

# **Supporting Information**

## **Deoxyfluorination with Sulfonyl Fluorides: Navigating Reaction Space with Machine Learning**

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## I. General Information

**Reagents and Methods.** Perfluorobutane-1-sulfonyl fluoride (PBSF) was purchased from Acros. 2-Pyridinesulfonyl fluoride (PyFluor), 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG), and *tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP) were purchased from Millipore-Sigma. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was obtained from both Sigma-Millipore and Acros. 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) was purchased from both Sigma-Millipore and TCI America. 4-Chlorobenzenesulfonyl fluoride (**3-Cl**), 4-(trifluoromethyl)benzene-sulfonyl fluoride (**3-CF<sub>3</sub>**), and 4-nitrobenzenesulfonyl fluoride (**3-NO<sub>2</sub>**) were synthesized as described in Section IV. PBSF and recently purchased bottles of DBU, MTBD, BTMG, and BTPP were stored sealed at room temperature. The remaining sulfonyl fluorides, PyFluor, **3-Cl**, **3-CF<sub>3</sub>**, and **3-NO<sub>2</sub>** were stored sealed in a fridge at 2 °C. Tetrahydrofuran (THF), toluene, and other common solvents were dispensed from a dry solvent system. Suppliers for all other materials are noted in the individual procedures. Reactions were monitored by thin-layer chromatography (TLC) on EMD Silica Gel 60 F254 plates, visualizing with UV-light (254 nm). Organic solutions were concentrated under reduced pressure using a rotary evaporator (23 °C, <50 torr). Automated column chromatography was performed using silica gel cartridges on a Biotage Isolera 4 (repacked with 40-53 µm silica from Silicycle).

**Instrumentation.** Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra and carbon nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded on a Bruker 500 AVANCE equipped with a cryoprobe (500 and 125 MHz, respectively). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl<sub>3</sub> = δ 7.26 ppm, CHDCl<sub>2</sub> = δ 5.32 ppm, C<sub>6</sub>HD<sub>5</sub> = δ 7.16 ppm, DMSO-*d*<sub>5</sub> = δ 2.50 ppm). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent peak (CDCl<sub>3</sub> = δ 77.16 ppm, CD<sub>2</sub>Cl<sub>2</sub> = δ 53.84 ppm, C<sub>6</sub>D<sub>6</sub> = δ 128.06 ppm, DMSO-*d*<sub>6</sub> = δ 39.52 ppm). <sup>19</sup>F fluorine spectra were recorded on either a Bruker 300 AVANCE (282 MHz) or a Bruker-adapted 400 MHz Oxford magnet (376 MHz); chemical shifts are reported in parts per million and are referenced to CFCl<sub>3</sub> (δ 0 ppm). NMR data are represented as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, m = multiplet), coupling constant in Hertz (Hz), integration). All NMR spectra were taken at 25 °C. High-resolution mass spectra were obtained on an Agilent 6220 LC/MS with an electrospray ionization time-of-flight (ESI-TOF) detector. FTIR and FT-ATR spectra were recorded on a Perkin-Elmer Spectrum 100 and are reported in terms of frequency of absorption (cm<sup>-1</sup>) and intensity (s = strong, m = moderate, w = weak, br = broad). Gas chromatography (GC) was performed on an Agilent 7890A series instrument equipped with a split-mode capillary injection system and a flame ionization detector. Liquid chromatography-mass spectrometry (LCMS) data was obtained on an Agilent 1260 Infinity instrument with a binary pump, a diode array detector, and an Agilent 6120 quadrupole detector.

## II. High Throughput Experimentation

Each of the 32 alcohols **1a – 1af** was evaluated under twenty distinct deoxyfluorination conditions in which five sulfonyl fluorides (**3-Cl**, PyFluor, **3-CF<sub>3</sub>**, **3-NO<sub>2</sub>**, and PBSF) were screened against four bases (DBU, MTBD, BTMG, and BTPP). The 640 resulting yields are tabulated below and were used to train and test the predictive ability of the random forest machine learning algorithm.

For each reaction, an 8 × 40 mm glass vial with a 5 mm Teflon stirbar was charged sequentially with a stock solution containing 0.1 mmol of the substrate alcohol in 125 µL THF, a stock solution containing 1.1 equiv sulfonyl fluoride in 125 µL THF, and 1.5 equiv base (resulting in a concentration of ~0.4 M). In cases where the substrate alcohol was not fully soluble in THF, the alcohol was added as a solid, followed by addition of 125 µL THF. The vials were capped and stirred at 600 rpm at room temperature for 48 hours. Yields were assessed by <sup>19</sup>F NMR following the addition of 1 equiv 1-fluoronaphthalene in 250 µL CDCl<sub>3</sub> as an external standard. The % yields are reported below as well as relevant diastereomeric or isomeric ratios.

In a few instances, assay yields greater than 100% are reported due to experimental error. We have chosen not to modify or correct the data set to avoid biasing the machine learning algorithm. To quantify <sup>19</sup>F NMR relative error, replicate reactions were performed for the highest yielding conditions for all substrates except **1a**, **1i**, and **1ab** (see Table S1), revealing an average variance of 4.8% yield. It should be noted that these were made from different stock solutions than in the initial 20-reaction screens. Within each individual 20-reaction screen, the relative error should be lower, although the use of stock solutions may result in systematic error for all yields within a screen.

The reported isolated yields demonstrated a larger root mean square variance of 7.1% yield from the NMR yields. The mean variance is -3.7% yield, indicating that the NMR yields are systematically higher than the isolated yields. However, as noted in the manuscript, some of the benzylic substrates and reactions employing PBSF underperformed on scale. In our experience, NMR yields for isolated samples did not deviate by more than ±2% yield from isolation on 1 mmol scale.

**Table S1.** Analysis of relative error among <sup>19</sup>F NMR yield replicates (using different stock solutions) and isolated yields.

product	conditions	Screening			Isolation	
		% yield	replicate	rel. error	% yield	isol. error
2b	3-CF <sub>3</sub> /BTPP	99	109	10	90	14
2c	PBSF/BTMG	89	85	4	84	3
2d	PBSF/MTBD	76	84	8	66	14
2e	3-CF <sub>3</sub> /BTPP	96	95	1	89	6.5
2f	PBSF/BTPP	22	21	1	18	3.5
2g	3-CF <sub>3</sub> /BTMG	106	95	11	96	4.5
2h	4-NsF/BTMG	82	78	4	77	3
2j	3-CF <sub>3</sub> /BTMG	80	80	0	82	-2
2k	PBSF/BTPP	94	97	3	86	9.5
2l	PBSF/MTBD	88	73	15	75	5.5
2m	PBSF/MTBD	80	70	10	88	-13

2n	PBSF/BTPP	106	111	5	94	14.5
2o	PBSF/BTMG	50	51	1	46	4.5
2p	PBSF/BTPP	13	16	3	15	-0.5
2q	PBSF/BTMG	52	56	4	53	1
2r	3-CF <sub>3</sub> /BTPP	97	94	3	85	10.5
2s	3-NO <sub>2</sub> /BTMG	49	47	2	41	7
2t	3-Cl/BTPP	66	63	3	57	7.5
2u	3-CF <sub>3</sub> /BTMG	57	59	2	60	-2
2v	PBSF/BTPP	82	90	8	90	-4
2w	3-CF <sub>3</sub> /BTPP	52	51	1	46	5.5
2x	3-CF <sub>3</sub> /BTPP	36	38	2	39	-2
2y	PBSF/BTPP	10	11	1	9	1.5
2z	3-NO <sub>2</sub> /BTMG	86	90	4	86	2
2aa	PBSF/BTMG	87	81	6	88	-4
2ac	PBSF/MTBD	92	88	4	78	12
2ad	3-CF <sub>3</sub> /BTPP	54	39	15	47	-0.5
2ae	PBSF/BTPP	28	31	3	24	5.5
2af	3-NO <sub>2</sub> /BTMG	52	57	5	54	0.5
		RMSE	6.2	RMSE	7.1	
		average	4.8	Average	-3.7	

THF was selected as the screening solvent because many of the more polar alcohols were insoluble in toluene, which was the solvent employed in our communication describing PyFluor.<sup>1</sup> In the supporting information of said communication, we demonstrated that substrate **1a** afforded product **2a** in 78% yield in toluene and 76% yield in THF. Under the current screening conditions, **1a** afforded at most 69% yield of **2a**, lower than we obtained with our original conditions, which were specifically and extensively optimized for this substrate.

Although we tried to avoid repeating substrates from our previous communication, we do have data for a few substrates under the original toluene conditions included in Table S2.

**Table S2.** Comparison of substrate performance in THF vs. toluene.

Substrate	Yield with PyFluor toluene (original) (2 eq MTBD)	Yield with PyFluor THF (current) (1.5 eq MTBD)	Difference
<b>1a</b>	79	69	-10%
<b>1e</b>	81	78	-3%
<b>1t</b>	39	41	+2%
<b>1w</b>	11	16	+5%
<b>1x</b>	14	13	-1%
<b>1aa</b>	43	38	-5%
<b>1ac</b>	28	72	+44%
<b>1ad</b>	31	53	+22%
<b>1ae</b>	9	8	-1%

With the exception of the acyclic secondary alcohol **1a**, there does not appear to be any marked preference for toluene over THF. In fact, substrates **1ac** and **1ad** perform much better under THF

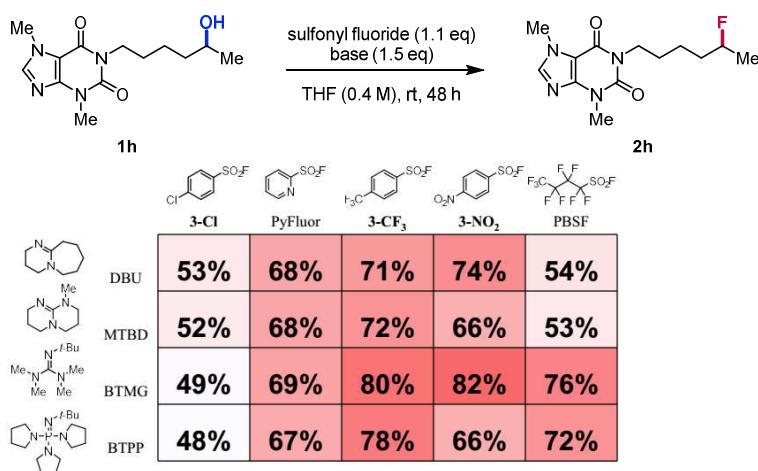
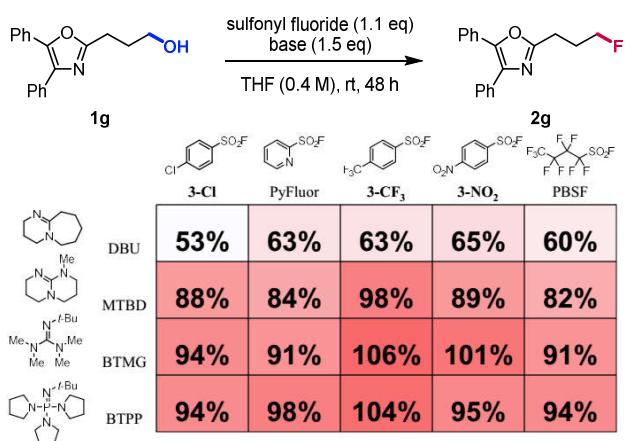
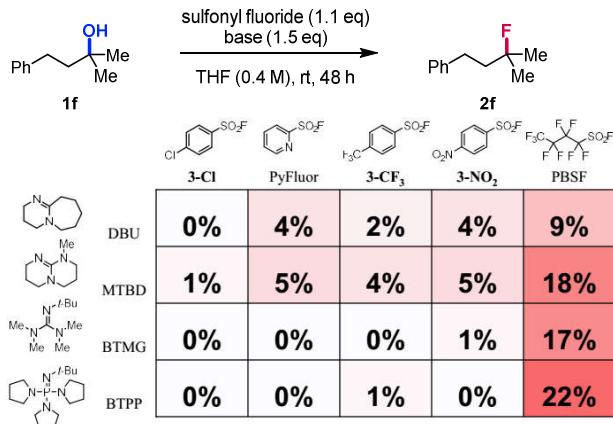
conditions, although this may arise from the reduction in base equivalents rather than solvent change. Again, THF was selected because it is generally a good solvent for this transformation, but it certainly is not the optimal solvent for all substrates.

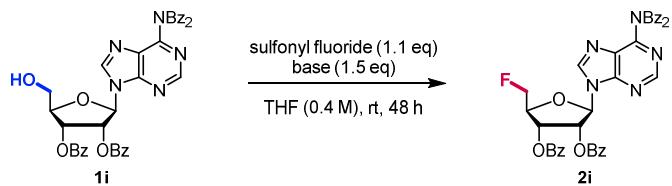
The random forest model described in Section VI was trained only on the screening reactions shown below, all of which were conducted in THF; however as shown in the table above, the reaction landscape may be complex with regards to solvent. We anticipate that expansion of our training set with new substrates and additional variables (*ie.* stoichiometry, concentration, solvent, and temperature) will lead to more accurate and comprehensive coverage of the sulfonyl fluoride deoxyfluorination reaction space.

<chem>CC(C)C(O)C1=CC=C(C=C1)C(F)F</chem> <b>1e</b>	sulfonyl fluoride (1.1 eq) base (1.5 eq) THF (0.4 M), rt, 48 h				
	<chem>Clc1ccc(S(=O)(=O)F)cc1</chem> 3-Cl	<chem>C#Cc1ccncc1S(=O)(=O)F</chem> PyFluor	<chem>C(F)(F)c1ccc(S(=O)(=O)F)cc1</chem> 3-CF <sub>3</sub>	<chem>O=[N+]([O-])c1ccc(S(=O)(=O)F)cc1</chem> 3-NO <sub>2</sub>	<chem>CC(F)(F)C(F)(F)C(F)(F)S(=O)(=O)F</chem> PBSF
DBU	<b>42%</b>	<b>48%</b>	<b>47%</b>	<b>52%</b>	<b>52%</b>
MTBD	<b>76%</b>	<b>78%</b>	<b>87%</b>	<b>82%</b>	<b>80%</b>
BTMG	<b>78%</b>	<b>79%</b>	<b>91%</b>	<b>87%</b>	<b>84%</b>
BTPP	<b>87%</b>	<b>88%</b>	<b>96%</b>	<b>83%</b>	<b>94%</b>

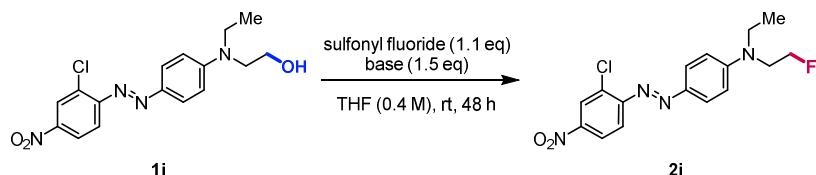
  

<chem>CC(C)COCC1=CC=C(C=C1)C(F)F</chem> <b>1a</b>	sulfonyl fluoride (1.1 eq) base (1.5 eq) THF (0.4 M), rt, 48 h				
	<chem>Clc1ccc(S(=O)(=O)F)cc1</chem> 3-Cl	<chem>C#Cc1ccncc1S(=O)(=O)F</chem> PyFluor	<chem>C(F)(F)c1ccc(S(=O)(=O)F)cc1</chem> 3-CF <sub>3</sub>	<chem>O=[N+]([O-])c1ccc(S(=O)(=O)F)cc1</chem> 3-NO <sub>2</sub>	<chem>CC(F)(F)C(F)(F)C(F)(F)S(=O)(=O)F</chem> PBSF
DBU	<b>40%</b>	<b>57%</b>	<b>52%</b>	<b>54%</b>	<b>39%</b>
MTBD	<b>54%</b>	<b>59%</b>	<b>69%</b>	<b>63%</b>	<b>60%</b>
BTMG	<b>41%</b>	<b>49%</b>	<b>57%</b>	<b>55%</b>	<b>61%</b>
BTPP	<b>42%</b>	<b>53%</b>	<b>60%</b>	<b>51%</b>	<b>65%</b>

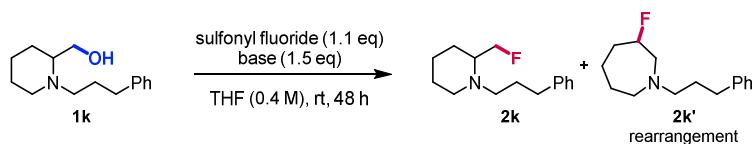




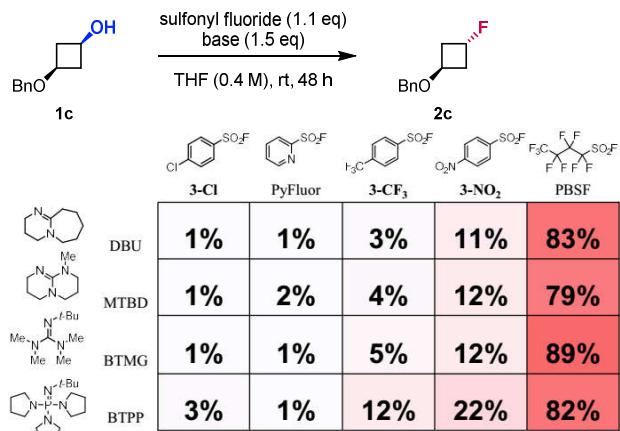
	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>6%</b>	<b>13%</b>	<b>14%</b>	<b>17%</b>	<b>29%</b>
MTBD	<b>17%</b>	<b>26%</b>	<b>30%</b>	<b>36%</b>	<b>38%</b>
BTMG	<b>21%</b>	<b>31%</b>	<b>34%</b>	<b>40%</b>	<b>49%</b>
BTPP	<b>32%</b>	<b>38%</b>	<b>45%</b>	<b>49%</b>	<b>47%</b>



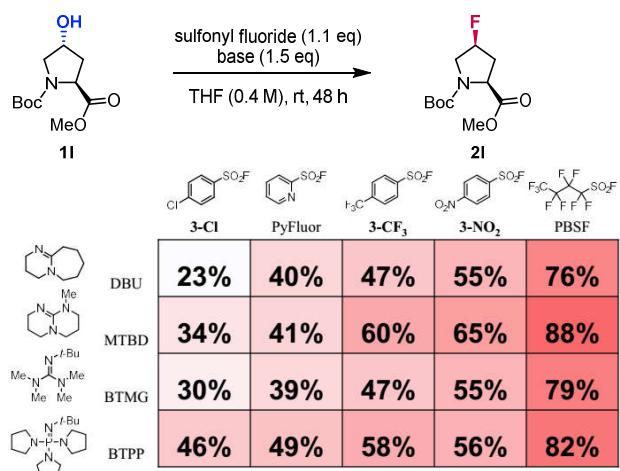
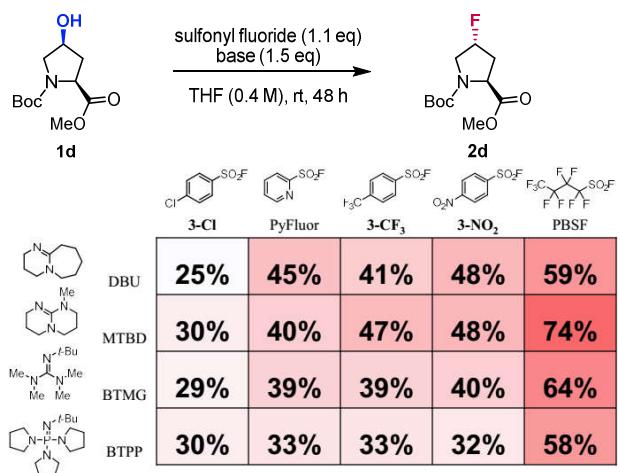
	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>43%</b>	<b>54%</b>	<b>54%</b>	<b>58%</b>	<b>52%</b>
MTBD	<b>72%</b>	<b>74%</b>	<b>80%</b>	<b>77%</b>	<b>65%</b>
BTMG	<b>73%</b>	<b>76%</b>	<b>80%</b>	<b>77%</b>	<b>56%</b>
BTPP	<b>66%</b>	<b>75%</b>	<b>67%</b>	<b>73%</b>	<b>46%</b>

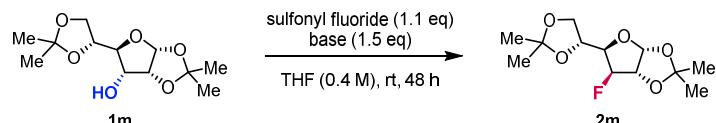


	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>6%</b> (16% rearr.)	<b>7%</b> (17% rearr.)	<b>8%</b> (21% rearr.)	<b>8%</b> (22% rearr.)	<b>10%</b> (31% rearr.)
MTBD	<b>21%</b> (46% rearr.)	<b>18%</b> (38% rearr.)	<b>22%</b> (47% rearr.)	<b>20%</b> (44% rearr.)	<b>23%</b> (49% rearr.)
BTMG	<b>26%</b> (53% rearr.)	<b>17%</b> (32% rearr.)	<b>28%</b> (56% rearr.)	<b>27%</b> (54% rearr.)	<b>30%</b> (57% rearr.)
BTPP	<b>27%</b> (50% rearr.)	<b>16%</b> (30% rearr.)	<b>31%</b> (54% rearr.)	<b>28%</b> (48% rearr.)	<b>36%</b> (58% rearr.)

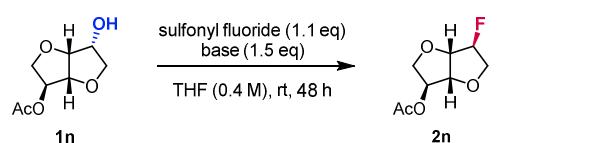


(\* Note: Starting material **1c** has a dr of 12:1.)

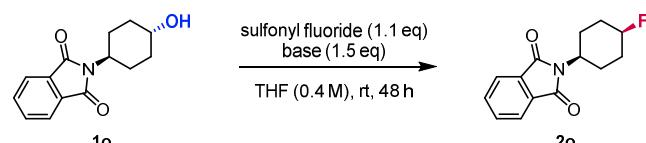




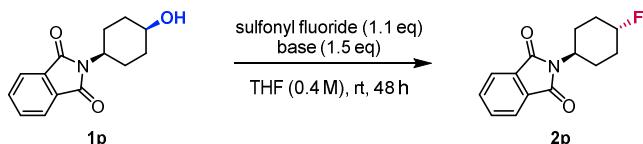
	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	0%	0%	0%	0%	65%
MTBD	0%	0%	0%	0%	80%
BTMG	0%	0%	0%	0%	70%
BTPP	0%	0%	0%	0%	70%



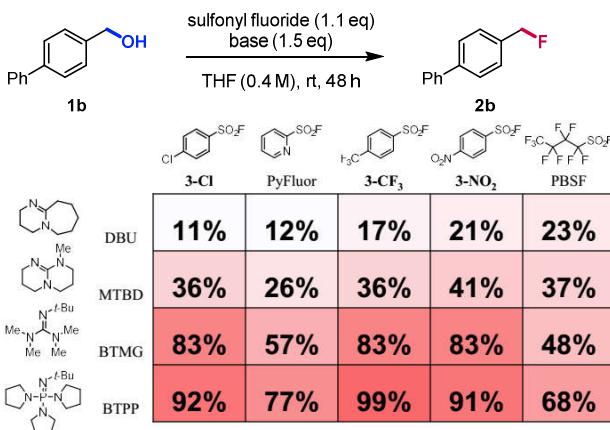
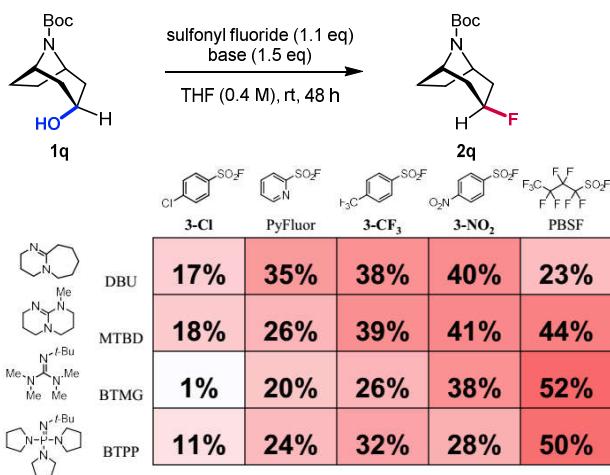
	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	0%	1%	3%	7%	91%
MTBD	2%	3%	7%	14%	105%
BTMG	2%	2%	6%	12%	97%
BTPP	8%	5%	23%	30%	106%

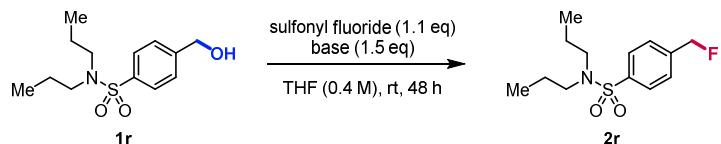


	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	1%	1%	5%	12%	40%
MTBD	2%	3%	6%	12%	48%
BTMG	2%	2%	5%	11%	50%
BTPP	2%	2%	9%	11%	45%

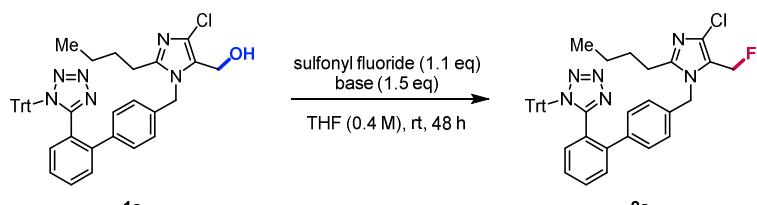


	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>4%</b>	<b>6%</b>	<b>7%</b>	<b>7%</b>	<b>8%</b>
MTBD	<b>5%</b>	<b>7%</b>	<b>9%</b>	<b>7%</b>	<b>11%</b>
BTMG	<b>1%</b>	<b>4%</b>	<b>6%</b>	<b>6%</b>	<b>12%</b>
BTPP	<b>2%</b>	<b>3%</b>	<b>6%</b>	<b>5%</b>	<b>13%</b>

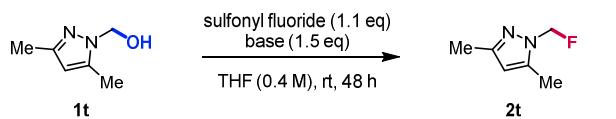




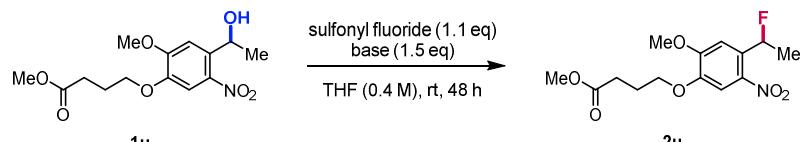
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DBU	<b>18%</b>	<b>17%</b>	<b>9%</b>	<b>28%</b>	<b>29%</b>
MTBD	<b>36%</b>	<b>41%</b>	<b>38%</b>	<b>42%</b>	<b>44%</b>
BTMG	<b>79%</b>	<b>74%</b>	<b>85%</b>	<b>84%</b>	<b>66%</b>
BTPP	<b>90%</b>	<b>85%</b>	<b>97%</b>	<b>89%</b>	<b>68%</b>



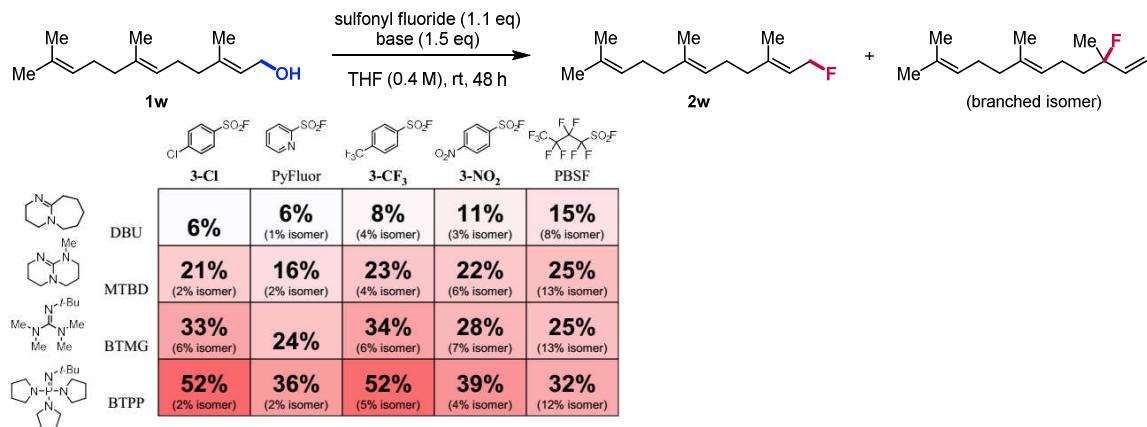
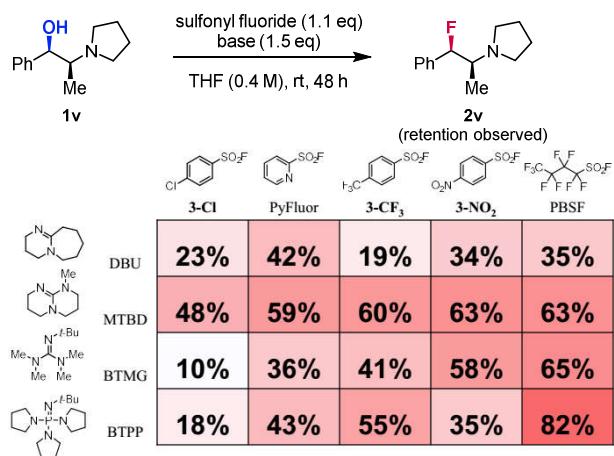
	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>33%</b>	<b>8%</b>	<b>36%</b>	<b>37%</b>	<b>33%</b>
MTBD	<b>38%</b>	<b>9%</b>	<b>38%</b>	<b>40%</b>	<b>39%</b>
BTMG	<b>45%</b>	<b>7%</b>	<b>44%</b>	<b>49%</b>	<b>39%</b>
BTPP	<b>47%</b>	<b>5%</b>	<b>44%</b>	<b>48%</b>	<b>47%</b>

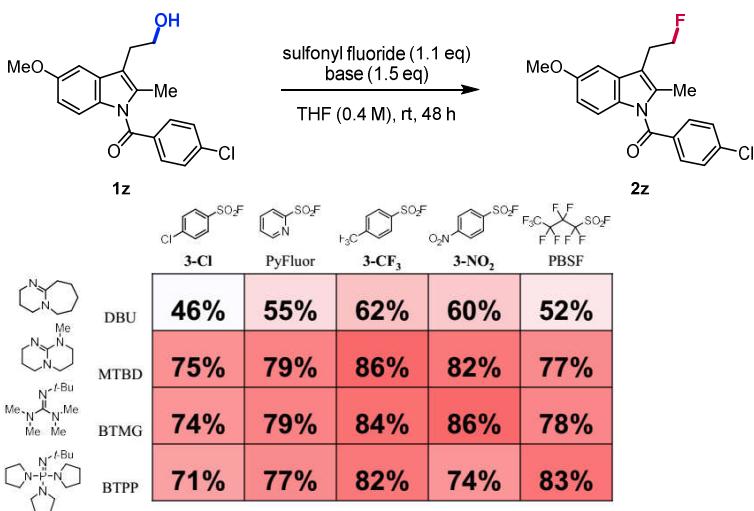
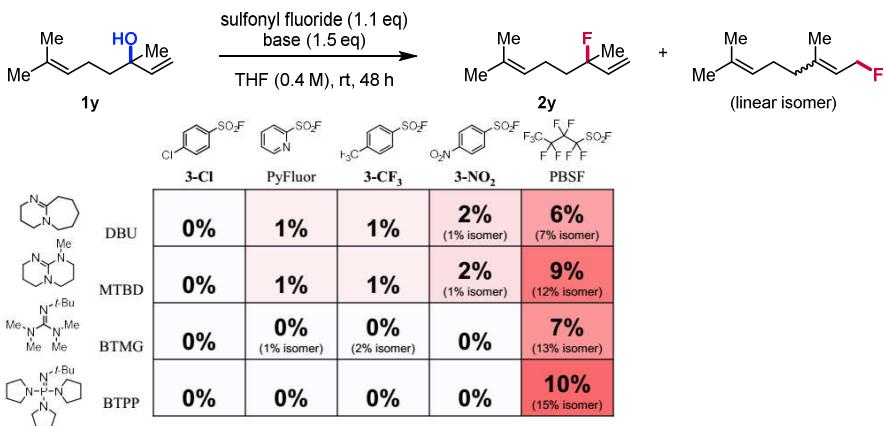
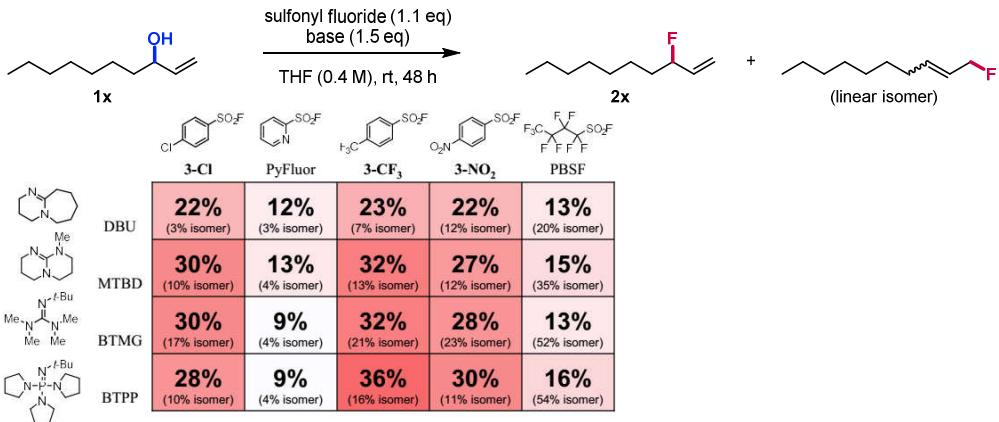


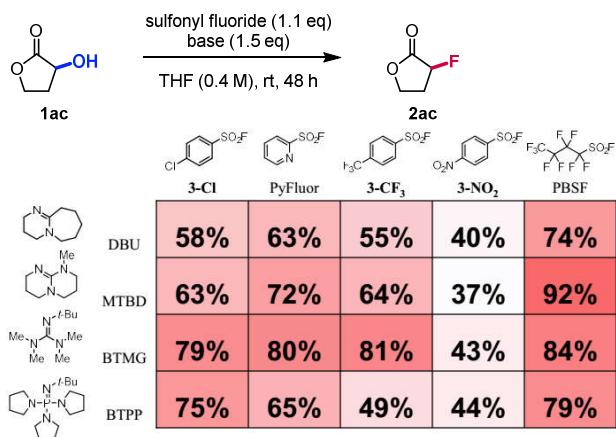
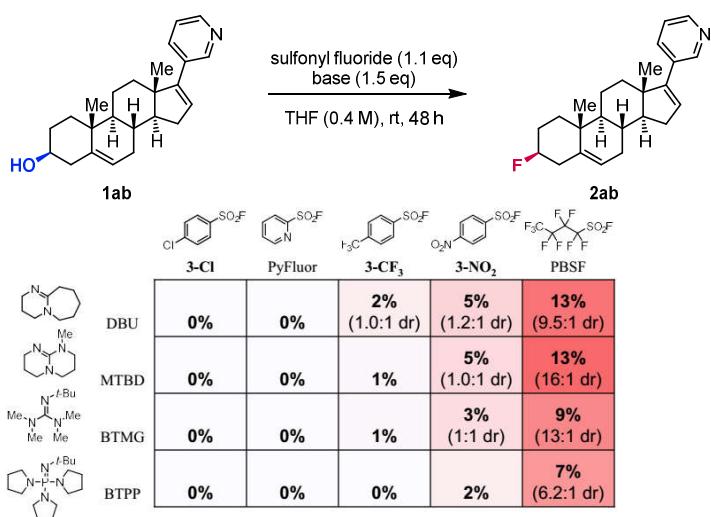
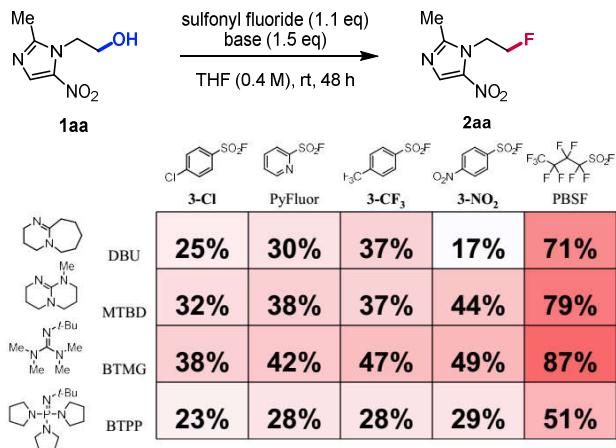
	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>38%</b>	<b>30%</b>	<b>43%</b>	<b>46%</b>	<b>47%</b>
MTBD	<b>59%</b>	<b>41%</b>	<b>58%</b>	<b>55%</b>	<b>55%</b>
BTMG	<b>62%</b>	<b>37%</b>	<b>59%</b>	<b>59%</b>	<b>52%</b>
BTPP	<b>66%</b>	<b>34%</b>	<b>65%</b>	<b>60%</b>	<b>57%</b>

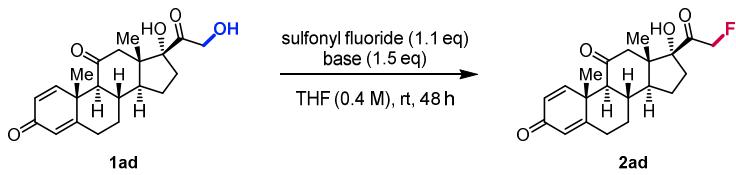


	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>28%</b>	<b>29%</b>	<b>40%</b>	<b>38%</b>	<b>25%</b>
MTBD	<b>38%</b>	<b>34%</b>	<b>47%</b>	<b>46%</b>	<b>18%</b>
BTMG	<b>49%</b>	<b>31%</b>	<b>57%</b>	<b>52%</b>	<b>18%</b>
BTPP	<b>41%</b>	<b>24%</b>	<b>52%</b>	<b>42%</b>	<b>9%</b>

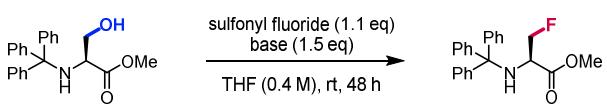




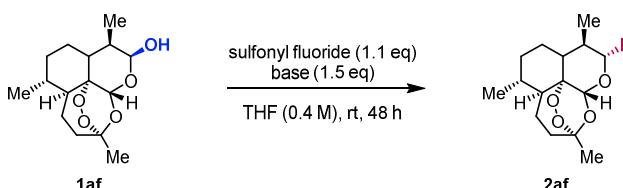




	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>32%</b>	<b>49%</b>	<b>40%</b>	<b>36%</b>	<b>31%</b>
MTBD	<b>43%</b>	<b>53%</b>	<b>42%</b>	<b>12%</b>	<b>31%</b>
BTMG	<b>41%</b>	<b>51%</b>	<b>53%</b>	<b>14%</b>	<b>42%</b>
BTPP	<b>35%</b>	<b>44%</b>	<b>54%</b>	<b>11%</b>	<b>43%</b>



	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>2%</b>	<b>3%</b>	<b>3%</b>	<b>3%</b>	<b>3%</b>
MTBD	<b>5%</b>	<b>8%</b>	<b>8%</b>	<b>9%</b>	<b>9%</b>
BTMG	<b>5%</b>	<b>5%</b>	<b>7%</b>	<b>10%</b>	<b>9%</b>
BTPP	<b>7%</b>	<b>5%</b>	<b>9%</b>	<b>11%</b>	<b>28%</b>

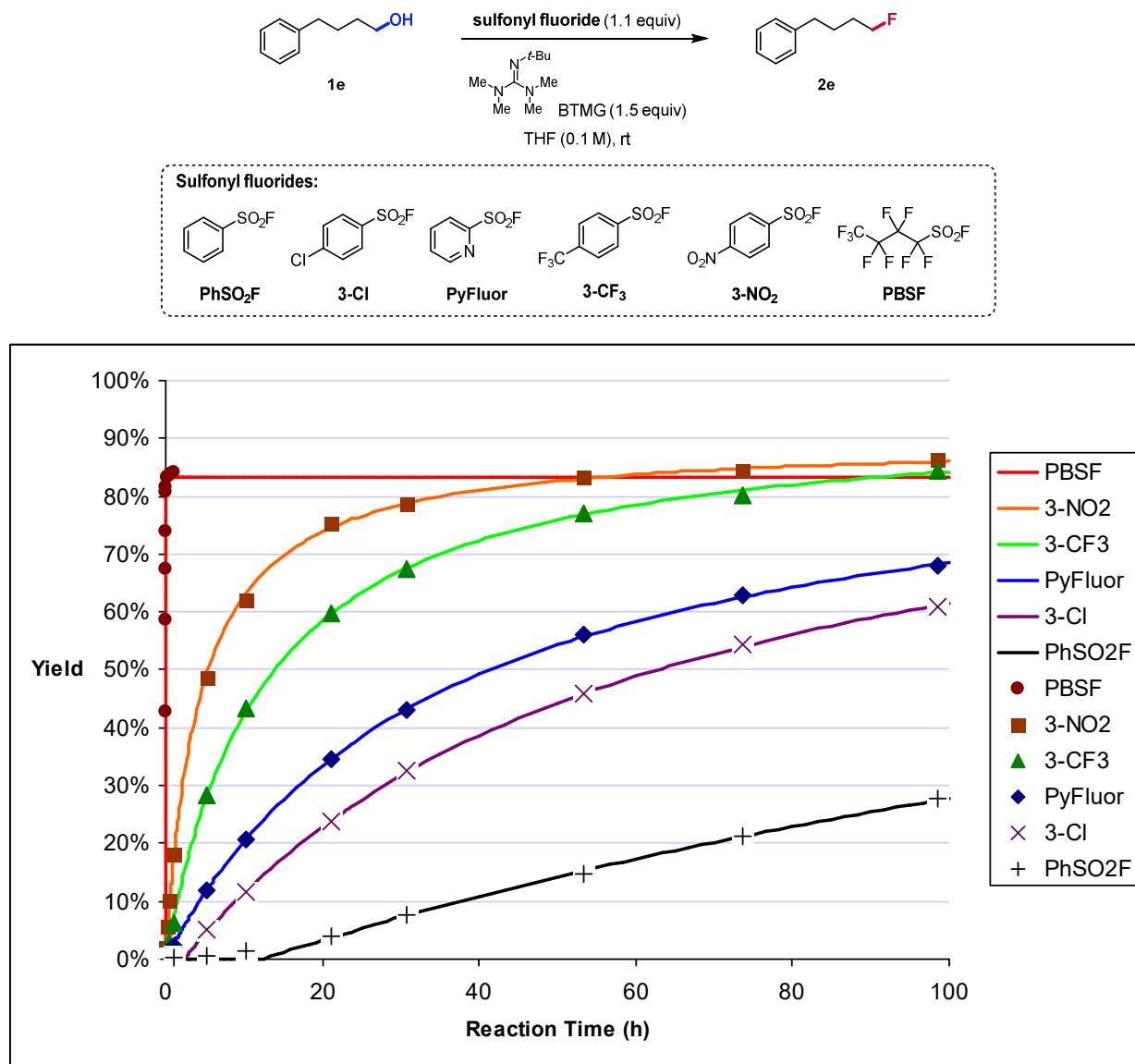


	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	<b>10%</b> *(1.3:1)	<b>38%</b> (0.4:1)	<b>32%</b> (2.0:1)	<b>41%</b> (2.2:1)	<b>33%</b> (0.9:1)
MTBD	<b>23%</b> (1.9:1)	<b>43%</b> (1.0:1)	<b>43%</b> (2.5:1)	<b>50%</b> (2.8:1)	<b>32%</b> (1.0:1)
BTMG	<b>15%</b> (2.2:1)	<b>39%</b> (2.2:1)	<b>41%</b> (3.0:1)	<b>52%</b> (3.1:1)	<b>38%</b> (1.3:1)
BTPP	<b>14%</b> (2.7:1)	<b>23%</b> (3.7:1)	<b>36%</b> (3.6:1)	<b>44%</b> (3.8:1)	<b>45%</b> (0.6:1)

\*(alpha : beta)

### III. Sulfonyl Fluoride Kinetics

To determine the relative reactivity of the sulfonyl fluorides employed in this study, the kinetic profile of the deoxyfluorination of 4-phenyl-1-butanol (**1e**) was measured with benzenesulfonyl fluoride (PhSO<sub>2</sub>F), **3-Cl**, PyFluor, **3-CF<sub>3</sub>**, **3-NO<sub>2</sub>**, and PBSF. The unactivated primary alcohol **1e** was selected to avoid mechanistic ambiguity—to the best of our knowledge, all sulfonate esters of **1e** react through an S<sub>N</sub>2 mechanism at room temperature. BTMG was selected over BTPP because the latter has a tendency to coagulate and precipitate solids when exposed to air. The reaction was diluted to 0.1 M so that accurate timepoints for PBSF could be obtained.



**Figure S1.** Sulfonyl fluoride reaction kinetics: Product yield as a function of reaction time. Experimental timepoints are overlaid with least-squares fit second order reaction profiles.

**Procedure:** For each sulfonyl fluoride, a separate reaction was assembled as follows: A 1-dram vial with Teflon-taped threads and a phenolic cap was charged with a stirbar, 1.1 equiv of the designated sulfonyl fluoride, a solution containing 4-phenyl-1-butanol substrate (60 mg, 0.4

mmol, Millipore-Sigma) in 4 mL THF (0.1 M), and finally BTMG (120  $\mu$ L, 1.5 equiv). Timepoints were taken by removing 25  $\mu$ L aliquots, diluting in ethyl acetate, and analyzing by gas chromatography (Agilent HP-5 column; Method: 300 °C injection, 80 °C [0 – 1 min], 80 – 120 °C [1 – 5 min]; retention time: (4-fluorobutyl)benzene (product): 4.05 min.) Time point data is tabulated below.

**Table S3.** Timepoint GC yield data for reaction of 4-phenyl-1-butanol with various sulfonyl fluorides.

time (minutes)	PBSF	PyFluor	<b>3-NO<sub>2</sub></b>	<b>3-CF<sub>3</sub></b>	<b>3-Cl</b>	PhSO <sub>2</sub> F
0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
5 seconds	42.9%					
15 seconds	58.5%					
30 seconds	67.5%					
1	74.0%					
2	80.8%					
4	81.6%					
6		0.4%	2.1%	0.6%	0.2%	0.1%
8	83.3%					
16	83.4%					
18		0.7%	5.6%	1.4%	0.3%	0.1%
30		1.4%	10.3%	2.9%	0.4%	0.1%
32	83.7%					
60		2.3%	18.0%	6.2%	0.6%	0.2%
64	84.0%					
312		12.0%	48.8%	28.2%	5.0%	0.6%
624		20.8%	62.0%	43.4%	11.6%	1.4%
1266		34.6%	75.3%	59.9%	23.8%	4.0%
1848		43.0%	78.7%	67.5%	32.4%	7.6%
3198		56.0%	83.3%	77.1%	45.9%	14.7%
4422		62.8%	84.4%	80.3%	54.4%	21.2%
5910		67.9%	86.4%	84.5%	60.9%	27.9%

**Fitting to 2<sup>nd</sup> order kinetics:** To estimate relative rates, each reaction was fit to a 2<sup>nd</sup> order reaction profile (on the premise that sulfonate ester formation occurs rapidly and results in a 1:1 mixture of fluoride nucleophile and sulfonate ester electrophile that react in a bimolecular rate determining step.) Functions approximating the reaction profile were generated by performing a non-linear least squares regression using Microsoft Excel Solver to the function shown below:

$$f(t) = A - \left( \frac{A}{[Akt + 1]} \right)$$

Where  $A$  is the maximum yield of the specified reaction (as a fraction of one),  $k$  is the second order rate constant (in yield<sup>-1</sup> · min<sup>-1</sup>), and  $t$  is the reaction time elapsed in minutes. In the reaction profiles for **3-Cl** and PhSF, the sigmoidal shape of the data points indicates that sulfonate ester formation is slow. To correct for this, an induction period ( $\phi$ ) was introduced and the profile was fit to the piecewise function shown below.

$$f(t) = \begin{cases} 0 & , \quad x \leq \phi \\ A - \left( \frac{A}{[Ak(t-\phi) + 1]} \right) & , \quad x > \phi \end{cases}$$

The variable values determined for each sulfonyl fluoride and  $R^2$  values are listed below:

**PBSF:**  $A = 0.833$   
 $k = 12.9 \text{ min}^{-1}$   
 $R^2 = 0.995$

**3-NO<sub>2</sub>:**  $A = 0.897$   
 $k = 0.00435 \text{ min}^{-1}$   
 $R^2 = 0.997$

**3-CF<sub>3</sub>:**  $A = 0.947$   
 $k = 0.00143 \text{ min}^{-1}$   
 $R^2 = 1.000$

**PyFluor:**  $A = 0.926$   
 $k = 0.000509 \text{ min}^{-1}$   
 $R^2 = 1.000$

**3-Cl:**  $A = .980$   
 $k = 0.000293 \text{ min}^{-1}$   
 $\phi = 137 \text{ min}$   
 $R^2 = 1.000$

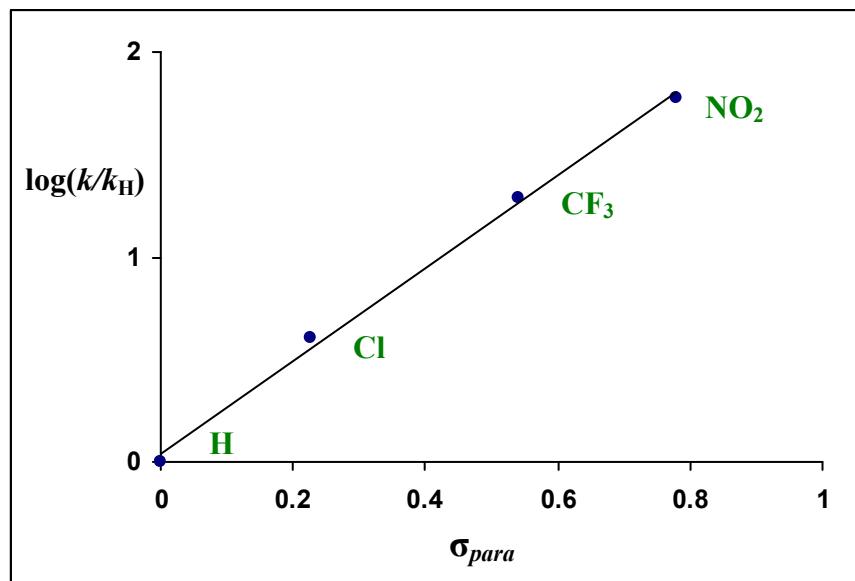
**PhSO<sub>2</sub>F:**  $A = 1.00$  (during regression, yield was constrained to  $\leq 100\%$ )  
 $k = 0.0000732 \text{ min}^{-1}$   
 $\phi = 733 \text{ min}$   
 $R^2 = 0.997$

Based on the 2<sup>nd</sup> order rate constants obtained from the regression, the relative reaction rates (compared to benzenesulfonyl fluoride, PhSO<sub>2</sub>F) of the various sulfonyl fluorides are shown below. Additionally, the  $t_{1/2}$  value (time at which reaction hits ½ of maximum yield  $A$ ) is listed. Since these reactions were diluted to 0.1 M concentration, these  $t_{1/2}$  values are a good estimate of the total reaction time under standard conditions at 0.4 M concentration.

	PhSO <sub>2</sub> F	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
<i>k<sub>rel</sub></i>	1	4.0	7.0	20	59	180,000
<i>t<sub>1/2</sub></i>	9.5 d	58 h	35 h	12 h	4.3 h	5.6 sec

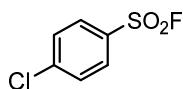
**Figure S2.** Relative reaction rates ( $k_{rel}$ ) and reaction half-lives ( $t_{1/2}$ ) based on the regression second order kinetic profile.

**Hammett Plot:** Based on the rate constants determined in the preceding section, a Hammett plot was generated by plotting the values of  $\log(k/k_H)$  against  $\sigma_{para}$  for PhSO<sub>2</sub>F, 3-Cl, 3-CF<sub>3</sub>, and 3-NO<sub>2</sub>. Linear regression affords a line described by the formula:  $y = 2.27x + 0.04$ . The  $\rho$  value of +2.27 indicates that this substitution is accelerated by increasingly electron-deficient substituents and is more sensitive to substituent effects than the ionization of substituted benzoic acids. For reference, the reactivity of PyFluor corresponds to a  $\sigma_{para}$  value of 0.35 (intermediate between chloro- and CF<sub>3</sub>- substituents) and the reactivity of PBSF corresponds to a  $\sigma_{para}$  value of 2.3 (more reactive than a *para*-substituted aryl diazonium salt.)



**Figure S3.** Hammett plot generated from the measured 2<sup>nd</sup> order rate constants.

## IV. Reagent and Substrate Synthesis

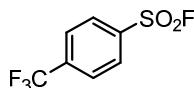


**4-chlorobenzenesulfonyl fluoride (3-Cl):** A 1000-mL round bottom flask was charged with a stirbar, 4-chlorobenzenesulfonyl chloride (5.00 g, 23.7 mmol, Acros), potassium bifluoride (9.25 g, 5 equiv, Millipore-Sigma), and 50 mL of 3:1 water:acetonitrile. The resulting suspension was stirred vigorously for five hours at room temperature. *Note: This reaction contains toxic hydrofluoric acid and will slowly etch glassware.* The mixture was diluted with 50 mL brine and extracted once with 100 mL ethyl acetate. The organic extract was directly filtered through 30 g of silica on a fritted filter, rinsing with an additional 50 mL ethyl acetate. The filtrate was concentrated to afford 4.38 g 4-chlorobenzenesulfonyl fluoride as a fluffy white solid (95% yield). Compound has been previously characterized.<sup>2</sup>

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.96 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 142.80, 131.53 (d, *J* = 25.7 Hz), 130.25, 130.00.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ 66.48 (s).

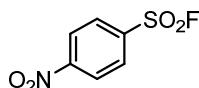


**4-(trifluoromethyl)benzenesulfonyl fluoride (3-CF<sub>3</sub>):** A 1000-mL round bottom flask was charged with a stirbar, 4-(trifluoromethyl)benzenesulfonyl chloride (9.60 g, 39.2 mmol, Oakwood), potassium bifluoride (15.33 g, 5 equiv, Millipore-Sigma), and 80 mL of 3:1 water:acetonitrile. The resulting suspension was stirred vigorously for one hour at room temperature. *Note: This reaction contains toxic hydrofluoric acid and will slowly etch glassware.* At one hour, the mixture was diluted with 50 mL brine and extracted once with 100 mL ethyl acetate. The organic extract was directly filtered through 30 g of silica on a fritted filter, rinsing with an additional 100 mL ethyl acetate. The filtrate was concentrated to afford 8.47 g 4-(trifluoromethyl) benzenesulfonyl fluoride as a fluffy white solid (95% yield). Compound has been previously characterized.<sup>2</sup>

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 8.17 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 137.33 (q, *J* = 33.5 Hz), 136.65 (d, *J* = 27.2 Hz), 129.26, 127.04 (q, *J* = 3.7 Hz), 122.87 (q, *J* = 273.5 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ 65.88 (s, 1F), -63.53 (s, 3F).



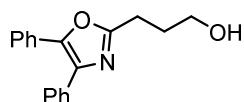
**4-nitrobenzenesulfonyl fluoride (3-NO<sub>2</sub>):** A 1000-mL round bottom flask was charged with a stirbar, 4-nitrobenzenesulfonyl chloride (5.00 g, 22.6 mmol, Oakwood), potassium bifluoride (8.81 g, 5 equiv, Millipore-Sigma), and 50 mL of 3:1 water:acetonitrile. The resulting suspension was stirred vigorously for one hour at room temperature. *Note: This reaction contains toxic hydrofluoric acid and will slowly etch glassware.*

*hydrofluoric acid and will slowly etch glassware.* At one hour, the mixture was diluted with 50 mL brine and extracted once with 100 mL ethyl acetate. The organic extract was directly filtered through 30 g of silica on a fritted filter, rinsing with an additional 50 mL ethyl acetate. The filtrate was concentrated to afford 4.20 g 4-nitrobenzenesulfonyl fluoride as a light brown solid (91% yield). Compound has been previously characterized.<sup>2</sup>

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 8.49 (d, *J* = 8.5 Hz, 2H), 8.25 (d, *J* = 8.9 Hz, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 151.92, 138.48 (d, *J* = 27.0 Hz), 130.15, 125.02.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ 66.21 (s).



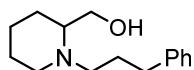
**3-(4,5-diphenyloxazol-2-yl)propan-1-ol (1g):** A flame-dried 500 mL round bottom flask with a stirbar was charged with lithium aluminum hydride (1.3 g, 5 equiv) and 30 mL dry diethyl ether. The vessel was then cooled to -78 °C under nitrogen. Oxaprozin methyl ester<sup>3</sup> (methyl 3-(4,5-diphenyloxazol-2-yl)propanoate, 2.1 g, 6.8 mmol) was dissolved in 20 mL dry diethyl ether and added dropwise to the reaction mixture over 10 minutes. The vessel was allowed to warm to room temperature over the course of 2 hours, after which the reaction was cooled to 0 °C and quenched by the slow, sequential addition of ethanol, methanol, and saturated ammonium chloride. The mixture was diluted with 100 mL water and extracted with 2 × 50 mL ethyl acetate. Organic extracts were dried with sodium sulfate, concentrated, and purified by automated column chromatography (50 g silica, 10 → 35% ethyl acetate in hexanes) to afford 1.65 g product as a fluffy white solid (87% yield).

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.66 – 7.61 (m, 2H), 7.60 – 7.55 (m, 2H), 7.39 – 7.29 (m, 6H), 3.79 (t, *J* = 5.9 Hz, 2H), 3.45 (s, 1H), 2.98 (t, *J* = 7.1 Hz, 2H), 2.10 (p, *J* = 6.8 Hz, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 163.64, 145.39, 134.86, 132.35, 128.99, 128.74, 128.67, 128.56, 128.20, 127.96, 126.53, 61.92, 29.60, 25.39.

**IR (ATR, cm<sup>-1</sup>):** 3329 (br, s), 3058 (w), 3034 (w), 2931 (w), 2871 (w), 2820 (w), 1606 (w), 1579 (w), 1569 (m), 1501 (w), 1443 (m), 1370 (2), 1323 (m), 1254 (w), 1220 (m), 1061 (s), 1024 (m), 989 (w), 964 (m), 921 (m), 757 (s), 722 (w), 693 (s), 674 (m).

**HRMS (ESI+):** Calculated for C<sub>18</sub>H<sub>18</sub>NO<sub>2</sub><sup>+</sup> [M + H]<sup>+</sup> : 280.1332; found: 280.1337.



**(±)-(1-(3-phenylpropyl)piperidin-2-yl)methanol (1k):** A flame-dried 100 mL round bottom flask with a stirbar and condenser was charged with (3-bromopropyl)benzene (1.70 g, 8.5 mmol, Millipore-Sigma), dry acetonitrile (35 mL), 2-piperidinemethanol (1.23 g, 1.25 equiv, Millipore-Sigma), and potassium carbonate (2.36 g, 5 equiv, Fisher). The mixture was heated to reflux for 4 hours and then filtered on a fritted funnel. The filtrate was concentrated and purified by automated column chromatography (50 g triethylamine-pretreated silica, 0 → 15% methanol in

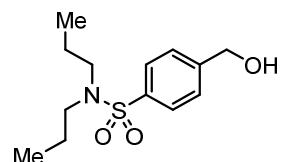
dichloromethane) to afford 1.41 g product as a light orange oil (71% yield). By NMR, the sample was found to contain 3 wt. % triethylamine.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.30 – 7.24 (m, 2H), 7.21 – 7.14 (m, 3H), 3.70 (dd, *J* = 10.7, 4.3 Hz, 1H), 3.44 (dd, *J* = 10.7, 4.2 Hz, 1H), 2.98 (dddd, *J* = 12.2, 5.1, 3.6, 1.1 Hz, 1H), 2.78 (dt, *J* = 12.9, 7.8 Hz, 2H), 2.69 – 2.53 (m, 2H), 2.44 (dt, *J* = 12.9, 7.1 Hz, 1H), 2.38 (dq, *J* = 8.2, 4.1 Hz, 1H), 2.25 (ddd, *J* = 12.4, 9.8, 3.0 Hz, 1H), 1.81 (p, *J* = 7.7 Hz, 2H), 1.72 – 1.48 (m, 4H), 1.47 – 1.26 (m, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 142.22, 128.47, 128.43, 125.92, 62.19, 60.53, 52.79, 50.68, 33.78, 28.43, 27.25, 24.28, 23.45.

**IR (film, cm<sup>-1</sup>):** 3357 (br, m), 3026 (w), 2930 (m), 2856 (w), 1655 (w), 1603 (w), 1496 (w), 1453 (m), 1376 (w), 1274 (w), 1033 (m), 992 (w), 909 (w), 839 (w), 746 (m), 697 (s).

**HRMS (ESI+):** Calculated for C<sub>15</sub>H<sub>24</sub>NO<sup>+</sup> [M + H]<sup>+</sup>: 234.1852; found: 234.1850.



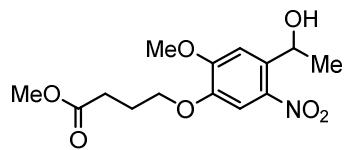
**4-(hydroxymethyl)-N,N-dipropylbenzenesulfonamide (1r):** To a solution of probenecid (2.85 g, 10 mmol, Alfa Aesar) in methanol (30 mL) was added trimethylsilyl chloride (2.56 mL, 2 equiv, Millipore-Sigma). The reaction was stirred at room temperature for 14 hours and then filtered through a 20 g silica plug with 50% ethyl acetate in hexanes. The filtrate was concentrated to afford crude methyl 4-(*N,N*-dipropylsulfamoyl)benzoate<sup>4</sup> as a colorless oil. Separately, a flame-dried 500 mL round bottom flask was charged with a stirbar and lithium aluminum hydride (1.585 g, 4.2 equiv, Millipore-Sigma), and 30 mL dry diethyl ether and cooled to -78 °C. The crude methyl ester was dissolved in 20 mL dry diethyl ether and added dropwise to the lithium aluminum hydride suspension while stirring rapidly. The reaction mixture was allowed to warm to room temperature over an hour and was then quenched at 0 °C by the slow sequential addition of ethanol, methanol and then water. The reaction was diluted with 50 mL water and extracted twice with 50 mL ethyl acetate. The extracts were dried with sodium sulfate, concentrated, and purified by automated column chromatography (50 g silica, 10 → 50% ethyl acetate in hexanes) to afford 1.87 g product as a white crystalline solid (82% yield).

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 4.69 (d, *J* = 3.7 Hz, 2H), 3.07 (s, 1H), 3.03 – 2.96 (m, 4H), 1.49 (dq, *J* = 14.9, 7.4 Hz, 4H), 0.82 (t, *J* = 7.4 Hz, 6H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 146.01, 138.48, 127.05, 126.94, 63.97, 50.07, 22.02, 11.20.

**IR (ATR, cm<sup>-1</sup>):** 3495 (s), 2966 (m), 2934 (w), 2875 (w), 1599 (w), 1467 (w), 1479 (m), 1321 (s), 1306 (w), 1190 (w), 1181 (m), 1146 (s), 1087 (s), 1052 (s), 1013 (w), 990 (s), 955 (w), 895 (w), 867 (m), 820 (m), 770 (s), 737 (s), 670 (s).

**HRMS (ESI+):** Calculated for C<sub>13</sub>H<sub>22</sub>NO<sub>3</sub>S<sup>+</sup> [M + Na]<sup>+</sup>: 272.1315; found: 272.1310.



**(±)-methyl 4-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoate (1u):** Trimethylsilyl chloride (1.7 mL, 2 equiv, Millipore-Sigma) was added to a solution of hydroxyethyl photolinker (4-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)butyric acid, 2.0 g, 6.7 mmol, Novabiochem) in dry methanol (20 mL). The reaction was stirred at room temperature for 16 hours. The mixture was then filtered through a 10 g silica plug rinsing with 1:1 ethyl acetate:hexanes, after which the filtrate was concentrated and purified by automated column chromatography (100 g silica, 10 → 50% ethyl acetate in hexanes) affording 2.03 g product as a yellow powder (97% yield).

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.56 (s, 1H), 7.29 (s, 1H), 5.55 (dt, *J* = 9.6, 5.1 Hz, 1H), 4.10 (td, *J* = 6.3, 2.1 Hz, 2H), 3.97 (s, 3H), 3.69 (s, 3H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.35 (d, *J* = 3.6 Hz, 1H), 2.18 (p, *J* = 6.8 Hz, 2H), 1.54 (d, *J* = 6.3 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 173.49, 154.24, 147.03, 139.66, 137.04, 109.18, 108.80, 68.34, 65.91, 56.47, 51.88, 30.50, 24.40, 24.38.

**IR (ATR, cm<sup>-1</sup>):** 3257 (br, m), 3004 (w), 2975 (w), 2953 (w), 2884 (w), 1725 (s), 1613 (w), 1578 (m), 1508 (s), 1466 (m), 1442 (w), 1408 (w), 1381 (m), 1322 (m), 1267 (s), 1217 (w), 1201 (s), 1172 (s), 1101 (s), 1055 (m), (1033 (w), 1016 (m), 995 (w), 975 (w), 933 (w), 899 (w), 868 (w), 852 (w), 815 (m), 758 (m), 660 (w).

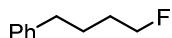
**HRMS (ESI+):** Calculated for C<sub>14</sub>H<sub>19</sub>NNaO<sub>7</sub><sup>+</sup> [M + Na]<sup>+</sup> : 336.1054; found: 336.1048.

## V. Isolation of Fluorinated Products

**General procedure:** A 2-dram vial with a stirbar is sequentially charged with the alcohol substrate (1 mmol), the specified sulfonyl fluoride (1.1 equiv), and dry THF (2 mL, 0.5 M). The contents are briefly stirred (~10 s) to dissolve or suspend substrate, followed by addition of the specified base (1.1 – 1.5 equiv).\* The reaction vessel is sealed by wrapping the vial threads with Teflon tape (prior to substrate addition) and affixing a phenolic cap. The reaction mixture is stirred at room temperature at 600 rpm for the designated reaction time (30 min – 48 hours). Purification is typically performed by concentrating the reaction mixture, loading onto a silica column with minimal dichloromethane, and purifying by automated silica column chromatography. All manipulations are performed on the benchtop. Aside from using dry solvent, no additional measures are taken to exclude air or moisture. Timepoint studies were conducted for selected substrates using the same procedure as outlined in Section III. The reaction orders and corresponding first- or second-order half-lives are reported in these cases (here half-lives are measured as the time to 50% of maximum yield).

\*Note on order of addition: The base is always added last. In cases where the substrate alcohol is a liquid, the reaction solvent is added prior to the sulfonyl fluoride addition. PBSF and PyFluor are added as a solution in the reaction solvent.

Note on condition selection: In the screening data in Section II, there were a handful of substrates for which multiple sets of conditions resulted in the highest yield when rounded to the nearest whole number. In these cases, we selected the set of conditions that gave the highest decimal yield from NMR integration (ie. 80.3% vs. 79.9%), although these differences are not statistically different based on the experimental error reported in Section II. In choosing a single set of conditions for isolation, our goal was to demonstrate comparatively high-yielding conditions across multiple substrate classes and to identify underlying reactivity trends. We do not claim to have identified the absolute highest yielding conditions for any substrate. Since the random forest model was trained on all screening results, our selection of isolation conditions did not bias the model output.



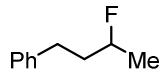
**(4-fluorobutyl)benzene (2e):** Following the general procedure, a 2-dram vial with a stirbar was sequentially charged with 4-phenyl-1-butanol (150.2 mg, 1 mmol, Combi-Blocks), THF (2 mL, 0.5 M), 3-CF<sub>3</sub> (251 mg, 1.1 equiv), and BTPP (460 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 24 hours, concentrated, taken up in hexanes, and purified by automated column chromatography (25 g silica, 0 → 5% ethyl acetate in hexanes). Product-containing fractions were concentrated by rotary evaporation at room temperature to afford 135.2 mg product as a colorless oil (89% yield). Product has been previously characterized.<sup>5</sup> At 0.4 M concentration, the reaction displays second order kinetics with a half-life of 1.9 hours ( $t_{98\% \text{ conversion}} = 46 \text{ h}$ ). Raw kinetic data: 0% yield at  $t = 0 \text{ min}$ ; 46% yield at  $t = 50 \text{ min}$ ; 83% yield at  $t = 254 \text{ min}$ ; 95% yield at  $t = 1488 \text{ min}$ . Best fit:

$$f(t) = A - \left( \frac{A}{[Ak t + 1]} \right) | f(t) = \text{yield (in decimal)}, A = 0.996, k = 0.0178 \text{ min}^{-1}$$

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.35 – 7.28 (m, 2H), 7.25 – 7.18 (m, 3H), 4.57 – 4.50 (m, 1H), 4.44 (t,  $J = 5.8 \text{ Hz}$ , 1H), 2.69 (t,  $J = 7.3 \text{ Hz}$ , 2H), 1.83 – 1.69 (m, 4H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 142.11, 128.53, 128.47, 125.97, 84.10 (d, *J* = 164.4 Hz), 35.54, 30.08 (d, *J* = 19.6 Hz), 27.12 (d, *J* = 5.1 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -218.31 (tt, *J* = 47.3, 25.2 Hz).

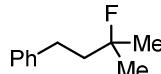


**(±)-(3-fluorobutyl)benzene (2a):** A 1-dram vial with a stirbar was sequentially charged with 4-phenyl-2-butanol (150.2 mg, 1 mmol, Millipore-Sigma), a solution of PyFluor (177 mg, 1.1 equiv, Millipore-Sigma) in toluene (1 mL, 1.0 M), and DBU (300 μL, 2 equiv). The reaction was stirred at 600 rpm at room temperature for 48 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (50 g silica, 0 → 10% ethyl acetate in hexanes). Fractions containing product were concentrated by rotary evaporation at room temperature to afford 120.7 mg product as a colorless oil (79% yield). Product has been previously characterized.<sup>6</sup>

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.20 (m, 3H), 4.67 (dm, *J* = 48.8 Hz, 1H), 2.83 (ddd, *J* = 14.8, 9.9, 5.3 Hz, 1H), 2.72 (ddd, *J* = 13.9, 9.6, 6.9 Hz, 1H), 2.07 – 1.95 (m, 1H), 1.85 (ddddd, *J* = 30.8, 13.9, 10.4, 6.9, 3.9 Hz, 1H), 1.37 (dd, *J* = 23.9, 6.2 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 141.63, 128.58, 128.57, 126.09, 90.20 (d, *J* = 164.9 Hz), 38.81 (d, *J* = 20.8 Hz), 31.52 (d, *J* = 4.8 Hz), 21.16 (d, *J* = 22.7 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -174.26 (ddqd, *J* = 48.0, 30.4, 23.9, 15.6 Hz).



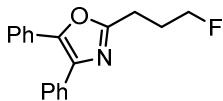
**(3-fluoro-3-methylbutyl)benzene (2f):** A 2-dram vial with a stirbar was sequentially charged with 2-methyl-4-phenyl-2-butanol (164.2 mg, 1 mmol, TCI), a solution of PBSF (332 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and BTTP (460 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 12 hours, concentrated, taken up in minimal hexanes, and purified by automated column chromatography (25 g silica, 0 → 9% ethyl acetate in hexanes) to afford 29.1 mg product as a colorless oil (18% yield). This product has been previously characterized.<sup>7</sup> At 0.4 M concentration, the reaction displays first order kinetics with a half-life of 1.5 hours, indicative of an S<sub>N</sub>1 mechanism (*t*<sub>98%</sub> conversion = 10 h). Raw kinetic data: 0% yield at *t* = 0 min; 5.3% yield at *t* = 50 min; 18.7% yield at *t* = 220 min; 21.1% yield at *t* = 540 min; 20.9 % yield at *t* = 1107 min. Best fit:

$$f(t) = A - Ae^{-kt} \quad |f(t) = \text{yield (in decimal)}, A = 0.214, k = 0.00763 \text{ min}^{-1}.$$

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.29 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.23 – 7.17 (m, 3H), 2.75 – 2.70 (m, 2H), 1.93 (dm, *J* = 19.5 Hz, 2H), 1.41 (d, *J* = 21.4 Hz, 6H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 142.18, 128.57, 128.43, 126.00, 95.47 (d, *J* = 165.6 Hz), 43.49 (d, *J* = 23.0 Hz), 30.41 (d, *J* = 5.3 Hz), 26.84 (d, *J* = 24.8 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -138.84 (hept/t, *J* = 21.4, 19.8, Hz).



**2-(3-fluoropropyl)-4,5-diphenyloxazole (2g):** Following the general procedure, a 2-dram vial with a stirbar was sequentially charged with 3-(4,5-diphenyloxazol-2-yl)propan-1-ol (**1g**) (279.3 mg, 1 mmol), **3-CF<sub>3</sub>** (251 mg, 1.1 equiv), THF (2 mL, 0.5 M), and BTMG (300  $\mu$ L, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 24 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (50 g silica, 0 → 30% ethyl acetate in hexanes) to afford 269.2 mg product as a white crystalline solid (96% yield). At 0.4 M concentration, the reaction displays second order kinetics with a half-life of 3.6 hours ( $t_{98\% \text{ conversion}} = 89 \text{ h}$ ). Raw kinetic data: 0% yield at  $t = 0 \text{ min}$ ; 37% yield at  $t = 60 \text{ min}$ ; 62% yield at  $t = 180 \text{ min}$ ; 92% yield at  $t = 900 \text{ min}$ ; 97% yield at  $t = 1620 \text{ min}$ ; 95% yield at  $t = 2400 \text{ min}$ . Best fit:

$$f(t) = A - \left( \frac{A}{[Ak t + 1]} \right) | f(t) = \text{yield (in decimal)}, A = 1.017, k = 0.00904 \text{ min}^{-1}.$$

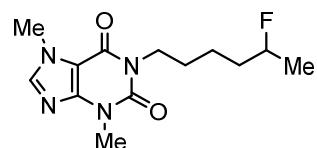
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.69 – 7.64 (m, 2H), 7.62 – 7.58 (m, 2H), 7.42 – 7.29 (m, 6H), 4.62 (dt,  $J = 47.1, 5.8 \text{ Hz}$ , 2H), 3.02 (t,  $J = 7.6 \text{ Hz}$ , 2H), 2.28 (dtt,  $J = 25.8, 7.5, 5.8 \text{ Hz}$ , 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  162.49, 145.42, 135.19, 132.57, 129.07, 128.74, 128.66, 128.52, 128.15, 127.99, 126.52, 82.91 (d,  $J = 165.7 \text{ Hz}$ ), 27.91 (d,  $J = 20.2 \text{ Hz}$ ), 24.18 (d,  $J = 5.6 \text{ Hz}$ ).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  –220.58 (tt,  $J = 47.4, 25.7 \text{ Hz}$ ).

**IR (ATR, cm<sup>-1</sup>):** 3067 (w), 2969 (w), 2899 (w), 1605 (w), 1590 (s), 1503 (w), 1485 (w), 1440 (m), 1384 (w), 1322 (w), 1290 (w), 1253 (w), 1216 (m), 1203 (m), 1144 (w), 1074 (w), 1058 (m), 1027 (s), 993 (m), 962 (m), 921 (m), 901 (w), 889 (s), 767 (s), 709 (w), 696 (s), 673 (m), 661 (w).

**HRMS (ESI+):** Calculated for C<sub>18</sub>H<sub>17</sub>FNO<sup>+</sup> [M + H]<sup>+</sup> : 282.1289; found: 282.1287.



**(±)-1-(5-fluorohexyl)-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione (2h):** A 1-dram vial with a stirbar was charged sequentially with (±)-lisofylline<sup>8</sup> (280.3 mg, 1 mmol), a solution of PyFluor (177 mg, 1.1 equiv) in toluene (1 mL, 1.0 M), and DBU (300  $\mu$ L, 2 equiv). The reaction was stirred at 600 rpm at room temperature for 48 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (50 g silica, 0 → 10% methanol in dichloromethane) affording 257.4 mg of an off-white solid. NMR analysis indicated that this consisted of 228.0 mg of the previously characterized title compound<sup>9</sup> (77% yield) and 29.4 mg of various elimination side products (11% elimination, 7.2:1 selectivity). Elimination side products were comprised of 19.8 mg (*E*)-1-(hex-4-en-1-yl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (8% *trans*-internal alkene), 3.0 mg (*Z*)-1-(hex-4-en-1-yl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (1% *cis*-internal alkene), and 6.6 mg 1-(hex-5-en-1-yl)-3,7-

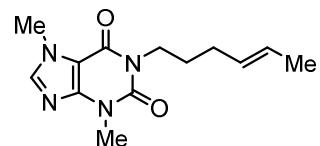
dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (3% terminal alkene). With 4-NsF and 1.5 equiv BTMG in 0.4 M THF, the reaction displays second order kinetics with a half-life of 4.6 hours ( $t_{98\% \text{ conversion}} = 110 \text{ h}$ ). Raw kinetic data: 0% yield at  $t = 0 \text{ min}$ ; 38% yield at  $t = 120 \text{ min}$ ; 66% yield at  $t = 600 \text{ min}$ ; 73% yield at  $t = 1260 \text{ min}$ ; 78% yield at  $t = 2640 \text{ min}$ . Best fit:

$$f(t) = A - \left( \frac{A}{[Ak t + 1]} \right) | f(t) = \text{yield (in decimal)}, A = .816, k = 0.00883 \text{ min}^{-1}.$$

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.47 (s, 1H), 4.60 (ddqd,  $J = 49.6, 7.9, 6.2, 4.3 \text{ Hz}$ , 1H), 3.96 (t,  $J = 7.6 \text{ Hz}$ , 2H), 3.94 (s, 3H), 3.52 (s, 3H), 1.68 – 1.32 (m, 6H), 1.26 (dd,  $J = 24.0, 6.2 \text{ Hz}$ , 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  155.29, 151.48, 148.76, 141.48, 107.67, 90.81 (d,  $J = 164.4 \text{ Hz}$ ), 41.17, 36.57 (d,  $J = 20.8 \text{ Hz}$ ), 33.62, 29.71, 27.84, 22.54 (d,  $J = 5.0 \text{ Hz}$ ), 21.04 (d,  $J = 22.8 \text{ Hz}$ ).

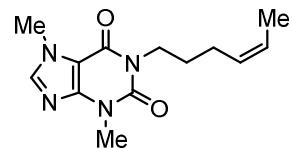
**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  –172.56 (ddqd,  $J = 48.8, 27.4, 23.9, 17.3 \text{ Hz}$ ).



**(E)-1-(hex-4-en-1-yl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione** (unresolved elimination side product):

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** [only alkenyl and adjacent peaks are identified]  $\delta$  5.43 – 5.38 (m, 2H), 2.13 – 2.02 (m, 2H), 1.66 – 1.61 (m, 3H).

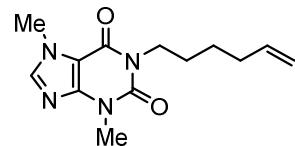
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** [only alkenyl and adjacent peaks are identified]  $\delta$  130.24, 125.41, 30.08, 27.69, 17.97.



**(Z)-1-(hex-4-en-1-yl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione** (unresolved elimination side product):

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** [only alkenyl and adjacent peaks are identified]  $\delta$  5.43 – 5.38 (m, 2H), 2.13 – 2.02 (m, 2H), 1.66 – 1.61 (m, 3H).

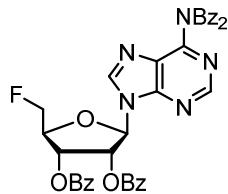
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** [only alkenyl and adjacent peaks are identified]  $\delta$  129.49, 124.55, 24.45, 12.87.



**1-(hex-5-en-1-yl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione** (unresolved elimination side product):

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** [only alkenyl and adjacent peaks are identified] δ 5.75 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.95 (dq, *J* = 17.0, 1.7 Hz, 1H), 4.88 (ddt, *J* = 10.1, 2.3, 1.3 Hz, 1H), 2.13 – 2.02 (m, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** [only alkenyl and adjacent peaks are identified] δ 138.60, 114.67, 33.52, 26.31.



**(2*R*,3*R*,4*S*,5*S*)-2-(6-(*N*-benzoylbenzamido)-9*H*-purin-9-yl)-5-(fluoromethyl)tetrahydrofuran-3,4-diyI dibenzoate (2i):** Following the general procedure, a 1-dram vial with a stirbar was sequentially charged with *N*<sup>6</sup>,*N*<sup>6</sup>,*O*<sup>2</sup>,*O*<sup>3</sup>-tetrabenzyloadenosine<sup>10</sup> (341.8 mg, 0.5 mmol), 3-NO<sub>2</sub> (113 mg, 1.1 equiv), THF (1 mL, 0.5 M), and BTPP (190 μL, 1.25 equiv). The reaction was stirred at 600 rpm at room temperature for 48 hours. The reaction mixture was concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 10 → 50% ethyl acetate in hexanes), affording 255.3 mg product as a white solid (75% yield).

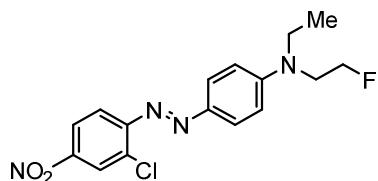
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 8.67 (s, 1H), 8.43 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 4H), 7.57 (dt, *J* = 15.7, 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.40 – 7.33 (m, 6H), 6.65 (d, *J* = 5.7 Hz, 1H), 6.13 (td, *J* = 5.7, 1.4 Hz, 1H), 6.07 (dd, *J* = 5.6, 3.7 Hz, 1H), 4.86 (dq, *J* = 47.7, 10.7, 2.6 Hz, 2H), 4.69 (dq, *J* = 29.4, 2.9 Hz, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 172.36, 165.46, 165.05, 153.08, 152.60, 152.18, 146.37, 134.07, 133.99, 133.98, 133.16, 129.99, 129.92, 129.59, 128.89, 128.73, 128.67, 128.65, 128.35, 127.68, 86.52, 82.52 (d, *J* = 18.5 Hz), 82.47 (d, *J* = 173.1 Hz), 74.60 (d, *J* = 2.5 Hz), 71.46 (d, *J* = 4.5 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -230.87 (td, *J* = 47.1, 29.3 Hz).

**IR (ATR, cm<sup>-1</sup>):** 3067 (w), 1718 (s), 1599 (m), 1579 (m), 1493 (w), 1450 (m), 1315 (w), 1241 (s), 1178 (m), 1092 (s), 1069 (m), 1025 (m), 1002 (w), 932 (w), 902 (w), 870 (w), 799 (w), 772 (w), 701 (s).

**HRMS (ESI+):** Calculated for C<sub>38</sub>H<sub>29</sub>FN<sub>5</sub>O<sub>7</sub><sup>+</sup> [M + H]<sup>+</sup> : 686.2046; found: 686.2051.



**(E)-4-((2-chloro-4-nitrophenyl)diazenyI)-N-ethyl-N-(2-fluoroethyl)aniline (2j):** Following the general procedure, a 2-dram vial with a stirbar was sequentially charged with Disperse

Red 13 (348.8 mg, 1 mmol, Aldrich), **3-CF<sub>3</sub>** (251 mg, 1.1 equiv), THF (2 mL, 0.5 M), and BTMG (300 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 24 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 50% ethyl acetate in hexanes with 5% triethylamine) to afford 288.8 mg product as a intensely dark red/purple solid (82% yield). At 0.4 M concentration, the reaction displays second order kinetics with a half-life of 3.2 hours (*t*<sub>98% conversion</sub> = 78 h). Raw kinetic data: 0% yield at *t* = 0 min; 23% yield at *t* = 30 min; 40% yield at *t* = 100 min; 60% yield at *t* = 265 min; 75% yield at *t* = 660 min; 80% yield at *t* = 1440 min; 78% yield at *t* = 3000 min. Best fit:

$$f(t) = A - \left( \frac{A}{[Ak t + 1]} \right) | f(t) = \text{yield (in decimal)}, A = .832, k = 0.0126 \text{ min}^{-1}.$$

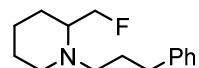
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 8.39 (d, *J* = 2.5 Hz, 1H), 8.15 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.94 (d, *J* = 9.3 Hz, 2H), 7.77 (d, *J* = 8.9 Hz, 1H), 6.77 (d, *J* = 9.2 Hz, 2H), 4.66 (dt, *J* = 47.0, 5.2 Hz, 2H), 3.77 (dt, *J* = 23.7, 5.2 Hz, 2H), 3.58 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 153.30, 151.81, 147.46, 144.70, 134.26, 127.17, 126.26, 122.85, 118.28, 111.74, 80.93, 50.83 (d, *J* = 21.7 Hz), 46.45, 12.39.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -221.69 (tt, *J* = 47.2, 23.8 Hz).

**IR (ATR, cm<sup>-1</sup>):** 3097 (w), 2972 (w), 2921 (w), 1597 (m), 1510 (s), 1403 (m), 1376 (w), 1329 (s), 1258 (w), 1234 (w), 1192 (w), 1137 (w), 1119 (s), 1041 (w), 999 (s), 888 (m), 821 (s), 796 (w), 746 (m), 726 (m).

**HRMS (ESI+):** Calculated for C<sub>16</sub>H<sub>17</sub>ClFN<sub>4</sub>O<sub>2</sub><sup>+</sup> [M + H]<sup>+</sup> : 351.1019; found: 351.1020.



**(±)-2-(fluoromethyl)-1-(3-phenylpropyl)piperidine (2k):** Following the general procedure, a 2-dram vial with a stirbar was sequentially charged with (1-(3-phenylpropyl)piperidin-2-yl)methanol (**1k**) (233.3 mg, 1 mmol), a solution of PBSF (332 mg, 1.1 equiv) in THF (10 mL, 0.1 M), and BTPP (460 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 24 hours. The reaction mixture was concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 3% triethylamine in hexanes). The products have low UV absorbance at 254 nm, but appear on TLC as bright yellow spots with permanganate stain. The rearranged isomer 3-fluoro-1-(3-phenylpropyl)azepane (**2k'**) eluted first followed by the title compound **2k**. Two samples were isolated—the first was determined by NMR to contain a mixture 127.9 mg **2k'** (54% yield **2k'**) as well as 15.1 mg **2k**. The second contained 61.0 mg of resolved title compound **2k** (32% overall yield **2k**). Both samples were colorless oils.

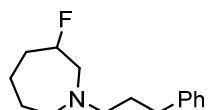
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.28 (t, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 3H), 4.56 – 4.27 (m, 2H), 2.89 (dt, *J* = 11.8, 4.1 Hz, 1H), 2.78 (ddd, *J* = 13.2, 9.6, 6.2 Hz, 1H), 2.67 – 2.55 (m, 2H), 2.51 (ddd, *J* = 13.6, 9.4, 5.6 Hz, 2H), 2.21 (td, *J* = 11.2, 3.1 Hz, 1H), 1.81 (ddt, *J* = 15.7, 8.8, 6.0 Hz, 2H), 1.71 (dt, *J* = 12.8, 4.2 Hz, 1H), 1.62 (tt, *J* = 13.5, 3.8 Hz, 2H), 1.51 (tdd, *J* = 14.3, 7.6, 3.8 Hz, 1H), 1.45 – 1.35 (m, 1H), 1.36 – 1.23 (m, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 142.40, 128.47, 128.41, 125.84, 85.99 (d, *J* = 170.2 Hz), 60.38 (d, *J* = 17.8 Hz), 54.23 (d, *J* = 2.0 Hz), 52.20, 33.95, 28.45 (d, *J* = 6.8 Hz), 27.55, 25.72, 23.72.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -221.12 (td, *J* = 47.7, 21.6 Hz).

**IR (film, cm<sup>-1</sup>):** 3026 (w), 2933 (m), 2857 (w), 2797 (w), 1603 (w), 1496 (w), 1454 (m), 1340 (w), 1278 (w), 1119 (w), 1084 (w), 1059 (w), 1011 (m), 984 (w), 944 (w), 907 (w), 875 (w), 744 (m) 698 (s).

**HRMS (ESI+):** Calculated for C<sub>15</sub>H<sub>23</sub>FN<sup>+</sup> [M + H]<sup>+</sup>: 236.1809; found: 236.1806.



**(±)-3-fluoro-1-(3-phenylpropyl)azepane (2k'): (partially resolved isomer)**

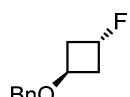
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.31 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 4.69 (ddt, *J* = 47.7, 11.9, 5.3 Hz, 1H), 2.93 – 2.80 (m, 2H), 2.67 – 2.57 (m, 4H), 2.57 – 2.51 (m, 2H), 2.04 (dddd, *J* = 19.8, 14.1, 8.4, 5.2, 2.3 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.78 (p, *J* = 7.6 Hz, 2H), 1.75 – 1.70 (m, 1H), 1.70 – 1.63 (m, 2H), 1.49 – 1.39 (m, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 142.54, 128.59, 128.40, 125.80, 92.98 (d, *J* = 168.5 Hz), 59.61 (d, *J* = 26.0 Hz), 58.21, 56.93, 33.59 (d, *J* = 21.3 Hz), 33.53, 29.64, 29.54, 20.76 (d, *J* = 9.2 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -170.74 (ddt, *J* = 47.7, 37.6, 19.5 Hz).

**IR (film, cm<sup>-1</sup>):** 3026 (w), 2932 (m), 2860 (w), 2812 (w), 1603 (w), 1496 (w), 1453 (m), 1356 (w), 1116 (w), 1086 (w), 1022 (m), 991 (m), 945 (w), 904 (w), 821 (w), 746 (m) 699 (s).

**HRMS (ESI+):** Calculated for C<sub>15</sub>H<sub>23</sub>FN<sup>+</sup> [M + H]<sup>+</sup> : 236.1809; found: 236.1805.

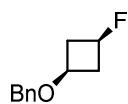


**((trans-3-fluorocyclobutoxy)methyl)benzene (2c):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with *cis*-3-(benzyloxy)cyclobutan-1-ol<sup>11</sup> (178.2 mg, 1 mmol, 12:1 dr), a solution of PBSF (332 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and then BTMG (220 μL, 1.1 equiv). Addition of base resulted in a substantial exotherm; on larger scale, it may be necessary to add BTMG slowly, dilute the reaction, or cool the mixture prior to addition. The reaction was stirred at 600 rpm at room temperature for 30 minutes, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (50 g silica, 0 → 10% ethyl acetate in hexanes) affording 151.8 mg product as a fragrant colorless oil (84% yield, 12:1 dr). This compound was previously characterized.<sup>11</sup> Additionally, <1% of a linear fluoride was detected by NMR with a splitting pattern suggestive of a cyclobutane ring-opening product; however, we were unable to isolate or identify this side product.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.40 – 7.28 (m, 5H), 5.25 (dtt, *J* = 56.4, 6.7, 3.7 Hz, 1H), 4.43 (s, 2H), 4.35 (ddt, *J* = 11.4, 6.9, 4.5 Hz, 1H), 2.55 – 2.36 (m, 4H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 137.98, 128.56, 127.91, 127.87, 87.07 (d, *J* = 198.6 Hz), 70.77, 70.04 (d, *J* = 9.1 Hz), 38.23 (d, *J* = 21.6 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -176.44 (dpd, *J* = 56.3, 20.7, 4.0 Hz).

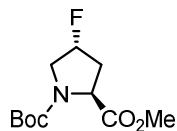


**((*cis*-3-fluorocyclobutoxy)methyl)benzene** (unresolved minor diastereomer):

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.40 – 7.28 (m, 5H), 4.70 (dp, *J* = 55.8, 6.6 Hz, 1H), 4.45 (s, 2H), 3.69 – 3.58 (m, 1H), 2.81 – 2.72 (m, 2H), 2.34 – 2.21 (m, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 137.94, 128.56, 127.98, 127.91, 80.44 (d, *J* = 211.7 Hz), 70.58, 63.34 (d, *J* = 23.8 Hz), 39.36 (d, *J* = 19.5 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -169.76 (dttd, *J* = 55.9, 25.3, 6.5, 4.1 Hz).

