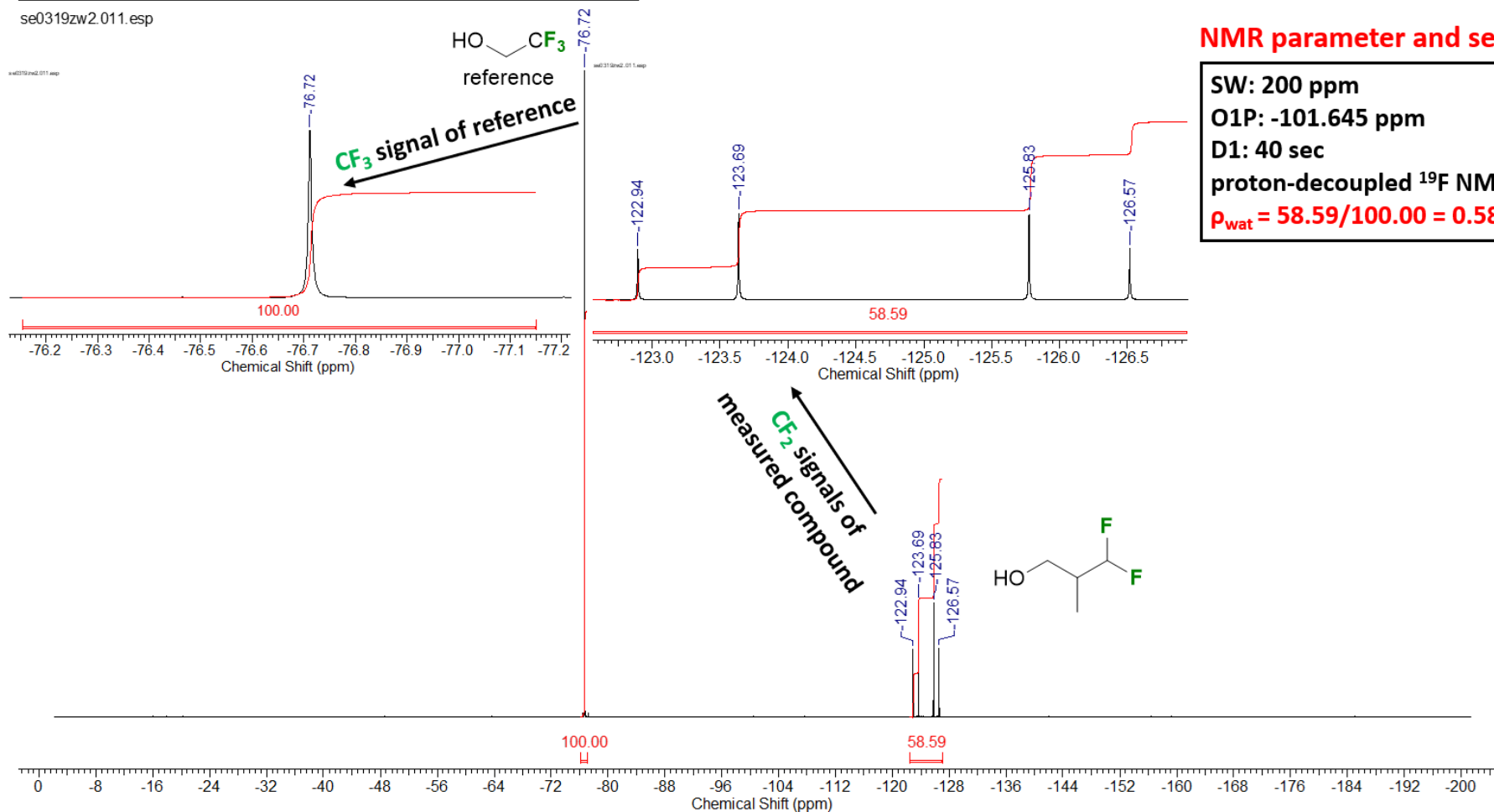
SFO2 400.1316005 MHz
 NUC2 ^1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 16.05800056 W
 PLW12 0.19825000 W

F2 - Processing parameters

SI 65536
 SF 376.4980709 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

Acquisition Time (sec)	0.8738	Comment	ZW8888-11-3 WAT	Date	03 Sep 2019 23:28:16
Date Stamp	03 Sep 2019 23:28:16				
File Name	\\isoton.ac.uk\udel\personalfiles\users\zw1m12\mydesktop\ZW8888 Labbook\ZW8888-11\se0319zw2\111.fid			Frequency (MHz)	376.46
Nucleus	19F	Number of Transients	64	Origin	spect
Owner	nmr	Points Count	262144	Pulse Sequence	zgfhigqn.2
SW(cyclical) (Hz)	75000.00	Solvent	Acetone	Spectrum Offset (Hz)	-38269.1406
Sweep Width (Hz)	74999.71	Temperature (degree C)	25.005	Spectrum Type	STANDARD

se0319zw2.011.esp



5 Conformational analysis in water and *n*-octanol medium.

5.1 General

Analogous as described in ref [7], the theoretical calculations were carried out with the Gaussian16 program.² The conformational analysis of the various compounds investigated was performed with the MN15 functional^{3, 4} in combination with the triple-zeta quality aug-cc-pVTZ basis set. Scans along the various rotatable bonds: C–C, C–O, and O–H bonds of the compounds have systematically been conducted. The solvent effects (octanol and water) were taken into account using the SMD solvation continuum model.⁵ The vibrational spectrum of each optimized conformer was computed to confirm its nature of true minimum and to obtain the correction to the free energies. Single point calculations at the SMD/MN15/aug-cc-pVTZ were finally carried out to obtain refined electronic energy values. The relative populations, p_i , of the various conformers were evaluated at 298 K from the computed free energies through a Boltzmann distribution:

$$p_i = \frac{e^{-\Delta G_i / RT}}{\sum_{i=1}^n e^{-\Delta G_i / RT}}$$

The theoretical molecular dipole moments were then computed for each conformer, and were weighted according to these populations (either for the compound as a whole or within a conformer series as in Tables 1,2). The fluorohydrin lipophilicity was then estimated from the above results through the calculations of the weighted SMD Gibbs energies obtained in water and in *n*-octanol at 298.15 K to obtain the standard free energy associated with the transfer between these two solvents. The octanol/water partition coefficient was then calculated according to Eq (2), and following the procedure proposed by Ribeiro for chloroform/water partition coefficient calculations:⁶

5.2 All values (Table S11)

$$\log P = -\frac{\Delta G_{o/w}^{\circ}}{2.303RT} = -\frac{G_o^{\circ} - G_w^{\circ}}{2.303RT}$$

Compound	$\log P_{\text{exp}}$	$\log P_{\text{theor}}$
D1	0.76	1.19
D2	0.1	1.2
D3	0.29	1.18
D4	0.58	1.26
D5	0.98	1.52
E2	-0.05	0.95
E3	-0.12	0.97
E4	0.04	0.96
E5	0.24	1.13
F2	-0.73	0.02
G1 ⁷	0.88	1.40
G2	0.26	1.39
G3	0.17	1.21
G4 ⁷	0.34	1.23
G7 ⁷	-0.12	1.06
G8 ⁷	0.27	1.30

5.3 Conformational analysis: relative energies and populations

For compounds **G1**, **G4**, **G7** and **G8**, see ref.⁷

5.3.1 Table S12. Relative Gibbs energy and populations of the energetic minima of **D1** (2-methylpropan-1-ol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol ⁻¹	%	D		kJ mol ⁻¹	%	D
D1_2	0.0	40.8%	2.33	D1_1	0.0	33.6%	2.30
D1_1	1.2	25.5%	2.49	D1_3	0.6	26.4%	1.98
D1_3	2.4	15.5%	2.16	D1_2	0.7	24.9%	2.16
D1_5	2.5	15.0%	2.46	D1_5	3.0	10.2%	2.27
D1_5bis	4.6	3.2%	2.34	D1_5bis	3.0	4.9%	2.14
			2.36				2.17

5.3.2 Table S13. Relative Gibbs energy and populations of the energetic minima of **D2** (2-fluoro-2-methylpropan-1-ol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol ⁻¹	%	D		kJ mol ⁻¹	%	D
D2_1	0.0	41.7%	2.47	D2_1	0.0	55.4%	2.29
D2_2	1.7	21.2%	4.73	D2_2	2.4	21.0%	4.41
D2_3	0.8	29.9%	4.31	D2_3	3.5	13.5%	3.89
D2_4	5.8	2.0%	2.19	D2_4	4.8	3.9%	2.18
D2_5	5.2	5.0%	2.55	D2_5	5.5	6.1%	2.38
			3.50				2.95

5.3.3 Table S14. Relative Gibbs energy and populations of the energetic minima of **D3** (3-fluoro-2-methylpropan-1-ol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Water				Octanol			
Conformer	ΔG	p_i	μ	Conformer	ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
D3_9	0.0	11.0%	4.42	D3_16	0.0	11.6%	4.06
D3_25	0.6	8.7%	2.56	D3_14	0.3	10.4%	2.11
D3_27	1.4	6.2%	1.73	D3_18	1.0	7.9%	2.07
D3_23	1.8	5.3%	4.41	D3_9	1.7	5.9%	4.13
D3_2	1.9	5.1%	4.27	D3_7	1.9	5.4%	2.38
D3_7	2.0	4.9%	2.46	D3_11	2.2	4.7%	2.04
D3_18	2.0	4.9%	2.22	D3_23	2.4	4.4%	4.13
D3_17	2.0	4.9%	4.54	D3_26	2.5	4.3%	3.89
D3_5	2.2	4.6%	1.78	D3_20	2.6	4.1%	1.90
D3_26	2.2	4.6%	4.16	D3_2	2.6	4.0%	4.01
D3_11	2.3	4.3%	2.21	D3_5	2.9	3.6%	1.59
D3_14	2.5	4.0%	2.24	D3_27	2.9	3.6%	1.59
D3_16	2.8	3.6%	4.28	D3_25	3.1	3.4%	2.41
D3_20	2.8	3.6%	2.10	D3_10	3.1	3.3%	3.83
D3_3	3.1	3.2%	1.88	D3_3	3.2	3.2%	1.64
D3_10	3.6	2.6%	4.05	D3_12	3.4	2.9%	1.60
D3_22	3.6	2.6%	2.65	D3_22	3.5	2.8%	2.57
D3_19	3.7	2.5%	1.93	D3_13	3.5	2.8%	4.02
D3_21	3.7	2.4%	4.20	D3_19	3.5	2.8%	1.88
D3_12	3.7	2.4%	1.81	D3_21	3.6	2.7%	3.91
D3_6	4.1	2.1%	4.14	D3_4	4.0	2.3%	2.24
D3_13	4.5	1.8%	4.21	D3_1	4.9	1.6%	2.17
D3_1	4.5	1.8%	2.29	D3_6	5.5	1.3%	3.83
D3_8	5.0	1.5%	3.93	D3_8	5.9	1.1%	3.64
D3_4	5.2	1.3%	2.35				
			3.13				2.85

