Palladium-catalyzed synthesis of monofluoroalkenes from 3,3-difluoropropenes using dimethylmalonate and derivatives as nucleophiles

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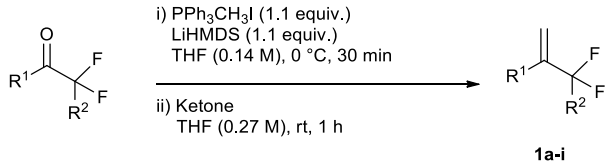
1. General information

The following includes general experimental procedures, specific details for representative reactions and isolation, and spectroscopic information for the new compounds prepared. All reactions were carried out under an argon atmosphere with dry solvents. Et_2O, THF, CH_3CN, CH_2Cl_2 and toluene were purified using a Vacuum Atmospheres Inc. Solvent Purification System. All other commercially available compounds were used as received. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Silicycle silica gel 60 Å F254 TLC plates, and visualized under UV (λ = 254 nm) or by staining with either potassium permanganate. Flash column chromatography was carried out on Silicycle silica gel 60 Å, 230–400 mesh. ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ at ambient temperature using Agilent DD2 500 and Varian Inova 400 spectrometers. ^1H, ^{13}C, and ^{19}F NMR chemical shifts are reported in ppm downfield of tetramethylsilane (^1H NMR) or residual $CHCl_3$ (^1H and ^{13}C NMR)

as the internal standard, or $CFCl_3$ (^{19}F NMR) as the external standard. Coupling constants (*J*) are measured in hertz (Hz). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, m = multiplet, bs = broad signal. High-resolution mass spectra were obtained on a LC/MS–TOF Agilent 6210 using electrospray ionization (ESI) or atmospheric pressure photoionization (APPI). Infrared spectra were recorded using a Thermo Scientific Nicolet 380 FT-IR spectrometer. Melting points were recorded on a Stanford Research System OptiMelt capillary melting point apparatus and are uncorrected. Optical rotation were measured on a Jasco DIP-360 Polarimeter with a sodium lamp at ambient temperature. Enantiomeric excesses were determined by HPLC analysis with a Hewlett Packard 1200 Series.

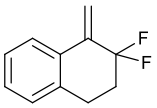
2. Synthesis of 3,3-difluoropropenes

a) Olefination of 3,3-difluoroketones

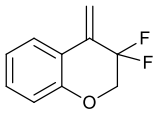


General protocol: The phosphonium salt was prepared by mixing methyl iodide (1.4 mL, 22.9 mmol) and triphenylphosphine (5.0 g, 19.1 mmol) in toluene (0.38 M) at room temperature for 5 hours. Removal of the excess of methyl iodide was done by washing with hexanes. Then, the phosphonium salt (1.1 equiv.) was deprotonated with LiHMDS (1.1 equiv.) (generated from HMDS and *n*-BuLi) in THF (0.14 M) at 0 °C over 30 min to provide the phosphonium ylide $PPh_3{=}CH_2$. The difluoroketone (1 equiv.) was diluted in THF (0.27 M) and slowly added to the Wittig reagent at 0 °C. The resulting solution was warmed up to rt and stirred for 1 h. The reaction was quenched with H_2O, extracted 3x with pentane and washed with sat. aq. $NaHCO_3$ sat. The combined organic layers were dried over $MgSO_4$ and concentrated.[1]

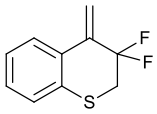
[1] X. Pigeon, M. Bergeron, F. Barabé, P. Dubé, H. N. Frost, and J.-F. Paquin, *Angew. Chem. Int. Ed.*, 2010, **49**, 1123.



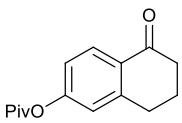
2,2-Difluoro-1-methylene-1,2,3,4-tetrahydronaphtalene (1a): Following the general protocol on a 5.49 mmol scale, the desired product (740 mg, 73%) was isolated as a colourless oil by flash chromatography (100% pentane). Spectroscopic data were in agreement with the literature.[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.58 (1H, m), 7.29-7.20 (2H, m), 7.16 (1H, m), 5.87 (1H, s), 5.78 (1H, t, *J* = 2.1 Hz), 3.05 (2H, t, *J* = 6.7 Hz), 2.32 (2H, tt, *J* = 13.5, 6.7 Hz).



3,3-Difluoro-4-methylenechroman (1b): Following the general protocol on a 1.29 mmol scale, the desired product (62 mg, 38%) was obtained as a yellow oil by flash chromatography (100% hexanes). Spectroscopic data were in agreement with the literature.[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J* = 7.9, 1.6 Hz), 7.26 (1H, m), 7.02 (1H, m), 6.95 (1H, dd, *J* = 8.3, 1.2 Hz), 5.86 (1H, s), 5.75 (1H, t, *J* = 2.3 Hz), 4.25 (2H, t, *J* = 10.5 Hz).



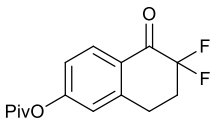
3,3-Difluoro-4-methylenethiochroman (1c): Following the general protocol on a 3.04 mmol scale, but at 70 °C overnight instead of 0 °C during 1 h, the desired product (277 mg, 46%) was obtained as a colourless oil by flash chromatography (100% pentane). Spectroscopic data were in agreement with the literature.[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (1H, dt, *J* = 7.8, 1.1 Hz), 7.23-7.09 (3H, m), 5.88-5.84 (2H, m), 3.33 (2H, t, *J* = 11.8 Hz).



5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl pivalate: PivCl (1.5 mL, 12.3 mmol, 1 equiv.) was added dropwise to a solution of 6-hydroxy-3,4-dihydro-1(*2H*)-naphtalenone (2.0 g, 12.3 mmol, 1 equiv.), DMAP (151 mg, 1.2 mmol, 0.1 equiv.) and Et_3N (1.7 mL, 12.3 mmol, 1 equiv.) in CH_2Cl_2 (41 mL, 0.3 M). The mixture was then stirred at room temperature for 7 h, then H_2O was added. The layers were separated and extracted 3x with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated.

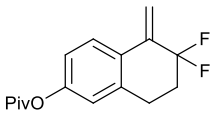
[2] J.-D. Hamel, M. Drouin, and J.-F. Paquin, *J. Fluorine. Chem.*, 2015, **174**, 81.

The crude residue was purified by flash chromatography (15% EtOAc/hexanes) to give the product (1.41 g, 72%) as an orange solid. mp = 44-46 °C; IR (neat) ν = 2974, 2935, 1745, 1676, 1602, 1478, 1276, 1230, 1110, 910 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (1H, d, *J* = 8.3 Hz), 7.01-6.96 (2H, m), 2.95 (2H, t, *J* = 6.1 Hz), 2.67-2.60 (2H, m), 2.13 (2H, dt, *J* = 12.6, 6.3 Hz), 1.36 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 176.5, 154.9, 146.2, 130.2, 129.0, 121.4, 120.1, 39.2, 38.9, 29.7, 27.0, 23.2; HRMS-ESI calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1329, found 247.1350.

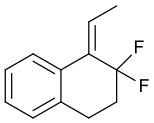


6,6-Difluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl pivalate: 5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (500 mg, 2.0 mmol, 1 equiv.) was added in THF (2.3 M), followed by HMDS (0.47 mL, 2.2 mmol, 1.1 equiv.). The reaction was cooled to 0 °C and *n*-BuLi (0.85 mL, 2.1 mmol, 1.05 equiv.) was added dropwise over 15 min. The mixture was stirred for 2 h at 0 °C. The resulting enolate solution was added dropwise over 15 min to a -78 °C solution of NFSI (703 mg, 2.2 mmol, 1.1 equiv.) in THF (0.38 M). The resulting solution was allowed to warm to room temperature over 16 h. Sat. aq. NH_4Cl was added to the reaction and the mixture was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification using flash chromatography (10% EtOAc/hexanes) gave a mixture of the ketone, the monofluoroketone and the difluoroketone.

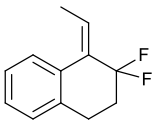
This mixture was then used without further purification to perform the second fluorination under the same conditions. Purification by flash chromatography (10% EtOAc/hexanes), followed by a second flash chromatography (10% EtOAc/hexanes), gave the difluoroketone as a yellow solid containing an unidentified impurity (116 mg over 2 steps). The product was used without further purification for the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (1H, d, *J* = 8.6 Hz), 7.10 (1H, dd, *J* = 8.6, 2.2 Hz), 7.05 (1H, m), 3.18 (2H, t, *J* = 6.3 Hz), 2.58 (2H, tt, *J* = 14.5, 6.3 Hz), 1.37 (9H, s); ^{19}F NMR (470 MHz, $CDCl_3$) δ -116.2 (2F, t, *J* = 14.9 Hz); HRMS-ESI calcd for $C_{15}H_{20}F_2NO_3$ $[M+NH_4]^+$ 300.1406, found 300.1423.



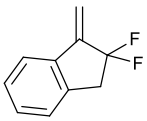
6,6-Difluoro-5-methylene-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (1d): Following the general protocol on a 0.42 mmol scale, but at 70 °C overnight instead of 0 °C during 1 h, the desired product (51 mg, 44%) was obtained as a yellow solid by flash chromatography (5% EtOAc/hexanes). mp = 67-68 °C; IR (neat) ν = 2974, 2875, 1739, 1606, 1477, 1413, 1397, 1262, 1153, 1061 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (1H, d, *J* = 8.6 Hz), 6.93 (1H, dd, *J* = 8.6, 2.4 Hz), 6.87 (1H, d, *J* = 2.5 Hz), 5.81 (1H, s), 5.75 (1H, t, *J* = 2.0 Hz), 3.01 (2H, t, *J* = 6.6 Hz), 2.29 (2H, tt, *J* = 13.6, 6.8 Hz), 1.37 (9H, s); ^{19}F NMR (470 MHz, $CDCl_3$) δ -98.4 (2F, t, *J* = 13.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 151.1, 138.4 (t, J_{C-F} = 22.3 Hz), 135.9, 129.2 (t, J_{C-F} = 3.0 Hz), 125.7, 121.4, 120.2, 119.1 (t, J_{C-F} = 240.5 Hz), 110.9 (t, J_{C-F} = 7.6 Hz), 39.11, 31.8 (t, J_{C-F} = 25.1 Hz), 27.1, 26.4 (t, J_{C-F} = 5.9 Hz); HRMS-ESI calcd for $C_{16}H_{19}F_2O_2$ $[M+H]^+$ 281.1348, found 281.1343.



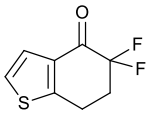
(*Z*)-1-Ethylidene-2,2-difluoro-1,2,3,4-tetrahydronaphtalene (1e/(*Z*)-4): Following the general protocol on a 6.0 mmol scale using $Ph_3P{=}CH_2CH_3$ (2.77 g, 6.6 mmol) instead of $Ph_3P{=}CH_3$, the desired product (388 mg, 33%) was isolated as a colourless oil by flash chromatography (100% pentane).[1] Spectroscopic data were in agreement with the literature.[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (1H, d, *J* = 1.5 Hz), 7.23-7.09 (3H, m), 6.50 (1H, qt, *J* = 7.5, 3.8 Hz), 2.84-2.79 (2H, m), 2.29-2.18 (2H, m), 2.14 (2H, dt, *J* = 7.4, 3.6 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -88.9 −-88.11(2F, m).



(*E*)-1-Ethylidene-2,2-difluoro-1,2,3,4-tetrahydronaphtalene ((*E*)-4): From the previous reaction (1e/(*Z*)-4), this minor isomer was isolated as a colourless oil (131 mg, 11%) using a second flash chromatography (100% pentanes). IR (neat) ν = 3063, 2939, 2856, 1713, 1640, 1443, 1256, 1062, 930, 779 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (1H, m), 7.26-7.15 (3H, m), 6.41 (1H, m), 2.94 (2H, t, *J* = 6.8 Hz), 2.29 (2H, tt, *J* = 14.3, 6.8 Hz), 2.03 (2H, dt, *J* = 7.2, 3.1 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -93.9 (2F, t, *J* = 14.4 Hz) ; ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 132.4 (t, J_{C-F} = 21.2 Hz), 132.2 (t, J_{C-F} = 2.5 Hz), 129.0, 128.2, 127.5, 125.8, 124.8 (t, J_{C-F} = 7.5 Hz), 121.0 (t, J_{C-F} = 241.4 Hz), 33.2 (t, J_{C-F} = 26.2 Hz), 26.6 (t, J_{C-F} = 5.2 Hz), 15.1; HRMS-ESI calcd for $C_{12}H_{12}F$ $[M-F]^+$ 175.0918, found 175.0911.

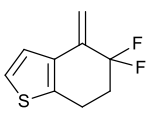


2,2-Difluoro-1-methylene-2,3-dihydro-1*H*-indene (1f): Following the general protocol on a 6.1 mmol scale, the desired product (293 mg, 29%) was obtained as a colourless oil by flash chromatography (100% hexanes). Spectroscopic data were in agreement with the literature.[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (1H, m), 7.39-7.22 (3H, m), 5.81 (1H, td, *J* = 3.4, 0.7 Hz), 5.67 (1H, t, *J* = 3.2 Hz), 3.46 (2H, t, *J* = 14.2 Hz).



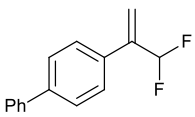
5,5-Difluoro-6,7-dihydrobenzo[*b*]thiophen-4-(5*H*)-one: 6,7-Dihydro-4-benzo[*b*]thiophenone (350 mg, 2.3 mmol, 1 equiv.) was added in THF (2.3 M), followed by HMDS (0.53 mL, 2.5 mmol, 1.1 equiv.). The reaction was cooled to 0 °C and *n*-BuLi (0.97 mL, 2.4 mmol, 1.05 equiv.) was added dropwise over 15 min. The mixture was stirred for 2 h at 0 °C. The resulting enolate solution was added dropwise over 15 min to a -78 °C solution of NFSI (798 mg, 2.5 mmol, 1.1 equiv.) in THF (0.38 M). The resulting solution was allowed to warm to room temperature over 16 h. Sat. aq. NH_4Cl was added to the reaction and the mixture was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification using flash chromatography (10% EtOAc/hexanes) gave a mixture of the ketone, the monofluoroketone and the difluoroketone.