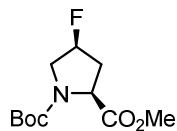


**1-(*tert*-butyl) 2-methyl (*2S,4R*)-4-fluoropyrrolidine-1,2-dicarboxylate (2d):** Following the general procedure, a 20-mL scintillation vial with a stirbar was charged sequentially with *N*-Boc-*cis*-4-hydroxy-L-proline methyl ester (245.3 mg, 1 mmol, Synthonix), a solution of PBSF (332 mg, 1.1 equiv) in THF (10 mL, 0.1 M), and MTBD (215 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 3 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 15% ethyl acetate in hexanes with 3% triethylamine). Product containing fractions were identified by LCMS and were concentrated to afford 162.1 mg product as a colorless oil (66% yield). Compound was previously identified.<sup>1</sup>

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** [1.6:1 ratio of two rotamers] δ 5.19 (dt, *J* = 52.4, 3.8 Hz, 1H), 4.48 – 4.32 (m, 1H), 3.94 – 3.76 (m, 1H), 3.73 (d, *J* = 7.0 Hz, 3H), 3.60 (ddd, *J* = 36.9, 12.9, 3.4 Hz, 1H), 2.63 – 2.50 (m, 1H), 2.09 (dddd, *J* = 38.8, 14.0, 9.5, 4.0 Hz, 1H), 1.42 (d, *J* = 22.9 Hz, 9H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** [1.6:1 ratio of two rotamers, minor rotamer denoted with \*] δ 173.26, 173.10\*, 154.24\*, 153.64, 92.01\* (d, *J* = 178.7 Hz), 91.19 (d, *J* = 178.7 Hz), 80.70, 80.68\*, 57.76, 57.40\*, 53.38\* (d, *J* = 22.8 Hz), 53.05 (d, *J* = 22.6 Hz), 52.50\*, 52.28, 37.66 (d, *J* = 22.7 Hz), 36.78\* (d, *J* = 22.6 Hz), 28.44\*, 28.32.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** [1.6:1 ratio of two rotamers, minor rotamer denoted with \*] δ -176.62 – -177.29\* (m), -177.54 (dtdd, *J* = 52.2, 38.2, 22.6, 18.6 Hz).



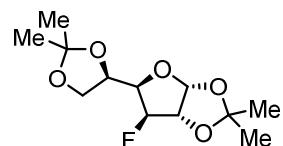
**1-(*tert*-butyl) 2-methyl (*2S,4S*)-4-fluoropyrrolidine-1,2-dicarboxylate (2l):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester (245.3 mg, 1 mmol, Alfa Aesar), a solution of PBSF (332 mg,

1.1 equiv) in THF (2 mL, 0.5 M), and MTBD (215  $\mu$ L, 1.5 equiv). Addition of base resulted in a substantial exotherm that resulted in a significant ~10% reduction in yield relative to screening scale. On larger scale, it may be necessary to add MTBD slowly, dilute the reaction, or cool the mixture prior to addition. The reaction was stirred at 600 rpm at room temperature for 30 minutes, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 15% ethyl acetate in hexanes with 3% triethylamine). Product containing fractions were identified by LCMS and were concentrated to afford 185.8 mg product as a colorless oil (75% yield). Compound has been previously characterized.<sup>12</sup>

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** [1.2:1 ratio of two rotamers]  $\delta$  5.19 (dq,  $J$  = 52.7, 3.7 Hz, 1H), 4.58 – 4.36 (m, 1H), 3.88 – 3.74 (m, 1H), 3.73 (s, 3H), 3.72 – 3.56 (m, 1H), 2.52 – 2.22 (m, 2H), 1.44 (d,  $J$  = 25.2 Hz, 9H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** [1.2:1 ratio of two rotamers, minor rotamer denoted with \*]  $\delta$  172.39, 171.99\*, 154.12\*, 153.74, 92.33\* (d,  $J$  = 177.3 Hz), 91.26 (d,  $J$  = 177.4 Hz), 80.53\*, 80.49, 57.74, 57.35\*, 53.29\* (d,  $J$  = 24.3 Hz), 52.97 (d,  $J$  = 24.3 Hz), 52.49\*, 52.35, 37.58 (d,  $J$  = 22.0 Hz), 36.71\* (d,  $J$  = 21.8 Hz), 28.49\*, 28.38.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** [1.2:1 ratio of two rotamers]  $\delta$  –172.34 – –173.70 (m).



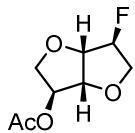
**(3a*R*,5*R*,6*S*,6a*S*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-fluoro-2,2-dimethyltetrahydro-furo[2,3-d][1,3]dioxole (2m):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with 1,2:5,6-di-*O*-isopropylidene- $\alpha$ -D-allofuranose (260.3 mg, 1 mmol, Ark Pharm), a solution of PBSF (332 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and then MTBD (215  $\mu$ L, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 12 hours. Upon completion, the mixture was concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (15 g silica, 0 → 20% ethyl acetate in hexanes) to afford 229.8 mg product as a colorless oil (88% yield). Compound was previously characterized.<sup>12</sup> At 0.4 M concentration, timepoint experiments suggest second order kinetics with a half-life of 32 minutes ( $t_{98\%}$  conversion = 13 h). Raw kinetic data: 0% yield at  $t$  = 0 min; 44% yield at  $t$  = 20 min; 70% yield at  $t$  = 120 min. Best fit:

$$f(t) = A - \left( \frac{A}{[Ak t + 1]} \right) \quad | f(t) = \text{yield (in decimal)}, A = .794, k = 0.0783 \text{ min}^{-1}.$$

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  5.93 (d,  $J$  = 3.7 Hz, 1H), 4.99 (dd,  $J$  = 49.8, 2.3 Hz, 1H), 4.68 (dd,  $J$  = 10.7, 3.8 Hz, 1H), 4.27 (ddd,  $J$  = 8.3, 6.1, 4.8 Hz, 1H), 4.10 (dd,  $J$  = 8.7, 6.1 Hz, 1H), 4.09 (ddd,  $J$  = 29.1, 8.2, 2.2 Hz, 1H), 4.01 (dd,  $J$  = 8.8, 4.8 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  112.48, 109.62, 105.30, 93.93 (d,  $J$  = 183.8 Hz), 82.66 (d,  $J$  = 32.8 Hz), 80.77 (d,  $J$  = 19.0 Hz), 72.01 (d,  $J$  = 7.2 Hz), 67.29 (d,  $J$  = 1.1 Hz), 26.98, 26.82, 26.30, 25.28.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):**  $\delta$  –207.60 (ddd,  $J$  = 49.9, 29.2, 10.9 Hz).



**(3*S*,3*a**R*,6*S*,6*a**S*)-6-fluorohexahydrofuro[3,2-*b*]furan-3-yl acetate (2n):** According to the general procedure, a 20-mL scintillation vial with a stirbar was charged sequentially with isosorbide-2-acetate (188.2 mg, 1 mmol, Combi-Blocks), a solution of PBSF (332 mg, 1.1 equiv) in THF (10 mL, 0.1 M), and BTTP (460  $\mu$ L, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 30 minutes, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0  $\rightarrow$  60% ethyl acetate in hexanes). The product is not particularly UV active and does not stain well; fractions containing product were identified by the condensate that appeared after partial evaporation. These fractions were concentrated by rotary evaporation at 0 °C to afford 188.8 mg of a colorless oil. This was determined by NMR to consist of 178.6 mg of the title compound (94% yield) and 10.2 mg *n*-hexane.

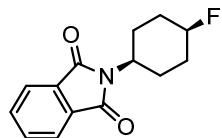
**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  5.15 (s, 1H), 5.04 (dd,  $J$  = 50.8, 2.9 Hz, 1H), 4.71 (dd,  $J$  = 8.1, 3.8 Hz, 1H), 4.66 (d,  $J$  = 3.8 Hz, 1H), 4.07 (dd,  $J$  = 24.7, 11.5 Hz, 1H), 3.90 – 3.76 (m, 3H), 2.05 (s, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  169.93, 95.05 (d,  $J$  = 180.7 Hz), 85.23, 84.91 (d,  $J$  = 30.6 Hz), 77.56, 72.64 (d,  $J$  = 22.2 Hz), 72.53, 20.91.

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  –186.35 (dddd,  $J$  = 49.9, 40.2, 24.8, 8.0 Hz).

**IR (film,  $\text{cm}^{-1}$ ):** 2965 (w), 2881 (w), 1742 (s), 1462 (w), 1434 (w), 1369 (m), 1228 (s), 1100 (w), 1067 (s), 1043 (m), 1016 (w), 989 (w), 967 (s), 922 (m), 860 (m), 842 (w), 780 (m).

**HRMS (ESI+):** Calculated for  $\text{C}_8\text{H}_{12}\text{FO}_4^+$  [ $\text{M} + \text{H}]^+$  : 191.0714; found: 191.0711.



**2-(*cis*-4-fluorocyclohexyl)isoindoline-1,3-dione (2o):** Following the general procedure, a 20-mL scintillation vial with a stirbar was charged sequentially with 2-(*trans*-4-hydroxycyclohexyl)isoindolin-1,3-dione<sup>13</sup> (122.6 mg, 0.5 mmol), a solution of PBSF (166 mg, 1.1 equiv) in THF (5 mL, 0.1 M), and BTMG (150  $\mu$ L, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 30 minutes, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0  $\rightarrow$  15% ethyl acetate in hexanes), affording 57.2 mg of a white solid. This was found by NMR to consist of 56.3 mg of the title compound (46% yield) and 0.9 mg of an unidentified primary fluoride rearrangement product. Additionally, substantial quantities of the elimination side product 2-(cyclohex-3-en-1-yl)isoindoline-1,3-dione were observed in the preceding fractions by LCMS, likely accounting for most of the mass balance.

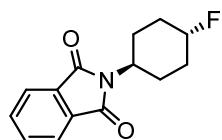
**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.82 (dd,  $J$  = 5.4, 3.1 Hz, 2H), 7.70 (dd,  $J$  = 5.4, 3.0 Hz, 2H), 4.86 (d,  $J$  = 47.1 Hz, 1H), 4.17 (t,  $J$  = 13.0 Hz, 1H), 2.64 (qd,  $J$  = 13.4, 4.3 Hz, 2H), 2.20 (t,  $J$  = 12.5 Hz, 2H), 1.71 – 1.51 (m, 4H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 168.38, 133.99, 132.12, 123.25, 86.98 (d, *J* = 169.3 Hz), 49.79, 30.57 (d, *J* = 21.5 Hz), 24.02.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -185.90 (qt, *J* = 45.7, 10.1 Hz).

**IR (ATR, cm<sup>-1</sup>):** 2940 (m), 2879 (w), 1771 (w), 1759 (w), 1701 (s), 1614 (w), 1469 (m), 1445 (w), 1432 (w), 1395 (w), 1380 (s), 1357 (m), 1336 (w), 1323 (w), 1271 (w), 1246 (m), 1157 (m), 1134 (w), 1079 (s), 1031 (m), 1017 (s), 1006 (m), 954 (w), 936 (m), 909 (m), 882 (s), 830 (m), 818 (w), 798 (m), 731 (w), 713 (s), 684 (w).

**HRMS (ESI+):** Calculated for C<sub>14</sub>H<sub>15</sub>FNO<sub>2</sub><sup>+</sup> [M + H]<sup>+</sup> : 248.1081; found: 248.1079.



**2-(*trans*-4-fluorocyclohexyl)isoindoline-1,3-dione (2p):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with 2-(*cis*-4-hydroxycyclohexyl)isoindoline-1,3-dione<sup>14</sup> (245.3 mg, 1 mmol), a solution of PBSF (332 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and BTTP (460 μL, 1.5 equiv). Addition of base resulted in a substantial exotherm; on larger scale, it may be necessary to add BTTP slowly, dilute the reaction, or cool the mixture prior to addition. The reaction was stirred at 600 rpm at room temperature for 30 minutes, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 10% ethyl acetate in hexanes), affording 43.4 mg of a white solid. This was found by NMR to consist of 36.9 mg of the title compound (15% yield) and 6.5 mg of the elimination side product 2-(cyclohex-3-en-1-yl)isoindoline-1,3-dione (accounting for 3% of mass balance). The elimination side product has been previously characterized.<sup>15</sup> A substantial amount of the elimination side product eluted before the product, likely accounting for most of the mass balance.

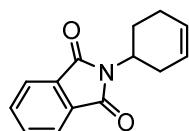
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.82 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H), 4.63 (dtt, *J* = 48.6, 11.1, 4.6 Hz, 1H), 4.16 (tt, *J* = 12.3, 4.0 Hz, 1H), 2.34 (q, *J* = 13.5 Hz, 2H), 2.28 – 2.18 (m, 2H), 1.88 – 1.74 (m, 2H), 1.71 – 1.57 (m, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 168.38, 134.09, 132.04, 123.30, 91.02 (d, *J* = 172.9 Hz), 49.29 (d, *J* = 1.7 Hz), 32.01 (d, *J* = 19.8 Hz), 26.90 (d, *J* = 12.5 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -172.58 (dtt, *J* = 48.9, 9.1, 4.7 Hz).

**IR (ATR, cm<sup>-1</sup>):** 3458 (w), 2936 (m), 2863 (w), 1765 (m), 1701 (s), 1611 (w), 1466 (w), 1455 (w), 1375 (s), 1332 (w), 1283 (w), 1255 (w), 1188 (w), 1167 (w), 1153 (w), 1112 (w), 1080 (m), 1032 (m), 984 (m), 939 (w), 898 (w), 856 (m), 795 (m), 712 (s), 652 (m).

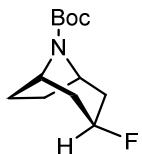
**HRMS (ESI+):** Calculated for C<sub>14</sub>H<sub>15</sub>FNO<sub>2</sub><sup>+</sup> [M + H]<sup>+</sup> : 248.1081; found: 248.1079.



**2-(cyclohex-3-en-1-yl)isoindoline-1,3-dione:** (partially resolved elimination side product)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.76 – 5.64 (m, 2H), 4.41 (dddd, *J* = 12.8, 11.1, 5.5, 3.2 Hz, 1H), 2.94 – 2.82 (m, 1H), 2.53 (tdd, *J* = 12.6, 10.1, 7.4 Hz, 1H), 2.32 – 2.19 (m, 2H), 2.19 – 2.08 (m, 1H), 1.80 (dp, *J* = 12.1, 2.5 Hz, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 168.56, 133.97, 132.18, 126.71, 125.15, 123.21, 47.66, 28.81, 26.44, 25.89.



**(±)-*tert*-butyl (1*R*,3*s*,5*S*)-3-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (2q):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with *N*-Boc-nortropine (227.3 mg, 1 mmol, Millipore-Sigma), a solution of PBSF (332 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and BTMG (300 μL, 1.5 equiv). Addition of base resulted in a substantial exotherm; on larger scale, it may be necessary to add BTMG slowly, dilute the reaction, or cool the mixture prior to addition. The reaction was stirred at 600 rpm at room temperature for 30 minutes, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g triethylamine-pretreated silica, 0 → 25% ethyl acetate in hexanes) to afford 122.4 mg product as a white solid (53% yield).

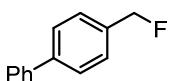
**<sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>):** δ 4.95 (dtt, *J* = 48.8, 10.6, 6.3 Hz, 1H), 4.29 – 4.16 (m, 2H), 2.12 – 2.01 (m, 2H), 2.00 – 1.88 (m, 2H), 1.82 – 1.69 (m, 2H), 1.64 – 1.55 (m, 2H), 1.45 (s, 9H).

**<sup>13</sup>C NMR (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>):** δ 153.43, 87.36 (d, *J* = 172.7 Hz), 79.64, 52.93 (d, *J* = 79.6 Hz), 37.84 (d, *J* = 98.2 Hz), 28.52, 28.43 (d, *J* = 97.0 Hz).

**<sup>19</sup>F NMR (282 MHz, CD<sub>2</sub>Cl<sub>2</sub>):** δ –179.80 (dtt, *J* = 48.8, 14.8, 4.7 Hz).

**IR (ATR, cm<sup>–1</sup>):** 2981 (w), 2957 (w), 2935 (w), 2893 (w), 2867 (w), 1682 (s), 1474 (w), 1463 (w), 1382 (s), 1369 (w), 1345 (m), 1325 (w), 1310 (w), 1296 (m), 1274 (w), 1257 (w), 1164 (s), 1103 (m), 1083 (s), 1036 (s), 995 (m), 967 (m), 918 (m), 878 (w), 869 (w), 844 (w), 826 (w), 803 (w), 777 (w), 757 (w), 739 (w).

**HRMS (ESI+):** Calculated for C<sub>8</sub>H<sub>13</sub>FNO<sub>2</sub><sup>+</sup> [M – C<sub>4</sub>H<sub>9</sub> + 2H]<sup>+</sup> : 174.0925; found: 174.0925.

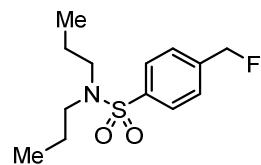


**4-(fluoromethyl)-1,1'-biphenyl (2b):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with biphenyl-4-ylmethanol (184.2 mg, 1 mmol, Oakwood), 3-CF<sub>3</sub> (251 mg, 1.1 equiv), THF (2 mL, 0.5 M), and then TPP (460 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 1 hour, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 5% ethyl acetate in hexanes) to afford 168.2 mg product as a white solid (90% yield). This compound has been previously characterized.<sup>16</sup>

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.68 – 7.60 (m, 4H), 7.52 – 7.45 (m, 4H), 7.39 (t, *J* = 7.4 Hz, 1H), 5.45 (d, *J* = 47.9 Hz, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 141.85 (d, *J* = 3.2 Hz), 140.70 (d, *J* = 1.1 Hz), 135.23 (d, *J* = 17.1 Hz), 128.96, 128.20 (d, *J* = 5.7 Hz), 127.66, 127.49 (d, *J* = 1.4 Hz), 127.28, 84.53 (d, *J* = 165.9 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ –206.15 (t, *J* = 47.9 Hz).



**4-(fluoromethyl)-N,N-dipropylbenzenesulfonamide (2r):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with 4-(hydroxymethyl)-N,N-dipropylbenzenesulfonamide (**1r**) (271.4 mg, 1 mmol), **3-CF<sub>3</sub>** (251 mg, 1.1 equiv), THF (2 mL, 0.5 M), and finally BTPP (460 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 3 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 5% ethyl acetate in hexanes) to afford 232.4 mg of the title compound as a translucent crystalline solid (85% yield).

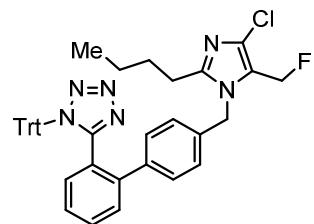
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 5.44 (d, *J* = 47.1 Hz, 2H), 3.07 (t, *J* = 7.7 Hz, 4H), 1.54 (h, *J* = 7.4 Hz, 4H), 0.86 (t, *J* = 7.4 Hz, 6H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 140.75 (d, *J* = 17.5 Hz), 140.38 (d, *J* = 2.4 Hz), 127.43, 127.22 (d, *J* = 6.7 Hz), 83.45 (d, *J* = 169.2 Hz), 50.12, 22.12, 11.28.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ –213.42 (t, *J* = 47.1 Hz).

**IR (ATR, cm<sup>-1</sup>):** 2965 (w), 2936 (w), 2876 (w), 1464 (m), 1410 (w), 1377 (w), 1335 (s), 1309 (w), 1212 (w), 1188 (w), 1155 (s), 1089 (m), 990 (s), 904 (w), 867 (w), 856 (w), 821 (m), 798 (w), 773 (m), 734 (s), 716 (w), 668 (s).

**HRMS (ESI+):** Calculated for C<sub>13</sub>H<sub>21</sub>FNO<sub>2</sub>S<sup>+</sup> [M + H]<sup>+</sup>: 274.1272; found: 274.1266.



**5-(4'-(2-butyl-4-chloro-5-(fluoromethyl)-1H-imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-yl)-1-trityl-1H-tetrazole (2s):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with *N*-trityl losartan<sup>17</sup> (332.6 mg, 0.5 mmol), **3-NO<sub>2</sub>** (113 mg, 1.1 equiv), THF (1 mL, 0.5 M), and BTMG (150 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 1 hour, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 30% ethyl acetate in hexanes) to afford

137.8 mg of a white solid. This was found by NMR to consist of 136.9 mg of the title compound (41% yield) and 0.9 mg ethyl acetate. In this case, the reaction may have been terminated prior to full conversion of sulfonate ester; a longer reaction time may lead to a moderate increase in yield.

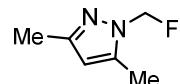
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.97 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.35 (t, *J* = 6.8 Hz, 4H), 7.26 (dd, *J* = 8.6, 7.1 Hz, 6H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 7.3 Hz, 6H), 6.75 (d, *J* = 7.9 Hz, 2H), 5.02 (s, 2H), 4.98 (d, *J* = 50.3 Hz, 2H), 2.52 (td, *J* = 8.4, 7.9, 2.4 Hz, 2H), 1.66 (p, *J* = 7.7 Hz, 2H), 1.31 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.87 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 163.98, 149.87 (d, *J* = 4.5 Hz), 141.39, 141.36, 141.30, 133.99, 131.02 (d, *J* = 8.0 Hz), 130.83, 130.35, 130.31, 130.11, 130.08, 128.44, 127.94, 127.76, 126.31, 125.33, 121.09 (d, *J* = 19.2 Hz), 82.98, 72.18 (d, *J* = 164.8 Hz), 47.43, 29.75, 26.88, 22.50, 13.88.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ –201.74 (t, *J* = 50.3 Hz).

**IR (ATR, cm<sup>-1</sup>):** 3060 (w), 2958 (w), 2929 (w), 1733 (w), 1570 (w), 1493 (w), 1446 (m), 1424 (w), 1358 (w), 1255 (s), 1188 (w), 1158 (w), 1073 (w), 1029 (w), 1004 (w), 948 (m), 904 (w), 880 (w), 821 (w), 784 (w), 746 (s), 697 (s), 678 (w).

**HRMS (ESI+):** Calculated for C<sub>41</sub>H<sub>37</sub>ClFN<sub>6</sub><sup>+</sup> [M + H]<sup>+</sup> : 667.2747; found: 667.2735.



**1-(fluoromethyl)-3,5-dimethyl-1*H*-pyrazole (2t):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with 3,5-dimethylpyrazole-1-methanol (126.2 mg, 1 mmol, Aldrich), **3-Cl** (214 mg, 1.1 equiv), THF (2 mL, 0.5 M), and then BTTP (460 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 1 hour. Following addition of 1-fluoronaphthalene as an external standard, the yield was determined by <sup>19</sup>F NMR in CDCl<sub>3</sub> to be 57% yield. We were unable to isolate the product using column chromatography. A crude sample was obtained by dissolving the concentrated reaction mixture in 5 mL CDCl<sub>3</sub>. After rinsing with 10 mL saturated aqueous sodium chloride, the organic layer was dried with sodium sulfate, concentrated to a light yellow oil, and analyzed by NMR. In addition to the product, peaks corresponding to BTTP and 4-chlorobenzenesulfonate species were observed as well.

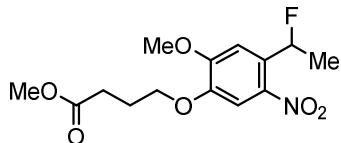
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.78 (d, *J* = 54.5 Hz, 2H), 5.77 (s, 1H), 2.18 (s, 3H), 2.08 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 147.93, 140.86 (d, *J* = 2.5 Hz), 107.56, 84.75 (d, *J* = 199.6 Hz), 13.25, 10.96.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ –162.39 (t, *J* = 54.3 Hz).

**IR (film, cm<sup>-1</sup>):** (crude reaction mixture) 2971 (w), 2875 (w), 1566 (w), 1475 (w), 1412 (w), 1394 (w), 1202 (s), 1083 (s), 1032 (m), 1020 (m), 1007 (s), 826 (w), 783 (m), 751 (s), 697 (w).

**HRMS (ESI+):** Calculated for C<sub>6</sub>H<sub>10</sub>FN<sub>2</sub><sup>+</sup> [M + H]<sup>+</sup> : 129.0823; found: 129.0823.



**(±)-methyl 4-(4-(1-fluoroethyl)-2-methoxy-5-nitrophenoxy)butanoate (2u):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with methyl 4-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoate (**1u**) (313.3 mg, 1 mmol), **3-CF<sub>3</sub>** (251 mg, 1.1 equiv), THF (2 mL, 0.5 M), and BTMG (300 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 24 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (50 g silica, 0 → 20% ethyl acetate in hexanes) to afford 187.9 mg product as a pale yellow solid (60% yield). Further elution resulted in the isolation of 75.4 mg of a yellow oil, which by NMR was determined to contain an mixture of elimination side product methyl 4-(2-methoxy-5-nitro-4-vinylphenoxy)butanoate (approx. 13% yield) as well as an unidentified primary fluoride (approx. 12% yield, assuming the molecular weight is identical to that of the title compound). The observed NMR splitting for the fluoride side product is consistent with methyl 4-(4-(2-fluoroethyl)-2-methoxy-5-nitrophenoxy)butanoate; however, we were unable to purify the compound through additional chromatography and assign definite NMR shifts. At 0.4 M concentration, the reaction displays second order kinetics with a half-life of 1.3 hours ( $t_{98\% \text{ conversion}} = 31 \text{ h}$ ). Raw kinetic data: 0% yield at  $t = 0 \text{ min}$ ; 27% yield at  $t = 30 \text{ min}$ ; 37% yield at  $t = 60 \text{ min}$ ; 53% yield at  $t = 208 \text{ min}$ ; 60% yield at  $t = 1440 \text{ min}$ ; 59% yield at  $t = 2190 \text{ min}$ . Best fit:

$$f(t) = A - \left( \frac{A}{[Akt + 1]} \right) \quad | f(t) = \text{yield (in decimal)}, A = .611, k = 0.0434 \text{ min}^{-1}.$$

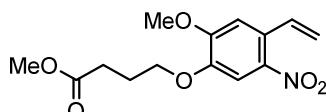
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.65 (s, 1H), 7.15 (s, 1H), 6.32 (dq,  $J = 48.4, 6.1 \text{ Hz}$ , 1H), 4.13 (td,  $J = 6.3, 2.7 \text{ Hz}$ , 2H), 3.98 (s, 3H), 3.70 (s, 3H), 2.56 (t,  $J = 7.2 \text{ Hz}$ , 2H), 2.19 (p,  $J = 6.7 \text{ Hz}$ , 2H), 1.68 (dd,  $J = 24.3, 6.1 \text{ Hz}$ , 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 173.45, 154.55 (d,  $J = 1.8 \text{ Hz}$ ), 147.45 (d,  $J = 1.3 \text{ Hz}$ ), 138.45 (d,  $J = 3.9 \text{ Hz}$ ), 134.00 (d,  $J = 20.9 \text{ Hz}$ ), 109.00, 107.86 (d,  $J = 16.6 \text{ Hz}$ ), 87.90 (d,  $J = 169.5 \text{ Hz}$ ), 68.35, 56.55, 51.89, 30.47, 24.36, 23.14 (d,  $J = 25.2 \text{ Hz}$ ).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -170.25 (dq,  $J = 48.6, 24.5 \text{ Hz}$ ).

**IR (ATR, cm<sup>-1</sup>):** 3106 (w), 2956 (w), 2887 (w), 1726 (s), 1614 (w), 1577 (m), 1517 (sm), 1501 (s), 1469 (w), 1449 (m), 1433 (w), 1409 (w), 1373 (m), 1315 (m), 1279 (m), 1264 (s), 1221 (s), 1197 (m), 1176 (s), 1105 (m), 1075 (s), 1054 (w), 1035 (m), 1013 (s), 990 (w), 971 (m), 884 (s), 852 (m), 813 (s), 758 (m), 705 (w), 681 (w), 660 (w).

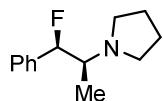
**HRMS (ESI+):** Calculated for C<sub>14</sub>H<sub>18</sub>NO<sub>6</sub><sup>+</sup> [M - F]<sup>+</sup>: 296.1129; found: 296.1125.



**methyl 4-(2-methoxy-5-nitro-4-vinylphenoxy)butanoate** (fully resolved elimination side product):

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** [only alkenyl peaks are identified] δ 7.31 (dd,  $J = 17.3, 10.9 \text{ Hz}$ , 1H), 5.63 (dd,  $J = 17.2, 1.0 \text{ Hz}$ , 1H), 5.43 (dd,  $J = 10.9, 1.0 \text{ Hz}$ , 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** [only alkenyl peaks are identified] δ 133.82, 117.63.



**1-((1*R*,2*S*)-1-fluoro-1-phenylpropan-2-yl)pyrrolidine (2v):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol (205.3 mg, 1 mmol, Aldrich), a solution of PBSF (332 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and BTPP (460 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 3 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 25% ethyl acetate in hexanes with 3% triethylamine) to afford 186.9 mg product as a colorless oil (90% yield). The <sup>3</sup>J<sub>(FH)</sub> and <sup>3</sup>J<sub>(HH)</sub> coupling constants are consistent with the *erythro*- diastereomer and overall retention of configuration, suggesting the formation of an aziridinium ion intermediate.<sup>18</sup>

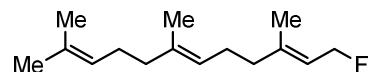
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.38 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.27 (m, 3H), 5.81 (dd, *J* = 48.2, 2.3 Hz, 1H), 2.83 – 2.69 (m, 5H), 1.90 – 1.80 (m, 4H), 1.04 (dd, *J* = 6.7, 1.4 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 139.30 (d, *J* = 20.4 Hz), 128.23 (d, *J* = 1.4 Hz), 127.61 (d, *J* = 0.5 Hz), 125.07 (d, *J* = 9.0 Hz), 94.39 (d, *J* = 179.9 Hz), 63.52 (d, *J* = 20.7 Hz), 51.18, 23.53, 10.13 (d, *J* = 6.7 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -199.69 (dd, *J* = 48.2, 28.2 Hz).

**IR (film, cm<sup>-1</sup>):** 3032 (w), 2967 (m), 2876 (w), 2791 (w), 1498 (w), 1451 (m), 1378 (w), 1351 (w), 1288 (w), 1200 (w), 1144 (w), 1091 (w), 1065 (w), 1031 (w), 1001 (m), 962 (m), 914 (w), 894 (w), 746 (s), 698 (s), 670 (m).

**HRMS (ESI+):** Calculated for C<sub>13</sub>H<sub>19</sub>FN<sup>+</sup> [M + H]<sup>+</sup> : 208.1496; found: 208.1495.



**(2*E*,6*E*)-1-fluoro-3,7,11-trimethyldodeca-2,6,10-triene (2w):** Following the general procedure, a 2-dram vial with a stirbar was sequentially charged with *trans,trans*-farnesol (222.4 mg, 1 mmol, Alfa Aesar), a solution of 3-CF<sub>3</sub> (251 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and BTPP (460 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 1 hour. Following addition of 1-fluoronaphthalene as an external standard, the yield was determined by <sup>19</sup>F NMR in CD<sub>2</sub>Cl<sub>2</sub> to be 46% yield. Additionally, 4% yield of the branched isomer (*E*)-3-fluoro-3,7,11-trimethyldodeca-1,6,10-triene was observed.

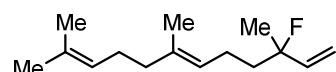
The product is prone to decomposition with elimination of fluoride. A sample was obtained by directly loading the reaction mixture onto an automated column (25 g triethylamine-pretreated silica) and removing the THF under a stream of air in the column-head space. The column was subjected to a gradient (0 → 15% ethyl acetate in hexanes) to afford a colorless oil. By NMR, this was found to contain the title compound in addition to 5 mol% of the branched isomer (*E*)-3-fluoro-3,7,11-trimethyldodeca-1,6,10-triene, 46 mol% of an unidentified farnesol derivative, and 3 mol% of an unidentified 4-trifluoromethanesulfonate derivative (<sup>19</sup>F NMR (282 MHz,

$\text{CD}_2\text{Cl}_2$ ):  $\delta$   $-63.89$ ). A separate fraction contained almost pure branched isomer and is also characterized. The title compound has been previously characterized.<sup>19</sup>

**$^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):**  $\delta$  5.48 (q,  $J = 7.2$  Hz, 1H), 5.15 – 5.06 (m, 2H), 4.88 (dd,  $J = 47.9, 7.2$  Hz, 2H), 2.17 – 2.01 (m, 6H), 2.01 – 1.94 (m, 2H), 1.72 (dd,  $J = 4.7, 1.4$  Hz, 3H), 1.67 (s, 3H), 1.60 (s, 6H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ ):**  $\delta$  144.56 (d,  $J = 11.4$  Hz), 135.92, 131.64, 124.66, 123.95, 119.36 (d,  $J = 17.0$  Hz), 79.80 (d,  $J = 155.9$  Hz), 40.09, 39.90 (d,  $J = 2.7$  Hz), 27.11, 26.53 (d,  $J = 3.6$  Hz), 25.79, 17.76, 16.55 (d,  $J = 4.7$  Hz), 16.08.

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_2\text{Cl}_2$ ):**  $\delta$   $-208.02$  (tdq,  $J = 47.9, 9.6, 4.8$  Hz).

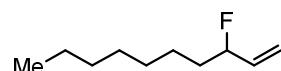


**( $\pm$ )-(E)-3-fluoro-3,7,11-trimethyldodeca-1,6,10-triene (branched isomer):**

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  5.89 (td,  $J = 17.7, 11.0$  Hz, 1H), 5.26 (d,  $J = 17.4$  Hz, 1H), 5.14 – 5.06 (m, 3H), 2.10 – 2.01 (m, 4H), 2.00 – 1.94 (m, 2H), 1.74 – 1.63 (m, 2H), 1.68 (s, 3H), 1.60 (s, 6H), 1.41 (d,  $J = 21.6$  Hz, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  140.91 (d,  $J = 22.7$  Hz), 135.64, 131.52, 124.42, 123.79, 113.40 (d,  $J = 11.3$  Hz), 96.18 (d,  $J = 169.2$  Hz), 40.45 (d,  $J = 23.2$  Hz), 39.81, 26.81, 25.85, 25.41 (d,  $J = 25.0$  Hz), 22.35 (d,  $J = 5.0$  Hz), 17.84, 16.08.

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$   $-148.15$  (dq,  $J = 39.9, 21.8, 18.0$  Hz).



**3-fluorodec-1-ene (2x):** Following the general procedure, a 2-dram vial with a stirbar was sequentially charged with 1-decen-3-ol (156.3 mg, 1 mmol, SAFC), THF (2 mL, 0.5 M), **3-CF<sub>3</sub>** (251 mg, 1.1 equiv), and BTPP (460  $\mu\text{L}$ , 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 24 hours. Following addition of 1-fluoronaphthalene as an external standard, the yield was determined by  $^{19}\text{F}$  NMR in  $\text{CDCl}_3$  to be 39% yield. Additionally, 10% yield of the linear isomer (*E*)-1-fluorodec-2-ene was observed.

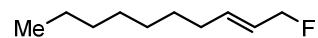
A sample was obtained by directly loading the reaction mixture onto an automated column (25 g silica) and removing the THF under a stream of air in the column-head space. The column was subjected to a gradient (0  $\rightarrow$  10% ethyl acetate in hexanes) to afford a volatile colorless oil. By NMR, this was found to contain title compound as well as 35 mol% of the linear isomer (*E*)-1-fluorodec-2-ene and some uncharacterized impurities. The title compound has been previously characterized.<sup>20</sup> At 0.4 M concentration, the reaction appears to exhibit first-order kinetics with a half-life of 2.1 hours ( $t_{98\% \text{ conversion}} = 14$  h). Raw kinetic data: 0% yield at  $t = 0$  min; 11% yield at  $t = 40$  min; 54% yield at  $t = 780$  min; 57% yield at  $t = 1575$  min; 54% yield at  $t = 2970$  min. Best fit:

$$f(t) = A - Ae^{-kt} \quad |f(t)| = \text{yield (in decimal)}, A = 0.553, k = 0.00546 \text{ min}^{-1}.$$

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.93 – 5.85 (m, 1H), 5.30 (ddd, *J* = 17.3, 3.4, 1.6 Hz, 1H), 5.20 (dd, *J* = 10.7, 1.4 Hz, 1H), 4.86 (ddd, *J* = 48.7, 12.6, 6.2 Hz, 1H), 1.78 – 1.57 (m, 2H), 1.47 – 1.17 (m, 10H), 0.94 – 0.79 (m, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 136.98 (d, *J* = 19.7 Hz), 116.82 (d, *J* = 11.9 Hz), 93.91 (d, *J* = 166.6 Hz), 35.40 (d, *J* = 22.0 Hz), 31.95, 29.53, 29.36, 24.85 (d, *J* = 4.6 Hz), 22.84, 14.27.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ –176.66 – –177.11 (m).

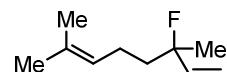


**(E)-1-fluorodec-2-ene** (linear isomer):

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.87 – 5.79 (m, 1H), 5.68 (dddd, *J* = 17.1, 8.6, 7.3, 4.1 Hz, 1H), 4.79 (dd, *J* = 47.5, 6.4 Hz, 2H), 2.08 (p, *J* = 6.7 Hz, 2H), 1.47 – 1.17 (m, 10H), 0.94 – 0.79 (m, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 137.94 (d, *J* = 12.0 Hz), 124.53, 83.89 (d, *J* = 160.1 Hz), 32.38 (d, *J* = 2.0 Hz), 31.98, 29.36, 29.31, 28.96, 22.82, 14.23.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ –207.35 (tm, *J* = 47.5 Hz).



**(±)-3-fluoro-3,7-dimethylocta-1,6-diene (2y):** Following the general procedure, a 2-dram vial with a stirbar was sequentially charged with linalool (154.2 mg, 1 mmol, Alfa Aesar), a solution of PBSF (332 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and BTPP (460 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 48 hours. Following addition of 1-fluoronaphthalene as an external standard, the yield was determined by <sup>19</sup>F NMR in CDCl<sub>3</sub> to be 9% yield. Additionally, 13% yield of the linear isomer (*E*)-1-fluoro-3,7-dimethylocta-2,6-diene was observed along with 1% yield (*Z*)-1-fluoro-3,7-dimethylocta-2,6-diene.

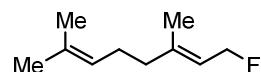
A sample was obtained by directly loading the reaction mixture onto an automated column (25 g silica) and removing the THF under a stream of air in the column-head space. The column was subjected to a gradient (0 → 15% ethyl acetate in hexanes) to afford a volatile colorless oil. By NMR, this was found to contain title compound as well as 65 mol% of the linear isomer (*E*)-1-fluoro-3,7-dimethylocta-2,6-diene, 6 mol% (*Z*)-1-fluoro-3,7-dimethylocta-2,6-diene, and several other uncharacterized impurities. The title compound has been previously characterized.<sup>21</sup> At 0.4 M concentration, the reaction appears to exhibit first-order kinetics with a half-life of 4.5 hours (*t*<sub>98% conversion</sub> = 30 h). Raw kinetic data (sum of all isomers): 0% yield at *t* = 0 min; 0% yield at *t* = 40 min; 12% yield at *t* = 180 min; 21% yield at *t* = 780 min; 27% yield at *t* = 1575 min. Best fit:

$$f(t) = A - Ae^{-kt} \quad |f(t)| = \text{yield (in decimal)}, \quad A = 0.265, \quad k = 0.00254 \text{ min}^{-1}.$$

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.89 (td, *J* = 17.7, 11.0 Hz, 1H), 5.27 (d, *J* = 17.4 Hz, 1H), 5.15 – 5.07 (m, 2H), 2.14 – 1.97 (m, 2H), 1.74 – 1.64 (m, 5H), 1.61 (s, 3H), 1.42 (d, *J* = 21.5 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 140.91 (d, *J* = 22.8 Hz), 132.08, 123.93, 113.35 (d, *J* = 11.4 Hz), 96.09 (d, *J* = 169.8 Hz), 40.46 (d, *J* = 23.2 Hz), 25.81, 25.41 (d, *J* = 25.0 Hz), 22.45 (d, *J* = 4.9 Hz), 17.72.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -148.51 (dqd, *J* = 39.6, 21.7, 17.6 Hz).

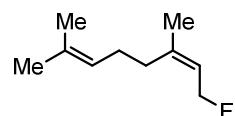


**(E)-1-fluoro-3,7-dimethylocta-2,6-diene (linear isomer):**

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.54 – 5.43 (m, 1H), 5.15 – 5.04 (m, 1H), 4.97 (dd, *J* = 40.9, 9.2 Hz, 2H), 2.16 – 1.96 (m, 4H), 1.73 (d, *J* = 8.3 Hz, 3H), 1.69 (s, 3H), 1.62 (s, 3H).

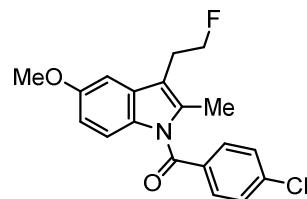
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 144.26 (d, *J* = 11.3 Hz), 132.00, 123.76, 119.09 (d, *J* = 16.9 Hz), 79.51 (d, *J* = 156.5 Hz), 39.70 (d, *J* = 2.7 Hz), 26.37 (d, *J* = 3.5 Hz), 25.83, 17.81, 16.58.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -207.73 (tdq, *J* = 47.8, 9.6, 4.8 Hz).



**(Z)-1-fluoro-3,7-dimethylocta-2,6-diene (linear isomer):**

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -206.55 (tm, *J* = 47.8 Hz).



**(4-chlorophenyl)(3-(2-fluoroethyl)-5-methoxy-2-methyl-1H-indol-1-yl)methanone (2z):**

Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with (4-chlorophenyl)(3-(2-hydroxyethyl)-5-methoxy-2-methyl-1H-indol-1-yl)methanone<sup>22</sup>

(343.8 mg, 1 mmol), **3-NO<sub>2</sub>** (226 mg, 1.1 equiv), THF (2 mL, 0.5 M), and BTMG (300 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 24 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 20% ethyl acetate in hexanes) to afford 295.8 mg product as a yellow solid (86% yield). At 0.4 M concentration, the reaction displays second order kinetics with a half-life of 1.8 hours (*t*<sub>98% conversion</sub> = 44 h). Raw kinetic data: 0% yield at *t* = 0 min; 35% yield at *t* = 36 min; 72% yield at *t* = 178 min; 90% yield at *t* = 1440 min. Best fit:

$$f(t) = A - \left( \frac{A}{[Ak t + 1]} \right) \quad f(t) = \text{yield (in decimal)}, A = .943, k = 0.0181 \text{ min}^{-1}.$$

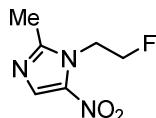
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.67 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.61 (dt, *J* = 47.0, 6.8 Hz, 2H), 3.84 (s, 3H), 3.08 (dt, *J* = 21.3, 6.8 Hz, 2H), 2.36 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 168.40, 156.11, 139.30, 135.79, 134.12, 131.26, 131.06, 130.98, 129.23, 115.16, 114.60 (d, *J* = 7.8 Hz), 111.45, 101.19, 82.83 (d, *J* = 170.2 Hz), 55.86, 25.66 (d, *J* = 21.8 Hz), 13.38.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -213.49 (tt, *J* = 47.0, 21.4 Hz).

**IR (ATR,  $\text{cm}^{-1}$ ):** 3105 (w), 3071 (w), 3038 (w), 2996 (w), 2954 (w), 2892 (w), 2834 (w), 1892 (w), 1673 (s), 1619 (w), 1597 (m), 1478 (w), 1465 (s), 1433 (m), 1402 (w), 1353 (s), 1329 (m), 1289 (m), 1251 (w), 1230 (m), 1211 (s), 1156 (m), 1142 (w), 1085 (m), 1064 (m), 1035 (s), 1014 (m), 1007 (m), 978 (m), 953 (w), 938 (m), 862 (m), 848 (s), 827 (w), 802 (s), 755 (s), 734 (w), 715 (w), 692 (w), 672 (w).

**HRMS (ESI+):** Calculated for  $\text{C}_{19}\text{H}_{18}\text{ClFNO}_2^+ [\text{M} + \text{H}]^+$  : 346.1005; found: 346.1001.

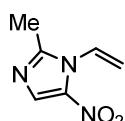


**1-(2-fluoroethyl)-2-methyl-5-nitro-1*H*-imidazole (2aa):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with metronidazole (171.2 mg, 1 mmol, Millipore-Sigma), a solution of PBSF (332 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and BTMG (220  $\mu\text{L}$ , 1.1 equiv). Addition of base resulted in a substantial exotherm; on larger scale, it may be necessary to add BTMG slowly, dilute the reaction, or cool the mixture prior to addition. The reaction was stirred at 600 rpm at room temperature for 30 minutes, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (50 g silica, 0  $\rightarrow$  10% methanol in dichloromethane) to afford 166.6 mg of a colorless oil. By NMR, this was determined to consist of 152.9 mg of the previously characterized title compound<sup>23</sup> (88% yield) and 13.7 mg of the elimination side product 2-methyl-5-nitro-1-vinyl-1*H*-imidazole<sup>24</sup> (9% yield, 9.9:1 selectivity).

**$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.97 (s, 1H), 4.75 (ddd,  $J = 47.0, 5.0, 4.0$  Hz, 2H), 4.61 (dt,  $J = 26.0, 4.4$  Hz, 2H), 2.50 (s, 3H).

**$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  151.74, 138.30, 133.40, 82.24 (d,  $J = 171.6$  Hz), 46.85 (d,  $J = 20.0$  Hz), 14.47 (d,  $J = 3.3$  Hz).

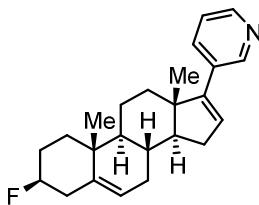
**$^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -224.07 (tt,  $J = 47.3, 26.1$  Hz).



**2-methyl-5-nitro-1-vinyl-1*H*-imidazole (unresolved elimination side product):**

**$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.92 (s, 1H), 7.05 (dd,  $J = 15.6, 8.2$  Hz, 1H), 5.64 (dd,  $J = 8.3, 1.3$  Hz, 1H), 5.41 (dd,  $J = 15.6, 1.3$  Hz, 1H), 2.51 (s, 3H).

**$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):** [nitro carbon not observed]  $\delta$  149.58, 131.90, 129.54, 116.49, 15.17.



**3-((3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-3-fluoro-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pyridine (2ab):** Following the general procedure, a 1-dram vial with a stirbar was sequentially charged with abiraterone (174.8 mg, 0.5 mmol), a solution of PBSF (166 mg, 1.1 equiv) in THF (1 mL, 0.5 M), and MTBD (108  $\mu$ L, 1.5 equiv). Addition of base resulted in a substantial exotherm; on larger scale, it may be necessary to add MTBD slowly, dilute the reaction, or cool the mixture prior to addition. The reaction was stirred at 600 rpm at room temperature for 30 minutes. The reaction mixture was concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g triethylamine-pretreated silica, 0  $\rightarrow$  15% ethyl acetate in hexanes) affording 49.2 mg of a white solid. By NMR, this was found to consist of 22.5 mg of the title compound (13% yield, 3.9:1 dr). Interestingly, the major diastereomer corresponds to retention of configuration, perhaps indicative of homoallylic neighboring group participation. Additionally, the sample contained 25.9 mg of the homoallylic rearrangement isomer, 3-((1*a**R*,3*a**R*,3*b**S*,5*a**S*,8*a**S*,8*b**R*,10*R*,10*a**R*)-10-fluoro-3*a*,5*a*-dimethyl-1,1*a*,2,3,3*a*,3*b*,4,5,5*a*,8,8*a*,8*b*,9,10-tetradecahydro-cyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl) pyridine (accounting for 15% of mass balance). This type of rearrangement has been previously documented in the literature.<sup>25</sup> By  $^{19}$ F NMR, the sample also contained an unidentified primary fluoride (triplet of triplets) present in 0.5% yield, which, assuming the mass is identical to that of the title compound, would account for 0.8 mg.

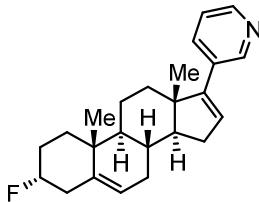
**$^1$ H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  8.62 (s, 1H), 8.46 (s, 1H), 7.64 (dq,  $J$  = 7.9, 1.8 Hz, 1H), 7.22 (dd,  $J$  = 8.0, 4.8 Hz, 1H), 5.99 (td,  $J$  = 3.3, 1.8 Hz, 1H), 5.43 (dd,  $J$  = 4.8, 2.8 Hz, 1H), 4.40 (dm,  $J$  = 50.4 Hz, 1H), 2.49 – 2.42 (m, 1H), 2.26 (dddd,  $J$  = 15.8, 6.6, 3.4, 1.6 Hz, 1H), 2.15 – 1.96 (m, 4H), 1.82 – 1.72 (m, 2H), 1.72 – 1.52 (m, 6H), 1.48 (tdd,  $J$  = 12.1, 5.1, 3.0 Hz, 1H), 1.09 (s, 3H), 1.08 – 1.04 (m, 4H), 0.93 (ddd,  $J$  = 13.8, 11.8, 7.9 Hz, 1H).

**$^{13}$ C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  151.77, 148.03, 148.00, 139.84 (d,  $J$  = 12.6 Hz), 133.81, 133.07, 129.36, 123.19, 122.82 (d,  $J$  = 1.1 Hz), 92.89 (d,  $J$  = 174.0 Hz), 57.61, 50.33 (d,  $J$  = 1.7 Hz), 47.46, 39.54 (d,  $J$  = 19.3 Hz), 36.86 (d,  $J$  = 1.2 Hz), 35.33, 33.07, 31.94, 31.67, 30.53, 28.88 (d,  $J$  = 17.7 Hz), 21.03, 19.40, 16.72.

**$^{19}$ F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -167.96 (dm,  $J$  = 50.2 Hz).

**IR (ATR, cm<sup>-1</sup>):** (1:1.2 mixture of product (3.9:1 dr):homoallylic rearrangement isomer): 3038 (w), 3010 (w), 2932 (m), 2856 (w), 1716 (w), 1599 (w), 1561 (w), 1474 (w), 1462 (w), 1442 (w), 1408 (w), 1399 (w), 1375 (m), 1319 (w), 1296 (w), 1280 (w), 1245 (w), 1192 (w), 1160 (w), 1128 (w), 1104 (w), 1080 (w), 1062 (w), 1050 (w), 1006 (s), 973 (m), 947 (m), 924 (w), 914 (w), 887 (w), 869 (m), 841 (w), 825 (w), 799 (s), 730 (w), 711 (s), 678 (w).

**HRMS (ESI+):** Calculated for C<sub>24</sub>H<sub>31</sub>FN<sup>+</sup> [M + H]<sup>+</sup>: 352.2435; found: 352.2440.

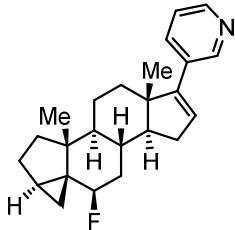


**3-((3*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-3-fluoro-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pyridine** (unresolved minor diastereomer):

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** (Only the C3 proton is distinguishable from diastereomer.) δ 8.62 (s, 1H), 8.46 (s, 1H), 7.64 (dq, *J* = 7.9, 1.8 Hz, 1H), 7.22 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.99 (td, *J* = 3.3, 1.8 Hz, 1H), 5.43 (dd, *J* = 4.8, 2.8 Hz, 1H), 4.84 (dm, *J* = 49.2 Hz, 1H), 2.49 – 2.42 (m, 1H), 2.26 (dddd, *J* = 15.8, 6.6, 3.4, 1.6 Hz, 1H), 2.15 – 1.96 (m, 4H), 1.82 – 1.72 (m, 2H), 1.72 – 1.52 (m, 6H), 1.48 (tdd, *J* = 12.1, 5.1, 3.0 Hz, 1H), 1.09 (s, 3H), 1.08 – 1.04 (m, 4H), 0.93 (ddd, *J* = 13.8, 11.8, 7.9 Hz, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 151.79, 148.03, 147.96, 138.34, 133.85, 133.08, 129.41, 123.19, 122.68, 89.64 (d, *J* = 168.7 Hz), 57.63, 50.18, 47.50, 37.65 (d, *J* = 23.1 Hz), 37.34, 35.33, 33.01, 31.91, 31.60, 30.48, 27.13 (d, *J* = 21.1 Hz), 20.69, 19.47, 18.81.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ –182.68 – –183.38 (m).

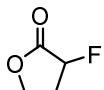


**3-((1*aR*,3*aR*,3*bS*,5*aS*,8*aS*,8*bR*,10*R*,10*aR*)-10-fluoro-3*a*,5*a*-dimethyl-1,1*a*,2,3,3*a*,3*b*,4,5,5*a*,8,8*a*,8*b*,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)pyridine** (unresolved homoallylic rearrangement isomer):

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 8.46 (s, 1H), 7.64 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.22 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.99 (td, *J* = 3.3, 1.8 Hz, 1H), 4.13 (dt, *J* = 48.4, 2.7 Hz, 1H), 2.15 – 1.96 (m, 2H), 1.88 (dq, *J* = 13.1, 4.0 Hz, 1H), 1.82 – 1.43 (m, 9H), 1.40 – 1.24 (m, 2H), 1.14 – 1.09 (m, 1H), 1.09 (s, 3H), 1.06 (s, 3H), 1.00 (td, *J* = 11.1, 4.9 Hz, 1H), 0.69 (t, *J* = 4.6 Hz, 1H), 0.53 (dd, *J* = 8.1, 5.3 Hz, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 151.92, 148.09, 148.03, 133.79, 133.05, 129.19, 123.16, 96.46 (d, *J* = 166.5 Hz), 57.51, 47.75, 47.66, 43.42 (d, *J* = 1.5 Hz), 36.60 (d, *J* = 25.5 Hz), 36.34 (d, *J* = 2.1 Hz), 36.29 (d, *J* = 37.1 Hz), 35.61, 31.84, 28.93, 25.09, 23.40 (d, *J* = 10.3 Hz), 22.49, 19.63, 16.98, 12.57 (d, *J* = 1.9 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ –170.90 (tm, *J* = 47.3).

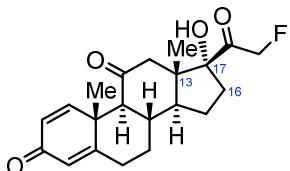


**( $\pm$ )-3-fluorodihydrofuran-2(3*H*)-one (2ac):** According to the general procedure, a 2-dram vial with a stirbar was charged sequentially with  $\alpha$ -hydroxy- $\gamma$ -butyrolactone (102.1 mg, 1 mmol, Sigma-Millipore), a solution of PBSF (332 mg, 1.1 equiv) in THF (2 mL, 0.5 M), and MTBD (215  $\mu$ L, 1.5 equiv). Addition of base resulted in a substantial exotherm that briefly raised the upper layer of solvent above the boiling point. On larger scale, it may be necessary to add MTBD slowly, dilute the reaction, or cool the mixture prior to addition. The reaction was stirred at 600 rpm at room temperature for 30 minutes, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0  $\rightarrow$  40% ethyl acetate in hexanes). The product is not UV active and was identified by taking crude  $^{19}\text{F}$  NMRs of the fractions at regular intervals. Product-containing fractions were concentrated by rotary evaporation at 0  $^{\circ}\text{C}$  to afford 81.4 mg product of a colorless oil (78% yield). This product has been previously characterized.<sup>26</sup>

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  5.08 (dt,  $J$  = 51.2, 7.7 Hz, 1H), 4.38 (td,  $J$  = 8.9, 3.9 Hz, 1H), 4.20 (q,  $J$  = 8.2 Hz, 1H), 2.57 (ttd,  $J$  = 14.1, 7.3, 3.8 Hz, 1H), 2.40 (ddq,  $J$  = 21.8, 13.4, 8.1 Hz, 1H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  171.82 (d,  $J$  = 20.8 Hz), 85.34 (d,  $J$  = 189.7 Hz), 64.97 (d,  $J$  = 5.9 Hz), 29.51 (d,  $J$  = 20.1 Hz).

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -195.68 (ddd,  $J$  = 51.0, 22.9, 13.8 Hz).



**(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-(2-fluoroacetyl)-17-hydroxy-10,13-dimethyl-7,8,9,10,12,13,14,15,16,17-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,11(6*H*)-dione (2ad):** Following the general procedure, a 2-dram vial with a stirbar was charged sequentially with prednisone (358.4 mg, 1 mmol, Sigma-Millipore), **3**-CF<sub>3</sub> (251 mg, 1.1 equiv), THF (2 mL, 0.5 M), and TPP (380  $\mu$ L, 1.25 equiv). The reaction was stirred at 600 rpm at room temperature for 3 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 10  $\rightarrow$  60% ethyl acetate in hexanes) to afford 229.7 mg of a white solid. Examination by NMR indicated that this consisted of a mixture of 170.2 mg of the title compound (47% yield), and 59.5 mg of the unconverted sulfonate ester intermediate 2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-hydroxy-10,13-dimethyl-3,11-dioxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-17-yl)-2-oxoethyl 4-(trifluoromethyl)benzenesulfonate (accounting for 11% of the mass balance). By HMBC, the alcohol proton peaks for both the title compound and sulfonate ester correlated with carbons 13, 16, and 17, indicating that the 17-hydroxy group is unprotected in both compounds and that the observed sulfonate ester is bound to the primary alcohol.

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.59 (d,  $J$  = 10.2 Hz, 1H), 6.10 (dd,  $J$  = 10.2, 1.9 Hz, 1H), 6.01 (t,  $J$  = 1.8 Hz, 1H), 5.82 (s, 1H), 5.39 (dd,  $J$  = 47.6, 17.3 Hz, 1H), 5.10 (dd,  $J$  = 47.2, 17.3 Hz,

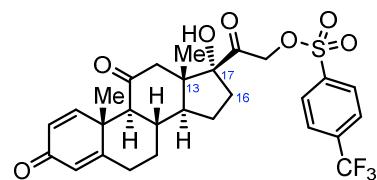
1H), 2.86 (d,  $J = 12.4$  Hz, 1H), 2.58 – 2.45 (m, 2H), 2.39 – 2.27 (m, 2H), 2.18 (d,  $J = 11.2$  Hz, 1H), 2.08 (s, 1H), 2.05 – 1.94 (m, 2H), 1.82 – 1.72 (m, 1H), 1.67 (ddd,  $J = 15.1, 9.6, 5.7$  Hz, 1H), 1.43 – 1.36 (m, 1H), 1.35 (s, 3H), 1.25 – 1.18 (m, 1H), 0.53 (s, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  210.01, 206.30 (d,  $J = 12.4$  Hz), 185.09, 167.18, 155.08, 127.04, 123.80, 87.41, 84.94 (d,  $J = 176.3$  Hz), 58.81, 50.74, 49.53, 48.83, 41.95, 35.51, 33.84, 33.15, 31.55, 22.84, 18.76, 15.43.

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  –231.16 (t,  $J = 47.4$  Hz).

**IR (ATR,  $\text{cm}^{-1}$ ):** (4.5:1 mixture of product:sulfonate ester) 3383 (br, s), 2941 (m), 1730 (m), 1704 (m), 1656 (s), 1616 (m), 1598 (w), 1445 (w), 1373 (w), 1354 (w), 1324 (w), 1301 (w), 1243 (m), 1185 (m), 1136 (m), 1116 (w), 1088 (m), 1063 (w), 1043 (s), 943 (w), 899 (s), 821 (s), 774 (w), 750 (w), 727 (w), 709 (w), 691 (m).

**HRMS (ESI+):** Calculated for  $\text{C}_{21}\text{H}_{26}\text{FO}_4^+ [\text{M} + \text{H}]^+$  : 361.1810; found: 361.1811.



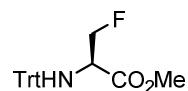
**2-((8S,9S,10R,13S,14S,17R)-17-hydroxy-10,13-dimethyl-3,11-dioxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl 4-(trifluoromethyl)benzenesulfonate (unresolved unconverted sulfonate ester):**

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.15 (d,  $J = 8.3$  Hz, 2H), 8.07 (d,  $J = 8.3$  Hz, 2H), 7.58 (dd,  $J = 10.2, 1.8$  Hz, 1H), 6.10 (dd,  $J = 10.2, 1.9$  Hz, 1H), 6.01 (t,  $J = 1.8$  Hz, 1H), 5.89 (s, 1H), 5.28 (d,  $J = 17.8$  Hz, 1H), 4.92 (d,  $J = 17.7$  Hz, 1H), 2.90 – 2.79 (m, 1H), 2.58 – 2.44 (m, 2H), 2.39 – 2.27 (m, 2H), 2.21 – 2.12 (m, 1H), 2.10 – 2.04 (m, 1H), 2.04 – 1.92 (m, 2H), 1.81 – 1.73 (m, 1H), 1.72 – 1.62 (m, 1H), 1.43 – 1.36 (m, 1H), 1.34 (s, 3H), 1.26 – 1.14 (m, 1H), 0.44 (s, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  209.75, 203.28, 185.09, 167.15, 155.03, 139.57, 133.90 (q,  $J = 32.4$  Hz), 128.77 (m), 128.68, 127.04, 125.43 (q,  $J = 273.1$  Hz), 123.80, 87.69, 73.58, 58.75, 50.88, 49.36, 48.76, 41.95, 35.51, 34.01, 33.15, 31.55, 22.79, 18.72, 15.17.

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  –61.92 (s).

**HRMS (ESI+):** Calculated for  $\text{C}_{28}\text{H}_{30}\text{F}_3\text{O}_7\text{S}^+ [\text{M} + \text{H}]^+$ : 567.1659; found: 567.1659.



**methyl (*R*)-3-fluoro-2-(tritylaminoo)propanoate (2ae):** According to the general procedure, a 20-mL scintillation vial with a stirbar was charged sequentially with *N*-trityl-L-serine methyl ester (361.4 mg, 1 mmol, TCI), a solution of PBSF (332 mg, 1.1 equiv) in THF (10 mL, 0.1 M), and BTPP (460  $\mu\text{L}$ , 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 3 hours, concentrated, taken up in minimal dichloromethane, and purified by automated column chromatography (25 g silica, 0 → 15% ethyl acetate in hexanes), affording 294.3 mg of a white foamy solid. By NMR, this was found to consist of 87.9 mg product (24% yield) and 206.4 mg of the side product methyl (*S*)-1-tritylaziridine-2-carboxylate<sup>27</sup> (60% of mass balance). Because

the selectivity does not appear to change over time, we suspect that aziridine is an unproductive side product (instead of an intermediate that forms product *via* ring-opening.)

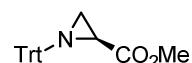
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.56 (d, *J* = 7.5 Hz, 6H), 7.32 (dt, *J* = 7.8, 5.7 Hz, 6H), 7.29 – 7.22 (m, 3H), 4.68 (ddd, *J* = 47.0, 8.8, 4.7 Hz, 1H), 4.50 (ddd, *J* = 47.1, 8.8, 6.1 Hz, 1H), 3.67 (dddd, *J* = 19.4, 10.6, 6.1, 4.7 Hz, 1H), 3.29 (s, 3H), 2.89 (d, *J* = 10.3 Hz, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 172.79 (d, *J* = 3.5 Hz), 145.61, 128.79, 128.07, 126.72, 85.01 (d, *J* = 176.7 Hz), 71.02, 56.70 (d, *J* = 21.1 Hz), 52.19.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -224.37 (td, *J* = 47.0, 19.4 Hz).

**IR (ATR, cm<sup>-1</sup>):** (1:2.5 mixture of product:aziridine) 3057 (w), 3028 (w), 2951 (w), 1740 (s), 1596 (w), 1489 (m), 1446 (m), 1392 (w), 1285 (w), 1241 (w), 1198 (s), 1177 (s), 1080 (m), 1032 (m), 1014 (w), 972 (w), 903 (w), 839 (w), 776 (w), 745 (s), 705 (s), 696 (w).

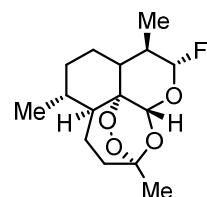
**HRMS (ESI+):** Calculated for C<sub>4</sub>H<sub>9</sub>FNO<sub>2</sub><sup>+</sup> [M – C(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub> + 2H]<sup>+</sup>: 122.0612; found: 122.0611.



**methyl (S)-1-tritylaziridine-2-carboxylate** (unresolved aziridine side product):

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.56 (d, *J* = 7.5 Hz, 6H), 7.32 (dt, *J* = 7.8, 5.7 Hz, 6H), 7.29 – 7.21 (m, 3H), 3.81 (s, 3H), 2.31 (dd, *J* = 2.7, 1.6 Hz, 1H), 1.95 (dd, *J* = 6.2, 2.7 Hz, 1H), 1.47 (dd, *J* = 6.2, 1.7 Hz, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 172.05, 143.71, 129.43, 127.77, 127.05, 74.51, 52.22, 31.81, 28.81.



**(3*R*,5*a**S*,6*R*,9*R*,10*S*,12*S*,12*a**R*)-10-fluoro-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromene (2af):** Following the general procedure, a 1-dram vial with a stirbar was charged sequentially with dihydroartemisinin (284.3 mg, 1.0 mmol, TCI), **3-NO<sub>2</sub>** (226 mg, 1.1 equiv), THF (2 mL, 0.5 M), and BTMG (300 μL, 1.5 equiv). The reaction was stirred at 600 rpm at room temperature for 30 minutes. Following addition of 1-fluoronaphthalene as an external standard, the yield was determined by <sup>19</sup>F NMR to be 54% yield with a 3.8:1 dr. Although the inverted diastereomer is favored, we suspect that the reaction proceeds *via* an oxocarbenium intermediate. The fluoride anion, which is coordinated to the protonated base, approaches primarily from the less-hindered face. This is supported in the screening results which show that diastereoselectivity increases when bulkier bases are employed.

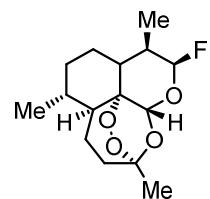
At least one of the product diastereomers decomposes readily on contact with acidic solution or silica, making purification a significant challenge. A sample was obtained by concentrating the reaction mixture, dissolving the residue in minimal dichloromethane, and rapidly purifying by automated column chromatography (25 g Florisil (EMD-Millipore), 0 → 25% ethyl acetate in

hexanes) to afford a white solid. By NMR, this was found to consist of the title compound, 5 mol% of the diastereomer (*3R,5aS,6R,9R,10R,12S,12aR*)-10-fluoro-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2] dioxepino[4,3-*i*]isochromene, and 20 mol% of the elimination side product (*3R,5aS,6R,12R,12aR*)-3,6,9-trimethyl-3,4,5,5a,6,7,8,8a-octahydro-12*H*-3,12-epoxy[1,2] dioxepino[4,3-*i*]isochromene. All three products have been characterized in the literature.<sup>28</sup>

**<sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>):** δ 5.10 (s, 1H), 5.02 (dd, *J* = 53.9, 9.0 Hz, 1H), 2.72 (dtdd, *J* = 14.0, 11.6, 8.0, 5.9 Hz, 1H), 2.30 (ddd, *J* = 14.4, 13.4, 4.0 Hz, 1H), 1.69 (ddd, *J* = 14.3, 5.0, 3.0 Hz, 1H), 1.55 – 1.49 (m, 1H), 1.35 (s, 3H), 1.31 – 1.12 (m, 4H), 1.04 – 0.95 (m, 1H), 0.93 – 0.84 (m, 1H), 0.80 – 0.73 (m, 1H), 0.71 – 0.66 (m, 6H), 0.53 – 0.47 (m, 1H).

**<sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>):** δ 108.68 (d, *J* = 208.3 Hz), 104.50, 91.39 (d, *J* = 6.2 Hz), 79.70, 51.44 (d, *J* = 0.5 Hz), 45.21 (d, *J* = 9.4 Hz), 36.98, 36.53, 34.24, 33.10 (d, *J* = 19.2 Hz), 25.93, 25.04, 21.85, 20.19, 11.71.

**<sup>19</sup>F NMR (282 MHz, C<sub>6</sub>D<sub>6</sub>):** δ –141.58 (ddd, *J* = 53.9, 10.7, 4.7 Hz).

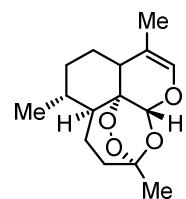


**(3*R*,5*aS*,6*R*,9*R*,10*R*,12*S*,12*aR*)-10-fluoro-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromene (unresolved minor diastereomer):**

**<sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>):** δ 5.58 (d, *J* = 1.9 Hz, 1H), 5.51 (d, *J* = 55.0 Hz, 1H), 2.60 (dddt, *J* = 35.7, 7.5, 5.2, 2.6 Hz, 1H), 2.34 – 2.27 (m, 1H), 1.74 – 1.63 (m, 1H), 1.60 – 1.39 (m, 3H), 1.37 (s, 3H), 1.31 – 1.15 (m, 3H), 1.03 (td, *J* = 11.3, 6.7 Hz, 1H), 0.83 – 0.66 (m, 1H), 0.65 (s, 6H), 0.62 – 0.47 (m, 1H).

**<sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>):** δ 111.08 (d, *J* = 222.0 Hz), 104.40, 88.93, 52.39, 43.83 (d, *J* = 2.0 Hz), 37.12, 36.56, 34.67, 31.05 (d, *J* = 22.9 Hz), 30.24, 26.00, 25.04, 24.35 (d, *J* = 5.8 Hz), 20.24, 12.30 (d, *J* = 1.6 Hz).

**<sup>19</sup>F NMR (282 MHz, C<sub>6</sub>D<sub>6</sub>):** δ –133.47 (dd, *J* = 55.2, 35.5 Hz).



**(3*R*,5*aS*,6*R*,12*R*,12*aR*)-3,6,9-trimethyl-3,4,5,5a,6,7,8,8a-octahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromene (unresolved elimination side product):**

**<sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>):** δ 6.28 (q, *J* = 1.5 Hz, 1H), 5.49 (s, 1H), 2.35 (ddd, *J* = 14.5, 13.3, 4.0 Hz, 1H), 1.74 – 1.65 (m, 2H), 1.59 – 1.52 (m, 2H), 1.43 – 1.30 (m, 7H), 1.25 – 1.16 (m, 2H), 0.95 – 0.81 (m, 2H), 0.74 – 0.63 (m, 4H).

**<sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>):** δ 136.13, 107.56, 104.51, 89.99, 78.91, 51.64, 44.82, 37.26, 36.61, 34.28, 30.08, 26.08, 24.86, 20.33, 16.32.

## VI. Development of Predictive Machine Learning Model

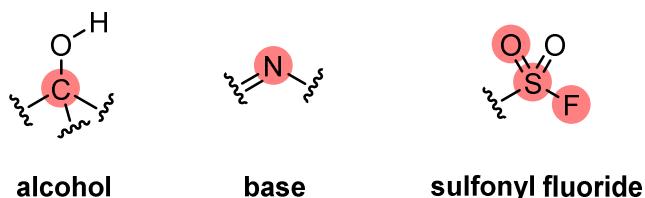
The 640 screening results Section II were used to train and test a random forest machine learning model. Model development and testing was carried out in the R Studio integrated development environment using with a modified version of the “rxnpredict” R script developed by Derek T. Ahneman in our previous publication.<sup>29</sup> The R script, input, and output files are included in the supplementary information in the compressed folder “rxnpredict.zip”. The procedure used to prepare data and train the model is described below:

- 1) The following programs and files were downloaded from the indicated source and installed:
  - R (<<https://cran.r-project.org/mirrors.html>>)
  - R Studio (<<https://www.rstudio.com/products/rstudio/download/>>)
  - The “rxnpredict” root directory included in the Supplementary Information as “rxnpredict.zip”.
- 2) In our previous publication, descriptors were automatically generated based on the shared atoms in substrate classes. In the current work, we found that having a large number of potentially irrelevant descriptors resulted in a model that predicted the internal test set with reasonable accuracy, but generated poor predictions for out-of-set substrates. Instead, we chose to manually select descriptors that are relevant to the expected nucleophilic substitution mechanism, although these could certainly be automatically extracted as well. Descriptors were generated according the following procedure:

### *Calculated descriptors:*

The 32 alcohols **1a–1af**; the five sulfonyl fluorides **3-Cl**, **PyFluor**, **3-CF<sub>3</sub>**, **3-NO<sub>2</sub>**, and **PBSF**; and the four bases **DBU**, **MTBD**, **BTMG**, and **BTPP** were submitted as calculations using Spartan '14 v. 1.1.14 (B3LYP, 6-31G\*). The following atomic and molecular descriptors were selected: (The atoms \*C1, \*N1, \*S1, \*O1, and \*F1 refer to the atoms highlighted in Figure S4.)

- Alcohol - \*C1 electrostatic charge
- Alcohol - \*C1 exposed area (Å<sup>2</sup>)
- Alcohol - electronegativity
- Base - \*N1 exposed area (Å<sup>2</sup>)
- Sulfonyl fluoride - \*S1 electrostatic charge
- Sulfonyl fluoride - \*F1 electrostatic charge
- Sulfonyl fluoride - \*O1 electrostatic charge



**Figure S4.** Designated atoms in the alcohol, sulfonyl fluoride, and base substrate classes.

*Categorical descriptors:*

For each alcohol, the following categorical descriptors were included. These are presented in binary format: if the category applies to a specific alcohol, the input is ‘1’, otherwise it is ‘0’.

- Alcohol - primary
- Alcohol - secondary
- Alcohol - tertiary
- Alcohol - cyclic
- Alcohol - 4-membered ring
- Alcohol - 5-membered ring
- Alcohol - 6-membered ring
- Alcohol - 7-membered ring
- Alcohol - benzylic
- Alcohol - allylic
- Alcohol - homobenzylic
- Alcohol - homoallylic
- Alcohol - alpha-carbonyl
- Alcohol - beta-carbonyl
- Alcohol - hemiacetal
- Alcohol - amino alcohol

These values were saved in the file “rxnpredict\R\_input\descriptor\_table.csv” within “rxnpredict.zip”. This file includes 23 columns corresponding to each of the descriptors, a header row containing the descriptor titles, and 640 rows corresponding to each reaction in the following order:

- 1 – alcohol **1e**, base **DBU**, sulfonyl fluoride **3-Cl**
- 2 – alcohol **1e**, base **DBU**, sulfonyl fluoride **PyFluor**
- 3 – alcohol **1e**, base **DBU**, sulfonyl fluoride **3-CF<sub>3</sub>**
- 4 – alcohol **1e**, base **DBU**, sulfonyl fluoride **3-NO<sub>2</sub>**
- 5 – alcohol **1e**, base **DBU**, sulfonyl fluoride **PBSF**
- 6 – alcohol **1e**, base **MTBD**, sulfonyl fluoride **3-Cl**
- 7 – alcohol **1e**, base **MTBD**, sulfonyl fluoride **PyFluor**
- 8 – alcohol **1e**, base **MTBD**, sulfonyl fluoride **3-CF<sub>3</sub>**
- 9 – alcohol **1e**, base **MTBD**, sulfonyl fluoride **3-NO<sub>2</sub>**
- 10 – alcohol **1e**, base **MTBD**, sulfonyl fluoride **PBSF**
- 11 – alcohol **1e**, base **BTMG**, sulfonyl fluoride **3-Cl**
- 12 – alcohol **1e**, base **BTMG**, sulfonyl fluoride **PyFluor**
- 13 – alcohol **1e**, base **BTMG**, sulfonyl fluoride **3-CF<sub>3</sub>**
- 14 – alcohol **1e**, base **BTMG**, sulfonyl fluoride **3-NO<sub>2</sub>**
- 15 – alcohol **1e**, base **BTMG**, sulfonyl fluoride **PBSF**
- 16 – alcohol **1e**, base **BTPP**, sulfonyl fluoride **3-Cl**
- 17 – alcohol **1e**, base **BTPP**, sulfonyl fluoride **PyFluor**
- 18 – alcohol **1e**, base **BTPP**, sulfonyl fluoride **3-CF<sub>3</sub>**

19 – alcohol **1e**, base **BTPP**, sulfonyl fluoride **3-NO<sub>2</sub>**  
20 – alcohol **1e**, base **BTPP**, sulfonyl fluoride **PBSF**  
21 – alcohol **1a**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
41 – alcohol **1f**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
61 – alcohol **1g**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
81 – alcohol **1h**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
101 – alcohol **1i**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
111 – alcohol **1j**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
141 – alcohol **1k**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
161 – alcohol **1c**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
181 – alcohol **1l**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
201 – alcohol **1d**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
221 – alcohol **1m**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
241 – alcohol **1n**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
261 – alcohol **1o**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
281 – alcohol **1p**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
301 – alcohol **1q**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
321 – alcohol **1b**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
341 – alcohol **1r**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
361 – alcohol **1s**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
381 – alcohol **1t**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
401 – alcohol **1u**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
421 – alcohol **1v**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
441 – alcohol **1w**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
461 – alcohol **1x**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
481 – alcohol **1y**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
501 – alcohol **1z**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
521 – alcohol **1aa**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]  
541 – alcohol **1ab**, base **DBU**, sulfonyl fluoride **3-Cl**  
[...]

561 – alcohol **1ac**, base **DBU**, sulfonyl fluoride **3-Cl**  
 [...]  
 581 – alcohol **1ad**, base **DBU**, sulfonyl fluoride **3-Cl**  
 [...]  
 601 – alcohol **1ae**, base **DBU**, sulfonyl fluoride **3-Cl**  
 [...]  
 621 – alcohol **1af**, base **DBU**, sulfonyl fluoride **3-Cl**  
 [...]  
 640 – alcohol **1af**, base **BTPP**, sulfonyl fluoride **PBSF**

3) Descriptors for an external test set corresponding to alcohols **1ag – 1ak** (see Section VII) were generated as in Step 2 and saved in “rxnpredict\R\_input\descriptor\_table\_external\_set.csv”. These alcohols do not appear in the training set under any conditions and are used to assess the ability of the model to predict reaction outcome of new, untested substrates.

4) The experimental reaction yields for alcohols **1a – 1af** from section II are included in the file ““rxnpredict\R\_input\observed\_yields.csv” as a single column with no header corresponding to the rows in “rxnpredict\R\_input\descriptor\_table.csv” as shown above. The experimental yields for alcohols **1ag – 1ak** are included in ““rxnpredict\R\_input\external\_set\_observed\_yields.csv”.

5) The “rxnpredict\rxnpredict.R” R script was opened in R Studio. User note: Line 9 should be modified to set the working directory as the location of the “rxnpredict” folder.

6) The “rxnpredict\rxnpredict.R” script was executed in R studio. The script with documentation is as follows:

```

# Install packages (if necessary) and load them.
if (!require("pacman")) install.packages("pacman")
pacman::p_load(ggplot2,
               caret,
               ModelMetrics,
               scales)

# Set the working directory to the location of the rxnpredict folder.
setwd("C:\\\\Users\\\\matt\\\\Desktop\\\\rxnpredict")

# =====#
# Load descriptor and yield data and prepare data for modeling.
# =====#

# Load user-created table containing reaction descriptors.
descriptor.table <- read.csv("R_input\\descriptor_table.csv", header=TRUE)

# Scale the descriptor data. Scale parameters are saved in descriptor.data.
descriptor.data <- scale(descriptor.table)
descriptor.scaled <- as.data.frame(descriptor.data)

# Load user-created yield data.
yield.data <- as.numeric(unlist(read.csv("R_input\\observed_yields.csv", header=FALSE, stringsAsFactors=FALSE)))

# Append the yield data to the descriptor table.
descriptor.scaled$yield <- yield.data

# =====#
# Split data and train random forest model.
# =====#

# Split into training and test set (70/30).
set.seed(1751)
size <- round(0.70*nrow(descriptor.scaled))
training <- sample(nrow(descriptor.scaled), size=size, replace=FALSE)
training.scaled <- descriptor.scaled[training,]
test.scaled <- descriptor.scaled[-training,]

# 10-fold cross-validation.

```

```

train_control <- trainControl(method="cv", number=10, savePredictions=TRUE)

# Train the random forest model.
rfFit <- train(yield ~ ., data=training.scaled, trControl=train_control, method="rf", importance=TRUE)

# Save the trained random forest model.
saveRDS(rfFit, "R_output\\rfFit.rds")

# =====
# Calculate R^2 and RMSE using test set and generate calibration plot.
# =====

# Predict yields for test set.
rf.pred <- predict(rfFit, test.scaled)

# Generate *.csv showing predicted and observed yields for the test set (saves to test_set_predicted_yields.csv).
predicted.yields <- as.data.frame(rf.pred)
predicted.yields$rf.pred <- round(predicted.yields$rf.pred, digits=1)
predicted.yields$yield <- test.scaled$yield
predicted.yields["Error"] <- predicted.yields$yield-predicted.yields$rf.pred
names(predicted.yields)[names(predicted.yields) == 'rf.pred'] <- 'Predicted Yield'
names(predicted.yields)[names(predicted.yields) == 'yield'] <- 'Observed Yield'
write.csv(predicted.yields, 'R_output\\test_set_predicted_yields.csv')

# Calculate R^2 and RMS error for test set.
rf.r2 <- cor(rf.pred, test.scaled$yield)^2
rf.rmse <- rmse(rf.pred, test.scaled$yield)

# Calculate R^2 and RMS error for training set (included to compare accuracy of training vs. test sets).
rftrain.pred <- predict(rfFit, training.scaled)
rftrain.r2 <- cor(rftrain.pred, training.scaled$yield)^2
rftrain.rmse <- rmse(rftrain.pred, training.scaled$yield)

# Generate calibration plot of test set (saves to test_set-calibration_plot.png).
df <- data.frame(x = rf.pred,
                  y = test.scaled$yield)
rsq <- paste(round(rf.r2, digits = 3))
rms <- paste(round(rf.rmse, digits = 1))
p1 <- ggplot(df, aes(x = x, y = y)) +
  geom_point(alpha = 0.4) +
  scale_x_continuous(breaks = seq(0,100,25), lim=c(0, 100)) +
  labs(x='Predicted Yield', y='Observed Yield', caption = bquote(R^2 ~ " = " ~ .(rsq) * "; RMS error = " ~ .(rms) * "%")) +
  theme(plot.caption = element_text(hjust = 0.5, size = 8)) +
  geom_segment(aes(x=0,xend=100,y=0,yend=100), linetype="dashed")
ggsave(file="R_output\\test_set-calibration_plot.png", width=5, height=4)

# =====
# Create Variable importance plot.
# =====

# Read in variable importance from trained rf model.
rf_imp <- importance(rfFit$finalModel)
rf.imp.df <- cbind(as.data.frame(rf_imp), names(rf_imp[, 1]))
colnames(rf.imp.df)[1] <- "IncMSE"
colnames(rf.imp.df)[3] <- "descriptor"

# For descriptor names, replace "_" with " " and "." with "*".
rf.imp.df$descriptor <- gsub("_", " ", rf.imp.df$descriptor)
rf.imp.df$descriptor <- gsub("[.]", "*", rf.imp.df$descriptor)

# Capitalize descriptor names.
simpleCap <- function(x) {
  s <- strsplit(x, " ")[[1]]
  paste(toupper(substring(s, 1, 1)), substring(s, 2),
        sep="", collapse=" ")
}
rf.imp.df$descriptor <- sapply(rf.imp.df$descriptor, simpleCap)

# Plot variable importance (saves to variable_importance_plot.png).
# USER: change '10' on next line to modify minimum percentage cutoff for IncMSE.
p2 <- ggplot(rf.imp.df[rf.imp.df$IncMSE>10, ], aes(x=reorder(descriptor, IncMSE), y=IncMSE)) +
  geom_bar(stat="identity") +
  scale_y_continuous(labels = comma) +

```

```

  labs(x="", y="Increase in Mean Squared Error (% yield)^2") +
  coord_flip()
# USER: change 'width' and 'height' parameter on next line to control plot dimensions.
ggsave(file="R_output\\variable_importance_plot.png", width=8, height=4)

# =====
# Load descriptors and predict yields for external test set.
# =====

# Load external test set.
externalset.table <- read.csv("R_input\\descriptor_table_external_set.csv", header=TRUE)

# Scale the external set data using the same scaling as for the training and test sets.
externalset.data <- scale(externalset.table, attr(descriptor.data,"scaled:center"),attr(descriptor.data,"scaled:scale"))
externalset.scaled <- as.data.frame(externalset.data)

# Predict yields for external test set.
rf.externalset <- predict(rfFit, externalset.scaled)

# Create table with predicted yields for external test set (saves to external_set_predicted_yields.csv).
externalset.predictedyields <- as.data.frame(rf.externalset)
externalset.predictedyields $rf.externalset <- round(externalset.predictedyields $rf.externalset, digits=1)
names(externalset.predictedyields )[names(externalset.predictedyields ) == 'rf.externalset'] <- 'Predicted Yield'
write.csv(externalset.predictedyields , 'R_output\\external_set_predicted_yields.csv')

# =====
# Calibration plots for external test substrates.
# =====

# Load external set observed yields.
external_obs <- as.numeric(unlist(read.csv("R_input\\external_set_observed_yields.csv", header=FALSE, stringsAsFactors=FALSE)))

# Store predicted yields for external substrates.
external_pred <- c(rf.externalset)

# Generate calibration plot for external substrates (saves to external-calibration_plot.png).
ex.r2 <- cor(external_pred, external_obs)^2
ex.rmse <- rmse(external_pred, external_obs)
alcohol <- rep(c("1ag", "1ah", "1ai", "1aj", "1ak"), times = c(20,20,20,20,20))
ex.df <- data.frame(x = external_pred,
                      y = external_obs,
                      substrate = alcohol)
exrsq <- paste(round(ex.r2, digits = 3))
exrms <- paste(round(ex.rmse, digits = 1))
ex.p1 <- ggplot(ex.df, aes(x = x, y = y, color = substrate)) +
  scale_color_manual(values=c("red", "darkorange1", "blue", "darkgreen", "purple3", "black")) +
  geom_point(alpha = 0.6) +
  scale_x_continuous(breaks = seq(0,100,25), lim=c(0, 100)) +
  labs(x='Predicted Yield', y='Observed Yield', caption = bquote(R^2 ~ " = " ~ .(exrsq) * "; RMS error = " ~ .(exrms) * "%")) +
  theme(plot.caption = element_text(hjust = 0.5, size = 8), legend.position="none") +
  geom_segment(aes(x=0,xend=100,y=0,yend=100,color="black"), linetype="dashed")
ggsave(file="R_output\\external-calibration_plot.png", width=5, height=4)

# Calculate R^2 and RMSE for external test substrates.
ex1.r2 <- cor(external_pred[1:20], external_obs[1:20])^2
ex1.rmse <- rmse(external_pred[1:20], external_obs[1:20])
ex2.r2 <- cor(external_pred[21:40], external_obs[21:40])^2
ex2.rmse <- rmse(external_pred[21:40], external_obs[21:40])
ex3.r2 <- cor(external_pred[41:60], external_obs[41:60])^2
ex3.rmse <- rmse(external_pred[41:60], external_obs[41:60])
ex4.r2 <- cor(external_pred[61:80], external_obs[61:80])^2
ex4.rmse <- rmse(external_pred[61:80], external_obs[61:80])
ex5.r2 <- cor(external_pred[81:100], external_obs[81:100])^2
ex5.rmse <- rmse(external_pred[81:100], external_obs[81:100])

# Generate table containing R^2 and RMSE for external test substrates (saves to external_set_stats.csv).
externalsetstats <-
  matrix(c(1,ex1.r2,ex1.rmse,2,ex2.r2,ex2.rmse,3,ex3.r2,ex3.rmse,4,ex4.r2,ex4.rmse,5,ex5.r2,ex5.rmse),ncol=3,byrow=TRUE)
colnames(externalsetstats) <- c("Ext. Substrate","R^2","RMS Error")
externalsetstats <- as.table(externalsetstats)
write.csv(externalsetstats , 'R_output\\external_set_stats.csv')

# =====

```

```

# Combined calibration plot (used to generate Figure 3 in manuscript).
# =====

# Generate calibration plot of test set and external substrates (saves to combined-calibration_plot.png).

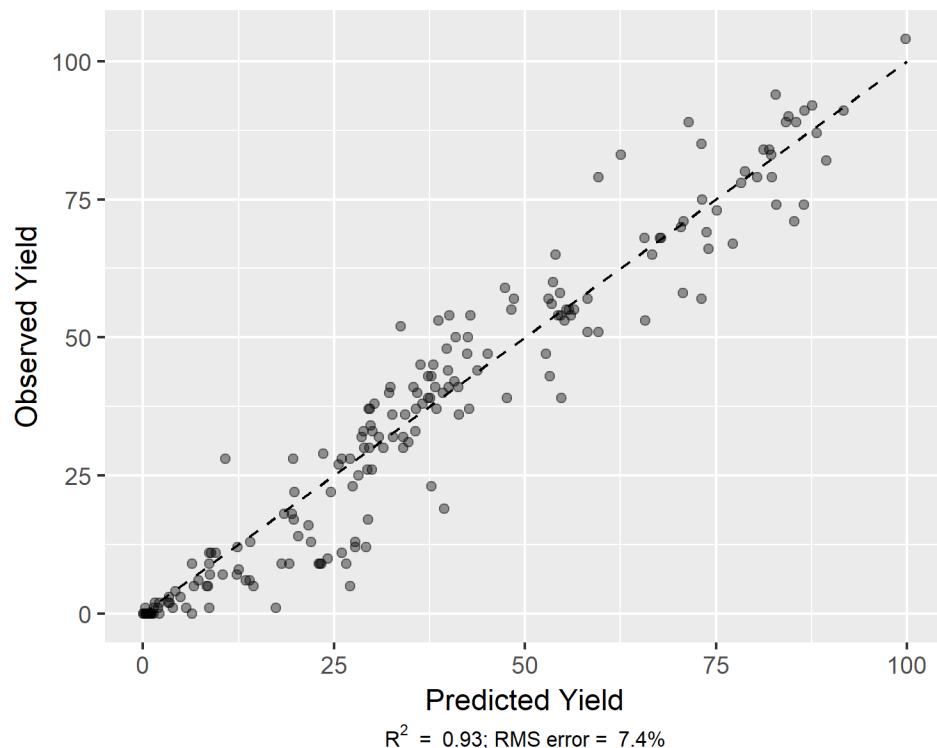
combined_obs <- c(external_obs,test.scaled$yield)
combined_pred <- c(external_pred,rf.pred)
combined_alcohol <- rep(c("1ag", "1ah", "1ai", "1aj","1ak","test set"), times = c(20,20,20,20,20,192))
combined.df <- data.frame(x = combined_pred,
                           y = combined_obs,
                           substrate = combined_alcohol)
combined.p1 <- ggplot(combined.df, aes(x = x, y = y, color = substrate, shape = substrate, fill = substrate)) +
  scale_color_manual(values=c("#ff3d3d", "#fc9f28", "#415ce2", "#1c9102", "#8841a8", "black", "black")) +
  scale_shape_manual(values=c(22, 24, 21, 25, 23, 20)) +
  scale_fill_manual(values=c("#ff3d3d", "#fc9f28", "#415ce2", "#1c9102", "#8841a8", "black")) +
  geom_point(alpha = 0.7) +
  theme_bw() +
  scale_x_continuous(breaks = seq(0,100,25), lim=c(0, 100)) +
  labs(x='Predicted Yield', y='Observed Yield', caption = bquote("Test set:" ~ R^2 ~ " = " ~ .(rsq) * " ; RMSE = " ~ .(rms) * "%"))
  +
  theme(plot.caption = element_text(hjust = 0.5, size = 8), legend.position="none") +
  geom_segment(aes(x=0,xend=100,y=0,yend=100,color="black"), linetype="dashed")
ggsave(file="R_output\\combined-calibration_plot.png", width=4, height=3.2, dpi=600)

```

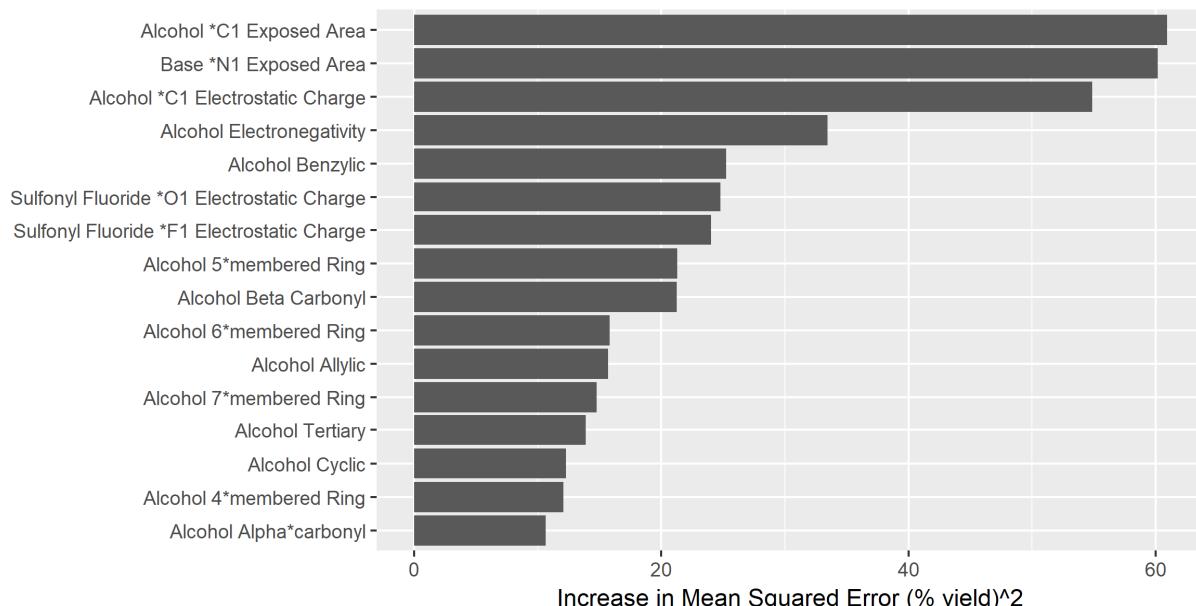
In summary, the executed script does the following:

- Loads and scales descriptor data and observed yields.
- Randomly splits the data into training (70%) and test (30%) sets.
- Trains a random forest algorithm using the training set.
- Predicts yields for the test set and generates a table showing the predicted *vs.* observed yields for the test set.
- Plots a calibration plot for the test set with  $R^2$  and RMS error values.
- Plots a variable importance plot for the model. The value of each variable is individually shuffled, and the resulting increase in mean squared error (MSE) is documented, providing a measure of variable importance. Without performing principle component analysis, these results can be misleading. For example, if multiple correlated variables are present, each will be underrepresented in the importance plot.
- Predicts the yields for an external set of reactions using the same scaling factors and generates a table showing the predicted yields.
- Loads the observed yields for external substrates and generates a calibration plot and a table containing the RMS error and  $R^2$  values for each substrate.