5.3.4 Table S15. Relative Gibbs energy and populations of the energetic minima of **D4** (3-fluoro-2-methylpropan-1-ol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
D4_20	0.0	9.4%	3.95	D4_11	0.0	15.8%	3.74
D4_11	0.2	8.8%	3.88	D4_20	0.7	12.0%	3.78
D4_4	0.3	8.2%	4.13	D4_13	0.7	12.0%	3.66
D4_2	0.5	7.6%	1.15	D4_4	2.2	6.5%	3.99
D4_26	1.0	6.3%	1.12	D4_19	2.8	5.1%	3.30
D4_13	1.5	5.2%	3.85	D4_16	2.9	4.8%	3.41
D4_5	1.7	4.6%	3.91	D4_2	3.0	4.8%	1.32
D4_1	1.8	4.5%	3.32	D4_17	3.2	4.3%	3.18
D4_7	1.9	4.4%	0.77	D4_8	3.7	3.6%	3.26
D4_22	2.0	4.2%	0.97	D4_7	3.8	3.4%	0.87
D4_16	2.4	3.6%	3.63	D4_1	3.9	3.3%	3.07
D4_27	2.6	3.3%	3.64	D4_18	4.1	3.1%	1.12
D4_23	2.8	3.1%	3.14	D4_22	4.2	3.0%	1.10
D4_17	2.8	3.1%	3.37	D4_24	4.3	2.7%	3.05
D4_8	2.9	2.9%	3.42	D4_9	4.4	2.7%	3.15
D4_3	3.0	2.8%	3.36	D4_3	4.5	2.6%	3.15
D4_10	3.1	2.7%	5.24	D4_27	5.2	1.9%	3.36
D4_19	3.2	2.6%	3.65	D4_10	5.2	1.9%	4.88
D4_18	3.3	2.5%	1.07	D4_5	5.4	1.8%	3.50
D4_24	3.6	2.2%	3.36	D4_12	5.5	1.7%	3.29
D4_14	3.8	2.0%	5.22	D4_25	5.6	1.7%	3.61
D4_9	3.8	2.0%	3.46	D4_14	5.9	1.4%	4.92
D4_25	4.2	1.8%	3.84				
D4_12	5.1	1.2%	3.87				
D4_15	5.6	1.0%	4.11				
			3.13				3.25

5.3.5 Table S16. Relative Gibbs energy and populations of the energetic minima of **D5** (3,3,3-trifluoro-2-methylpropan-1-ol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
D5_3	0.0	16.7%	2.20	D5_9	0.0	18.4%	2.82
D5_6	0.3	15.0%	2.11	D5_7	0.2	16.9%	4.47
D5_1	0.8	12.4%	4.62	D5_8	0.6	14.7%	2.73
D5_8	1.1	10.9%	2.76	D5_3	1.3	10.9%	2.07
D5_5	1.2	10.2%	4.92	D5_6	1.8	8.9%	1.96
D5_9	1.3	9.9%	2.95	D5_1	2.0	8.1%	4.35
D5_7	1.3	9.7%	4.80	D5_2	2.2	7.7%	4.48
D5_4	1.7	8.5%	2.39	D5_4	2.2	7.7%	2.31
D5_2	2.3	6.7%	4.71	D5_5	2.5	6.7%	4.69
			3.33				3.26

5.3.6 Table S17. Relative Gibbs energy and populations of the energetic minima of **E2** (2-fluoro-2-c-propyl-ethanol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
E2_3	0.0	42.4%	4.30	E2_2	0.0	52.5%	1.91
E2_2	0.2	38.5%	2.06	E2_3	1.9	24.4%	4.03
E2_1	2.3	16.8%	3.94	E2_1	2.5	19.0%	3.63
E2_4	8.1	1.6%	2.28	E2_5	7.1	1.5%	2.22
E2_5	8.5	0.7%	2.25	E2_4	7.5	2.6%	2.16
			3.33				2.77

5.3.7 Table S18. Relative Gibbs energy and populations of the energetic minima of **E3** (2-(2'-*syn*-fluoro-*c*-propyl)-ethanol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
E3_8	0.0	25.1%	4.70	E3_7	0.0	30.7%	2.95
E3_7	0.2	23.6%	3.14	E3_8	1.2	18.7%	4.42
E3_9	1.2	15.2%	3.20	E3_9	1.8	14.6%	2.92
E3_3	1.3	15.2%	2.84	E3_3	1.9	14.0%	2.70
E3_2	1.9	11.7%	3.78	E3_2	2.7	10.4%	3.61
E3_1	2.9	7.8%	1.10	E3_1	3.0	9.3%	0.99
E3_4	7.1	1.4%	3.35	E3_4	6.5	2.3%	3.09
			3.33				3.07

5.3.8 Table S19. Relative Gibbs energy and populations of the energetic minima of **E4** (2-(2'-*anti*-fluoro-*c*-propyl)-ethanol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
E4_7	0.0	22.0%	2.68	E4_3	0.0	19.5%	2.27
E4_3	0.4	18.7%	2.41	E4_7	0.0	19.1%	2.46
E4_9	0.8	15.8%	4.58	E4_8	0.4	16.8%	2.89
E4_2	1.2	13.8%	1.14	E4_9	0.9	13.6%	4.33
E4_8	1.3	13.2%	3.06	E4_2	1.4	10.9%	1.12
E4_1	2.3	8.6%	3.46	E4_1	1.7	10.0%	3.29
E4_6	4.4	3.7%	3.33	E4_5	3.4	5.0%	3.74
E4_4	5.7	2.2%	1.40	E4_6	4.9	2.7%	3.24
E4_5	6.0	1.9%	3.87	E4_4	5.2	2.4%	1.46
			2.85				2.75

5.3.9 Table S20. Relative Gibbs energy and populations of the energetic minima of **E5** (2-(2',2'-difluoro-c-propyl)-ethanol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
E5_7	0.0	26.5%	2.92	E5_7	0.0	36.4%	2.74
E5_9	0.9	18.4%	4.93	E5_9	1.8	17.3%	4.61
E5_8	1.0	17.6%	4.92	E5_8	2.6	13.0%	4.63
E5_3	1.4	15.0%	2.38	E5_1	3.1	10.4%	2.53
E5_1	2.6	9.3%	2.56	E5_3	3.5	9.0%	2.32
E5_2	2.6	9.3%	2.86	E5_2	3.6	8.6%	2.80
E5_4	6.7	1.8%	2.04	E5_4	6.9	2.3%	1.92
E5_6	7.5	1.3%	4.94	E5_5	7.3	1.9%	3.99
E5_5	8.3	0.9%	4.45	E5_6	8.9	1.0%	4.67
			3.54				3.28

5.3.10 Table S21. Relative Gibbs energy and populations of the energetic minima of **F2** (2-fluoro-2-oxetanyl-ethanol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
F2_1	0.0	40.9%	2.15	F2_1	0.0	53.3%	1.95
F2_2	1.6	21.8%	1.85	F2_2	2.8	17.0%	1.74
F2_3	1.2	25.3%	3.41	F2_3	2.3	21.0%	3.18
F2_5	4.3	3.6%	3.85	F2_5	4.9	3.7%	3.65
F2_8	3.9	8.3%	2.40	F2_8	5.9	5.0%	2.18
			2.48				2.25

5.3.11 Table S22. Relative Gibbs energy and populations of the energetic minima of **G2** (2-fluorobutan-1-ol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Conformer	Water			Conformer	Octanol		
	ΔG	p_i	μ		ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
G2_5	0.0	15.0%	2.60	G2_5	0.0	24.6%	2.43
G2_26	1.0	10.3%	2.13	G2_26	2.3	9.8%	1.91
G2_23	1.3	9.0%	4.53	G2_4	2.5	9.0%	2.36
G2_27	1.6	7.8%	1.97	G2_6	2.6	8.7%	2.57
G2_6	1.7	7.6%	2.71	G2_27	3.1	7.1%	1.77
G2_14	1.7	7.6%	4.28	G2_23	3.2	6.7%	4.23
G2_15	2.3	6.1%	4.33	G2_14	3.3	6.5%	3.97
G2_4	2.3	6.1%	2.52	G2_24	3.6	5.7%	4.36
G2_24	2.6	5.3%	4.62	G2_17	4.4	4.2%	3.76
G2_22	2.7	5.0%	4.52	G2_22	4.6	3.8%	4.22
G2_17	3.3	3.9%	4.12	G2_13	5.6	2.5%	3.82
G2_8	3.5	3.7%	4.58	G2_8	5.7	2.4%	4.28
G2_13	3.7	3.4%	4.14	G2_18	6.0	2.2%	3.75
G2_18	4.0	3.0%	4.05	G2_11	6.1	2.1%	2.24
G2_9	4.6	2.3%	4.66	G2_20	6.2	2.0%	2.57
G2_20	5.4	1.7%	2.71	G2_2	6.5	1.8%	1.94
G2_11	6.4	1.1%	2.31	G2_9	7.9	1.0%	4.39
				G2_5	0.0	24.6%	2.43
			3.38				2.91

5.3.12 Table S23. Relative Gibbs energy and populations of the energetic minima of **G3** (3-fluorobutan-1-ol) identified at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

Water				Octanol			
Conformer	ΔG	p_i	μ	Conformer	ΔG	p_i	μ
	kJ mol^{-1}	%	D		kJ mol^{-1}	%	D
G3_8	0.0	11.3%	4.46	G3_11	0.0	15.9%	1.87
G3_20	0.0	11.2%	1.96	G3_2	0.6	12.6%	4.17
G3_2	0.4	9.6%	4.47	G3_8	1.2	9.8%	4.17
G3_11	0.4	9.5%	2.02	G3_14	1.5	8.7%	1.95
G3_5	0.5	9.4%	2.33	G3_20	1.5	8.6%	1.78
G3_14	1.1	7.4%	2.14	G3_5	1.7	8.0%	2.13
G3_23	1.3	6.8%	4.48	G3_23	2.7	5.4%	4.21
G3_18	2.6	3.9%	4.37	G3_18	3.5	3.9%	4.16
G3_27	2.8	3.7%	1.97	G3_27	3.6	3.7%	2.01
G3_6	2.8	3.7%	2.22	G3_15	4.2	2.9%	4.26
G3_24	3.3	3.0%	2.55	G3_24	4.4	2.7%	2.44
G3_26	3.5	2.8%	4.11	G3_6	4.6	2.4%	2.10
G3_15	3.8	2.4%	4.51	G3_12	5.2	2.0%	4.10
G3_4	4.6	1.8%	4.60	G3_3	5.3	1.9%	1.92
G3_3	4.6	1.7%	1.85	G3_17	5.4	1.8%	4.30
G3_17	4.7	1.7%	4.68	G3_4	5.5	1.8%	4.33
G3_9	4.8	1.7%	2.81	G3_22	5.7	1.6%	1.99
G3_13	4.9	1.6%	2.98	G3_13	5.7	1.6%	2.76
G3_22	4.9	1.6%	2.20	G3_16	5.8	1.5%	1.57
G3_12	5.1	1.5%	4.31	G3_26	6.3	1.2%	3.75
G3_19	5.2	1.4%	4.48	G3_19	6.5	1.2%	4.21
G3_25	5.7	1.1%	3.92	G3_9	6.8	1.0%	2.67
G3_7	5.7	1.1%	2.24				
			3.18				2.92

6 Synthesis

6.1 General methods.

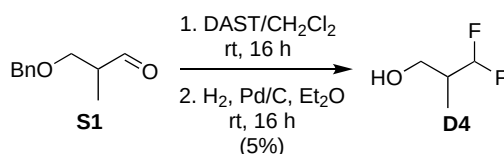
All chemical reagents were obtained from commercial sources and used without further purification. Anhydrous solvents were purchased from commercial sources. All glassware was flame-dried under vacuum and cooled under Ar prior to use. Water or air sensitive reactions were performed under inert atmosphere, using dry solvents. Reactions were monitored by TLC (Merck Kieselgel 60 F₂₅₄, aluminium sheet) and spots were visualized by UV and/or by exposure to a basic solution of KMnO₄, followed by brief heating. Flash column chromatography was performed on silica gel (Merck silica gel 60, particle size 40–63 μm). All reported solvent mixtures are volume measures. Nuclear magnetic resonance spectra were recorded using either a Bruker Ultrashield 400 MHz or 500 MHz spectrometer. The chemical shift (δ) is given in ppm using the residual solvent peak as an internal standard. The coupling constants (J) are given in Hertz (Hz). IR spectra were recorded on a Thermo Scientific™ Nicolet iS5 as films and absorption peaks are given in cm⁻¹. Low resolution electrospray mass spectra were recorded with a Waters Acquity TQD mass tandem quadrupole mass spectrometer. HRMS spectra were measured on a Bruker Daltonics MaXis time of flight (TOF) mass spectrometer or, for volatile compounds, a Thermo MAT900 XP double focusing sector mass spectrometer. All compounds subjected to biological assays were of >95% purity (liquid chromatography–UV).