This mixture was then used without further purification to perform the second fluorination under the same conditions. Purification by flash chromatography (10% EtOAc/hexanes) gave the difluoroketone as a colourless oil containing an unindentified impurity (93 mg over 2 steps). The product was used without further purification for the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* = 5.4 Hz), 7.21 (1H, dt, *J* = 5.3, 0.6 Hz), 3.28 (2H, t, *J* = 6.1 Hz), 2.64 (2H, tt, *J* = 14.5, 6.1 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -111.6 (2F, t, *J* = 14.5 Hz); HRMS-ESI calcd for $C_8H_7F_2OS$ $[M+H]^+$ 189.01802, found 189.0185.

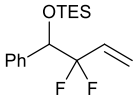


5,5-Difluoro-4-methylene-4,5,6,7-tetrahydrobenzo[*b*]thiophene (1g): Following the general protocol on a 0.495 mmol scale, but at 70 °C overnight instead of 0 °C

during 1 h, the desired product (39 mg, 42%) was obtained as a colourless oil by flash chromatography (100% hexanes). IR (neat) ν = 3114, 2938, 2853, 1824, 1640, 1399, 1358, 1167, 936, 907 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15-7.12 (2H, m), 5.64 (1H, t, *J* = 2.2 Hz), 5.54 (1H, s), 3.05 (2H, t, *J* = 6.4 Hz), 2.36 (2H, tt, *J* = 13.5, 6.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -100.2 (t, *J* = 13.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5 (t, J_{C-F} = 6.0 Hz), 136.0 (t, J_{C-F} = 22.9 Hz), 133.6 (t, J_{C-F} = 3.5 Hz), 124.7, 123.4 (t, J_{C-F} = 1.3 Hz), 119.1 (t, J_{C-F} = 241.9 Hz), 108.6 (t, J_{C-F} = 7.1 Hz), 32.5 (t, J_{C-F} = 25.8 Hz), 22.1 (t, J_{C-F} = 6.0 Hz); HRMS data could not be obtained either using ESI or APPI.



4-(3,3-Difluoroprop-1-en-2-yl)-1,1'-biphenyl (1h): The product was synthesized following a literature protocol. Spectroscopic data were in agreement with the literature.[3] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64-7.54 (5H, m), 7.45 (2H, t, *J* = 7.7 Hz), 7.36 (1H, m), 6.43 (1H, t, *J* = 55.3 Hz), 5.73 (2H, dt, *J* = 52.5, 2.1 Hz).

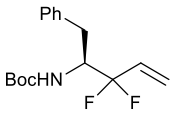


Triethylsilyl 2,2-difluoro-1-phenylbut-3-en-1-ol (1i): The alcohol[4] (285 mg, 1.6 mmol, 1 equiv.) was added at room temperature to CH_2Cl_2 (0.3 M), followed by imidazole (148 mg, 2.2 mmol, 1.4 equiv.). At 0 °C, TESOTf was added dropwise (0.52 mL, 1.9 mmol, 1.2 equiv.). The reaction was warmed to room temperature and stirred for 1 h. Sat. aq. $NaHCO_3$ was added and the reaction was extracted 3x with CH_2Cl_2, and then washed with brine. The organic layers were dried over $MgSO_4$ and concentrated. Purification by flash chromatography (100% hexanes) afforded the final product as a colourless oil (399 mg, 88%). IR (neat) ν = 2956, 2878, 1455, 1418, 1193, 1103, 1071, 998, 839, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.29 (5H, m), 5.90 (1H, ddt, *J* = 17.1, 12.7, 10.8 Hz), 5.47 (1H, d, *J* = 17.3 Hz), 5.39 (1H, d, *J* = 11.1 Hz), 4.85 (1H, t, *J* = 8.7 Hz), 0.89 (9H, t, *J* = 7.9 Hz), 0.65-0.49 (6H, m); ^{19}F NMR (470 MHz, $CDCl_3$) δ -104.1 (1F, dt, *J* = 243.9, 9.9 Hz), -109.7 (1F, ddd, *J* = 243.7, 13.6, 8.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8 (d, J_{C-F} = 4.8 Hz), 129.7 (t, J_{C-F} = 25.7 Hz),

[3] M, Bergeron, T. Johnson and J.-F. Paquin, *Angew. Chem. Int. Ed.*, 2011, **50**, 11112.
[4] M. Kirihara, T. Takuwa, S. Takizawa, T. Momose and H. Nemoto, *Tetrahedron*, 2000, **56**, 8275.

128.3, 127.8 (2C, m), 127.7, 120.8 (t, $J_{C\text{-}F}$ = 9.1 Hz), 118.6 (t, $J_{C\text{-}F}$ = 244.9 Hz), 76.5 (d, $J_{C\text{-}F}$ = 2.9 Hz), 76.3, 6.6, 4.7; HRMS-ESI calcd for $C_{16}H_{28}F_2NOSi$ $[M+NH_4]^+$ 316.1903, found 316.1905.

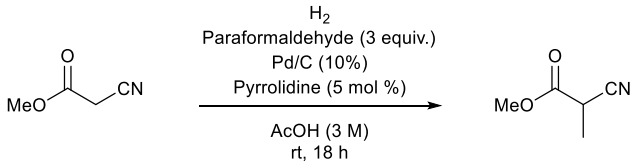
b) Deoxofluorination

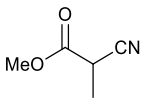


(*S*)-*tert*-Butyl (3,3-difluoro-1-phenylpent-4-en-2-yl)carbamate (1j): Deoxofluor (50% in toluene, 2.4 mL, 5.5 mmol, 5 equiv.) was added to the corresponding enone[5] (300 mg, 1.1 mmol, 1 equiv.) under inert atmosphere. The reaction was stirred at 30 °C for 60 h. The mixture was then dissolved with EtOAc and sat. aq. $NaHCO_3$ was added dropwise to quench the solution, which was stirred during 15 min. The organic layer was separated, dried over $MgSO_4$ and concentrated. Purification by flash chromatography (3% EtOAc/hexanes) gave the product (103 mg, 32%) as a white solid. mp = 82-83°C; IR (neat) ν = 2985, 2937, 1693, 1603, 1521, 1454, 1351, 1210, 1026, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.26 (2H, m), 7.24-7.18 (3H, m), 5.97 (1H, ddt, *J* = 17.3, 12.3, 11.0 Hz), 5.74 (1H, dtd, *J* = 17.4, 2.4, 0.8 Hz), 5.51 (1H, d, *J* = 11.0 Hz), 4.53 (1H, d, *J* = 10.6 Hz), 4.36-4.24 (1H, m), 3.18 (1H, dd, *J* = 14.8, 3.8 Hz), 2.64 (1H, dd, *J* = 14.4, 10.7 Hz), 1.28 (9H, s); ^{19}F NMR (470 MHz, $CDCl_3$) δ -106.3 (1F, dt, *J* = 247.1, 9.5 Hz), -111.5 (1F, dt, *J* = 246.9, 15.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 136.7, 130.8 (t, $J_{C\text{-}F}$ = 26.0 Hz), 129.2, 128.4, 126.6, 121.0 (t, $J_{C\text{-}F}$ = 9.4 Hz), 120.0 (t, $J_{C\text{-}F}$ = 244.2 Hz), 79.8, 55.4 (dd, $J_{C\text{-}F}$ = 30.8, 25.6 Hz), 34.6, 28.1; HRMS-ESI calcd for $C_{16}H_{22}F_2NO_2$ $[M+H]^+$ 298.1613, found 298.1616.

[5] T. Nguyen, R. A. Coover, J. Verghese, R. G. Moran and K. C. Ellis, *ACS Med. Chem. Lett.*, 2014, **5**, 462.

3. Synthesis of nucleophiles





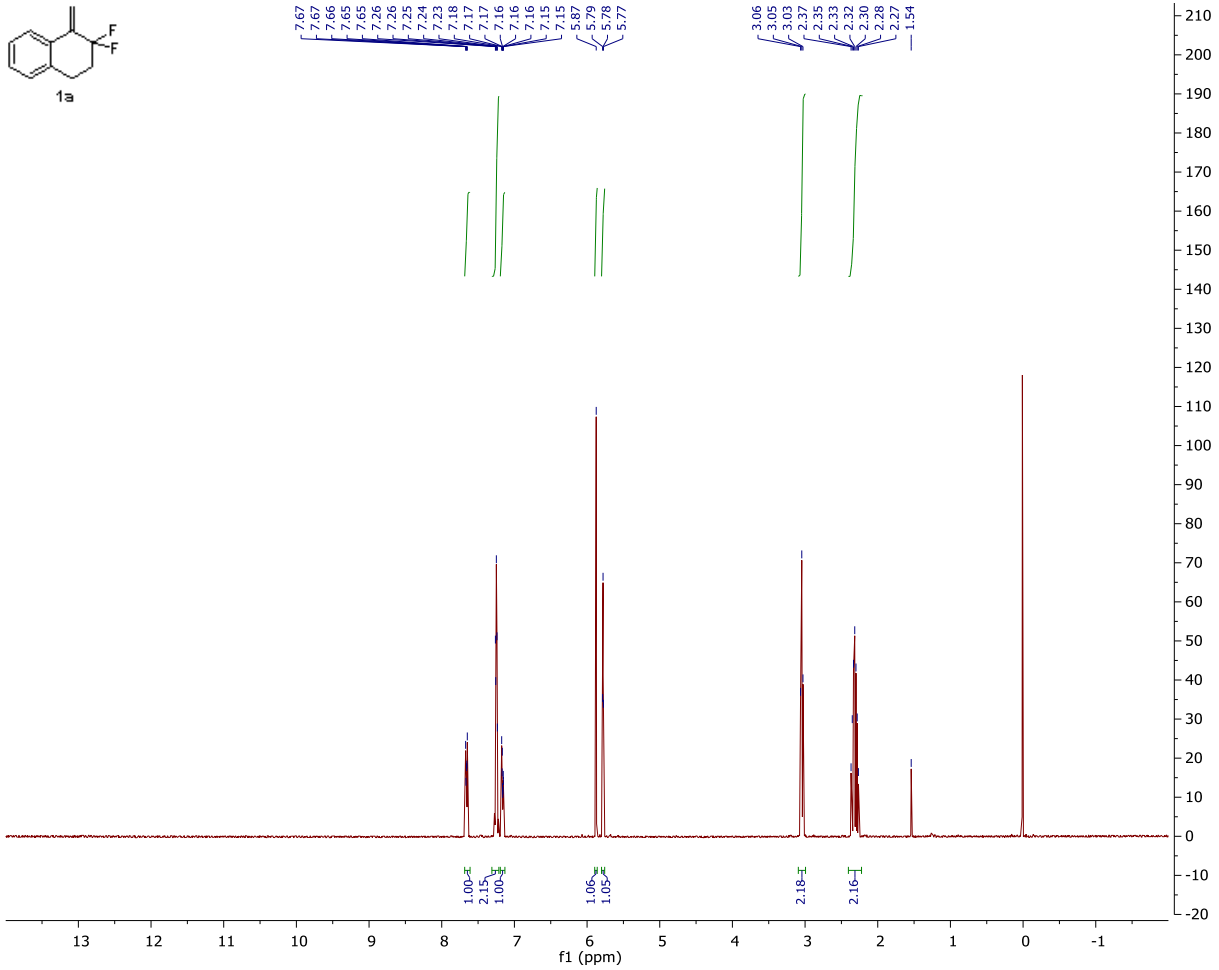
Methyl 2-cyanopropanoate[6]: Methyl cyanoacetate (1 mL, 11.3 mmol, 1 equiv.) and paraformaldehyde (1.0 g, 33.9 mmol, 3 equiv.) were added to AcOH (4 mL, 3M). Then, Pd/C (10 %, 38 mg) and pyrrolidine (28 μL, 0.6 mmol, 5 mol %) were added. The mixture was stirred under H_2 atmosphere for 16 h. Then, the reaction was filtered on a celite pad, Et_2O was added and the organic layer was washed 3x with brine and 1x with sat. aq. $NaHCO_3$. The organic layers were dried over $MgSO_4$ and concentrated. The desired product (153.5 mg, 12%) was obtained as a colourless oil by flash chromatography (20% EtOAc/hexanes). IR (neat) ν = 2958, 2251, 1743, 1701, 1457, 1436, 1268, 1206, 1110, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (3H, s), 3.58 (1H, q, *J* = 7.4 Hz), 1.60 (3H, d, *J* = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 117.3, 53.5, 31.3, 15.3; HRMS-ESI calcd for $C_5H_8NO_2$ $[M+H]^+$ 114.0550, found 114.0548.

[6] E. S. Stratford and R. W. Curley, *J. Med. Chem.*, 1983, **26**, 1463.