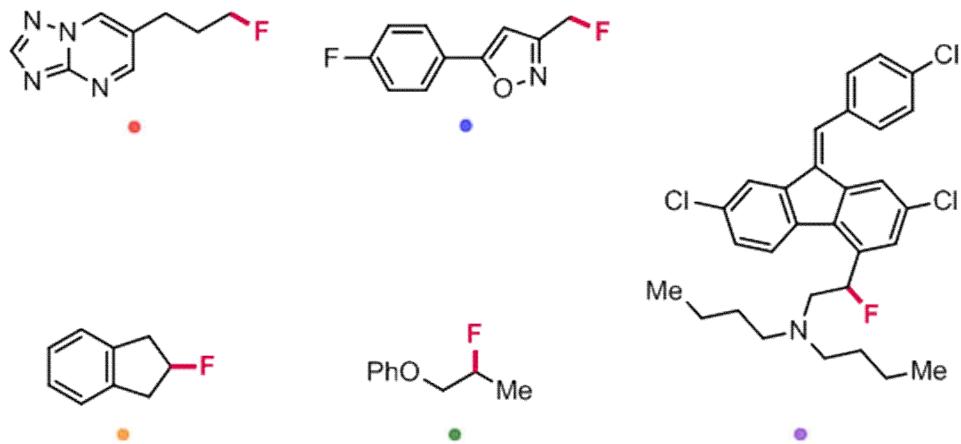
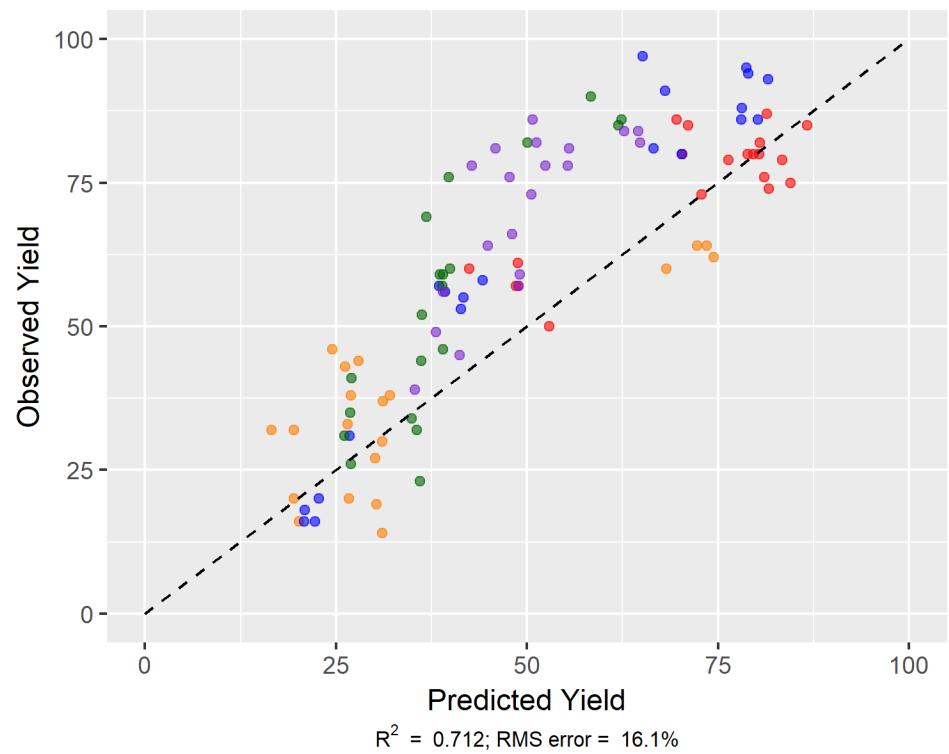
The output for the executed program is saved in “rxnpredict\R\_output”. The plots are shown below.



**Figure S5.** Calibration plot of observed vs. predicted yield for internal test set.



**Figure S6.** Variable importance plot. Significant variables are determined by randomly shuffling the values of a specific variable, retraining the model, and measuring the increase in the mean squared error in test set prediction.

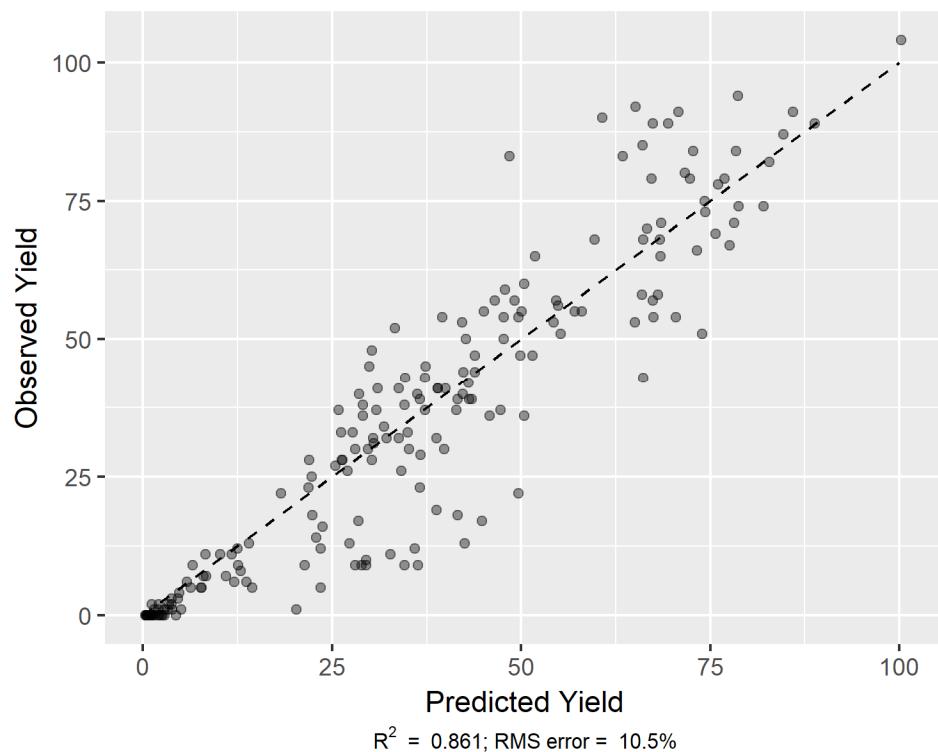


**Figure S7.** Plot of observed vs. predicted yield for the external test set.

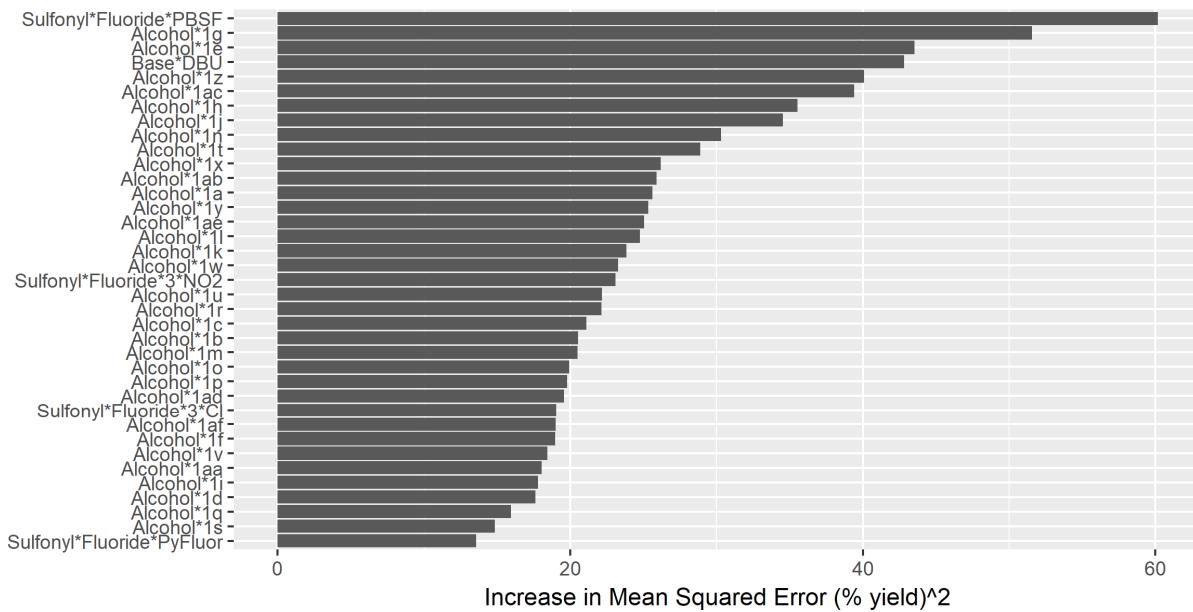
## Results for Model Developed with One-Hot Encoding

In order to evaluate the significance of the chemical descriptors in our model, we trained and evaluated a separate model using one-hot encoding. In a one-hot encoded model, the descriptor contains  $n$  columns where  $n$  is equal to the total number of reagents. In this embodiment, our descriptor table contained 41 columns, one for each of 32 alcohols, 4 bases, and 5 sulfonyl fluorides. In any given row, all columns are assigned a value of ‘0’ except for the three columns corresponding to the alcohol, base, and sulfonyl fluoride employed in the corresponding reaction, which are assigned a value of ‘1’. As such, the model is not trained with any chemical descriptors, but relies solely on discrete reagent identity. The input files and R script are saved in the directory “rxnpredict\One-Hot-Encoding\_Controls”.

Using the same training set as in the original model, the test set calibration plot for the one-hot encoded model is shown in Figure S8. The observed RMSE of 10.5% ( $R^2 = 0.861$ ) shows a moderate decrease in accuracy from the descriptor model (7.4% RMSE,  $R^2 = 0.930$ ). However, the model predicts the test set with reasonable accuracy. Again, because ~70% of the entries for each reagent are featured in the training set, this level of accuracy using discrete reagent identifiers is unsurprising as most trends would be expected to apply to the remaining test entries. In effect, the variable importance plot in Figure S9 identifies which reagents provide yields that deviate the most from the average yield of other reagents in the same class. For example, the sulfonyl fluoride PBSF on average affords substantially higher yields than other sulfonyl fluorides and has a high  $\Delta\text{MSE} \approx 60$  (%yield)<sup>2</sup>. Likewise, the base DBU provides much lower yields than the other bases and displays a  $\Delta\text{MSE} \approx 45$  (%yield)<sup>2</sup>.



**Figure S8.** Calibration plot of observed vs. predicted yield for internal 70/30 test set using a model trained with one-hot encoding input.



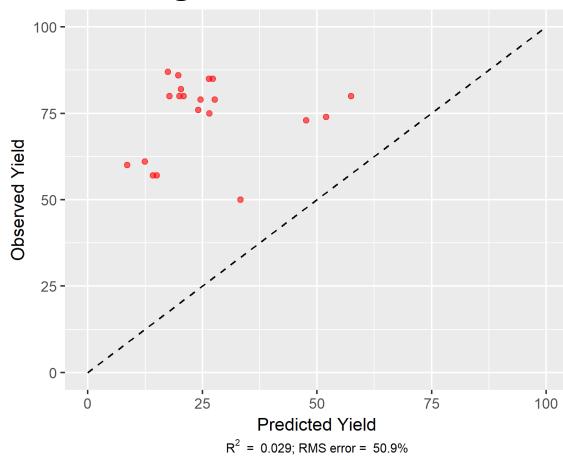
**Figure S9.** Variable importance plot for the one-hot encoded model.

The one-hot encoded model is incapable of providing specific predictions for out-of-set reagents. For example, for any number of external alcohol substrates, the one-hot encoding will predict the same yield for each combination of sulfonyl fluoride and base.

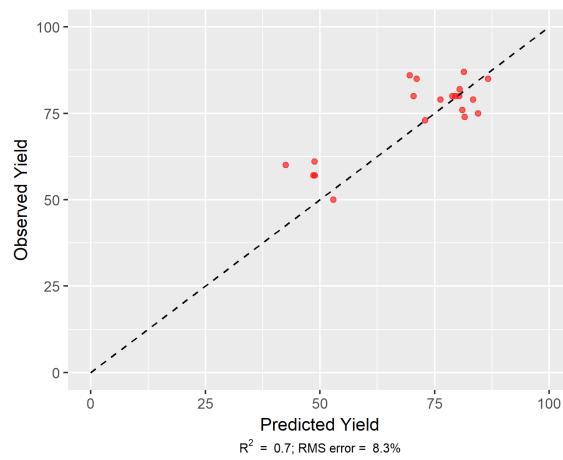
In Figure S10 below, the plots of predicted vs. observed yield for each of the external substrates are shown side-by-side for both the one-hot encoded model (left) and the original descriptor model (right). In the one-hot encoding plots, the *x*-axis horizontal positions of the points corresponding to each combination of base and sulfonyl fluoride are identical for all five plots. The substantial variation in *y*-axis vertical positions indicates that the alcohol identity has a significant impact on reaction outcome that cannot be predicted by simply averaging the performance with any base/sulfonyl fluoride pair. As shown in each of the comparisons, the descriptor-based model is far more accurate with an overall RMSE of 16.1% across all five substrates than the one-hot encoded model (40.2% overall RMSE). The success of the descriptor model on these test substrates provides strong evidence that the chemical descriptors are significant as continuous variables, and are not simply aggregated by the model as discrete reagent identifiers.

### One-hot encoded model.

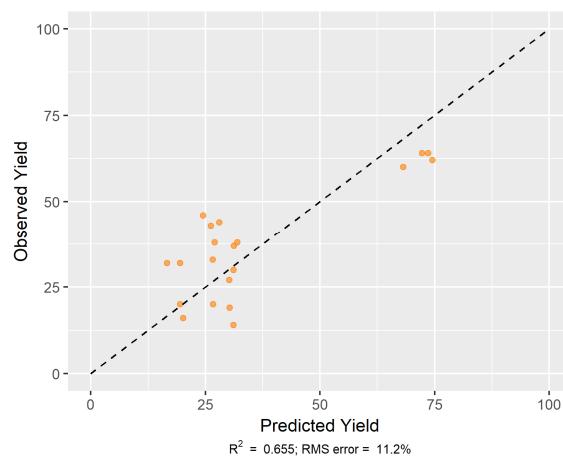
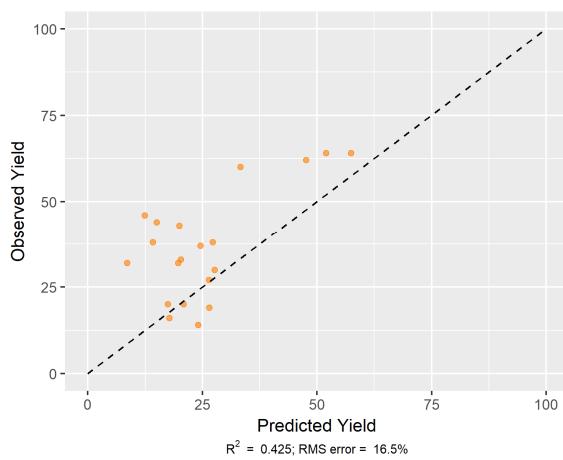
#### Substrate 2ag:



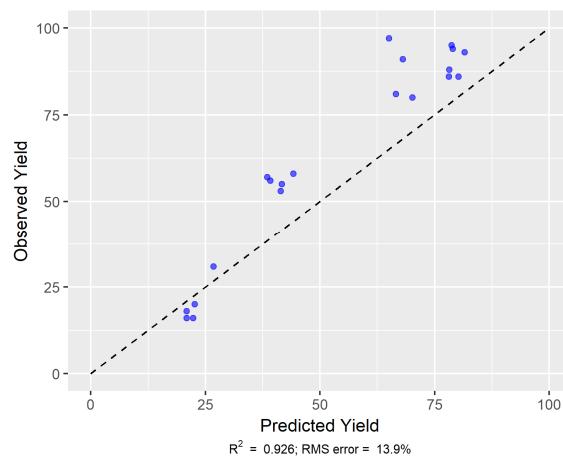
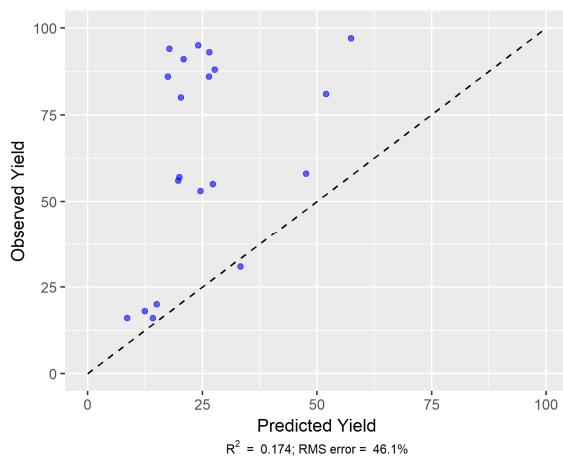
### Original descriptor model.



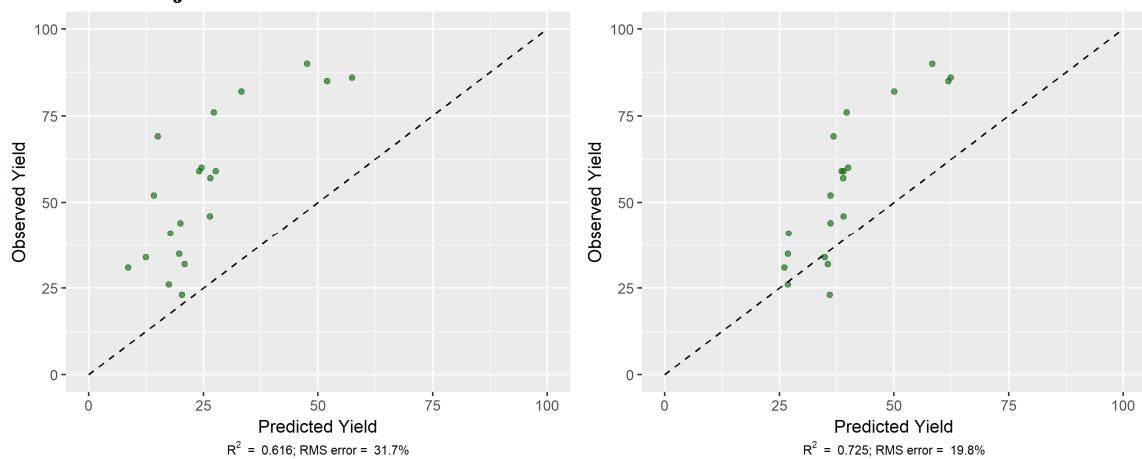
#### Substrate 2ah:



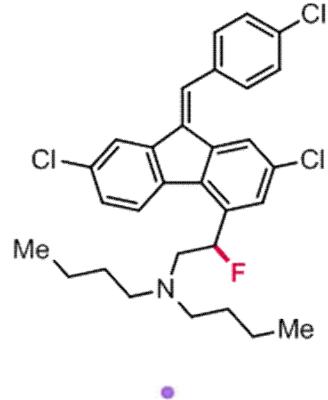
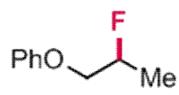
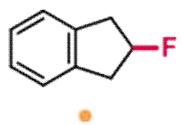
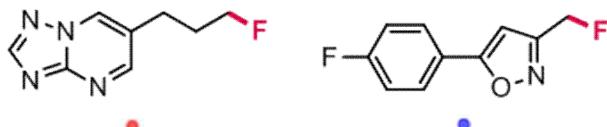
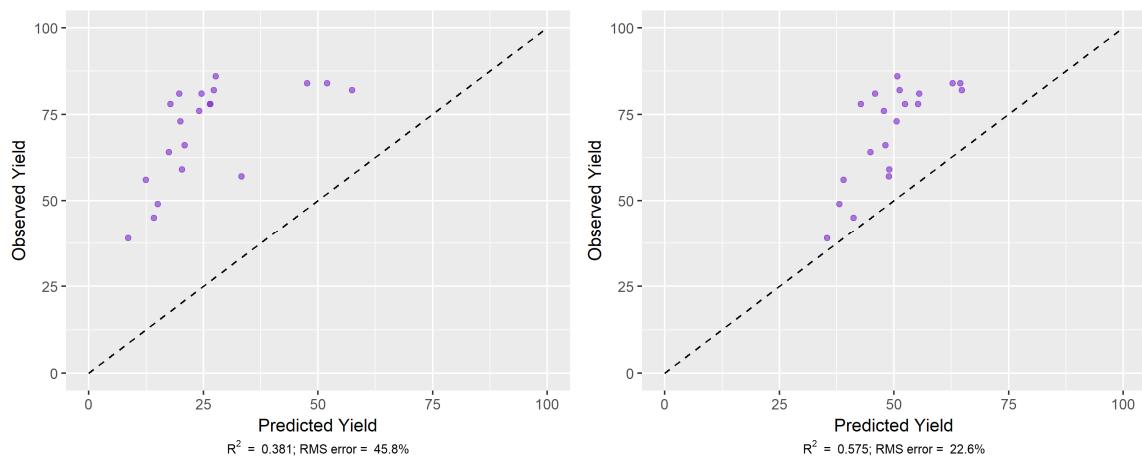
#### Substrate 2ai:



### Substrate 2aj:



### Substrate 2ak:



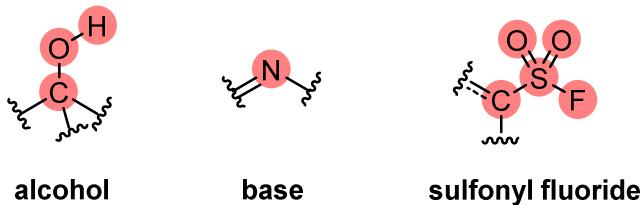
**Figure S10.** Comparison of the plots of observed vs. predicted yield for each substrate in the external test set using the one-hot encoded model (left) and the original descriptor model (right).

## **Results for Model Developed with Automated Descriptor Extraction**

In our previous publication,<sup>29</sup> computational atomic, molecular, and vibrational descriptors were automatically extracted using a Python script (original code is available at <<https://github.com/doylelab/rxnpredict>>). With the current data set, these computational descriptors enabled fairly accurate modeling of the test set, but provided poor predictions for external substrates. Using this procedure; following 43 atomic and molecular descriptors were extracted: (The designated atoms are highlighted in Figure S11.)

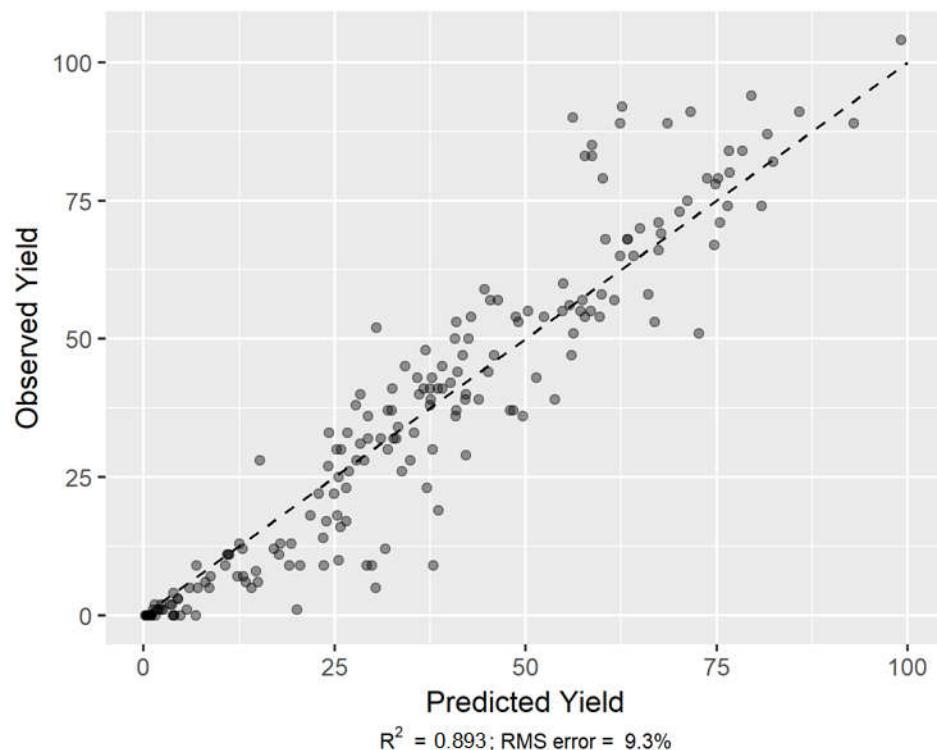
- Alcohol - \*C1 NMR shift
- Alcohol - \*C1 electrostatic charge
- Alcohol - \*H1 NMR shift
- Alcohol - \*H1 electrostatic charge
- Alcohol - \*O1 electrostatic charge
- Alcohol - E HOMO
- Alcohol - E LUMO
- Alcohol - dipole moment
- Alcohol - electronegativity
- Alcohol - hardness
- Alcohol - molecular volume
- Alcohol - molecular weight
- Alcohol - ovality
- Alcohol - surface\_area
- Base - \*N1 electrostatic charge
- Base - E HOMO
- Base - E LUMO
- Base - dipole moment
- Base - electronegativity
- Base - hardness
- Base - molecular volume
- Base - molecular weight
- Base - ovality
- Base - surface\_area
- Sulfonyl fluoride - \*C1 NMR shift
- Sulfonyl fluoride - \*C1 electrostatic charge
- Sulfonyl fluoride - \*F1 electrostatic charge

- Sulfonyl fluoride - \*O1 electrostatic charge
- Sulfonyl fluoride - \*O2 electrostatic charge
- Sulfonyl fluoride - \*S1 electrostatic charge
- Sulfonyl fluoride - E HOMO
- Sulfonyl fluoride - E LUMO
- Sulfonyl fluoride - V1 frequency
- Sulfonyl fluoride - V1 intensity
- Sulfonyl fluoride - V2 frequency
- Sulfonyl fluoride - V2 intensity
- Sulfonyl fluoride - dipole moment
- Sulfonyl fluoride - electronegativity
- Sulfonyl fluoride - hardness
- Sulfonyl fluoride - molecular volume
- Sulfonyl fluoride - molecular weight
- Sulfonyl fluoride - ovality
- Sulfonyl fluoride - surface area

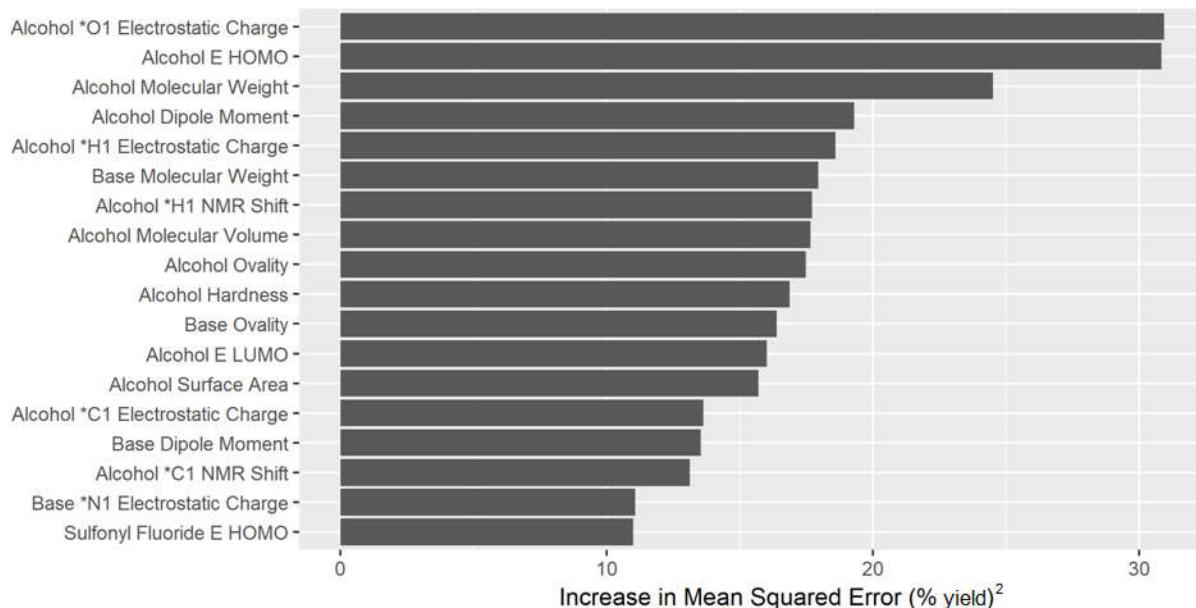


**Figure S11.** Designated atoms for automated descriptor extraction.

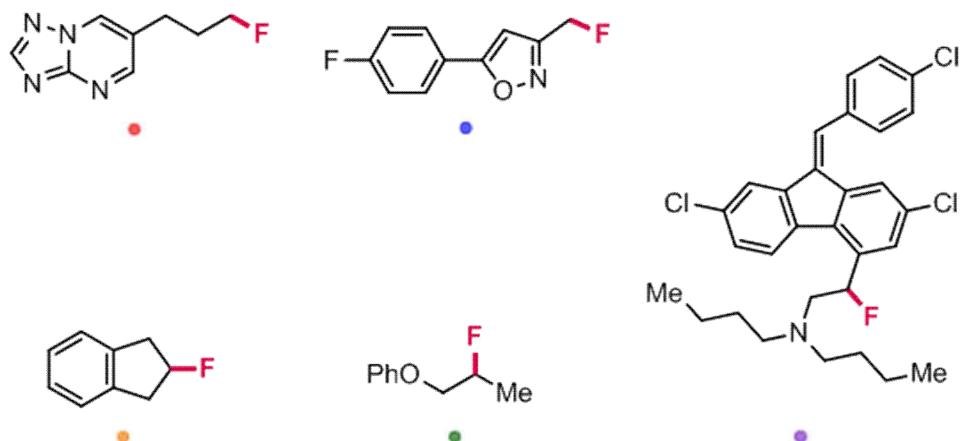
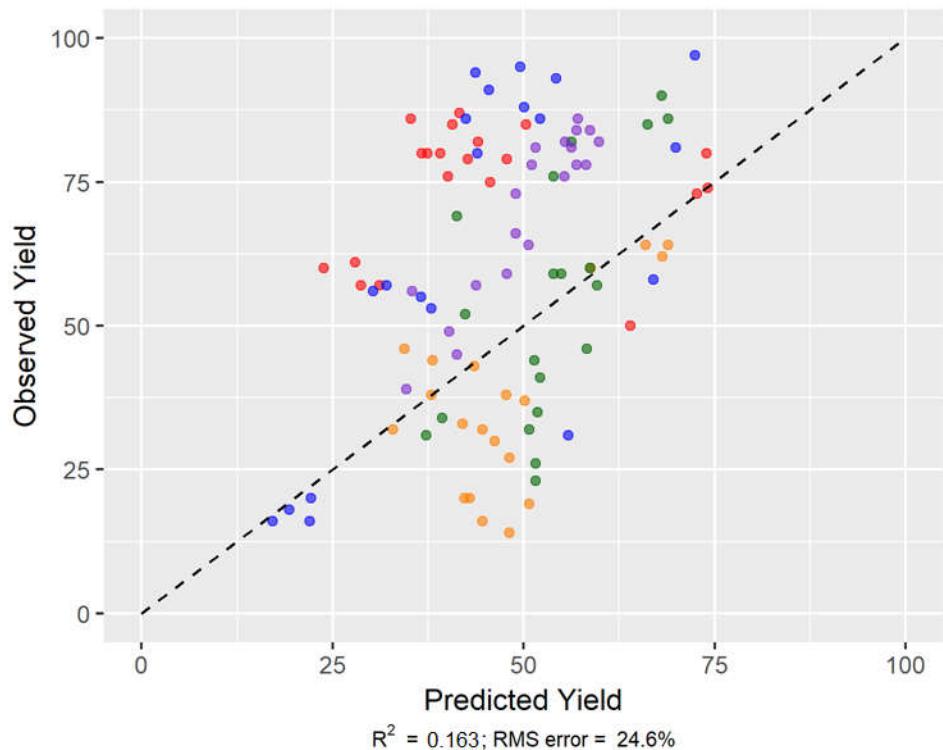
Statistics for the model trained on the automatically extracted descriptors are displayed in Figures S12 - S14. Notably, the RMSE for the test set was 9.3%, nearly 2% worse than with the selected computational and categorical descriptors (Figure S12). The variable importance plot also highlighted unexpected and chemically irrelevant variables (*i.e.* alcohol and base molecular weights), which we interpret to be a sign of overfitting (Figure S13). Care should be taken in interpreting variable important plots, especially when correlated variables have not been removed. Finally, the calibration plot for the external validation substrates show poor correlation with an overall RMSE of 24%, which is 8% higher than with our hand-selected descriptors (Figure S14). For each substrate, PBSF was predicted to be the optimal sulfonyl fluoride, suggesting that model simply averaged all of the experimental screening results and failed to identify reactivity trends in new substrates. We suspect that overfitting arose from employing 43 descriptors for a data set containing only 32 distinct alcohols. In all likelihood, the trained model treated each combination of descriptors as a discrete reagent identifier (similar to in one-hot encoding) rather than treating the descriptors as continuous variables.



**Figure S12.** Plot of observed vs. predicted yield for internal test set using automatically extracted descriptors.



**Figure S13.** Variable importance plot with automatically extracted descriptors. Care should be taken in interpreting variable importance plots when principal component analysis has not been performed. If multiple correlated variables are present, each will individually appear to have less importance.

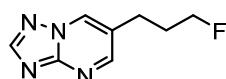


**Figure S14.** Plot of observed vs. predicted yield for the external test set with automatically extracted descriptors.

We were able to dramatically remove the predictive ability of the model by *removing* most of the computational descriptors except those relevant to the nucleophilic substitution mechanism and adding categorical descriptors as shown on pages S48 – S49. Interestingly, models trained on the full set of computational and categorical descriptors *actually performed worse*, suggesting that the random forest model (under default parameters in the R caret package) suffers when many superfluous or uncorrelated variables are present.

## VII. External Validation Substrates

**General procedure:** The four alcohols **1ag – 1ak** were evaluated under the same twenty deoxyfluorination conditions used for the substrates in Section II. For each reaction, an  $8 \times 40$  mm glass vial with a 5 mm Teflon stirbar was charged sequentially with a stock solution containing 0.1 mmol of the substrate alcohol in 125  $\mu\text{L}$  THF, a stock solution containing 1.1 equiv sulfonyl fluoride in 125  $\mu\text{L}$  THF, and 1.5 equiv base (resulting in a concentration of ~0.4 M). In cases where the substrate alcohol was not fully soluble in THF, the alcohol was added as a solid, followed by addition of 125  $\mu\text{L}$  THF. The vials were capped and stirred at 600 rpm at room temperature for 48 hours. Yields were assessed by  $^{19}\text{F}$  NMR following the addition of 1 equiv. 1-fluoronaphthalene in 250  $\mu\text{L}$   $\text{CDCl}_3$  as an external standard. For each substrate, two tables are reported containing the observed yields and those predicted by the trained random forest algorithm.



**6-(3-fluoropropyl)-[1,2,4]triazolo[1,5-a]pyrimidine (2ag):** 3-[1,2,4]Triazolo[1,5-a]pyrimidin-6-ylpropan-1-ol (Millipore-Sigma) was evaluated according to the general procedure. A sample for characterization was obtained by subjecting the crude reaction mixtures to automated column chromatography (25 g silica, 30  $\rightarrow$  70% ethyl acetate in hexanes), which afforded the title compound as a white solid.

		(observed)					(predicted)						
		3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF	DBU		3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU		60%	61%	57%	57%	50%			43%	49%	49%	49%	53%
MTBD		86%	80%	79%	85%	73%			70%	70%	76%	71%	73%
BTMG		87%	82%	85%	79%	74%			81%	81%	87%	83%	82%
BTPP		80%	80%	75%	76%	80%			80%	79%	85%	81%	80%

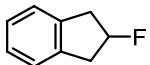
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  8.74 (s, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 4.54 (dt,  $J$  = 47.1, 5.6 Hz, 2H), 2.94 (t,  $J$  = 7.7 Hz, 2H), 2.10 (dm,  $J$  = 27.6 Hz, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  156.62, 156.28, 154.53, 134.05, 123.92, 82.26 (d,  $J$  = 166.7 Hz), 31.33 (d,  $J$  = 20.1 Hz), 25.85 (d,  $J$  = 4.7 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -221.05 (tt,  $J$  = 47.3, 26.4 Hz).

**IR (ATR, cm<sup>-1</sup>):** 3104 (w), 3063 (w), 2966 (w), 2924 (w), 2904 (w), 1891 (w), 1626 (m), 1569 (w), 1537 (m), 1511 (s), 1449 (w), 1439 (m), 1425 (w), 1391 (m), 1361 (m), 1319 (m), 1288 (w), 1268 (s), 1250 (s), 1236 (w), 1221 (w), 1176 (s), 1124 (m), 1094 (w), 1067 (w), 1021 (s), 950 (m), 923 (m), 889 (s), 843 (m), 785 (s), 757 (w), 740 (w), 666 (s).

**HRMS (ESI+):** Calculated for C<sub>8</sub>H<sub>10</sub>FN<sub>4</sub><sup>+</sup> [M + H]<sup>+</sup>: 181.0884; found: 181.0884.



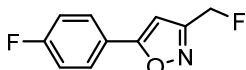
**2-fluoro-2,3-dihydro-1*H*-indene (2ah):** 2-Indanol (Millipore-Sigma) was evaluated according to the general procedure. A sample for characterization was obtained by subjecting the crude reaction mixtures to automated column chromatography (25 g silica, 0 → 25% ethyl acetate in hexanes), which afforded the title compound as a volatile colorless oil. This compound has been previously characterized.<sup>30</sup>

		(observed)					(predicted)					
		3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF	3-Cl		PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	32%	46%	38%	44%	60%		17%	25%	27%	28%	68%	
	32%	43%	37%	38%	62%		20%	26%	31%	32%	75%	
	20%	33%	27%	30%	64%		20%	27%	30%	31%	72%	
	16%	20%	19%	14%	64%		20%	27%	30%	31%	74%	
MTBD												
BTMG												
BTPP												

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.31 – 7.26 (m, 2H), 7.24 – 7.17 (m, 2H), 5.58 – 5.41 (m, 1H), 3.32 – 3.23 (m, 2H), 3.22 – 3.18 (m, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 140.11, 127.00, 124.97, 94.85 (d, *J* = 176.7 Hz), 40.70 (d, *J* = 23.1 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ –173.84 (dtt, *J* = 53.3, 31.6, 28.7 Hz).



**3-(fluoromethyl)-5-(4-fluorophenyl)isoxazole (2ai):** 5-(4-Fluorophenyl)isoxazole-3-methanol (Millipore-Sigma) was evaluated according to the general procedure. A sample for characterization was obtained by subjecting the crude reaction mixtures to automated column chromatography (25 g silica, 0 → 15% ethyl acetate in hexanes), which afforded the title compound as a white solid.

		(observed)					(predicted)					
		3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF	3-Cl		PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
DBU	16%	18%	16%	20%	31%		21%	21%	22%	23%	27%	
	56%	57%	53%	55%	58%		39%	39%	41%	42%	44%	
	86%	80%	86%	88%	81%		78%	70%	80%	78%	67%	
	94%	91%	93%	95%	97%		79%	68%	82%	79%	65%	
MTBD												
BTMG												
BTPP												

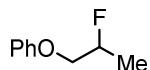
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.81 – 7.72 (m, 2H), 7.20 – 7.12 (m, 2H), 6.59 (s, 1H), 5.49 (d, *J* = 46.9 Hz, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 169.98, 164.00 (d, *J* = 251.6 Hz), 160.54 (d, *J* = 23.1 Hz), 128.08 (d, *J* = 8.6 Hz), 123.50 (d, *J* = 3.4 Hz), 116.41 (d, *J* = 22.2 Hz), 98.36, 76.19 (d, *J* = 166.8 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -108.96 (tt, *J* = 8.5, 5.2 Hz, 1F), -221.36 (t, *J* = 46.8 Hz, 1F).

**IR (ATR, cm<sup>-1</sup>):** 3120 (w), 2973 (w), 1915 (w), 1619 (m), 1601 (m), 1513 (m), 1462 (m), 1439 (m), 1371 (w), 1306 (w), 1236 (m), 1186 (w), 1161 (m), 1095 (w), 1047 (w), 1035 (s), 992 (s), 949 (w), 909 (m), 844 (s), 817 (s), 754 (s), 724 (w), 679 (m).

**HRMS (ESI+):** Calculated for C<sub>10</sub>H<sub>8</sub>F<sub>2</sub>NO<sup>+</sup> [M + H]<sup>+</sup>: 196.0568; found: 196.0565.



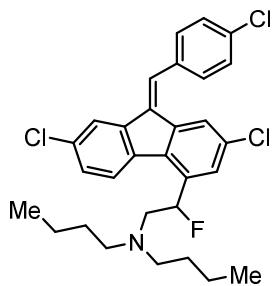
**(±)-(2-fluoropropoxy)benzene (2aj):** 1-Phenoxy-2-propanol (TCI) was evaluated according to the general procedure. A sample for characterization was obtained by subjecting the crude reaction mixtures to automated column chromatography (25 g silica, 0 → 10% ethyl acetate in hexanes), which afforded the title compound as a colorless oil. This compound has been previously characterized.<sup>31</sup> Small amounts of the isomer ((1-fluoropropan-2-yl)oxy)benzene were detected by NMR. This may arise from formation of an oxiranium ion intermediate or may be due to the presence of 2-phenoxy-1-propanol impurity in the starting material (listed as >95.0% purity).

		(observed)					(predicted)				
		3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF	26%	35%	36%	37%	50%
	DBU	31%	34%	52%	69%	82%	26%	35%	36%	37%	50%
	MTBD	35%	44%	60%	76%	90%	27%	36%	40%	40%	58%
	BTMG	26%	23%	46%	59%	85%	27%	36%	39%	39%	62%
	BTTP	41%	32%	57%	59%	86%	27%	36%	39%	39%	62%

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.34 – 7.27 (m, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 2H), 5.07 (dpd, *J* = 48.6, 6.3, 3.5 Hz, 1H), 4.15 – 3.96 (m, 2H), 1.47 (dd, *J* = 23.6, 6.4 Hz, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 158.61, 129.65, 121.32, 114.73, 88.60 (d, *J* = 169.3 Hz), 70.81 (d, *J* = 23.5 Hz), 17.60 (d, *J* = 22.3 Hz).

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -180.43 (dtq, *J* = 48.5, 23.5, 19.7 Hz).



**( $\pm$ )-(Z)-N-butyl-N-(2-(2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl)-2-fluoroethyl)butan-1-amine (2ak):** Lumefantrine (Acros) was evaluated according to the general procedure. A sample for characterization was obtained by subjecting the crude reaction mixtures to automated column chromatography (25 g silica, 0 → 20% ethyl acetate in hexanes), which afforded the title compound as a yellow solid. This compound has been previously characterized.<sup>23</sup> In most of the screens, a second fluorine peak of identical splitting and similar shift is observed to varying extents. The interaction of the chloroarene group with the dichlorofluorene may result in atropisomerism, resulting in two product diastereomers.

		(observed)					(predicted)				
		3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF	3-Cl	PyFluor	3-CF <sub>3</sub>	3-NO <sub>2</sub>	PBSF
	DBU	39%	56%	45%	49%	57%	35%	39%	41%	38%	49%
	MTBD	81%	73%	81%	82%	84%	46%	51%	56%	51%	63%
	BTMG	64%	59%	78%	86%	84%	45%	49%	55%	51%	65%
	BTPP	78%	66%	78%	76%	82%	43%	48%	52%	48%	65%

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.73 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.60 (s, 1H), 7.49 (d, *J* = 1.9 Hz, 1H), 7.46 (s, 4H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.34 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.14 (ddd, *J* = 48.3, 7.6, 2.3 Hz, 1H), 3.01 – 2.91 (m, 1H), 2.91 – 2.77 (m, 1H), 2.70 – 2.61 (m, 2H), 2.60 – 2.50 (m, 2H), 1.48 – 1.38 (m, 4H), 1.38 – 1.30 (m, 4H), 0.92 (t, *J* = 7.3 Hz, 6H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 141.48, 138.43, 136.04 (d, *J* = 20.8 Hz), 135.74, 134.93, 134.84, 134.64 (d, *J* = 5.1 Hz), 134.12, 133.42, 132.87, 130.66, 129.23, 128.72, 128.28, 125.90 (d, *J* = 13.1 Hz), 124.55 (d, *J* = 2.7 Hz), 123.74, 120.75, 92.21 (d, *J* = 175.9 Hz), 59.37 (d, *J* = 22.2 Hz), 54.40 (d, *J* = 1.4 Hz), 29.09, 20.76, 14.25.

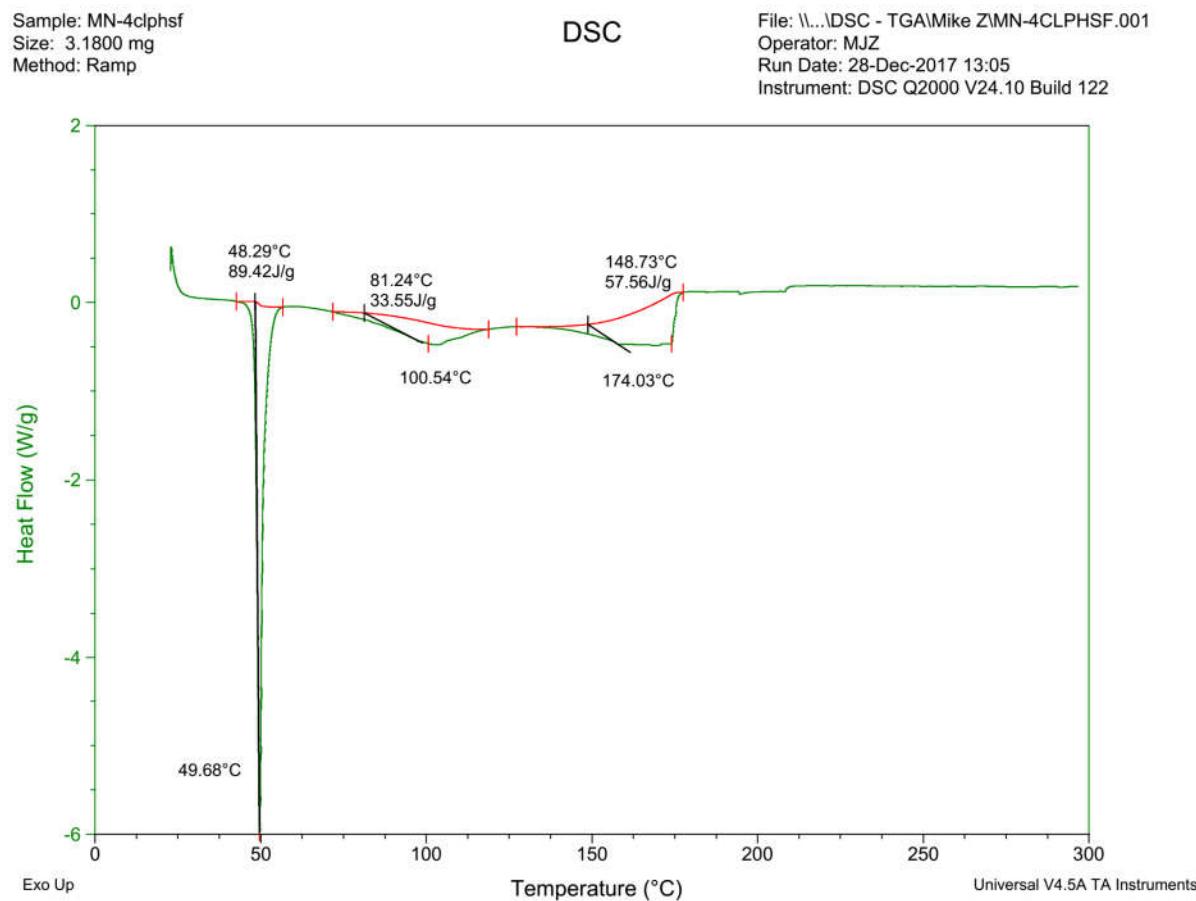
**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -180.14 (ddd, *J* = 48.2, 33.2, 21.6 Hz).

## VIII. DSC Traces for 3-Cl, 3-CF<sub>3</sub>, and 3-NO<sub>2</sub>

The stability of deoxyfluorination reagents has typically been assessed by differential scanning calorimetry (DSC).<sup>12,32</sup> We previously reported the DSC trace for PyFluor, which displays no exothermic decomposition between 0 and 350 °C.<sup>Error! Bookmark not defined.</sup> Stability studies for PBSF have also been published.<sup>33</sup>

Here, we report DSC data for the newly-disclosed reagents **3-Cl**, **3-CF<sub>3</sub>**, and **3-NO<sub>2</sub>**. Measurements were performed in crimped Tzero aluminum pans using the indicated sample masses. Sharp endotherms attributed melting were observed for each reagent (**3-Cl**: 89 J/g at 48 °C; **3-CF<sub>3</sub>**: 63 J/g at 69 °C; **3-NO<sub>2</sub>**: 63 J/g at 79 °C). A number of other artifacts were observed, potentially corresponding to impurities or endothermic decomposition. Crimped Tzero aluminum pans are not airtight, so the highest temperature artifact likely arises from premature evaporation, which would occur well below the actual boiling point. **Importantly, no exothermic decomposition was observed on between 0 and 300 °C, indicating that these reagents have high thermal stability similar to that of PyFluor.**

### 3-Cl:

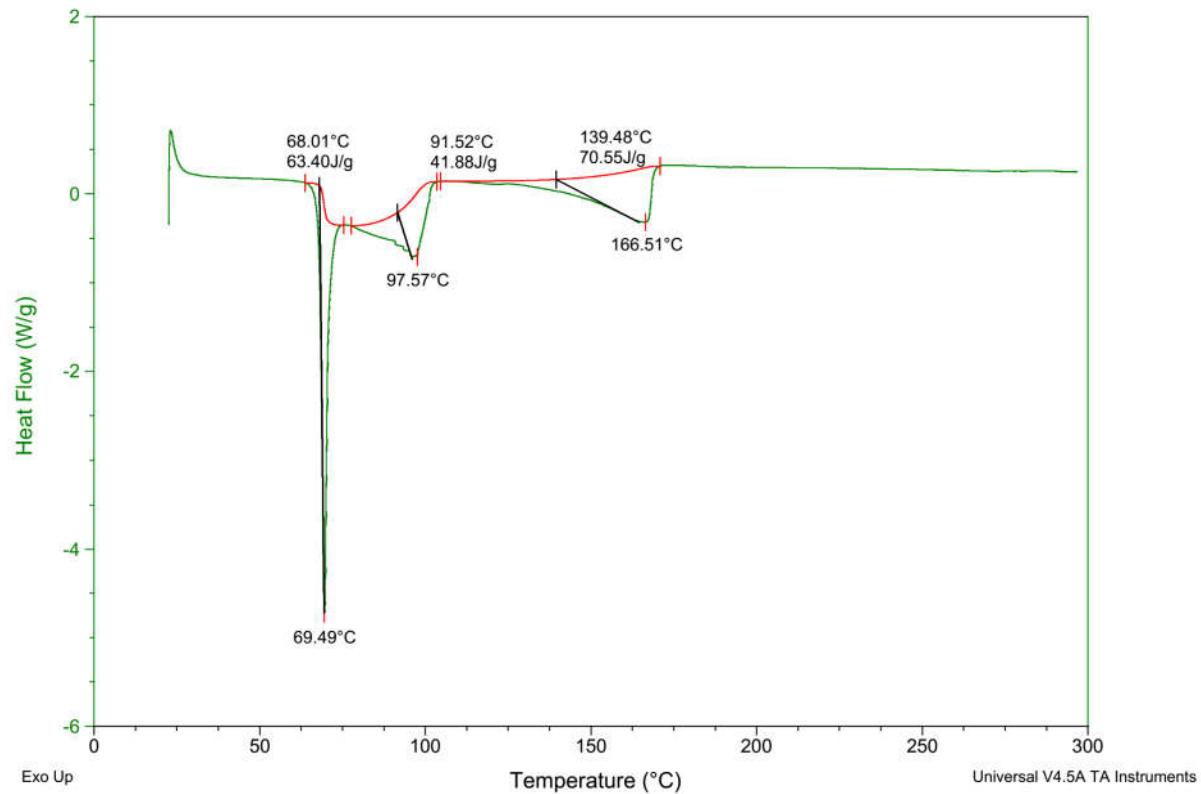


### 3-CF<sub>3</sub>:

Sample: MN-4cf3phSF  
Size: 2.0900 mg  
Method: Ramp

DSC

File: \\...\\DSC - TGA\\Mike Z\\MN-4CF3PHSF.001  
Operator: MJZ  
Run Date: 28-Dec-2017 11:56  
Instrument: DSC Q2000 V24.10 Build 122

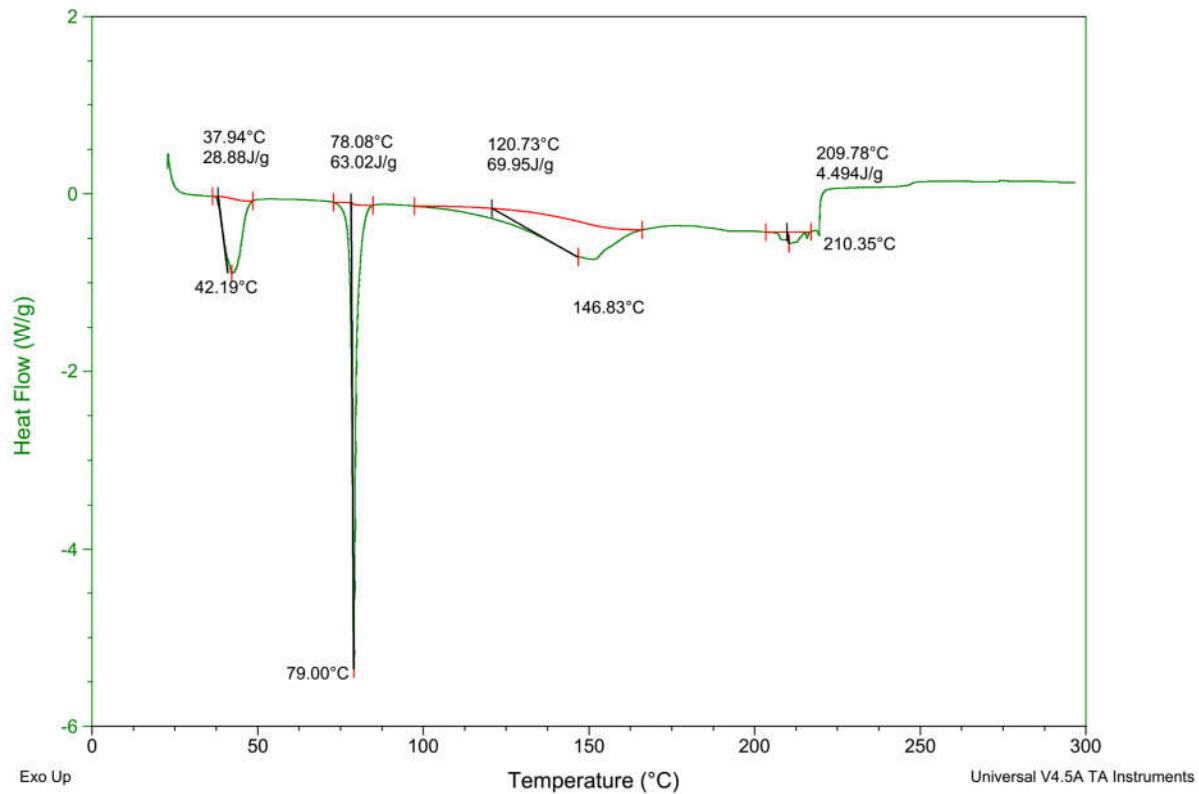


### 3-NO<sub>2</sub>:

Sample: MN-4nsf  
Size: 3.2600 mg  
Method: Ramp

DSC

File: \\...\\DSC - TGA\\Mike Z\\MN-4NSF.001  
Operator: MJZ  
Run Date: 28-Dec-2017 13:40  
Instrument: DSC Q2000 V24.10 Build 122

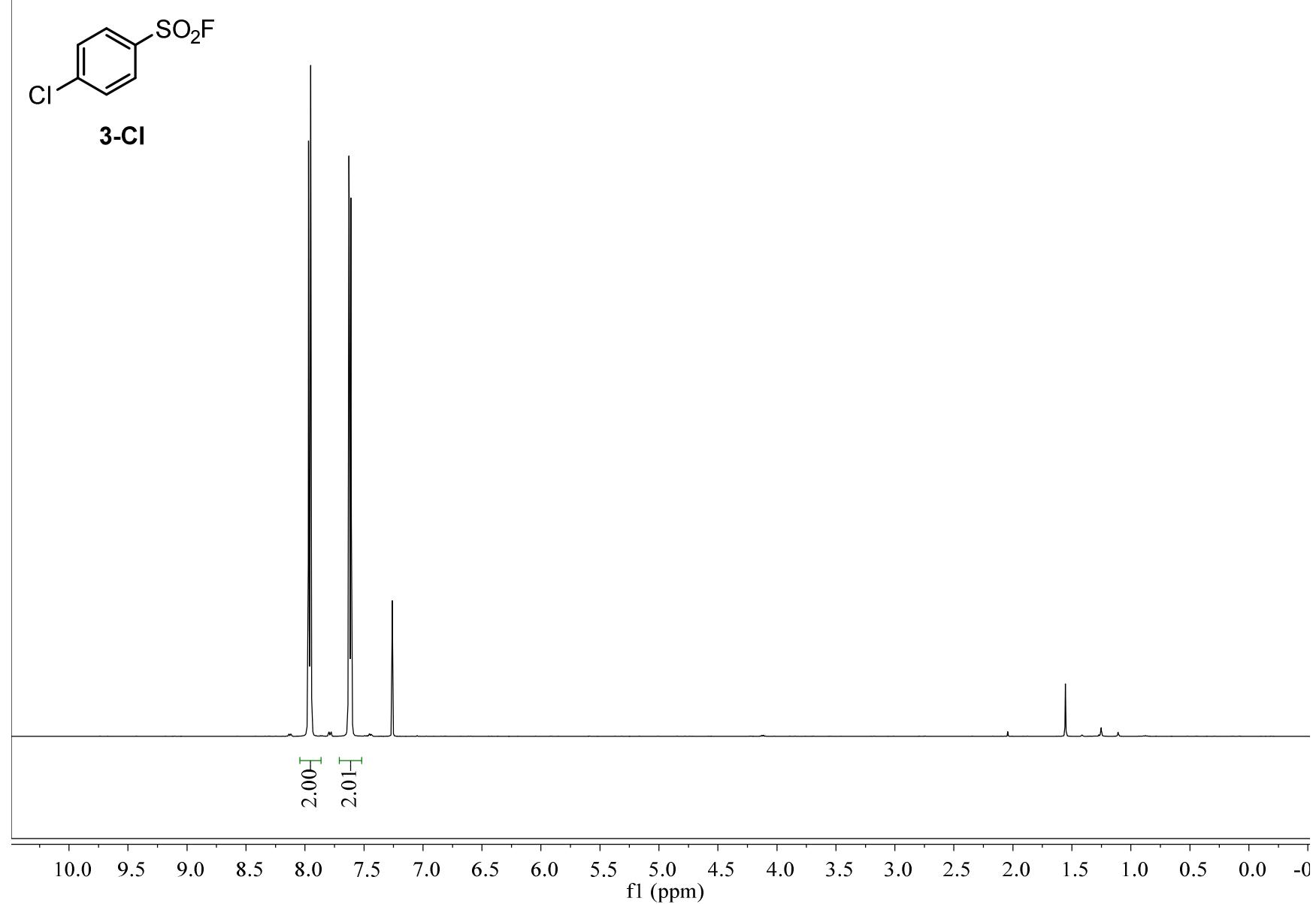


## IX. References

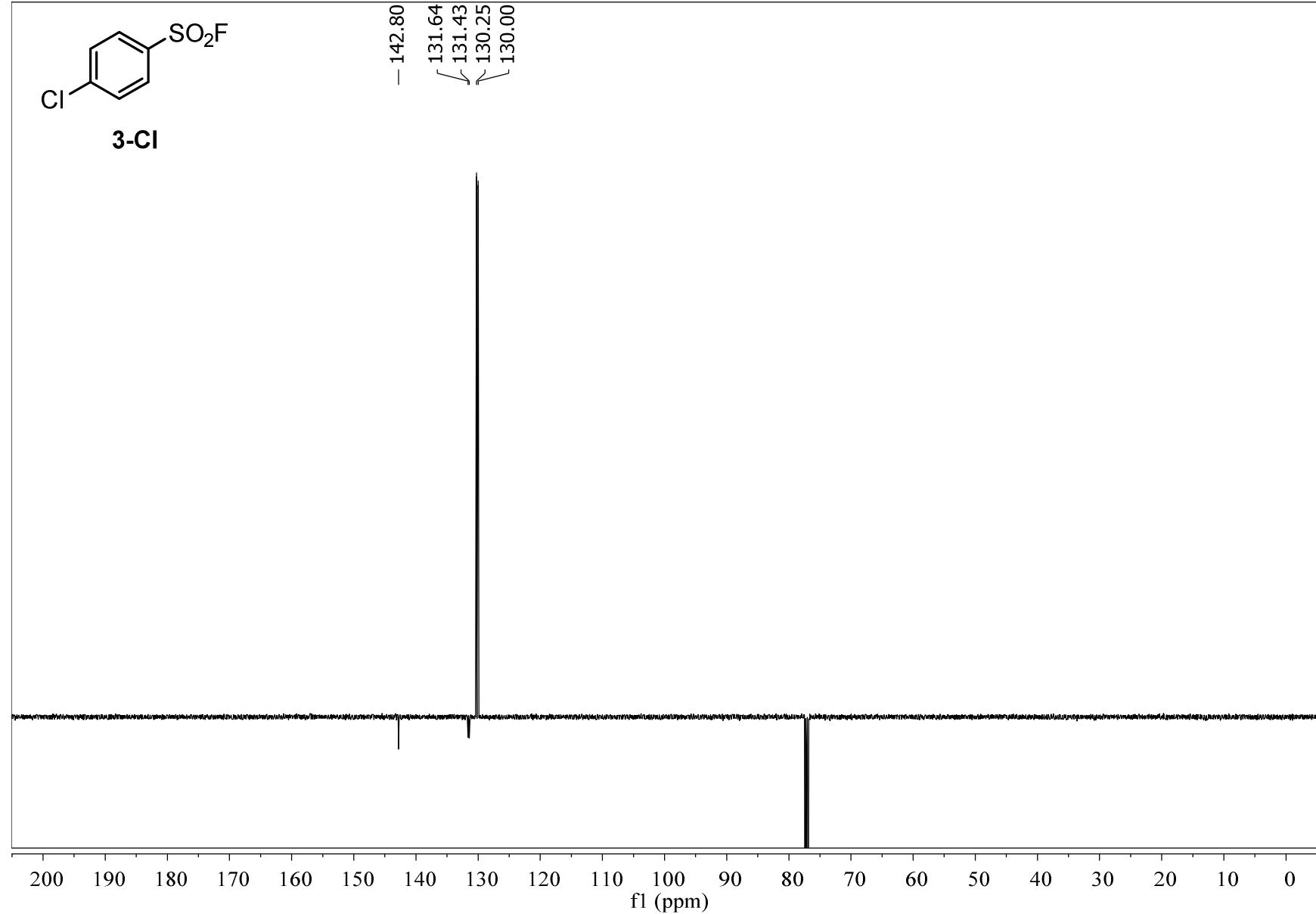
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## X. NMR Spectra

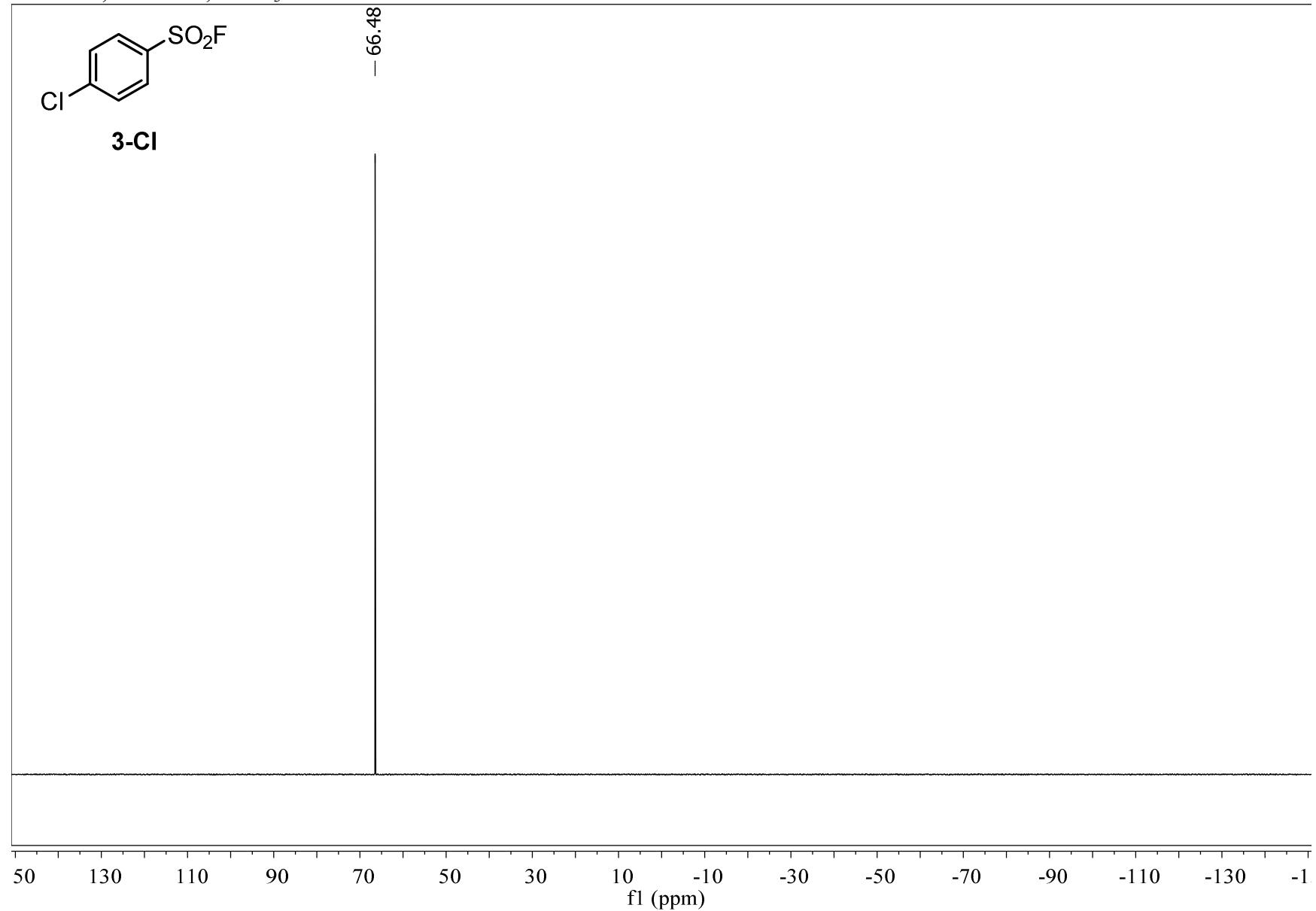
$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$



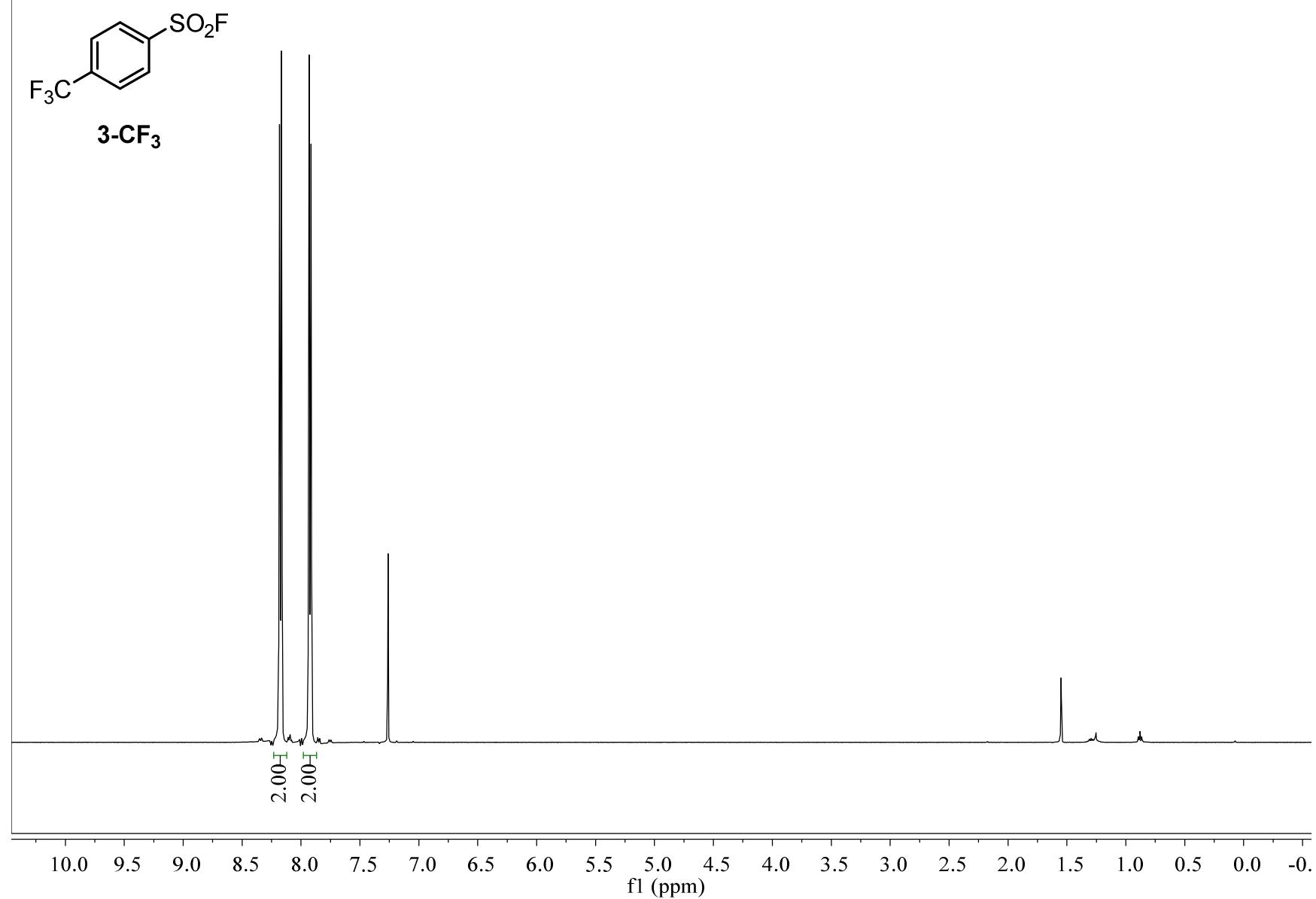
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



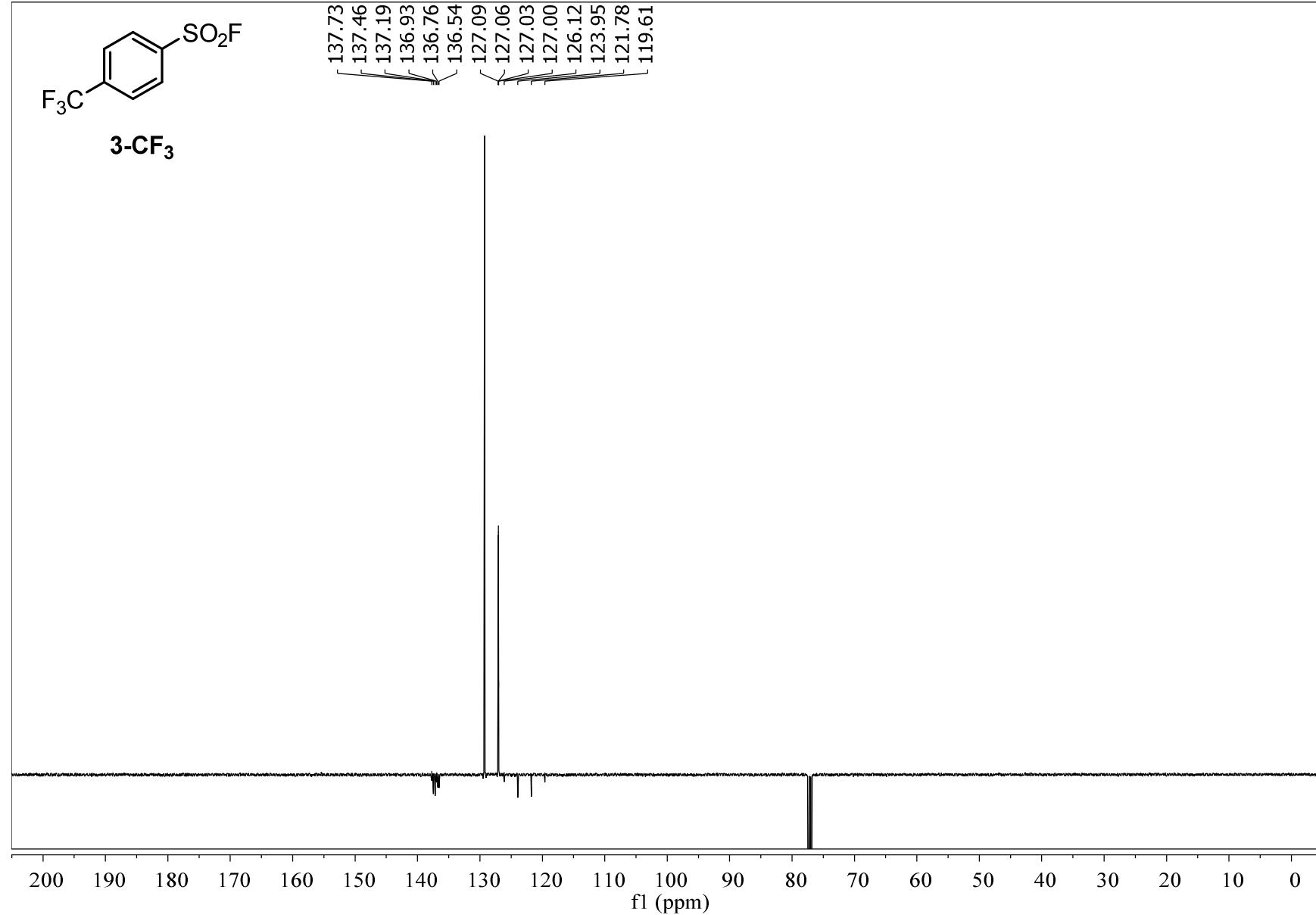
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



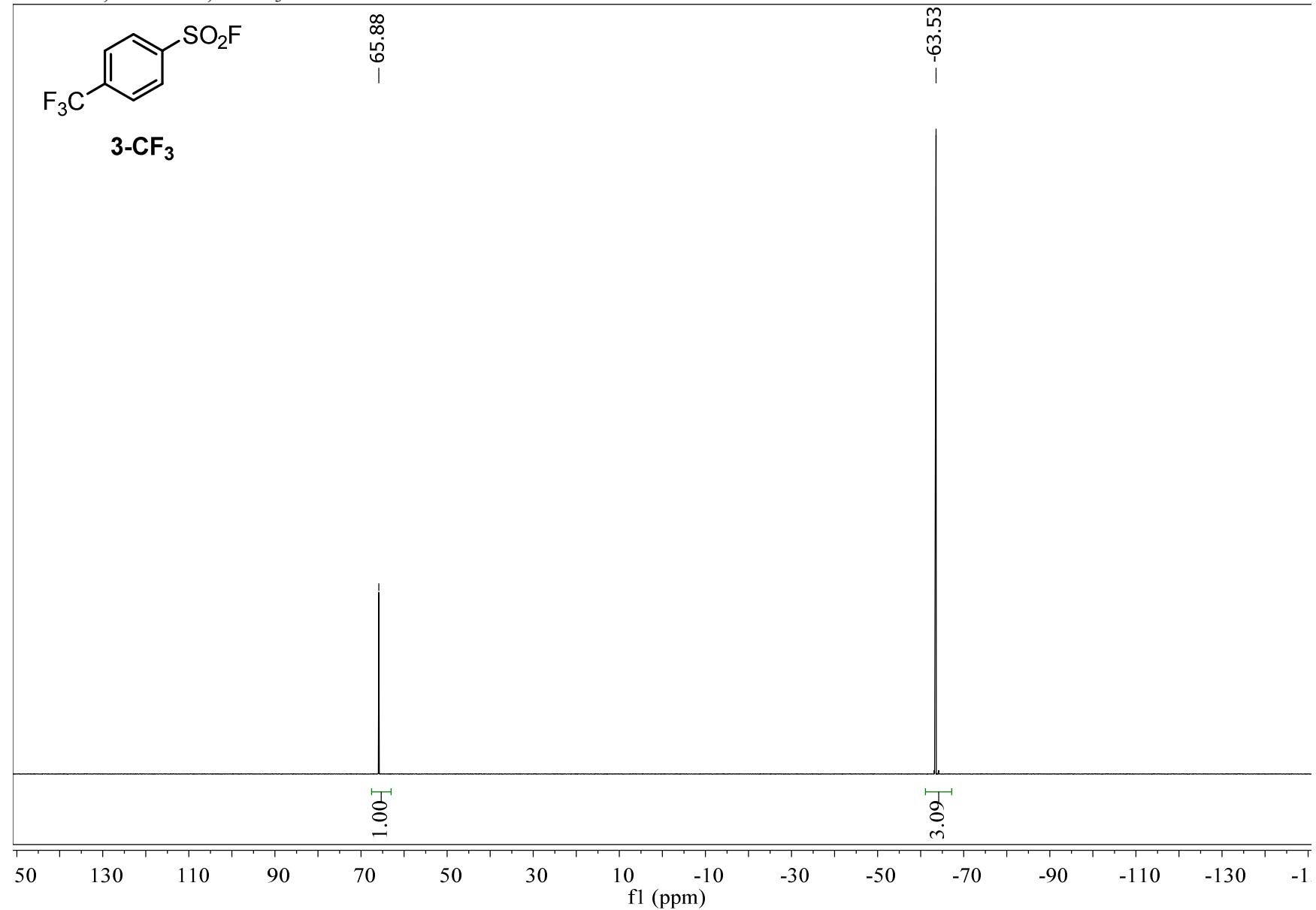
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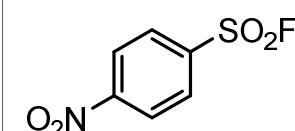
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>

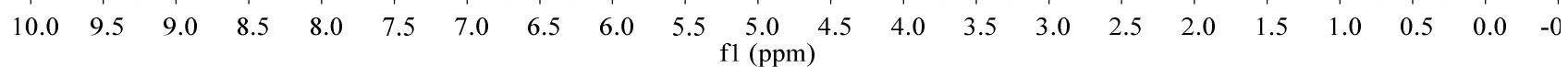


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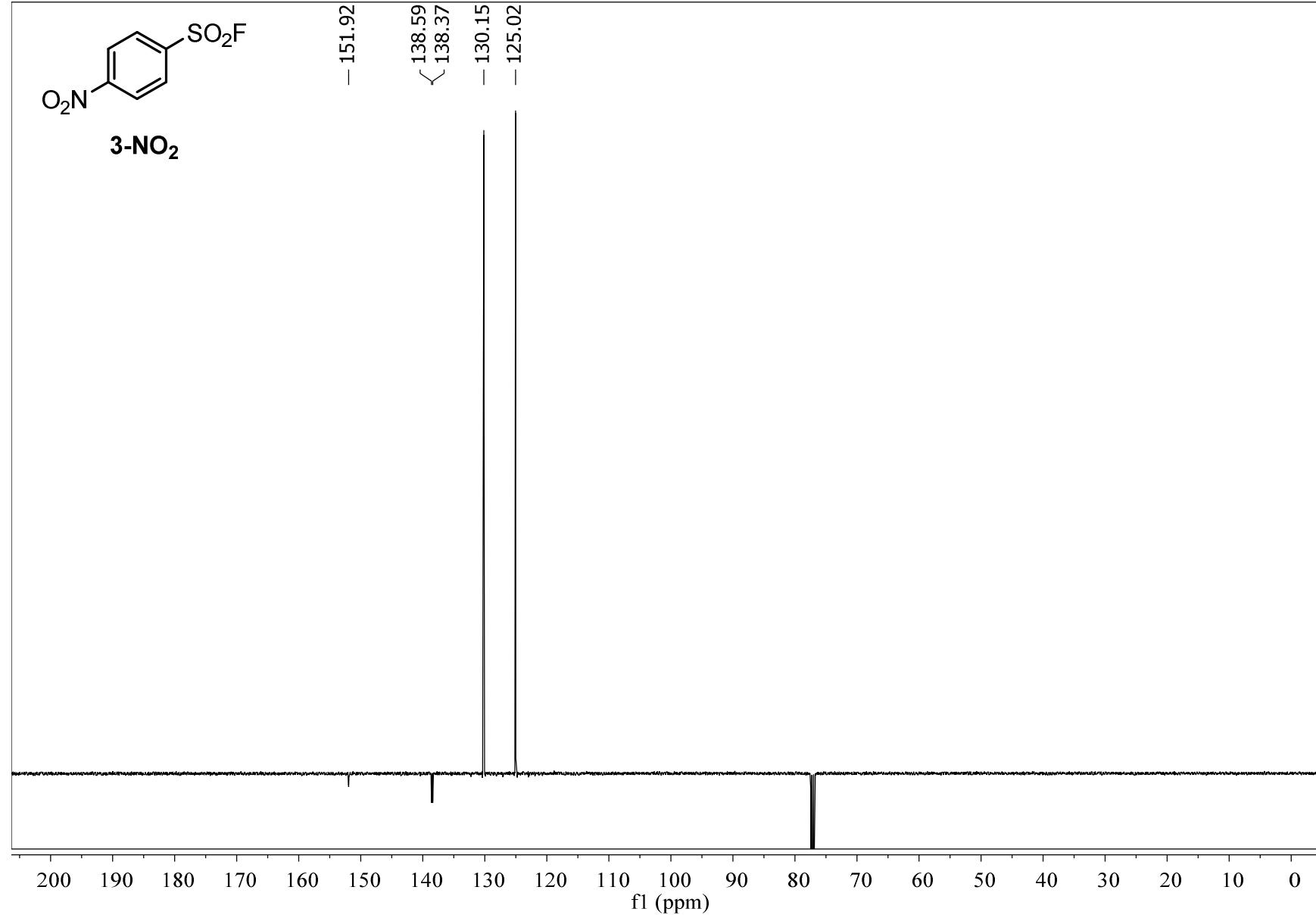


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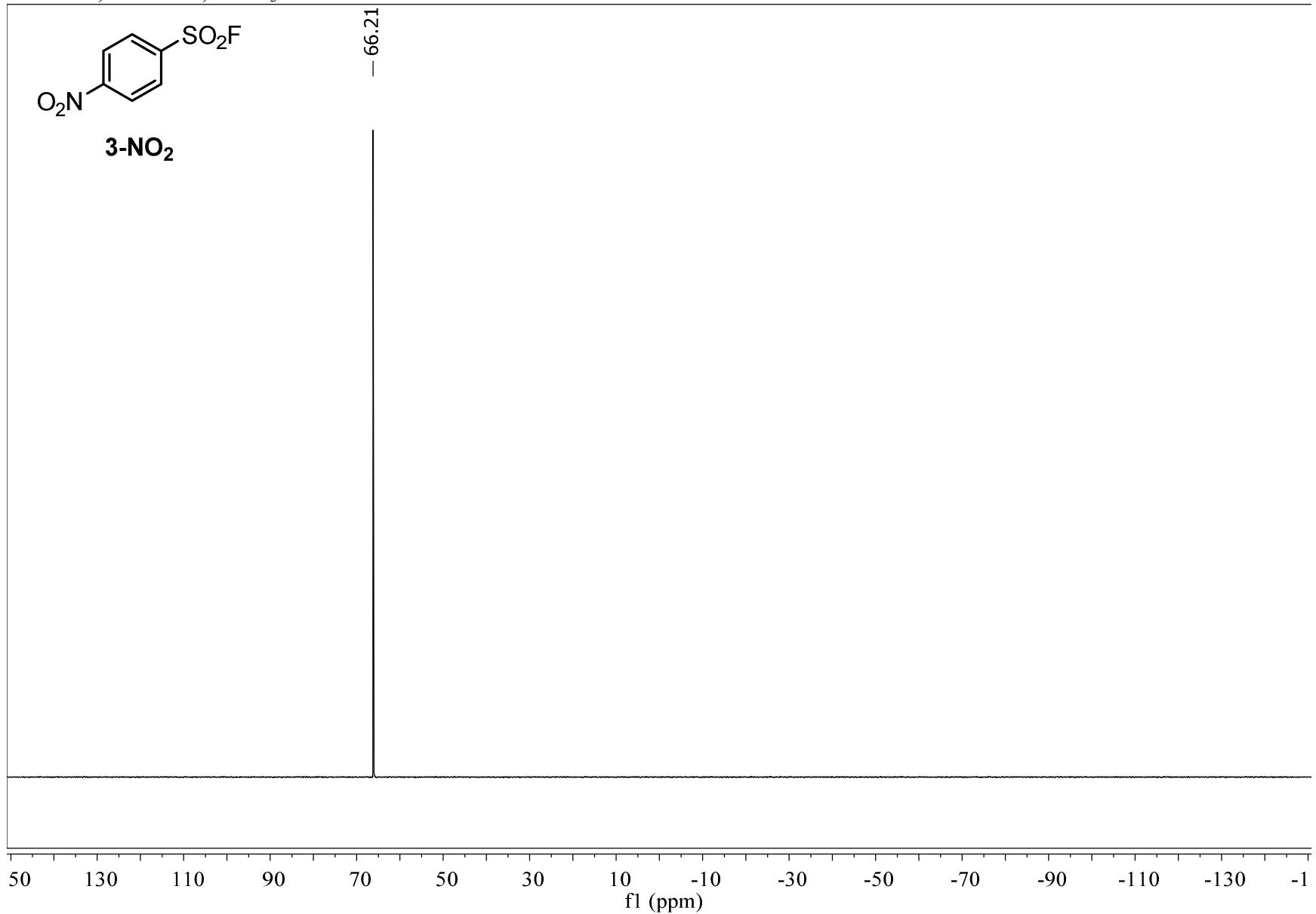
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2.02



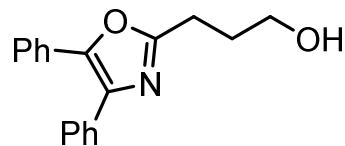
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



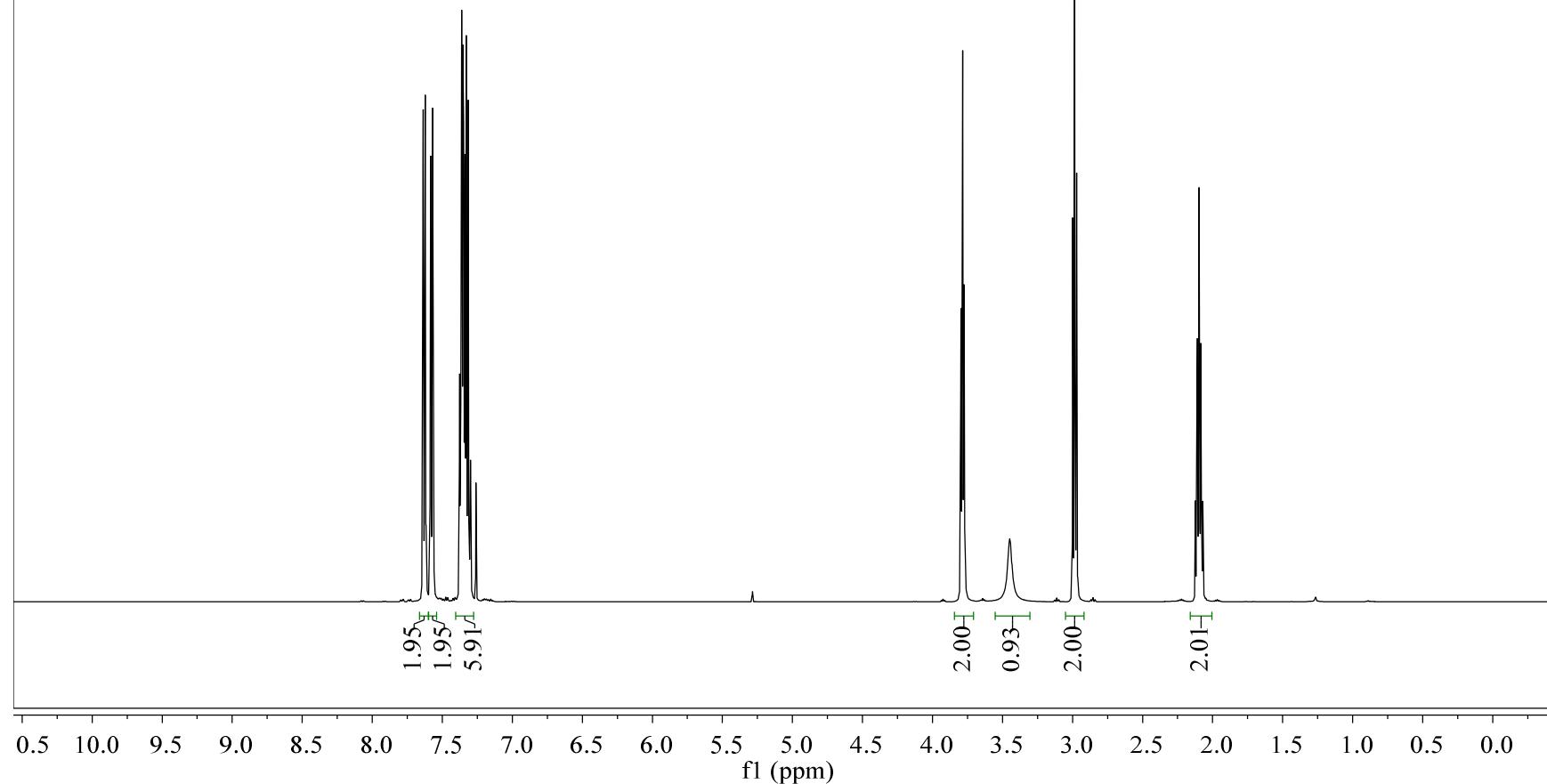
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