6.2 Compounds available

Compounds **D1–D3**, **D5**, **F2** were commercially available.

6.3 Synthesis of novel compounds

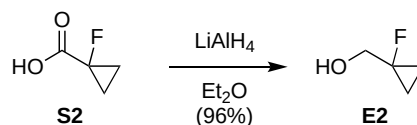
6.3.1 Synthesis of 3,3-difluoro-2-methylpropan-1-ol (**D4**)



To a 250 mL two-neck round-bottom flask were added 3-benzyloxy-2-methylpropanal **S1**⁸ (2.37 g, 13.3 mmol, 1.0 equiv) and anhydrous CH₂Cl₂ (80 mL). The resulting mixture was cooled to 0 °C, followed by slow addition of (diethylamino)sulfur trifluoride (5.27 mL, 39.9 mmol, 3.0 equiv) at this temperature. The reaction mixture was warmed to room temperature and stirred for 16 h. Upon completion as indicated by TLC analysis, the reaction mixture was slowly quenched with sat. aq. NaHCO₃ solution (150 mL), followed by extraction with CH₂Cl₂ (100 mL × 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated. The crude mixture was purified by flash chromatography (eluent: CH₂Cl₂/petroleum ether 20/80 – 25/75) to obtain the desired difluorinated

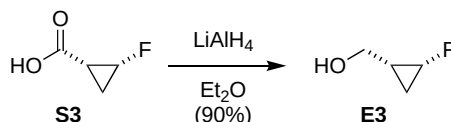
intermediate (not pure). This intermediate was treated with Pd/C (10wt% loading, 700 mg) in Et₂O (40 mL) under argon. The resulting mixture was degassed with H₂ gas and then stirred under H₂ at room temperature overnight. Upon completion was indicated by TLC analysis, the reaction mixture was loaded directly into a column for purification (eluent: pentane 100% – CH₂Cl₂/pentane 50/50 – Et₂O/CH₂Cl₂ 10/90) to afford the desired product in solution. This solution was concentrated at 700 mbar/35 °C and further dried by slow evaporation at atmospheric pressure to obtain the desired product **D4** (72 mg, 0.65 mmol, 5%) as a colourless oil. The low yield was due to the volatility of the product. ¹H NMR (400 MHz, CDCl₃) δ 5.86 (1H, td, *J* 56.7, 3.9 Hz, H-3), 3.63 – 3.76 (2H, m, H-1), 2.05 – 2.25 (1H, m, H-2), 1.64 (1H, t, *J* 4.2 Hz, OH), 1.05 (3H, d, *J* 7.1 Hz, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 118.0 (t, *J* 242.1 Hz, C-3), 62.6 (dd, *J* 6.2, 4.8 Hz, C-1), 39.8 (t, *J* 19.3 Hz, C-2), 9.3 (t, *J* 5.3 Hz, CH₃) ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -124.0 (1F, ddd, *J* 281.8, 56.8, 12.1 Hz, F-3), -126.8 (1F, ddd, *J* 282.6, 56.9, 18.2 Hz, F-3') ppm; ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -124.0 (1F, d, *J* 281.8 Hz, F-3), -126.8 (1F, d, *J* 282.6 Hz, F-3') ppm; IR (neat) 3356 (br. m), 2982 (m), 2957 (w), 2896 (w), 1467 (m), 1399 (m), 1154 (m), 1086 (s), 1025 (s), 988 (s), 942 (m) cm⁻¹.

6.3.2 Synthesis of (1-fluorocyclopropyl)methanol (**E2**)



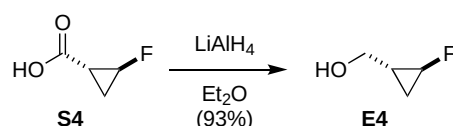
A solution of **S2** (250 mg, 1 equiv) in Et₂O (2 mL) was added to a slurry of LiAlH₄ (273 mg, 3 equiv) in Et₂O (6 mL) at 0 °C dropwise. The reaction was allowed to warm to room temperature and stirred for 16 h. It was then cooled to 0 °C and water (0.27 mL) was added dropwise, followed by aq. NaOH (15% wt., 0.27 mL) then water (0.81 mL). To this MgSO₄ was added and after stirring for 15 min the mixture was filtered and the resultant filtrate was carefully concentrated at 750 mbar/30 °C to afford **E2** as a colourless oil (208 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ 3.84 (d, *J*=22.0 Hz, 2H, H1), 1.88 (br. s, 1H, OH), 1.17–1.04 (m, 2H, H3' + H4'), 0.75–0.67 (m, 2H, H3'' + H4'') ppm; ¹³C NMR (101 MHz, CDCl₃) δ 79.9 (d, *J*=216.4 Hz, C2), 66.1 (d, *J*=22.0 Hz, C1), 9.2 (d, *J*=11.7 Hz, C3 and C4 overlapped) ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -191.3 (ttt, *J*=22.0, 18.6, 8.7 Hz, 1F) ppm; ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -191.3 (s, 1F) ppm; IR (neat) 3339 (br. w), 2931 (w), 2872 (w), 1416 (m), 1200 (m), 1038 (s), 1013 (s) cm⁻¹; HRMS (CI) for C₄H₈FO (M+H)⁺, calculated 91.0554, found 91.0544. Data consistent with literature.⁹

6.3.3 Synthesis of (rac-(1R,2R)-2-fluorocyclopropyl)methanol (**E3**)



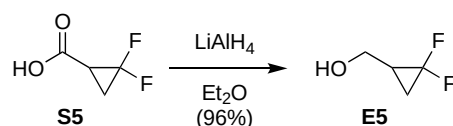
A solution of **S3** (250 mg, 1 equiv) in Et₂O (2 mL) was added to a slurry of LiAlH₄ (273 mg, 3 equiv) in Et₂O (6 mL) at 0 °C dropwise. The reaction was allowed to warm to room temperature and stirred for 16 h. It was then cooled to 0 °C and water (0.27 mL) was added dropwise, followed by aq. NaOH (15% wt., 0.27 mL) then water (0.81 mL). To this MgSO₄ was added and after stirring for 15 min the mixture was filtered and the resultant filtrate was carefully concentrated at 750 mbar/30 °C to afford **E3** as a colourless oil (195 mg, 90%). ¹H NMR (500 MHz, CDCl₃) δ 4.74 (dtd, J=65.2, 5.9, 2.7 Hz, 1H, H4), 3.94 (br. d, J=4.3 Hz, 1H, H1'), 3.69–3.60 (m, 1H, H1''), 1.52 (br. s, 1H, OH), 1.34–1.15 (m, 1H, H2), 0.92–0.71 (m, 2H, H3) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 72.3 (d, J=218.8 Hz, C4), 61.1 (d, J=9.2 Hz, C1), 18.7 (d, J=11.0 Hz, C2), 9.4 (d, J=10.1 Hz, C3) ppm; ¹⁹F NMR (471 MHz, CDCl₃) δ -227.4 (dddd, J=65.0, 23.4, 11.3, 5.2 Hz, 1F) ppm; ¹⁹F {¹H} NMR (471 MHz, CDCl₃) δ -227.4 (s, 1 F) ppm; IR (neat) 3334 (br. w), 2943 (w), 2888 (w), 1445 (m), 1200 (s), 1016 (s), 982 (s) cm⁻¹; HRMS (CI) for C₄H₈FO (M+H)⁺, calculated 91.0554, found 91.0544.

6.3.4 Synthesis of (rac-(1R,2S)-2-fluorocyclopropyl)methanol (**E4**)



A solution of **S4** (250 mg, 1 equiv) in Et₂O (2 mL) was added to a slurry of LiAlH₄ (273 mg, 3 equiv) in Et₂O (6 mL) at 0 °C dropwise. The reaction was allowed to warm to room temperature and stirred for 16 h. It was then cooled to 0 °C and water (0.27 mL) was added dropwise, followed by aq. NaOH (15% wt., 0.27 mL) then water (0.81 mL). To this MgSO₄ was added and after stirring for 15 min the mixture was filtered and the resultant filtrate was carefully concentrated at 750 mbar/30 °C to afford **E4** as a colourless oil (201 mg, 93%). ¹H NMR (400 MHz, CDCl₃) δ 4.47 (ddt, J=64.1, 6.2, 2.3 Hz, 1H, H4), 3.55–3.42 (m, 2H, H1), 1.63–1.51 (m, 1H, H2), 1.48 (br. t, J=4.5 Hz, 1H, OH), 1.15–1.04 (m, 1H, H3'), 0.62 (app. dq, J=10.3, 6.7 Hz, 1H, H3') ppm; ¹³C NMR (101 MHz, CDCl₃) δ 72.5 (d, J=220.6 Hz, C4), 62.7 (C1), 20.2 (d, J=10.1 Hz, C2), 9.7 (d, J=11.0 Hz, C3) ppm; ¹⁹F NMR (471 MHz, CDCl₃) δ -210.2 (dtdd, J=64.2, 20.8, 10.4, 1.7 Hz, 1F) ppm; ¹⁹F {¹H} NMR (471 MHz, CDCl₃) δ -210.2 (s, 1F) ppm; IR (neat) 3335 (br. w), 2930 (w), 2881 (w), 1453 (m), 1135 (s), 1031 (s), 982 (s) cm⁻¹; HRMS (CI) for C₄H₈FO (M+H)⁺, calculated 91.0554, found 91.0545.

6.3.5 Synthesis of (2,2-difluorocyclopropyl)methanol (**E5**)



A solution of **S5** (250 mg, 1 equiv) in Et₂O (2 mL) was added to a slurry of LiAlH₄ (233 mg, 3 equiv) in Et₂O (6 mL) at 0 °C dropwise. The reaction was allowed to warm to room temperature and stirred