4. NMR spectra

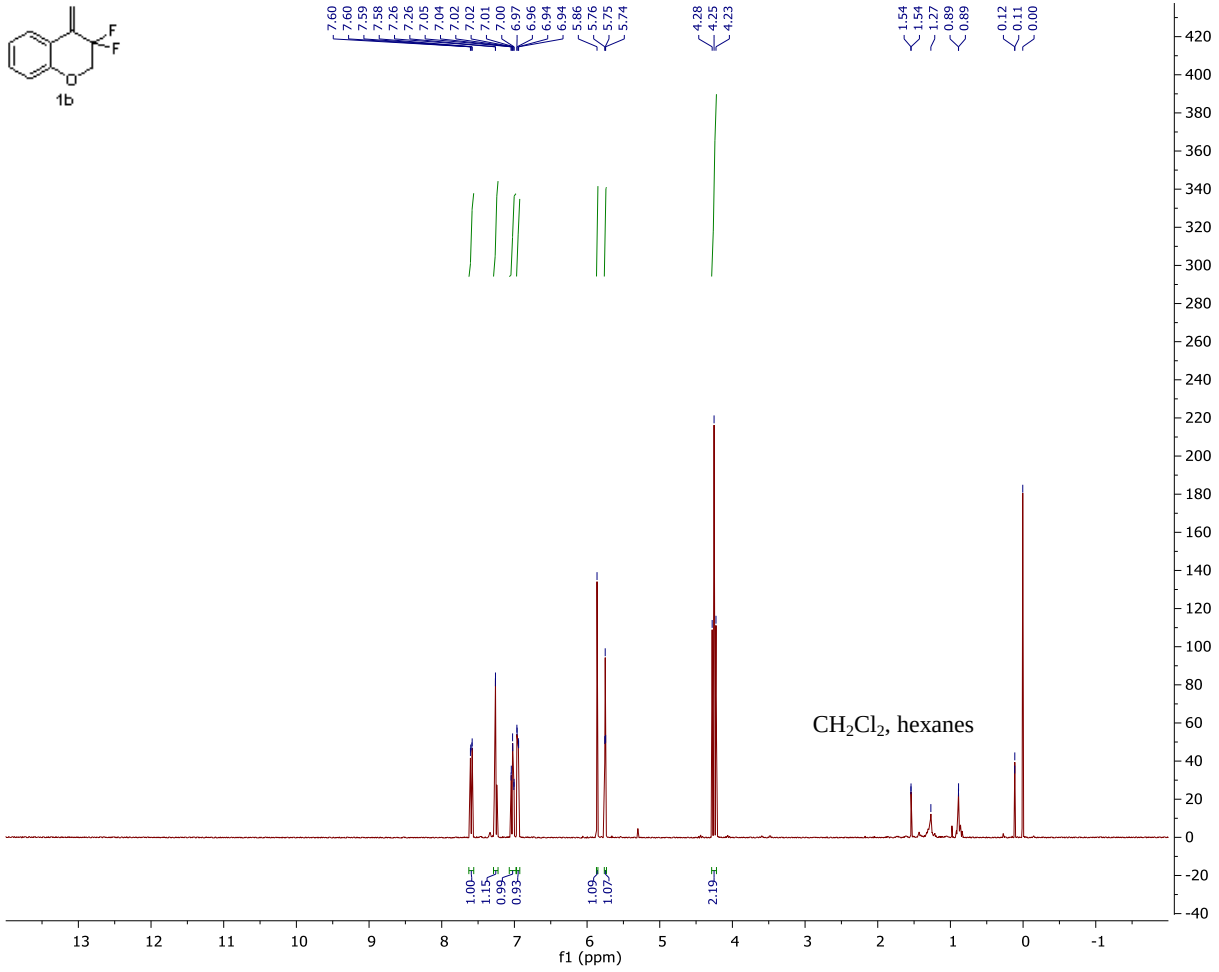
2,2-Difluoro-1-methylene-1,2,3,4-tetrahydronaphtalene (1a)

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



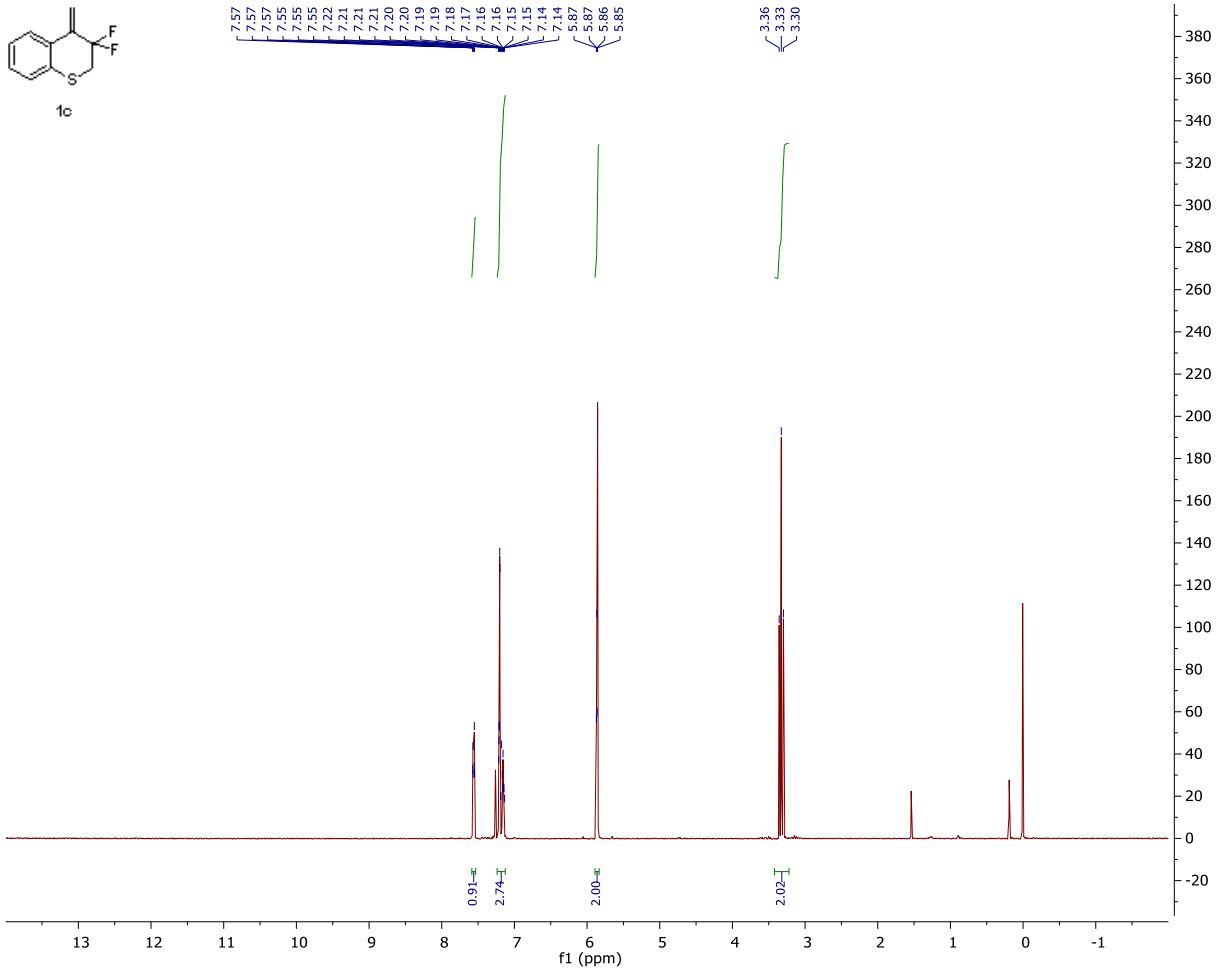
3,3-Difluoro-4-methylenechroman (1b)

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



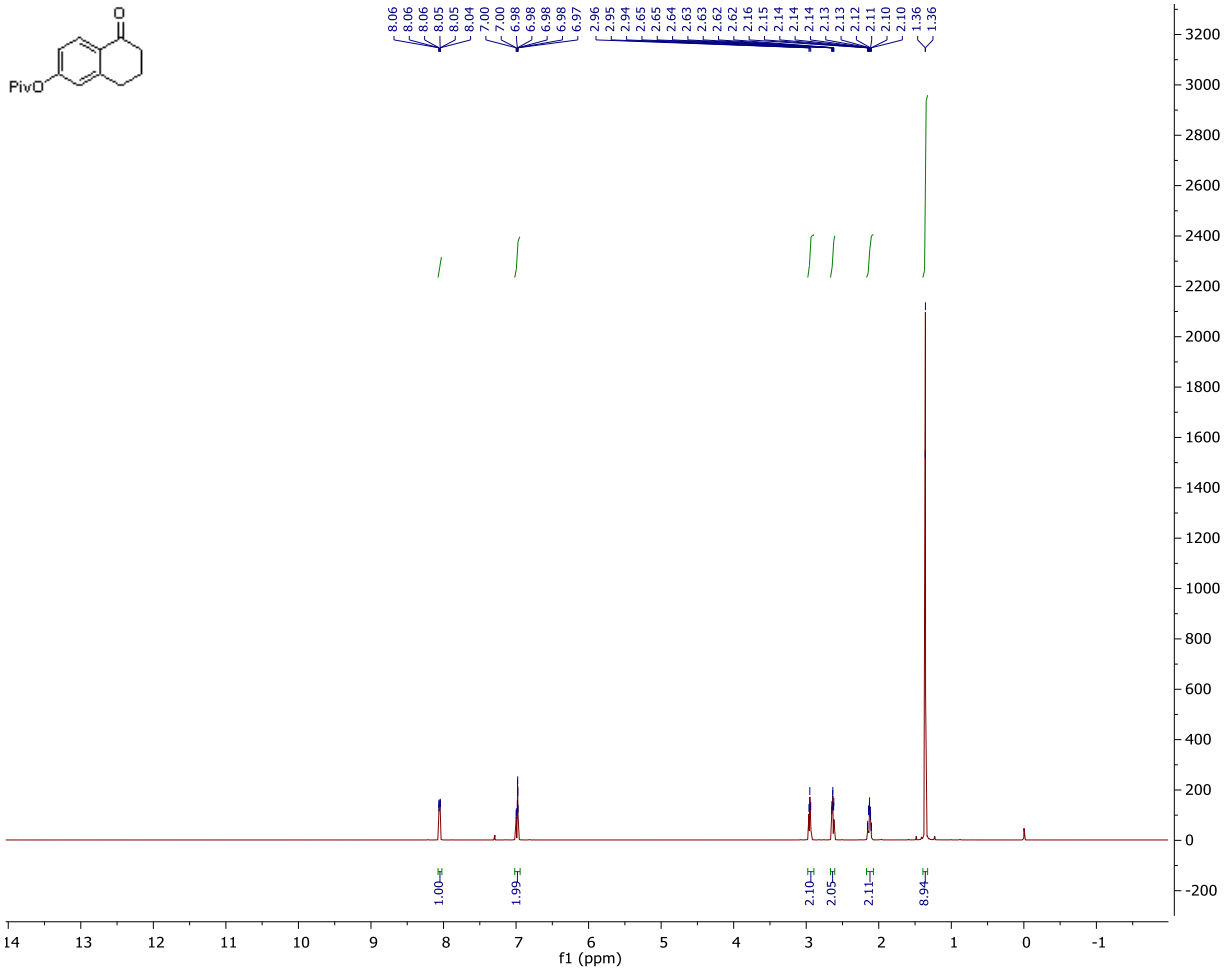
3,3-Difluoro-4-methylenethiochroman (1c)