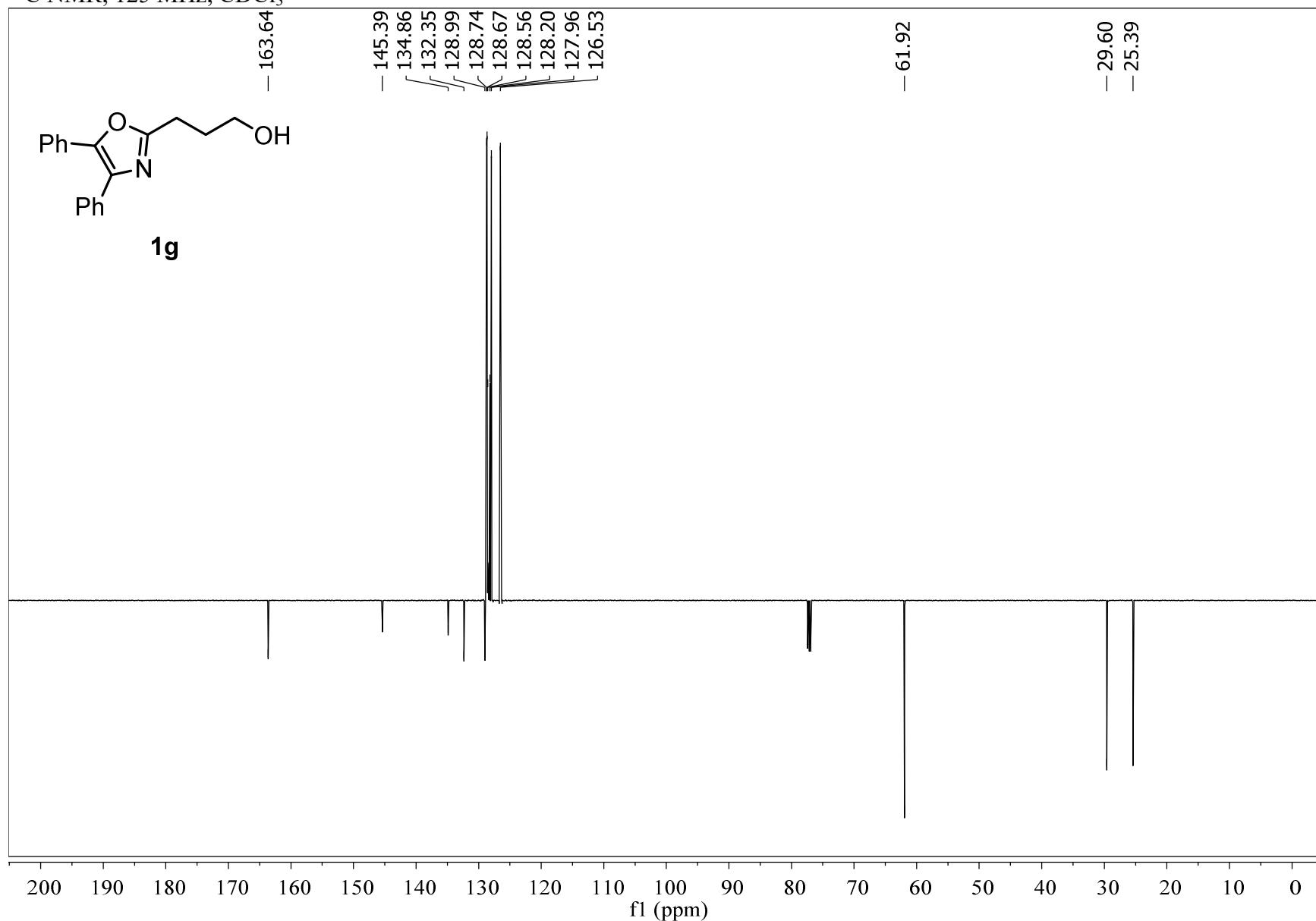
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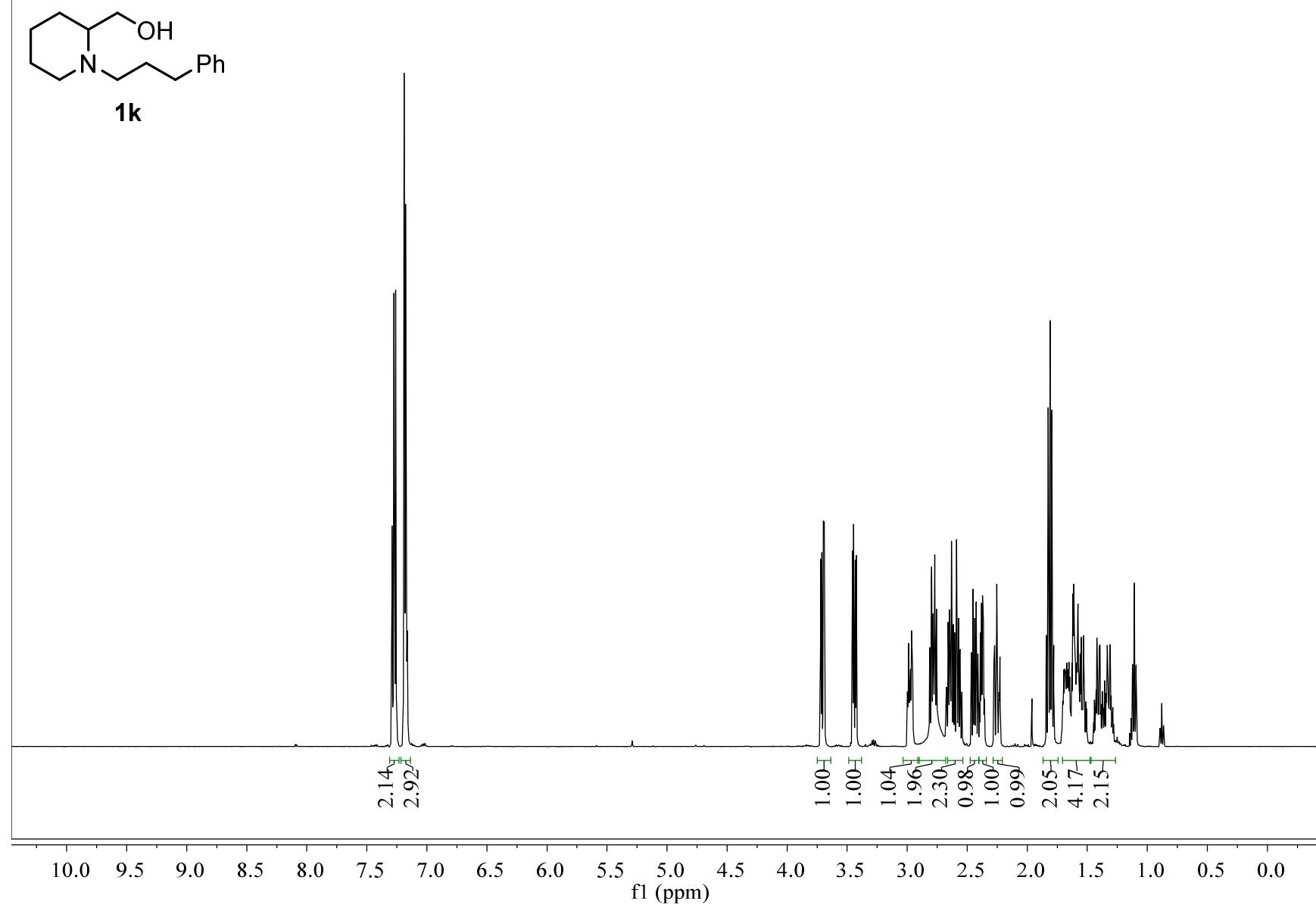
**1g**



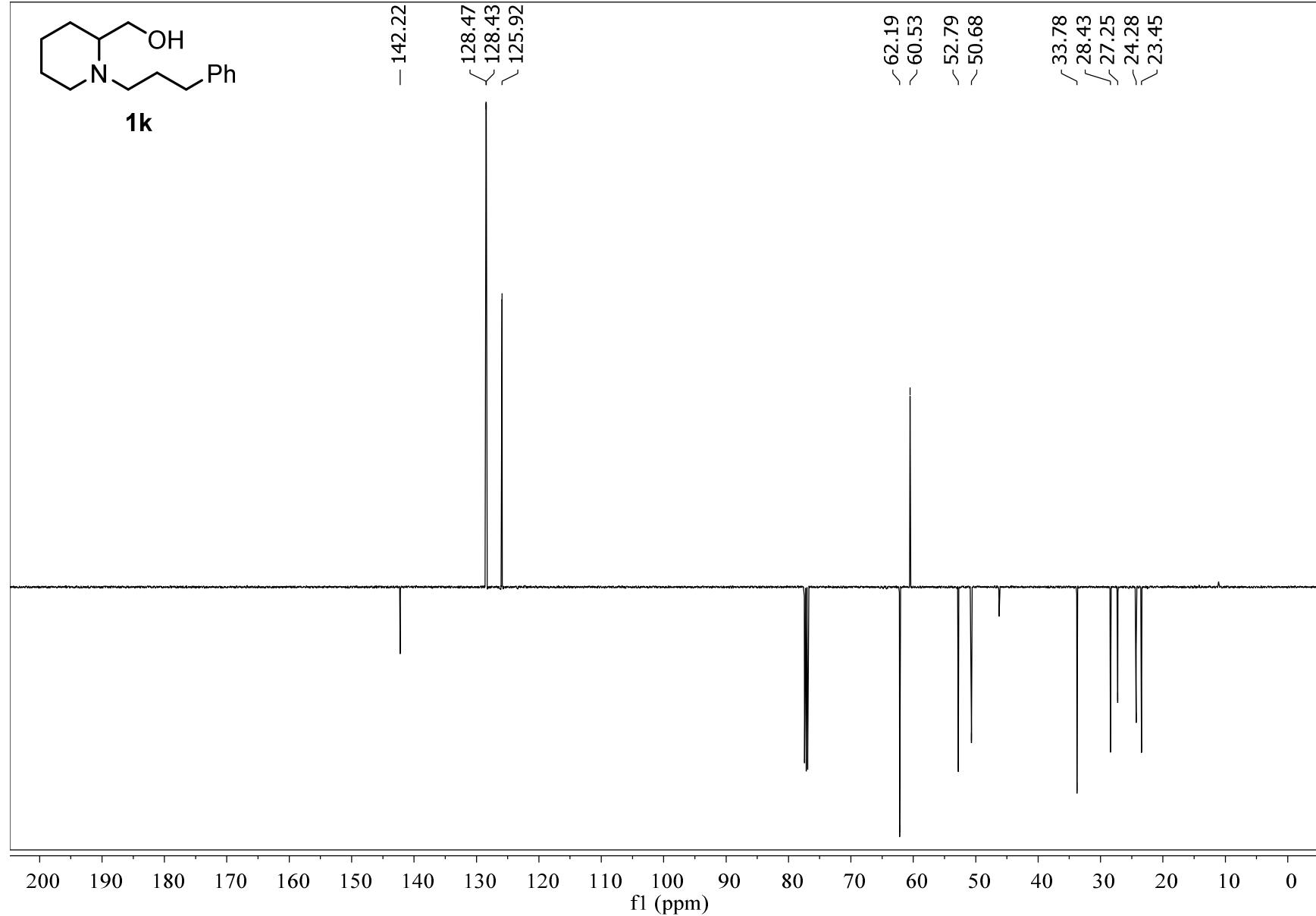
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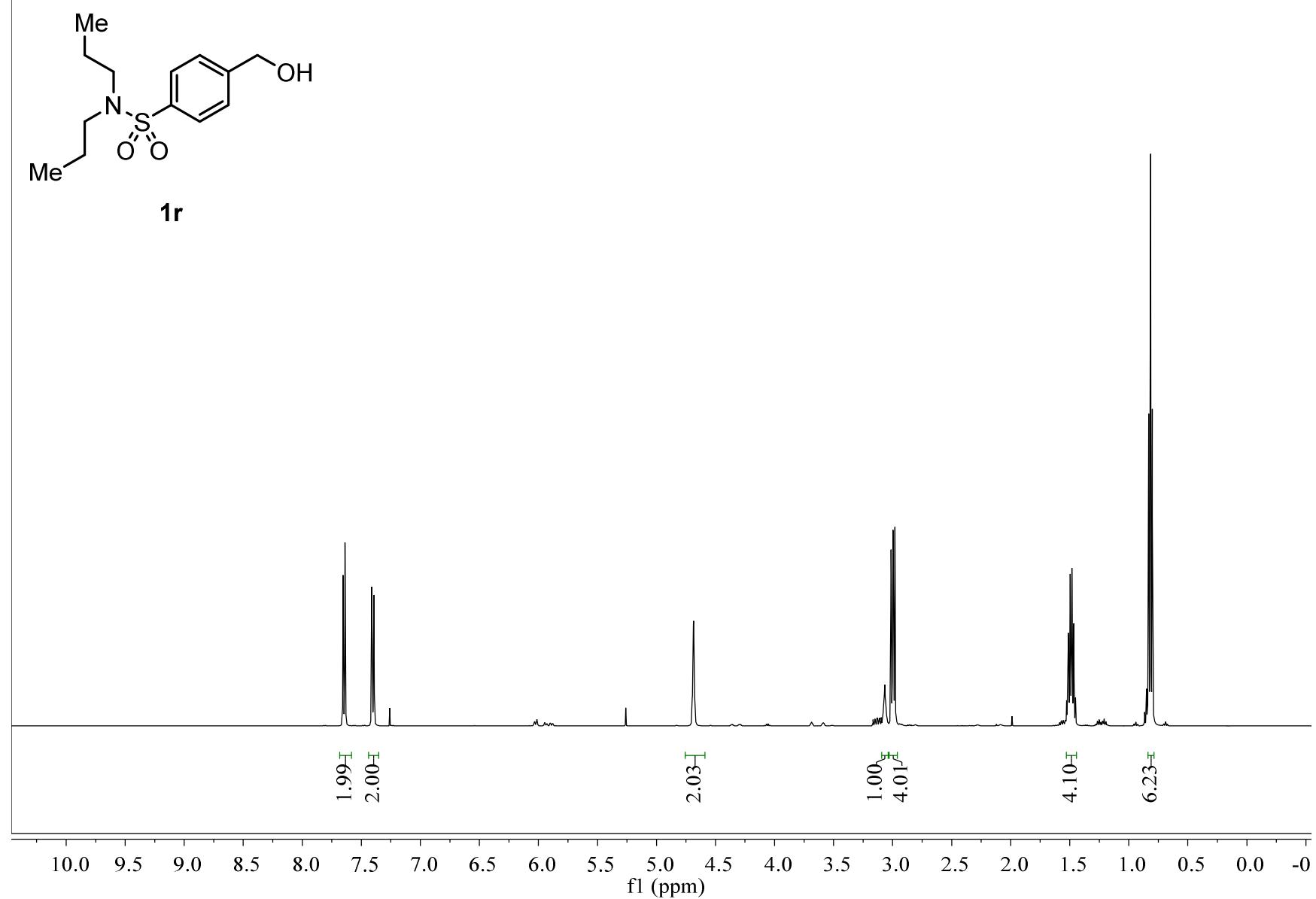
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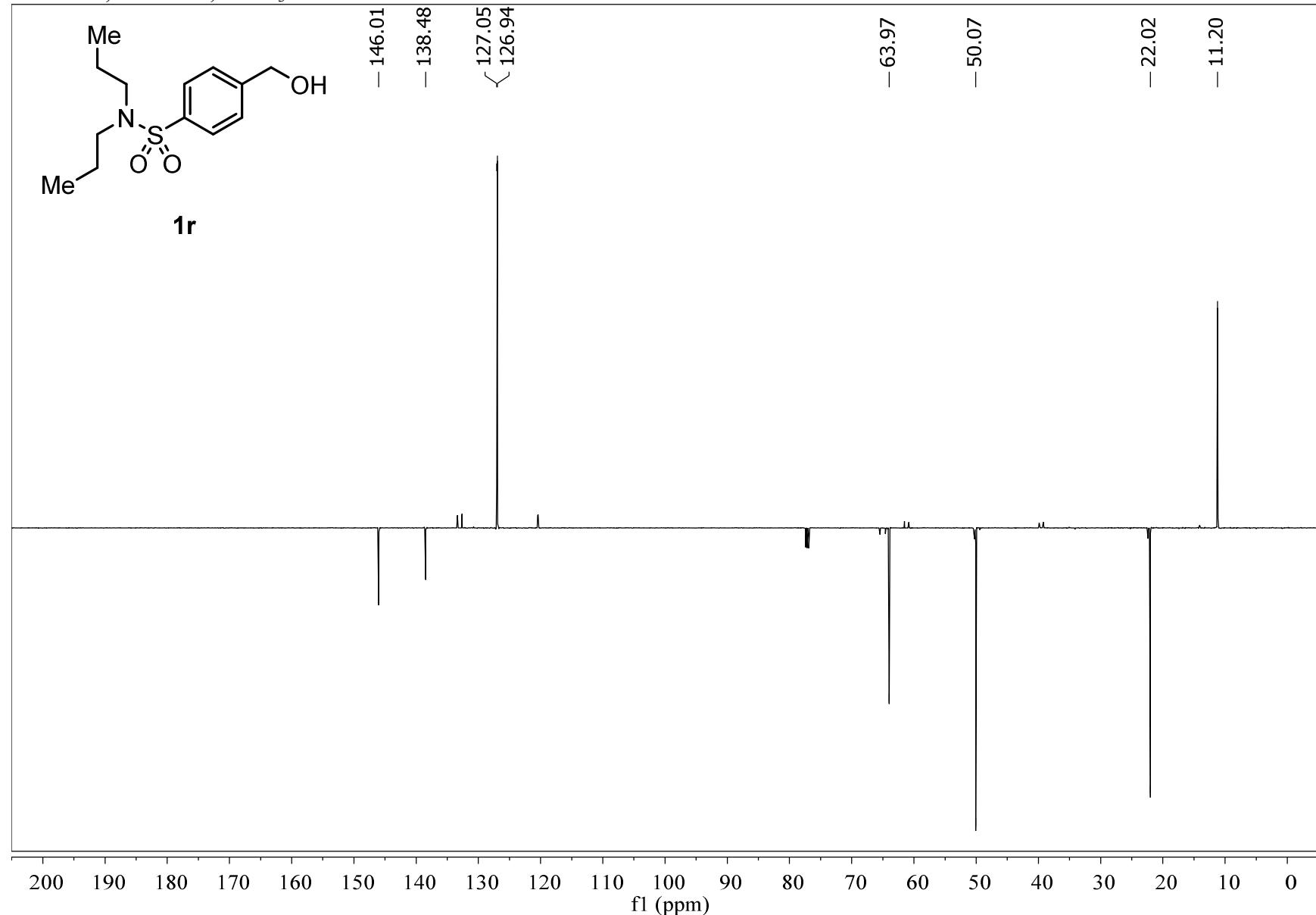
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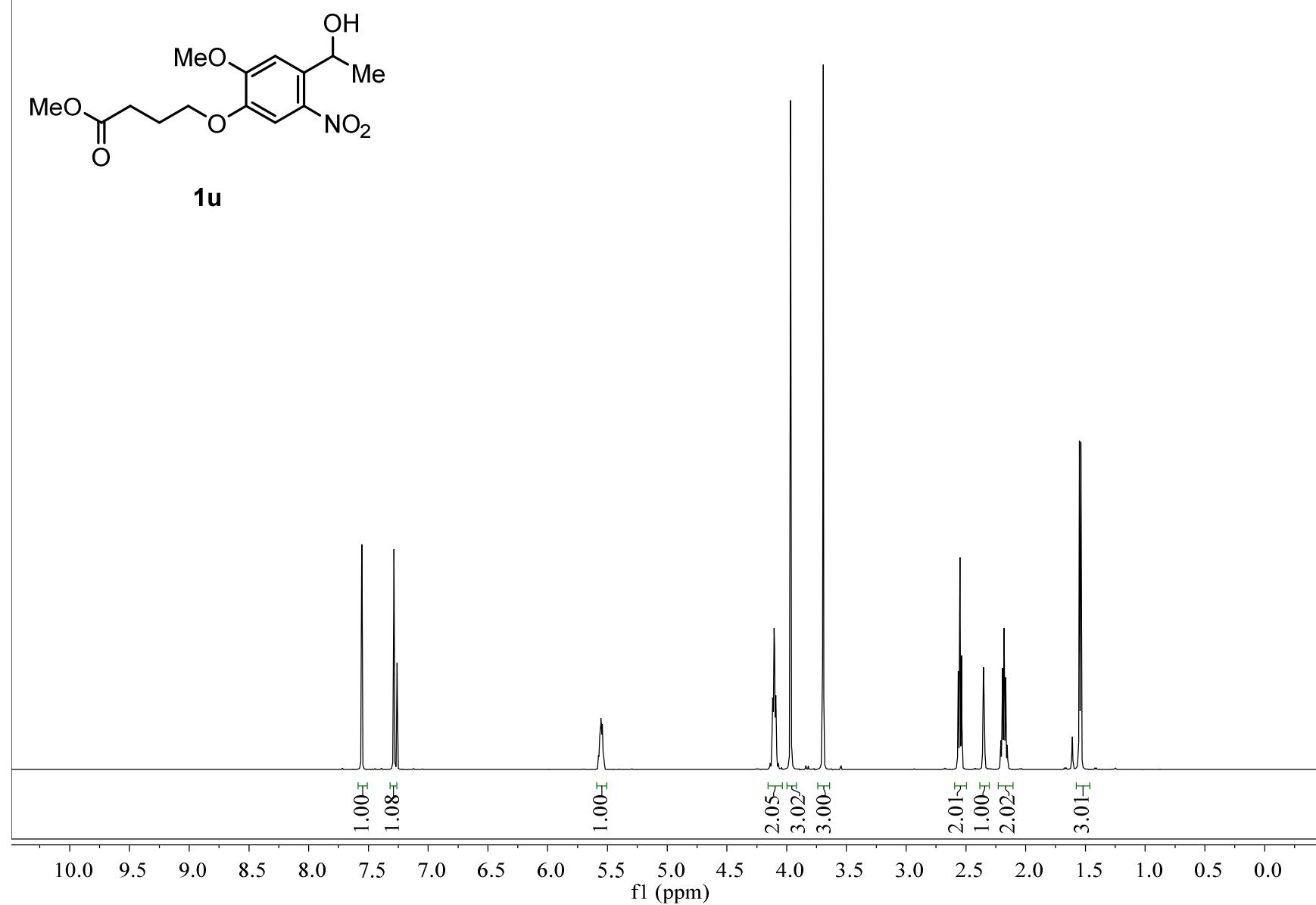
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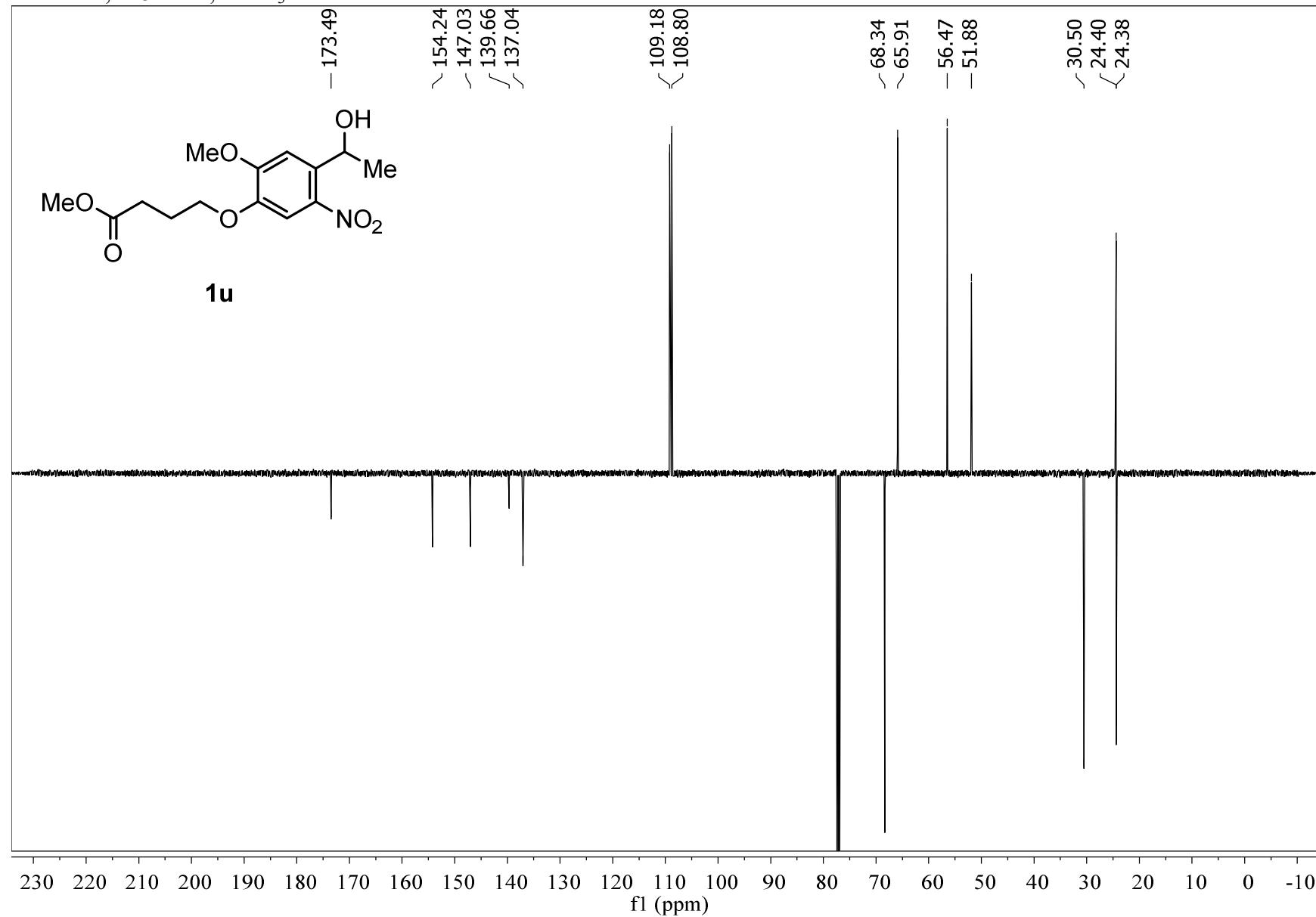
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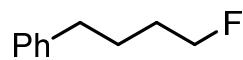
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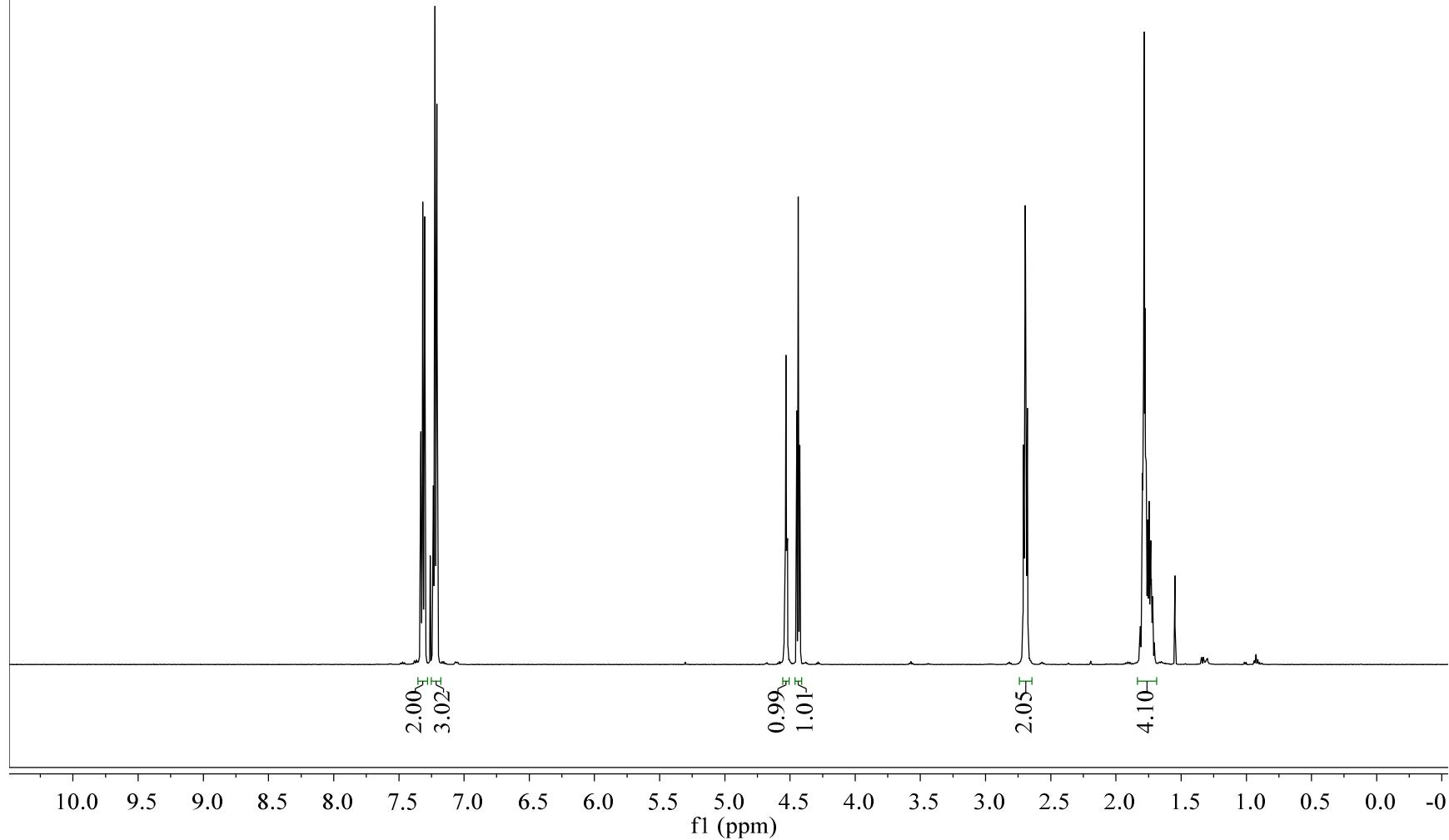
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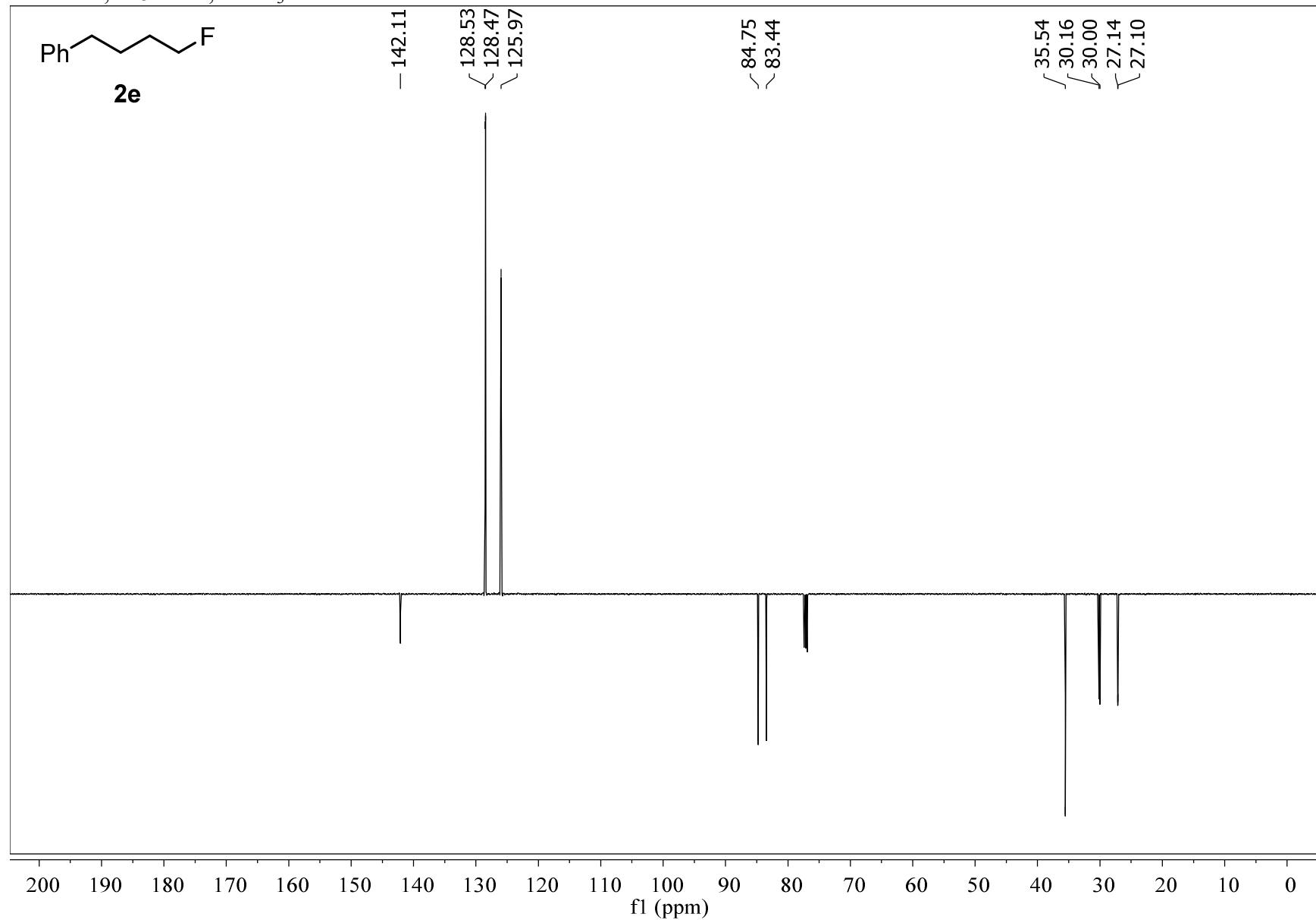
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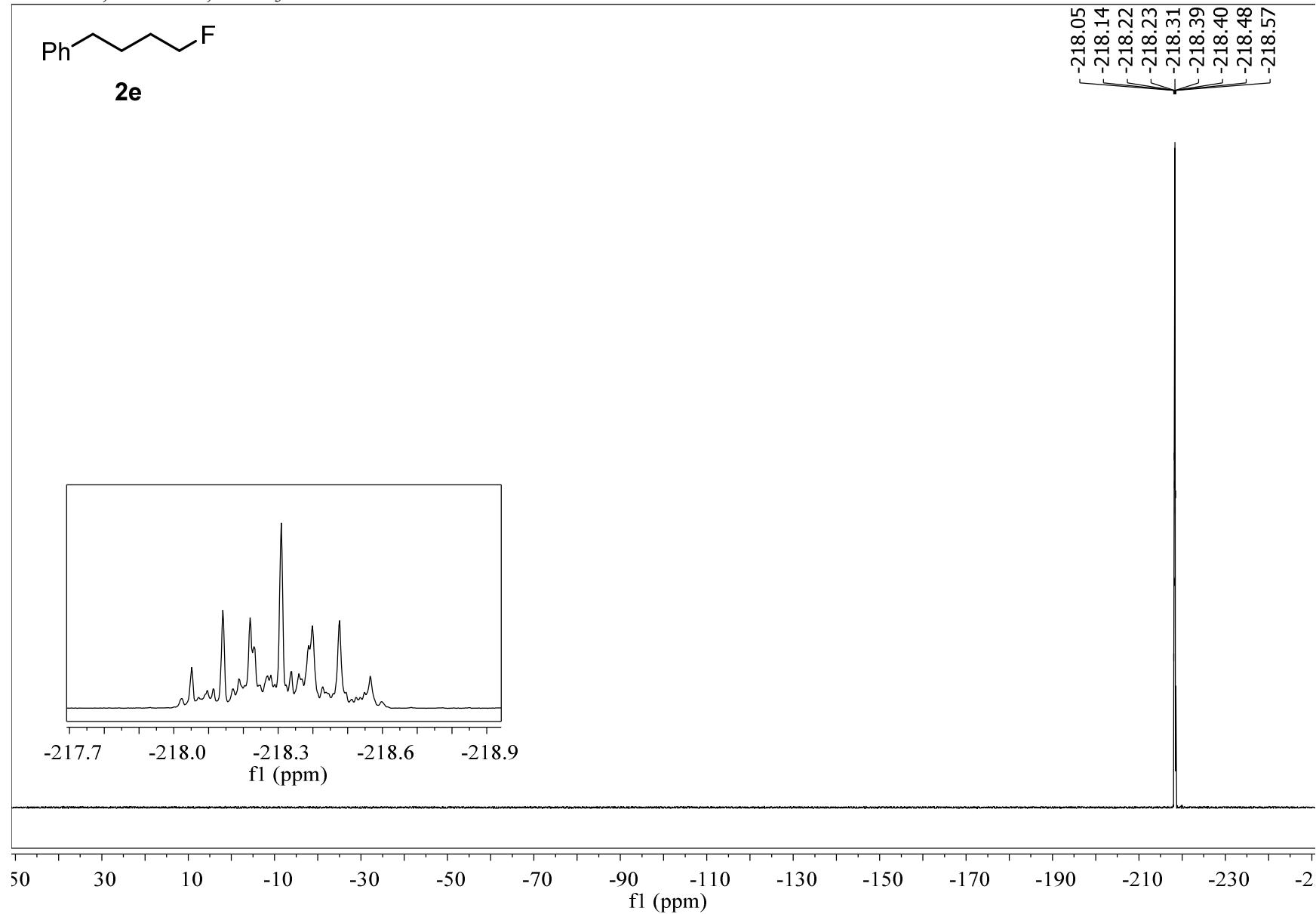
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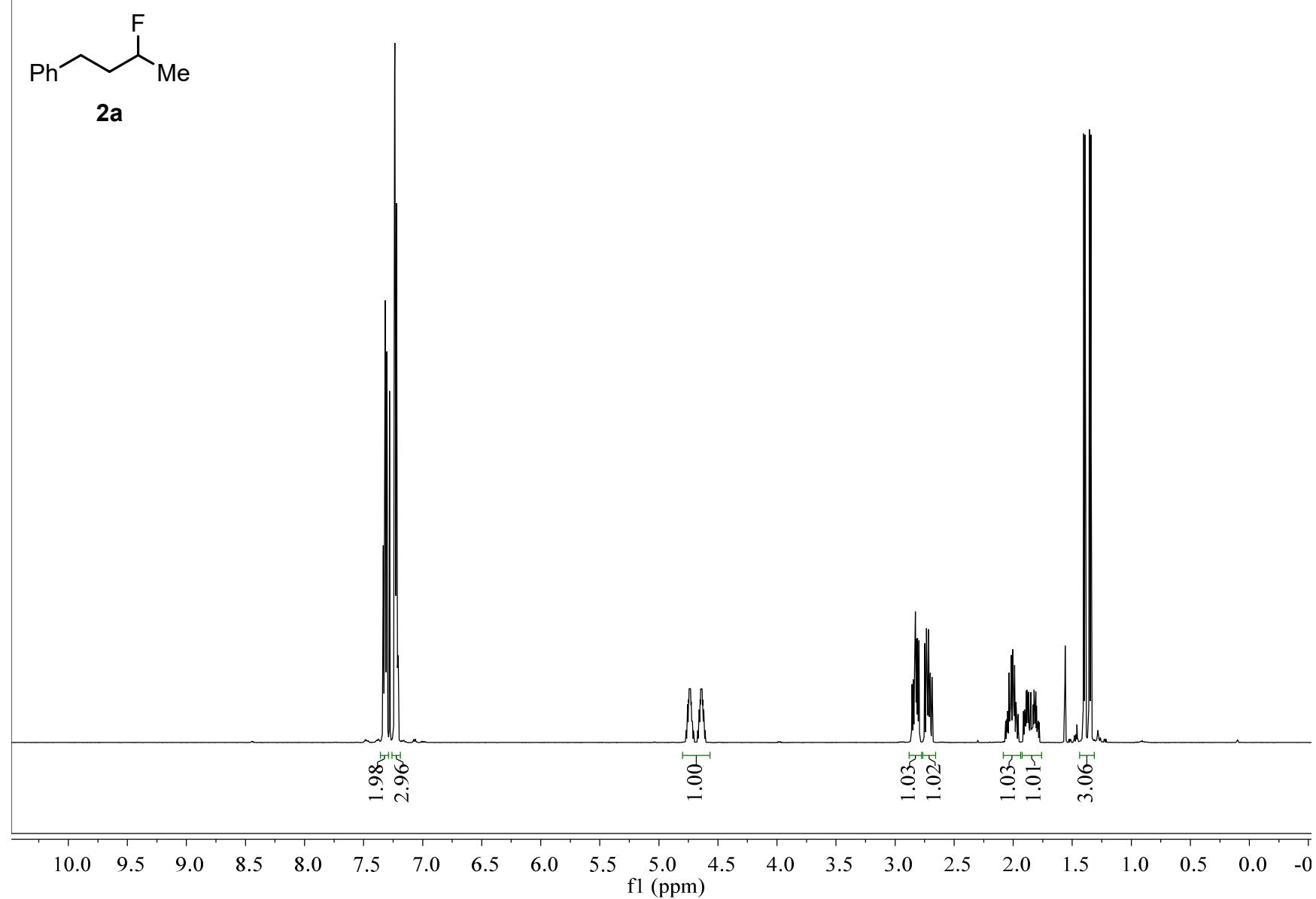
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



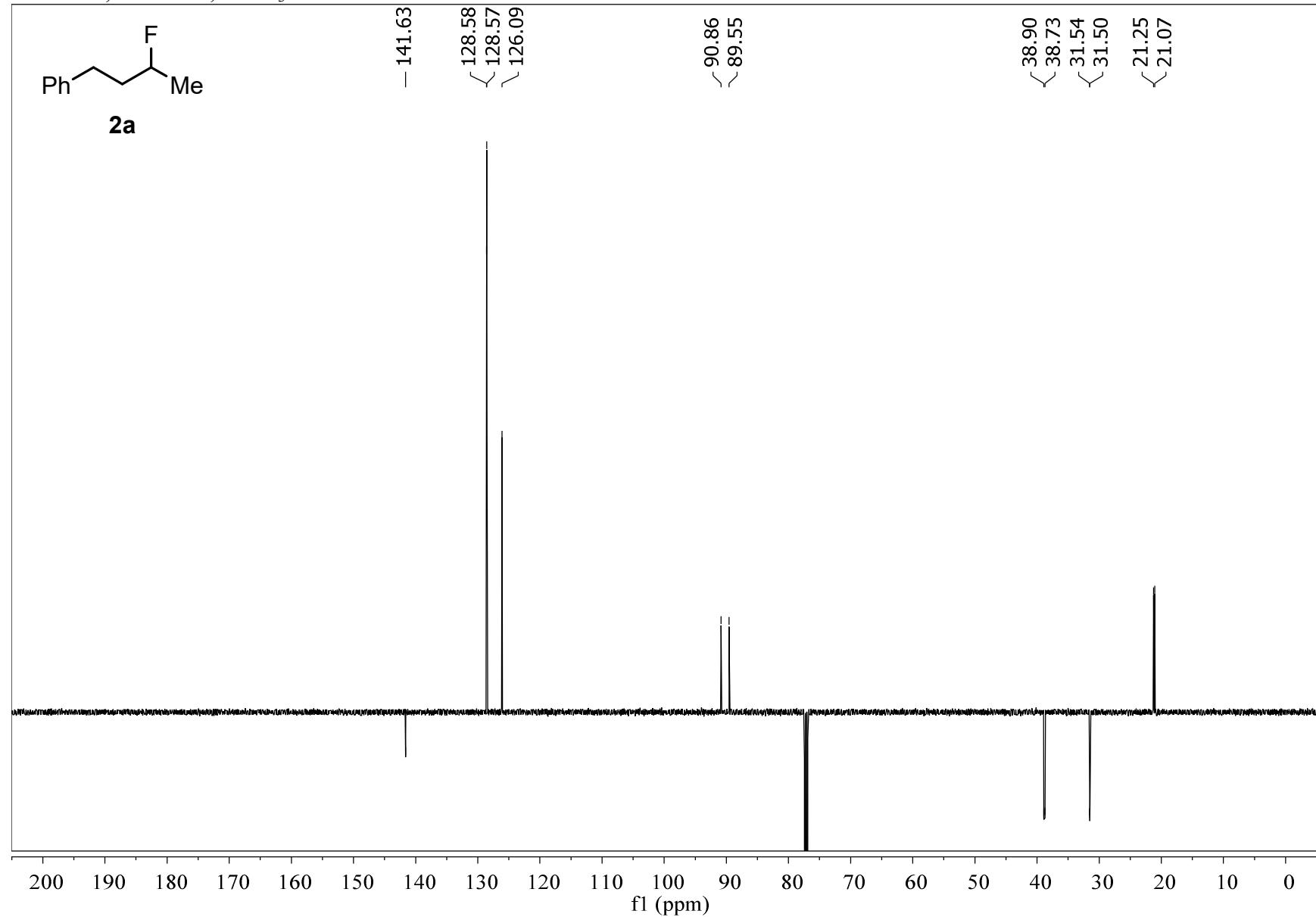
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



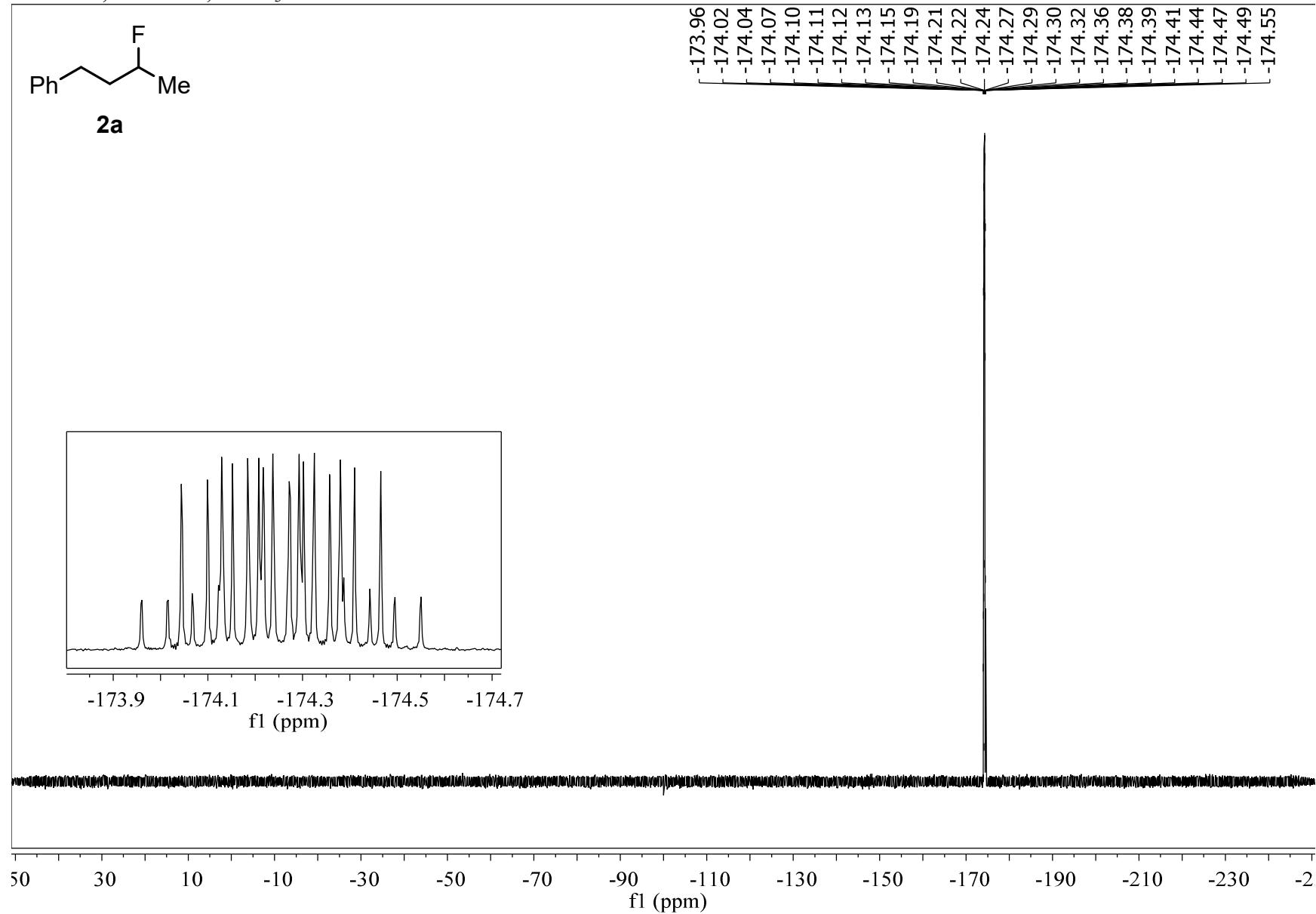
$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$



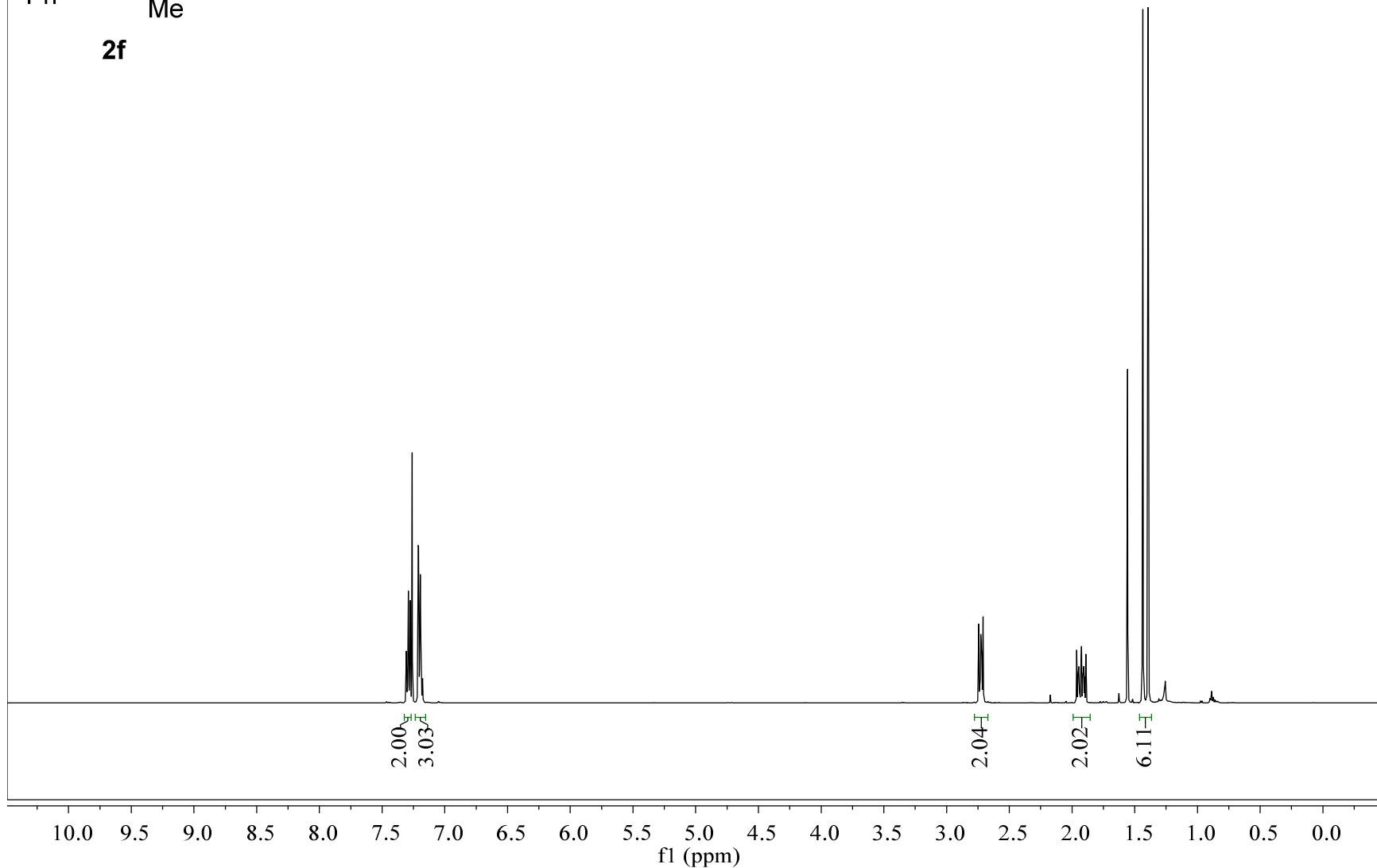
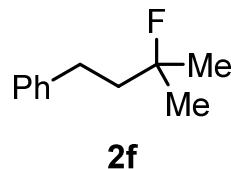
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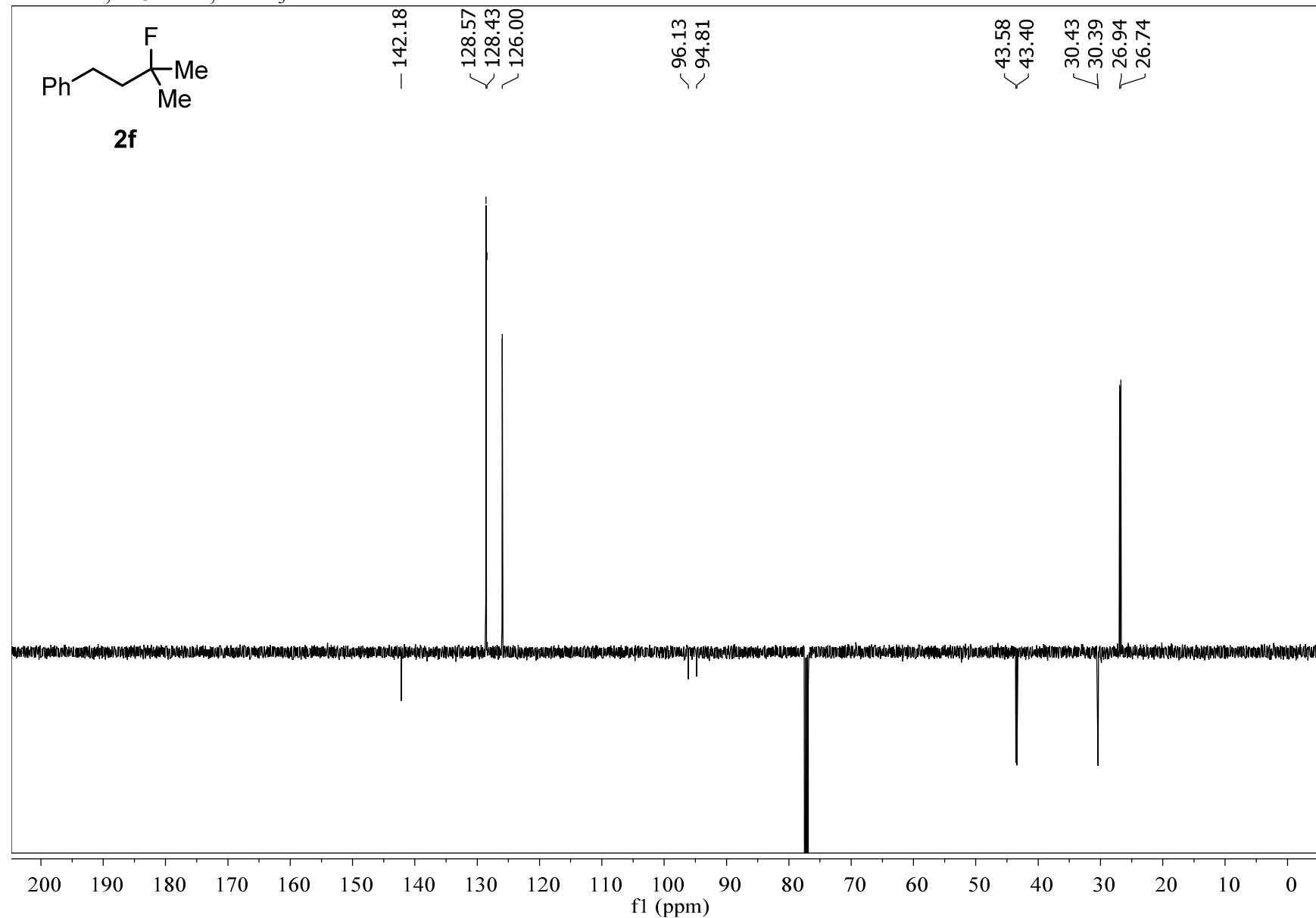
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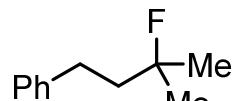
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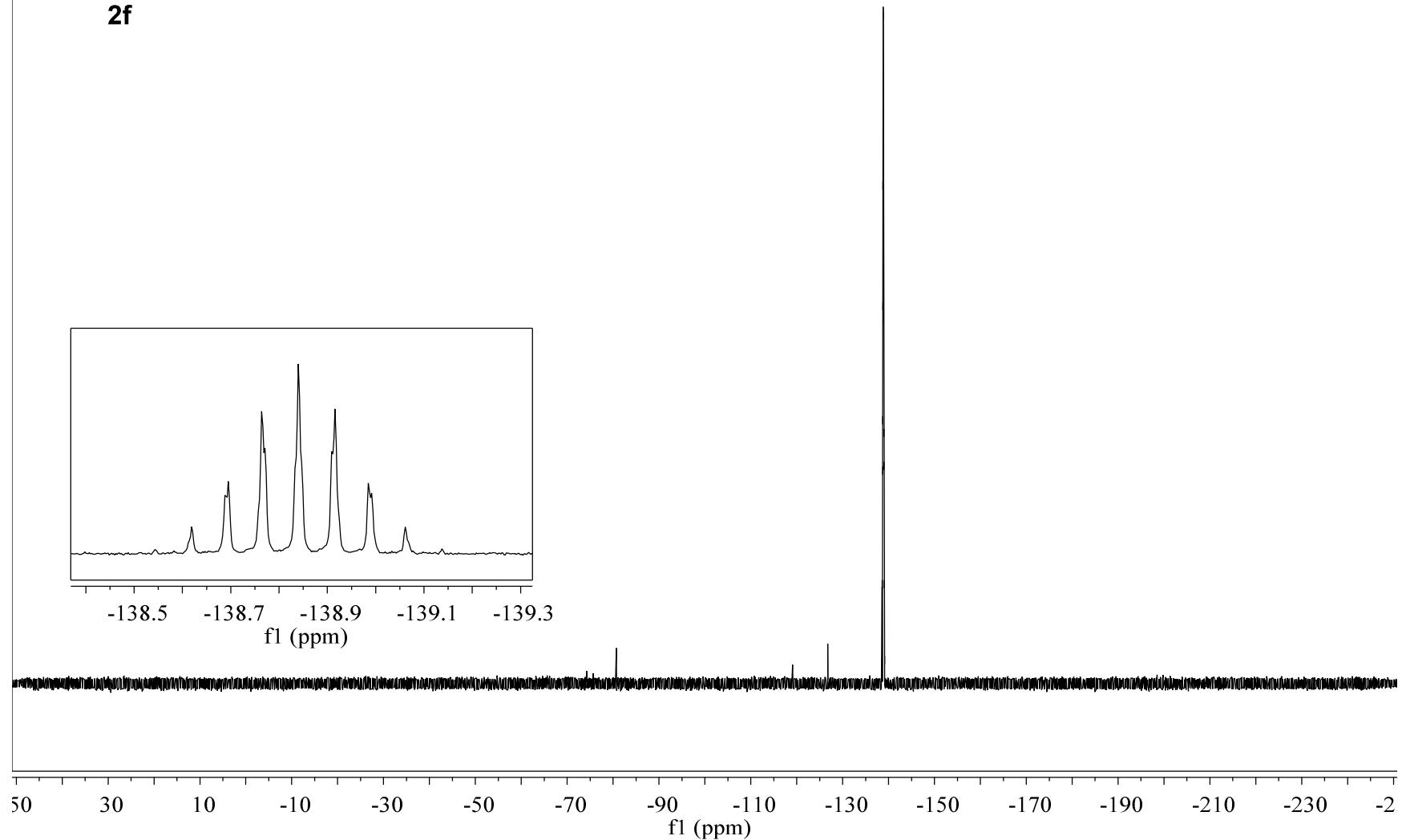
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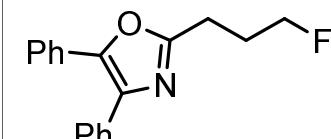
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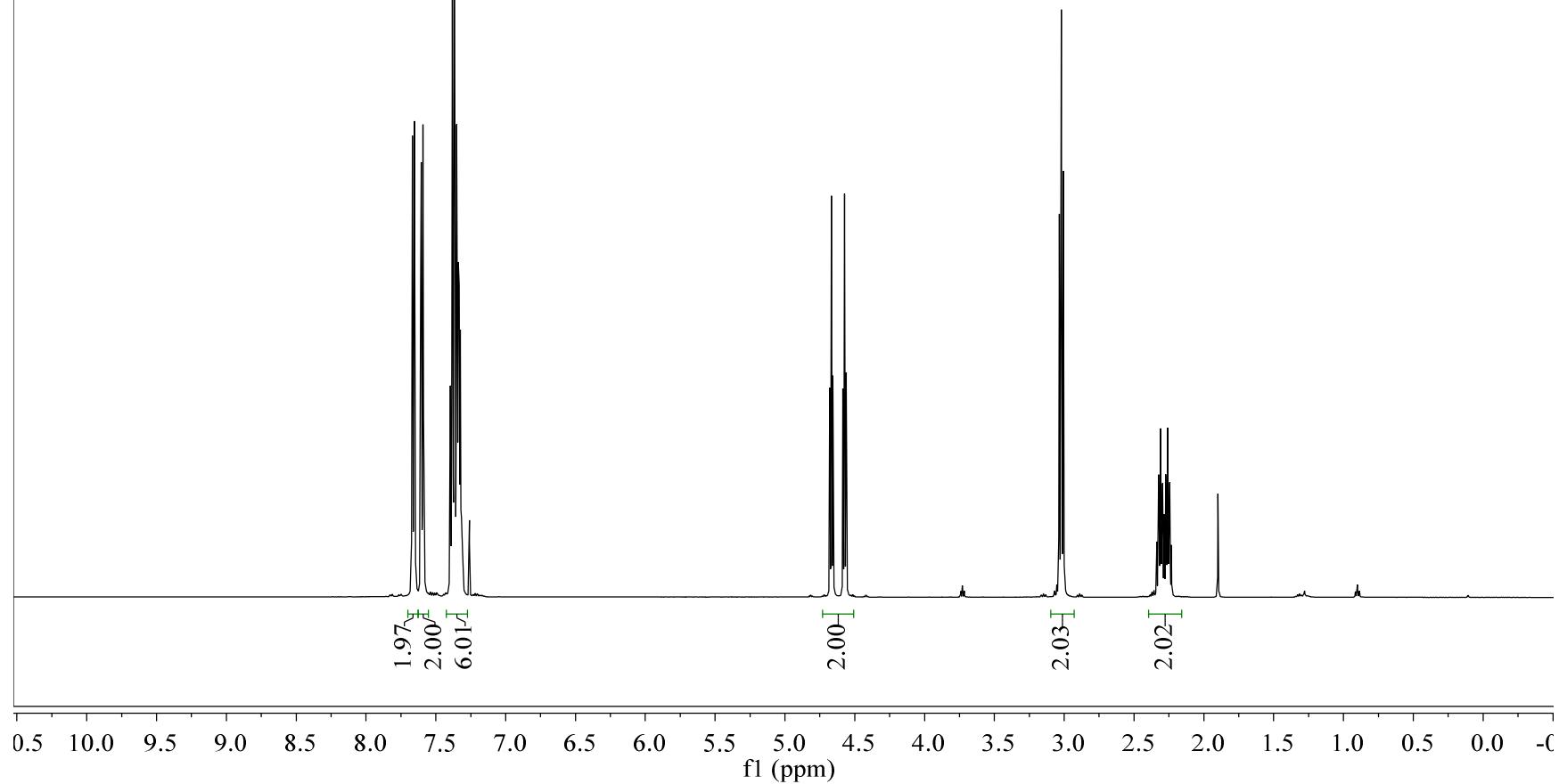
**2f**