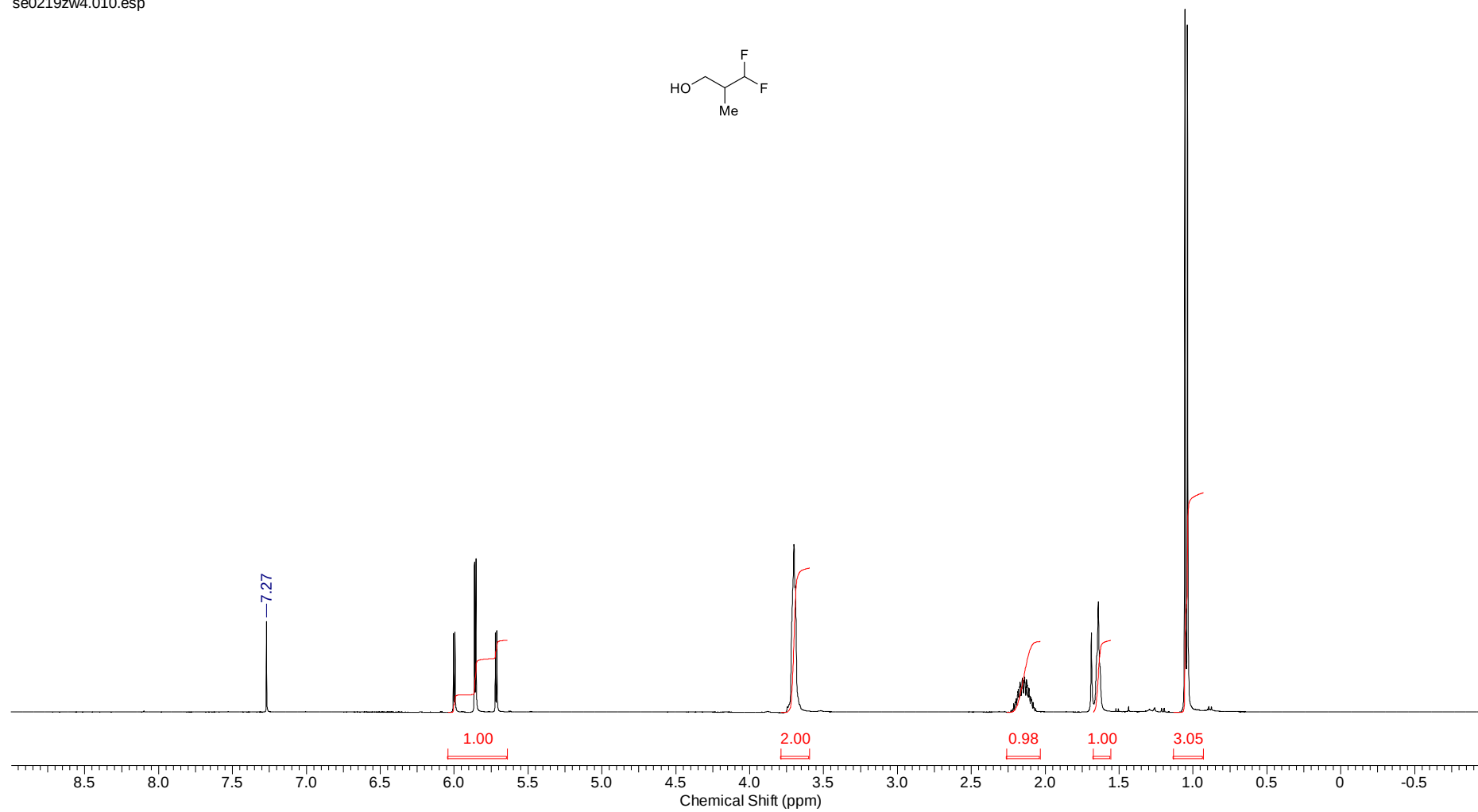
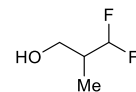
for 16 h. It was then cooled to 0 °C and water (0.23 mL) was added dropwise followed by aq. NaOH (15% wt., 0.23 mL) then water (0.69 mL). To this MgSO₄ was added and after stirring for 15 min the mixture was filtered and the resultant filtrate was carefully concentrated at 750 mbar/30 °C to afford **E5** as a colourless oil (214 mg, 97%). ¹H NMR (400 MHz, CDCl₃) δ 3.98–3.54 (m, 2H, H1), 1.99–1.83 (m, 1H, H2), 1.48 (tdd, J=11.9, 7.6, 4.2 Hz, 1H, H3'), 1.18 (dtd, J=13.3, 7.6, 3.8 Hz, 1H, H3'') ppm; ¹³C NMR (101 MHz, CDCl₃) δ 113.6 (t, J=281.7 Hz, C4), 60.1 (d, J=5.9 Hz, C1), 24.3 (t, J=10.6 Hz, C2), 14.5 (t, J=11.4 Hz, C3) ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -128.8 (app. dtt, J=161.3, 12.1, 3.5 Hz, 1F, F4'), -144.5 (app. ddd, J=160.8, 13.4, 4.3 Hz, 1F, F4'') ppm; ¹⁹F {¹H} NMR (376 MHz, CDCl₃) δ -128.8 (d, J=161.3 Hz, 1F, F4'), -144.5 (d, J=161.3 Hz, 1F, F4'') ppm. Data consistent with literature.¹⁰

7 NMR spectra for novel compounds

7.1 3,3-Difluoro-2-methylpropan-1-ol (D4)

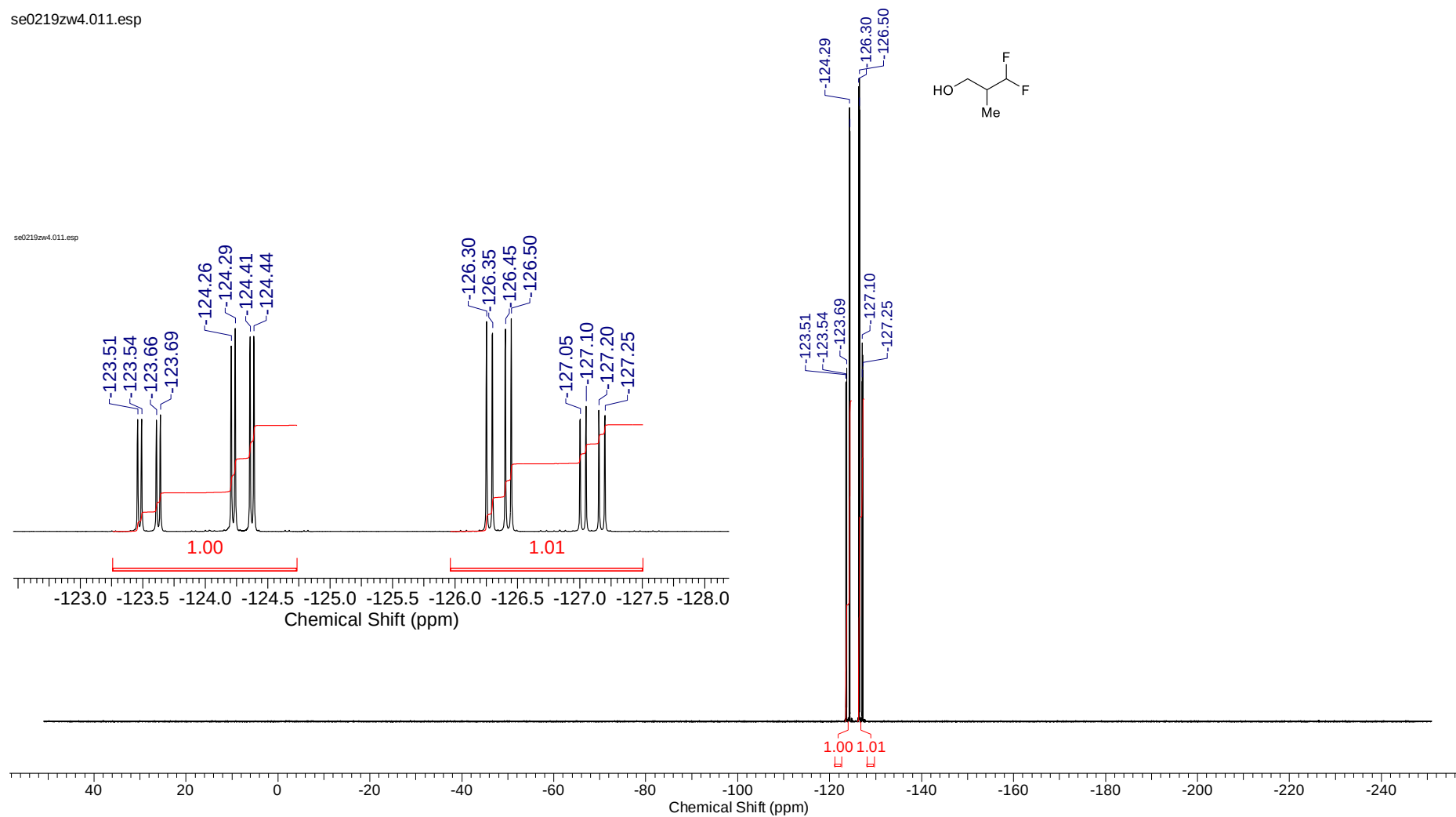
7.1.1 3,3-Difluoro-2-methylpropan-1-ol (D4) (^1H NMR, CDCl_3 , 400 MHz)

se0219zw4.010.esp



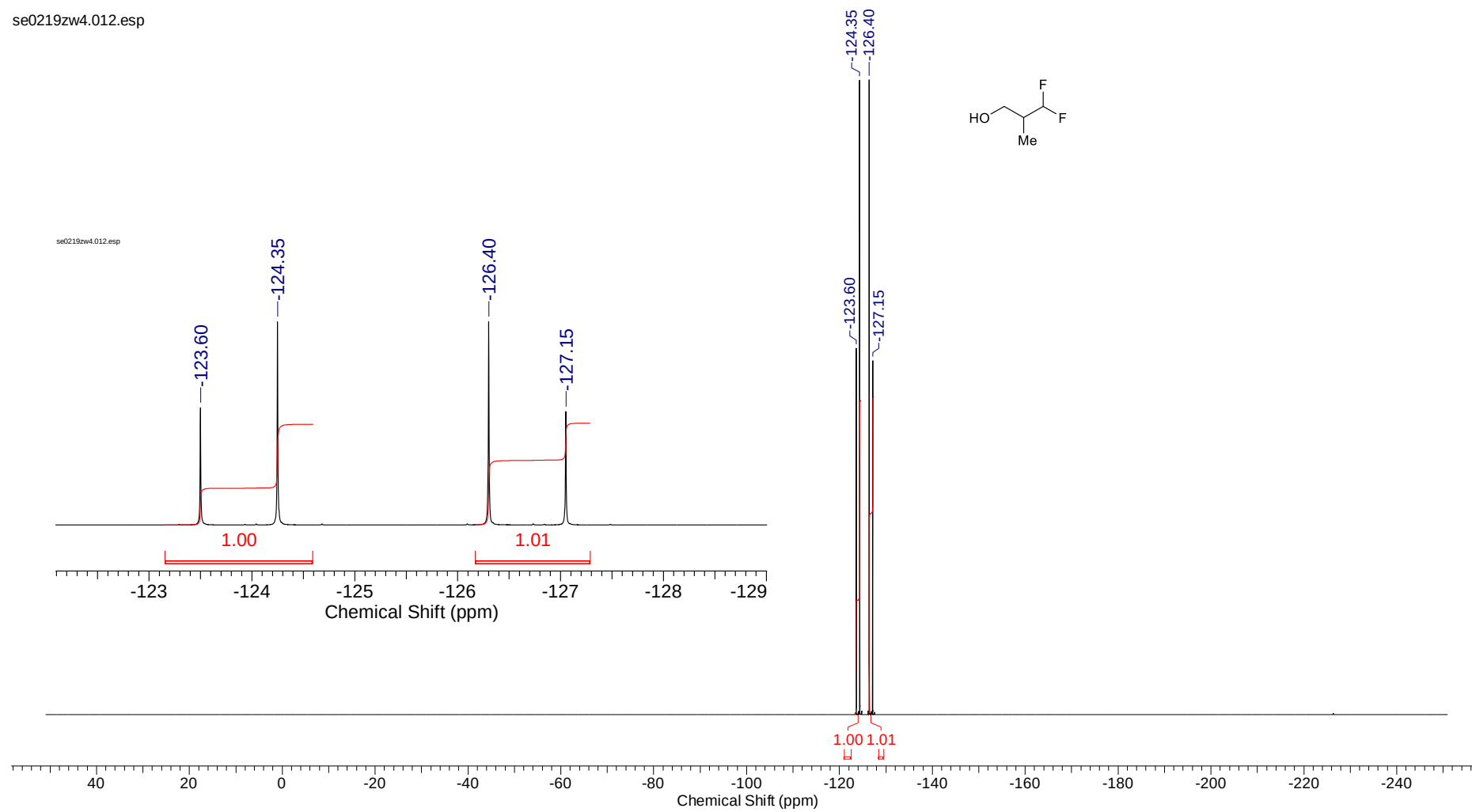
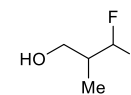
7.1.2 3,3-Difluoro-2-methylpropan-1-ol (**D4**) (^{19}F NMR, CDCl_3 , 376 MHz)

se0219zw4.011.esp



7.1.3 3,3-Difluoro-2-methylpropan-1-ol (**D4**) ($^{19}\text{F}\{^1\text{H}\}$ NMR, CDCl_3 , 376 MHz)