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

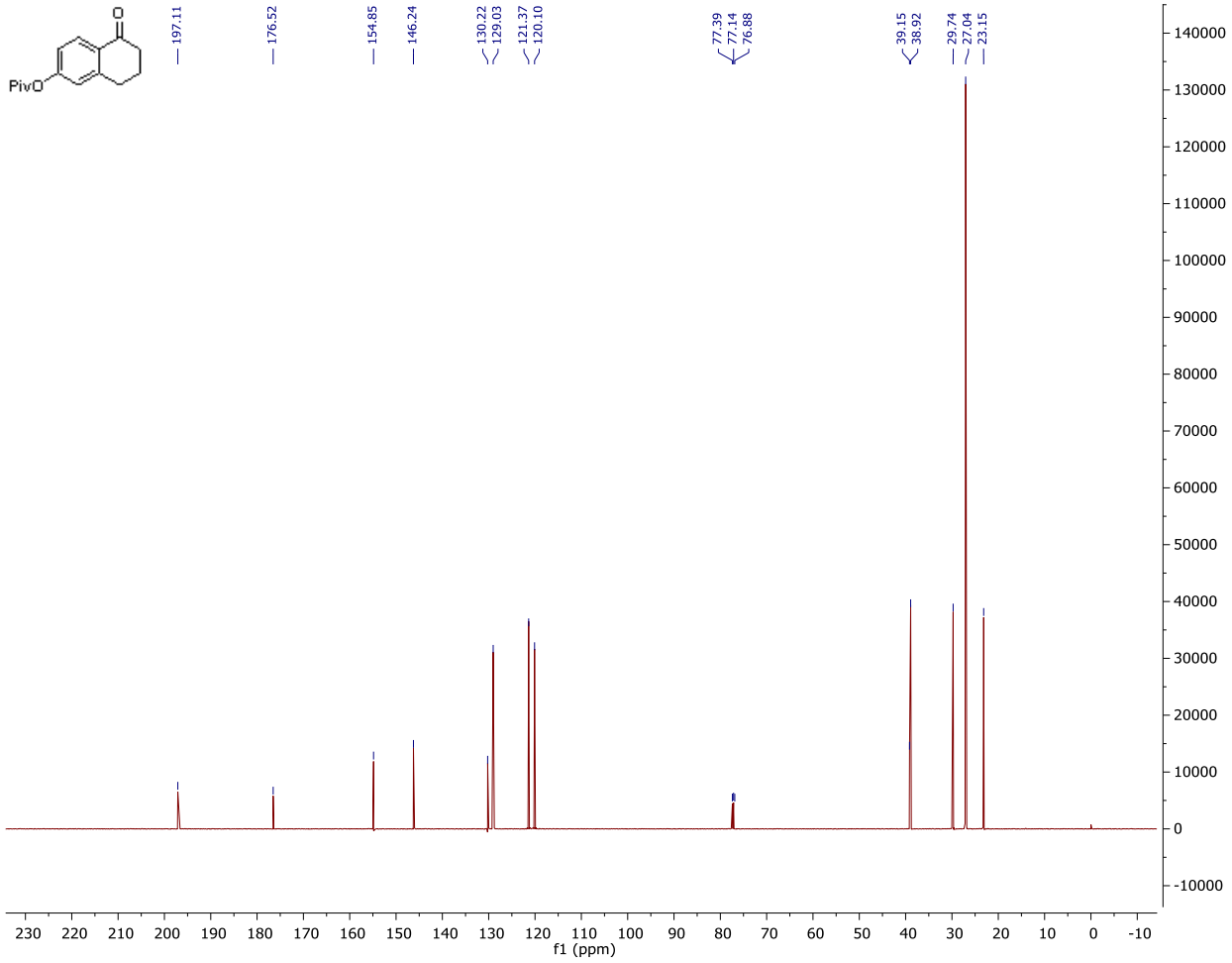


5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl pivalate

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

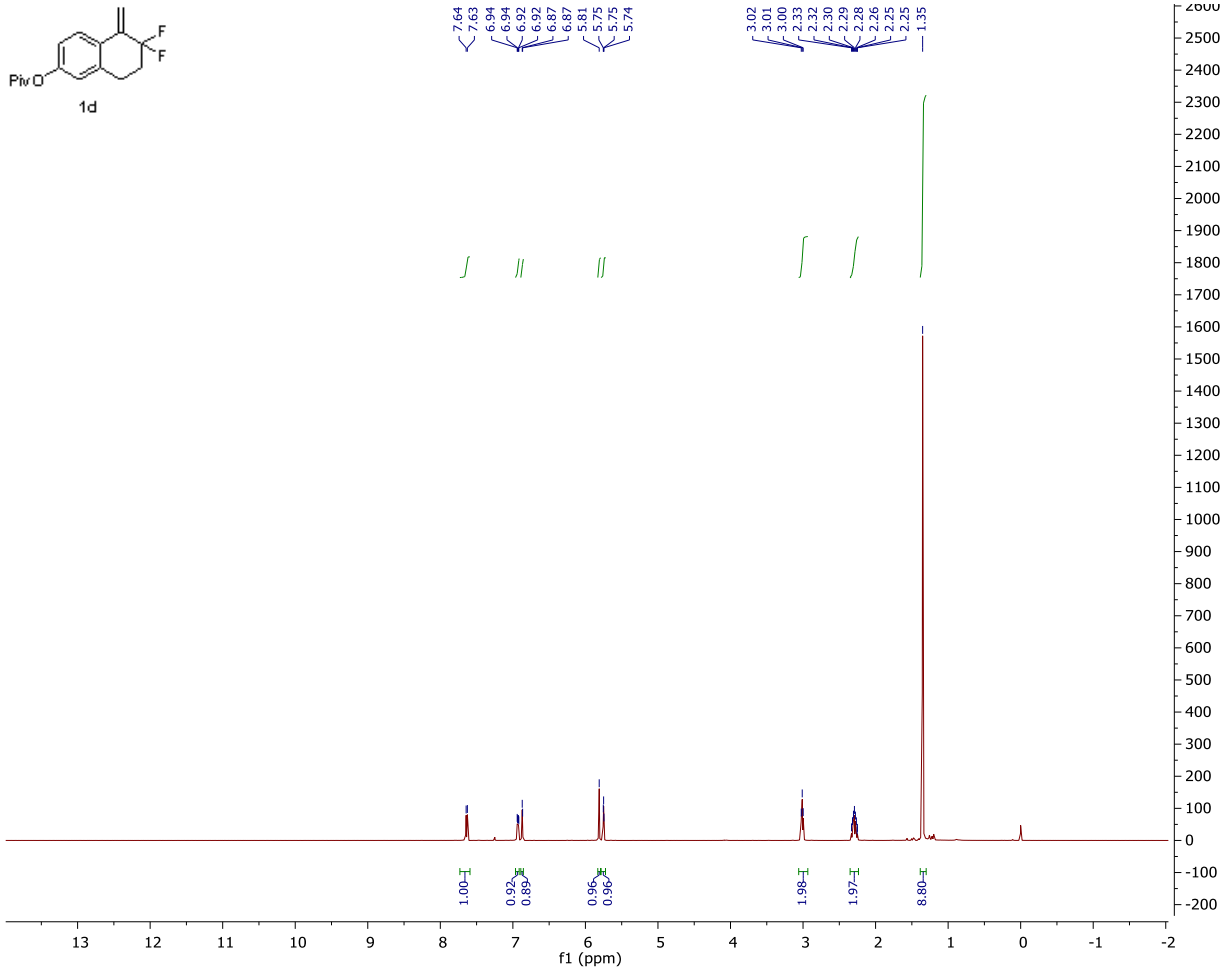


^{13}C (126 MHz, $CDCl_3$)

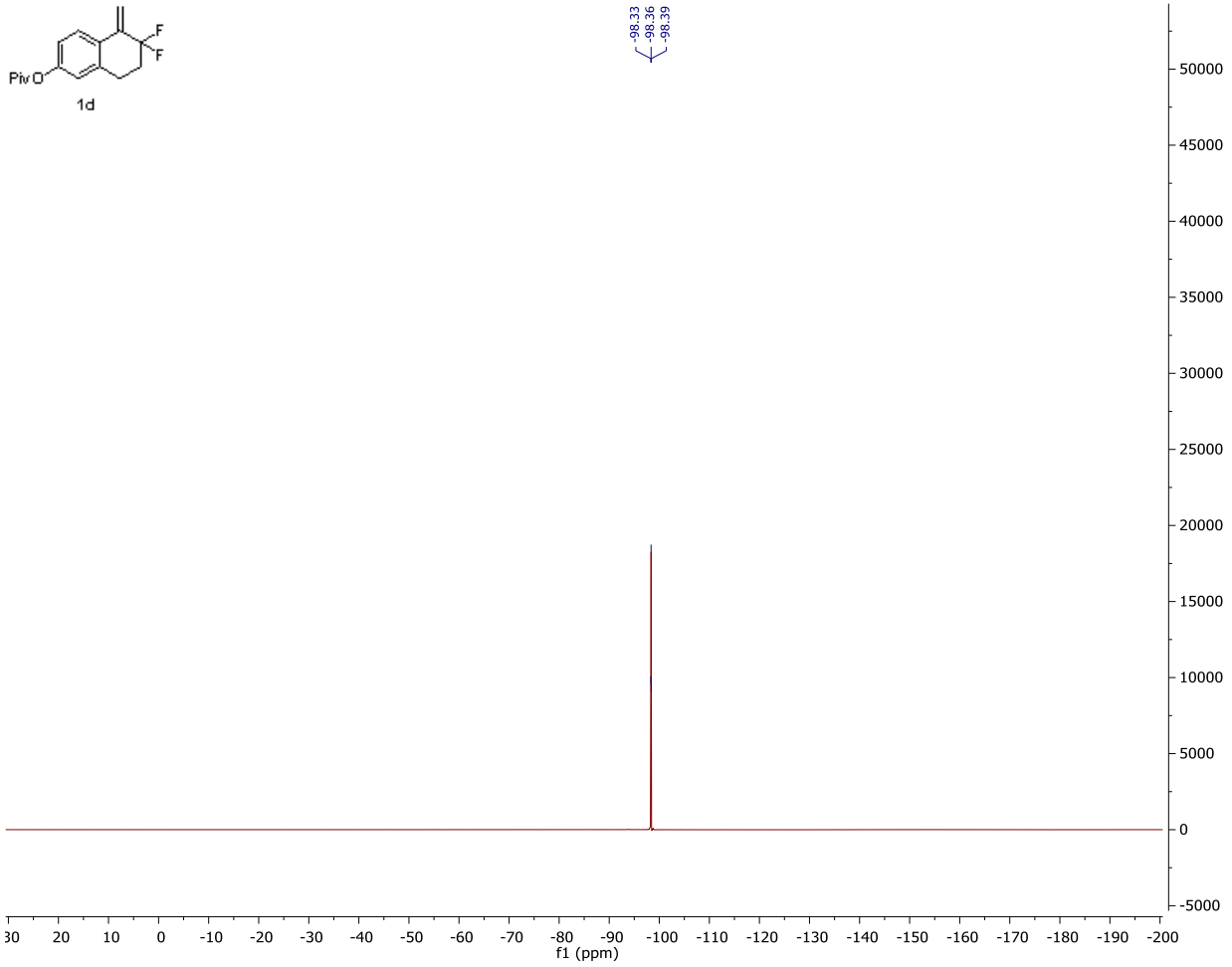


6,6-Difluoro-5-methylene-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (1d)

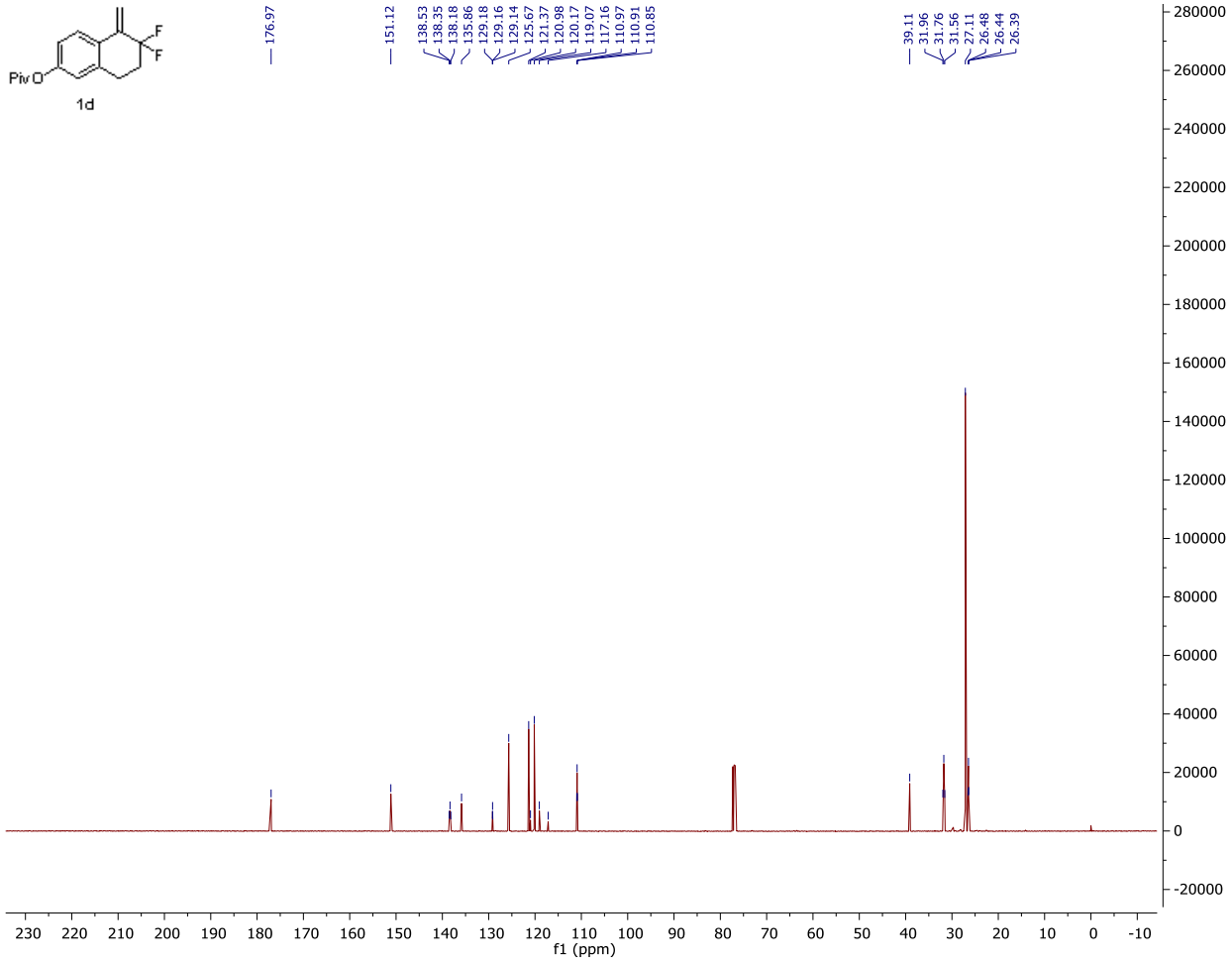
^{1}H (500 MHz, $CDCl_3$)



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

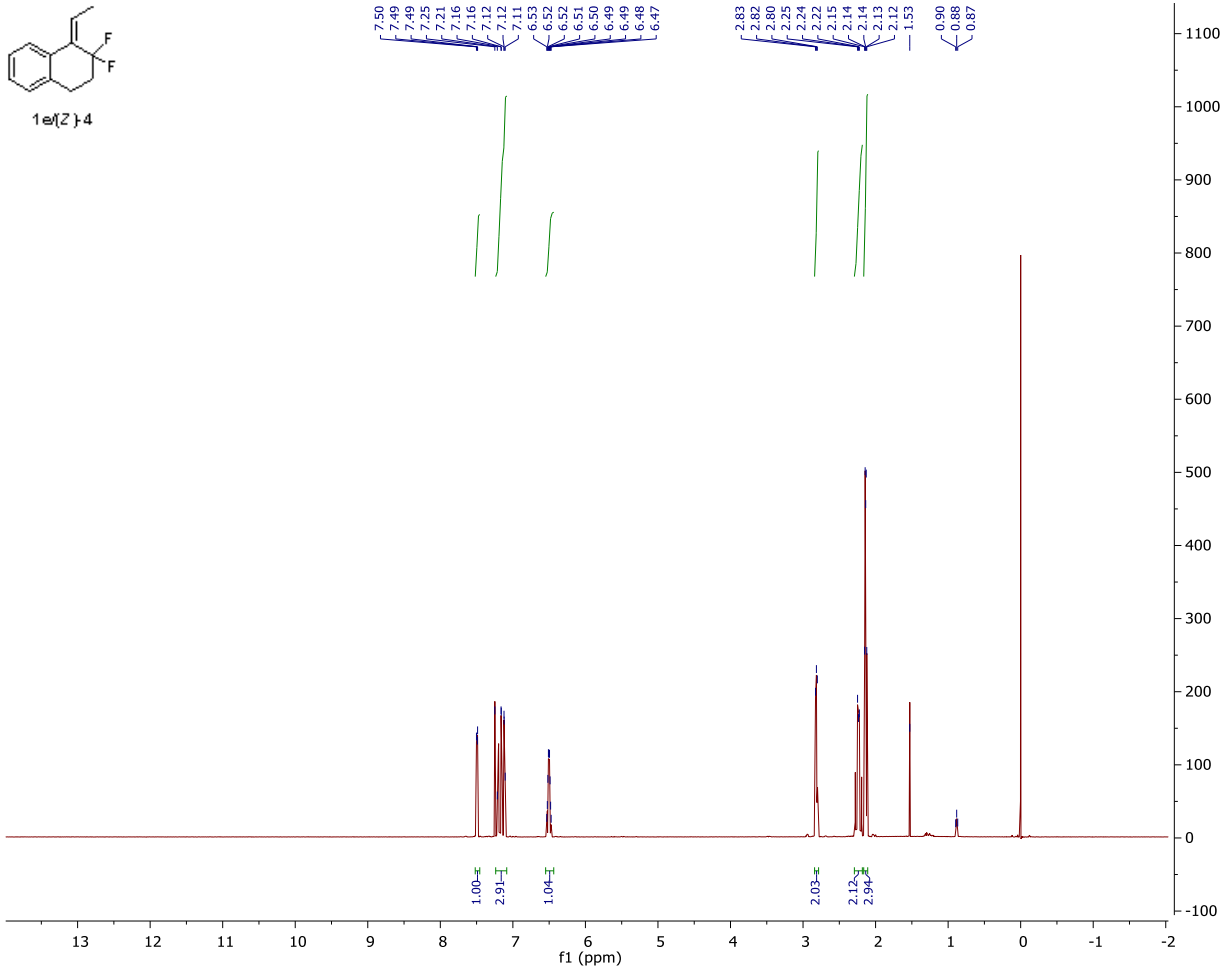


^{13}H (126 MHz, $CDCl_3$)