<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

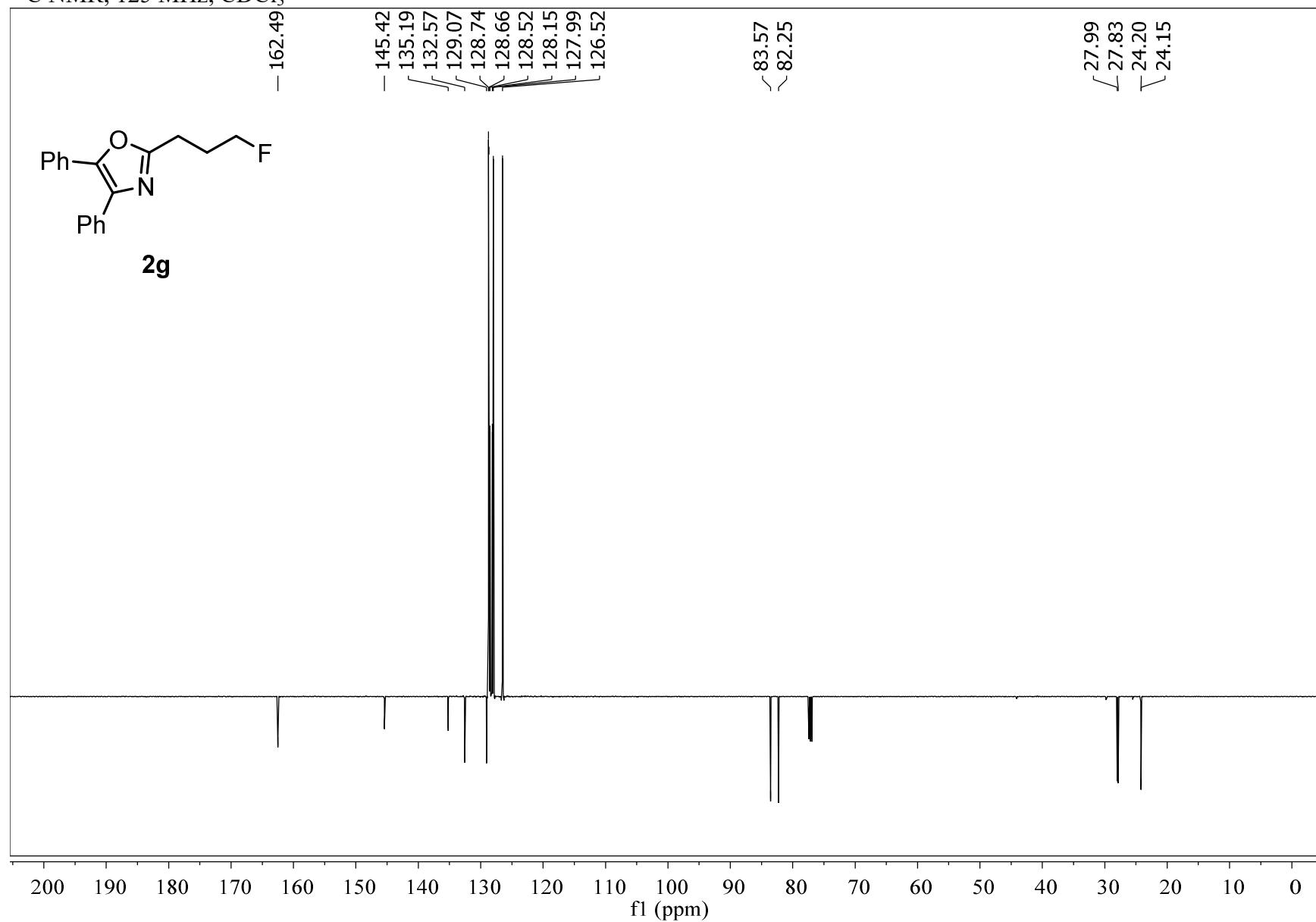


**2g**

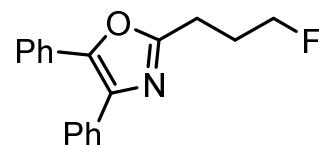


S-102

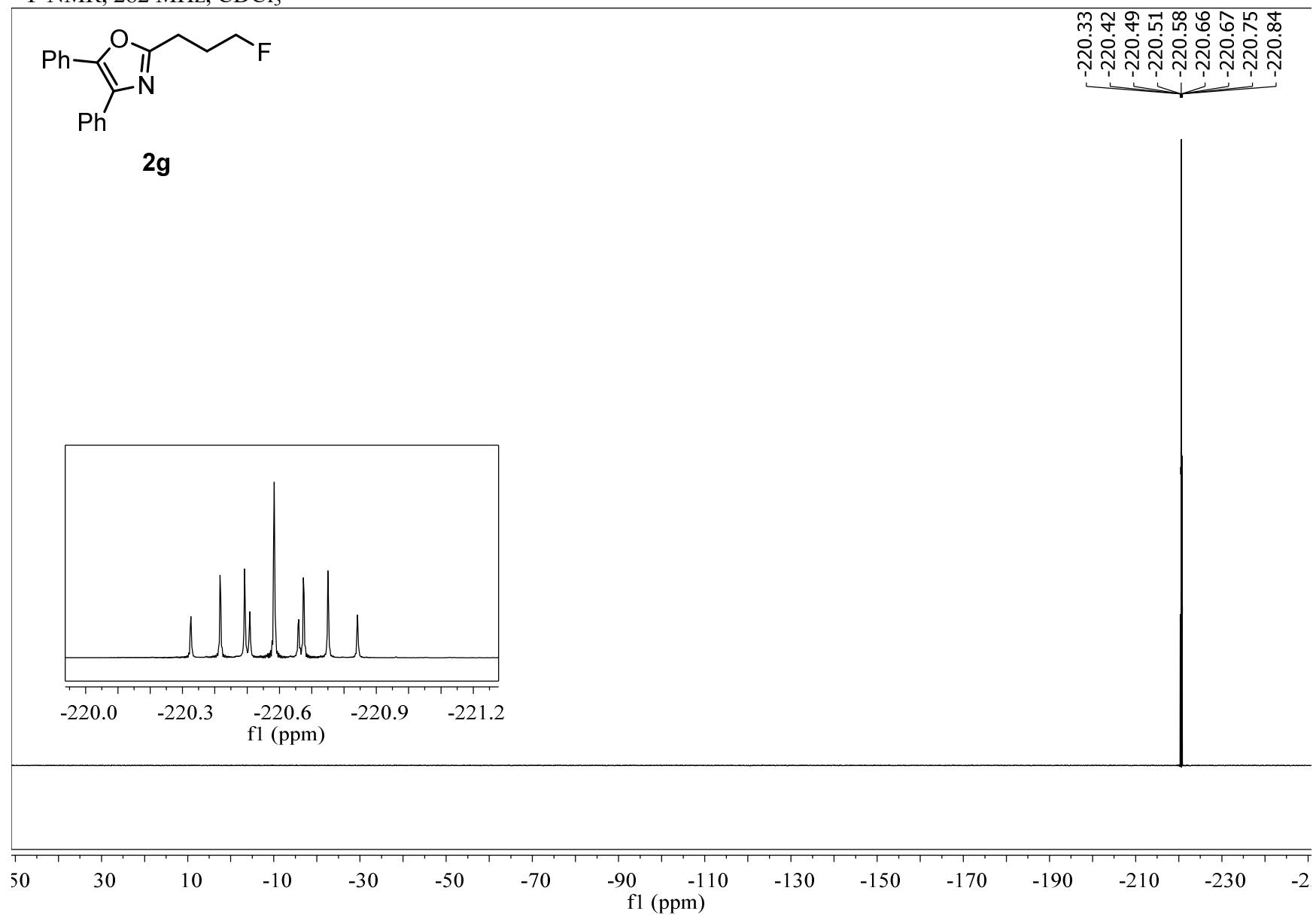
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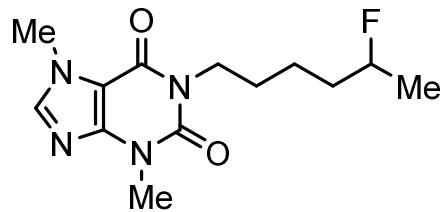
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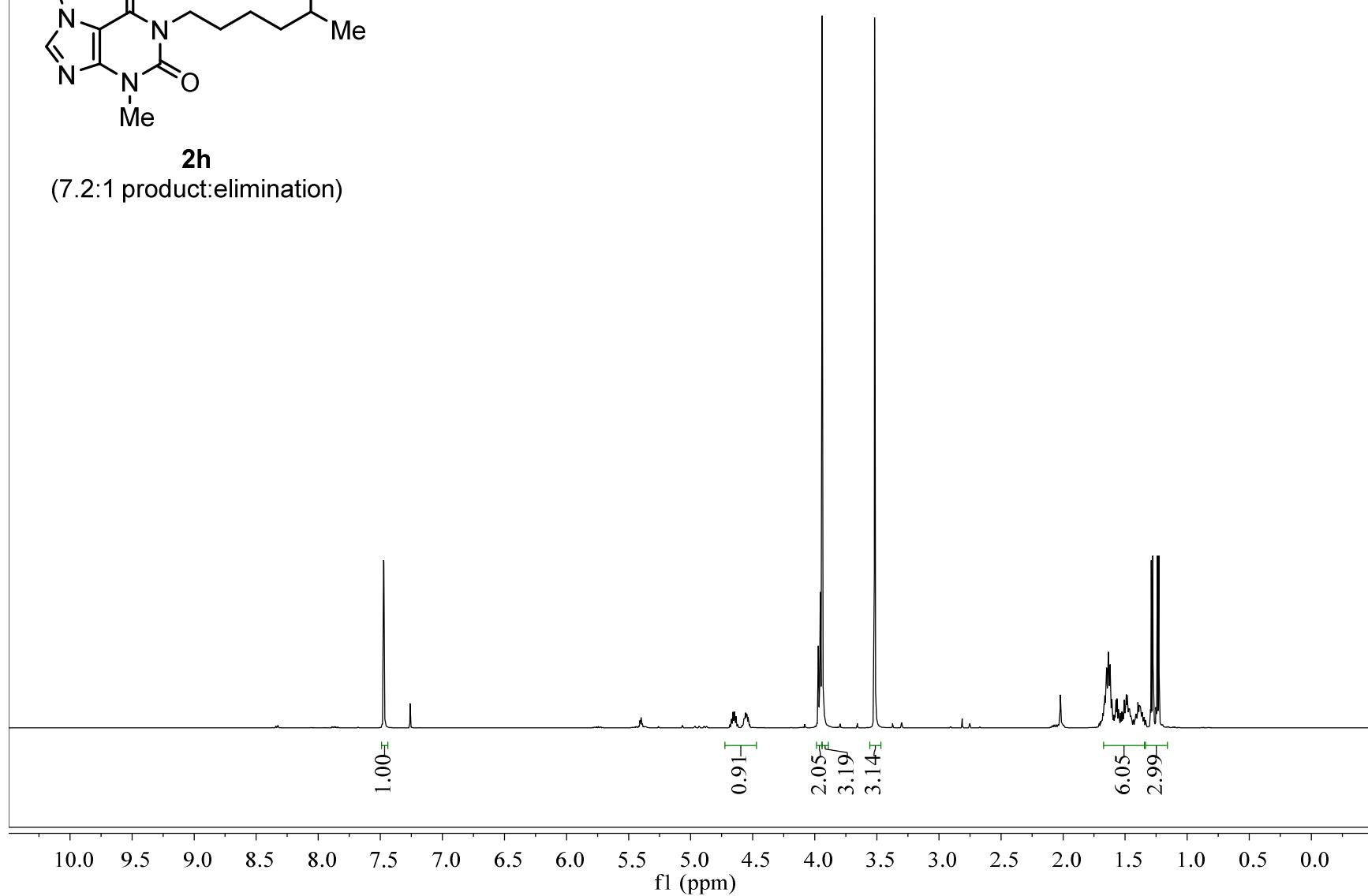
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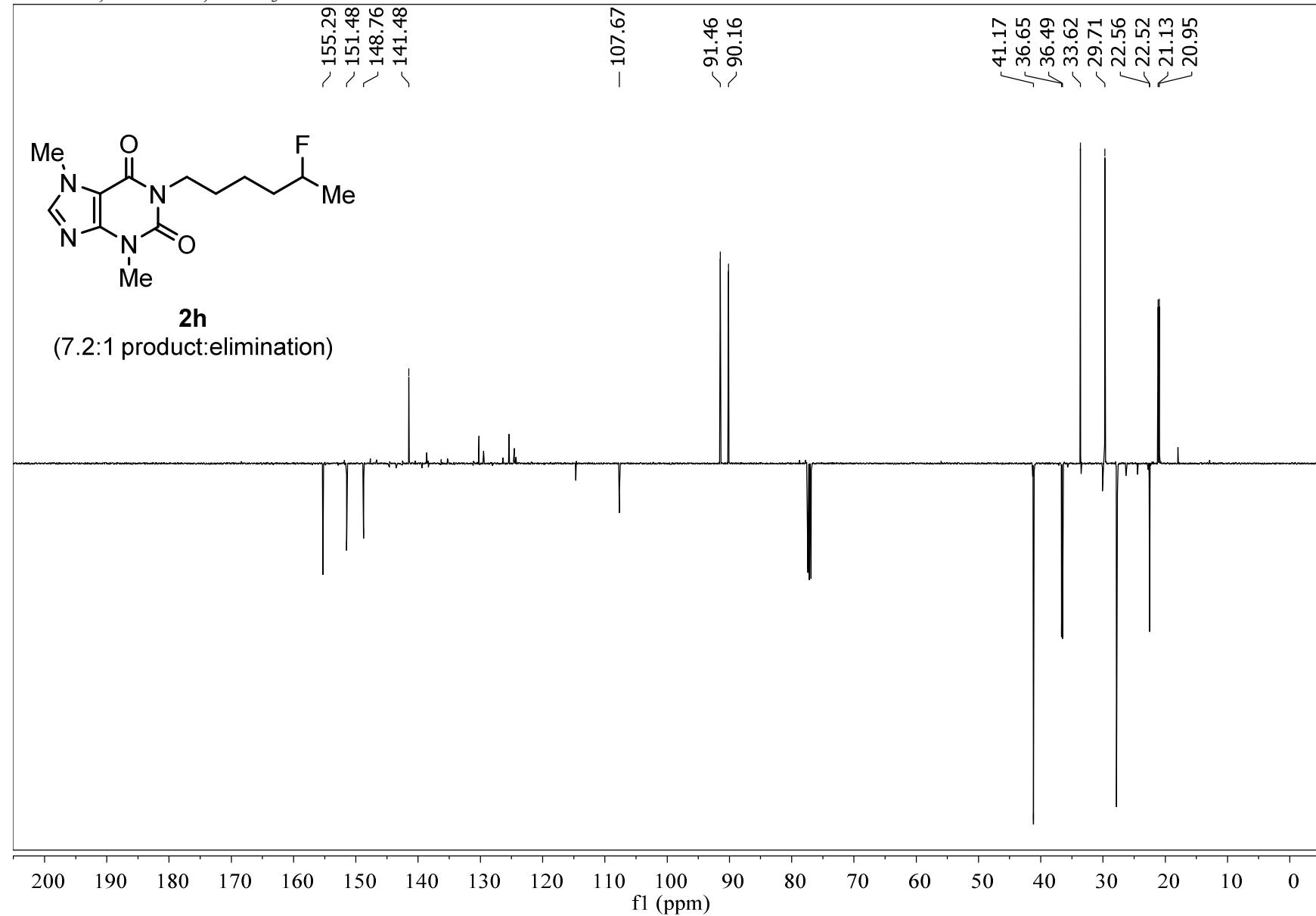
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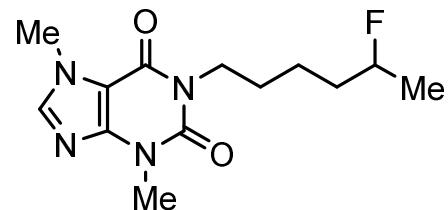
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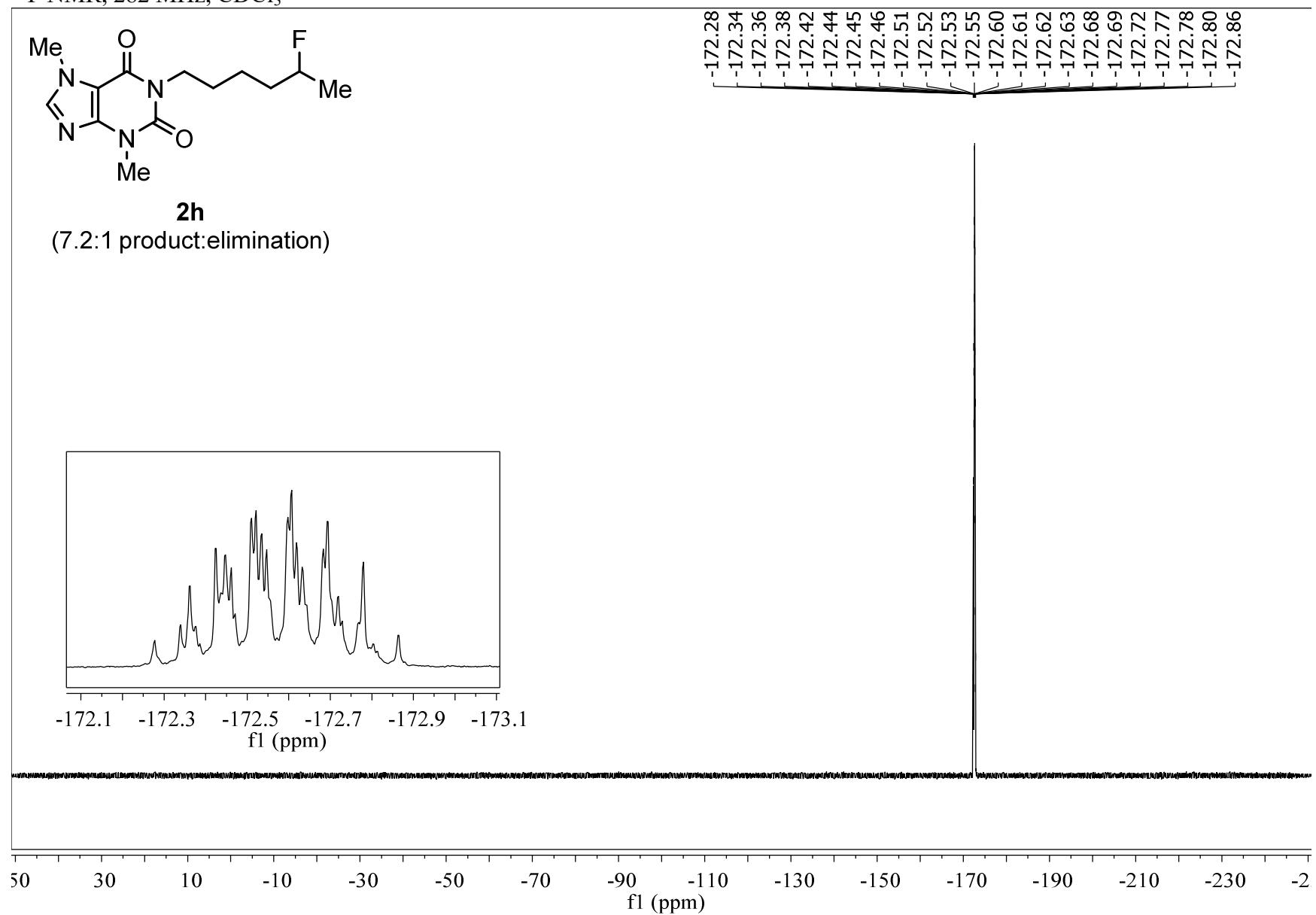
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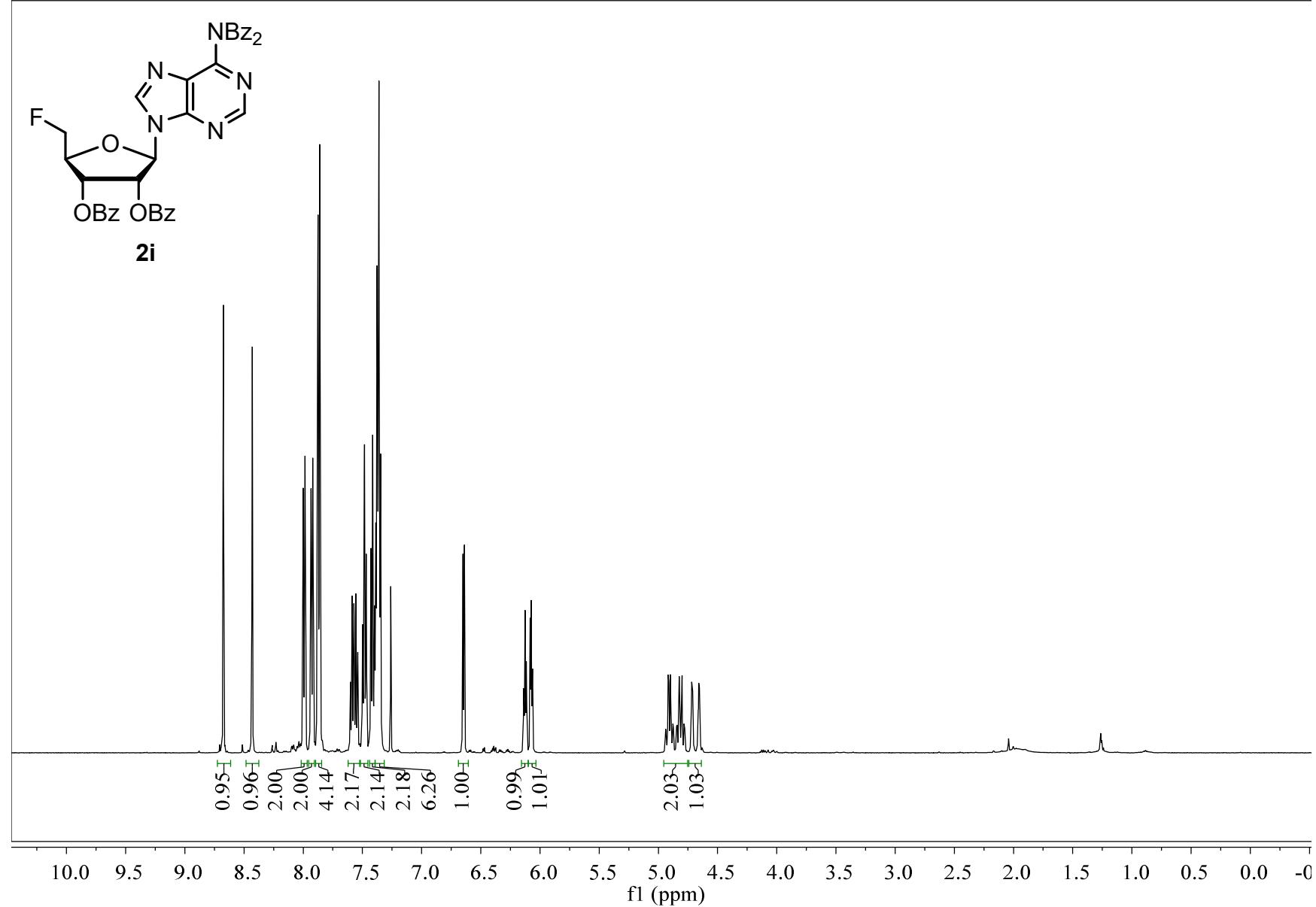
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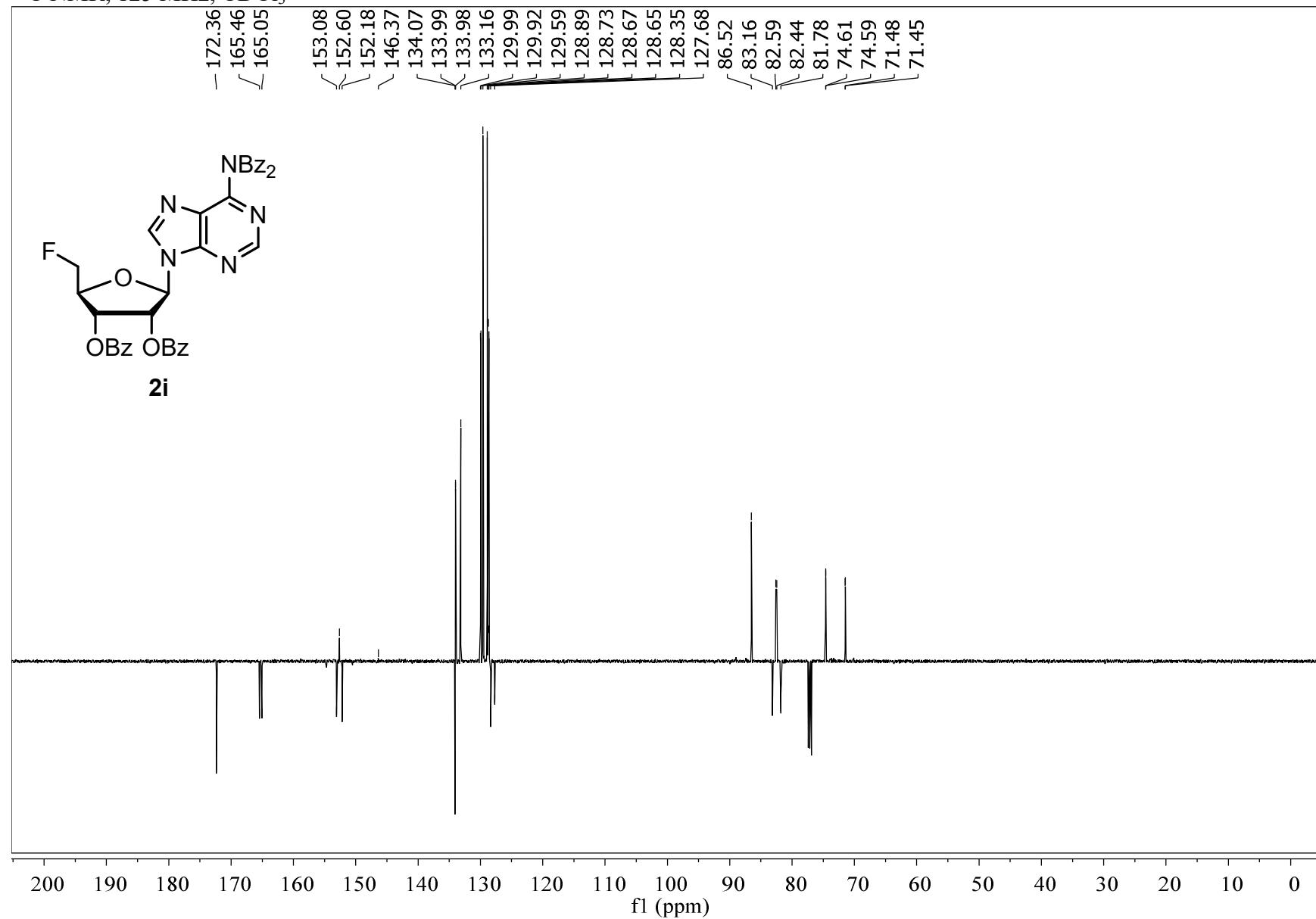
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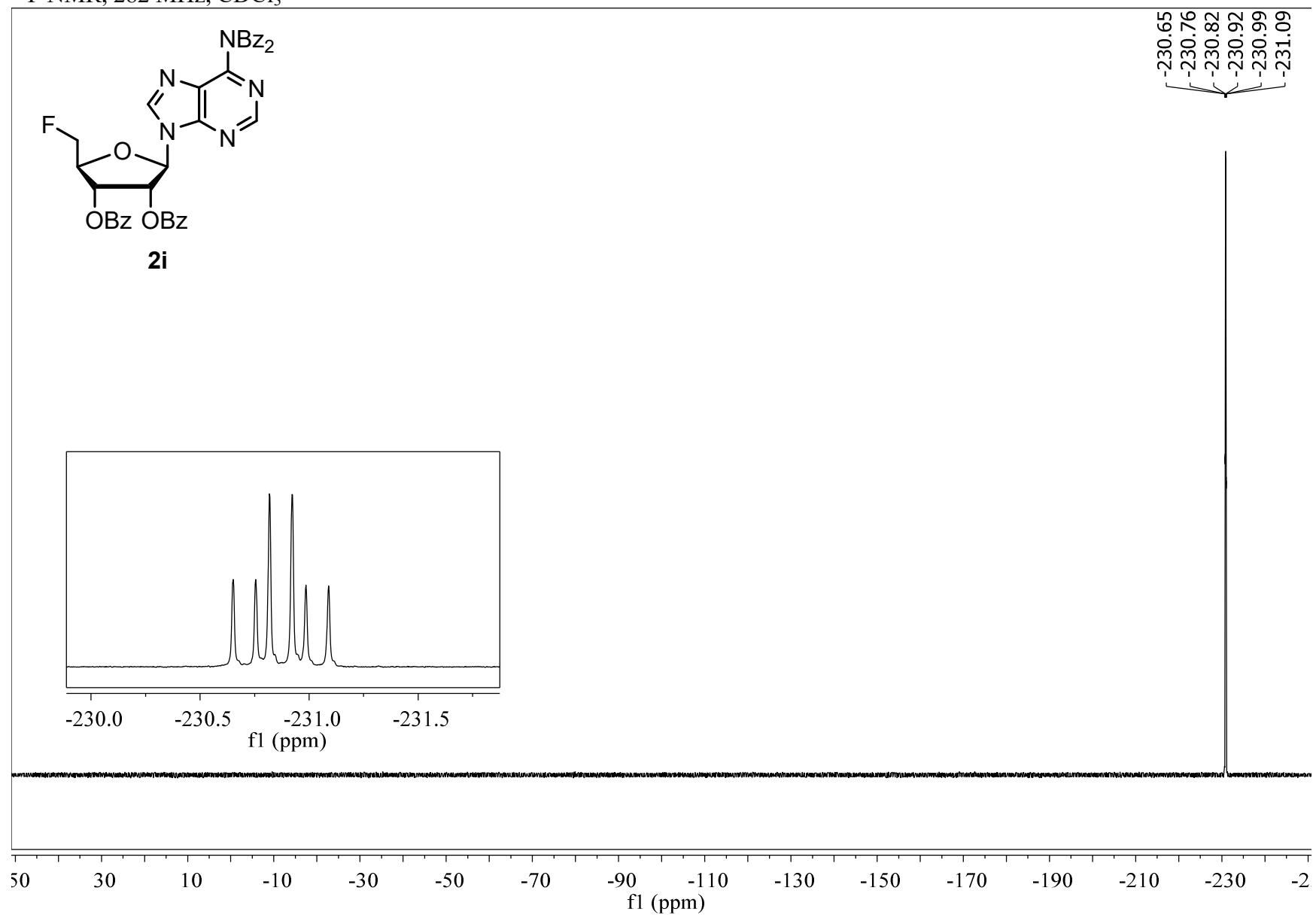
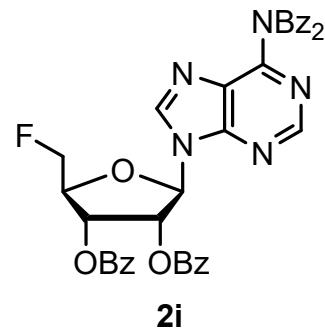
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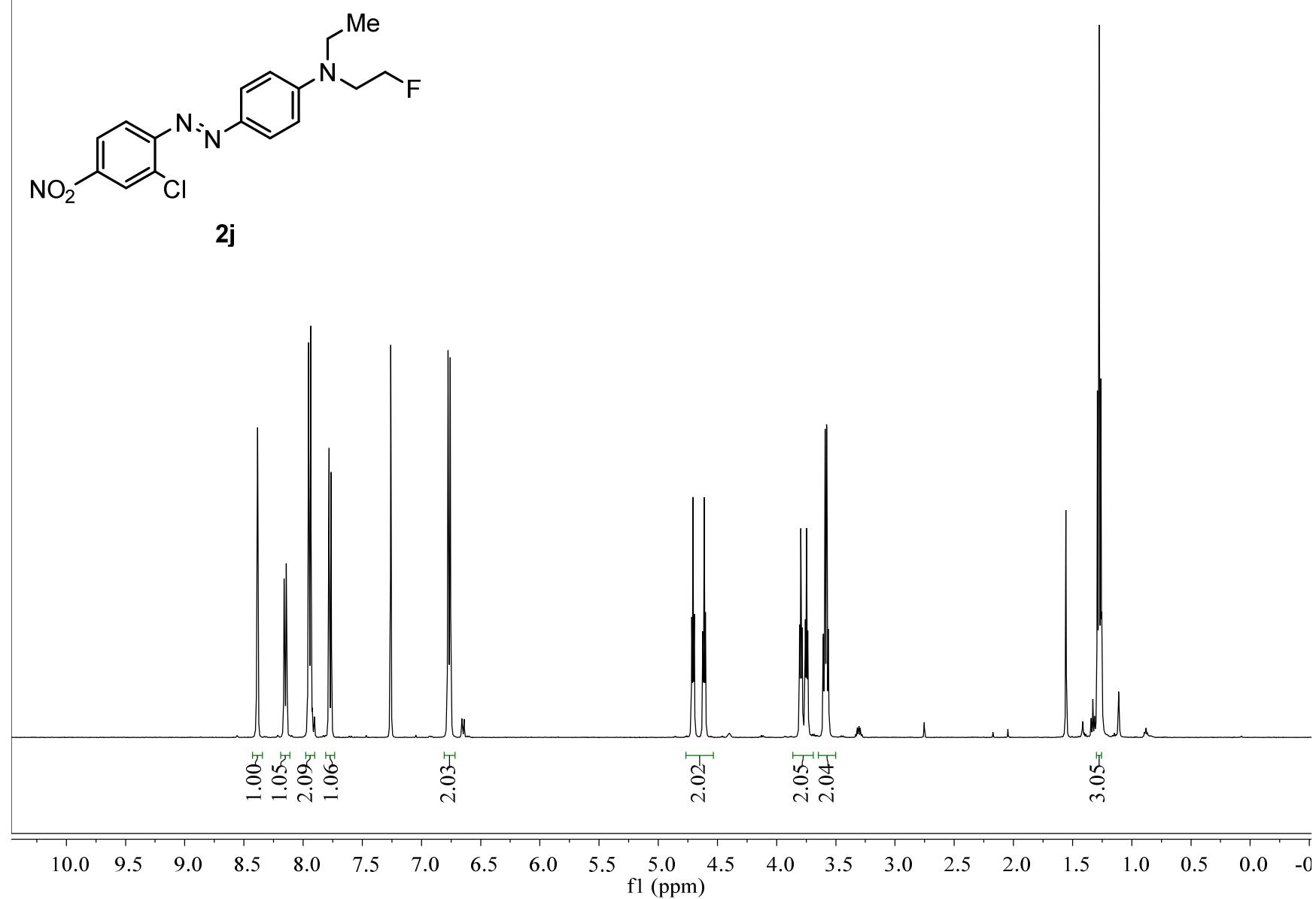
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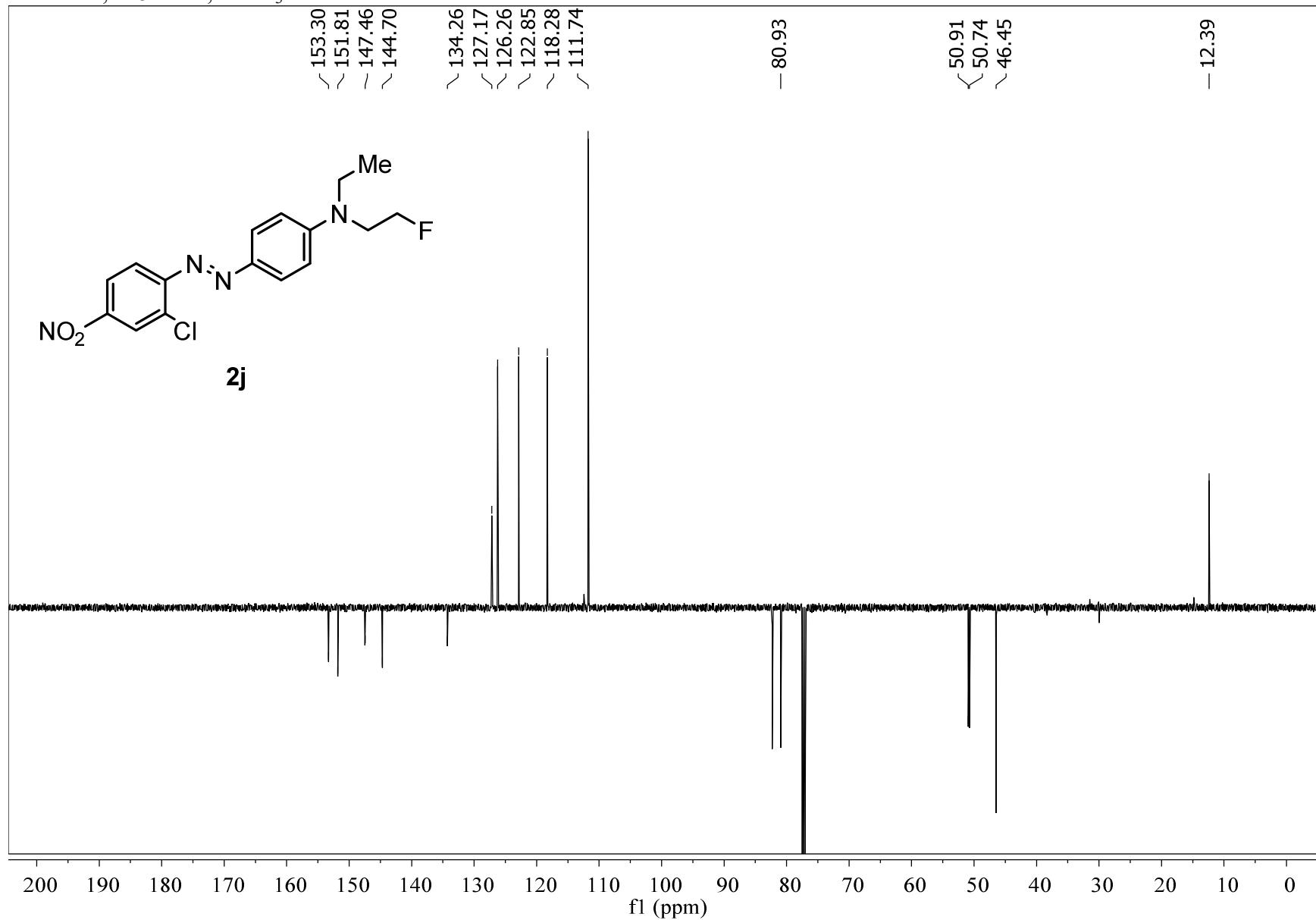
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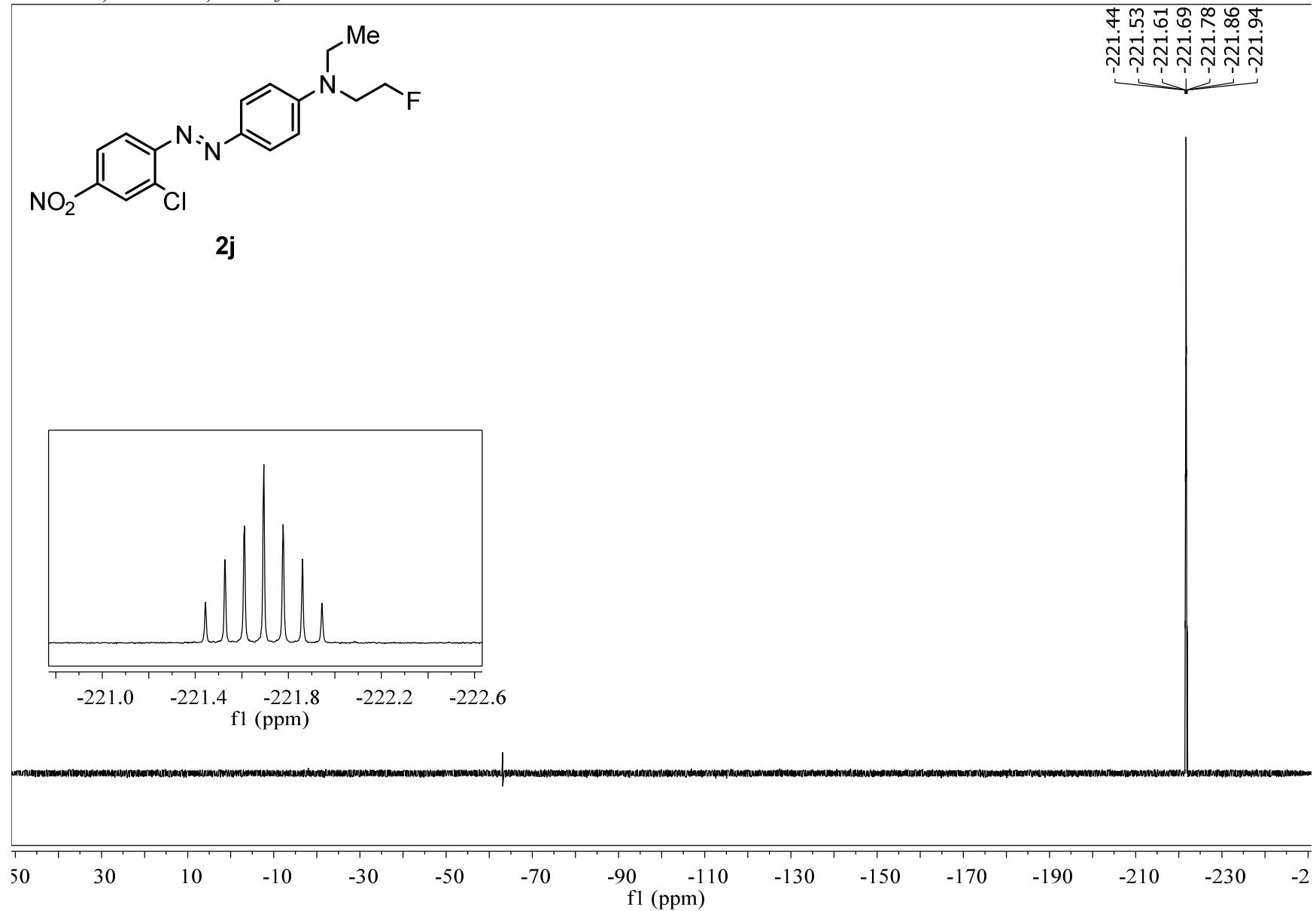
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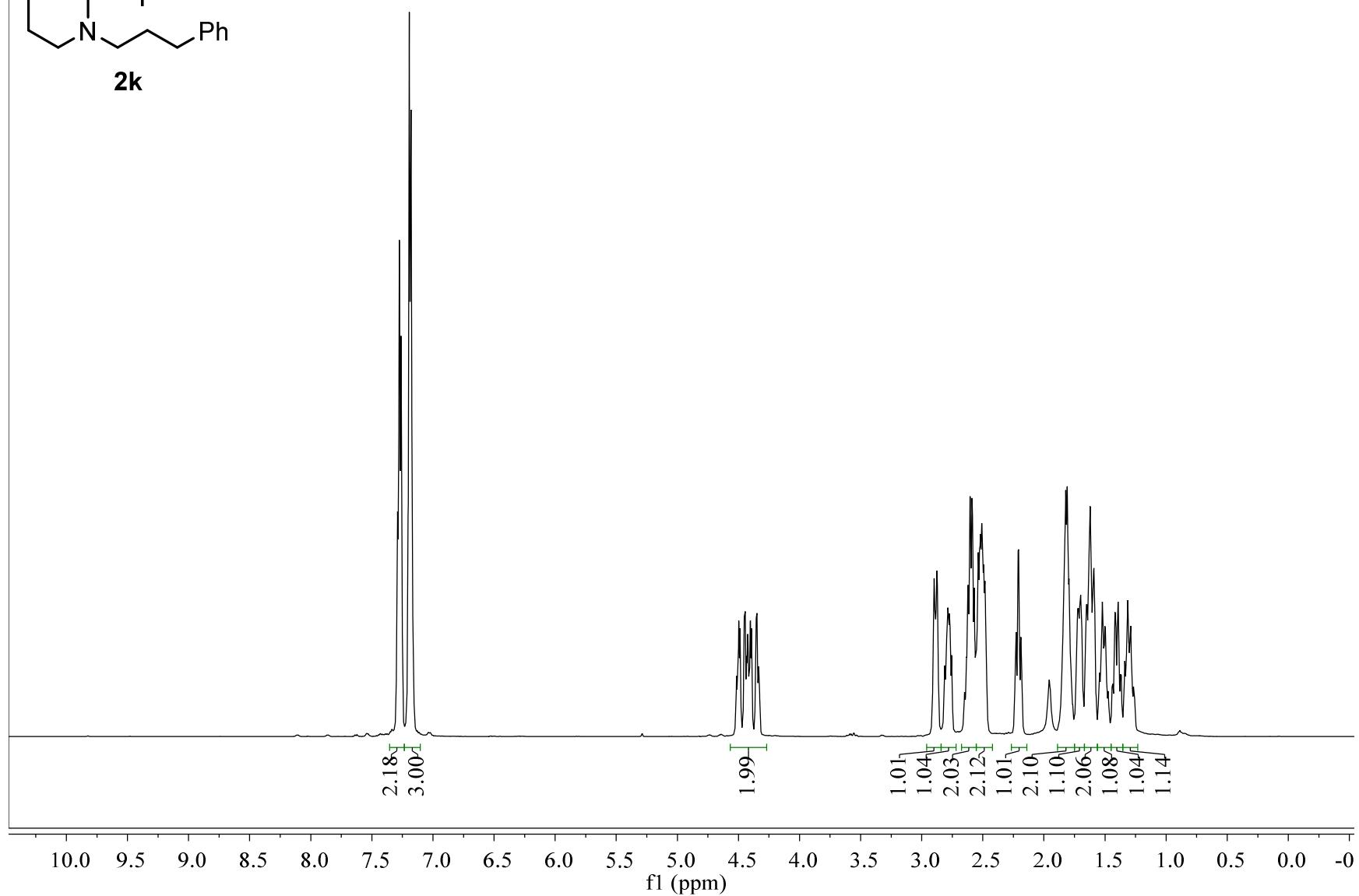
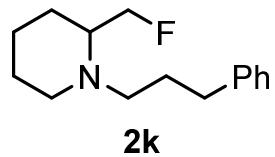
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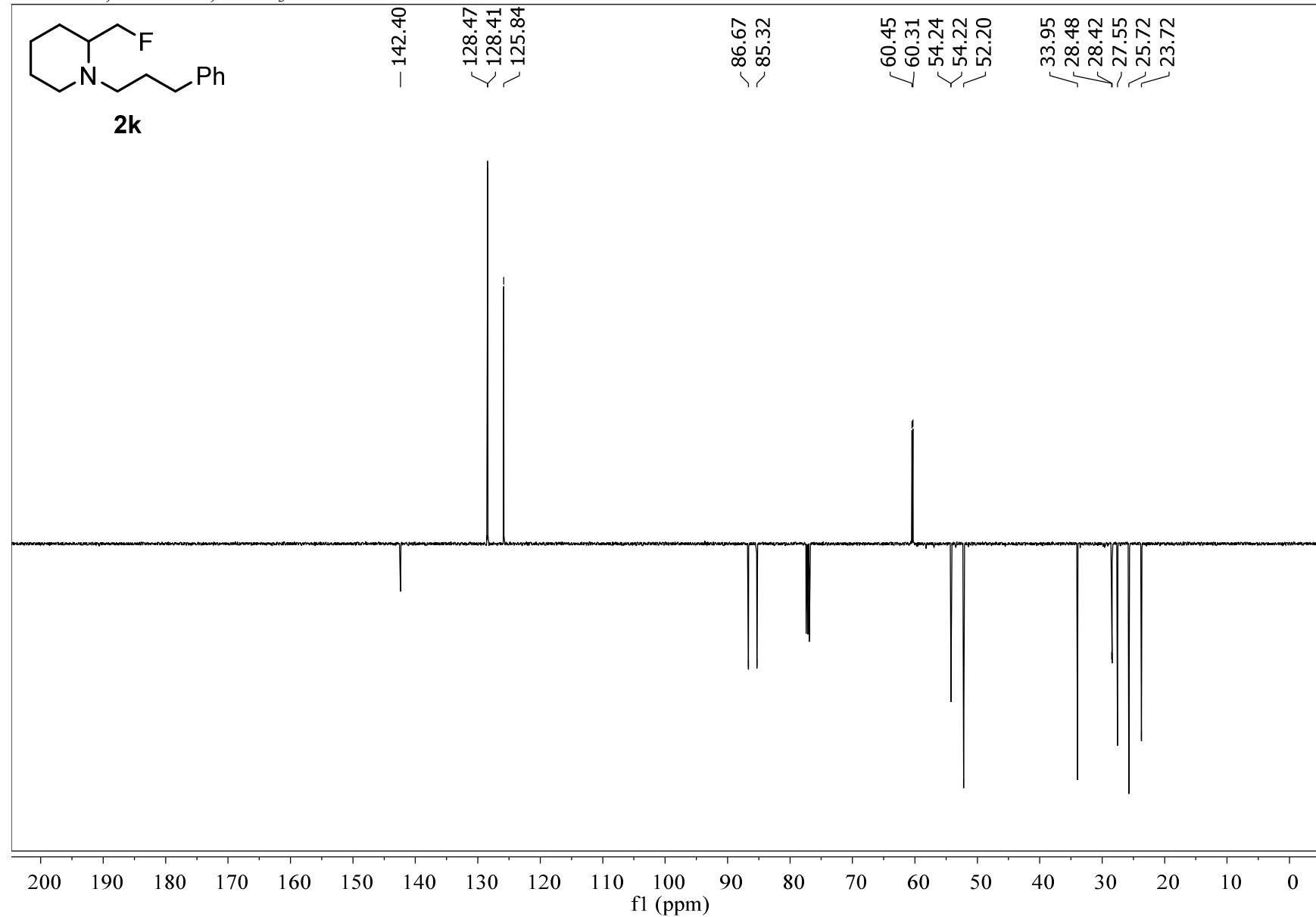
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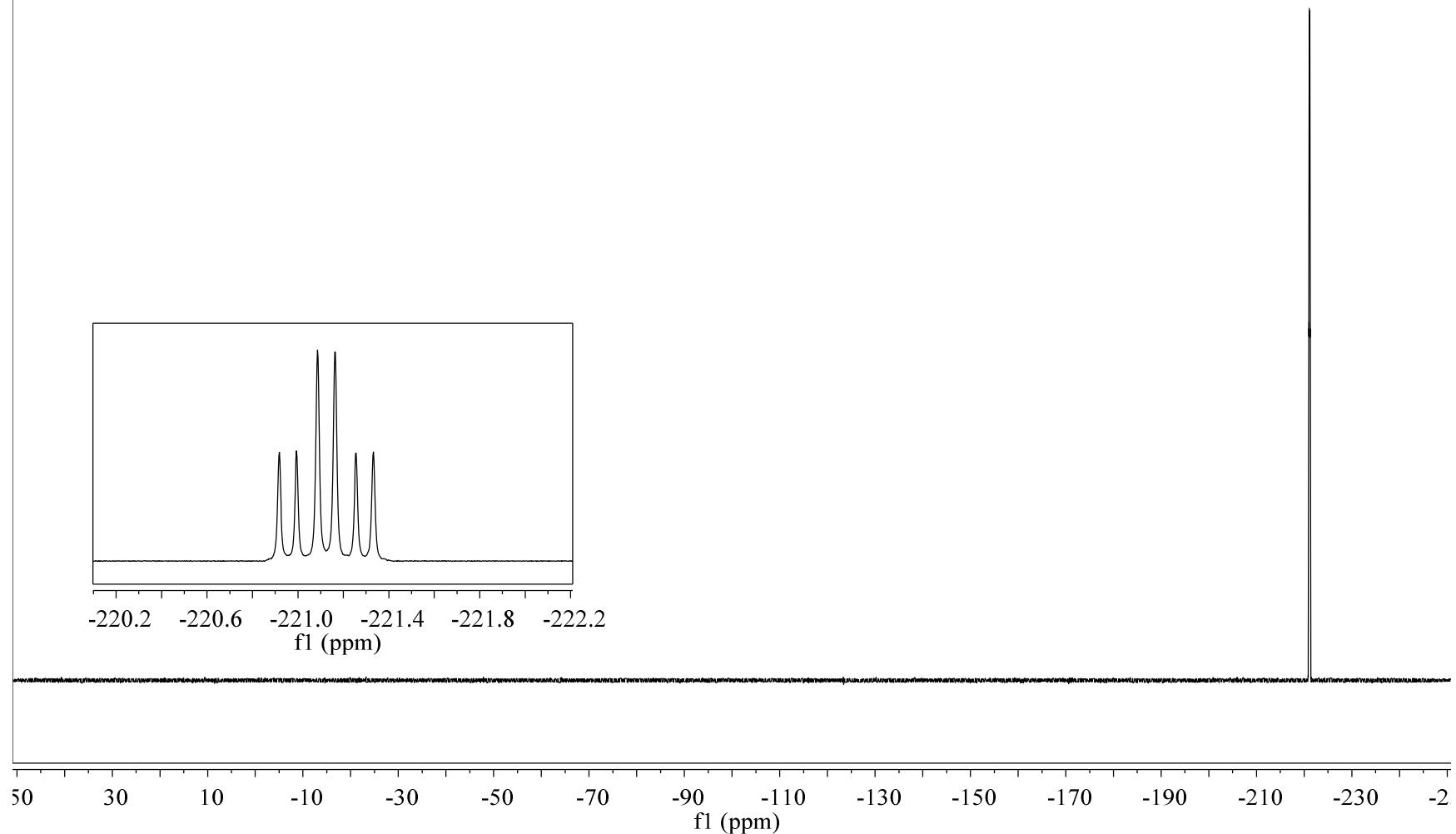
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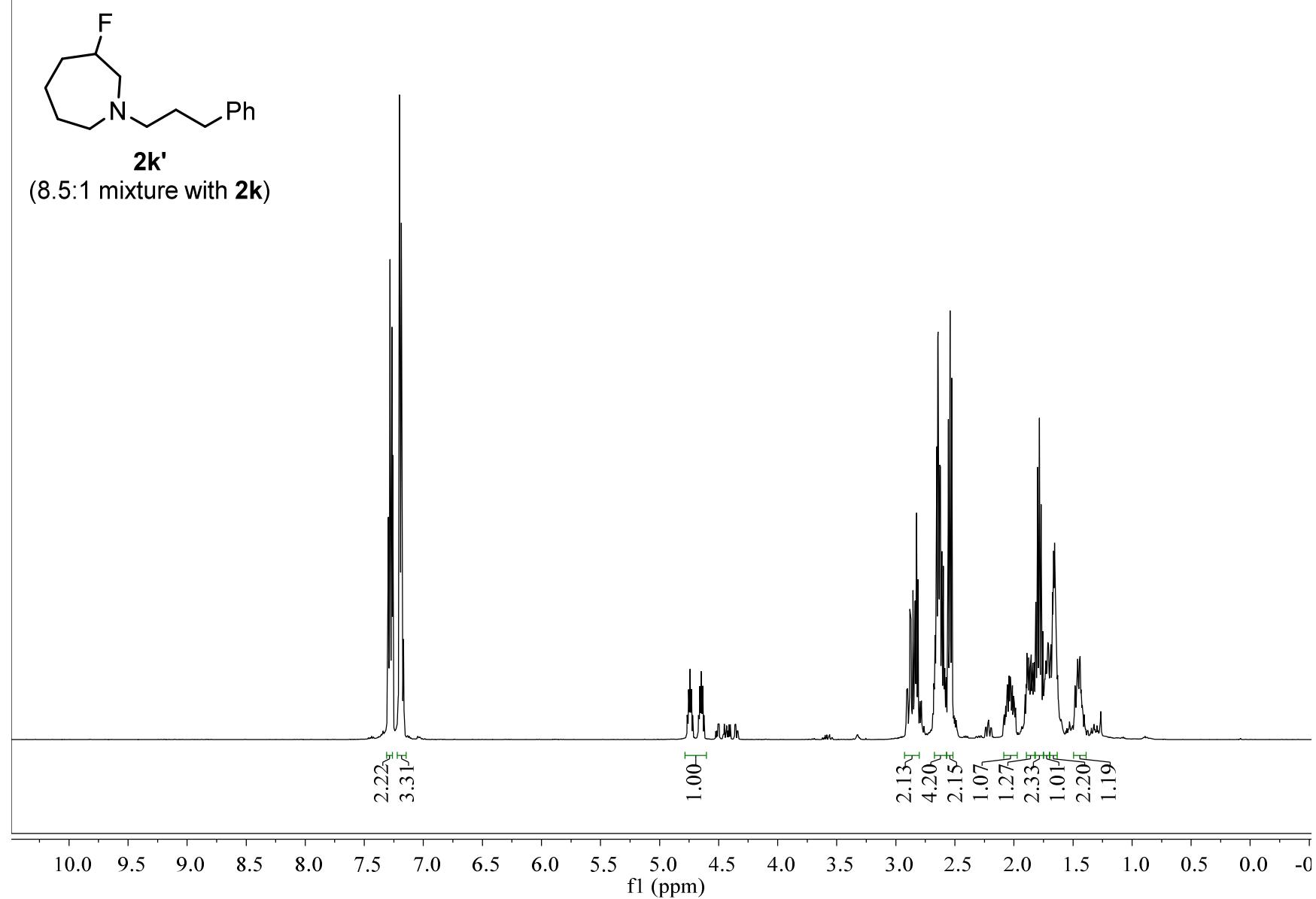
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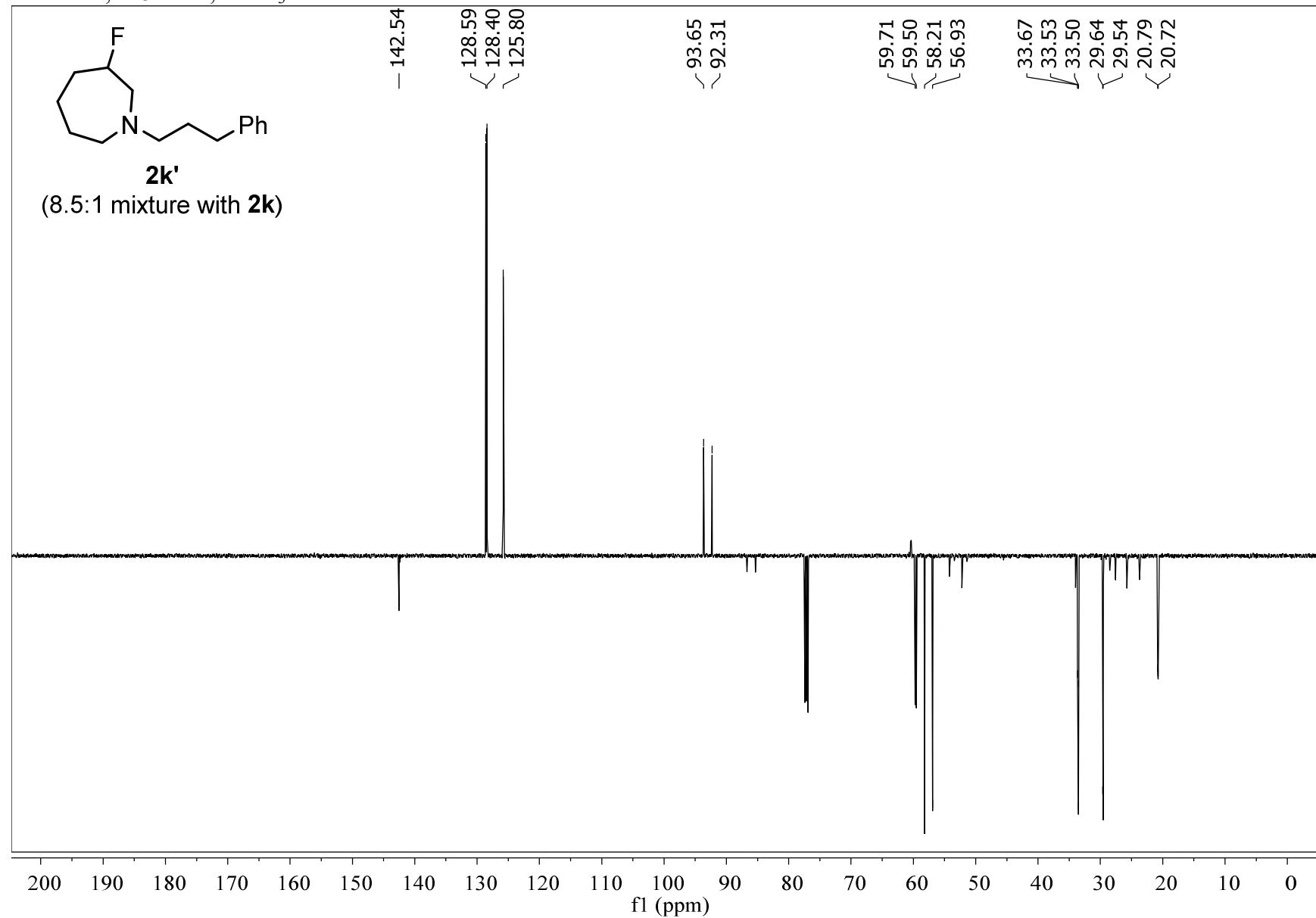
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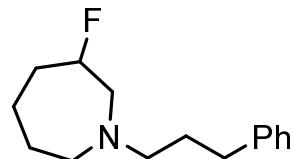
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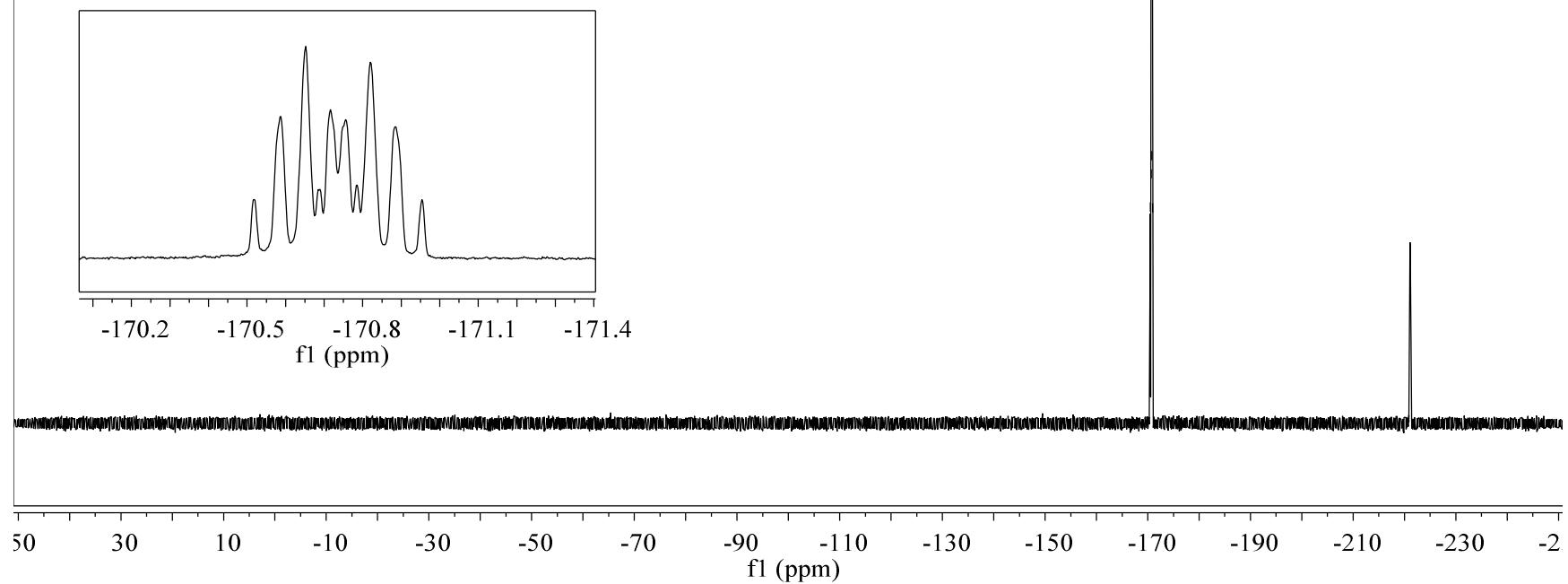
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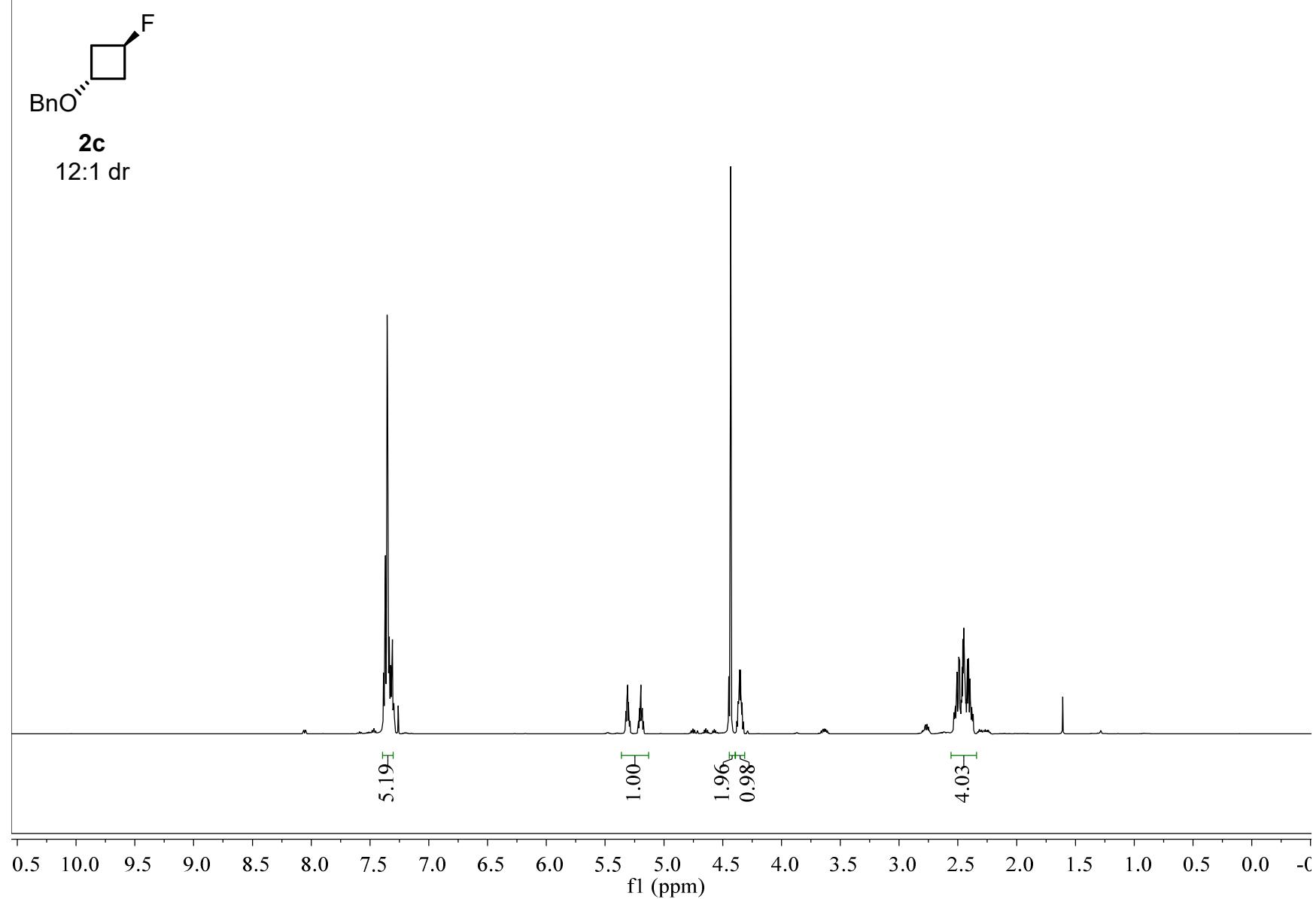
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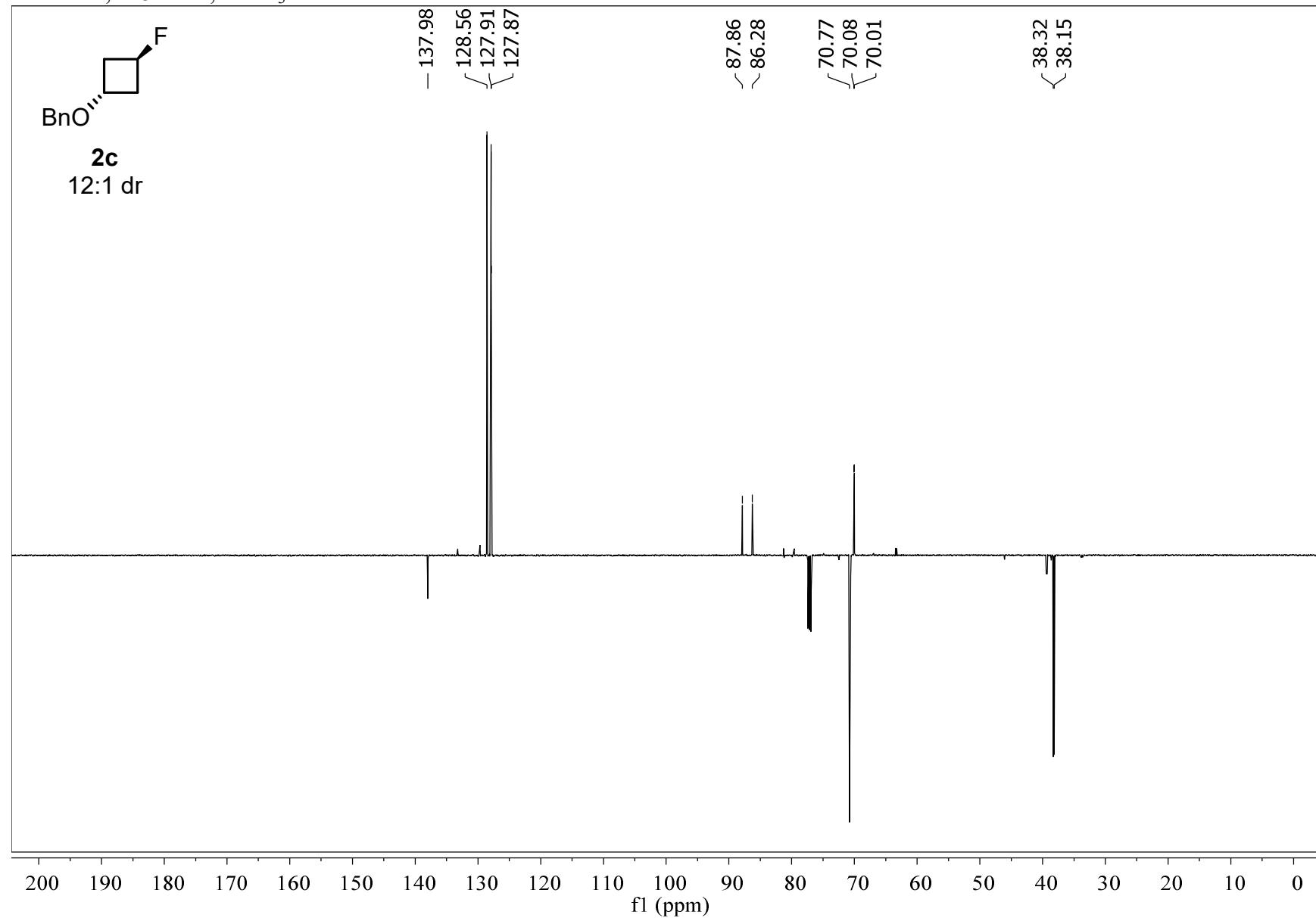
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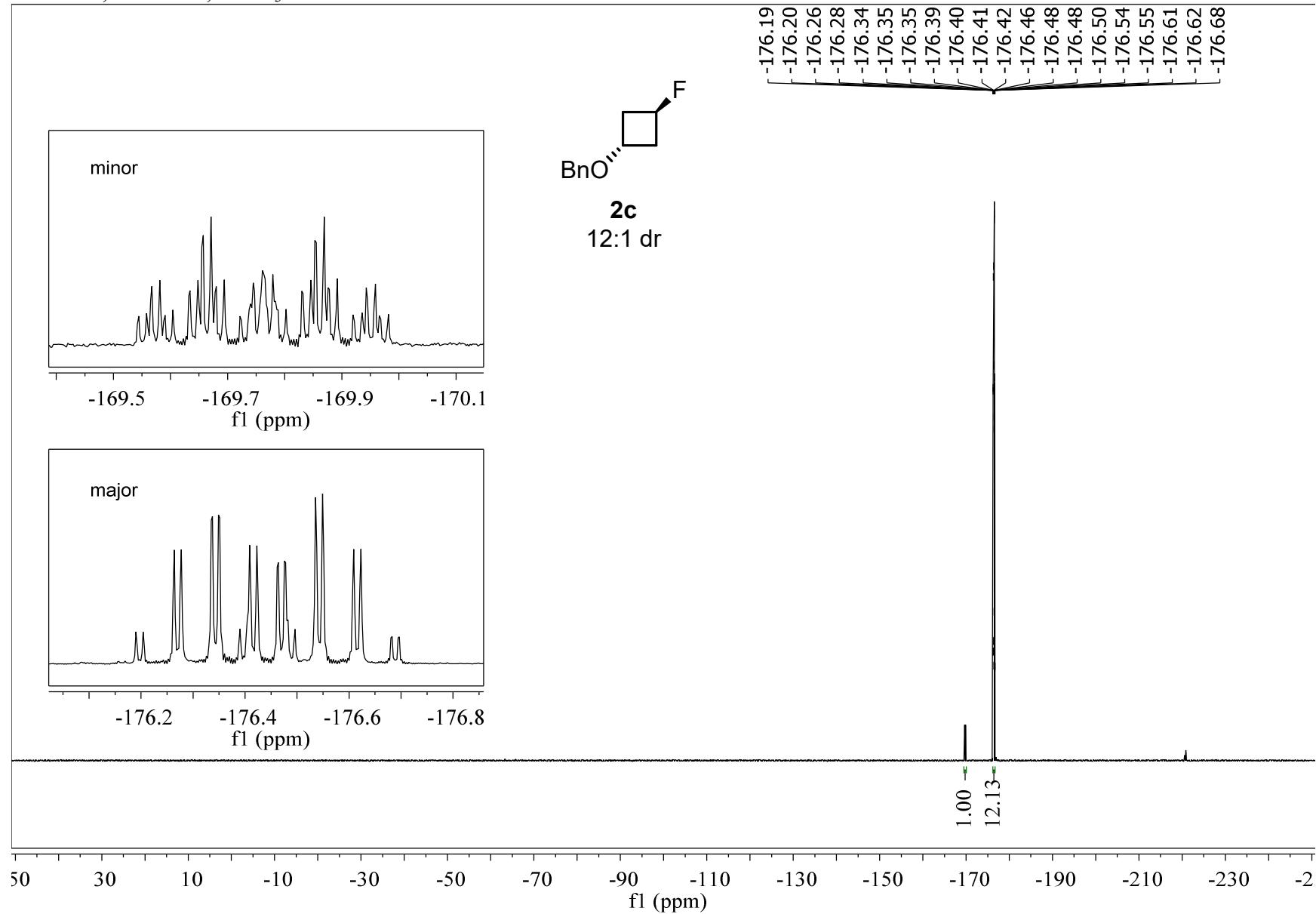
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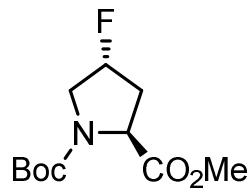
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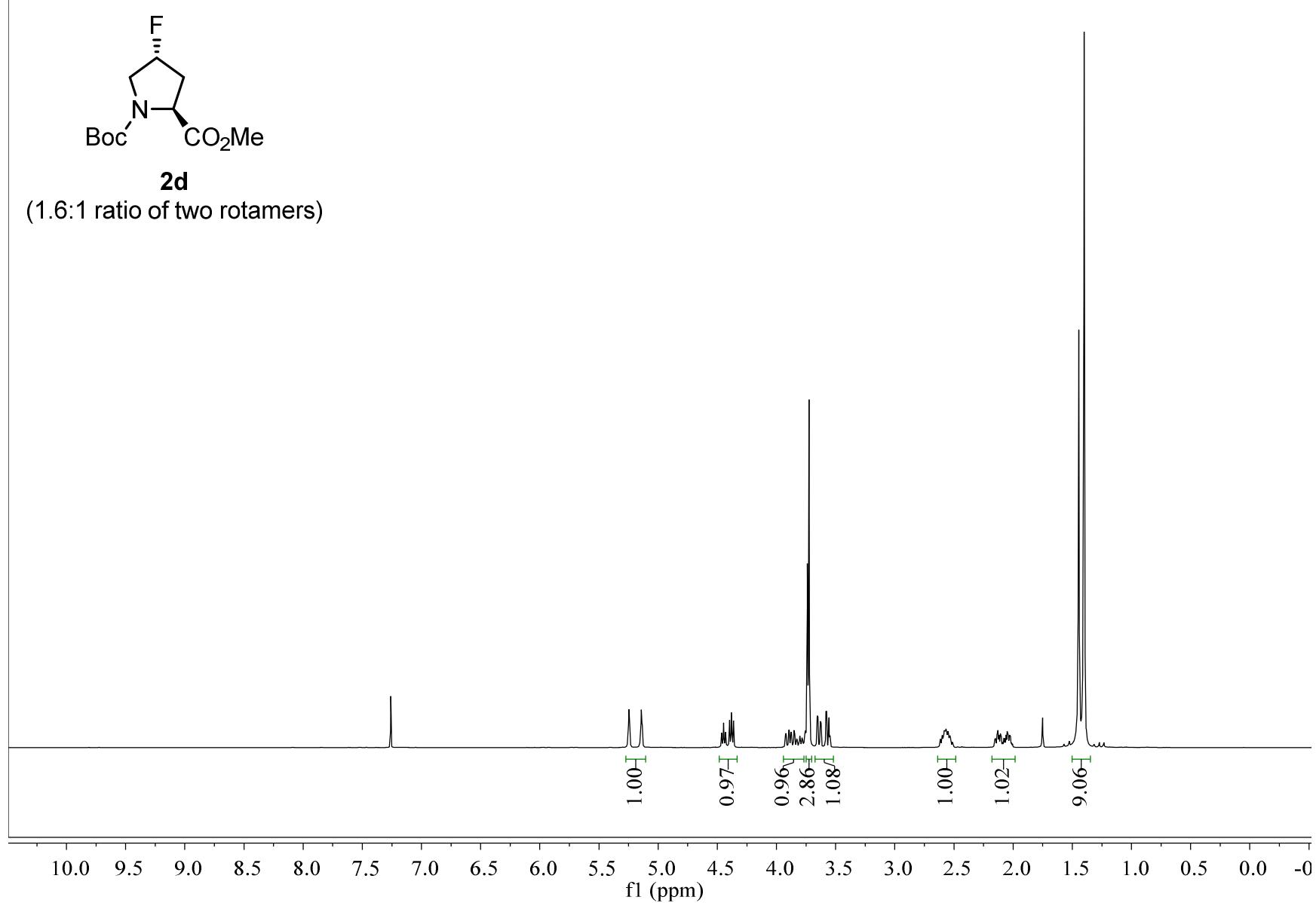


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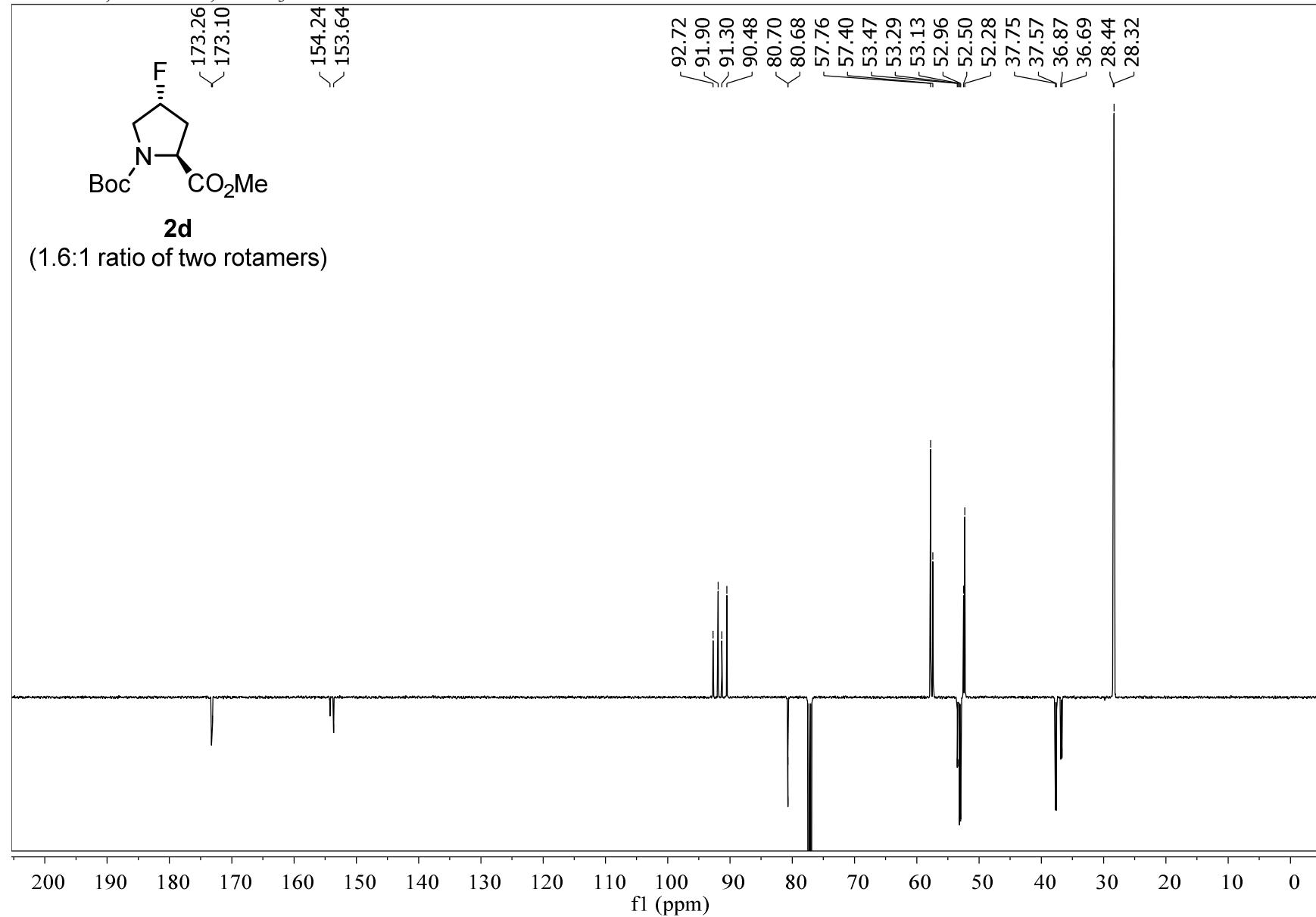


**2d**

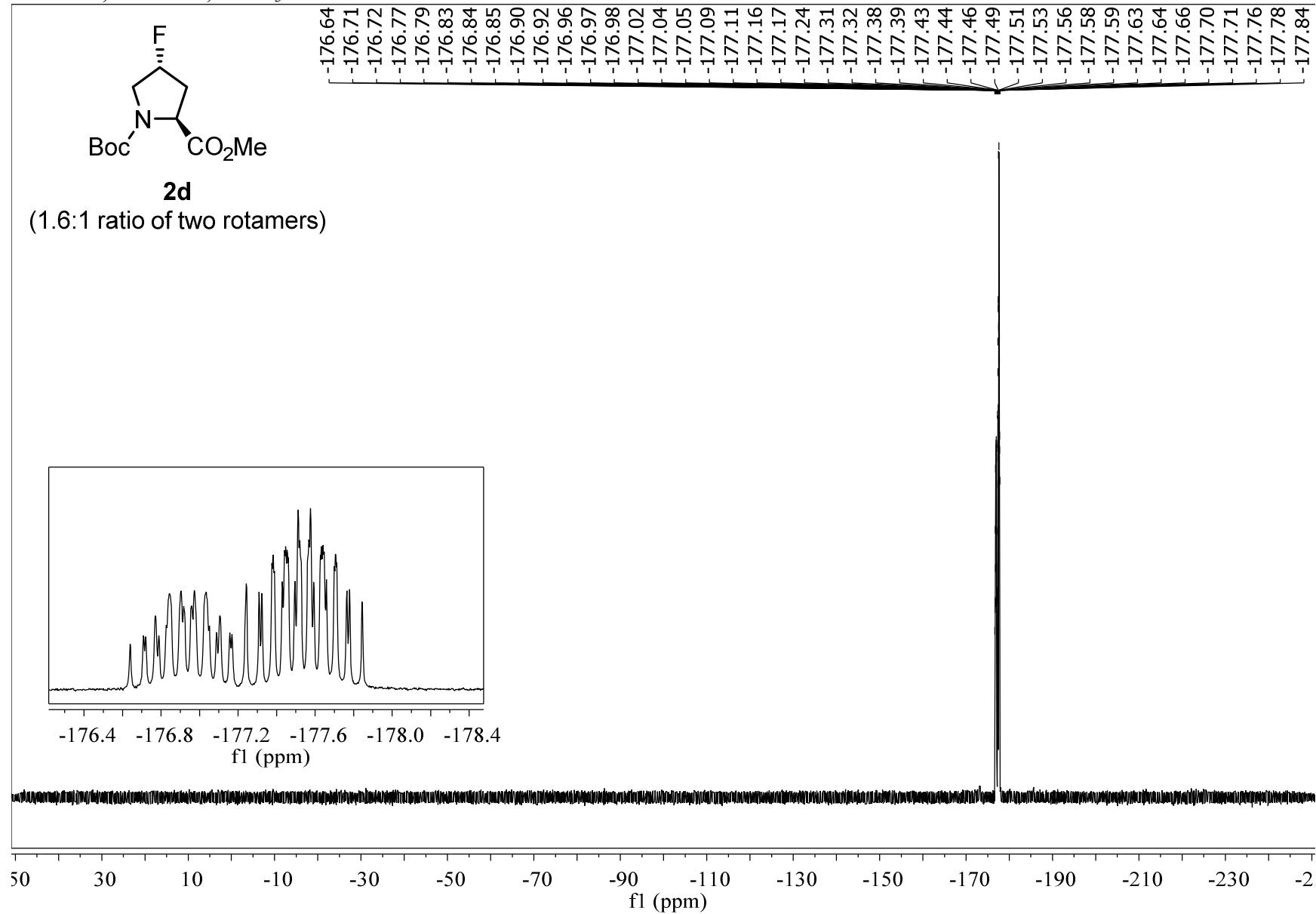
(1.6:1 ratio of two rotamers)



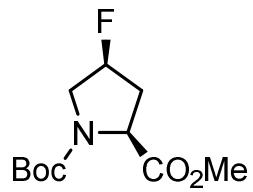
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



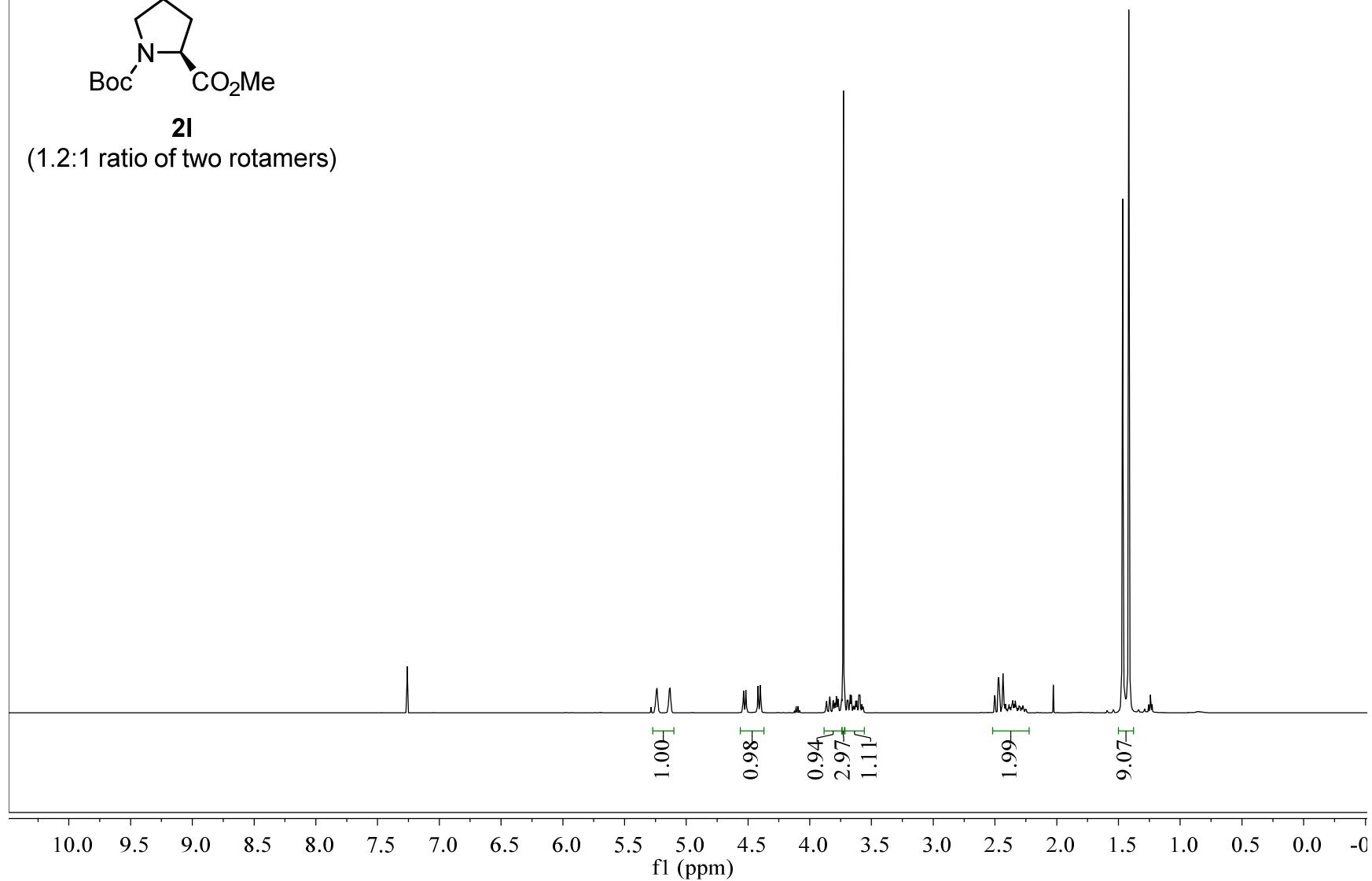
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



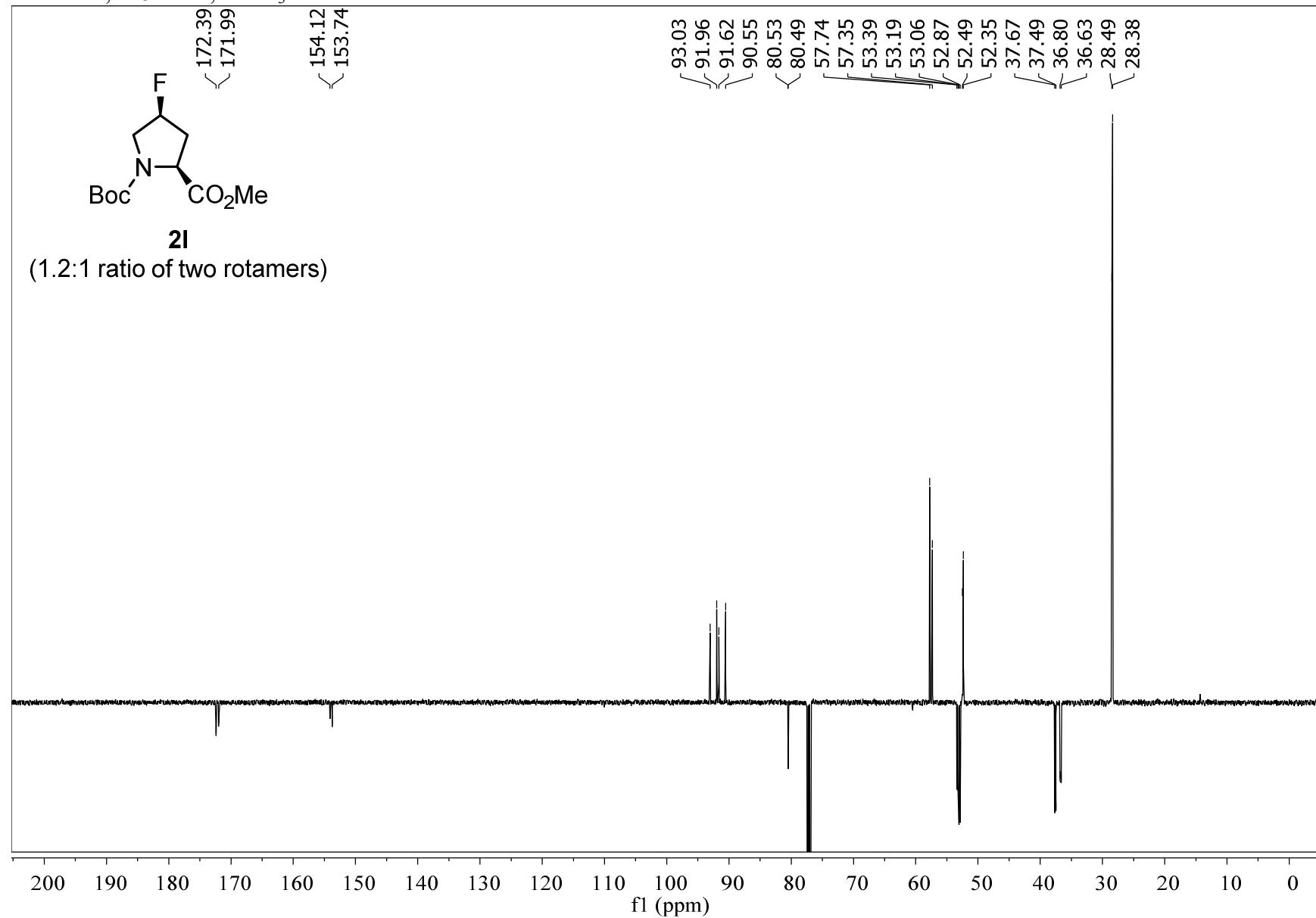
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



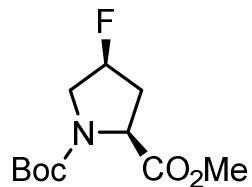
(1.2:1 ratio of two rotamers)



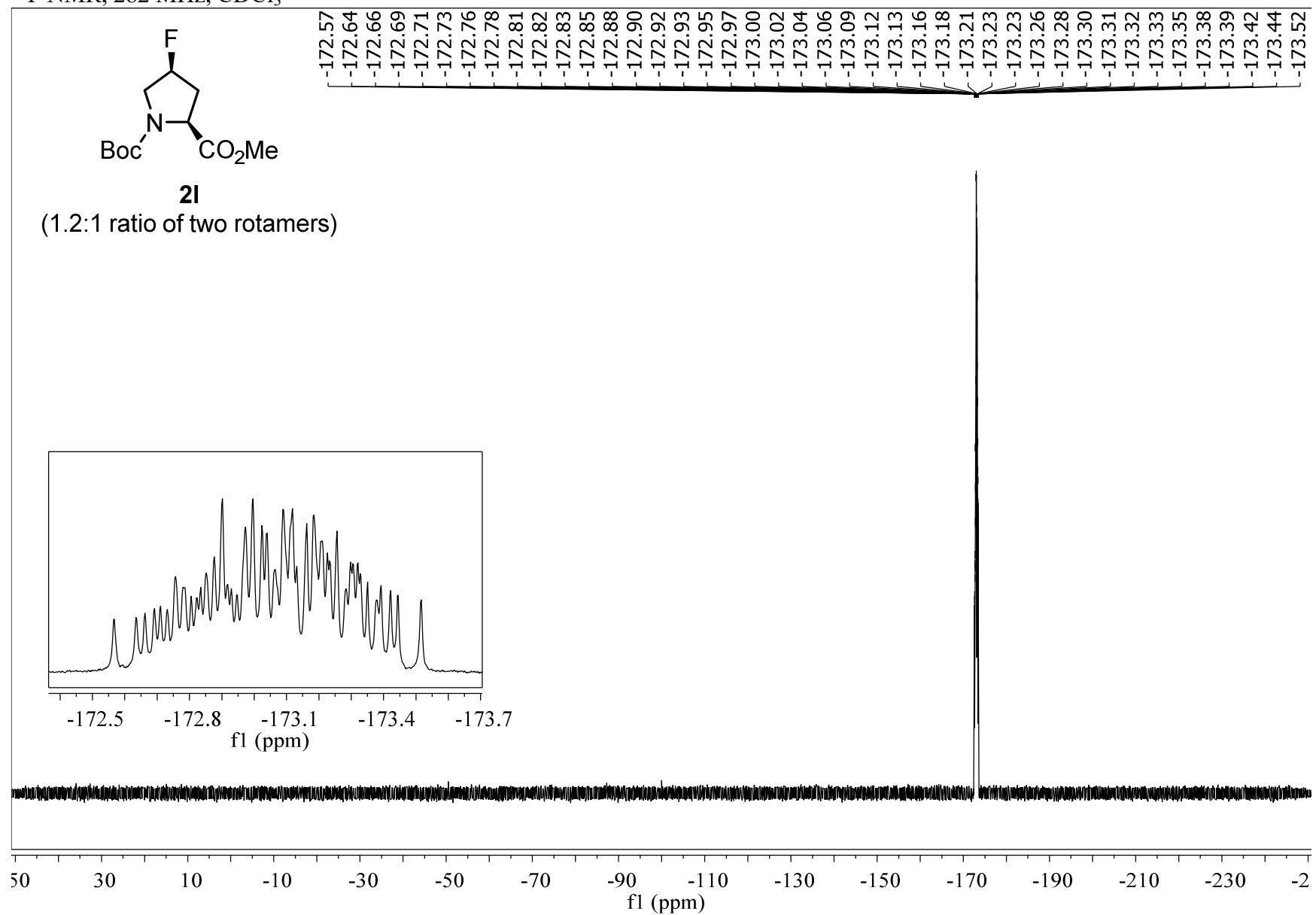
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



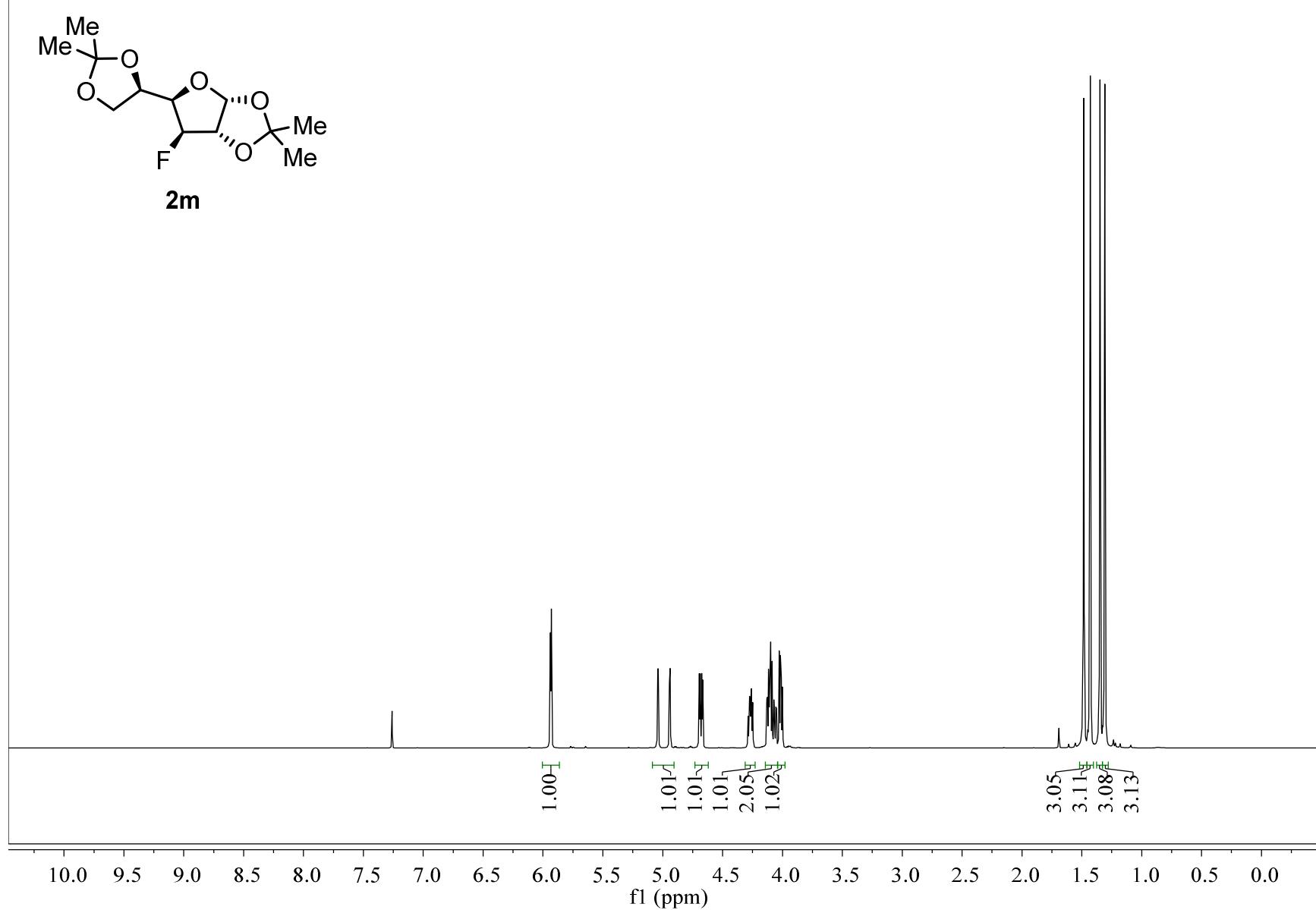
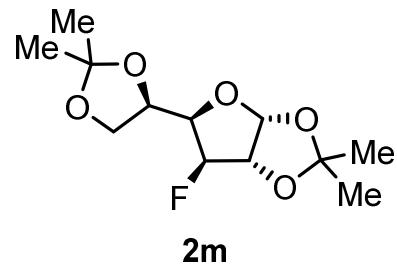
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



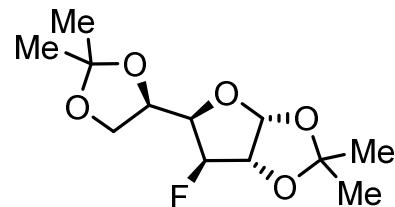
**2l**  
(1.2:1 ratio of two rotamers)



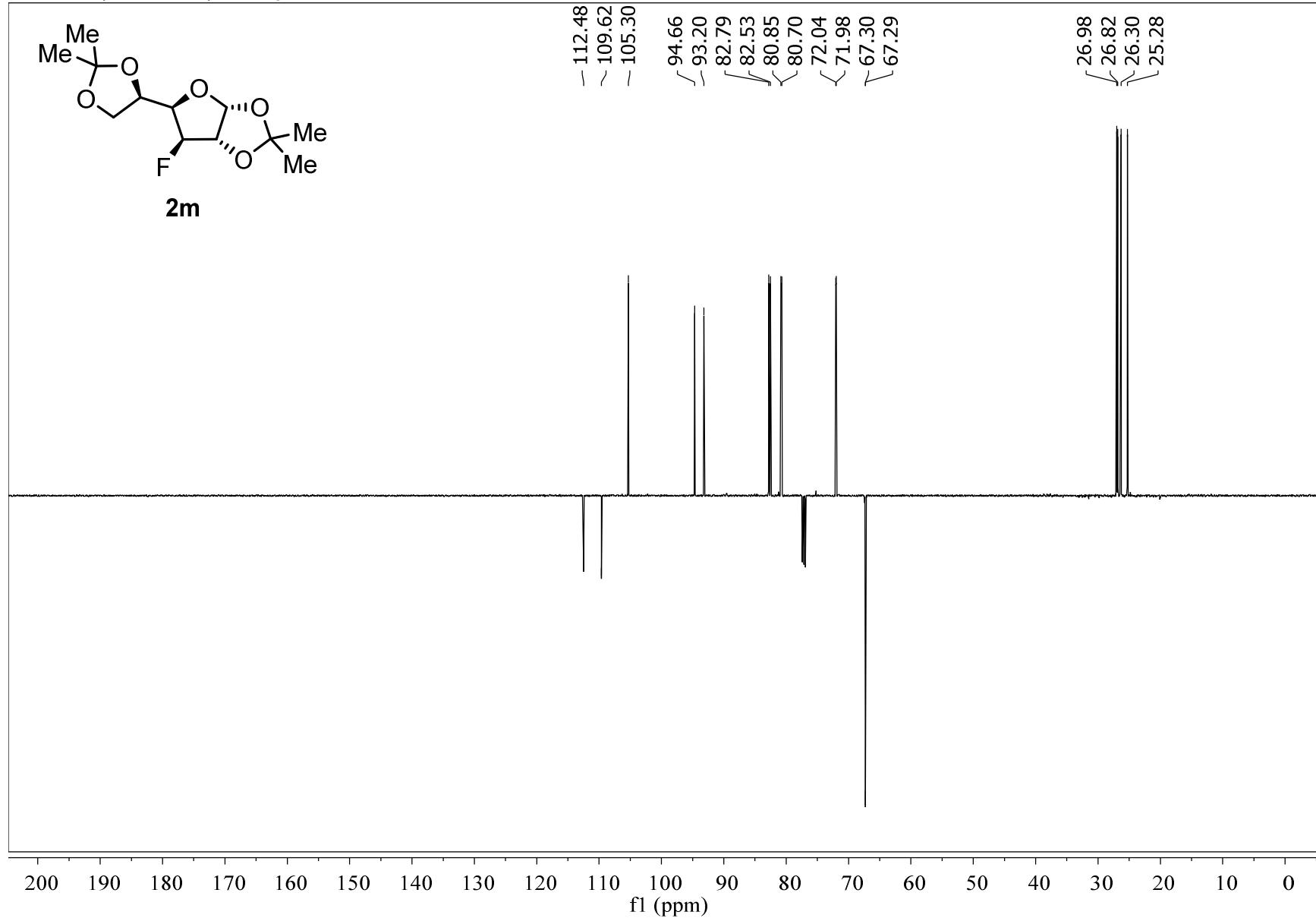
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



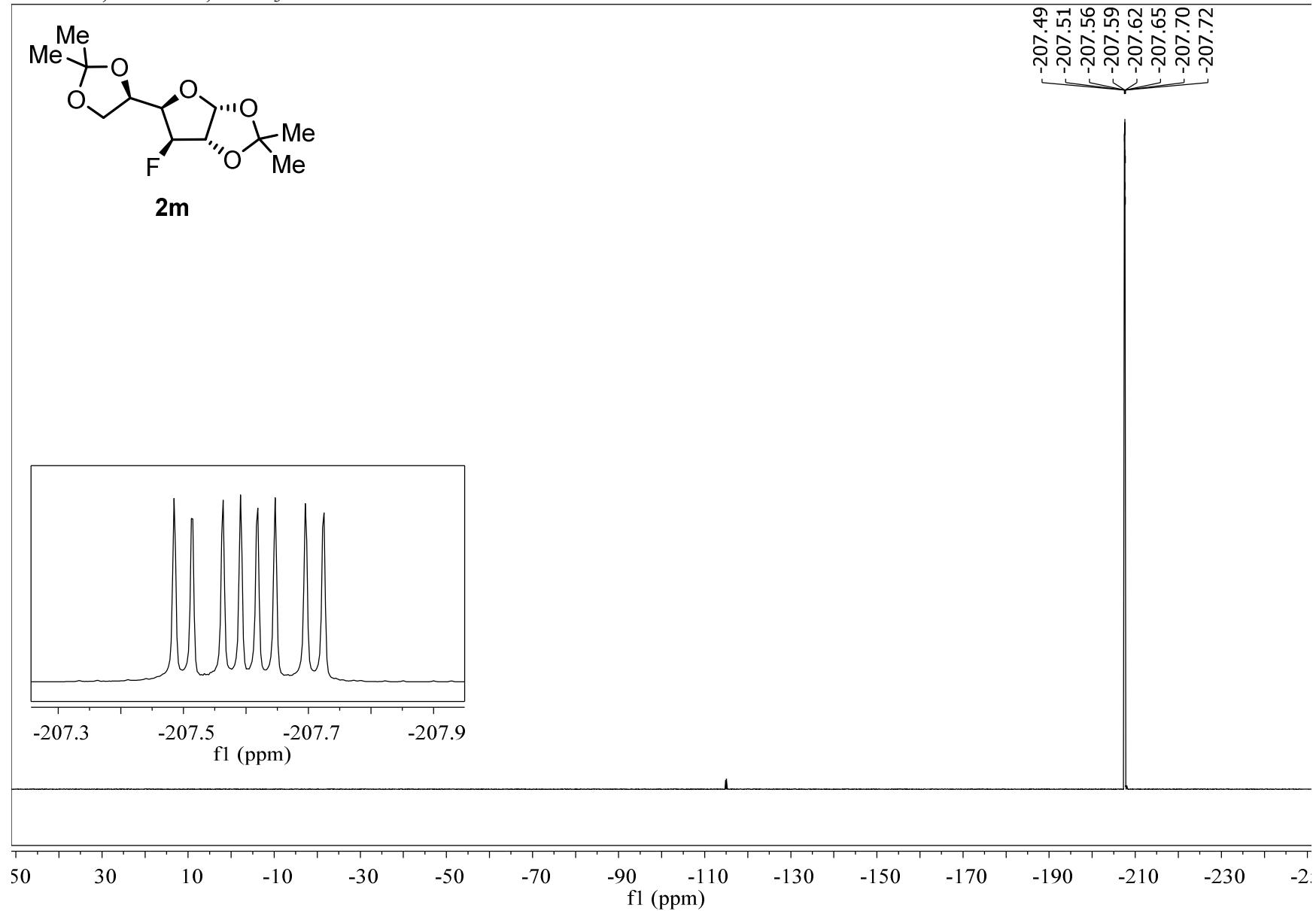
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



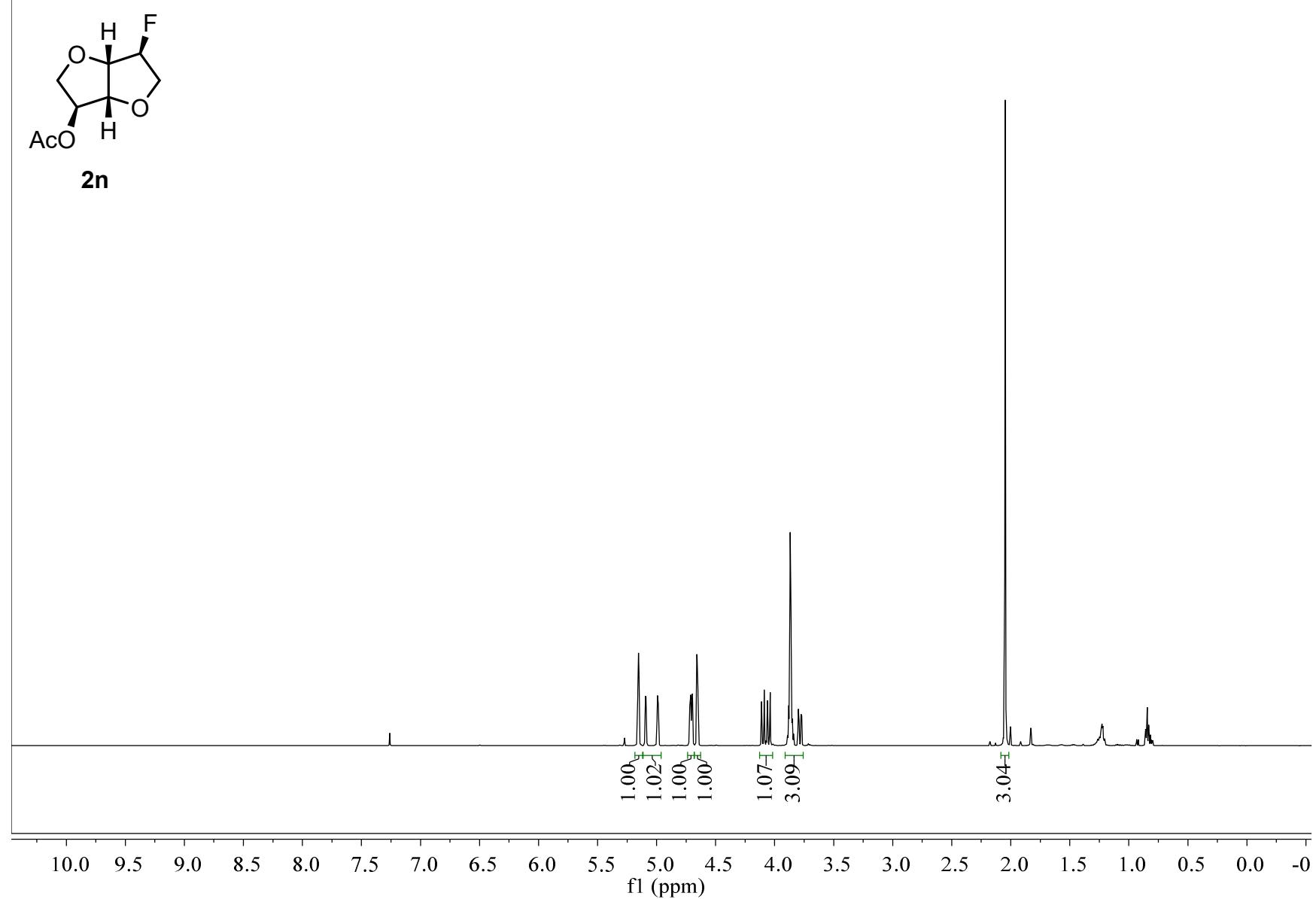
2m



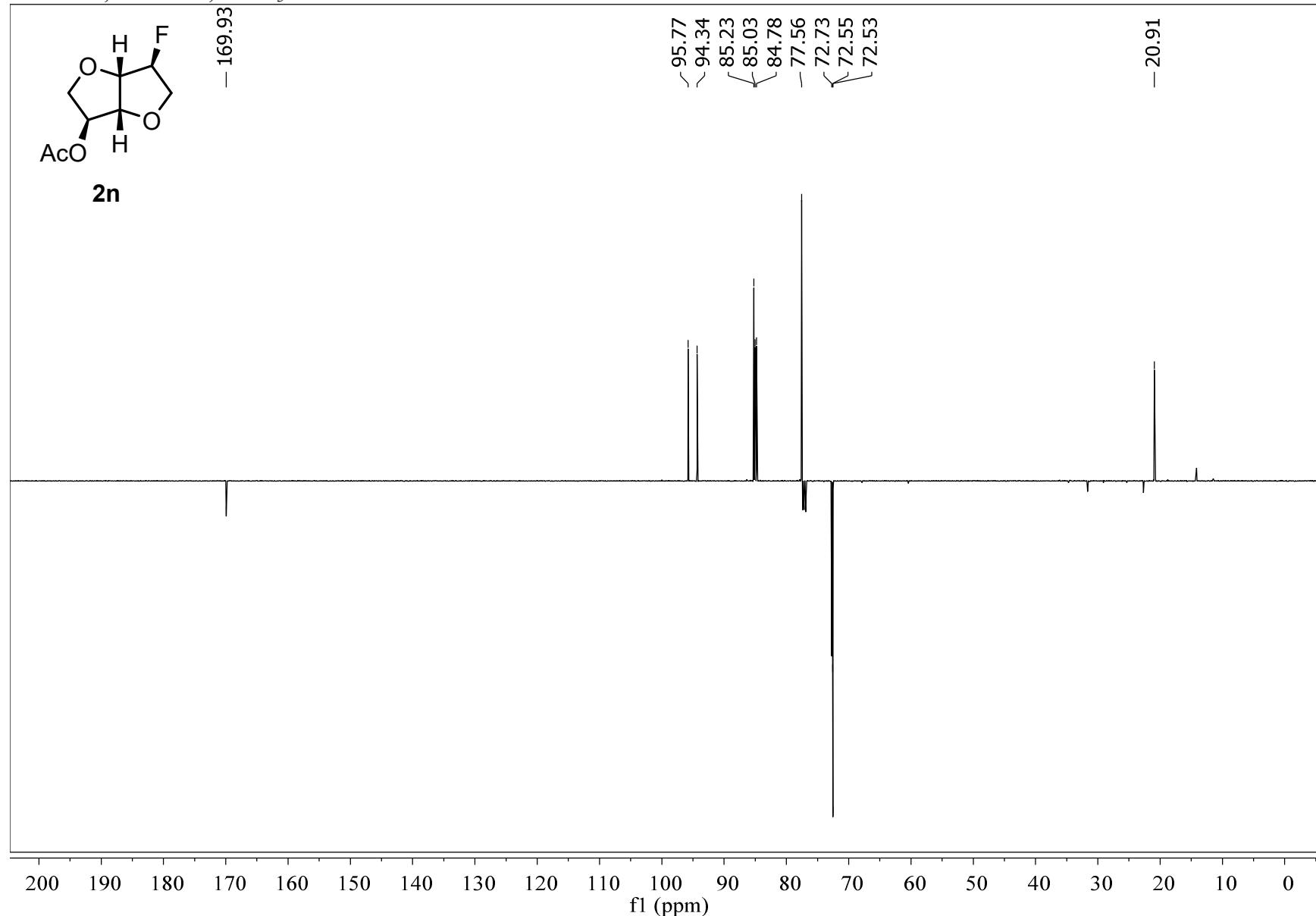
<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>



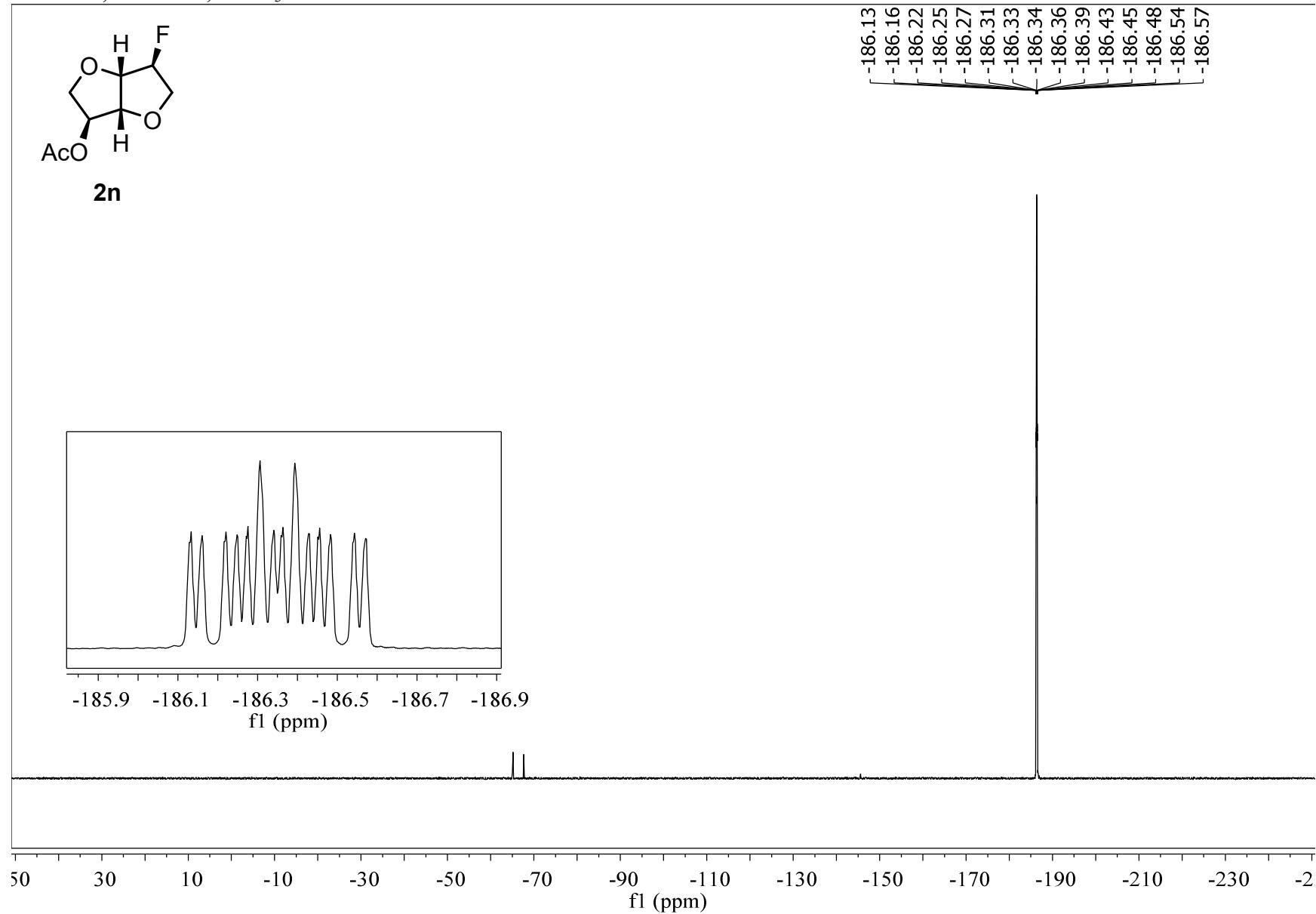
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