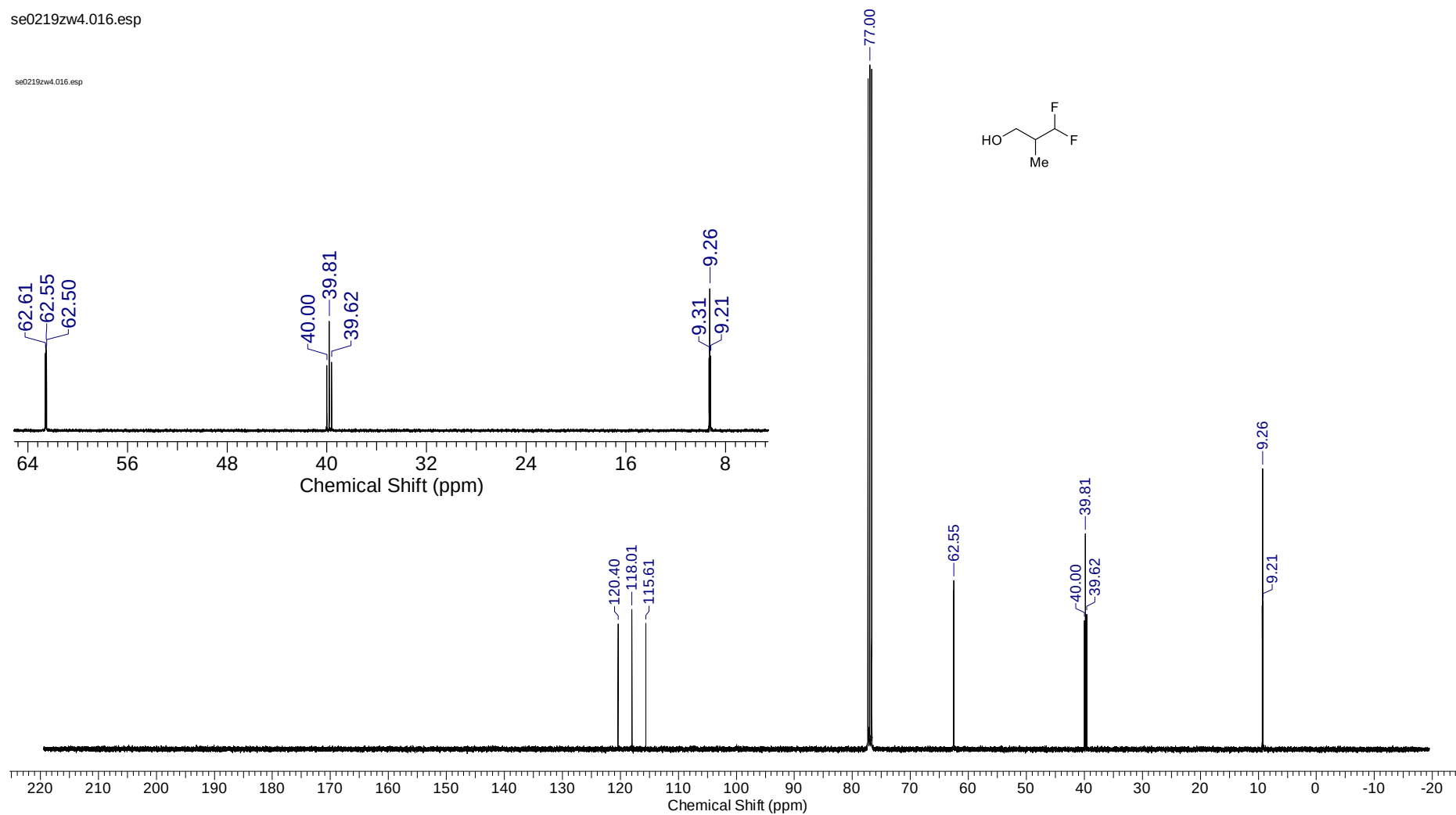
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7.1.4 3,3-Difluoro-2-methylpropan-1-ol (**D4**) (^{13}C NMR, CDCl_3 , 101 MHz)

se0219zw4.016.esp

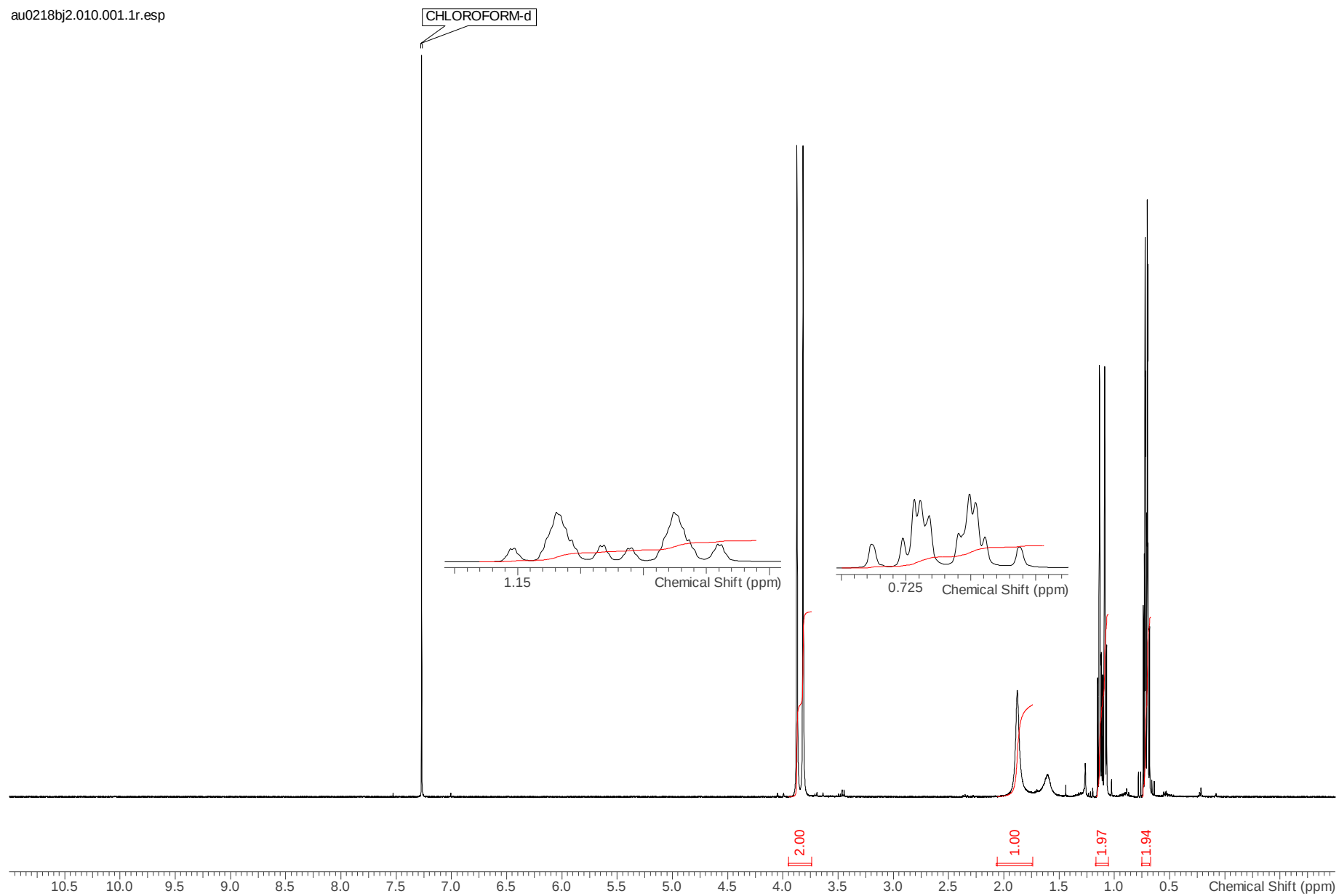
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7.2 (1-Fluorocyclopropyl)methanol (E2)

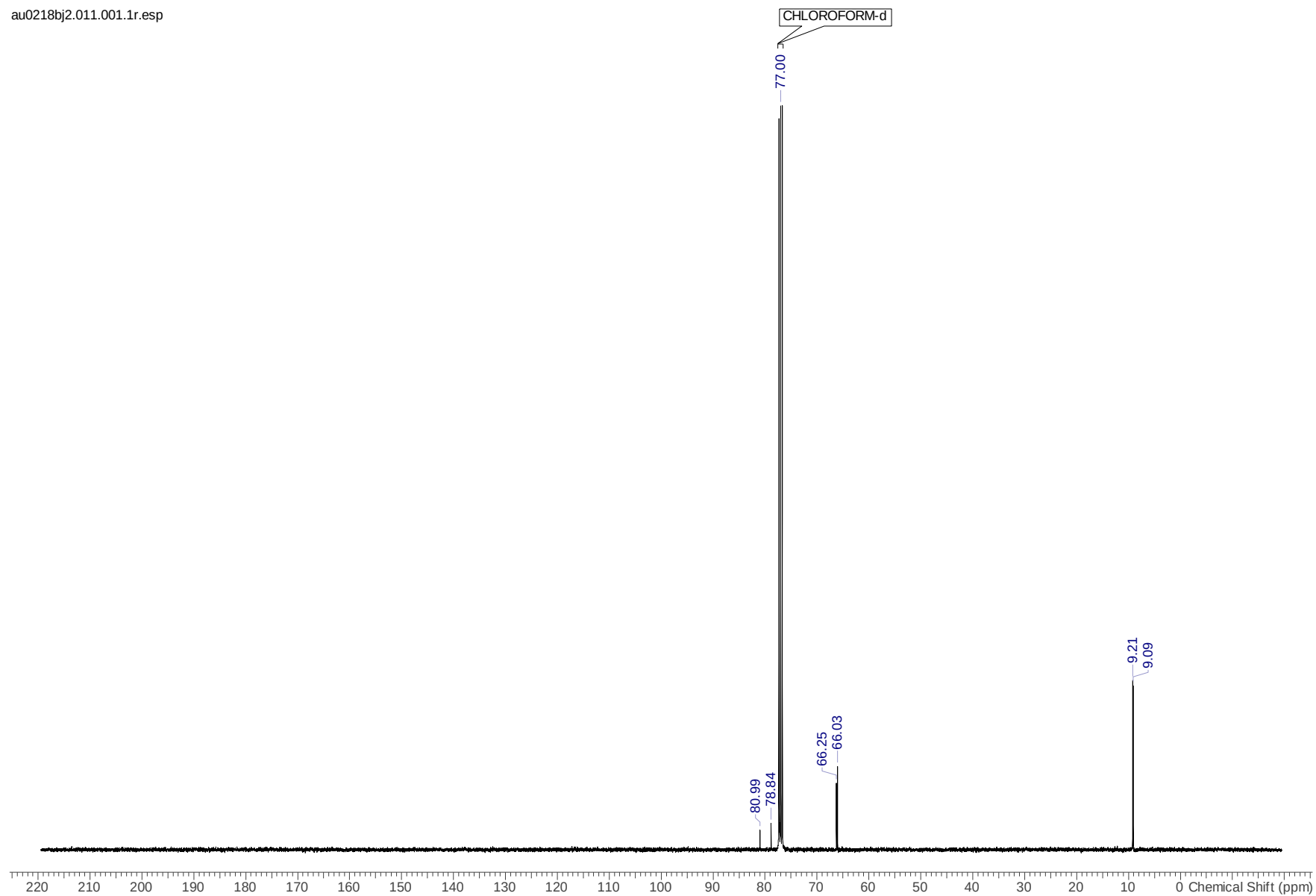
7.2.1 (1-Fluorocyclopropyl)methanol (E2) (^1H NMR, CDCl_3 , 400 MHz)