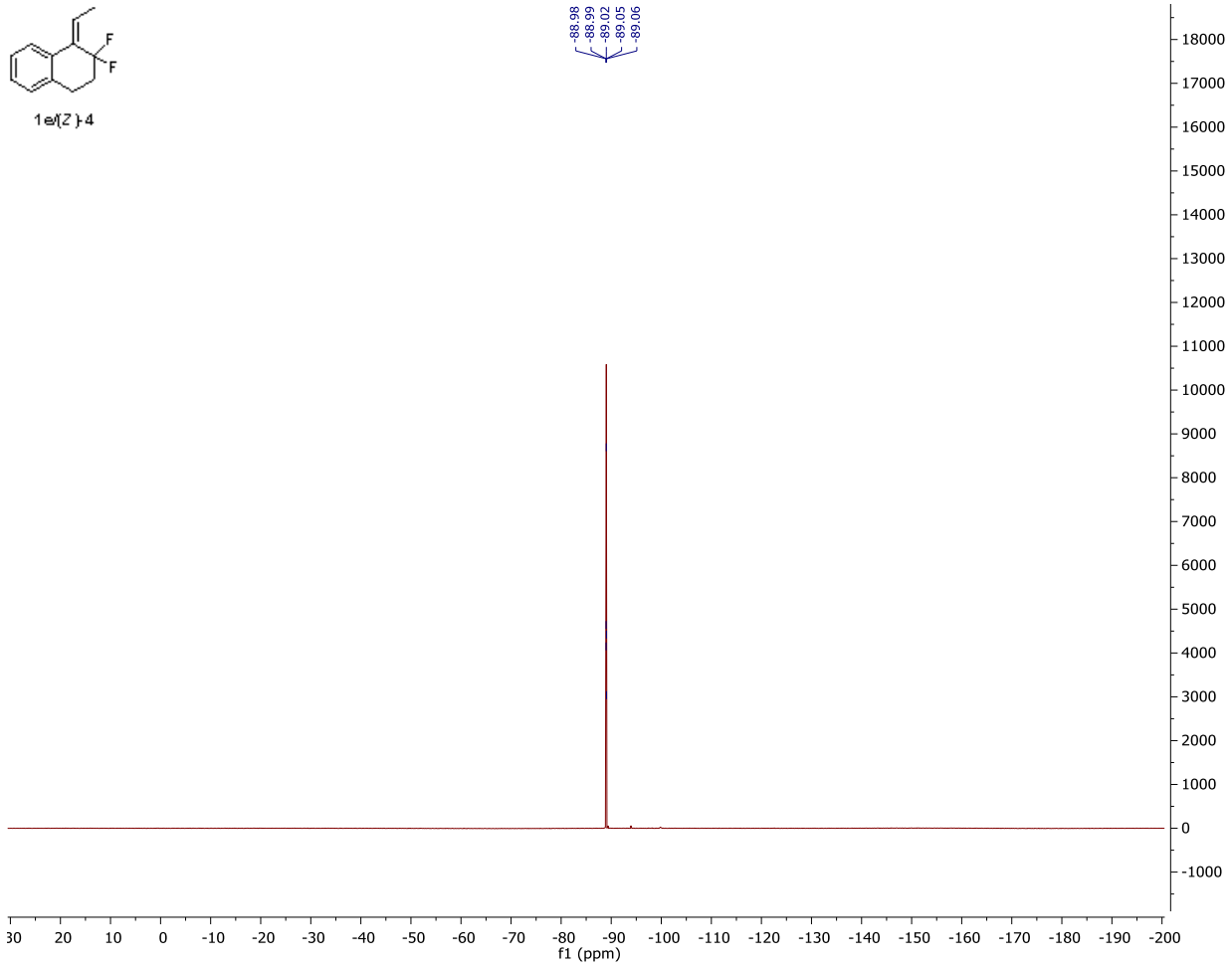


(*Z*)-1-Ethylidene-2,2-difluoro-1,2,3,4-tetrahydronaphtalene (1e/(*Z*)-4)

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

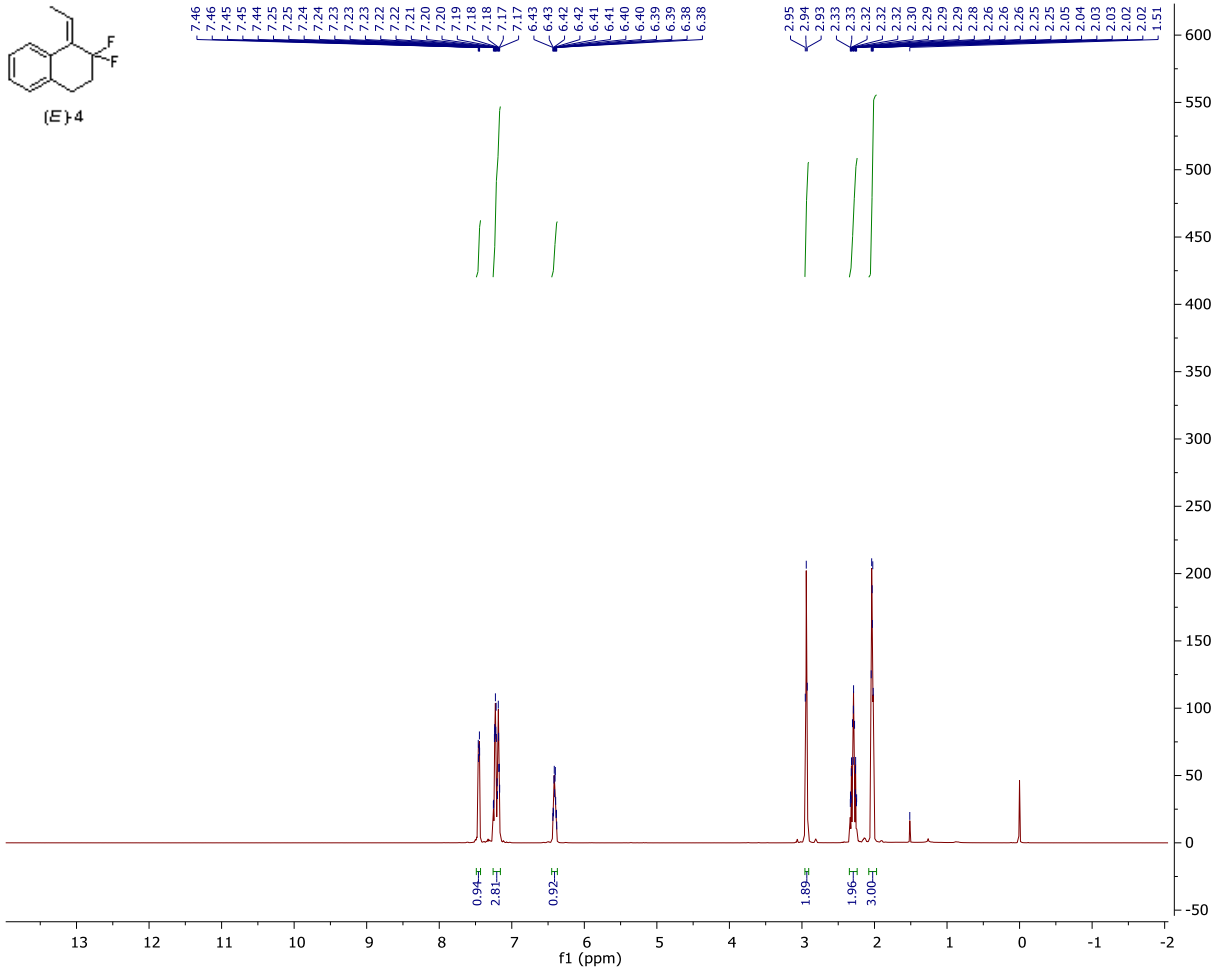


^{19}F (470 MHz, $CDCl_3$)

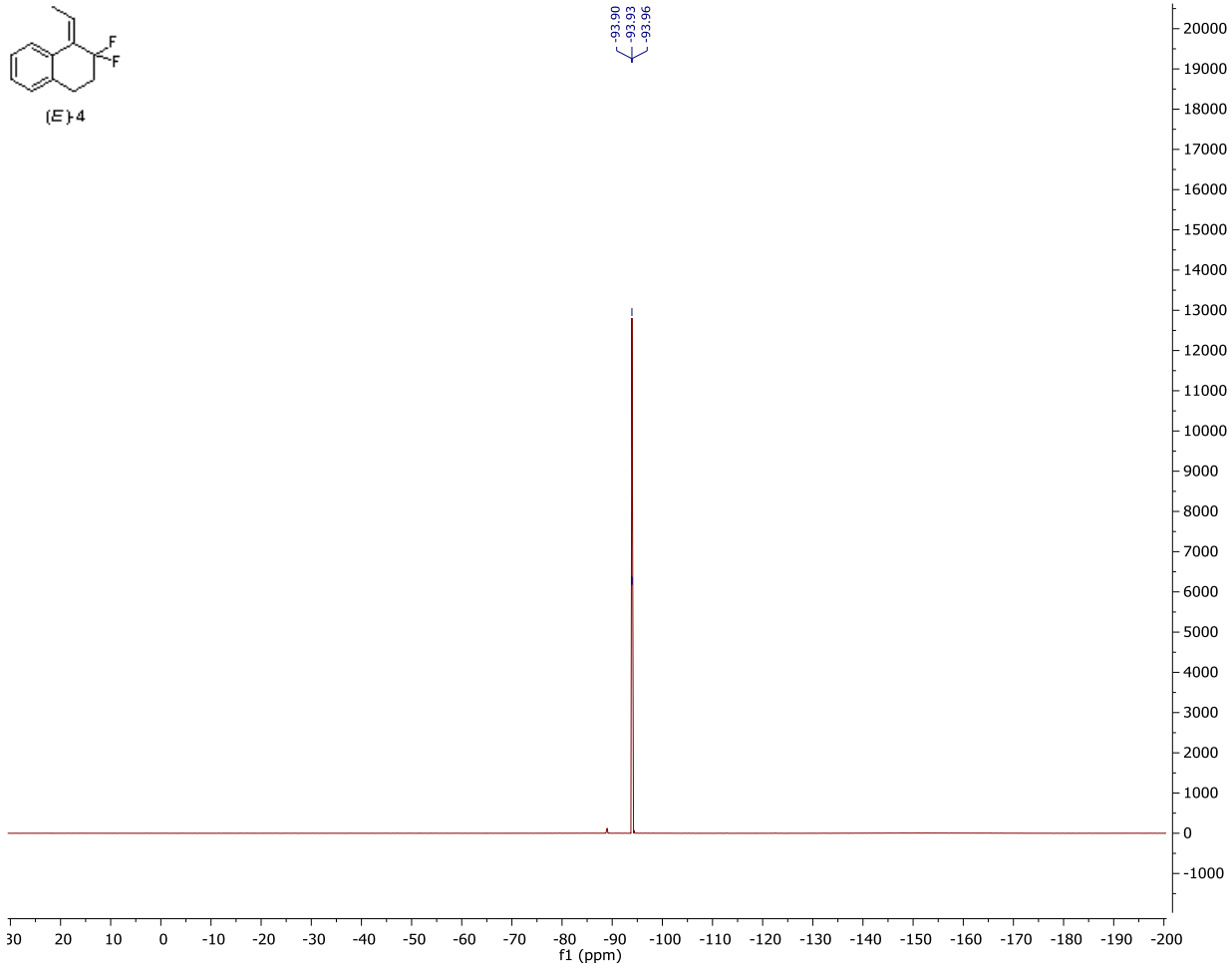


(*E*)-1-Ethylidene-2,2-difluoro-1,2,3,4-tetrahydronaphtalene ((*E*)-4)