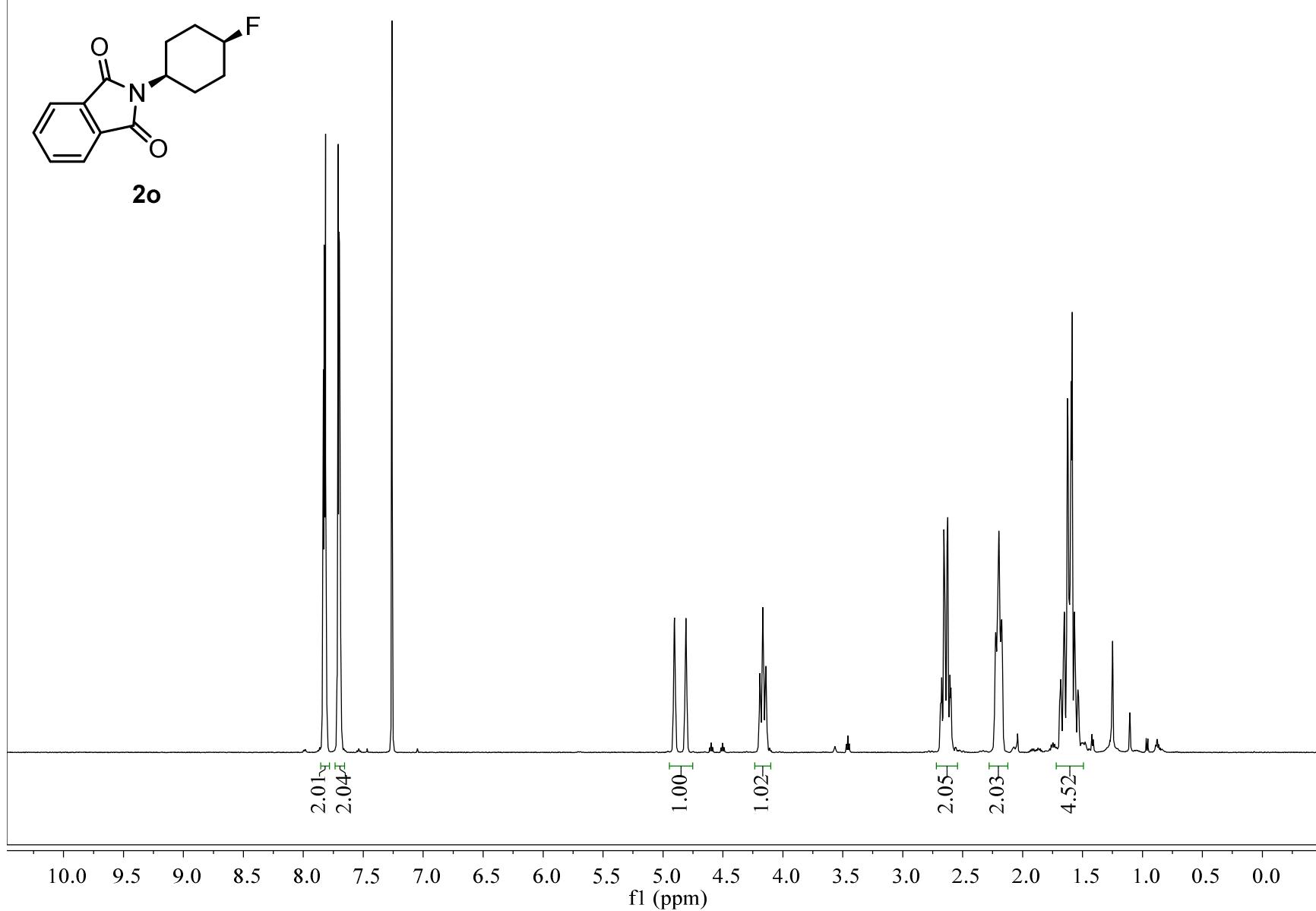
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



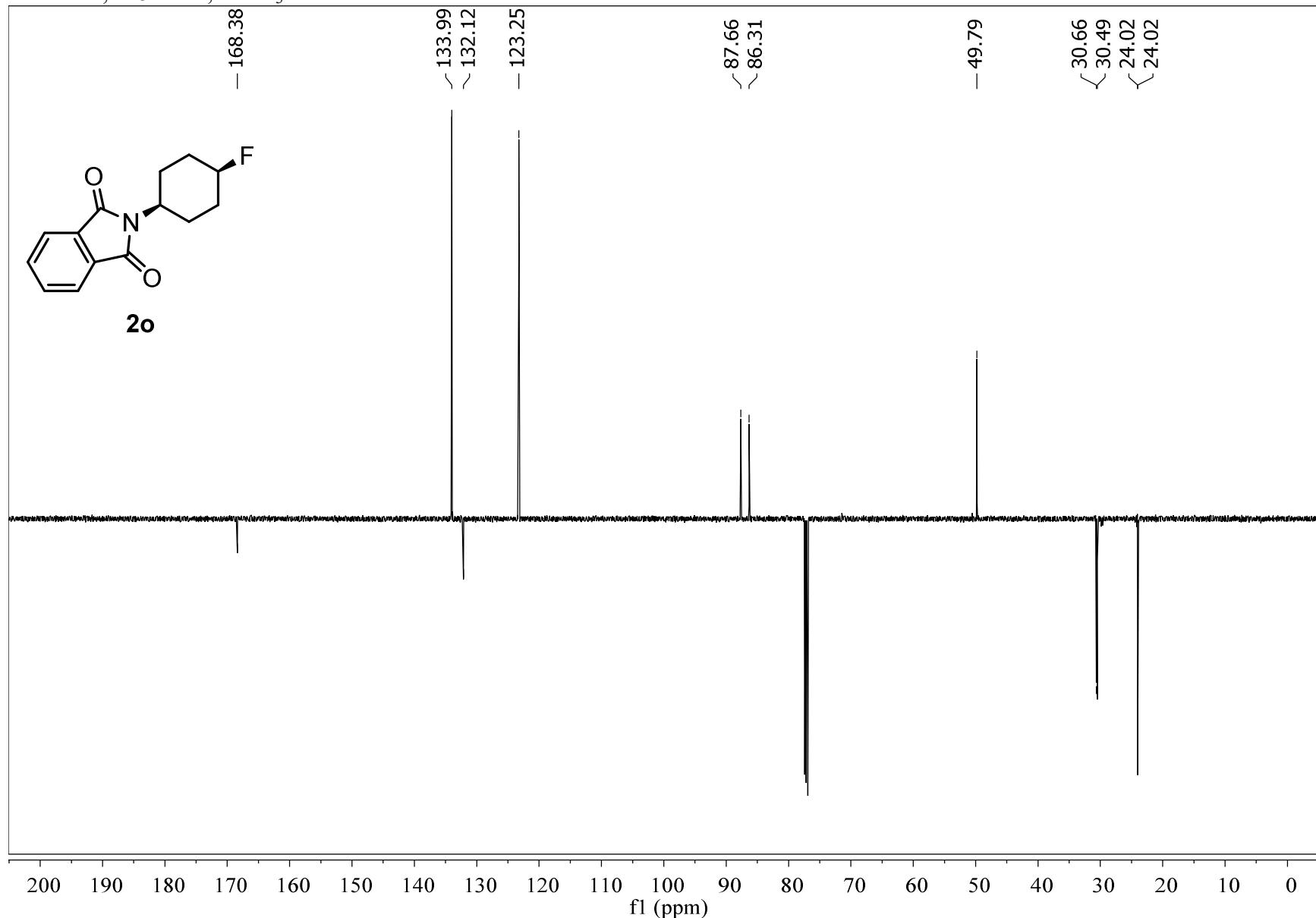
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



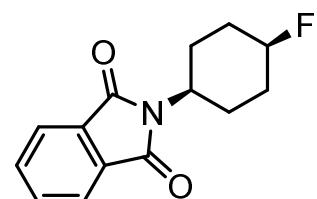
$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$



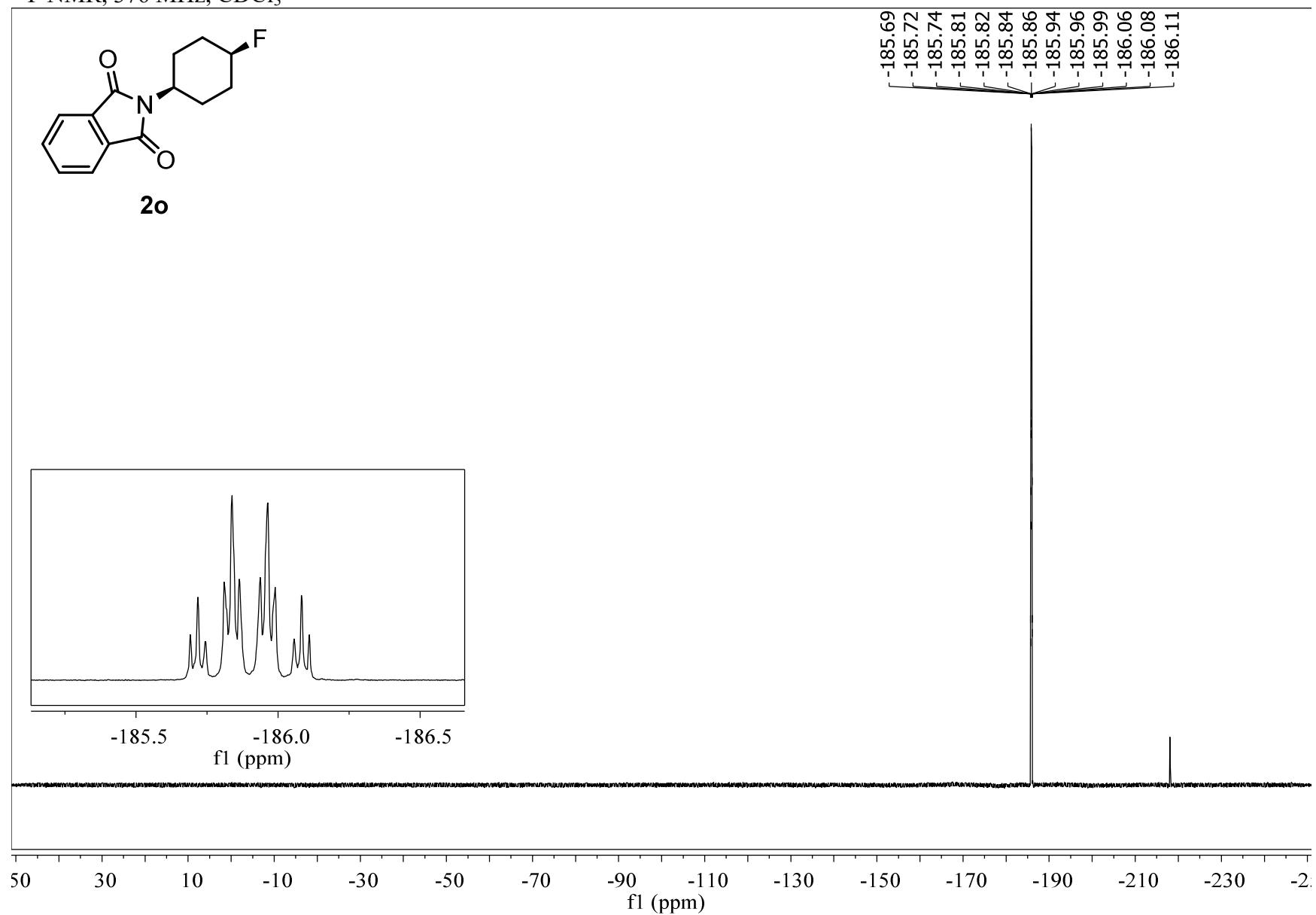
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



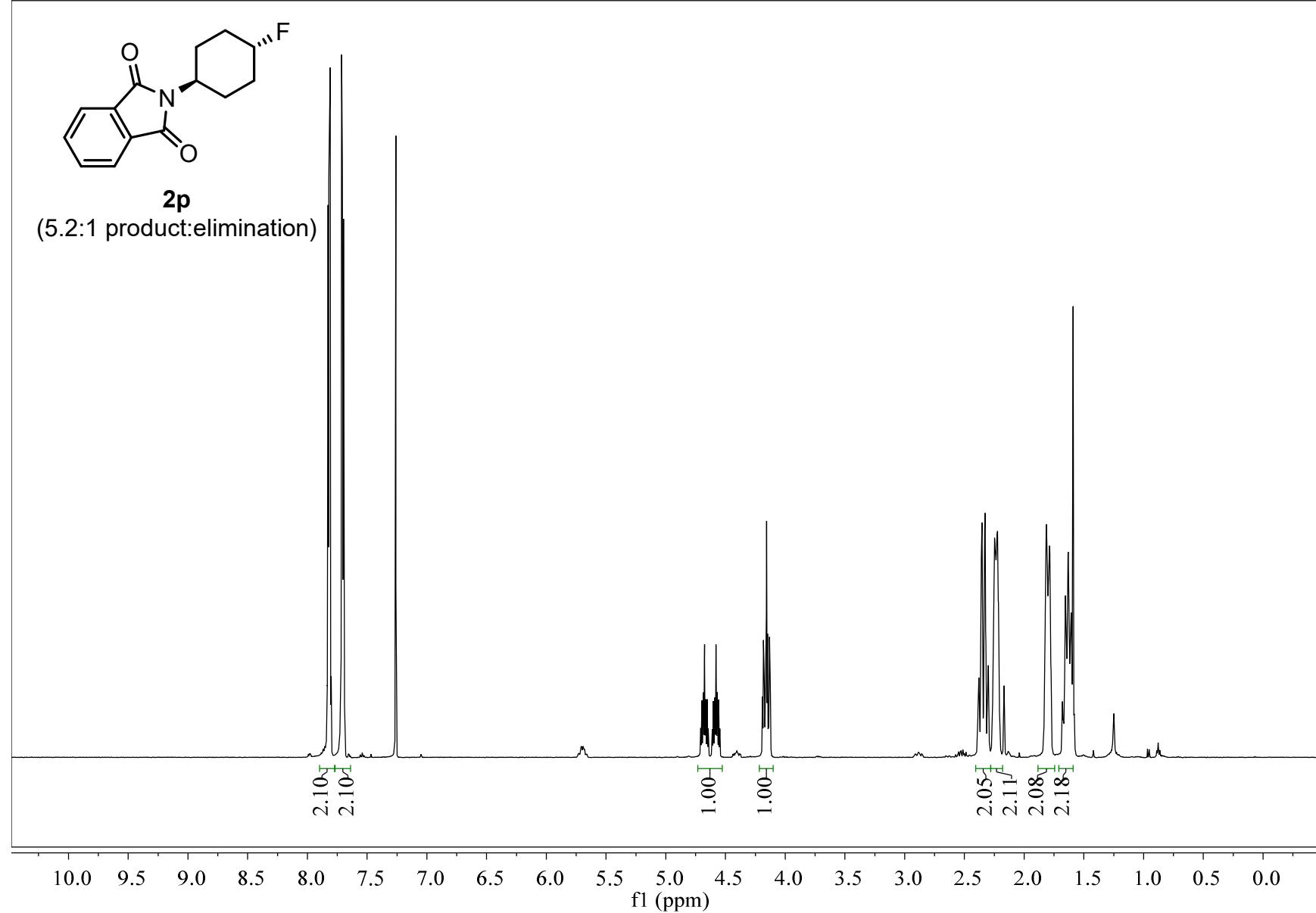
<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>



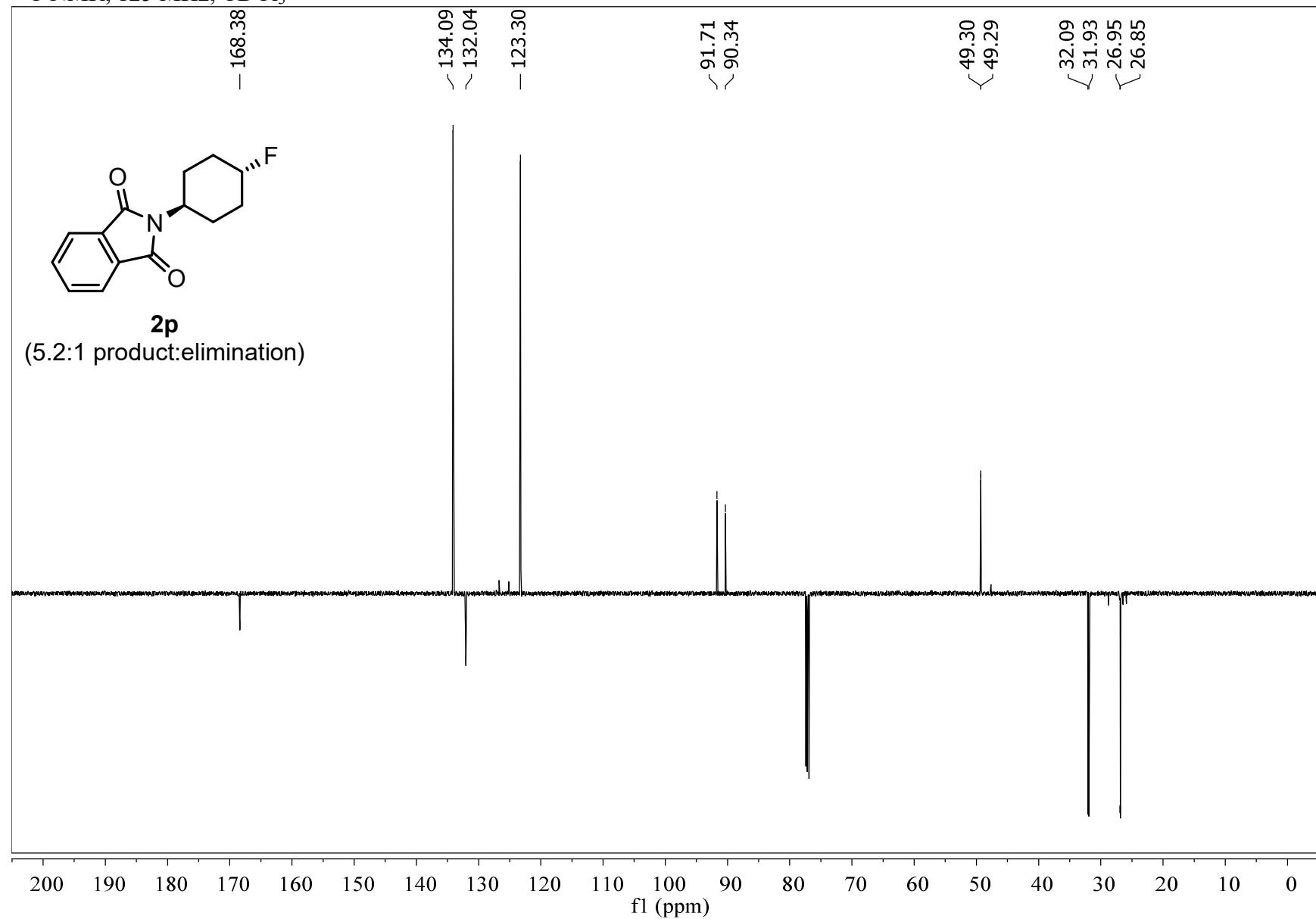
**2o**



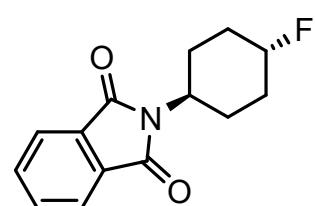
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



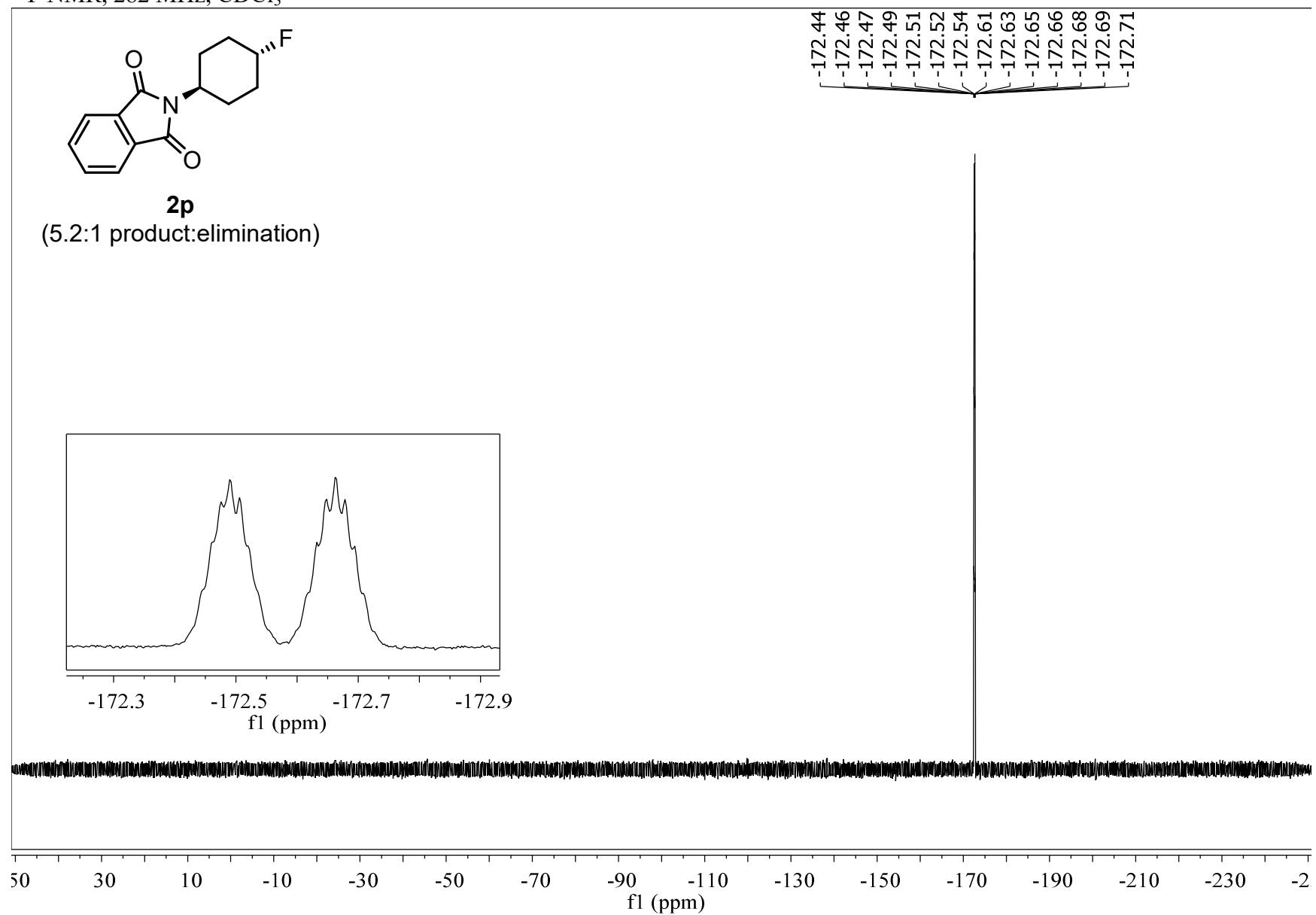
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



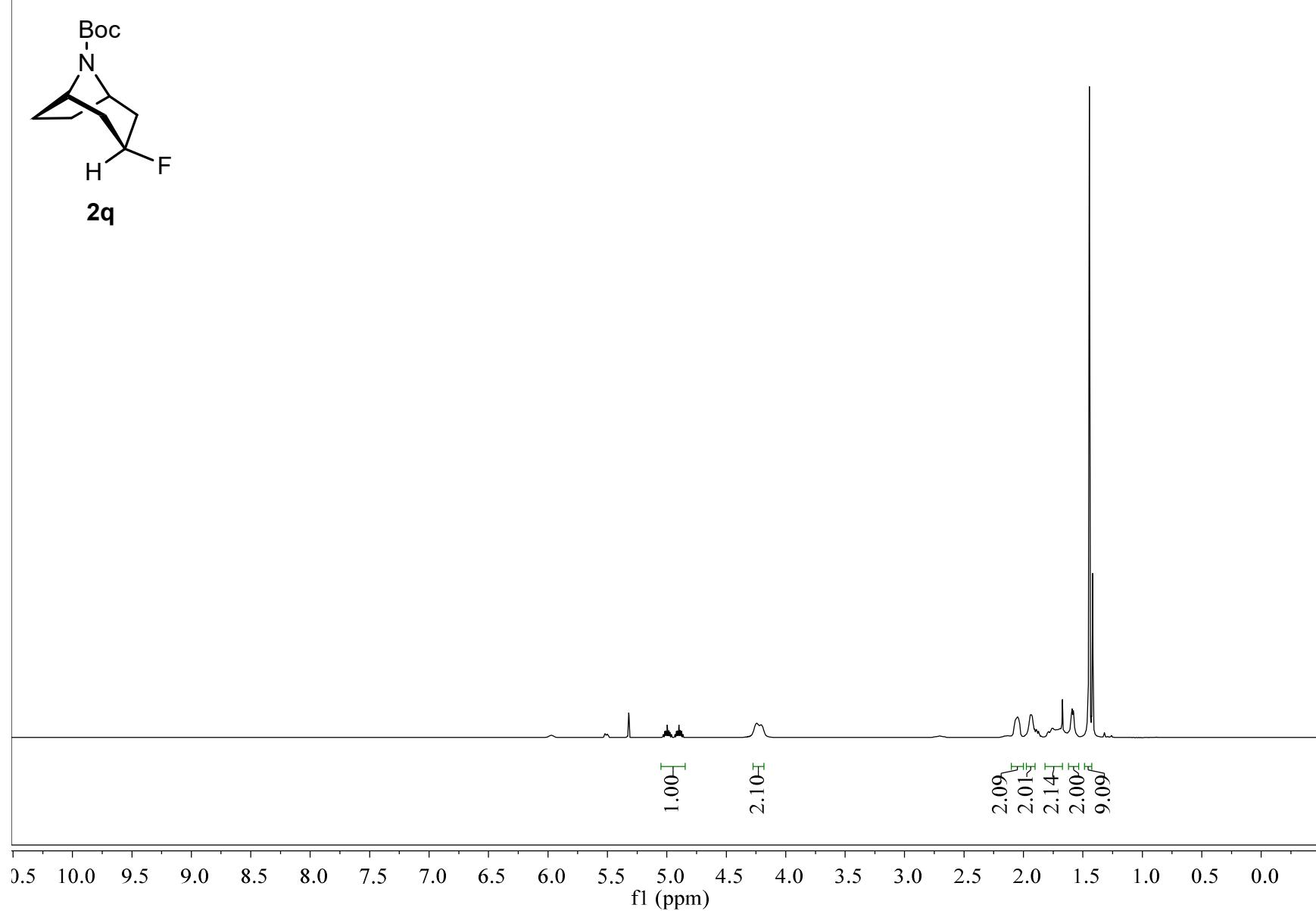
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



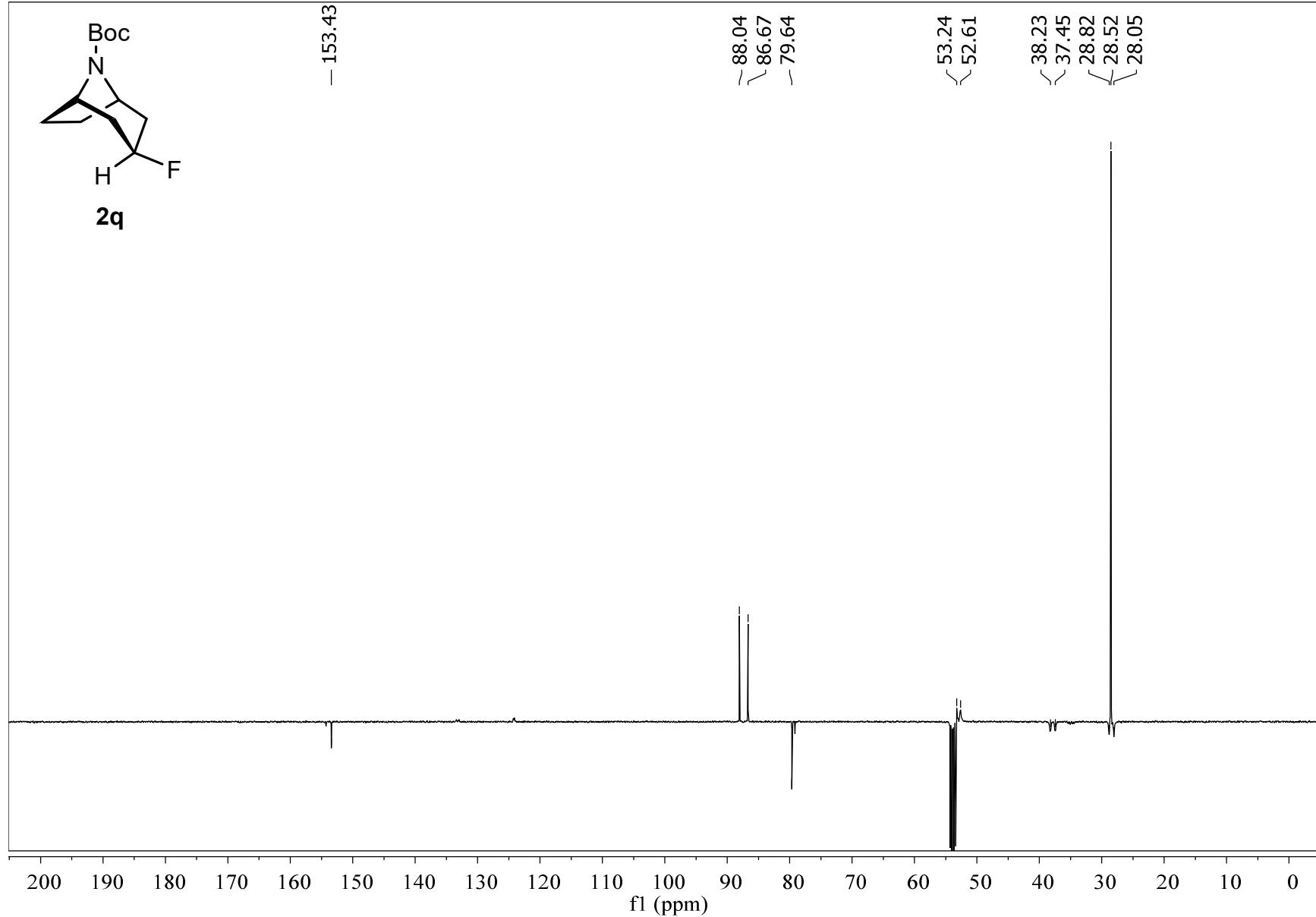
**2p**  
(5.2:1 product:elimination)



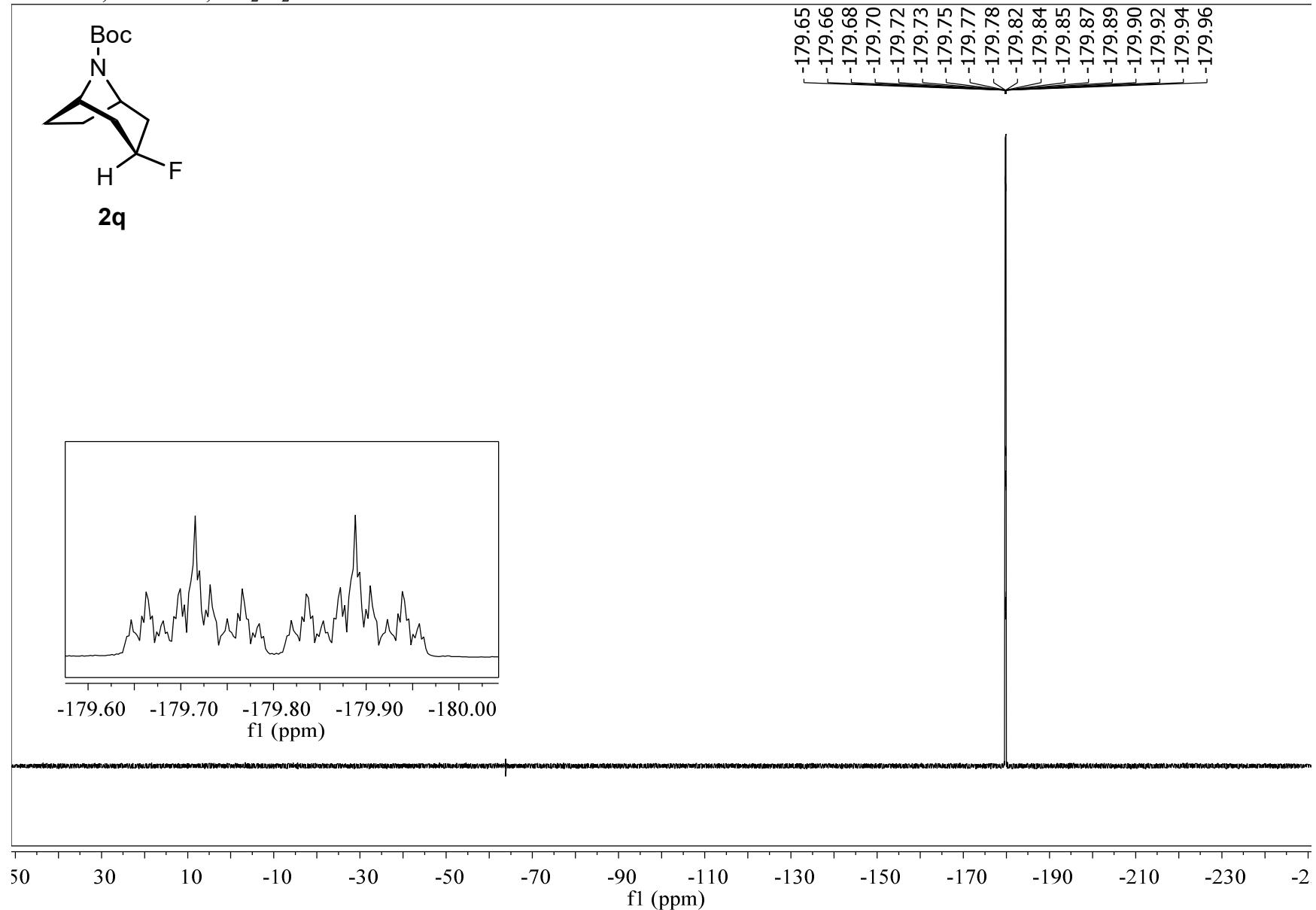
<sup>1</sup>H NMR, 500 MHz, CD<sub>2</sub>Cl<sub>2</sub>



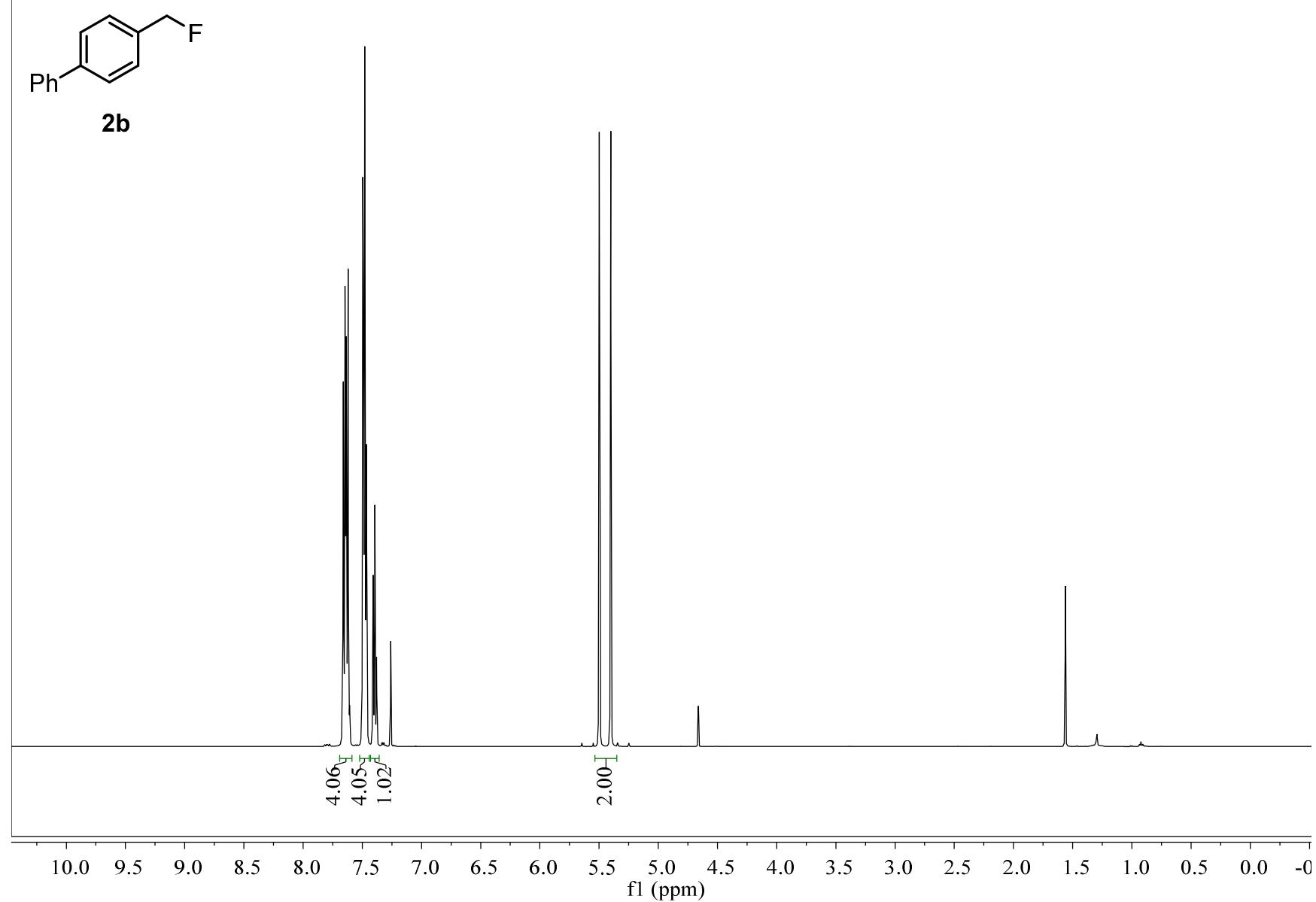
<sup>13</sup>C NMR, 125 MHz, CD<sub>2</sub>Cl<sub>2</sub>



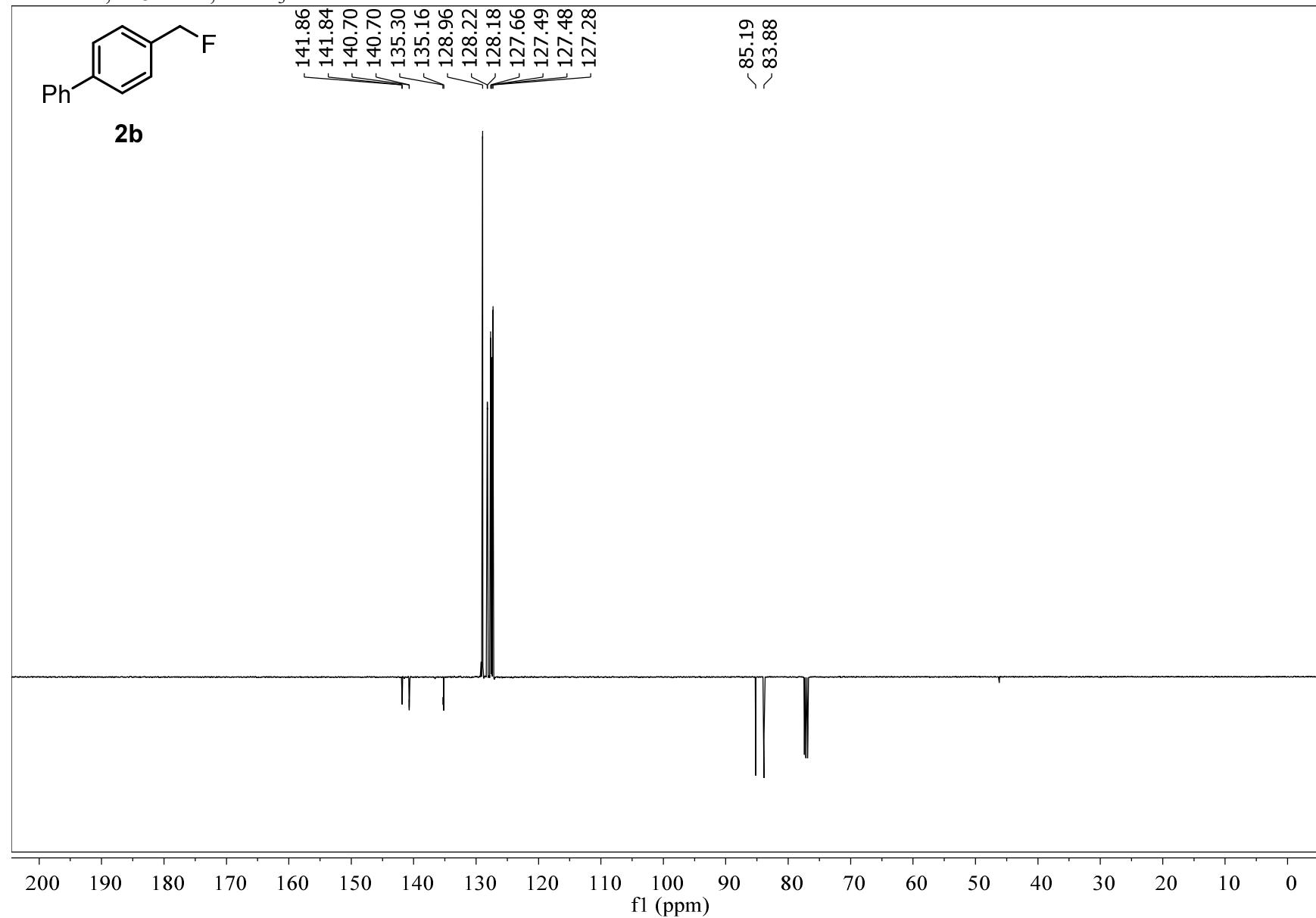
<sup>19</sup>F NMR, 282 MHz, CD<sub>2</sub>Cl<sub>2</sub>



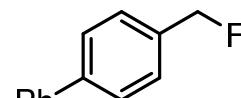
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

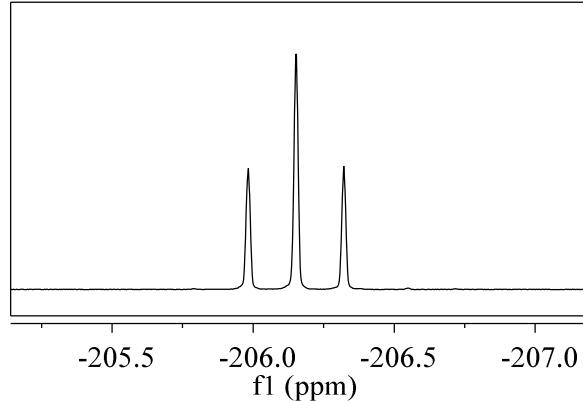


<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



**2b**

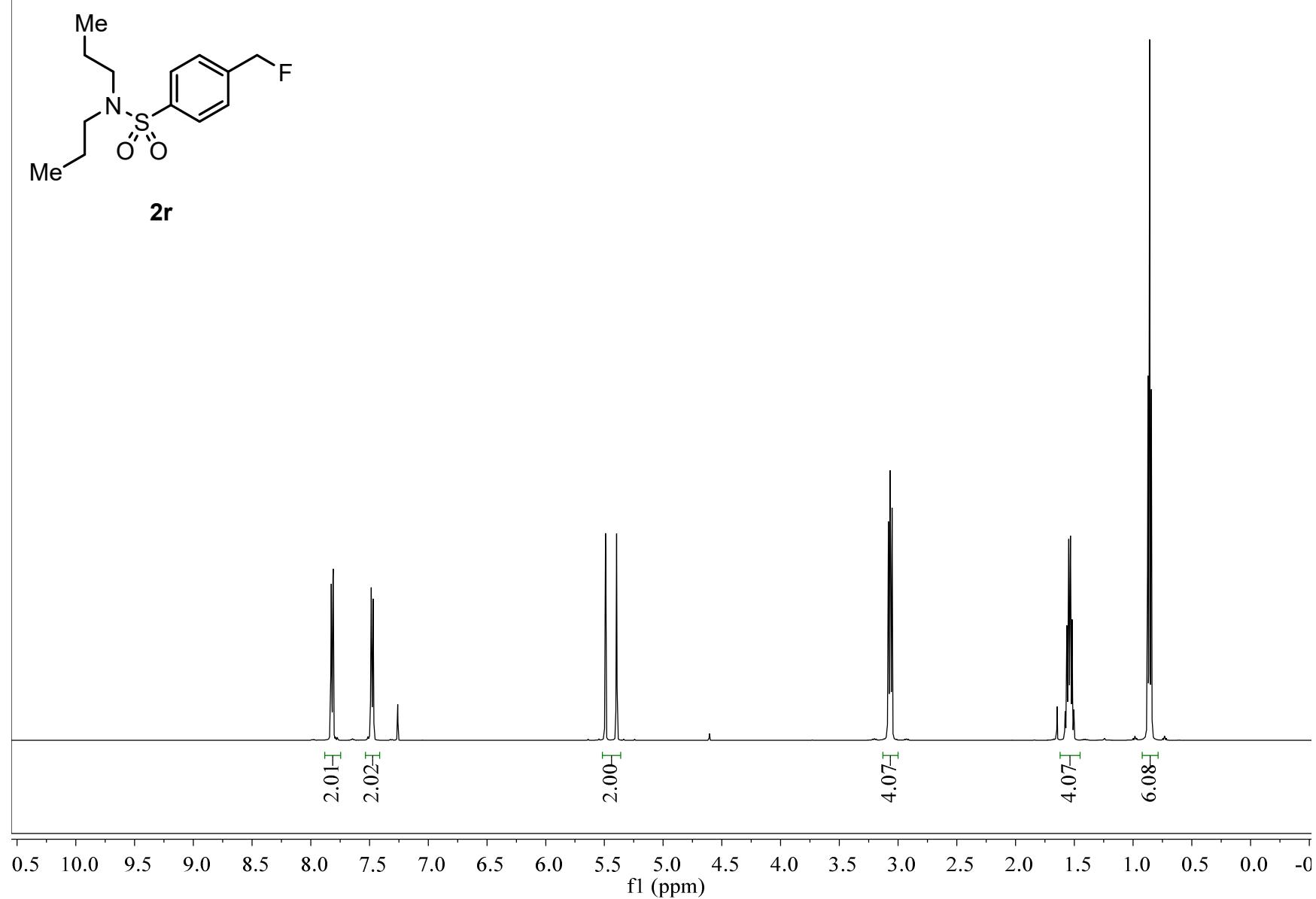
-205.98  
-206.15  
-206.32



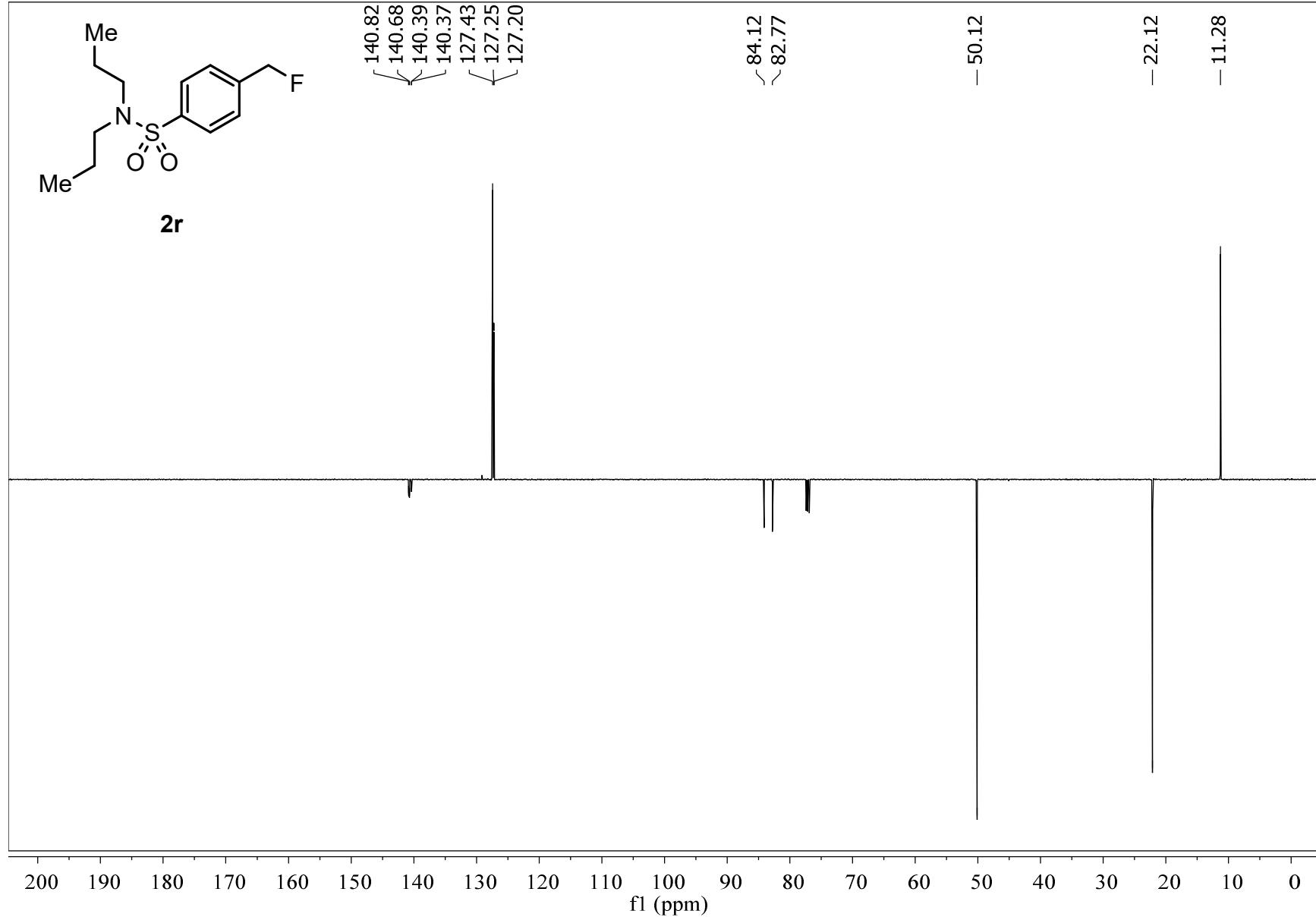
-205.5    -206.0    -206.5    -207.0  
f1 (ppm)

50    30    10    -10    -30    -50    -70    -90    -110    -130    -150    -170    -190    -210    -230    -2  
f1 (ppm)

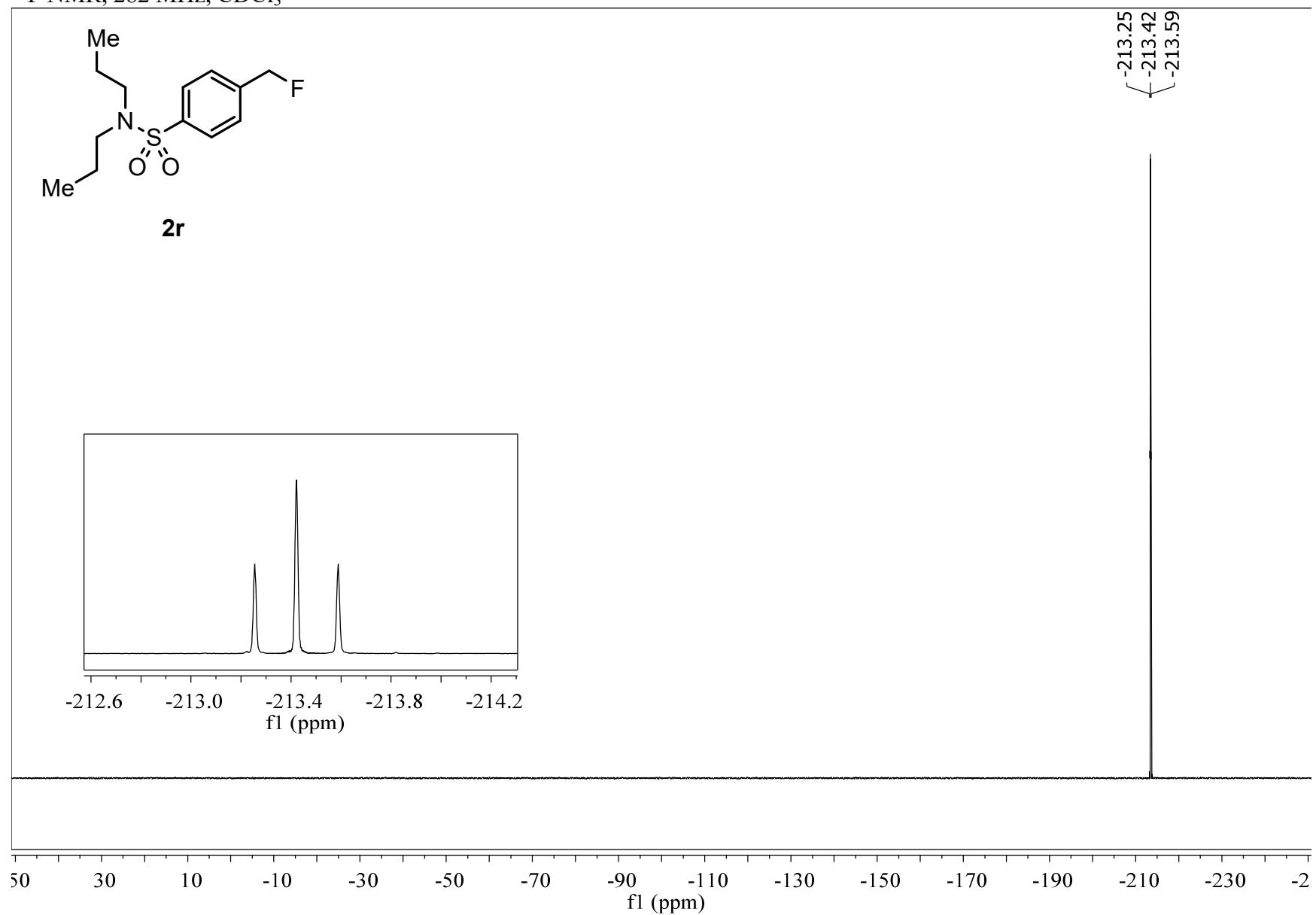
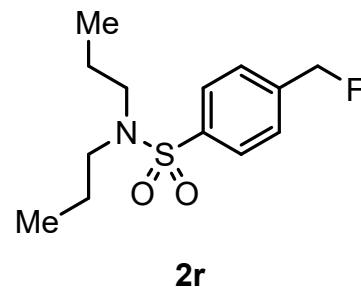
$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$



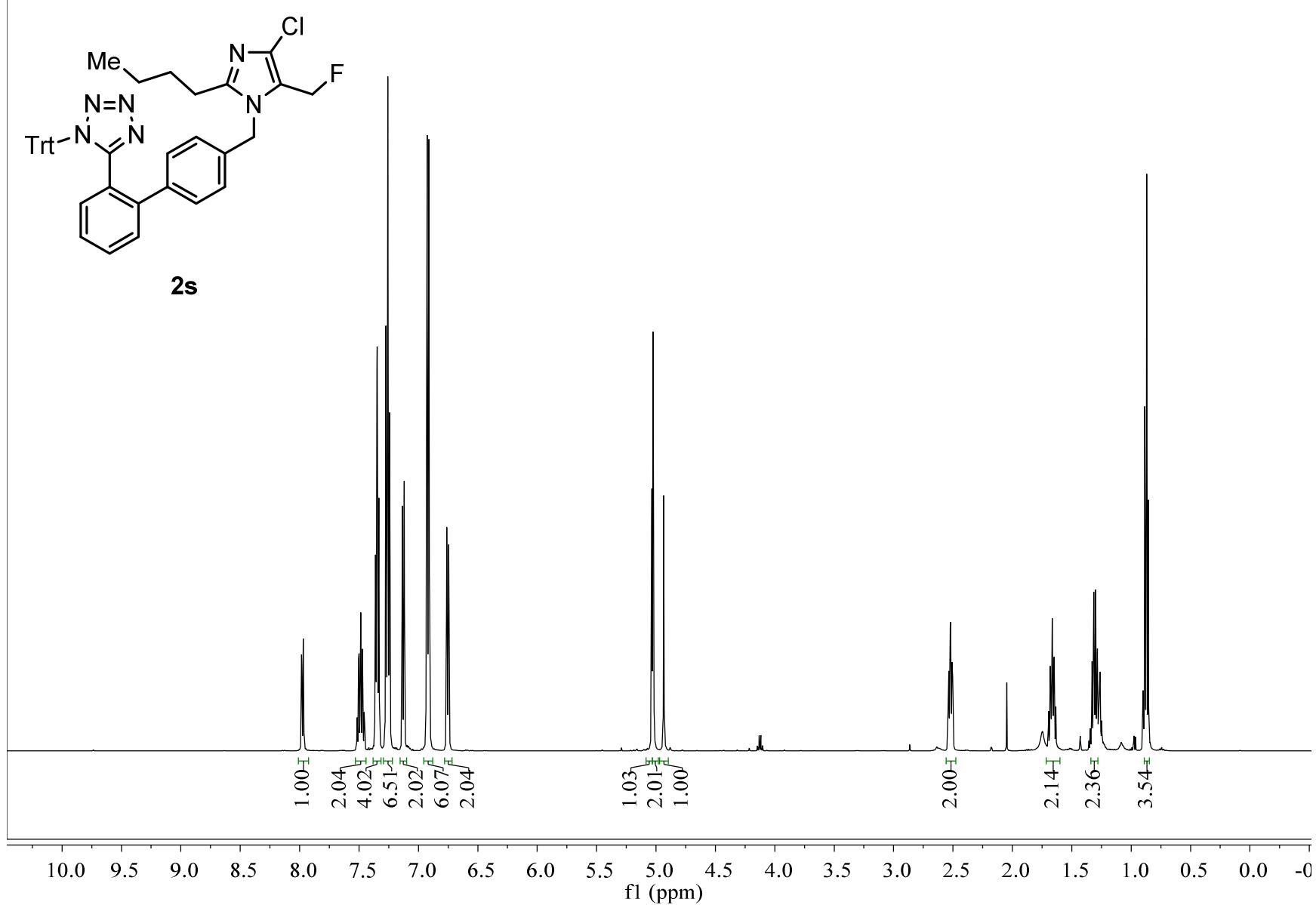
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



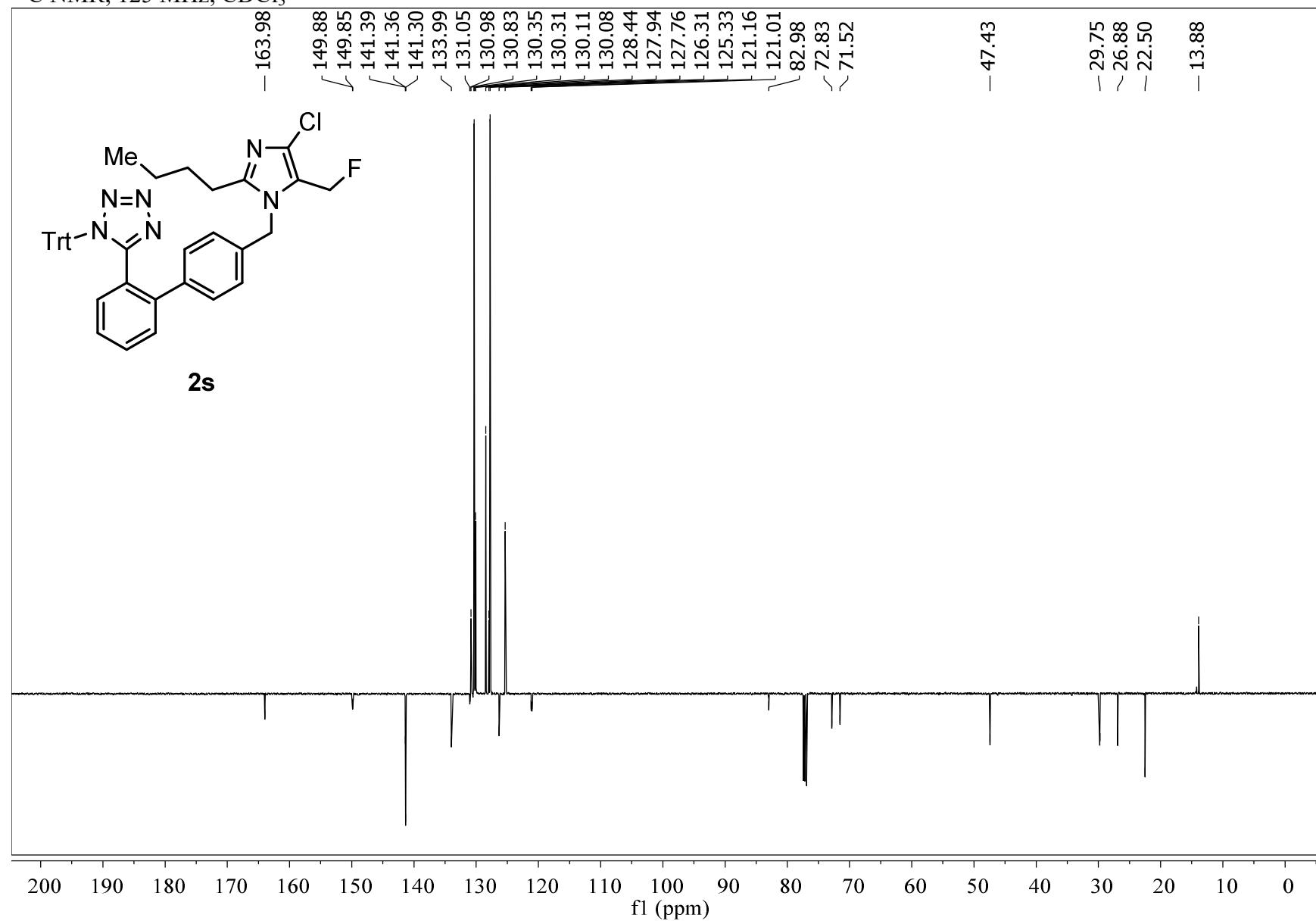
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



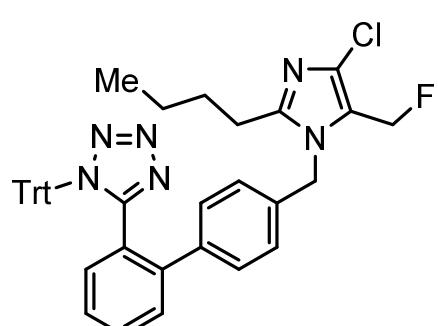
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

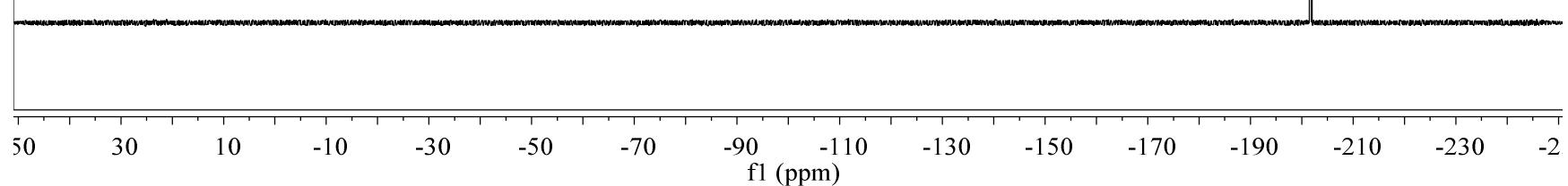
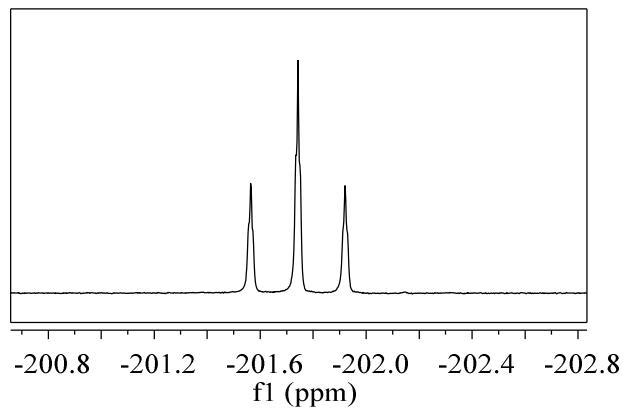


<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>

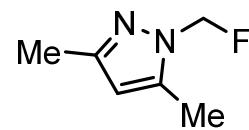


**2s**

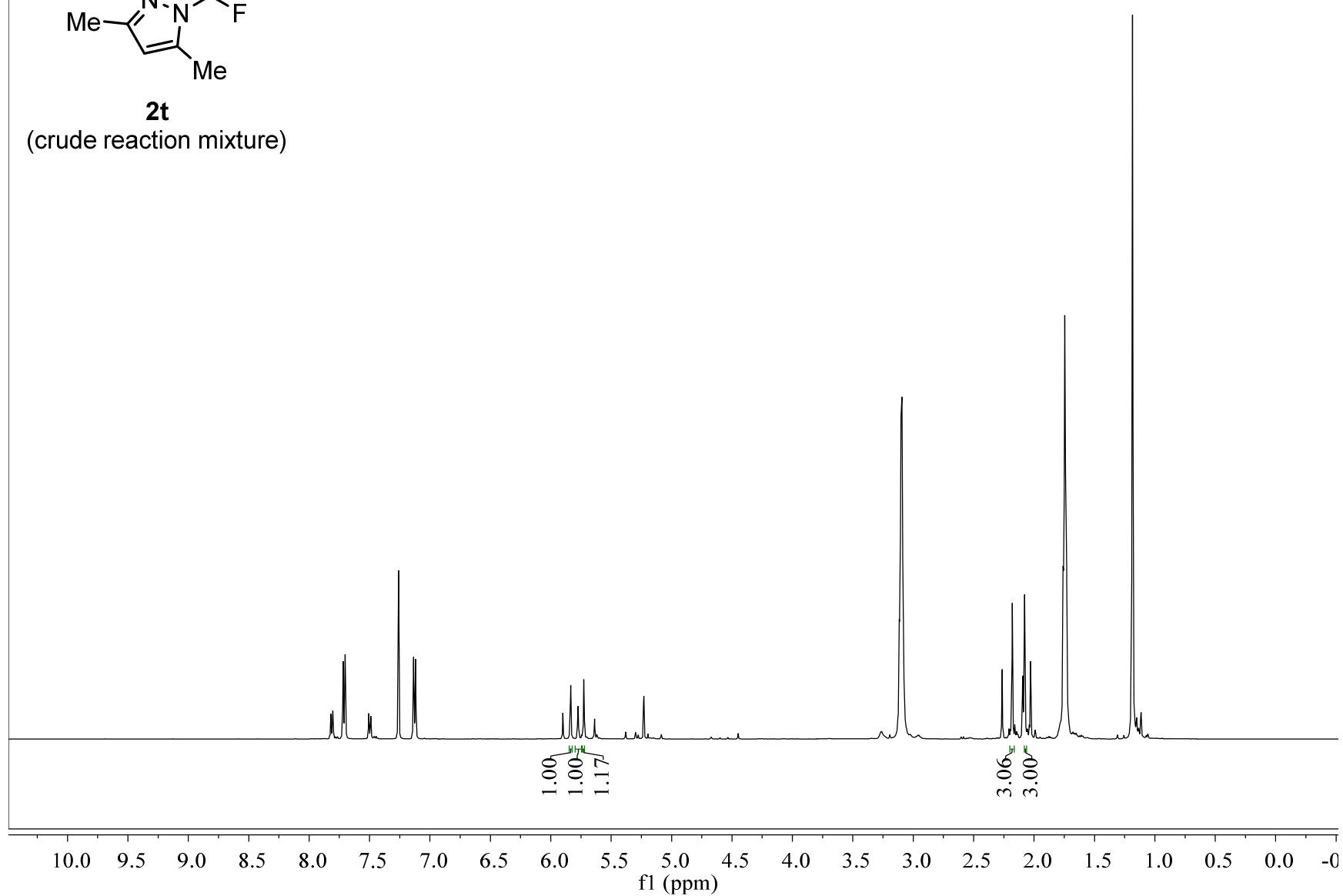
-201.56  
-201.74  
-201.92



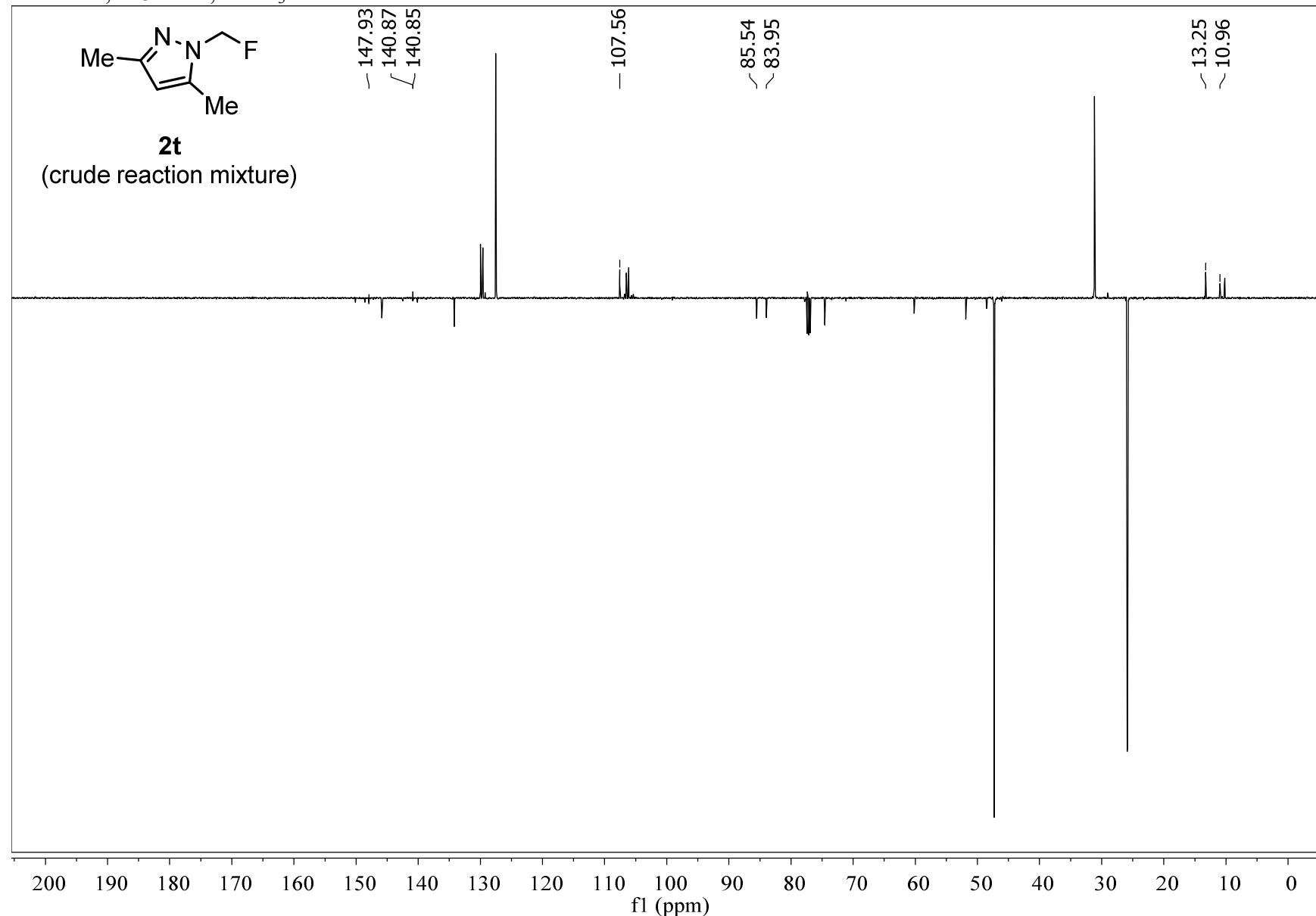
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



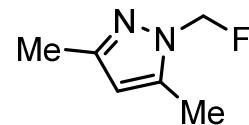
**2t**  
(crude reaction mixture)



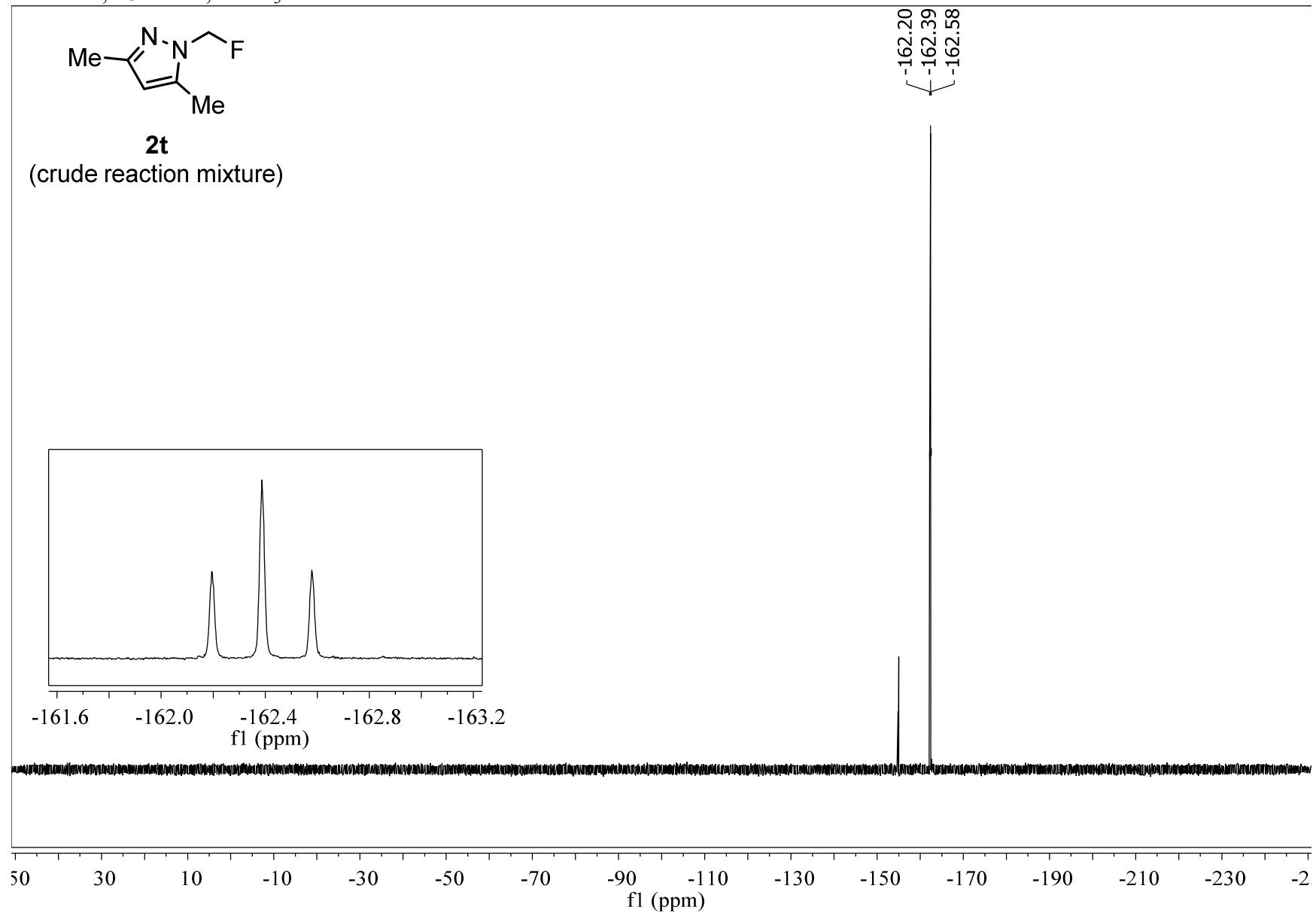
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



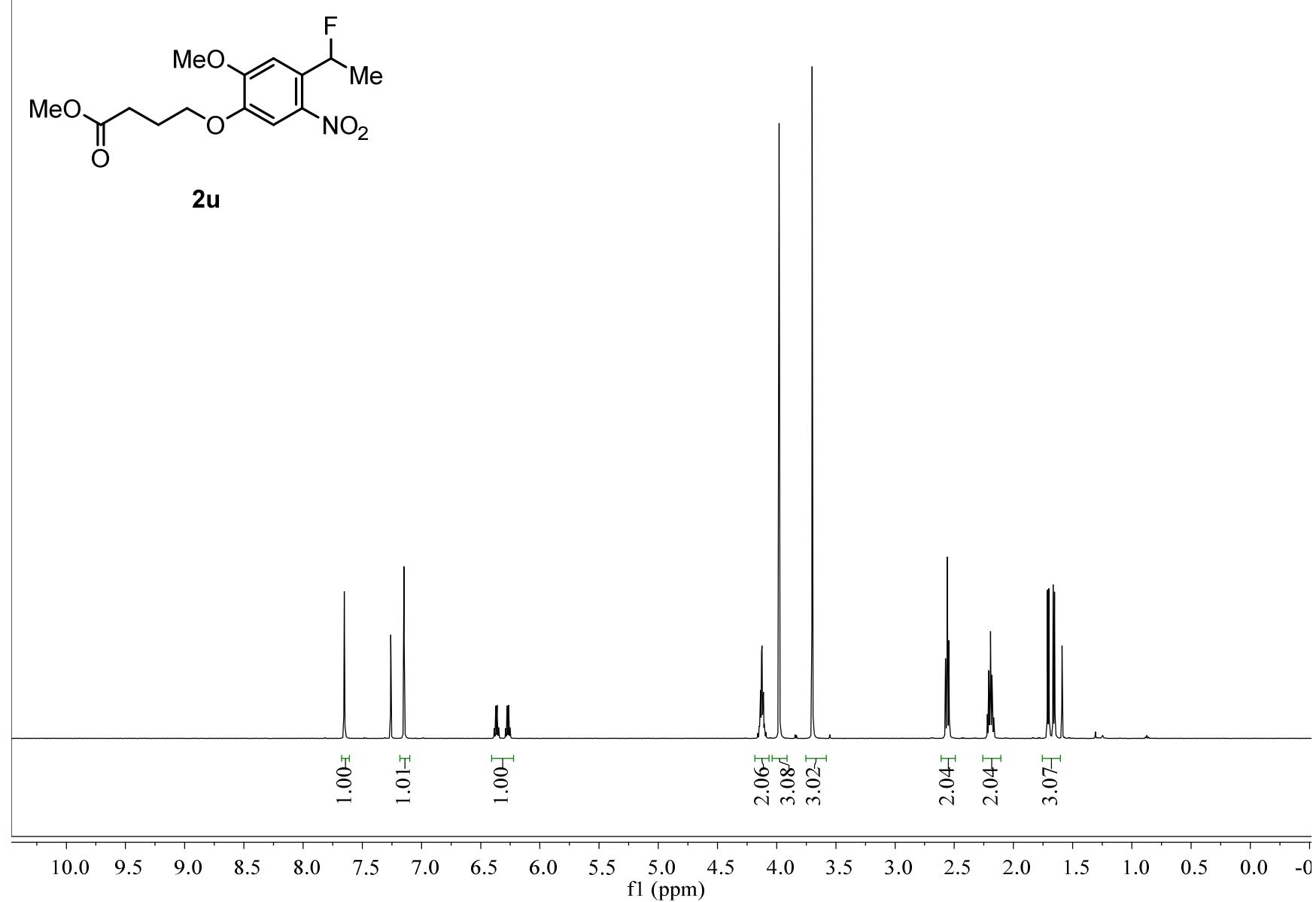
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



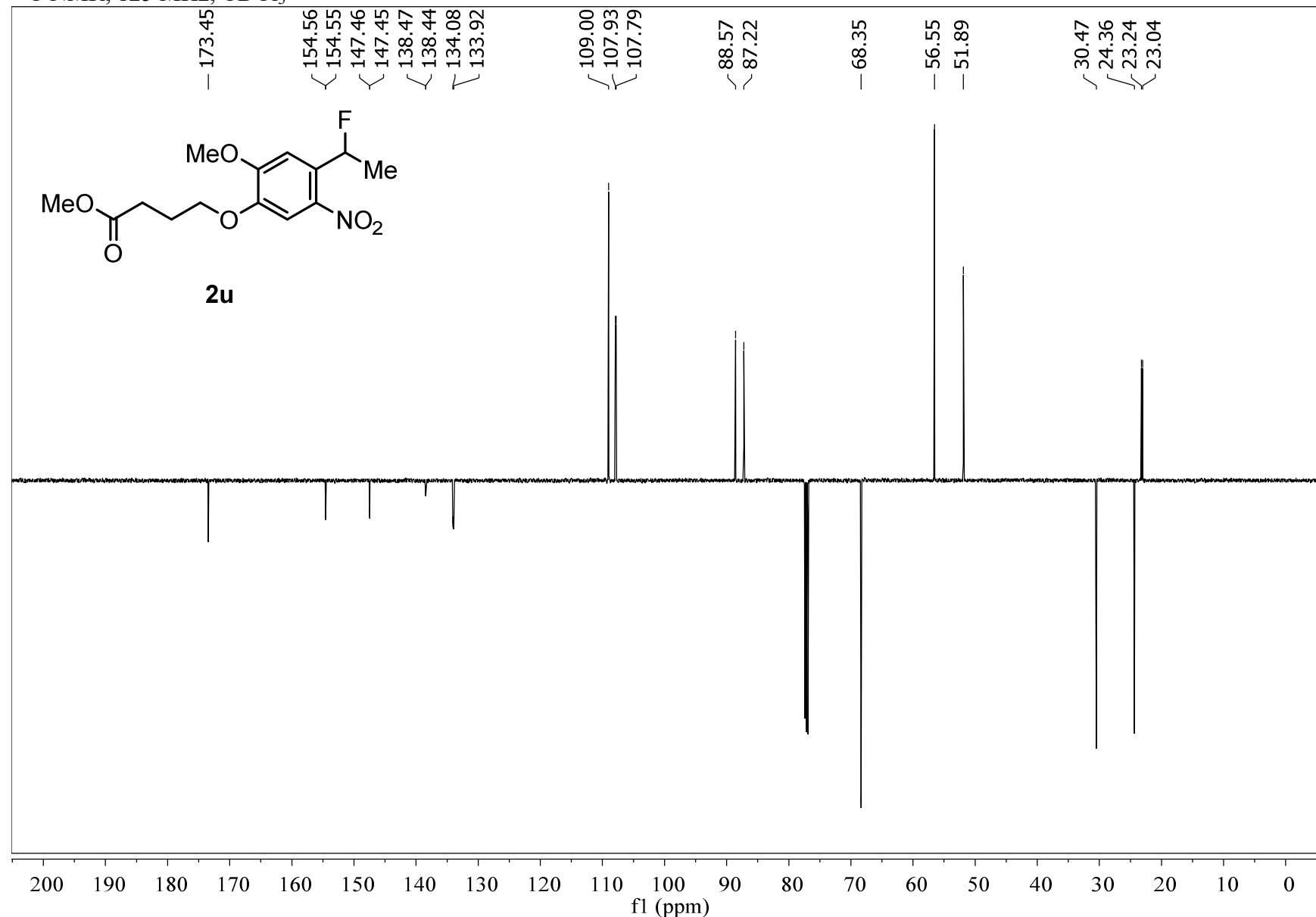
**2t**  
(crude reaction mixture)



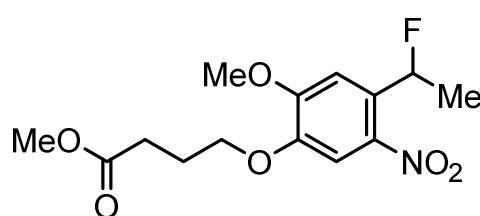
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



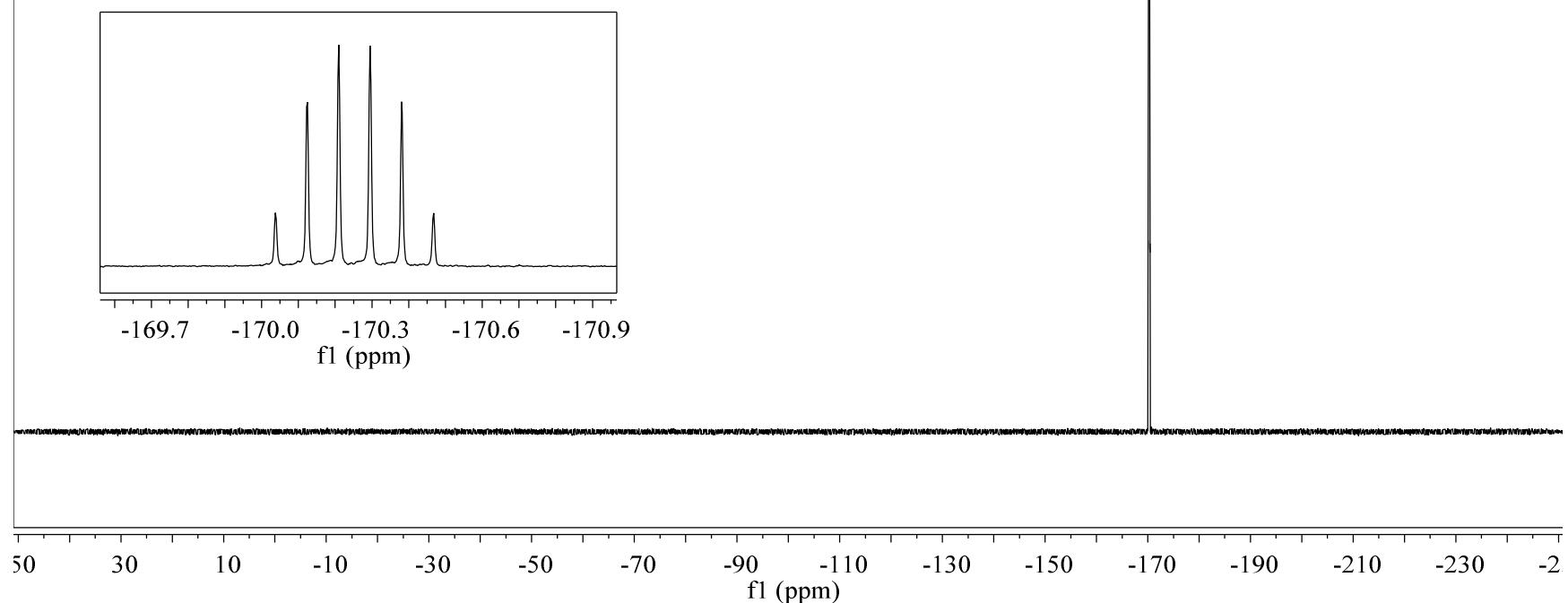
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



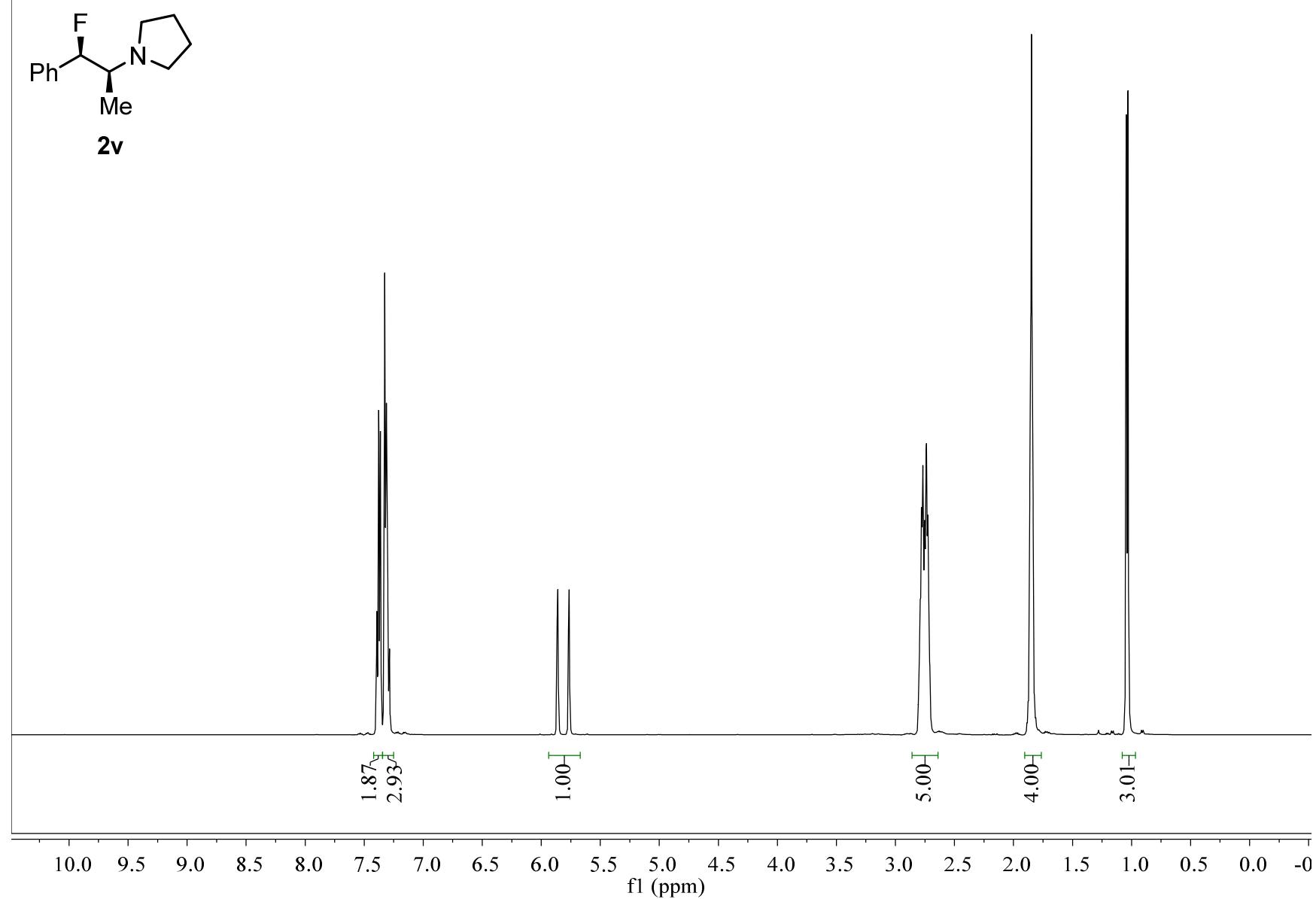
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