au0218bj2.010.001.1r.esp



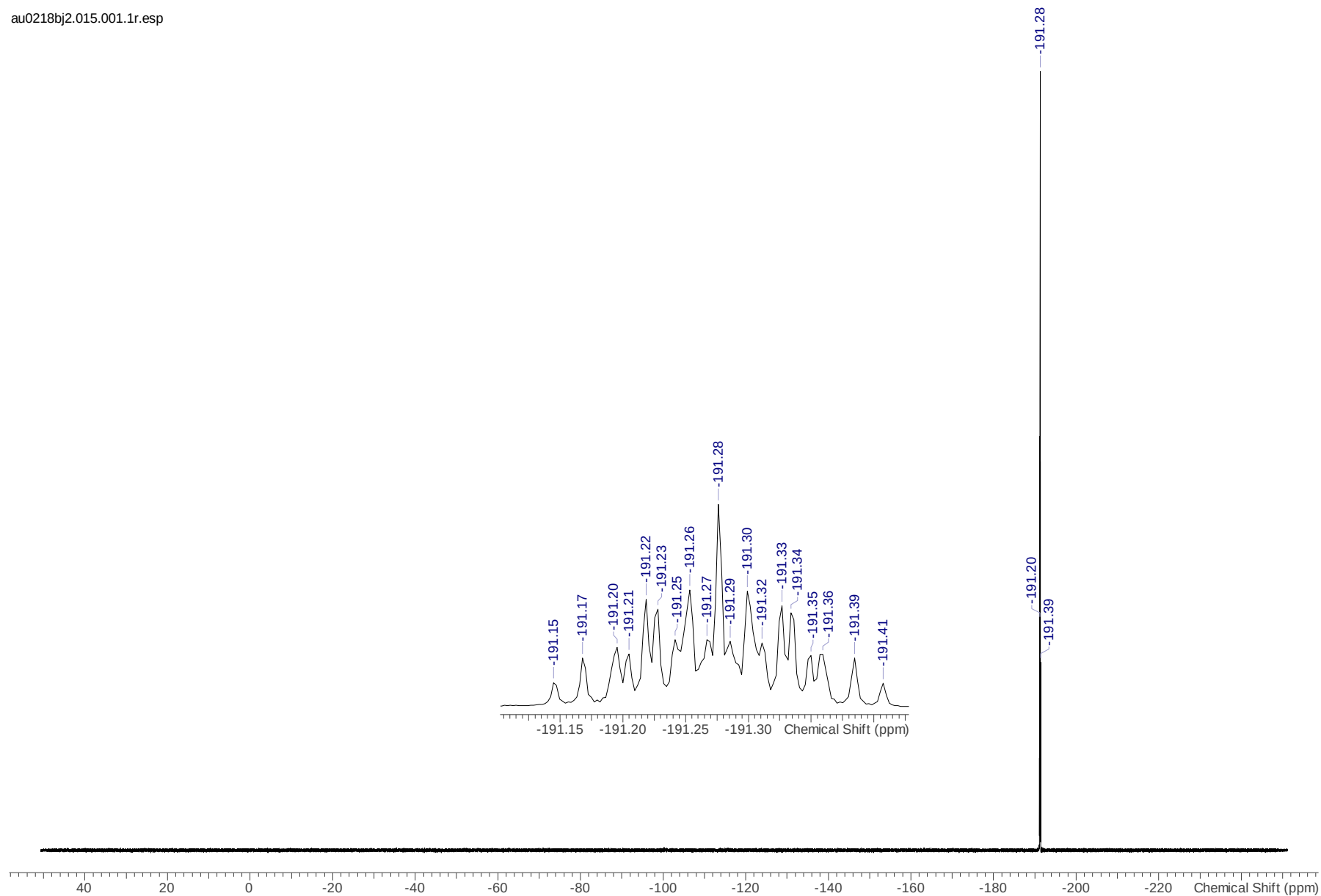
7.2.2 (1-Fluorocyclopropyl)methanol (**E2**) (^{13}C NMR, CDCl_3 , 101 MHz)

au0218bj2.011.001.1r.esp



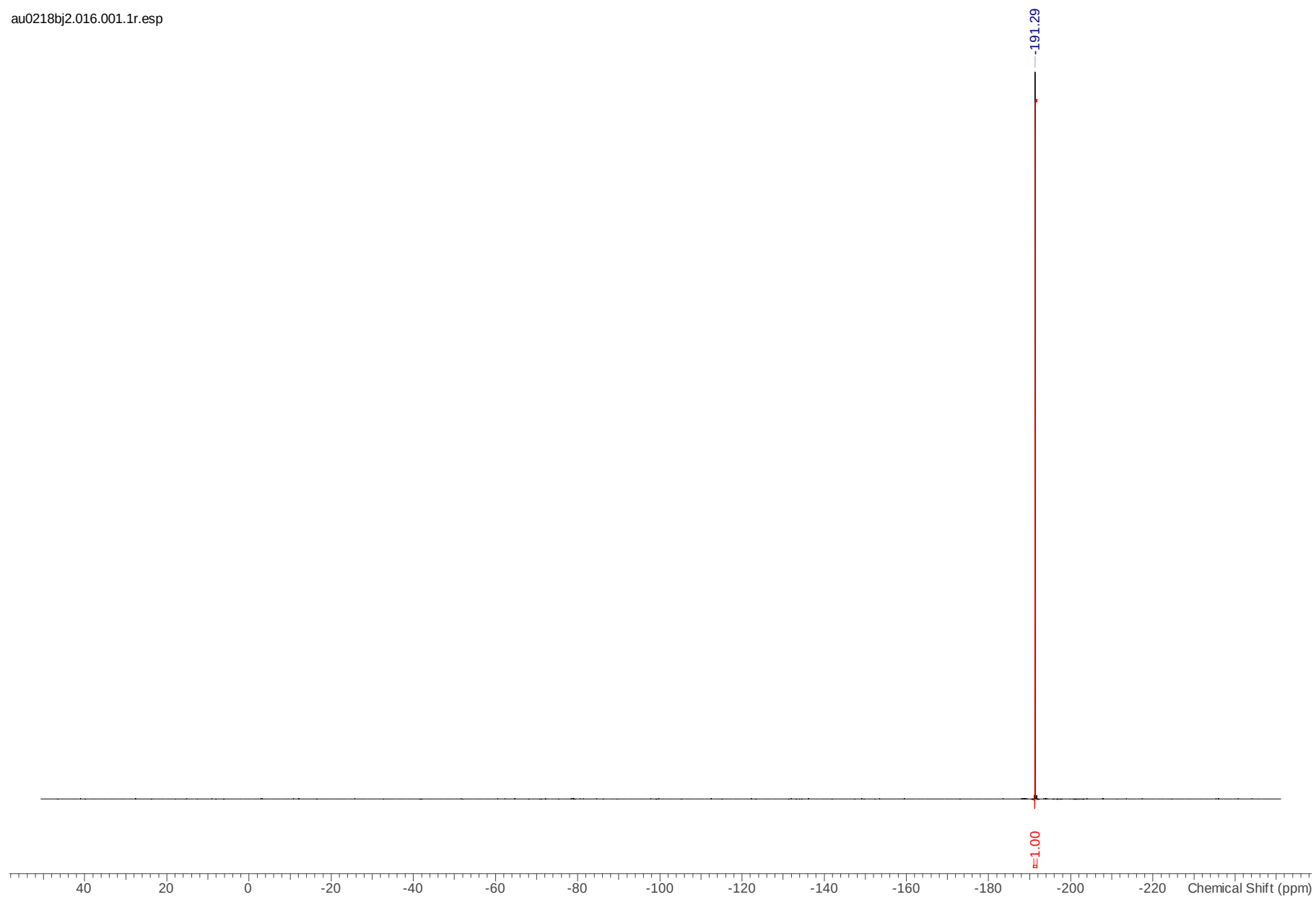
7.2.3 (1-Fluorocyclopropyl)methanol (**E2**) (^{19}F NMR, CDCl_3 , 376 MHz)

au0218bj2.015.001.1r.esp



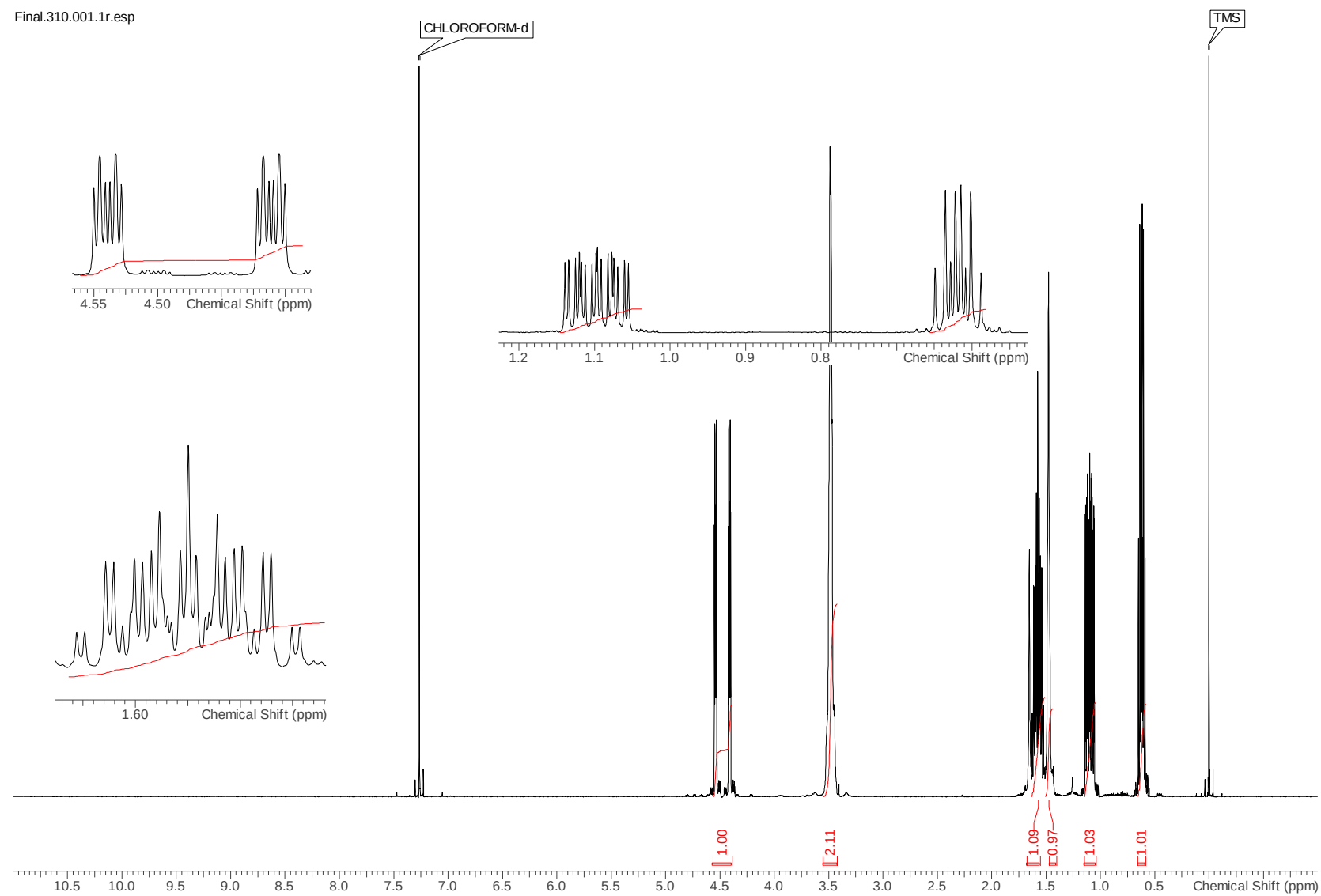
7.2.4 (1-Fluorocyclopropyl)methanol (**E2**) (^{19}F { ^1H } NMR, CDCl_3 , 376 MHz)