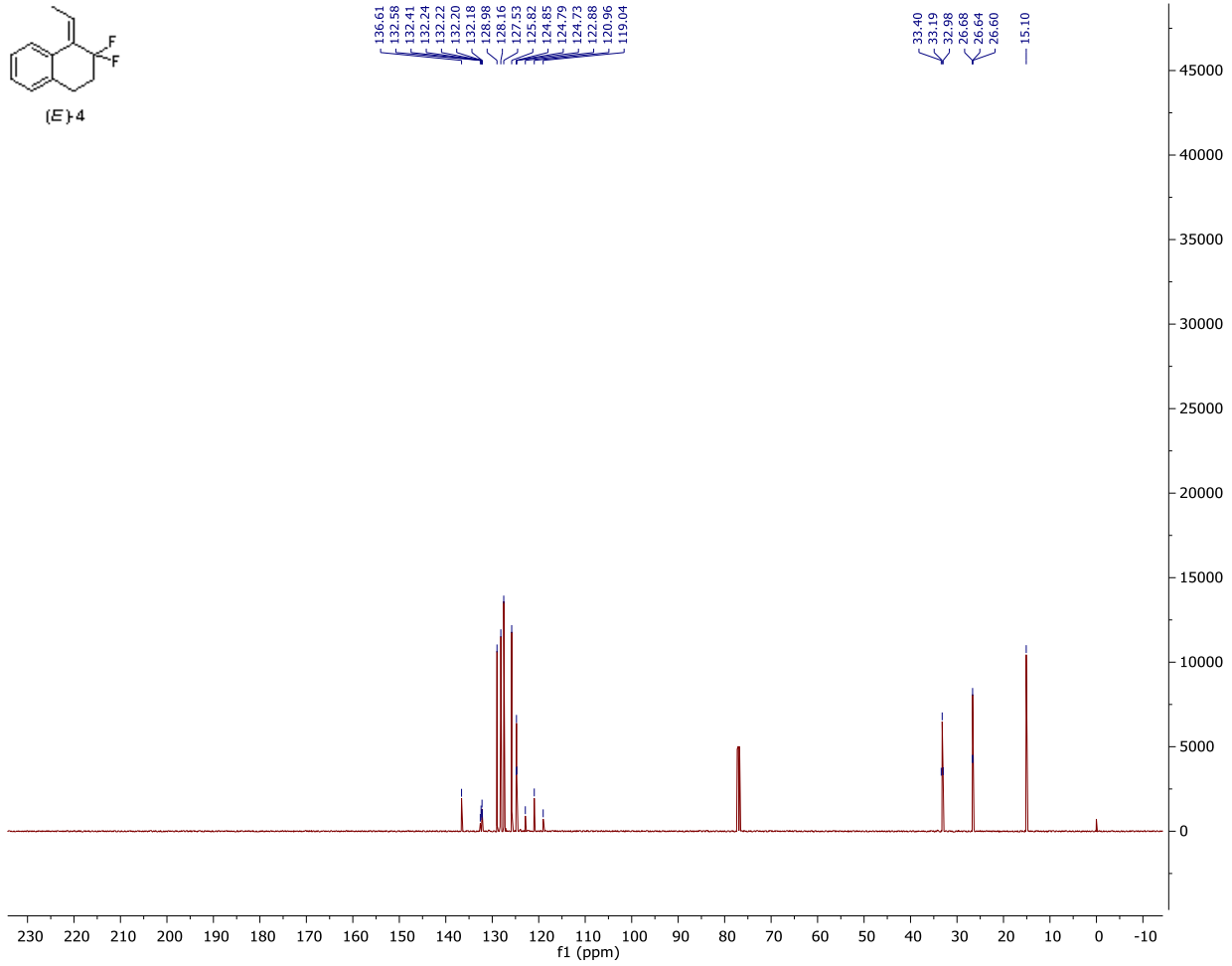
^{1}H (500 MHz, $CDCl_3$)



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

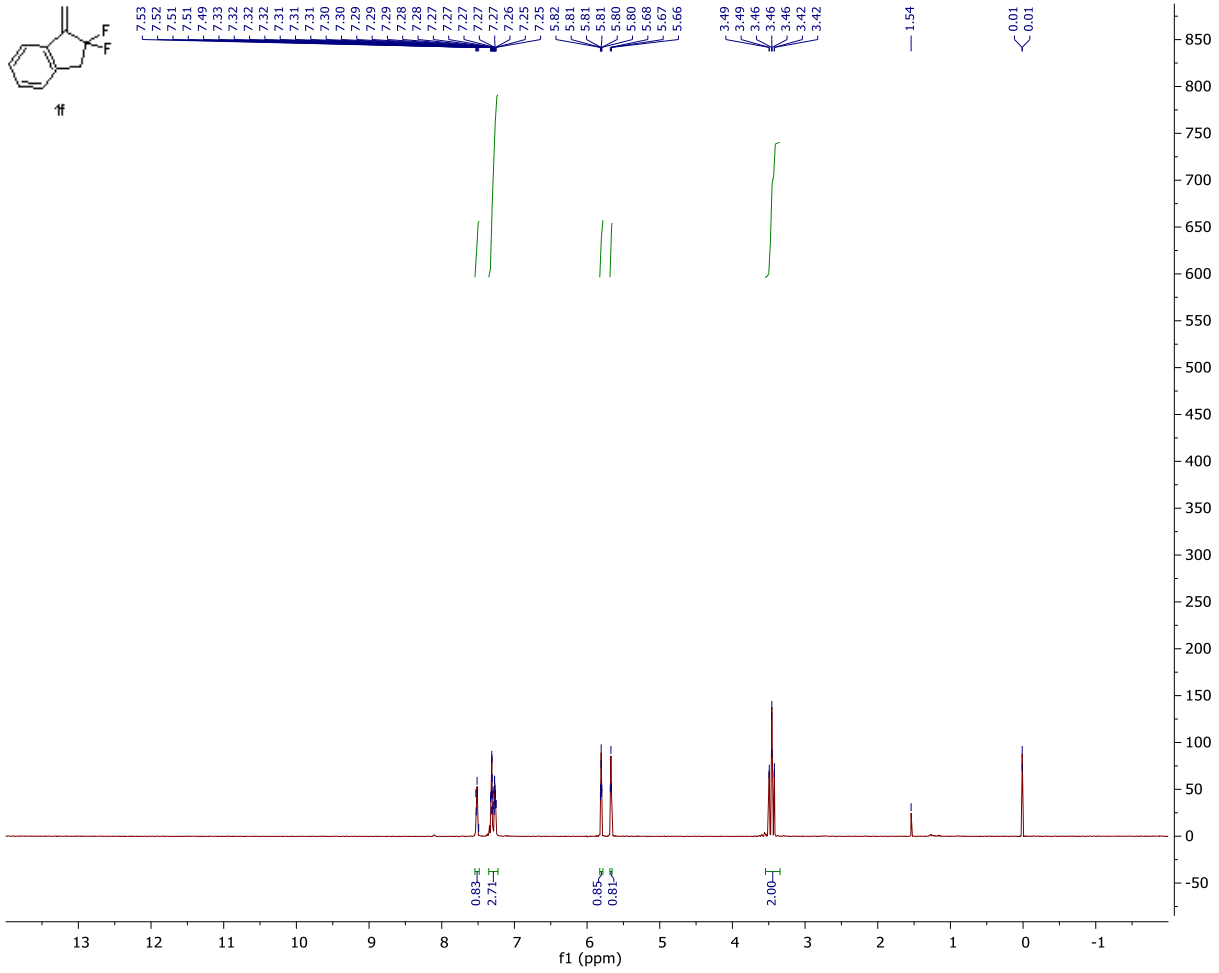


^{13}C (126 MHz, $CDCl_3$)



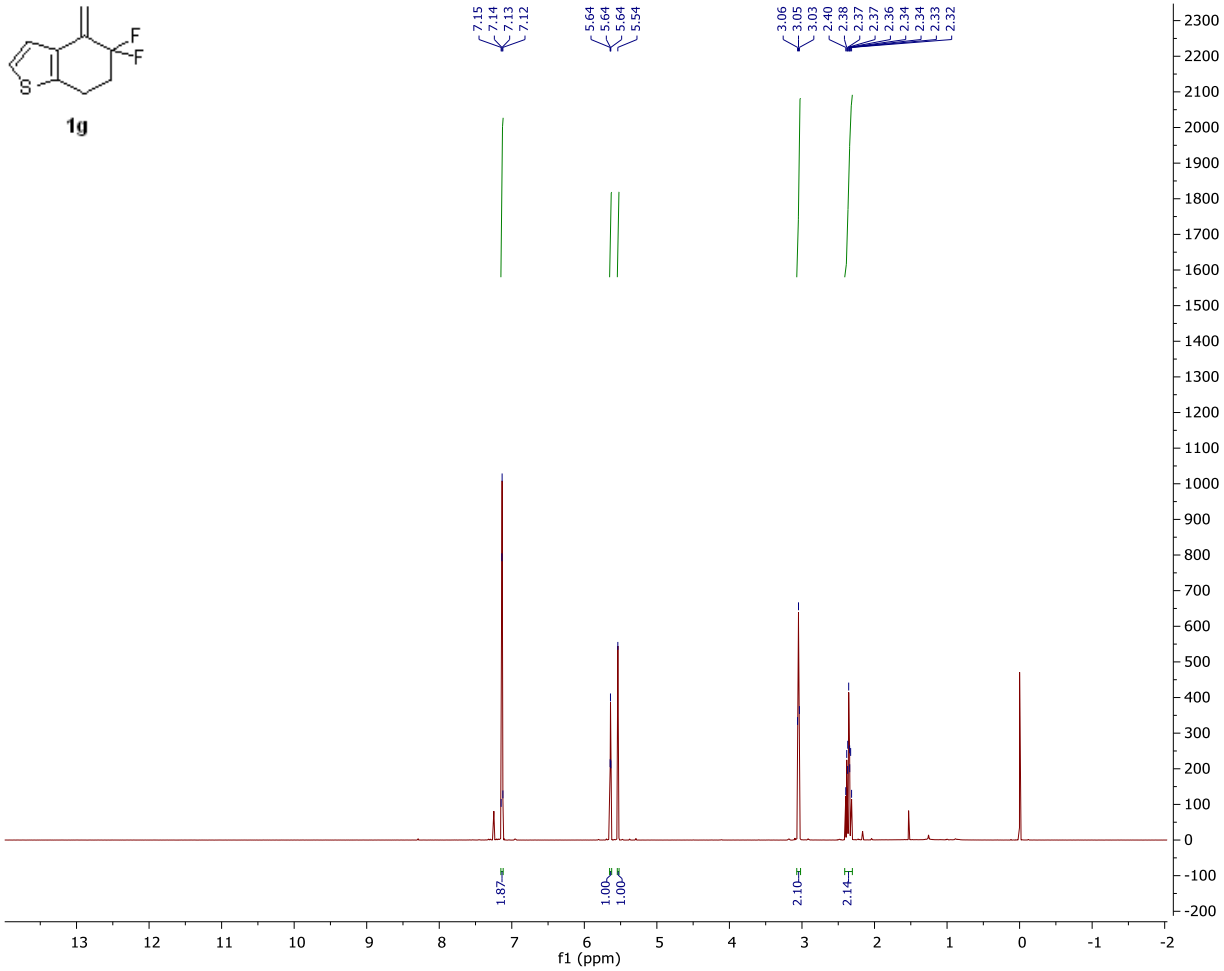
2,2-Difluoro-1-methylene-2,3-dihydro-1*H*-indene (1f)

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

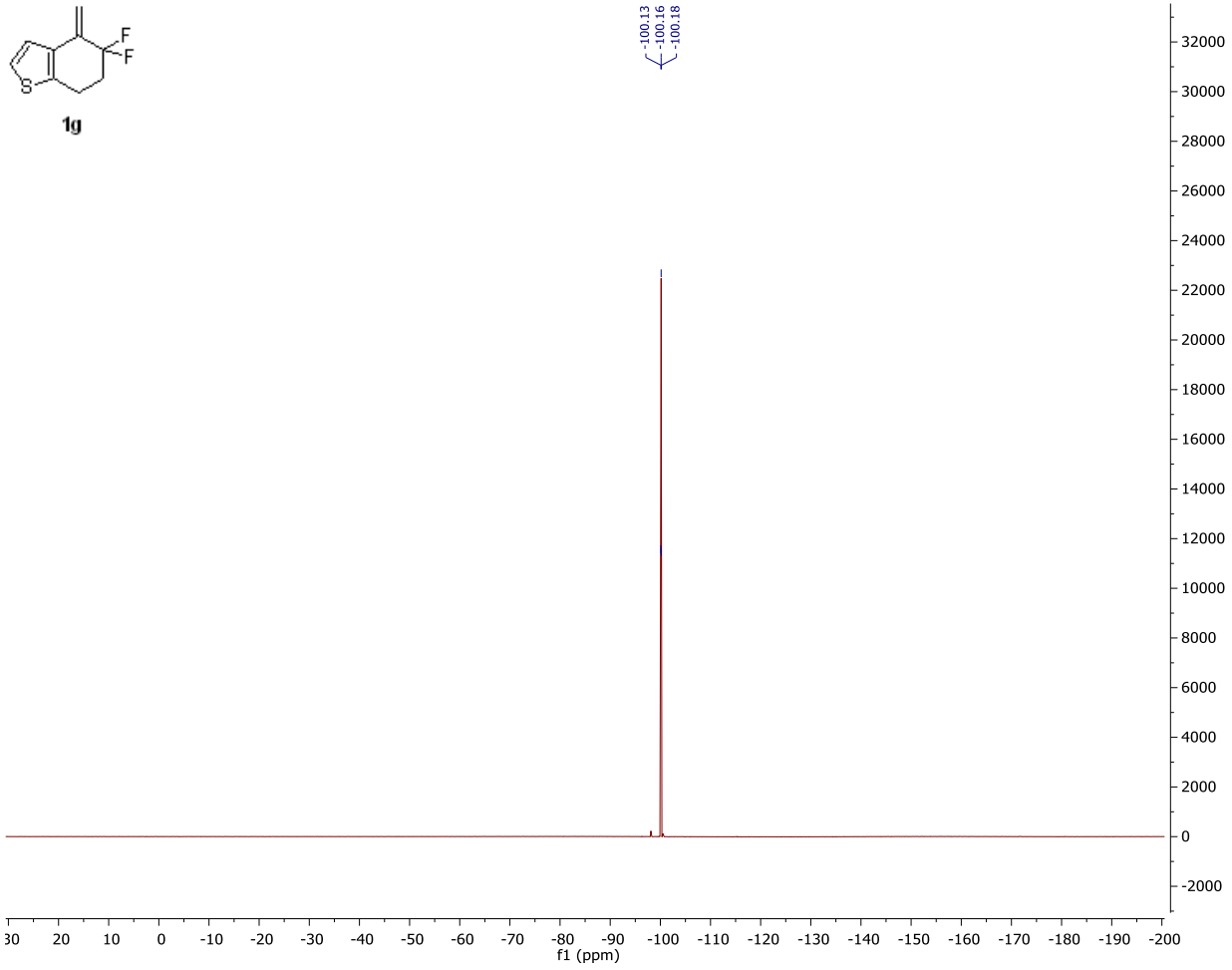


5,5-Difluoro-4-methylene-4,5,6,7-tetrahydrobenzo[*b*]thiophene (1g)