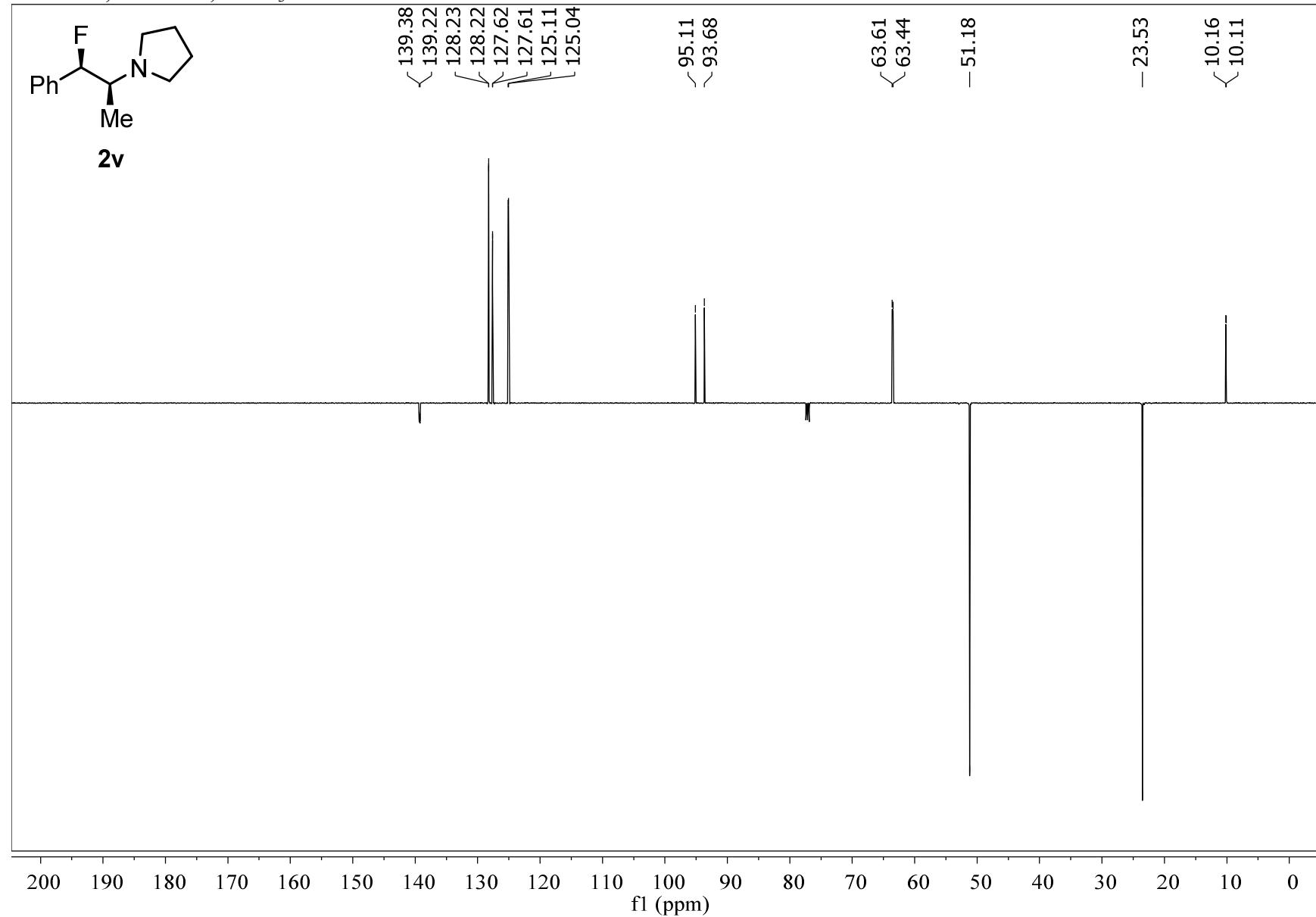
**2u**



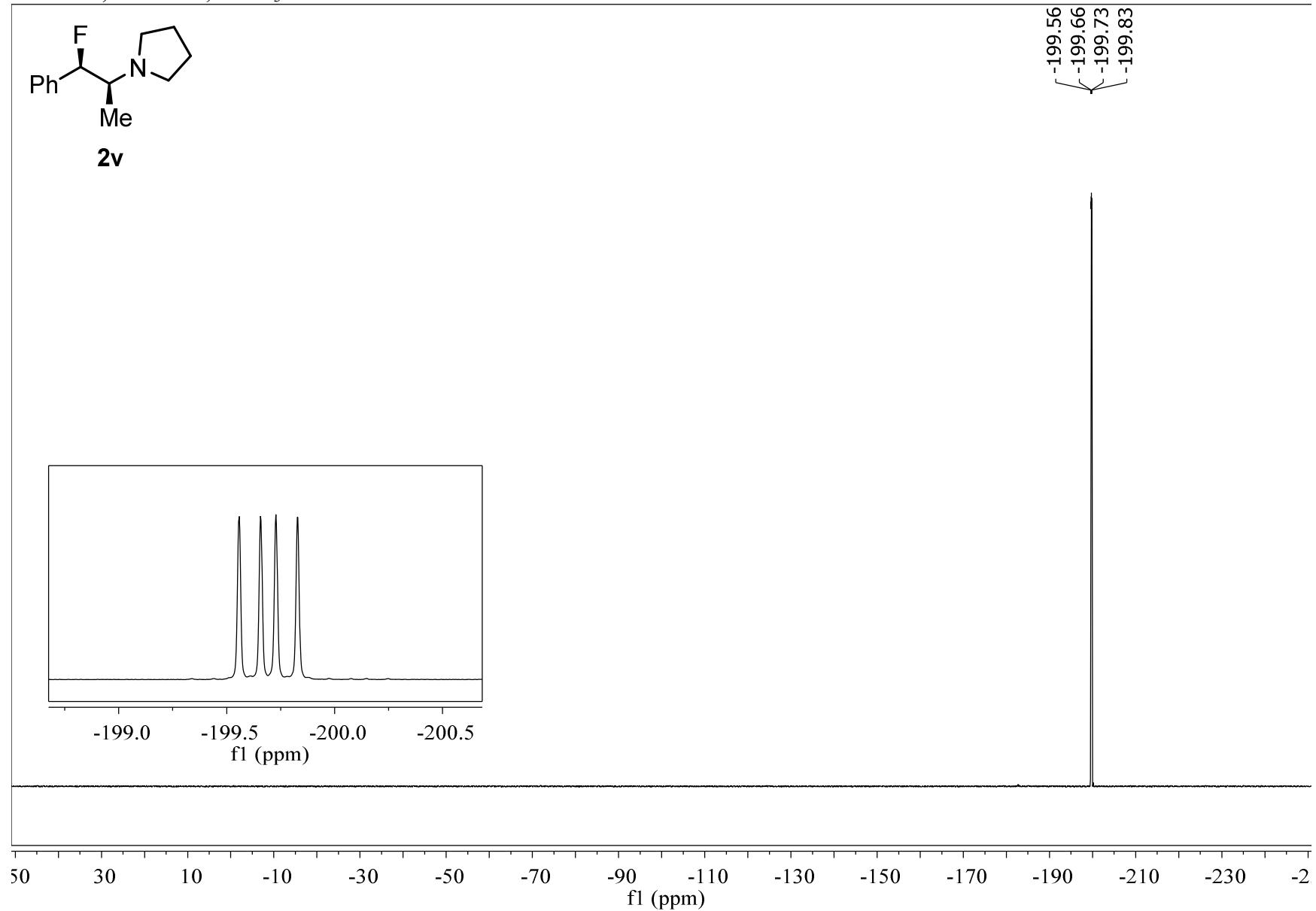
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



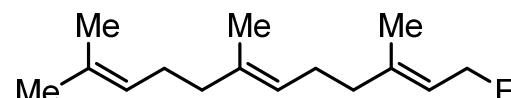
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>

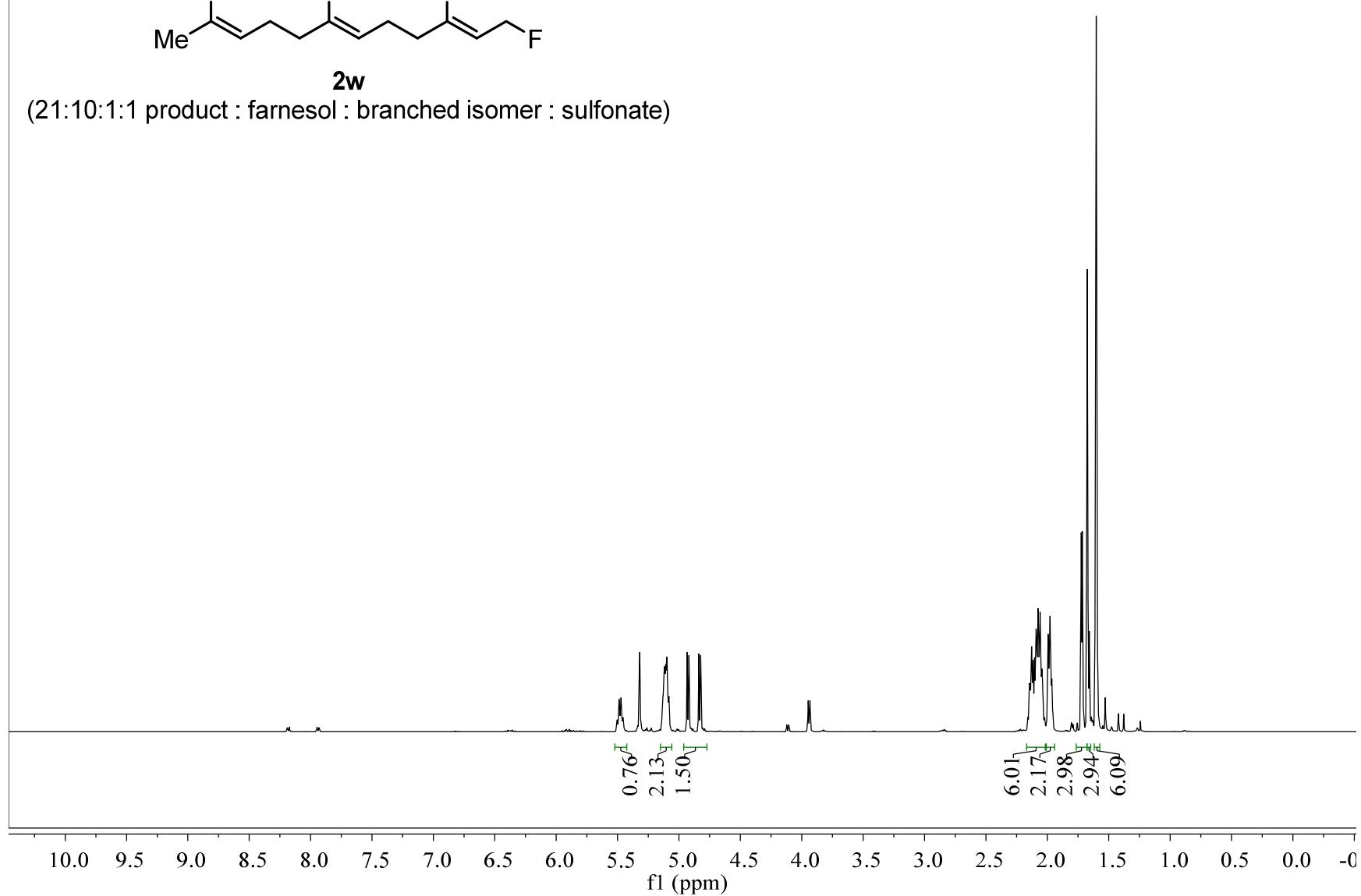


<sup>1</sup>H NMR, 500 MHz, CD<sub>2</sub>Cl<sub>2</sub>

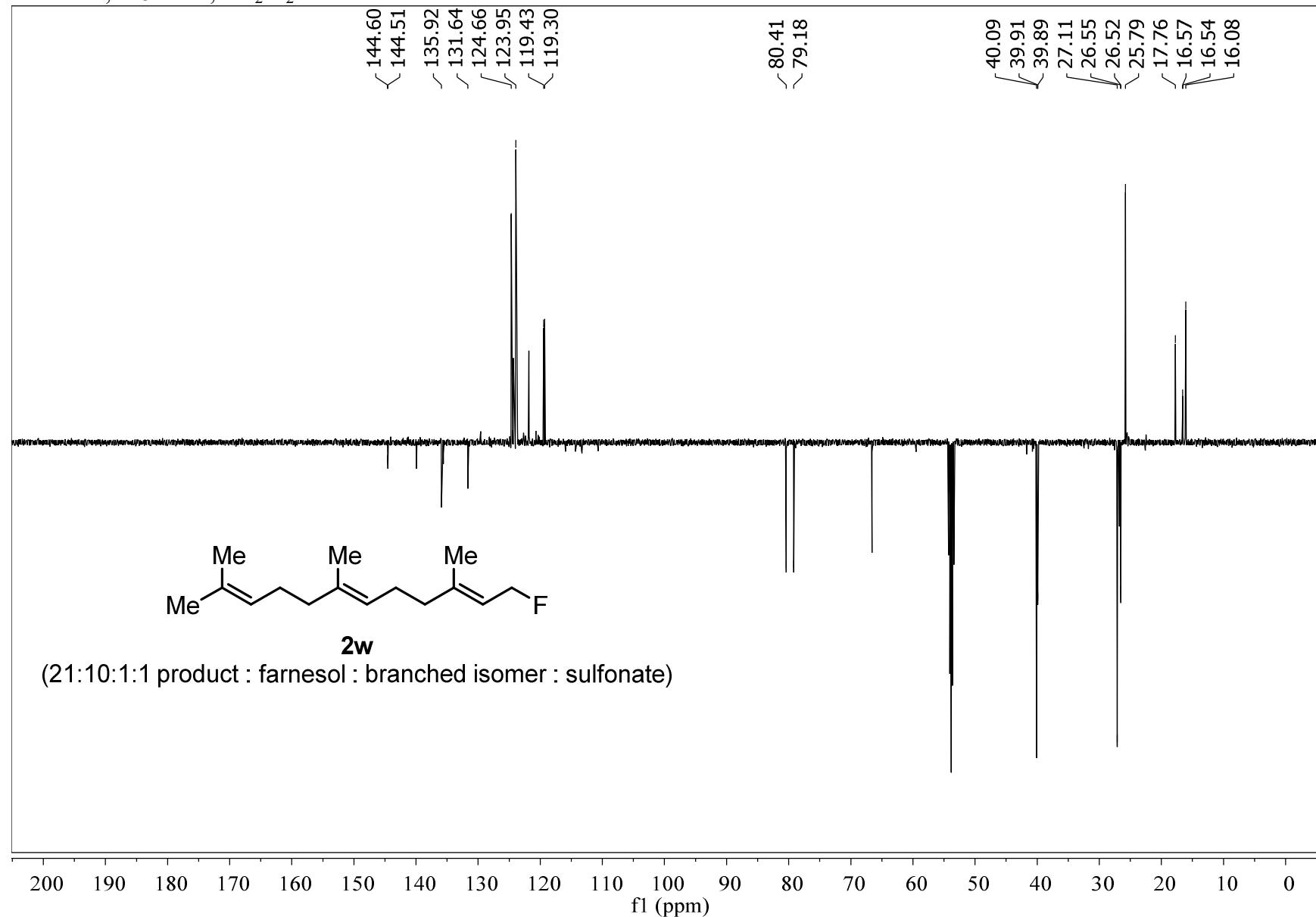


**2w**

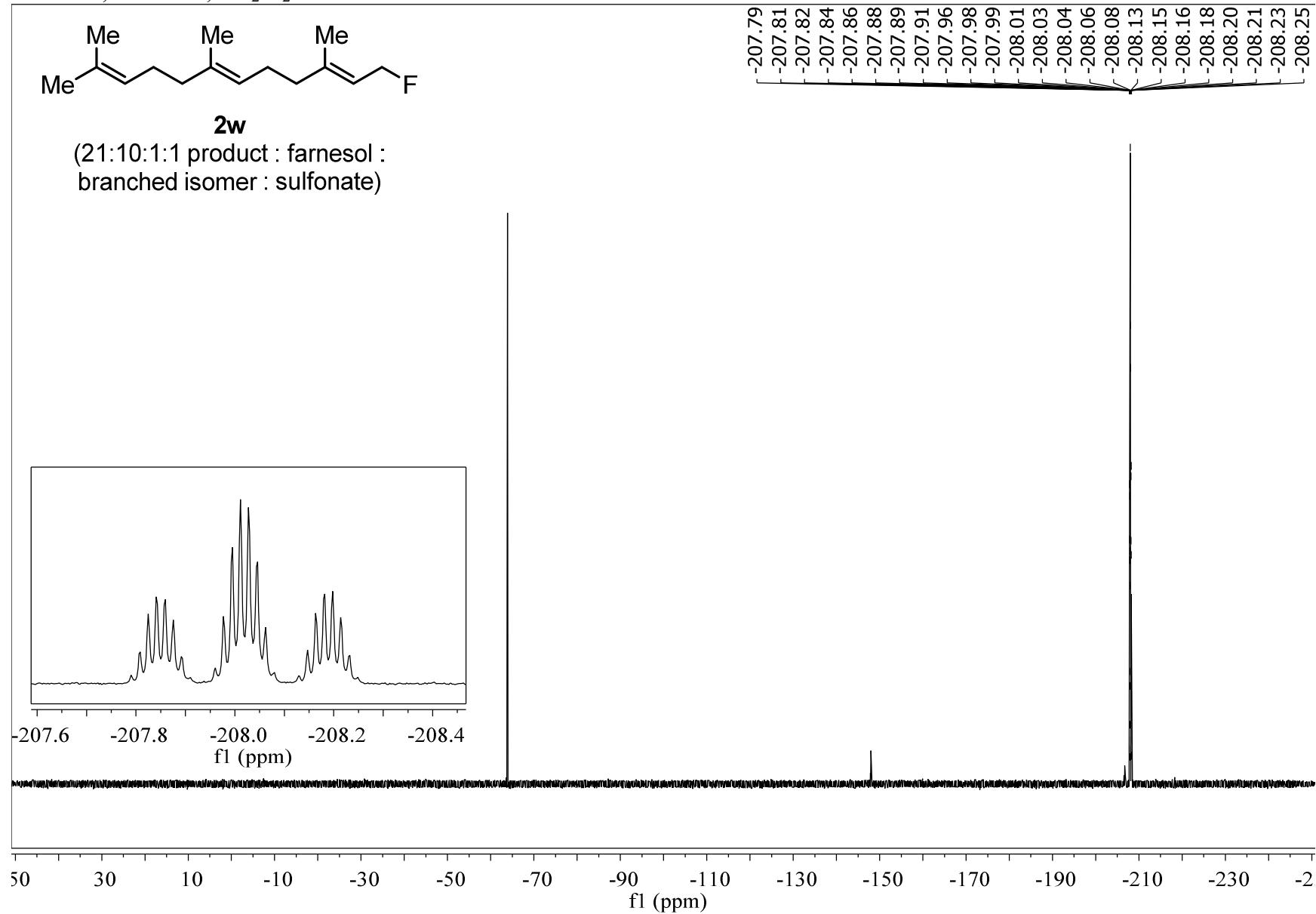
(21:10:1:1 product : farnesol : branched isomer : sulfonate)



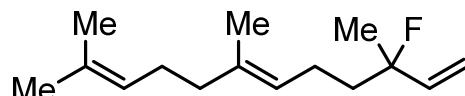
<sup>13</sup>C NMR, 125 MHz, CD<sub>2</sub>Cl<sub>2</sub>



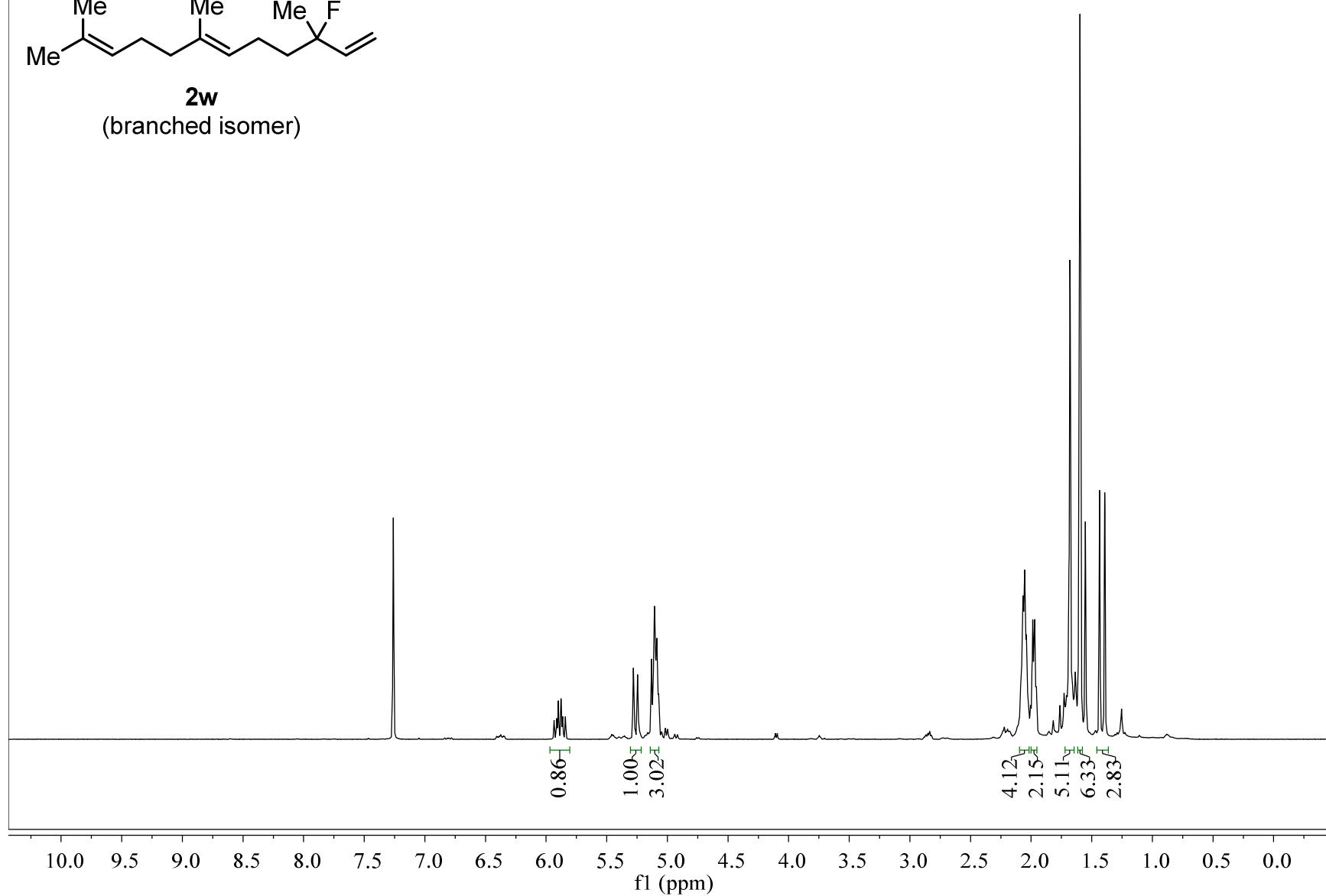
<sup>19</sup>F NMR, 282 MHz, CD<sub>2</sub>Cl<sub>2</sub>



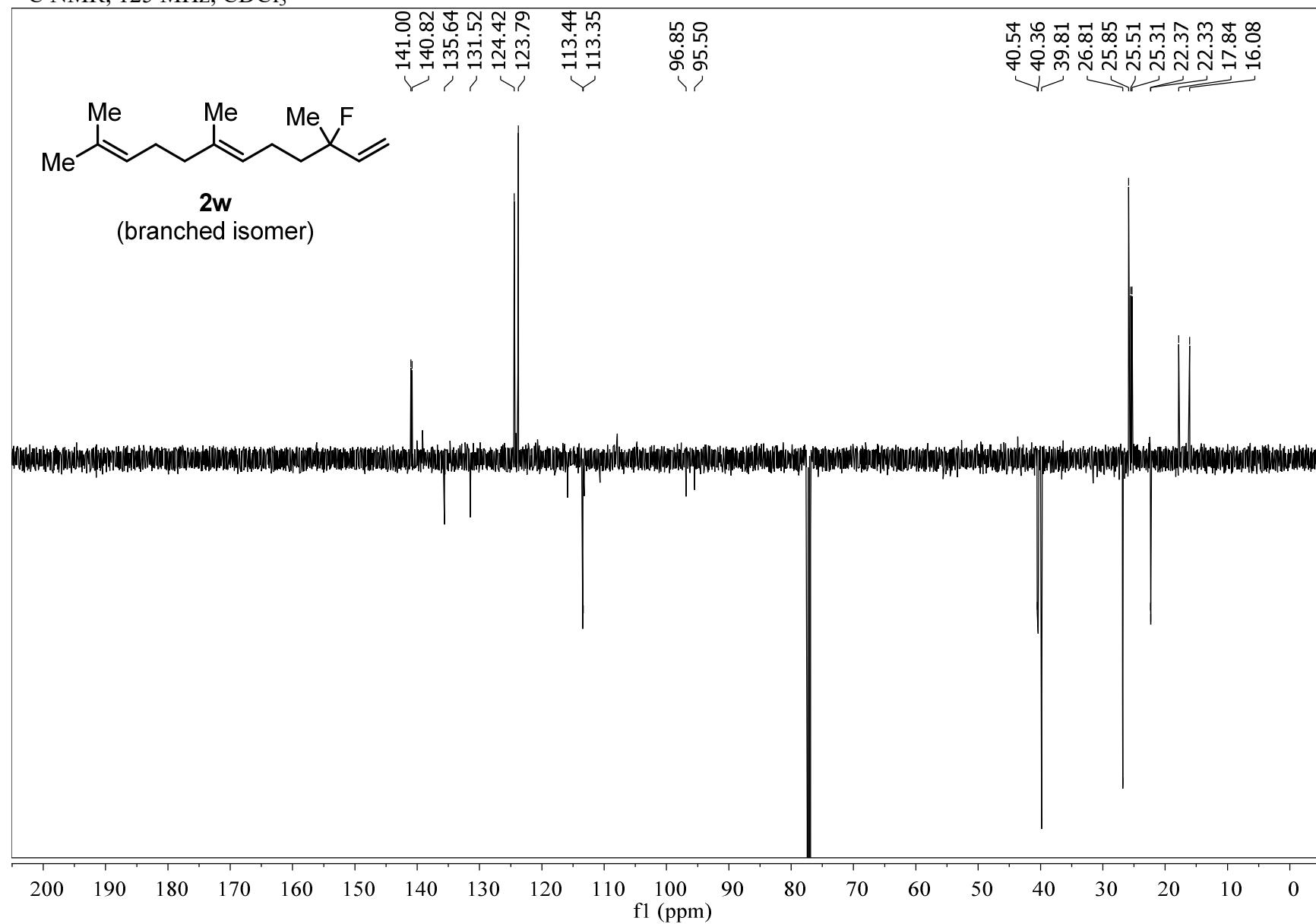
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



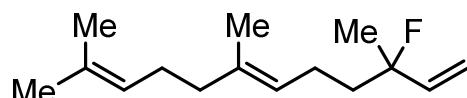
**2w**  
(branched isomer)



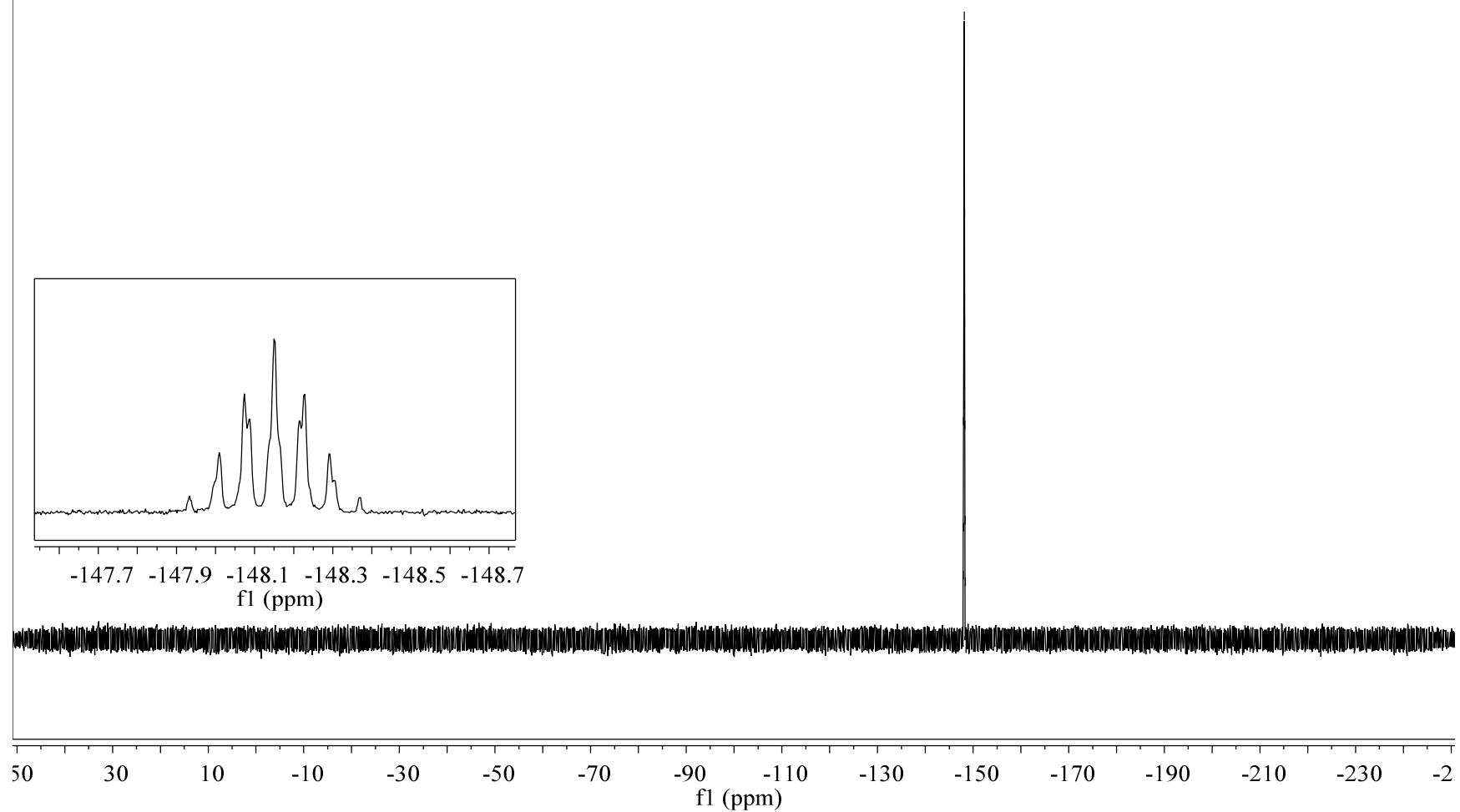
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



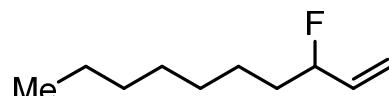
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



**2w**  
(branched isomer)

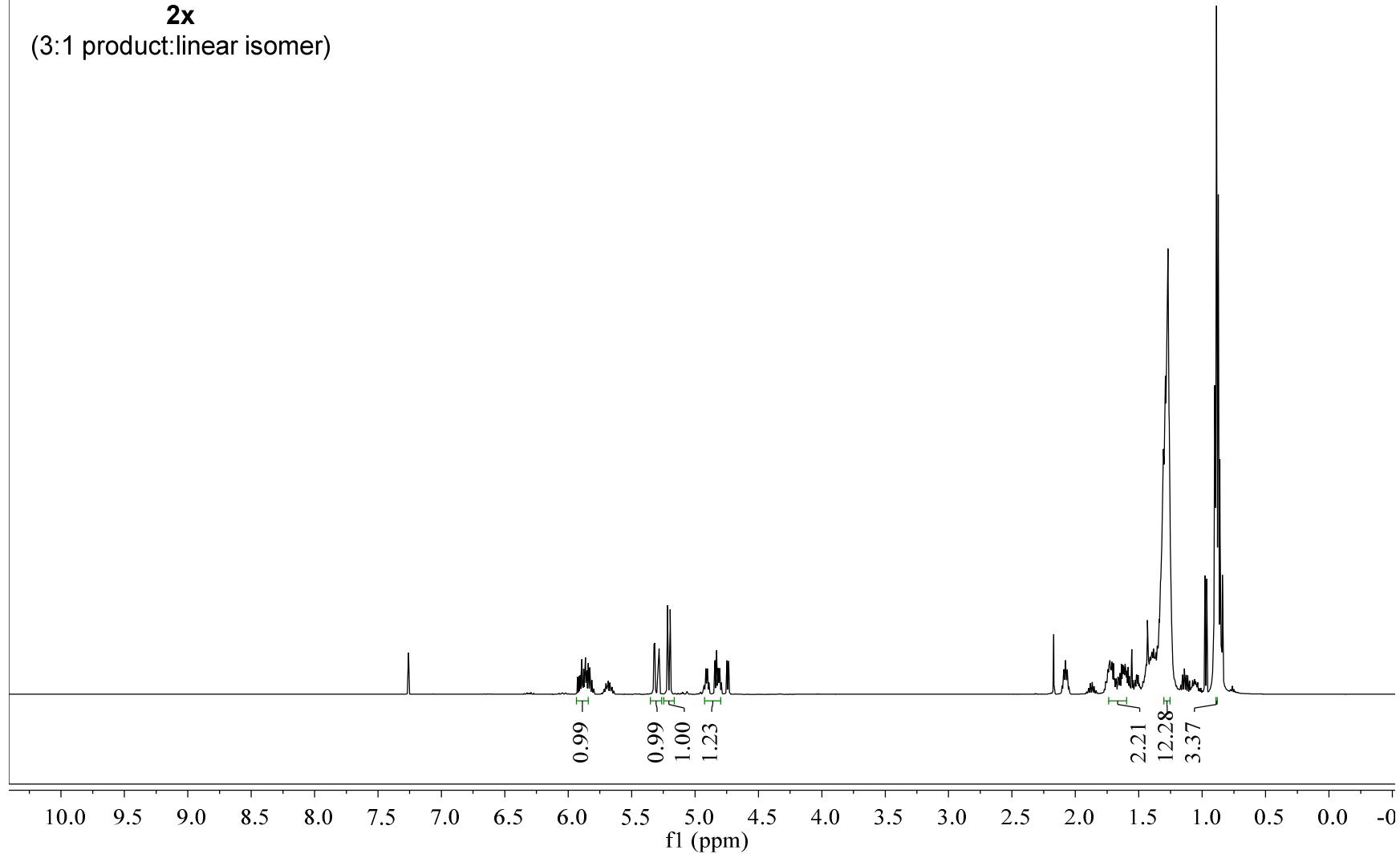


<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

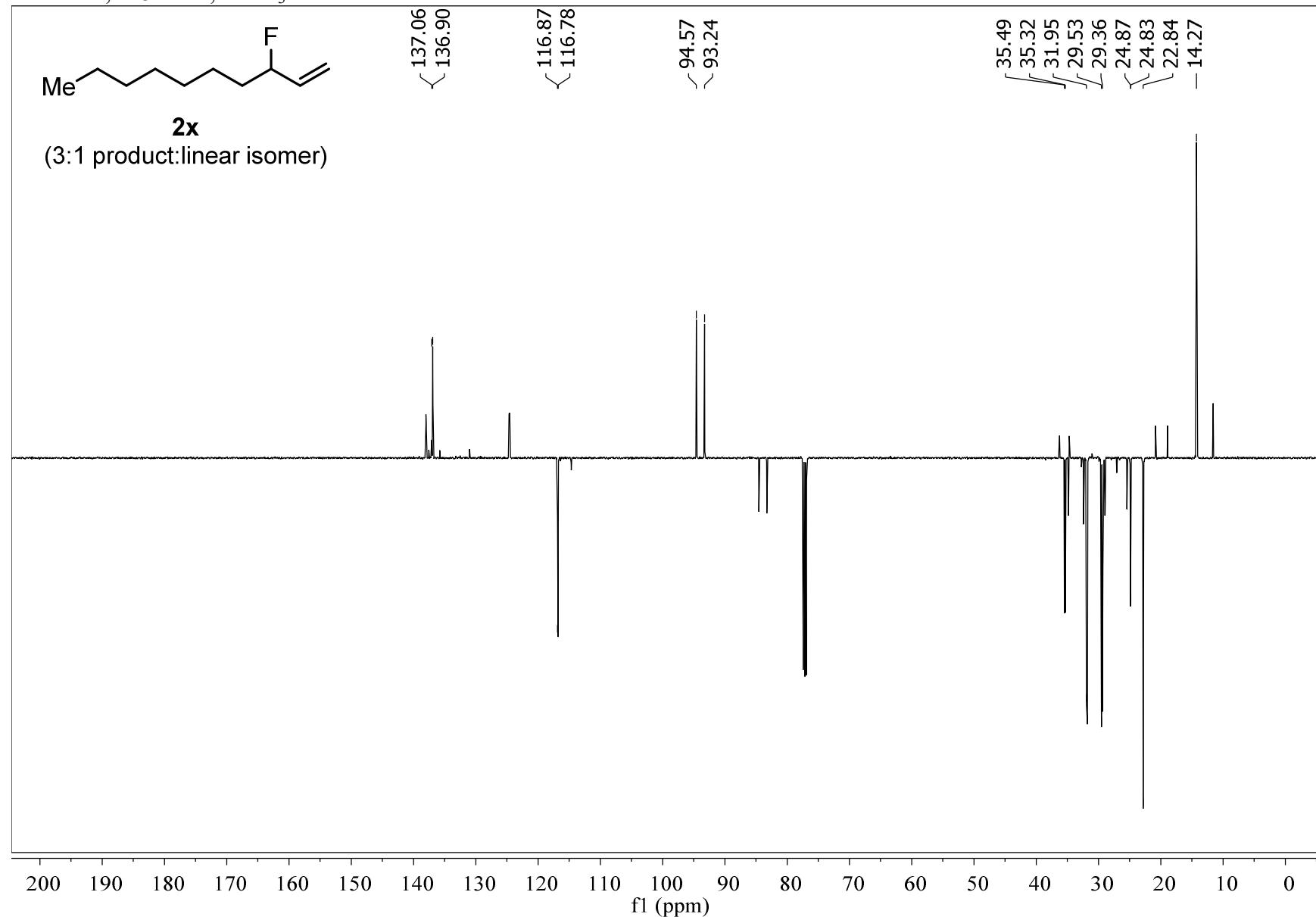


**2x**

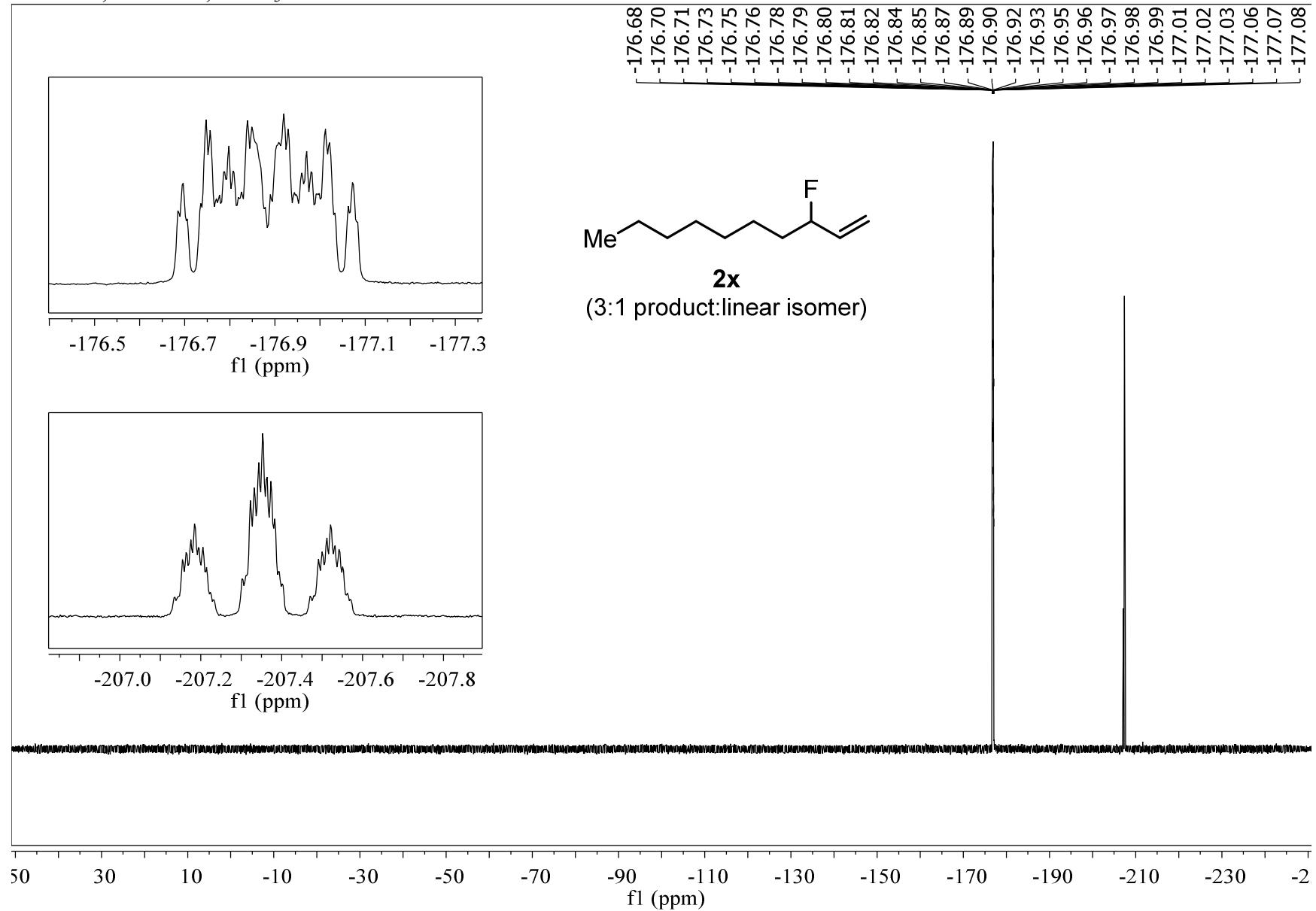
(3:1 product:linear isomer)



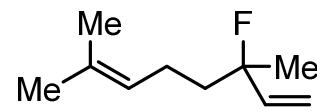
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>

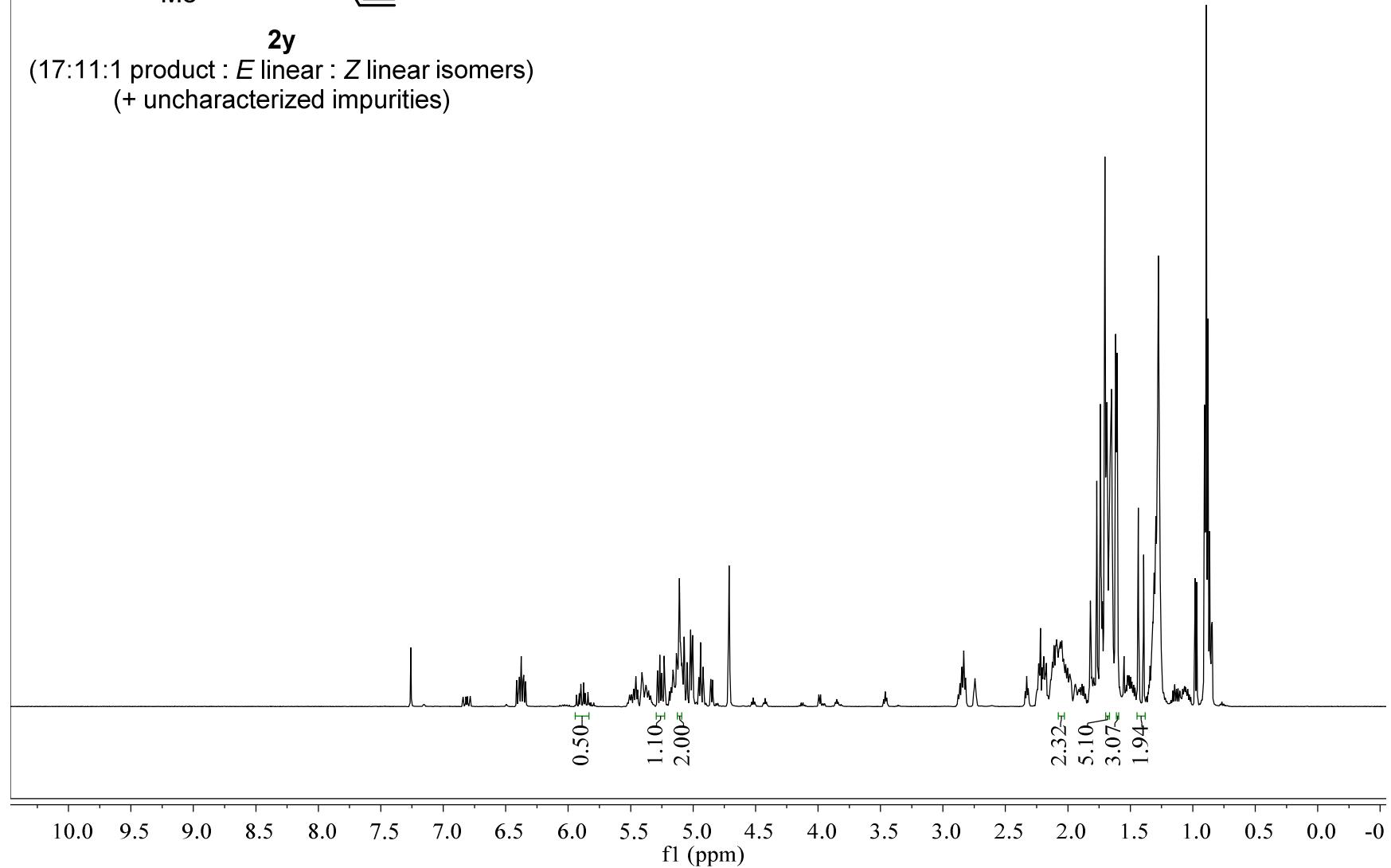


<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

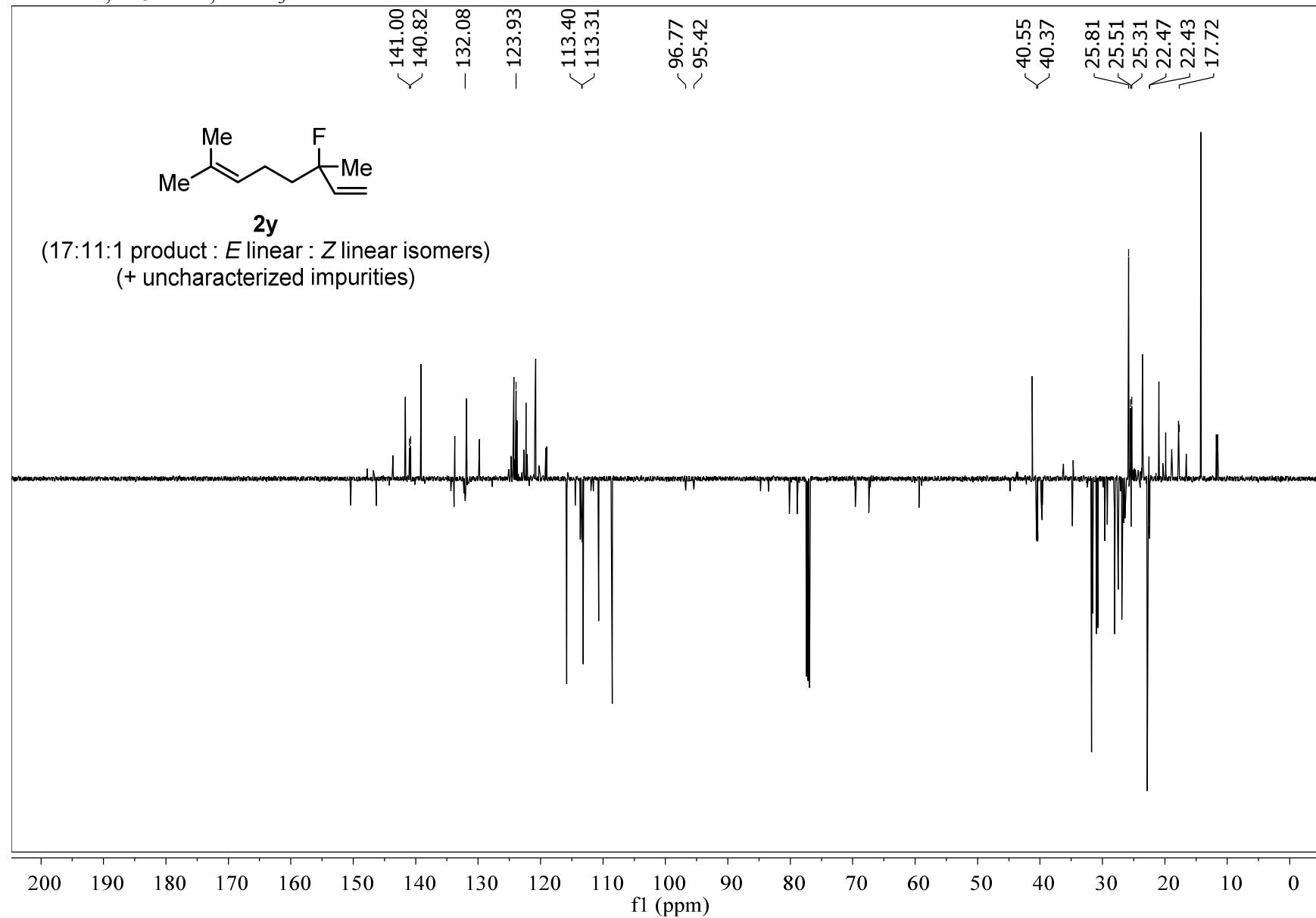


**2y**

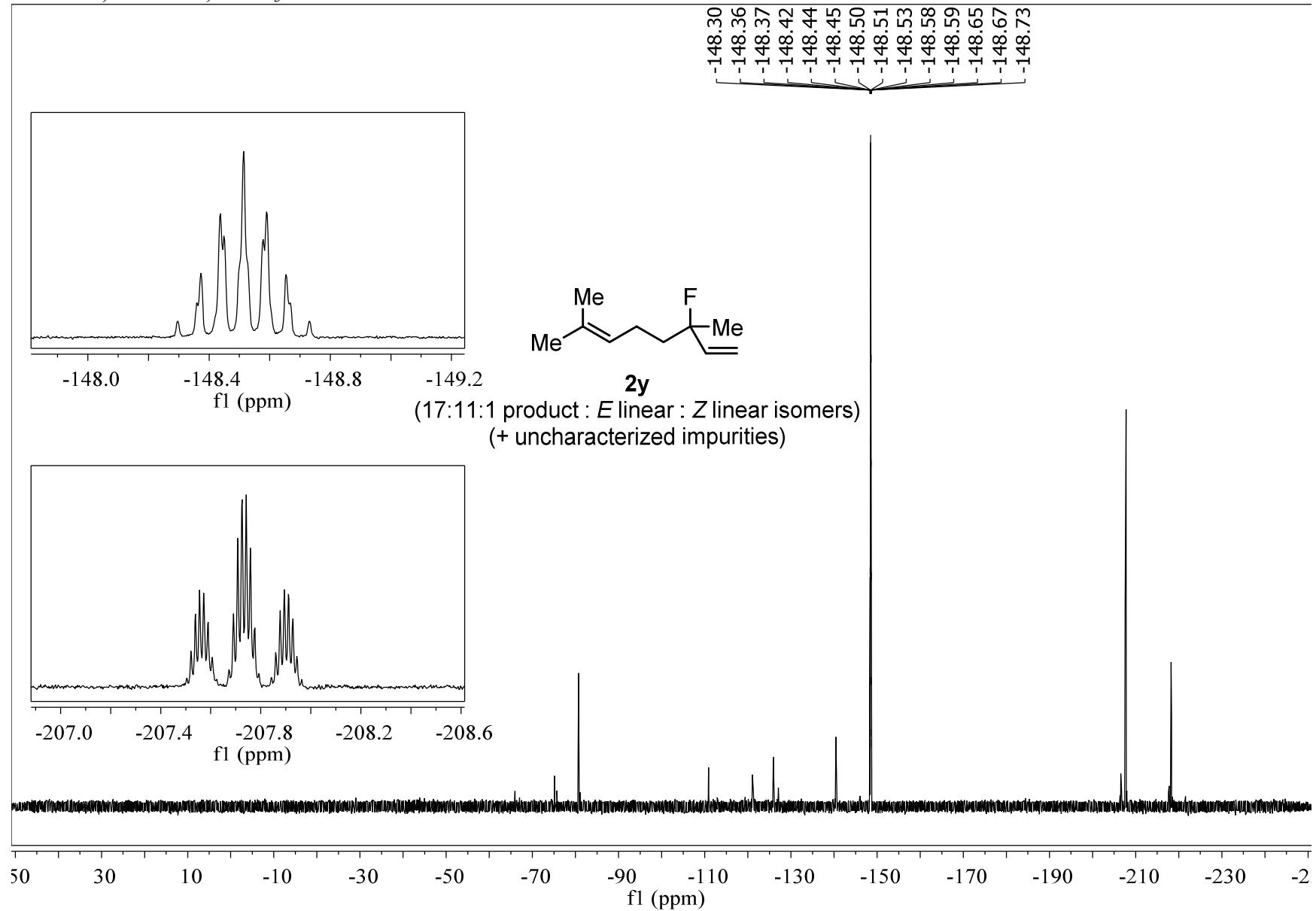
(17:11:1 product : *E* linear : *Z* linear isomers)  
(+ uncharacterized impurities)



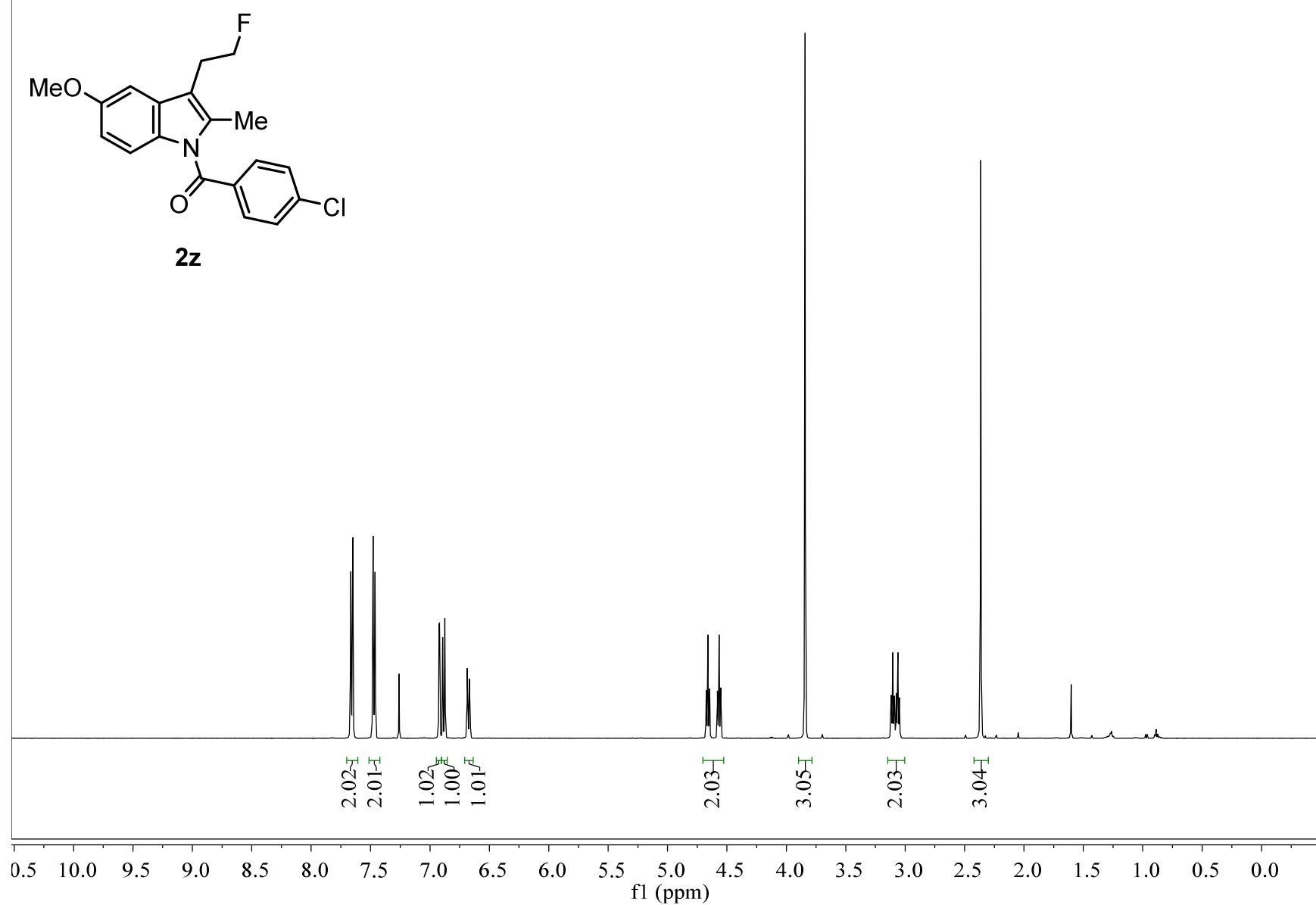
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



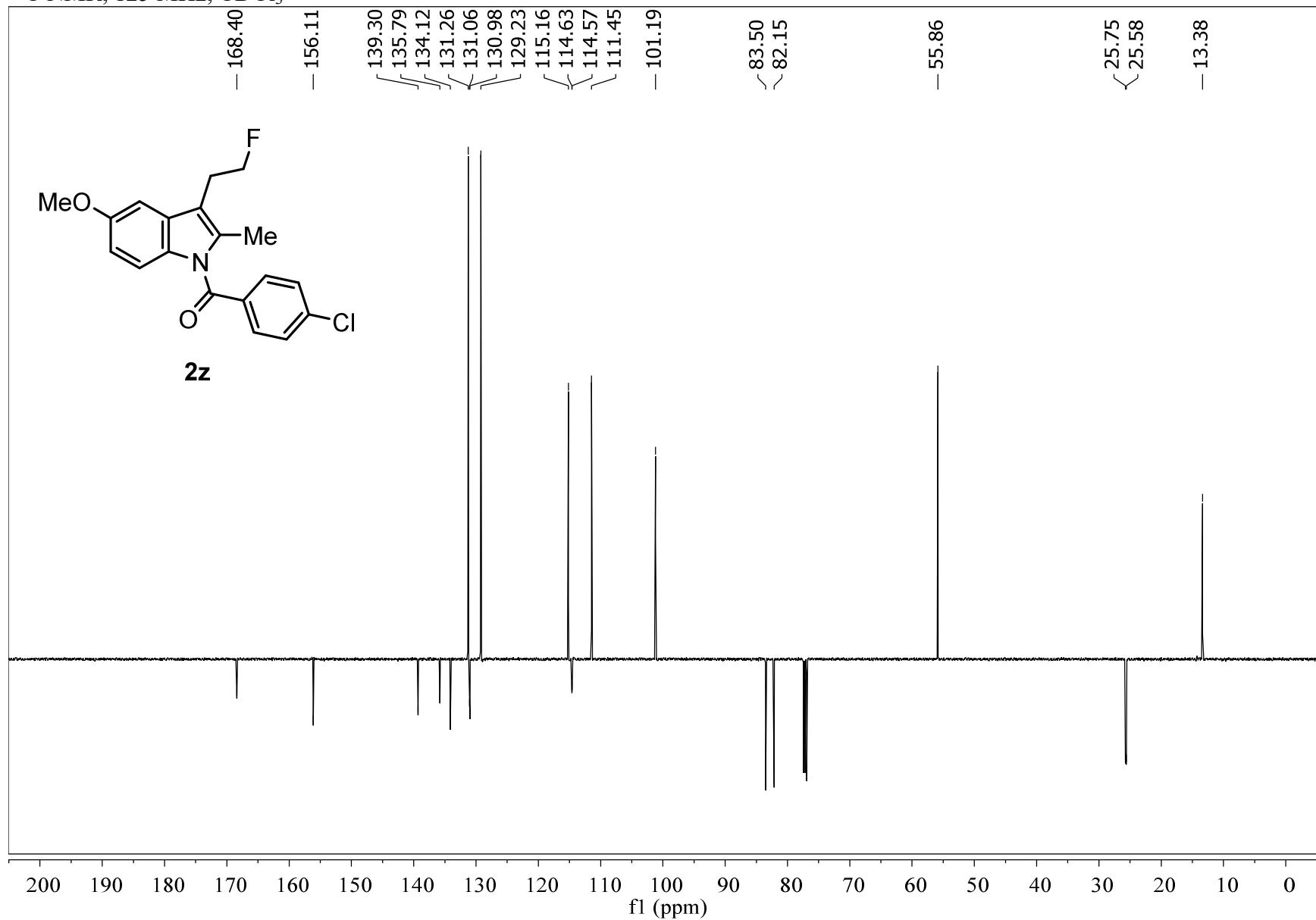
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



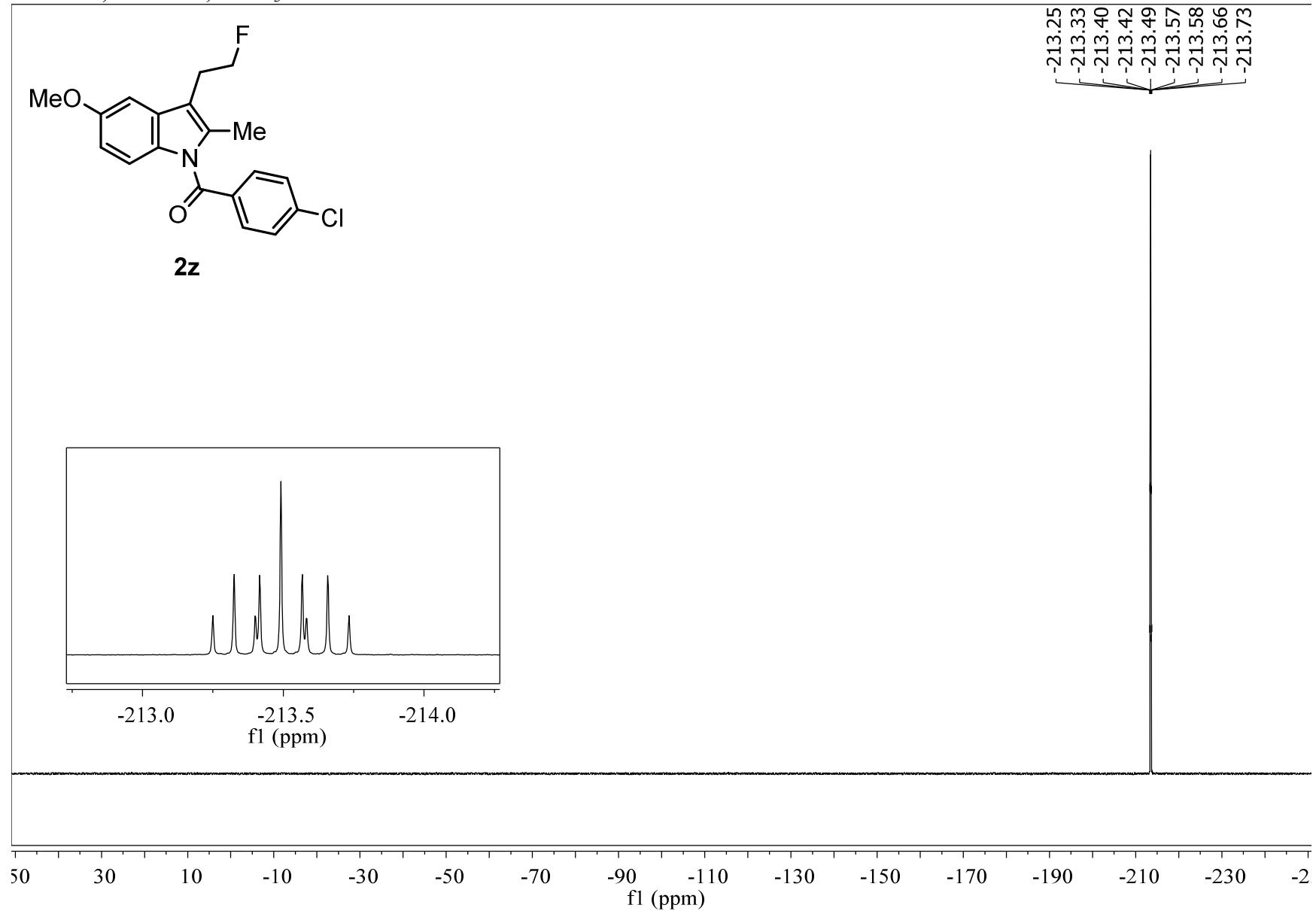
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



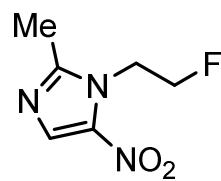
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>

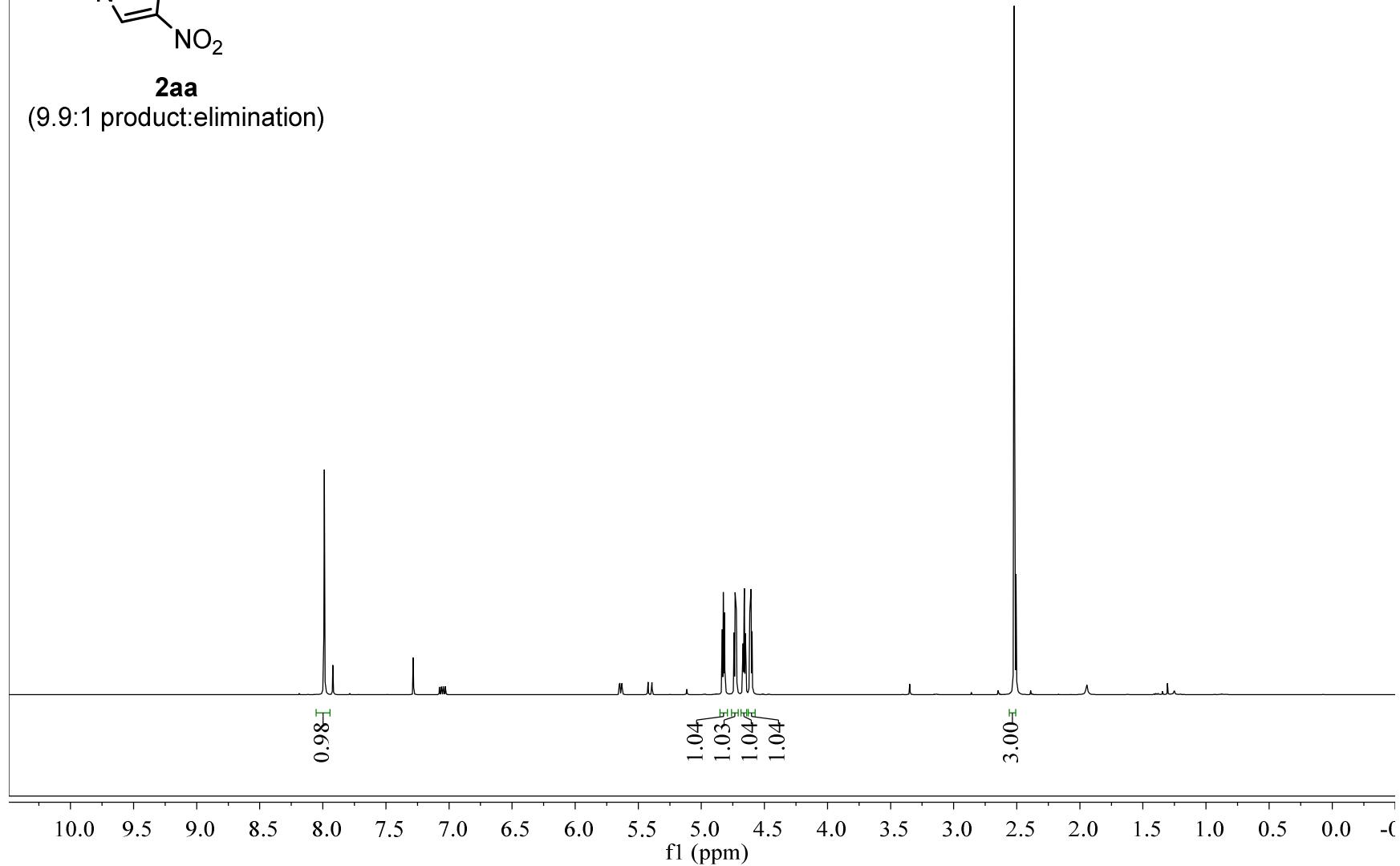


<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

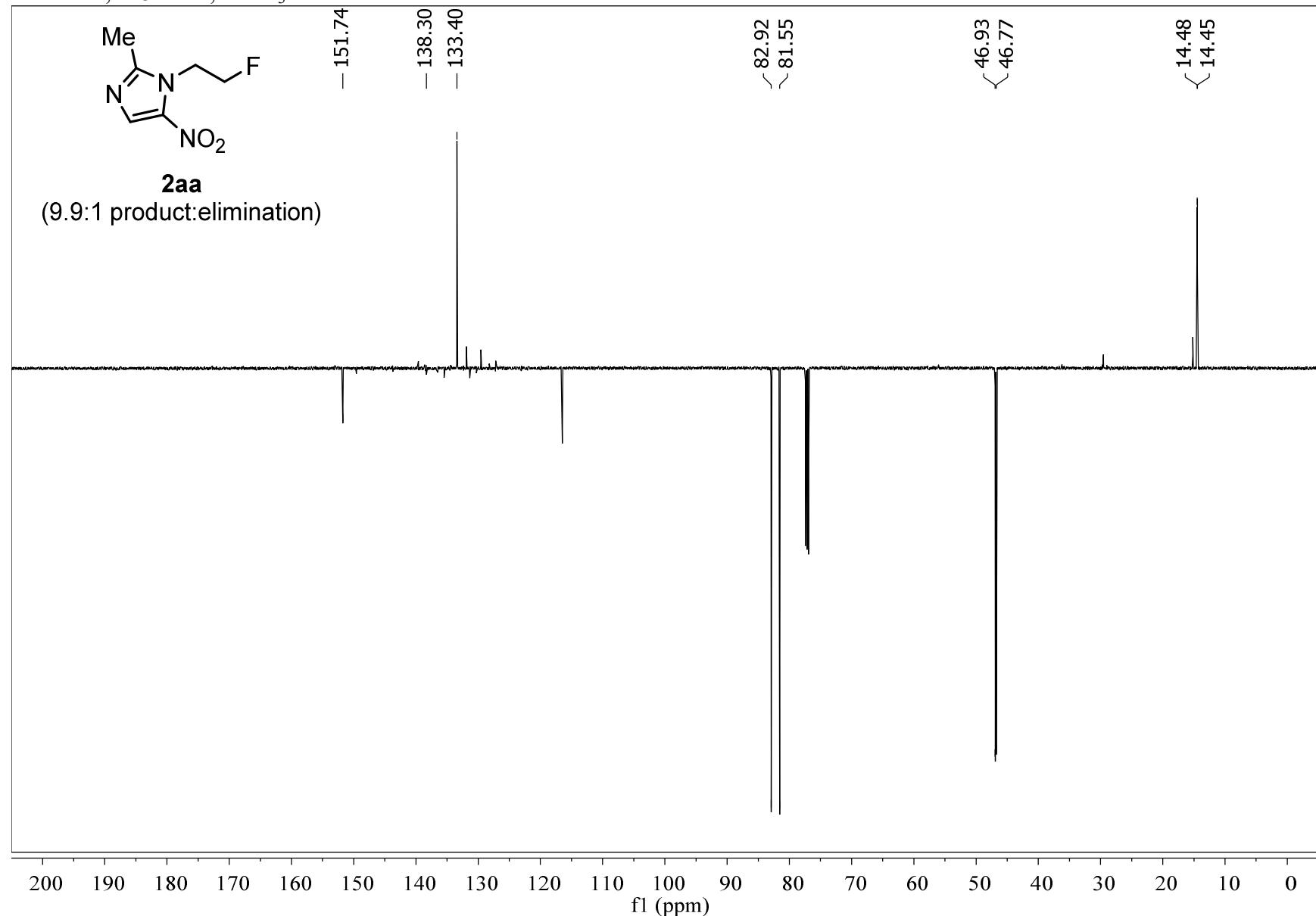


**2aa**

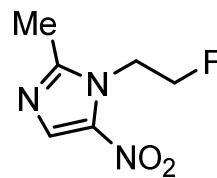
(9.9:1 product:elimination)



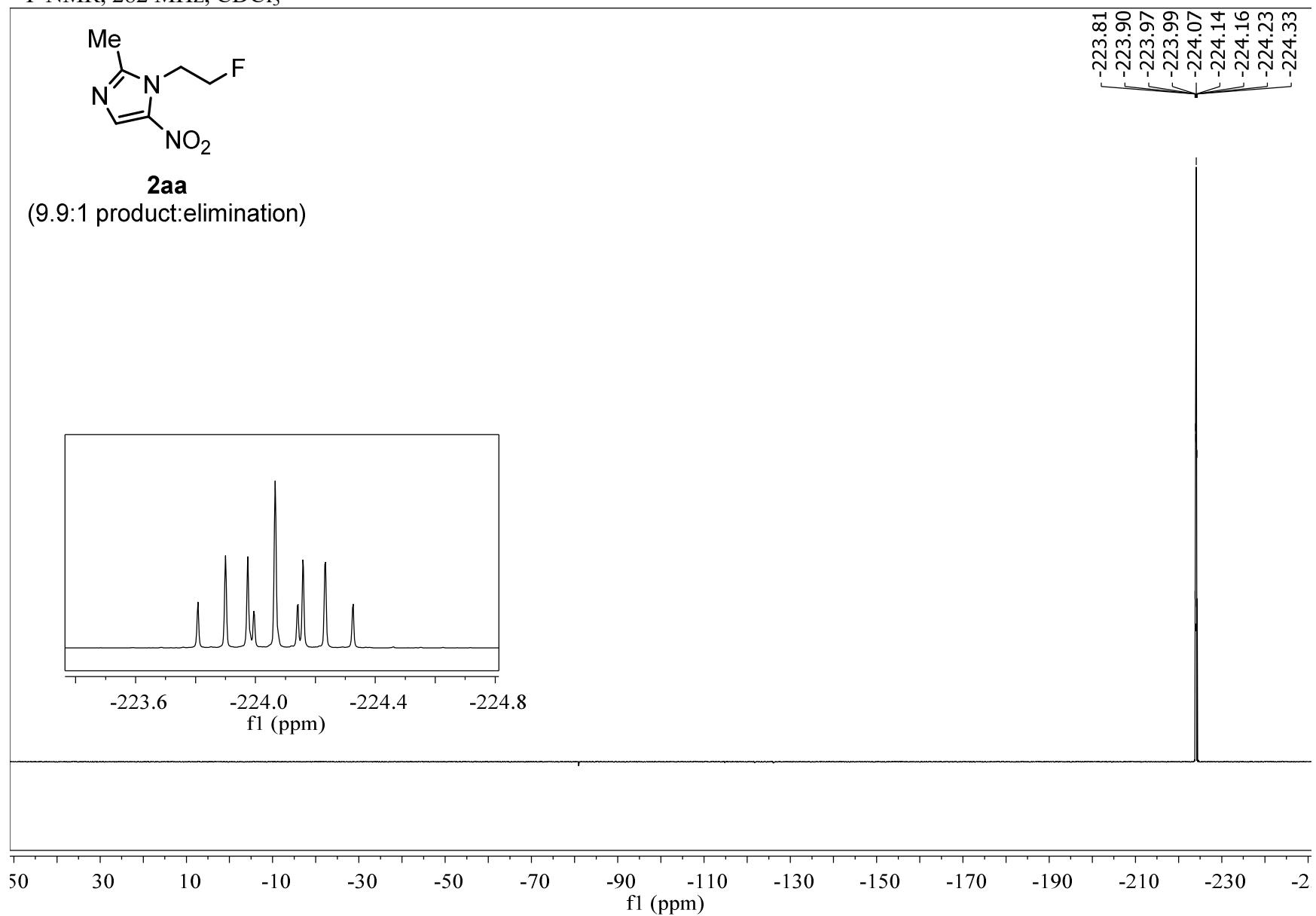
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



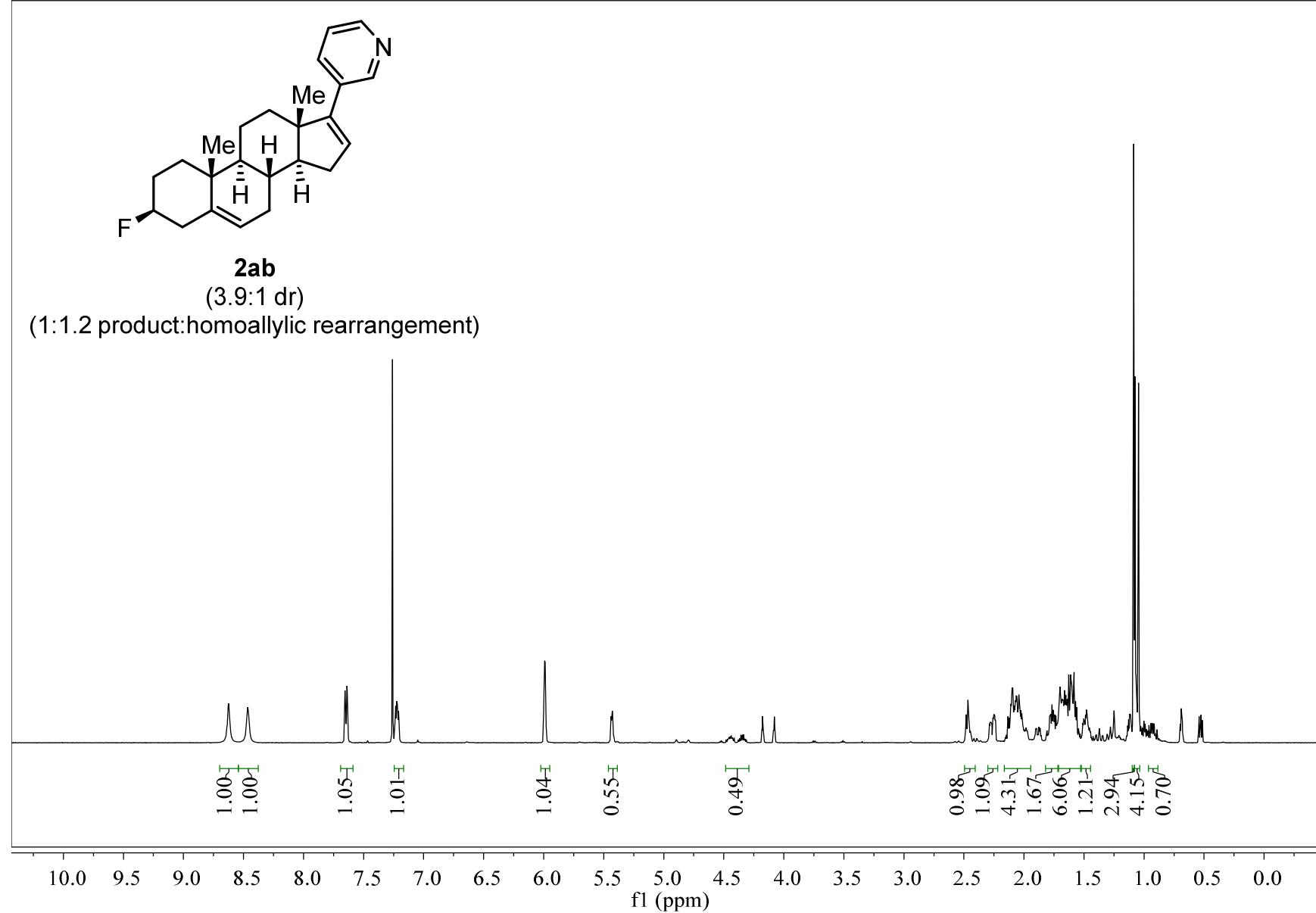
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



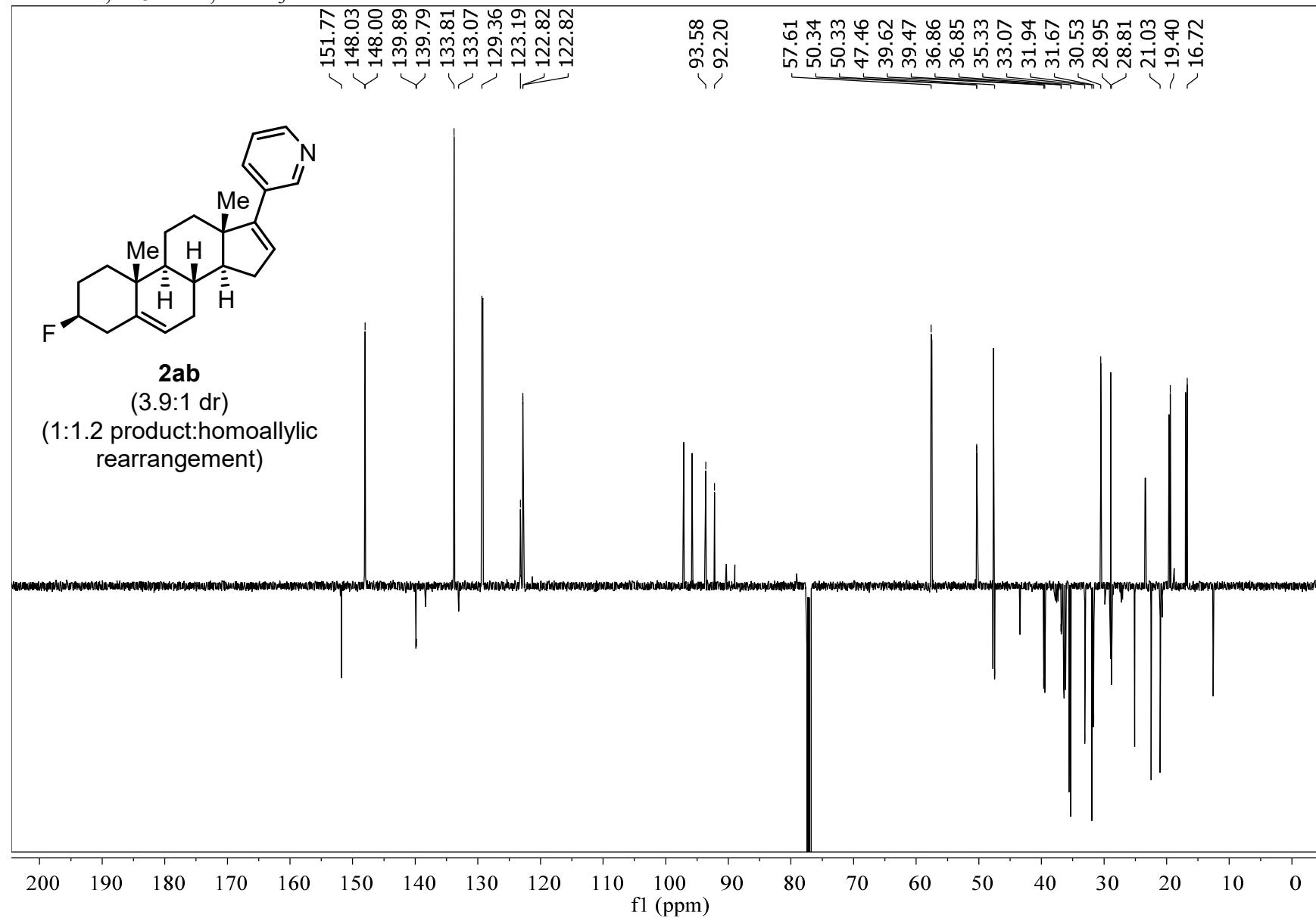
**2aa**  
(9.9:1 product:elimination)



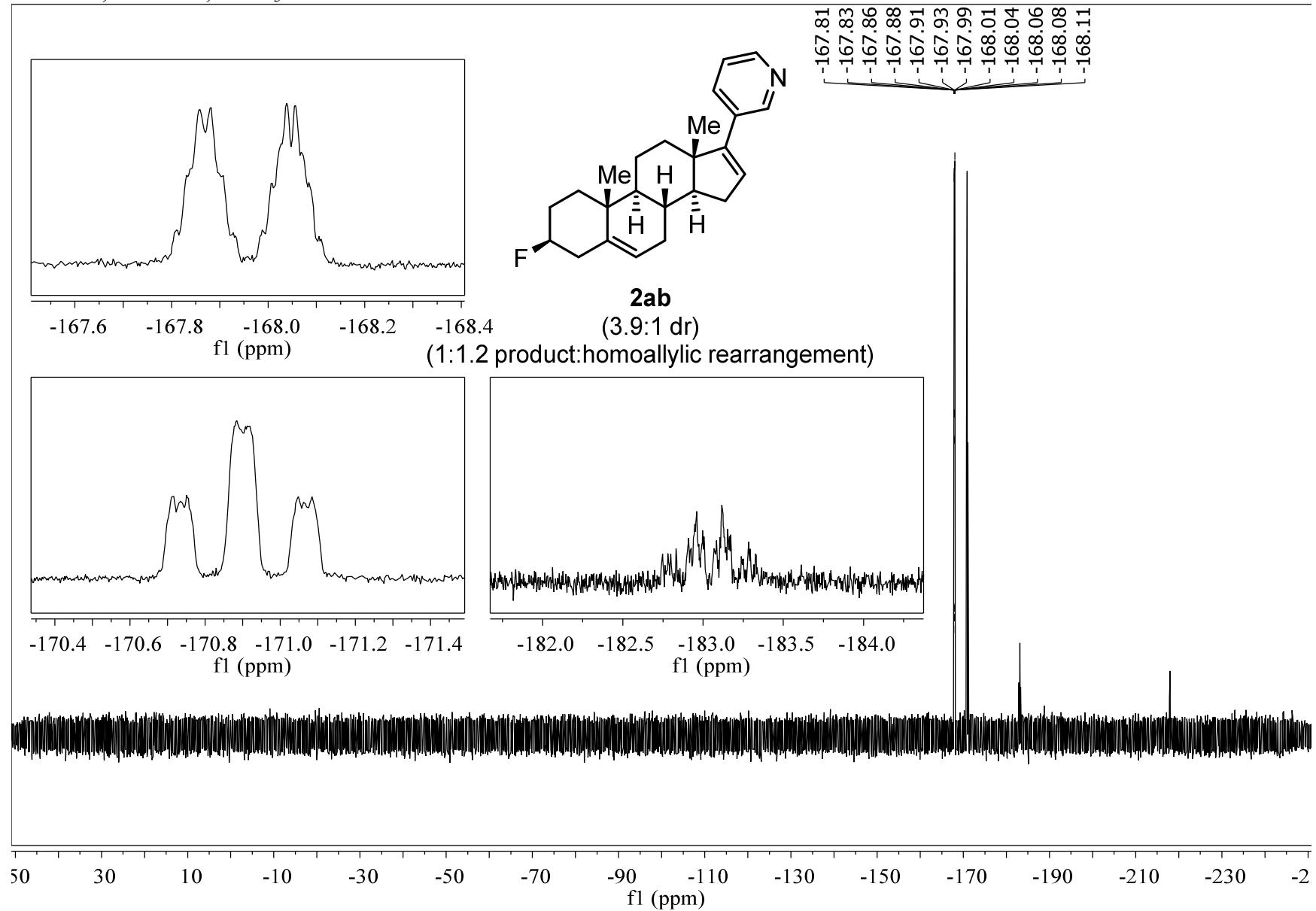
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



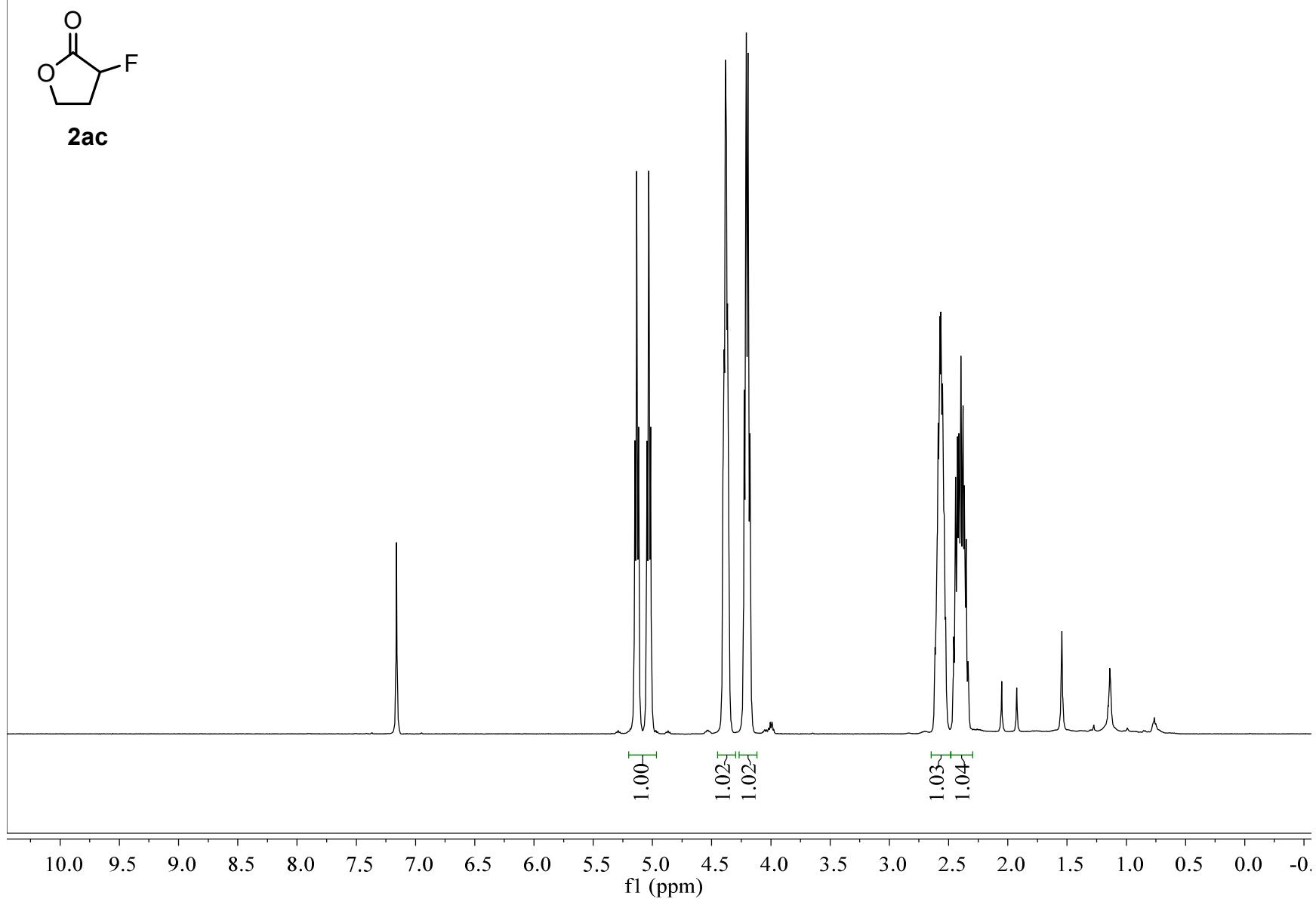
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



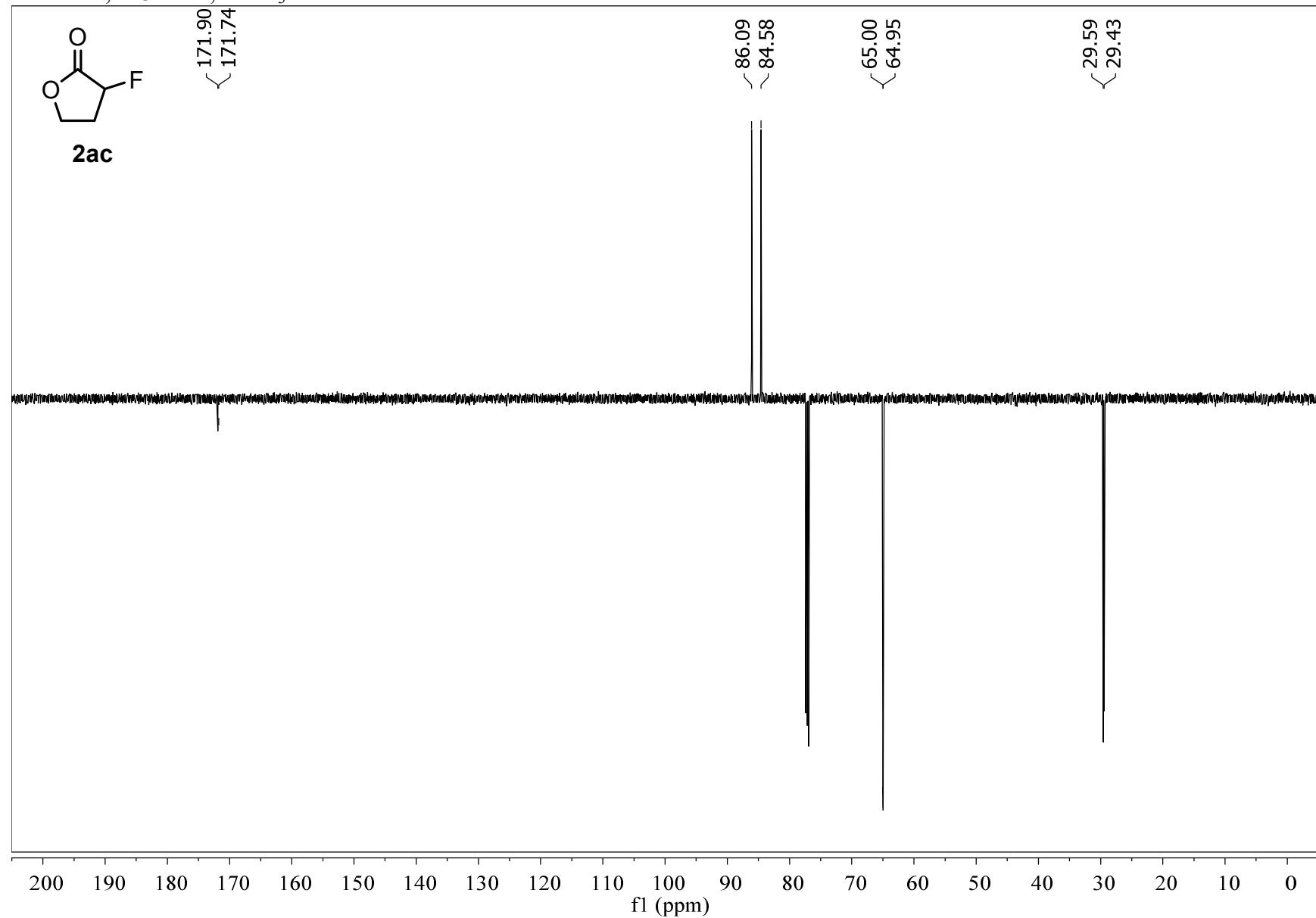
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