au0218bj2.016.001.1r.esp



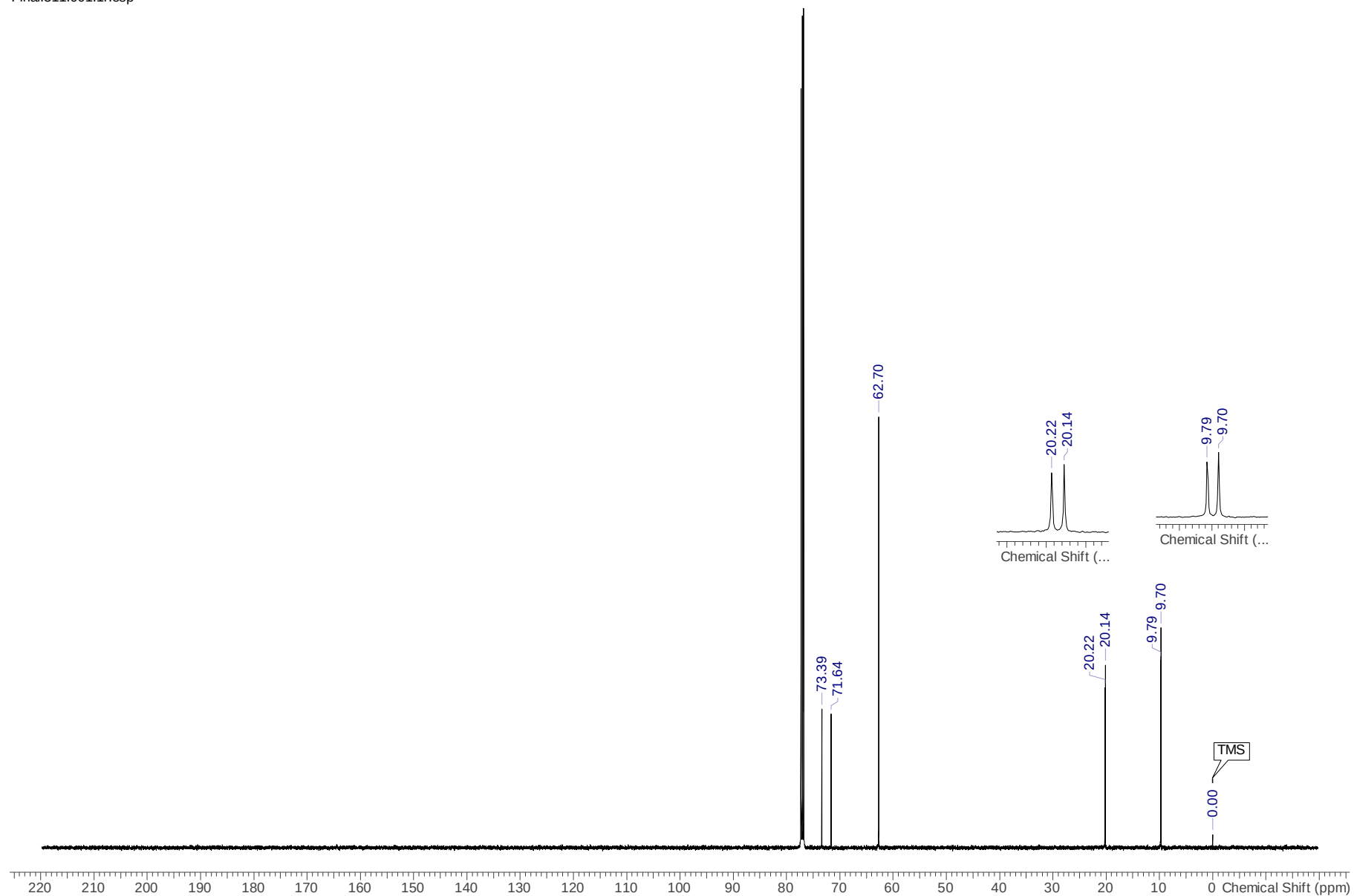
7.3 *rac*-(1*R*,2*R*)-(2-Fluorocyclopropyl)methanol (**E3**)

7.3.1 *rac*-(1*R*,2*R*)-2-Fluorocyclopropyl)methanol (**E3**) (^1H NMR, CDCl_3 , 400 MHz)



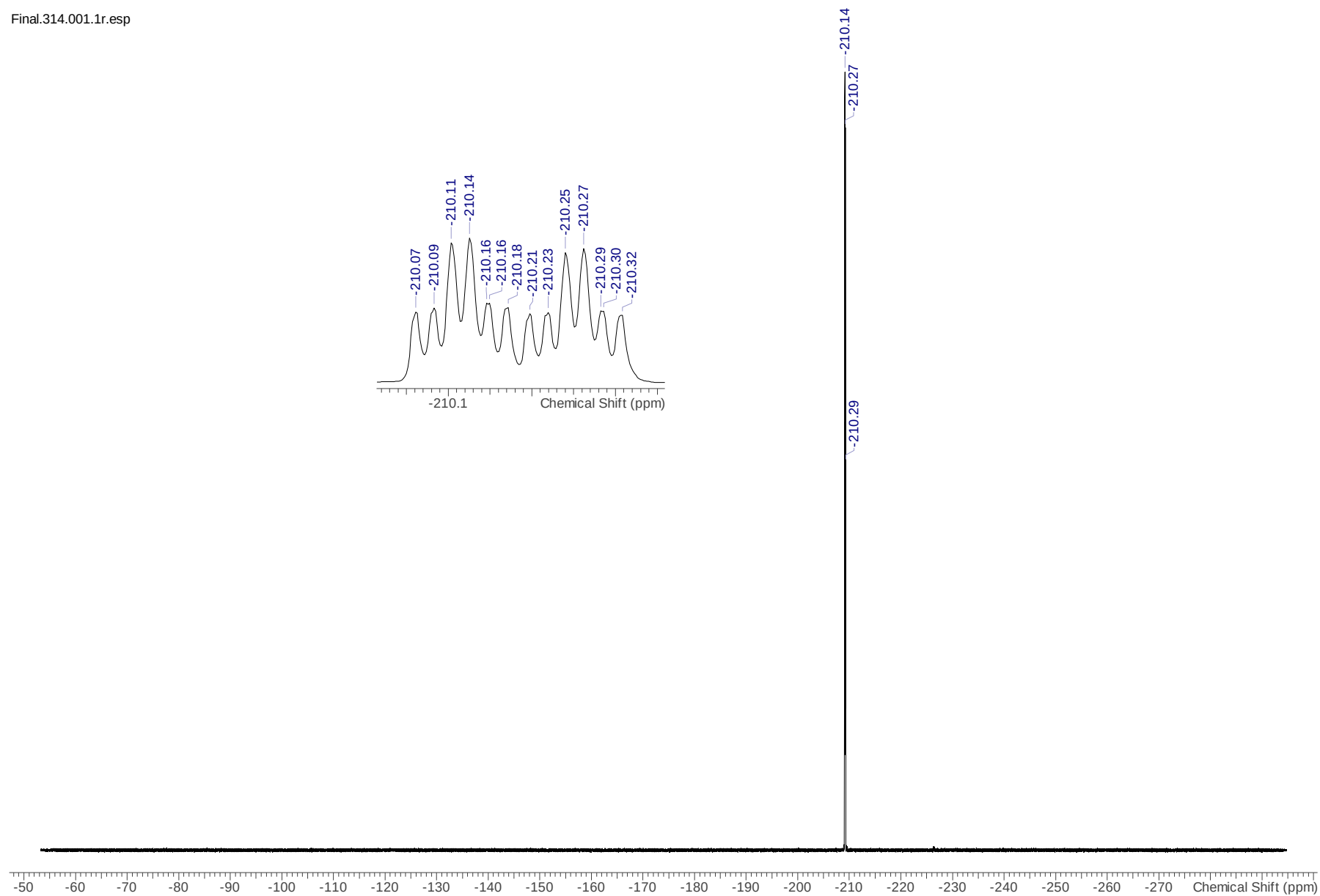
7.3.2 *rac*-(1*R*,2*R*)-(2-Fluorocyclopropyl)methanol (**E3**) (^{13}C NMR, CDCl_3 , 126 MHz)

Final.311.001.1r.esp



7.3.3 *rac*-(1*R*,2*R*)-(2-Fluorocyclopropyl)methanol (**E3**) (^{19}F NMR, CDCl_3 , 471 MHz)

Final.314.001.1r.esp



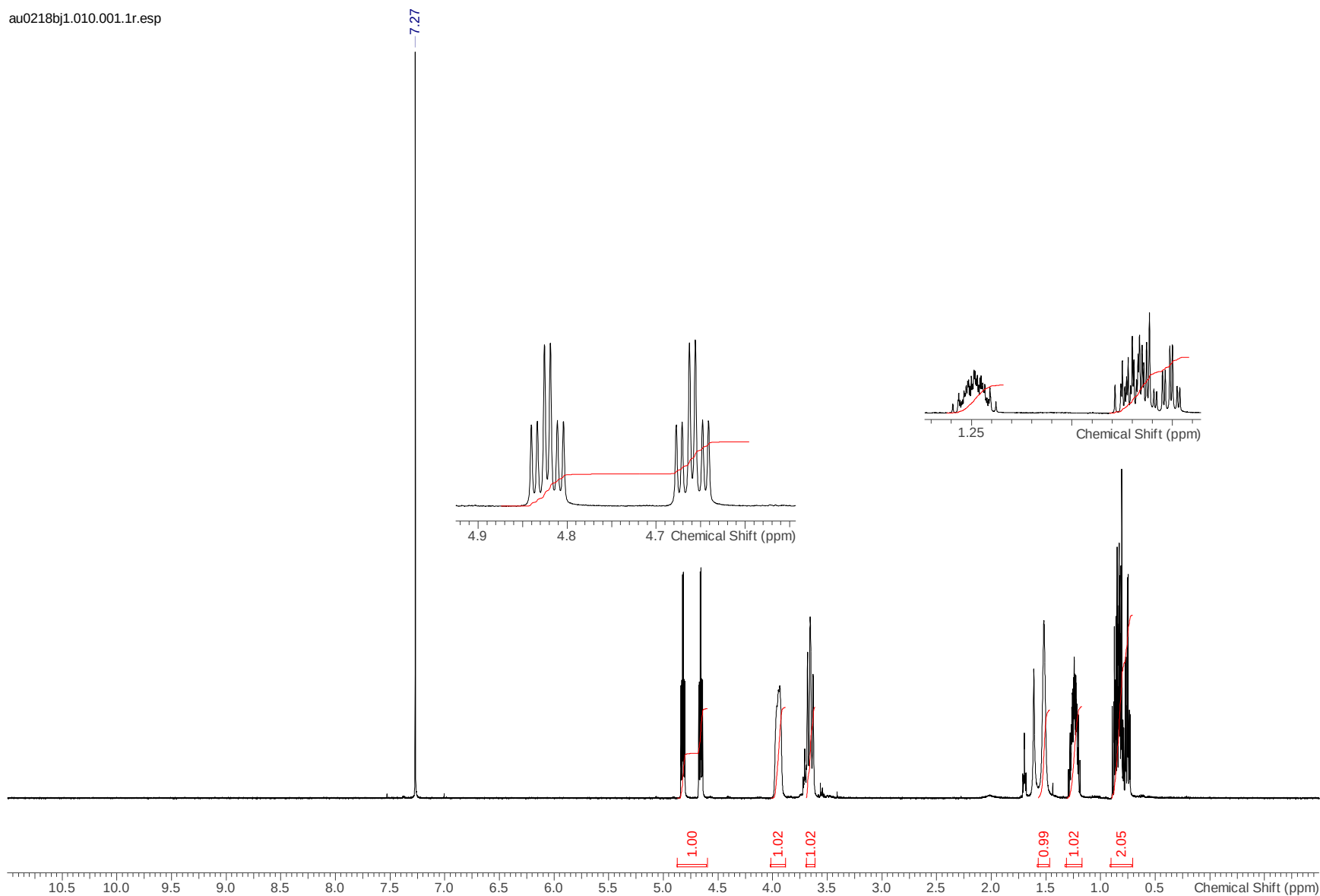
7.3.4 *rac*-(1*R*,2*R*)-(2-Fluorocyclopropyl)methanol (**E3**) (^{19}F { ^1H } NMR, CDCl_3 , 471 MHz)