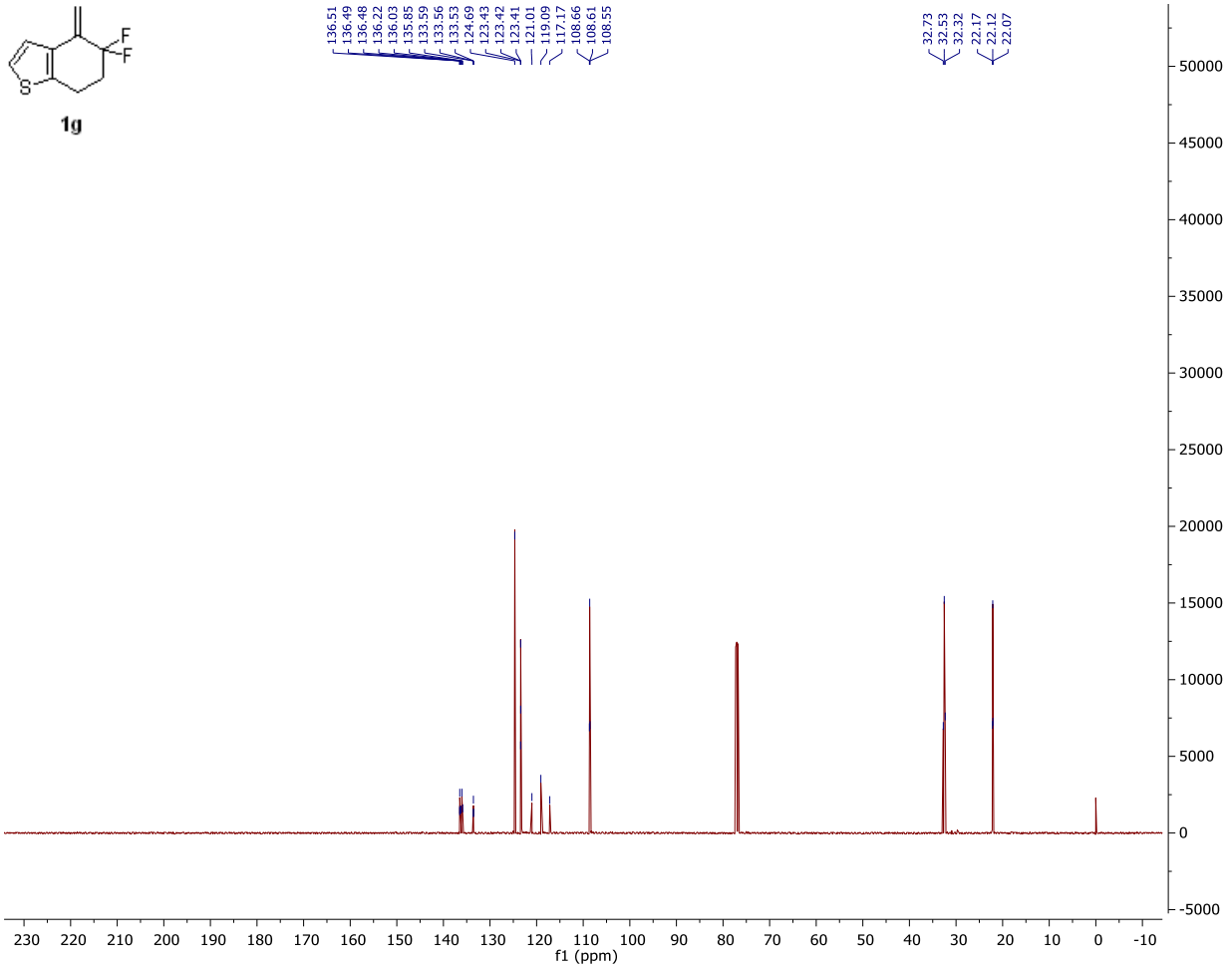
^{1}H (500 MHz, $CDCl_3$)



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

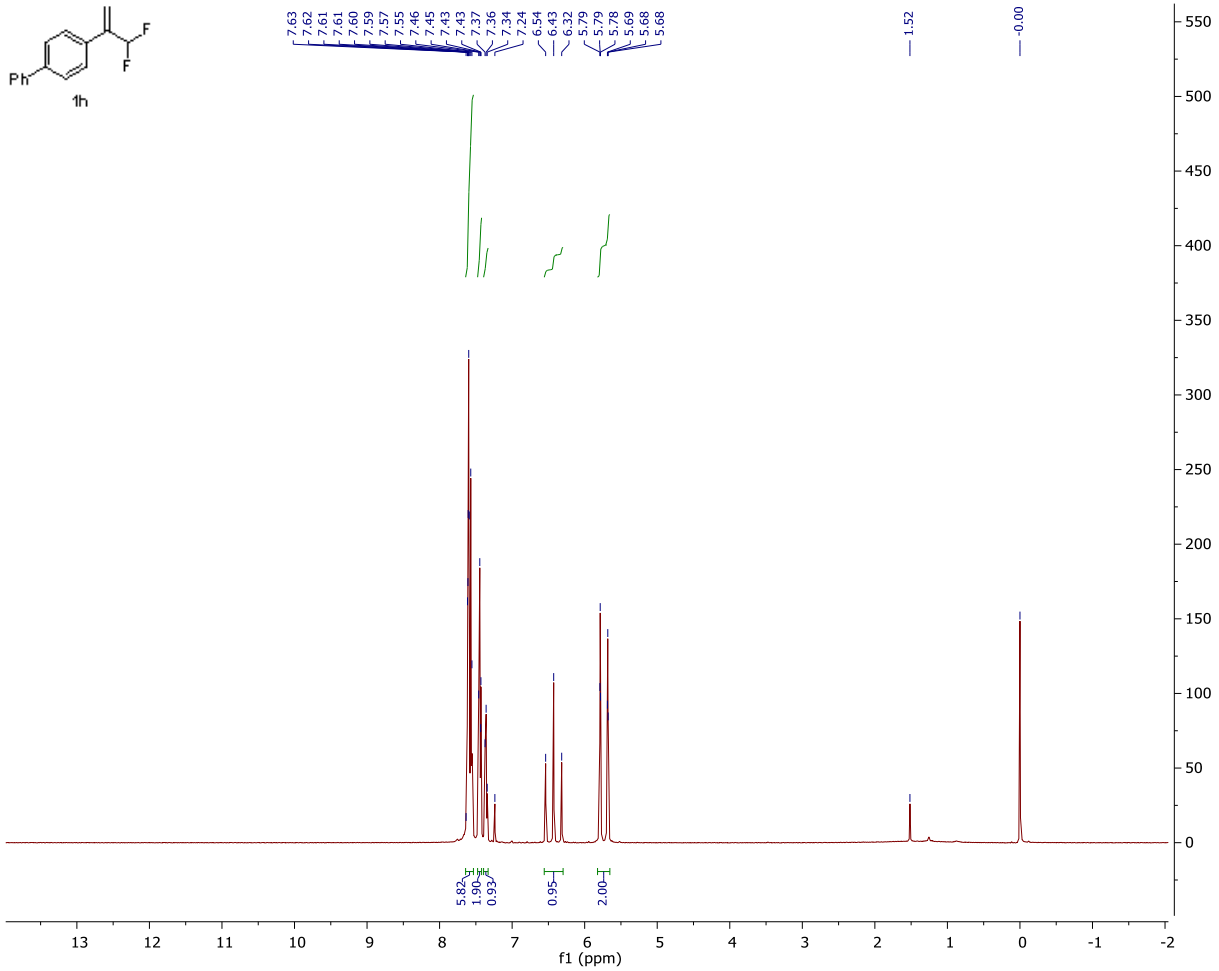


^{13}C (126 MHz, $CDCl_3$)



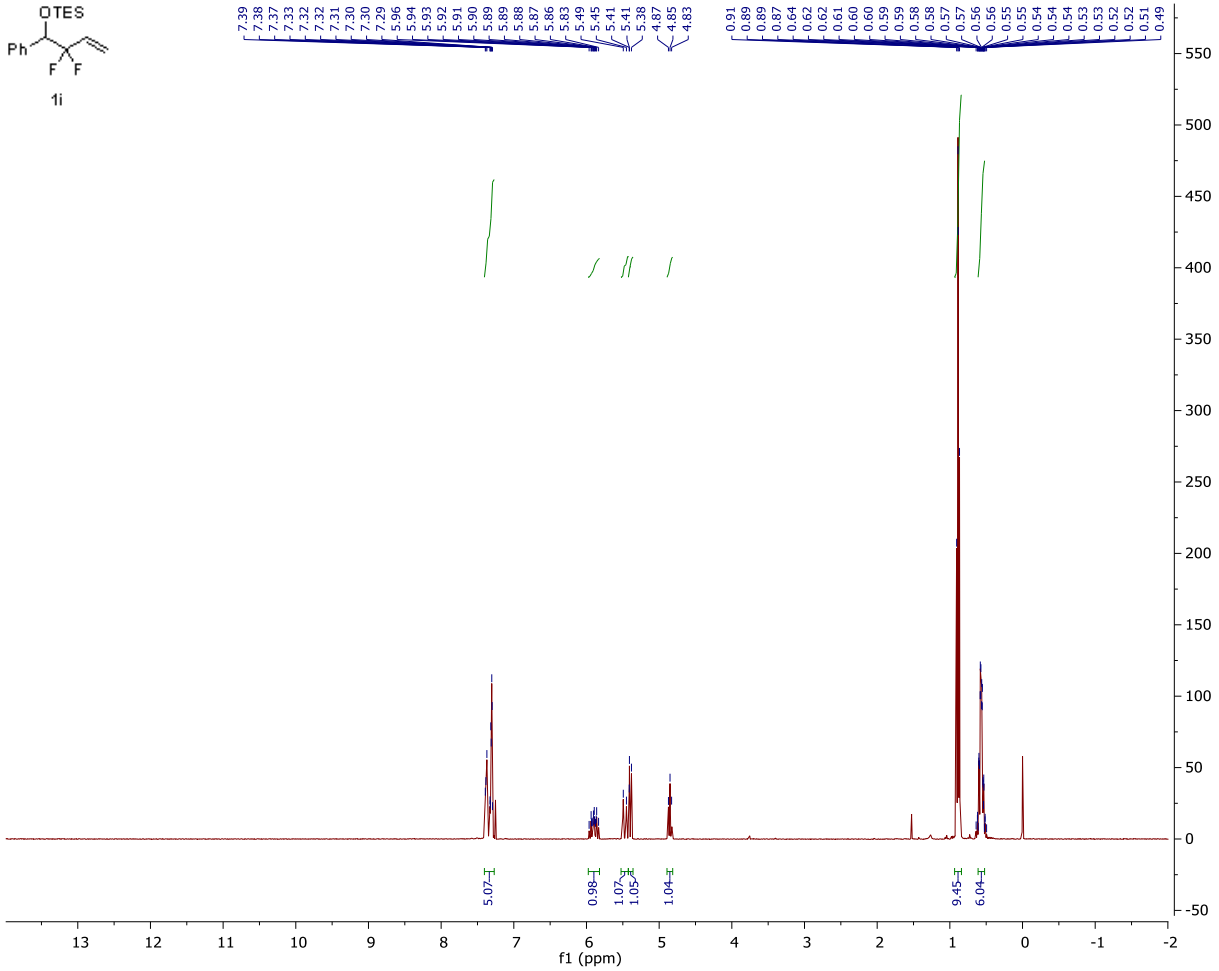
4-(3,3-Difluoroprop-1-en-2-yl)-1,1'-biphenyl (1h)