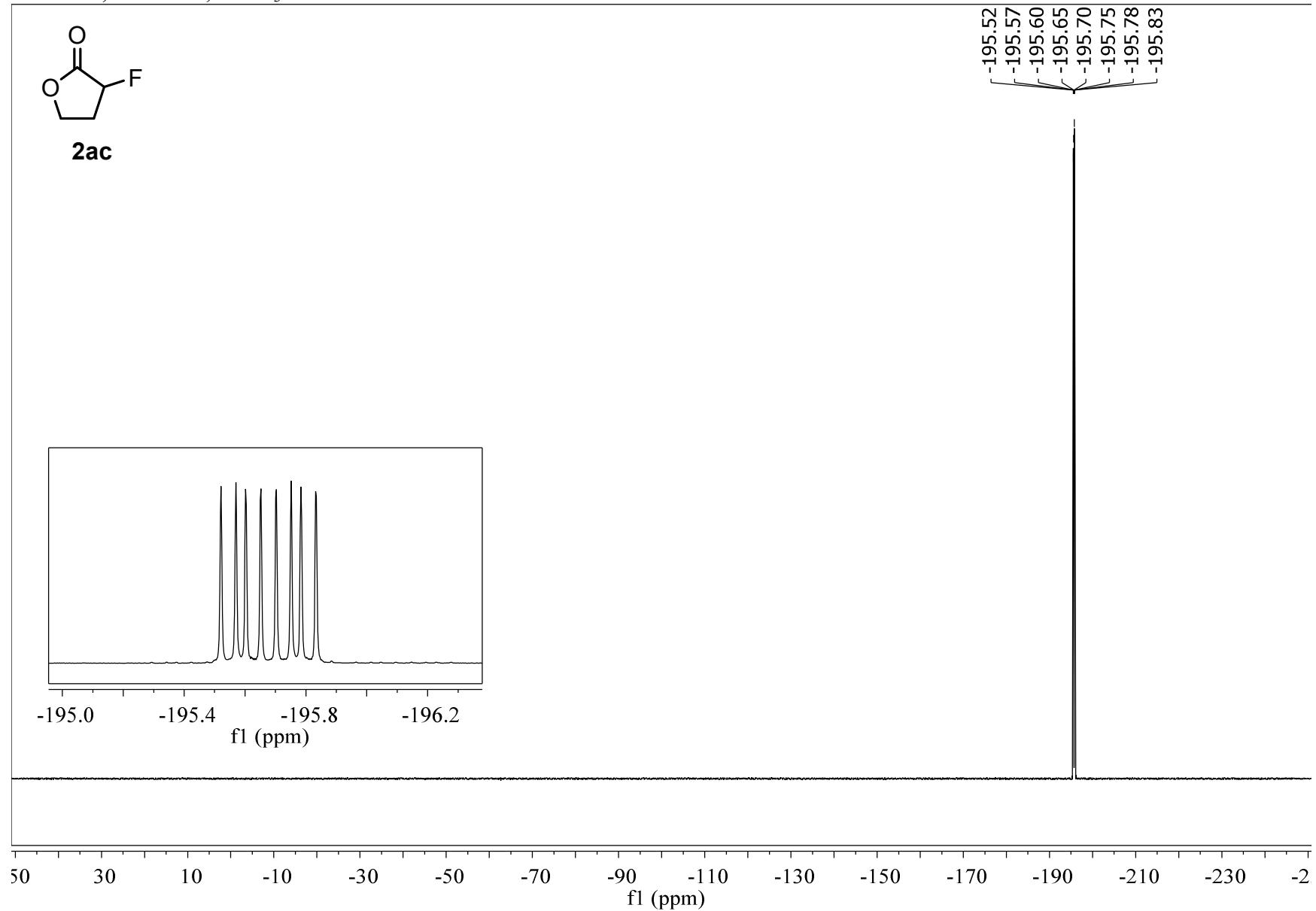
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



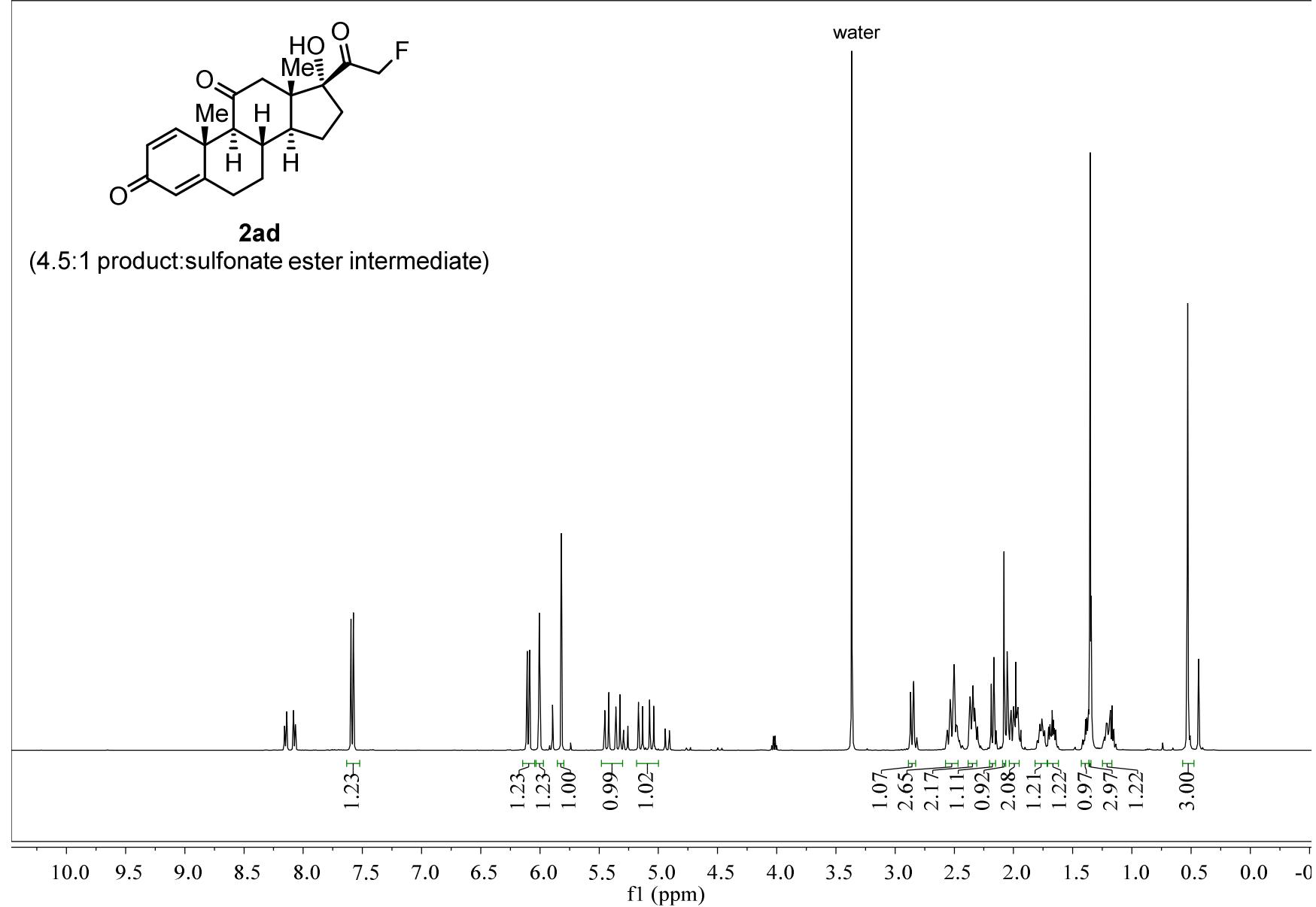
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



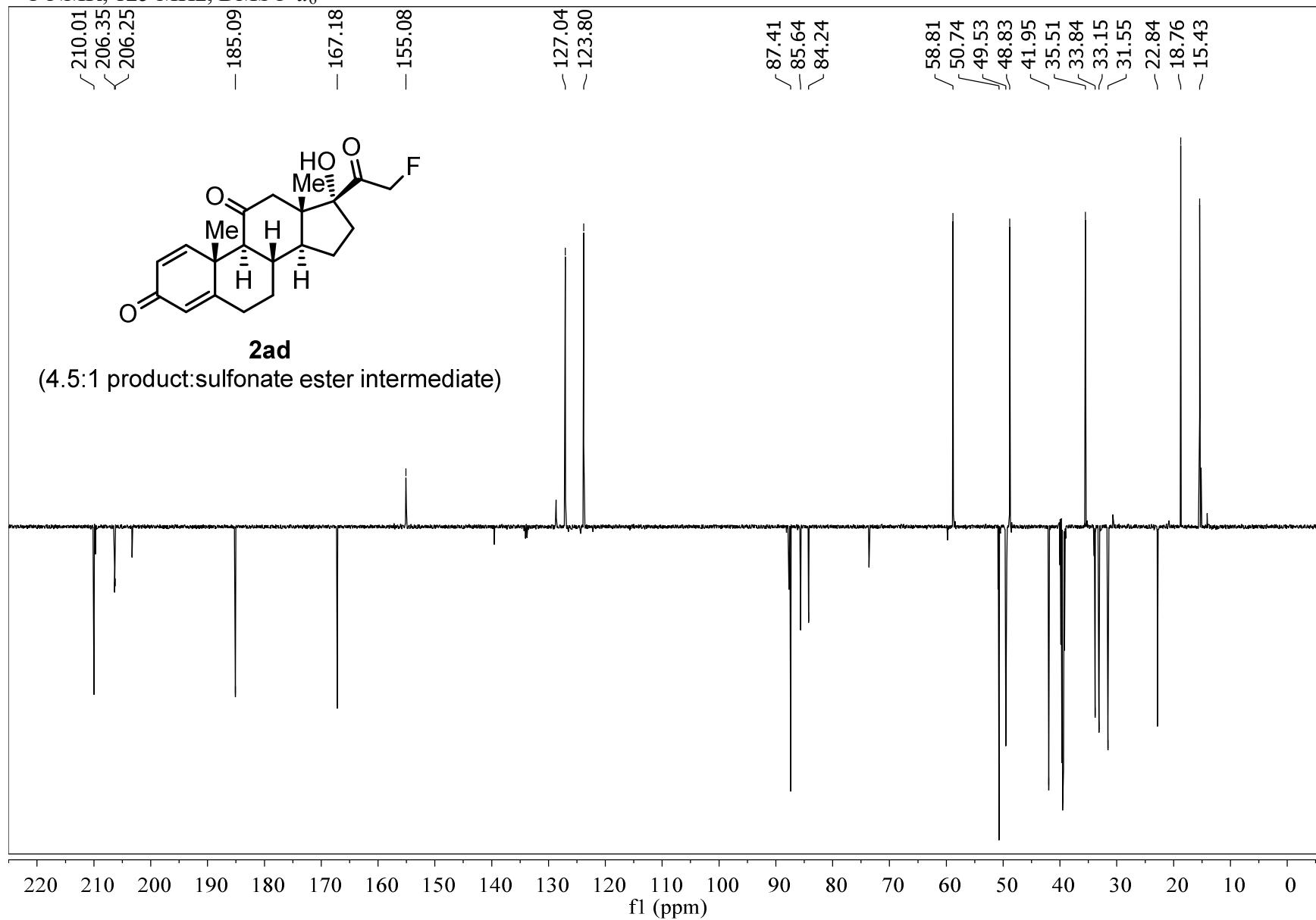
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



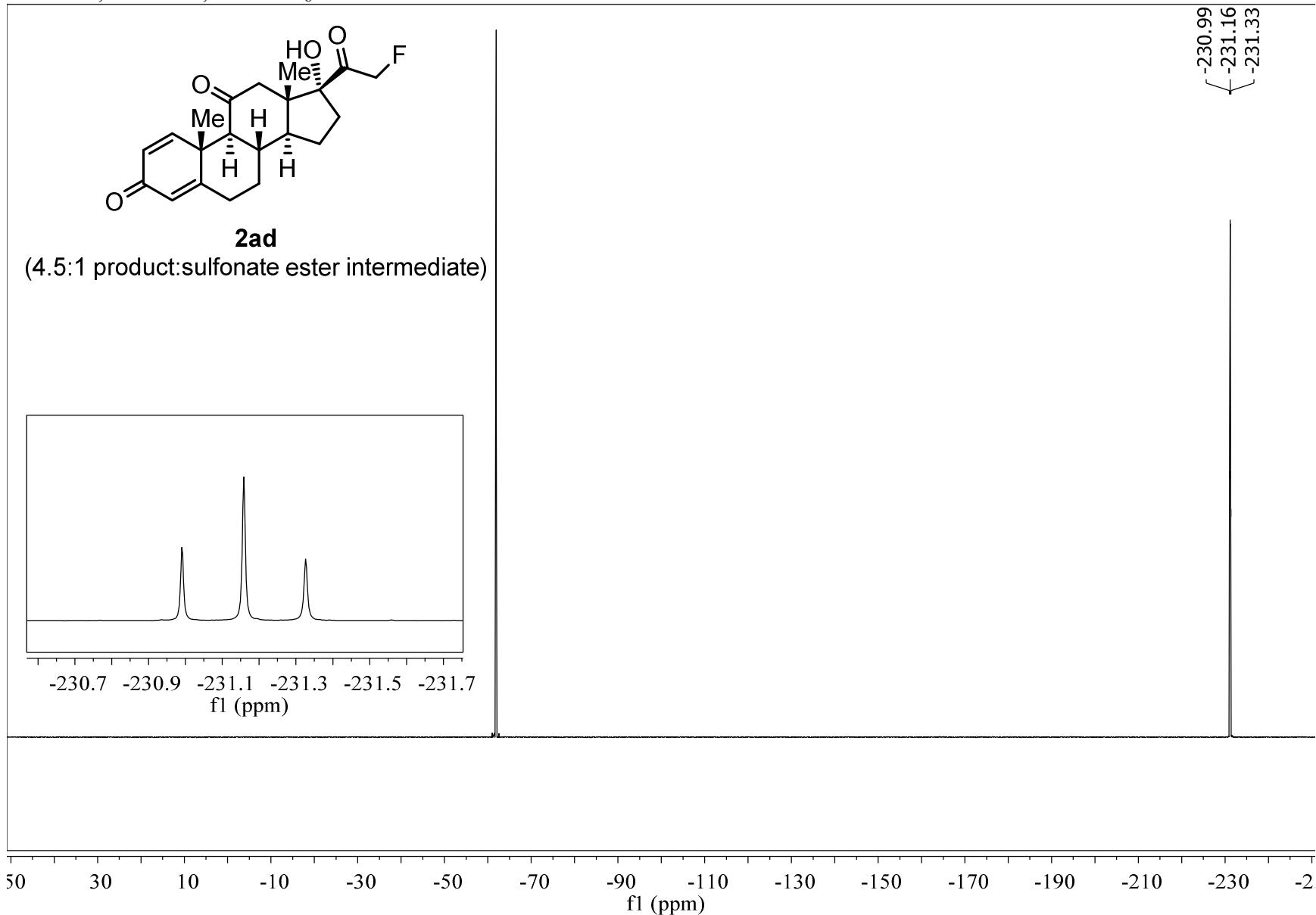
<sup>1</sup>H NMR, 500 MHz, DMSO-*d*<sub>6</sub>



<sup>13</sup>C NMR, 125 MHz, DMSO-*d*<sub>6</sub>



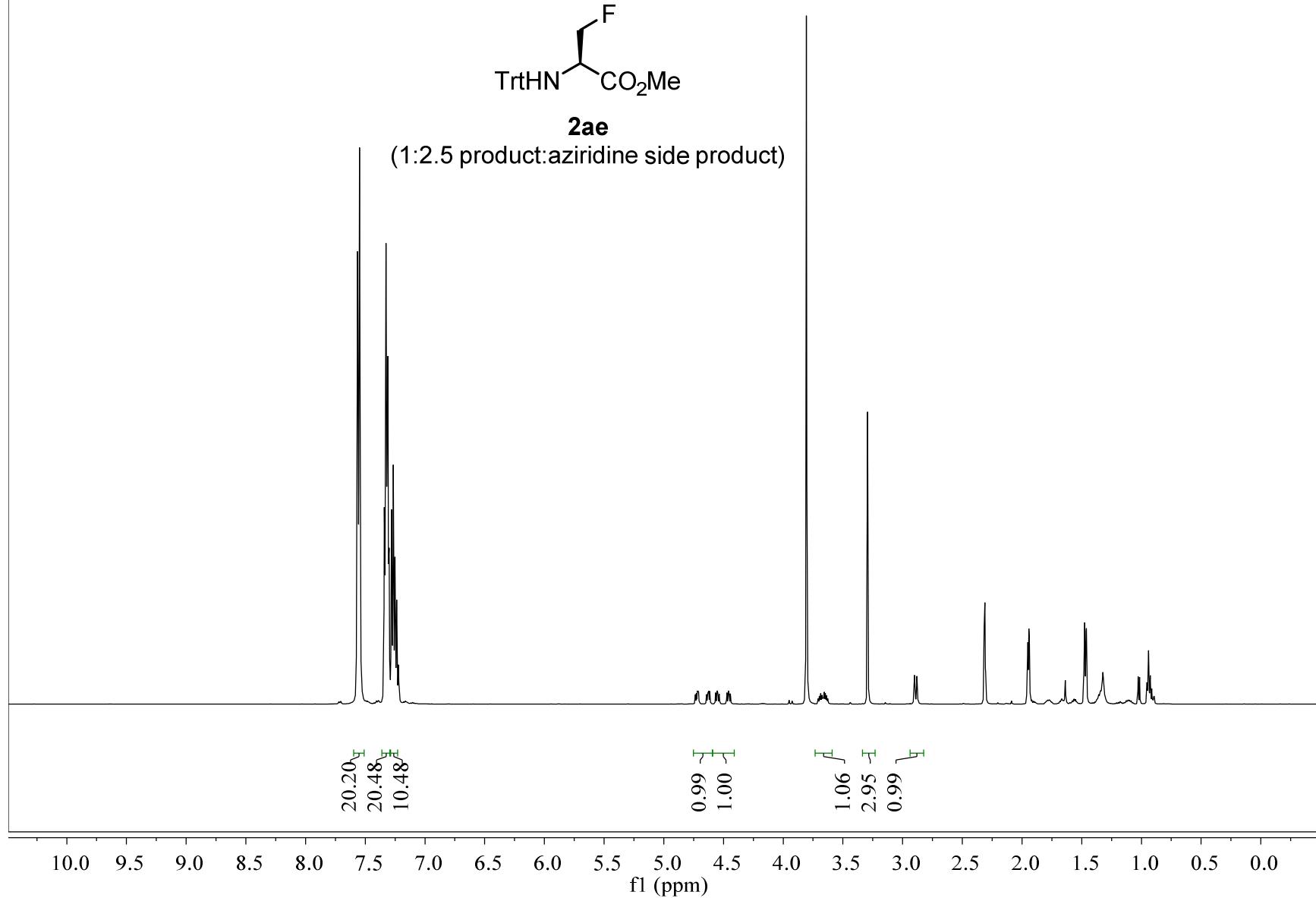
<sup>19</sup>F NMR, 282 MHz, DMSO-*d*<sub>6</sub>



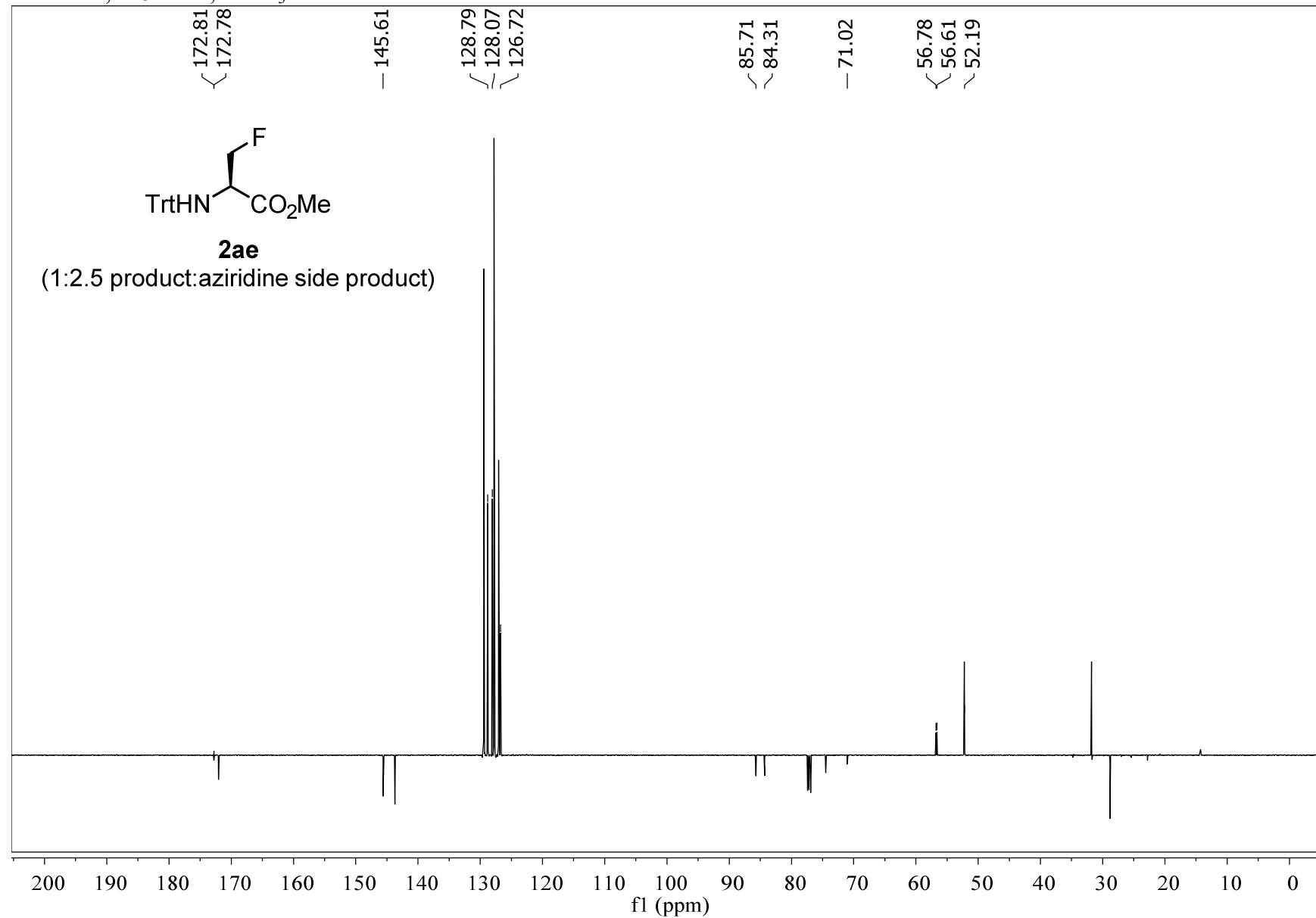
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



2ae  
(1:2.5 product:aziridine side product)



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

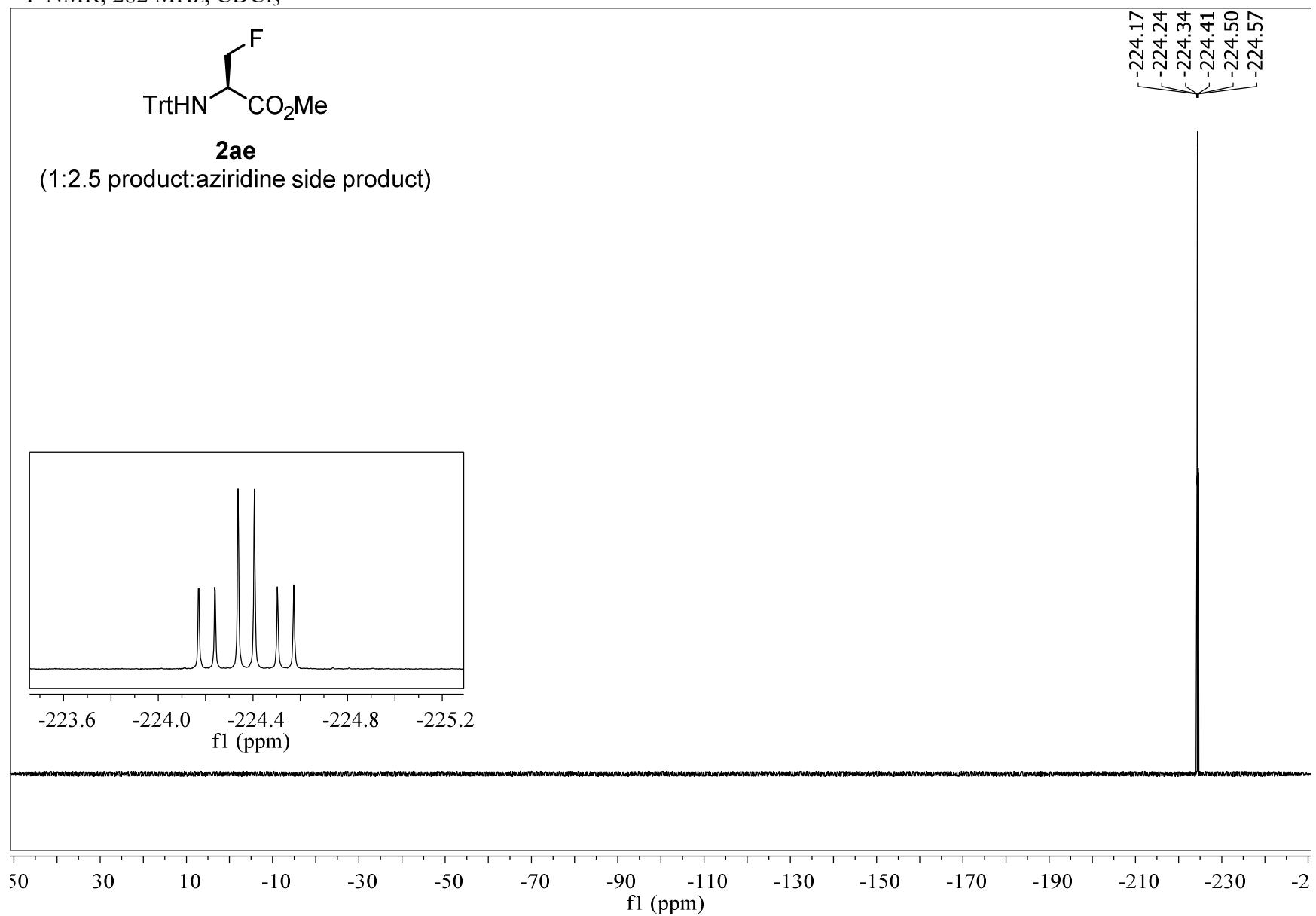


<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>

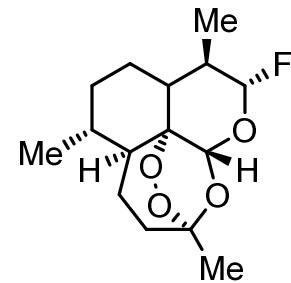


**2ae**

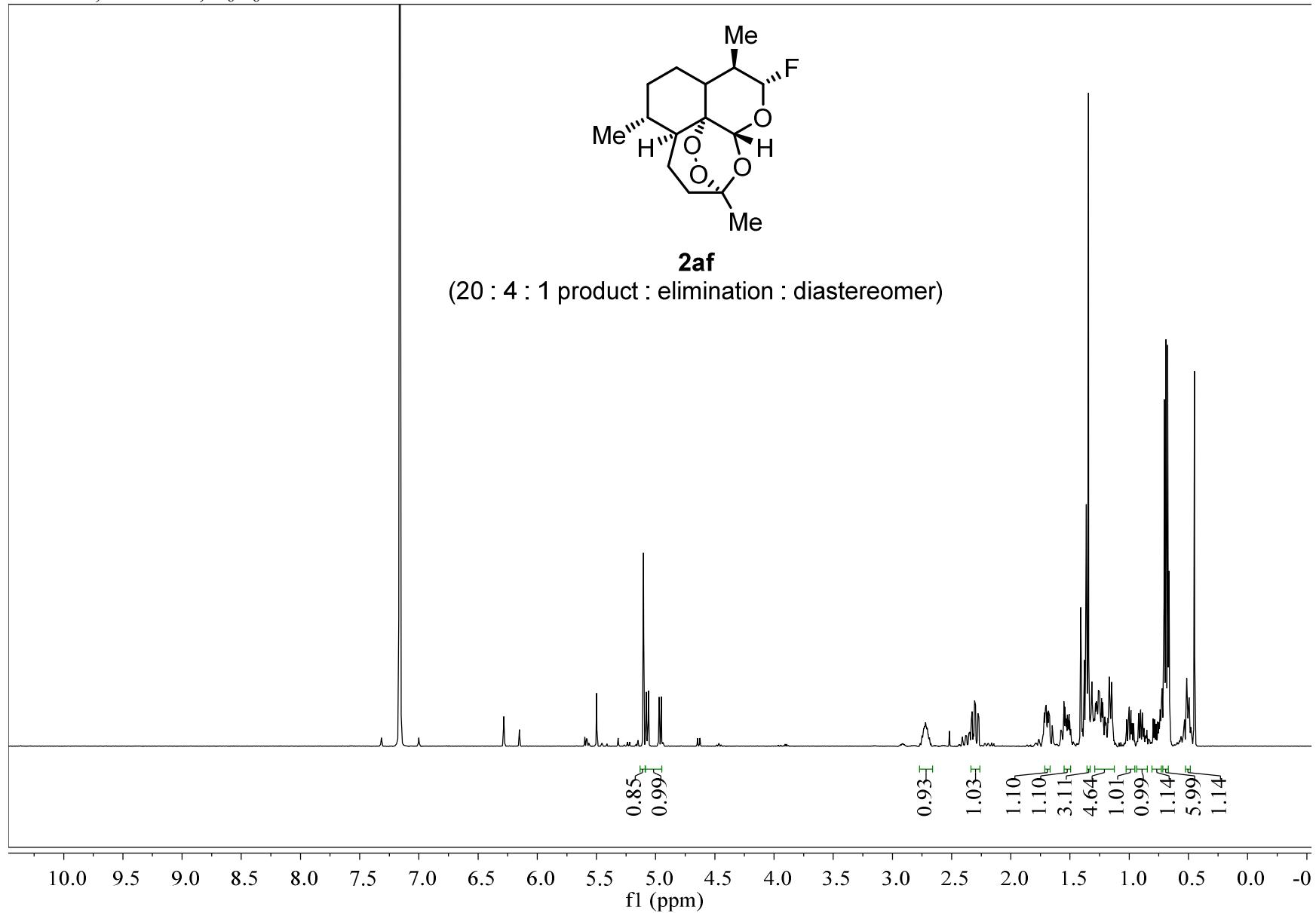
(1:2.5 product:aziridine side product)



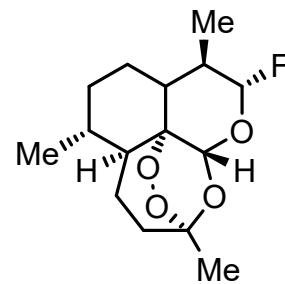
<sup>1</sup>H NMR, 500 MHz, C<sub>6</sub>D<sub>6</sub>



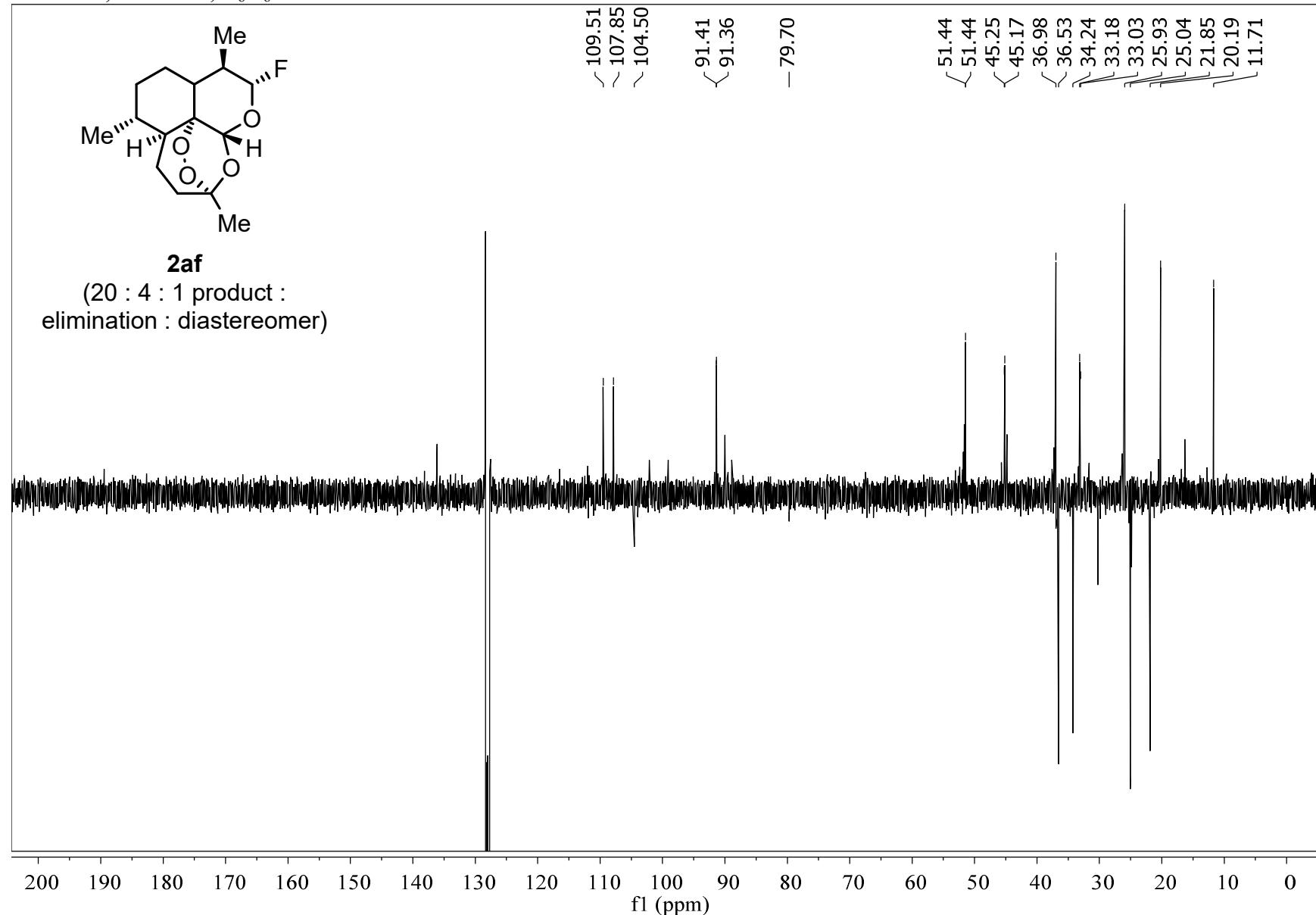
**2af**  
(20 : 4 : 1 product : elimination : diastereomer)



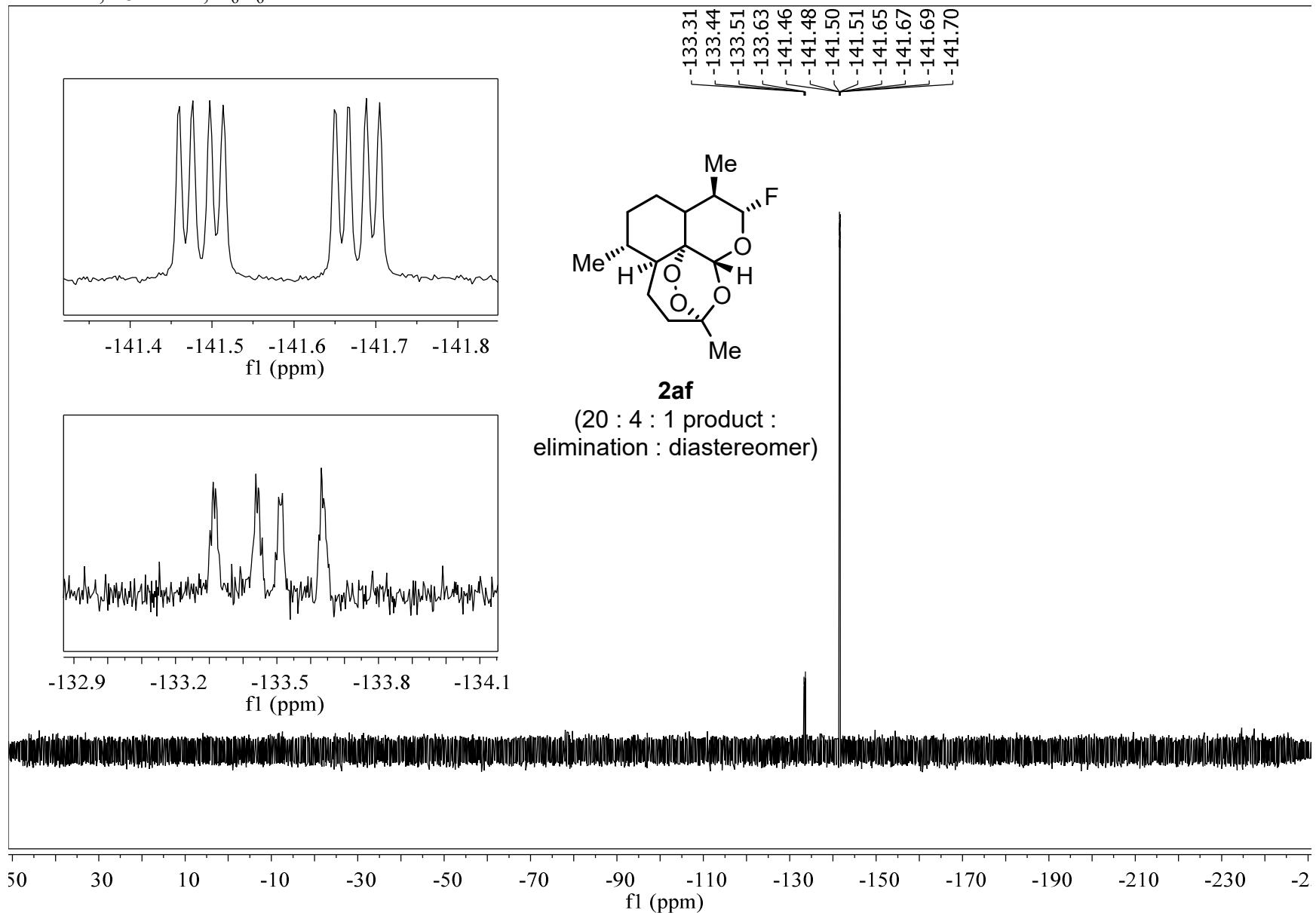
<sup>13</sup>C NMR, 125 MHz, C<sub>6</sub>D<sub>6</sub>



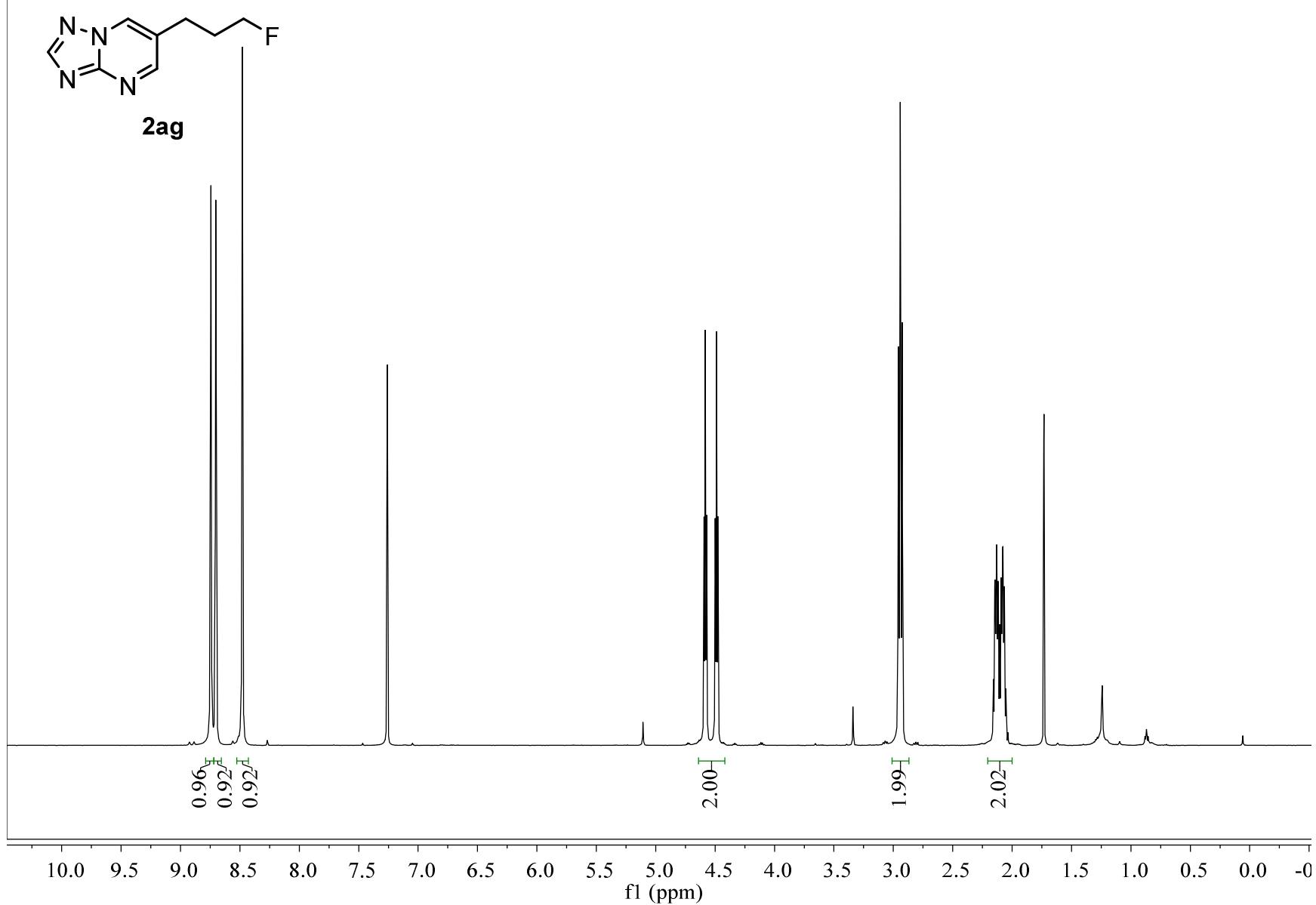
**2af**  
(20 : 4 : 1 product :  
elimination : diastereomer)



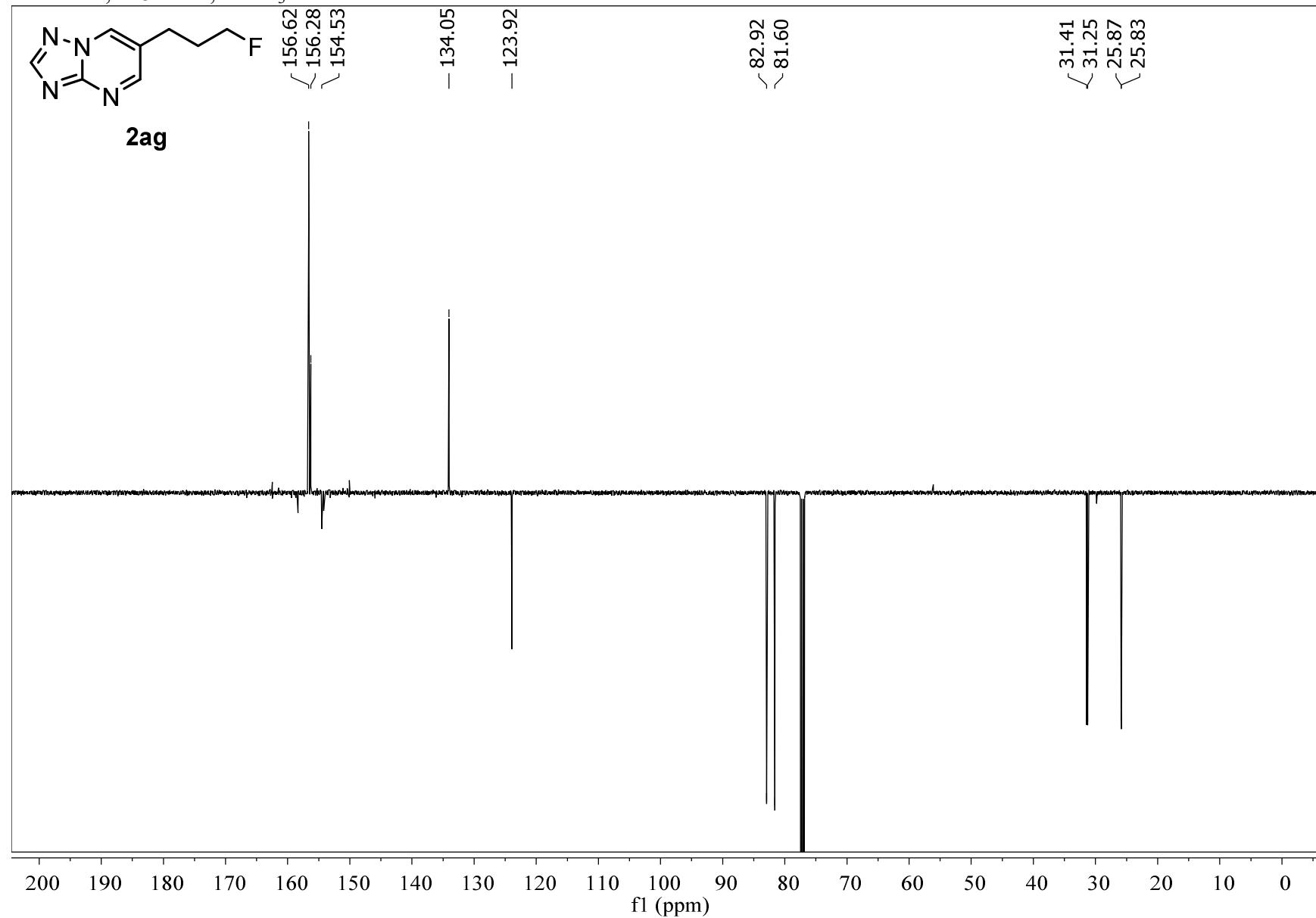
<sup>19</sup>F NMR, 282 MHz, C<sub>6</sub>D<sub>6</sub>



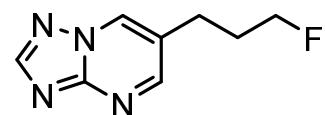
$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

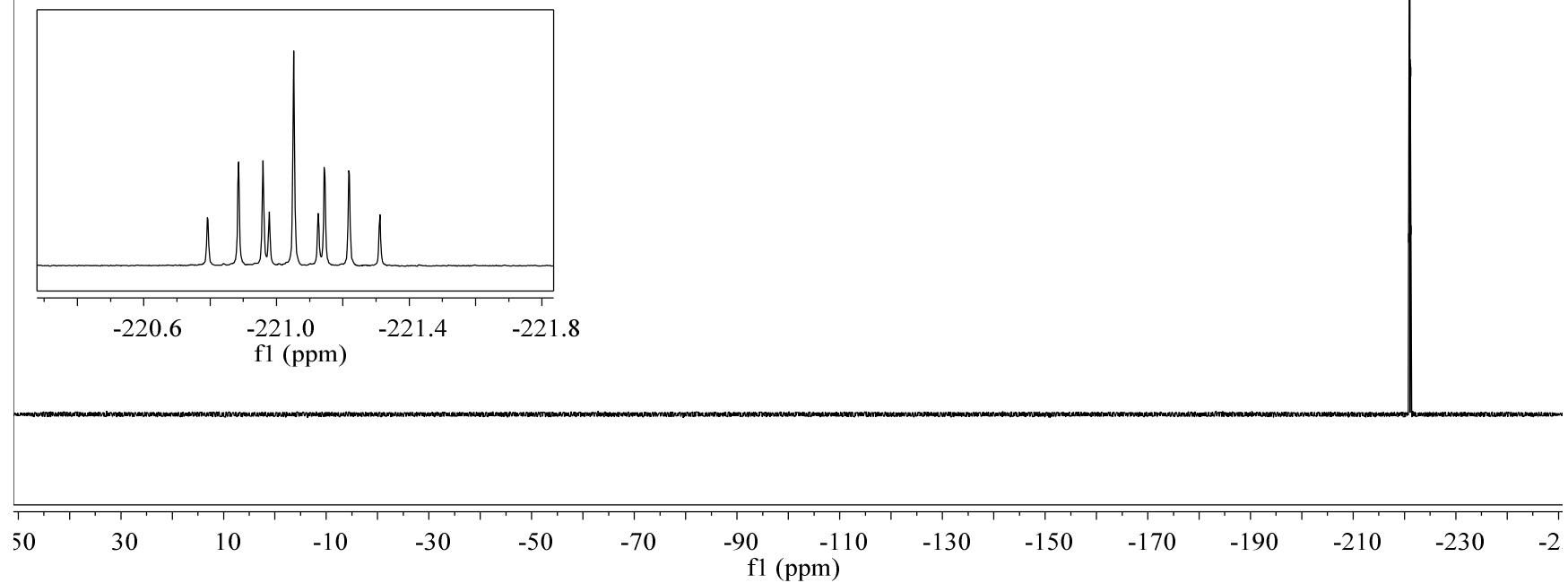


<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>

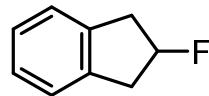


2ag

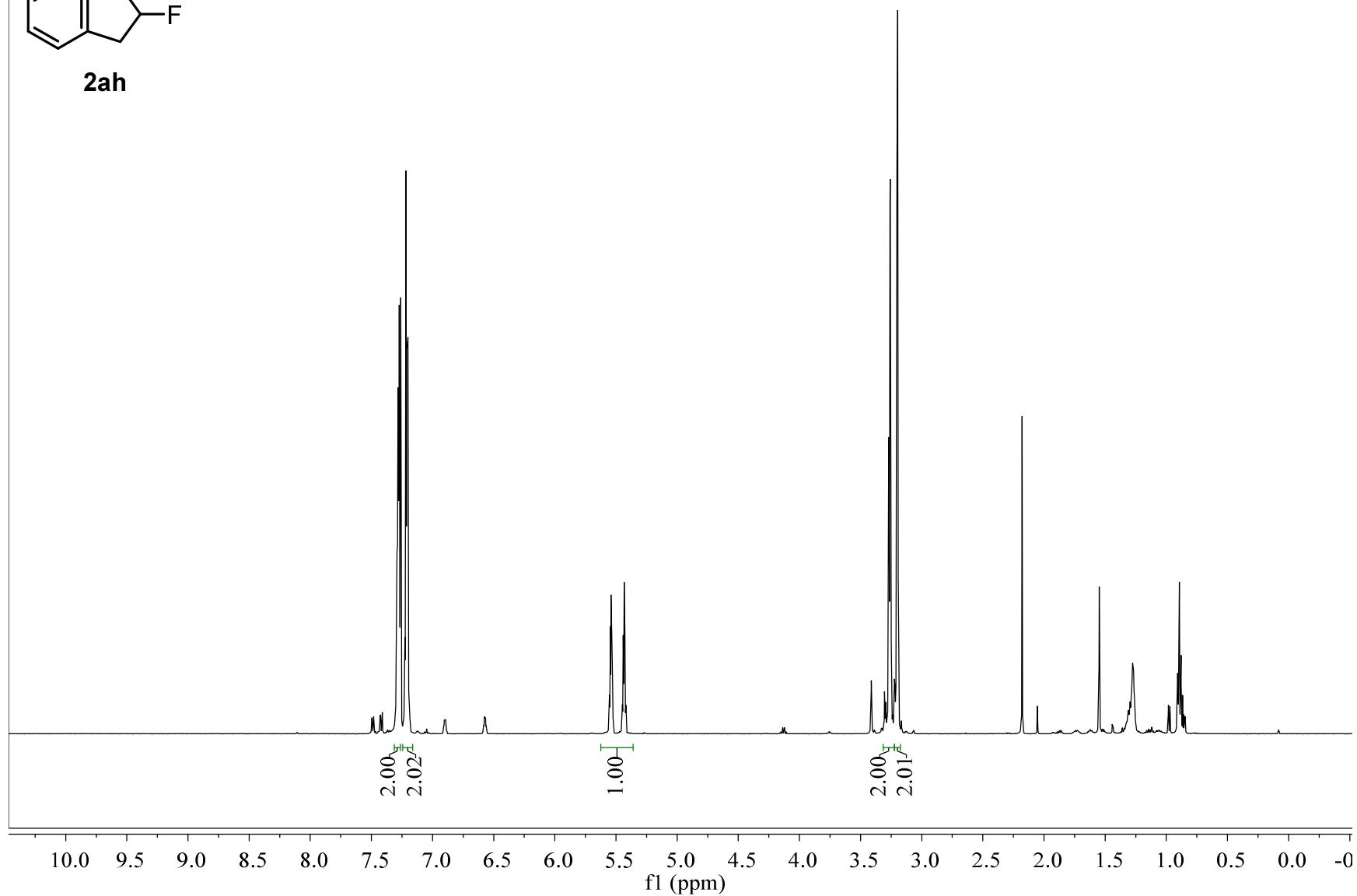
-220.79  
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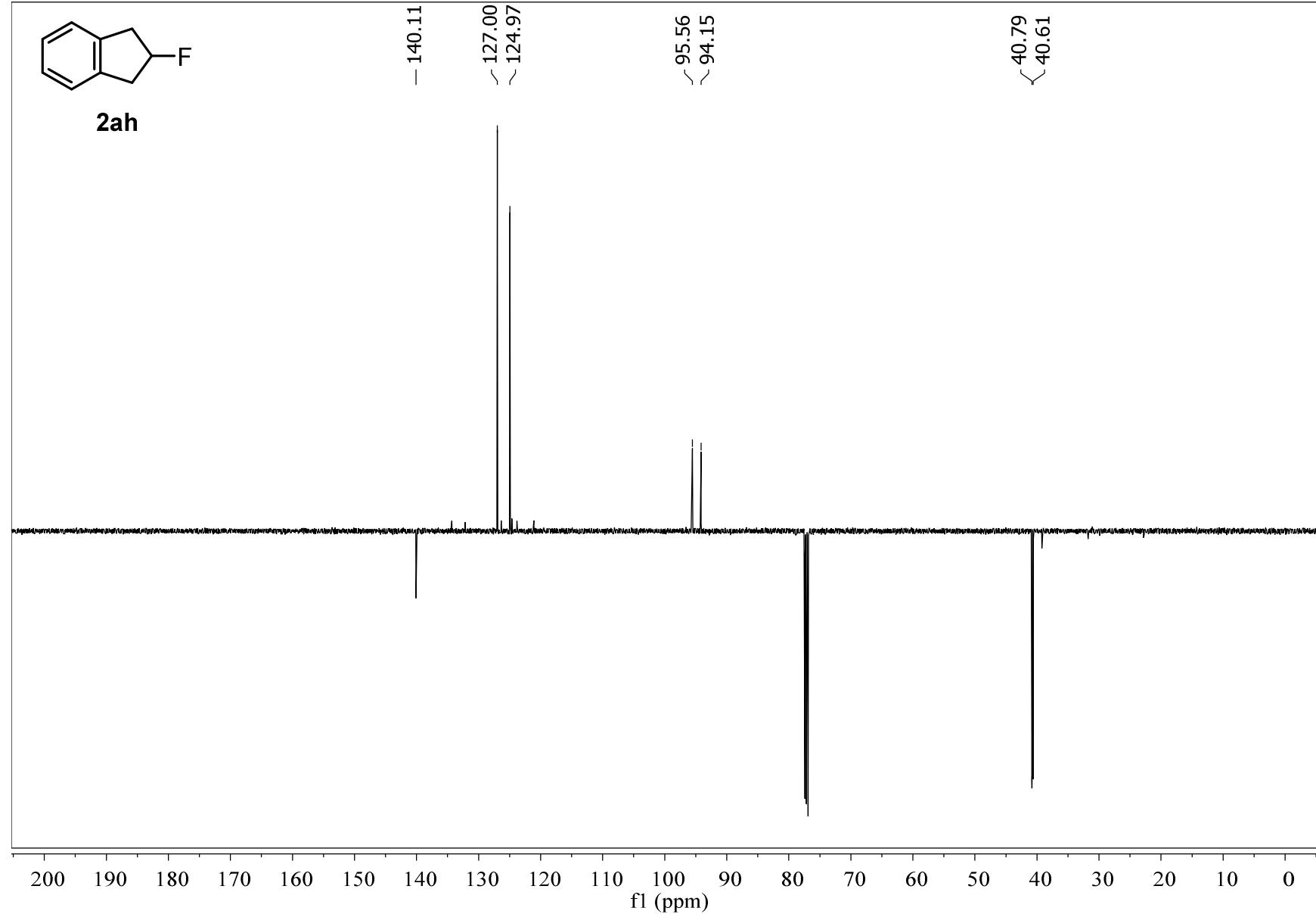
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



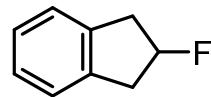
**2ah**



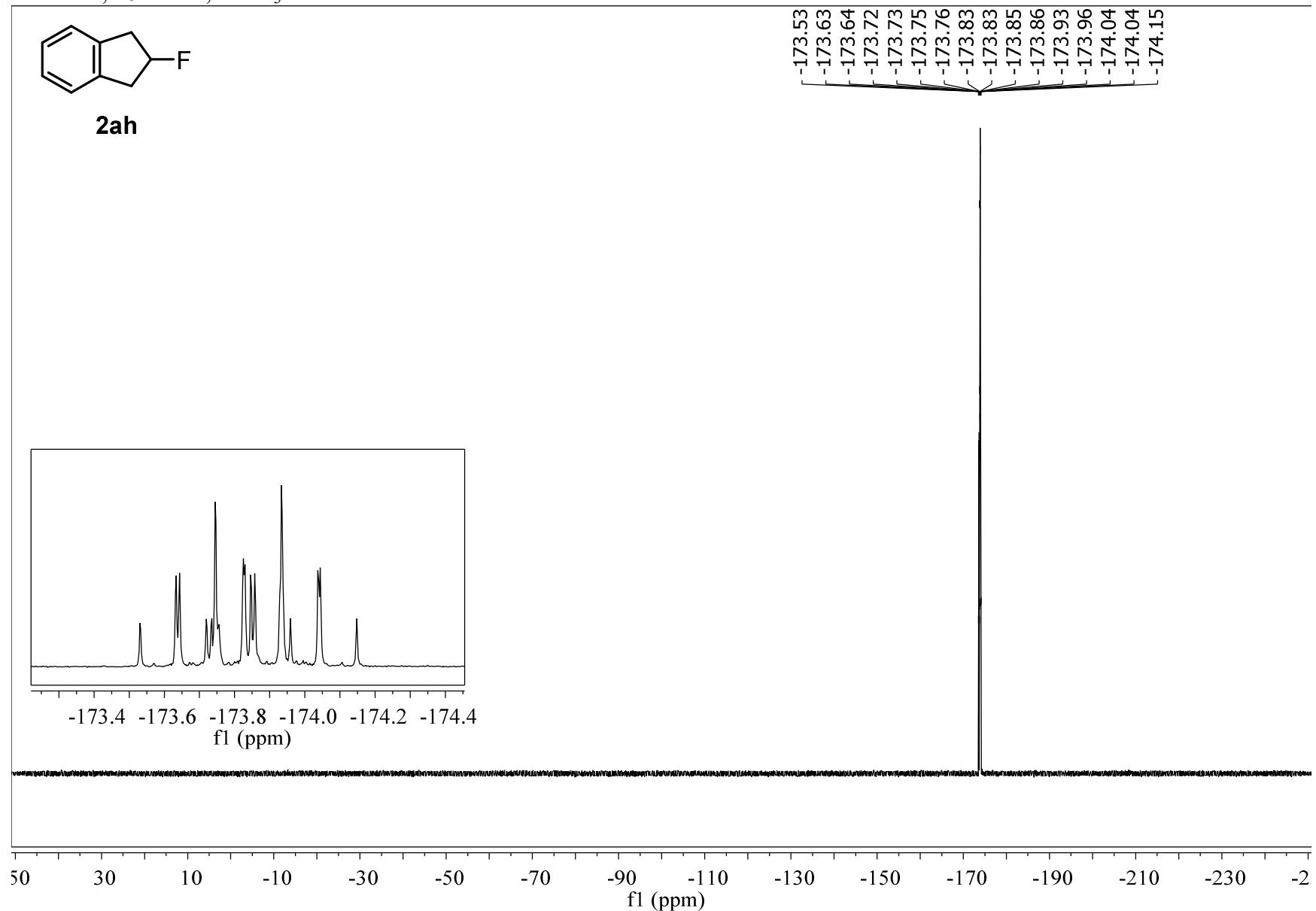
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



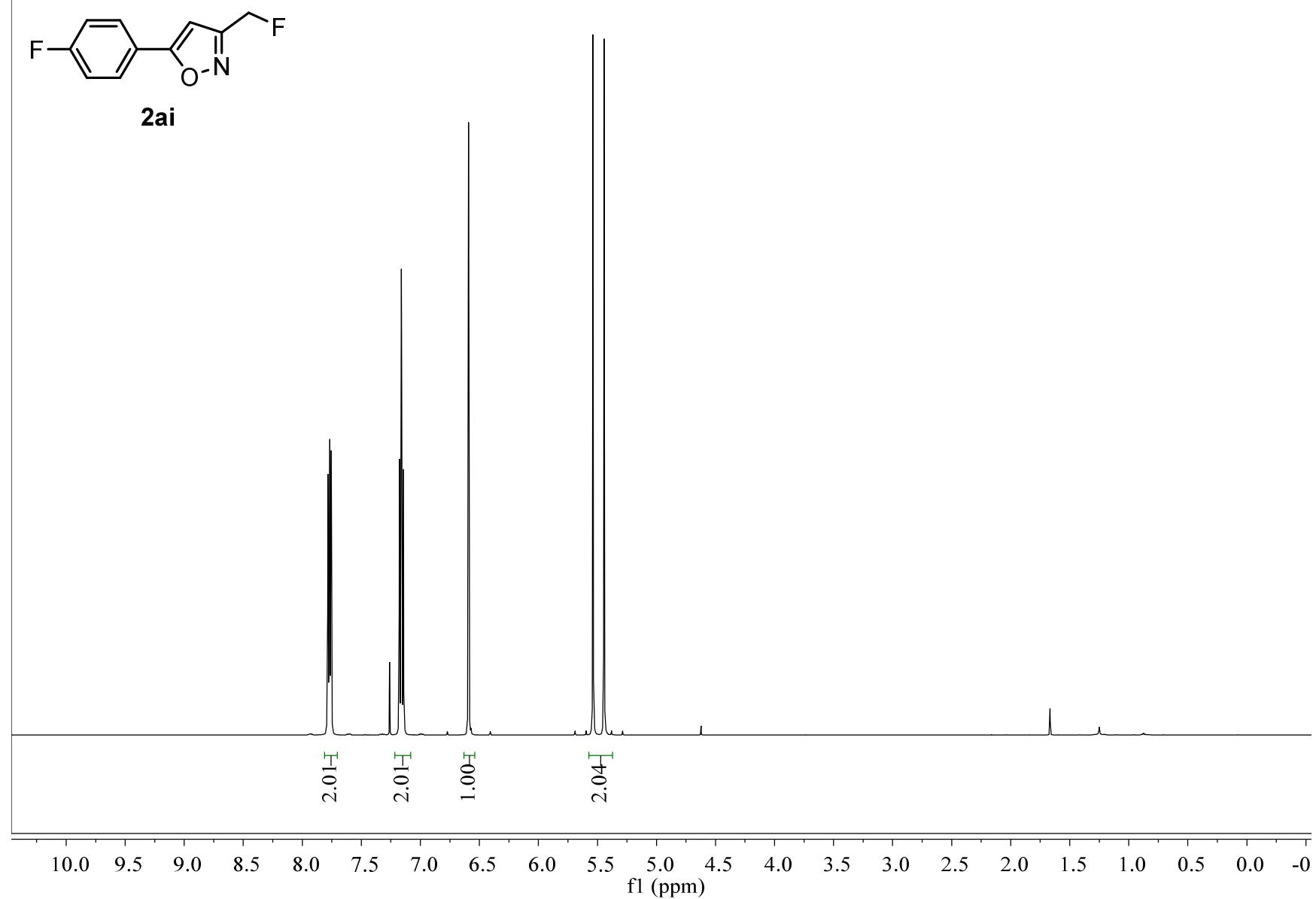
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



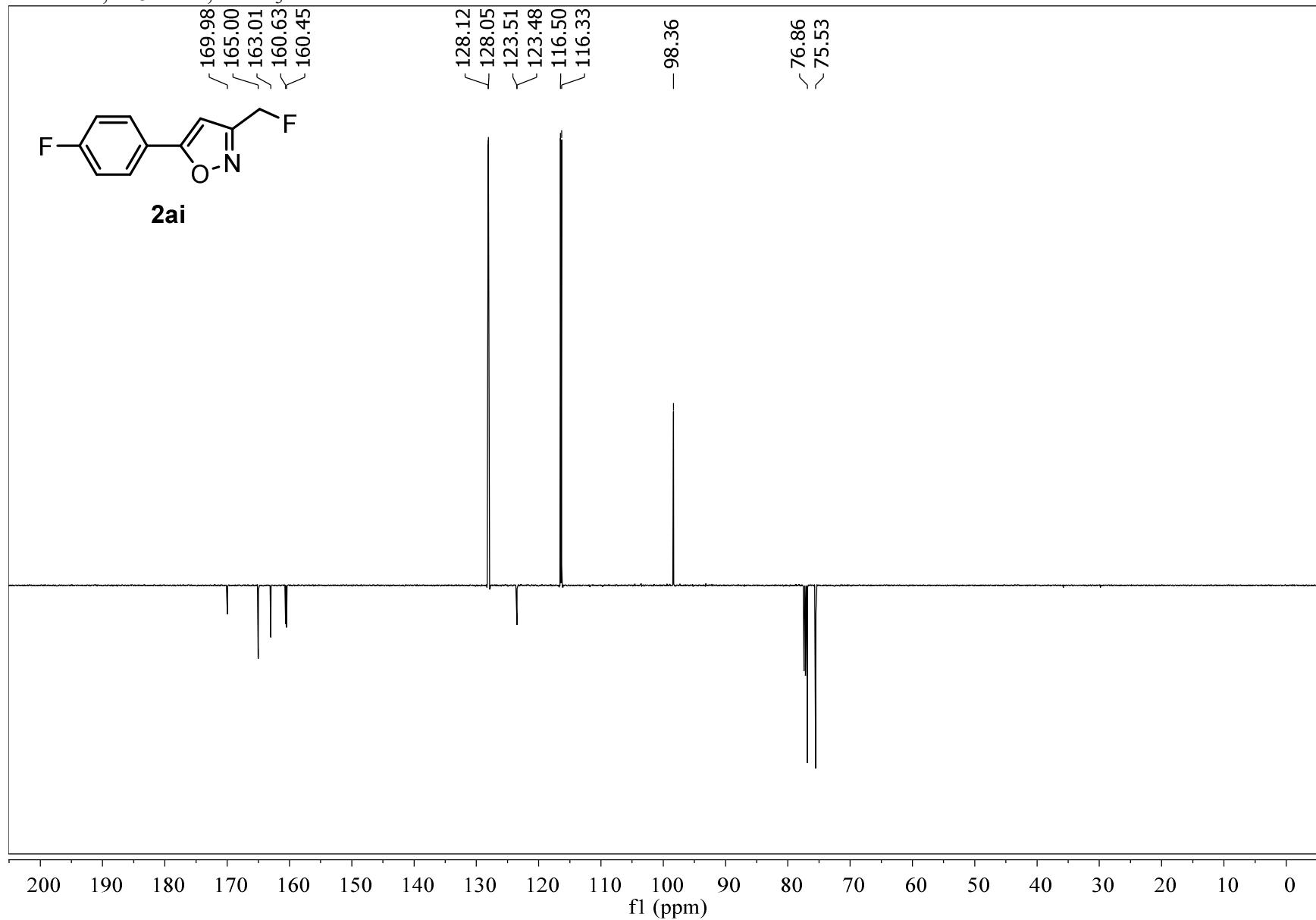
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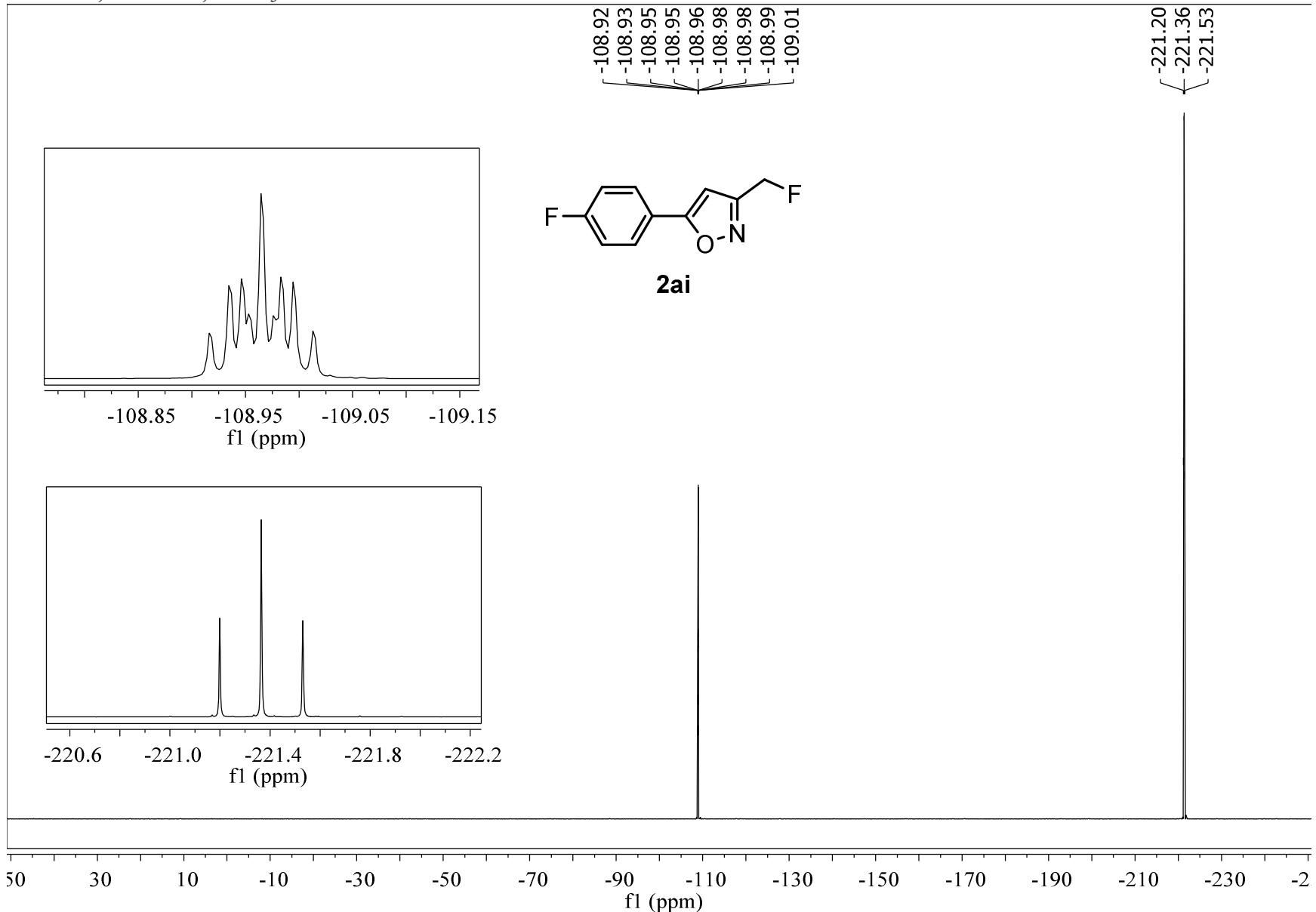
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



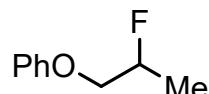
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



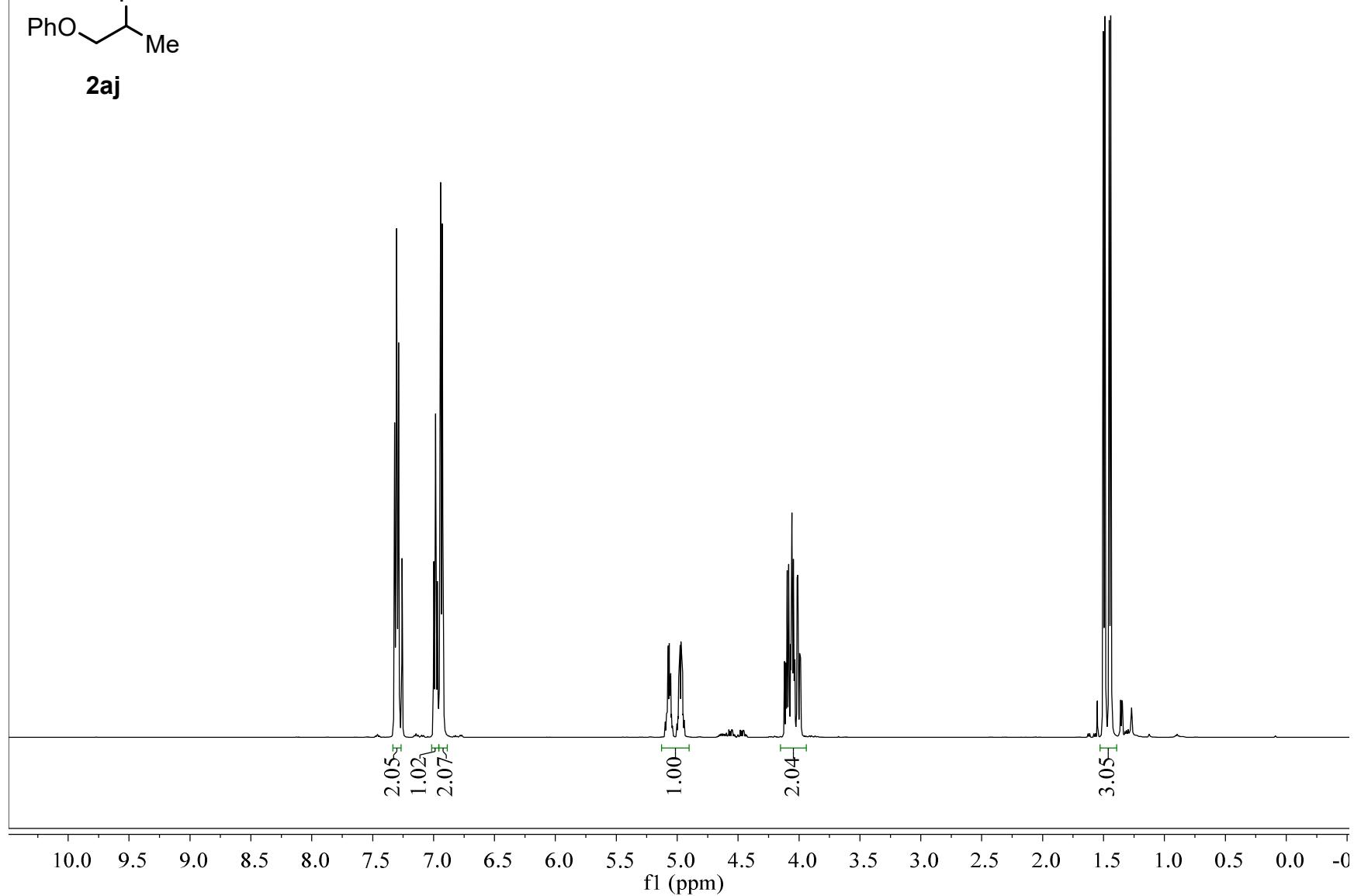
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

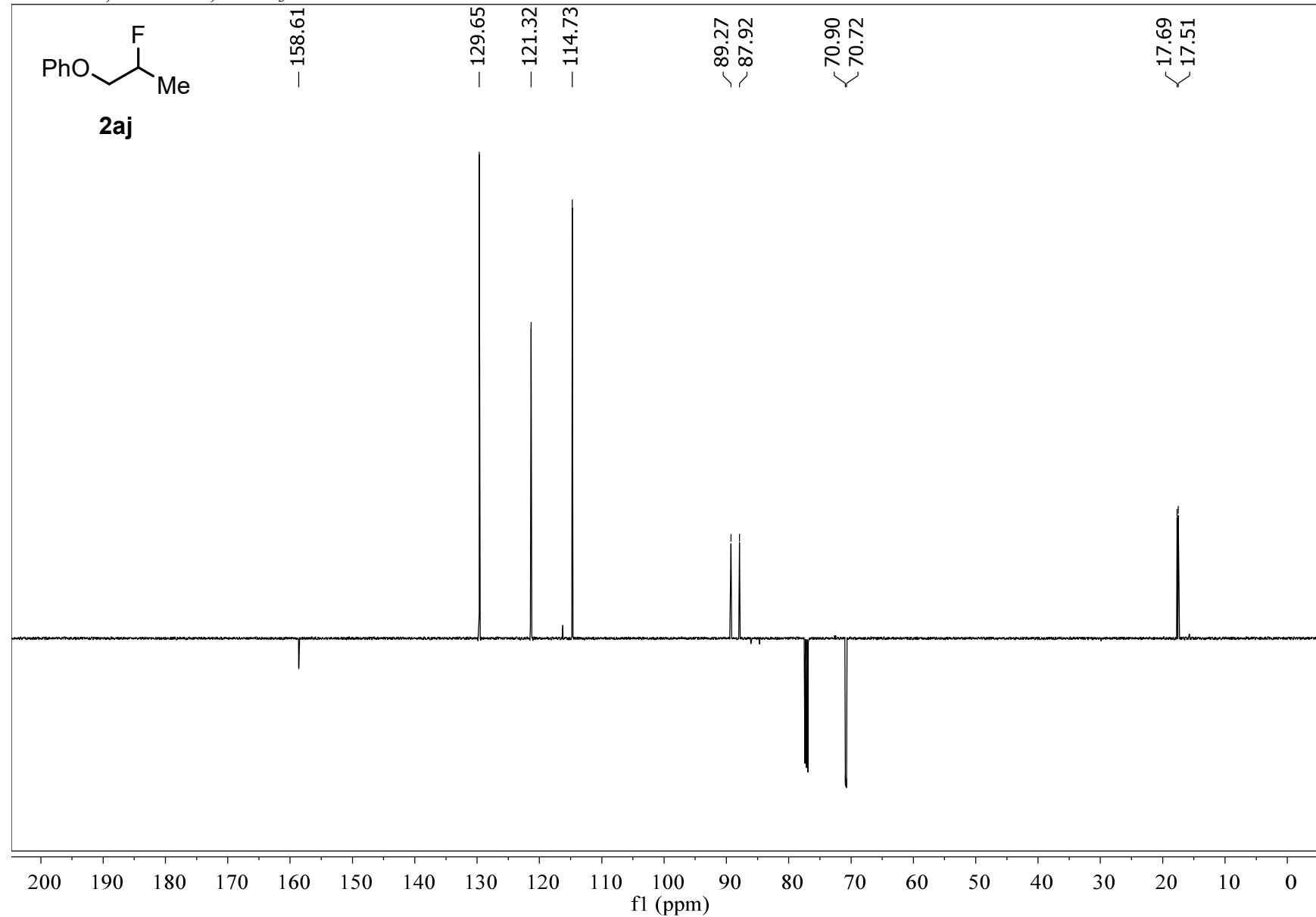


**2aj**

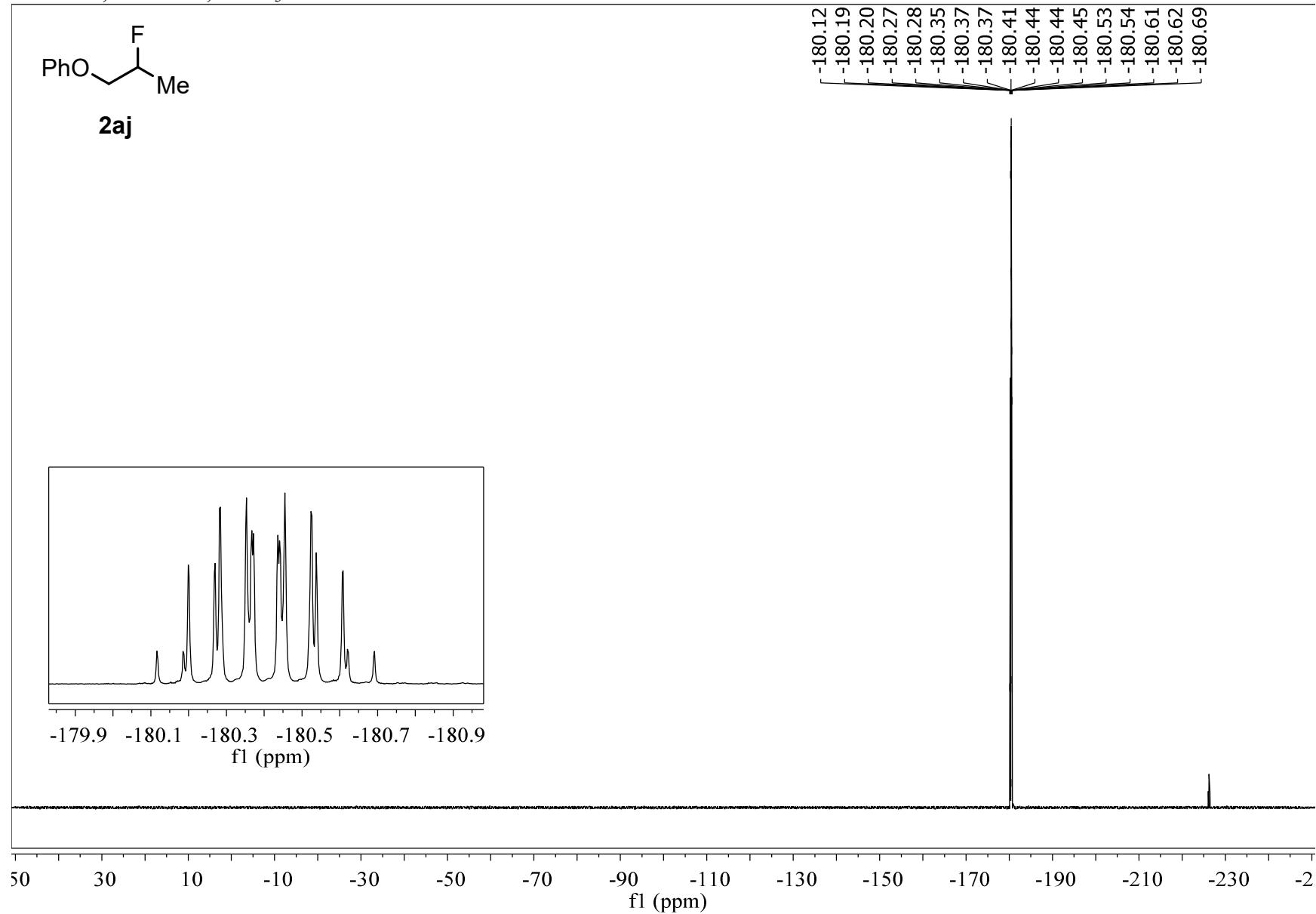


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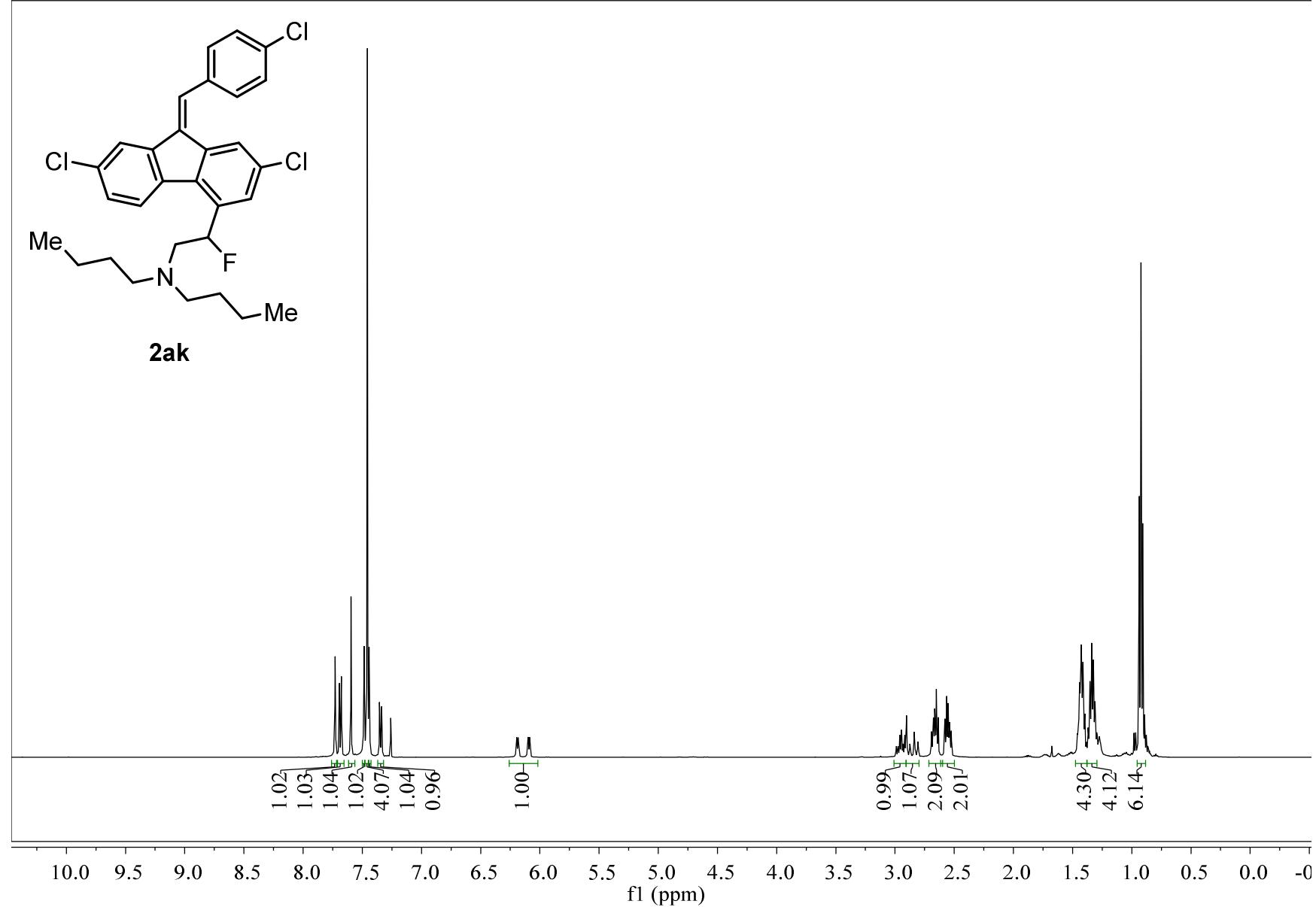
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



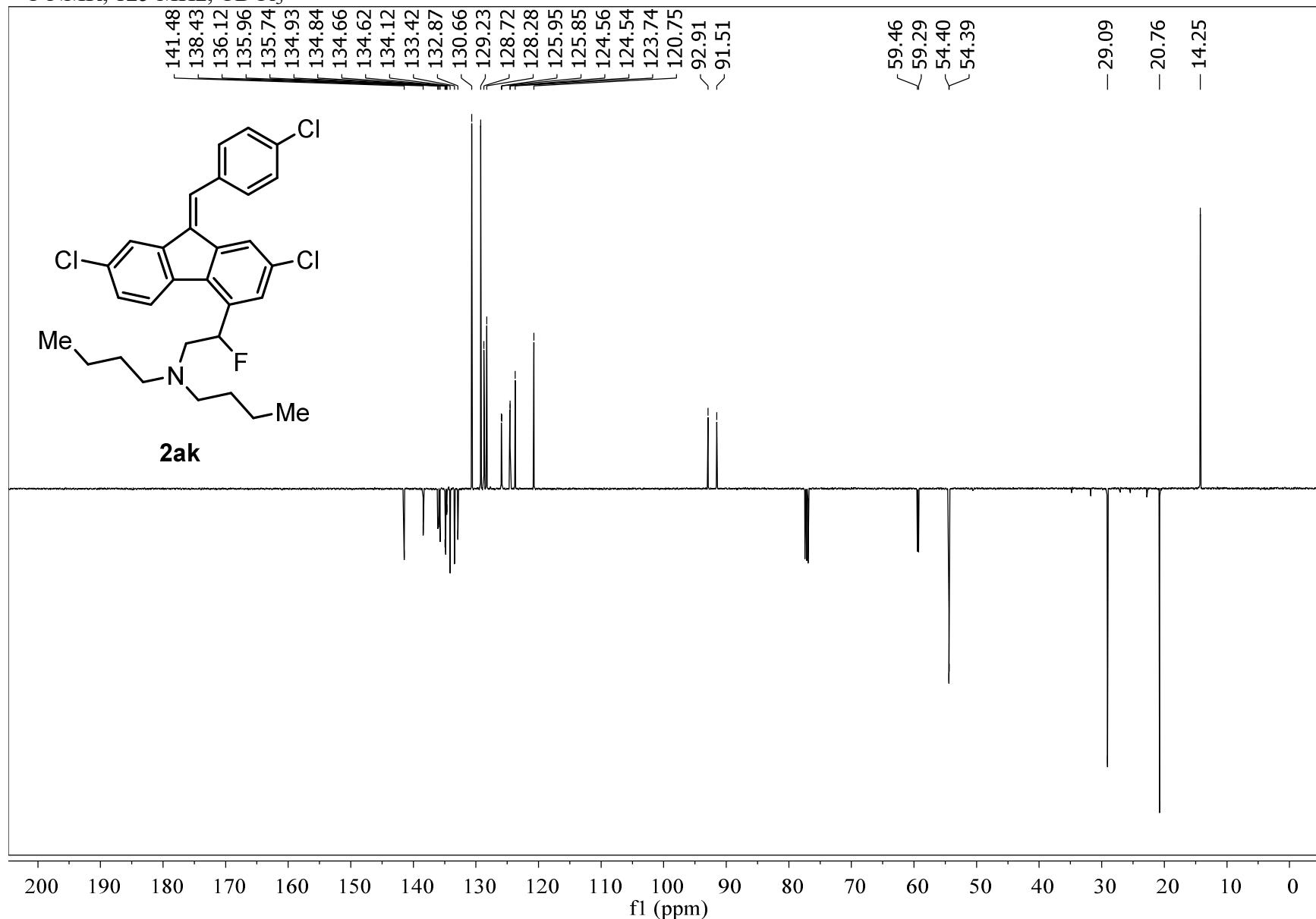
<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>



<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



<sup>19</sup>F NMR, 282 MHz, CDCl<sub>3</sub>