Final.315.001.1r.esp



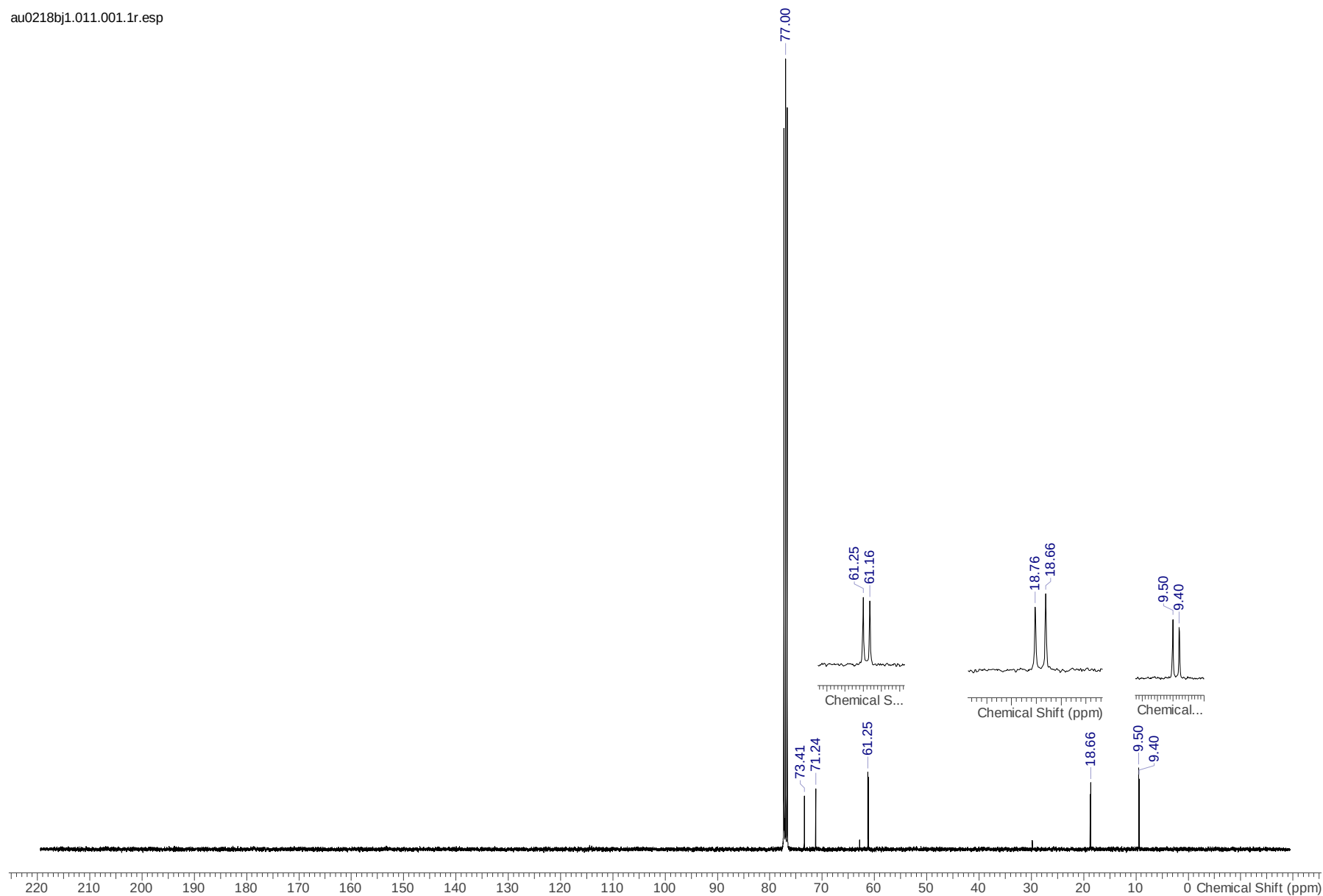
7.4 *rac*-(1*R*,2*S*)-(2-fluorocyclopropyl)methanol (E4)**7.4.1 *rac*-(1*R*,2*S*)-(2-fluorocyclopropyl)methanol (E4) (¹H NMR, CDCl₃, 400 MHz)**

au0218bj1.010.001.1r.esp



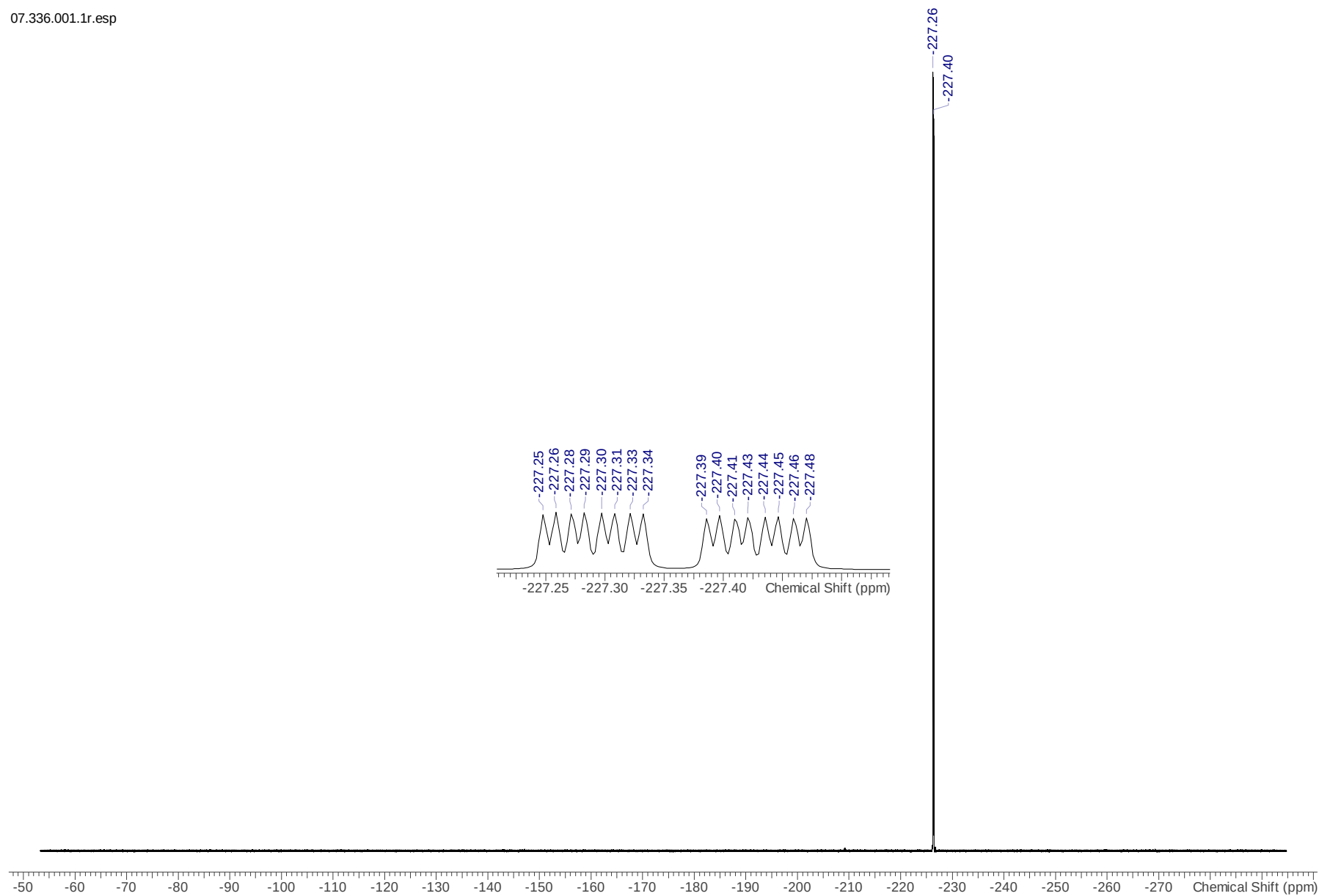
7.4.2 *rac*-(1*R*,2*S*)-(2-fluorocyclopropyl)methanol (**E4**) (^{13}C NMR, CDCl_3 , 101 MHz)

au0218bj1.011.001.1r.esp



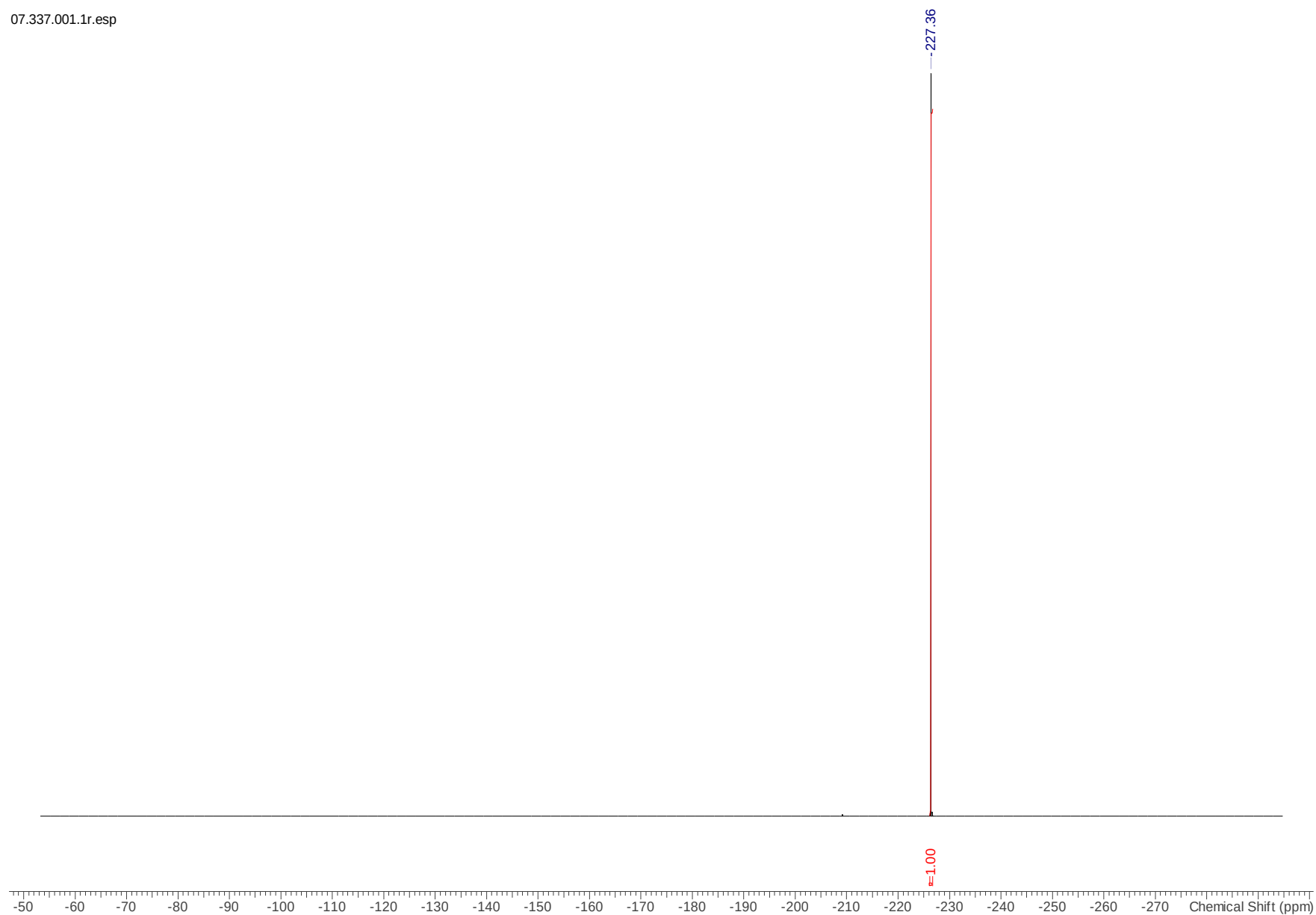
7.4.3 *rac*-(1*R*,2*S*)-(2-fluorocyclopropyl)methanol (**E4**) ^{19}F NMR, CDCl_3 , 471 MHz

07.336.001.1r.esp



7.4.4 *rac*-(1*R*,2*S*)-(2-fluorocyclopropyl)methanol (**E4**) ^{19}F {1H} NMR, CDCl_3 , 471 MHz

07.337.001.1r.esp



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