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

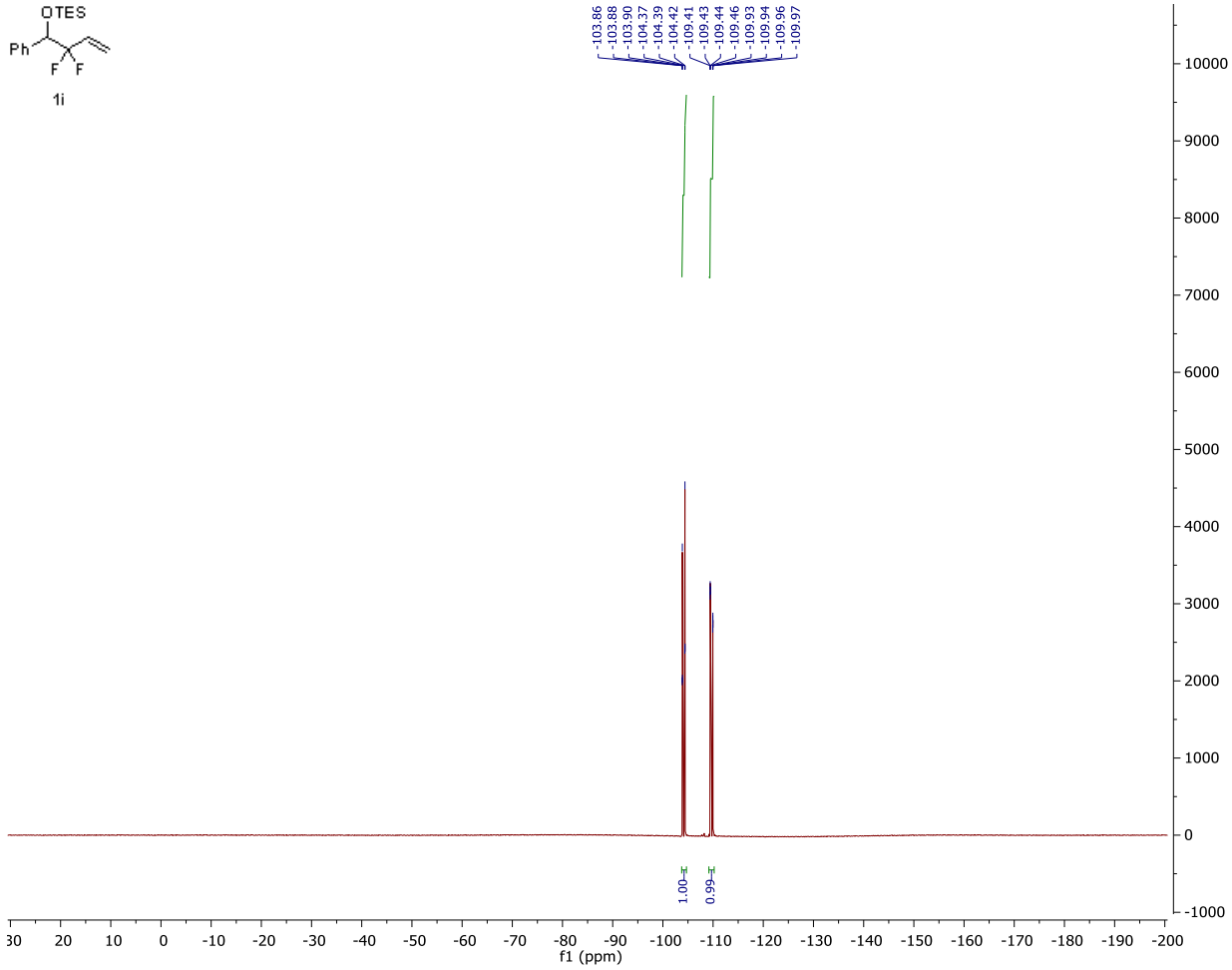


Triethylsilyl 2,2-difluoro-1-phenylbut-3-en-1-ol (1i)

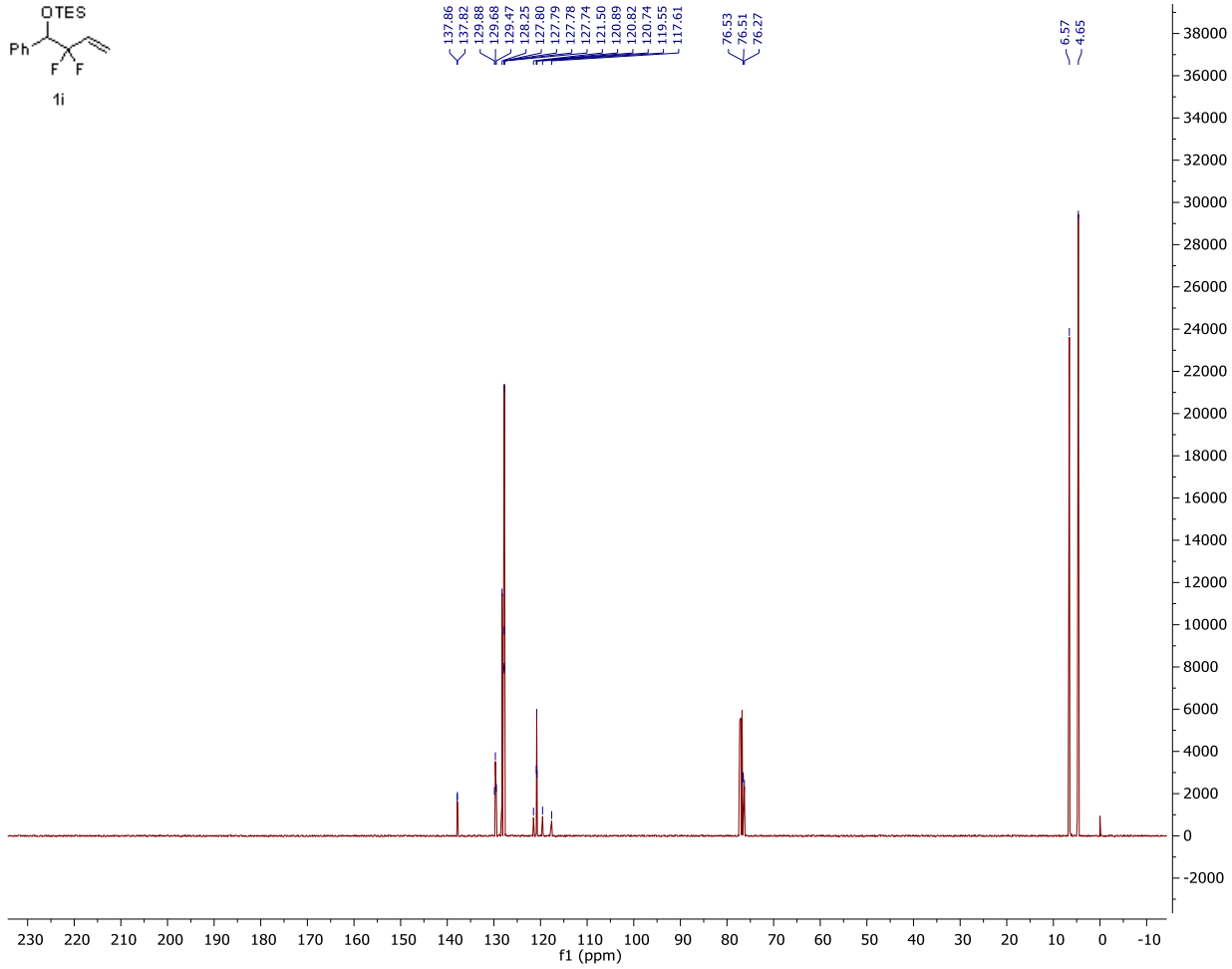
^{1}H (500 MHz, $CDCl_3$)



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

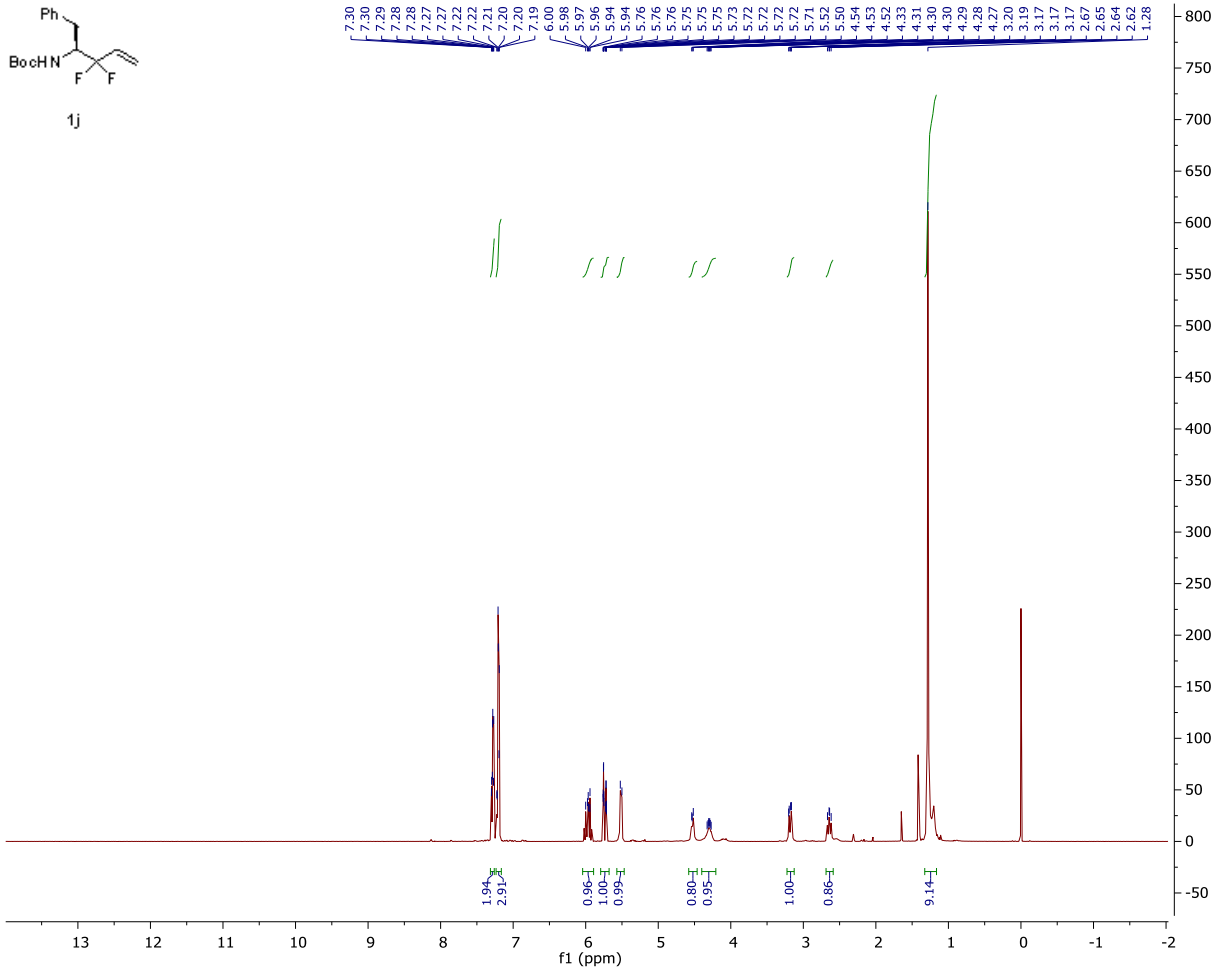


^{13}C (126 MHz, $CDCl_3$)



(*S*)-*tert*-Butyl (3,3-difluoro-1-phenylpent-4-en-2-yl)carbamate (1j)

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



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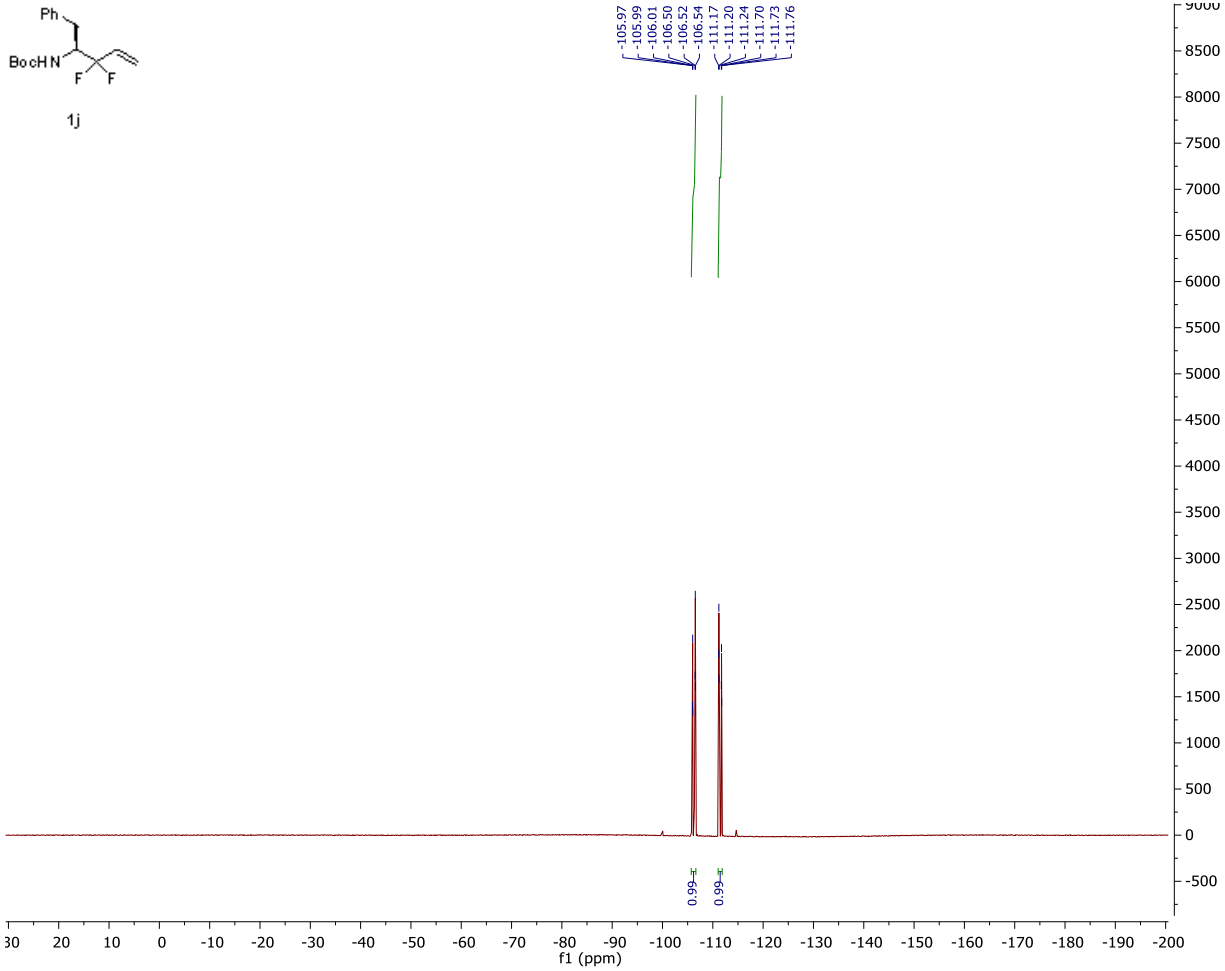

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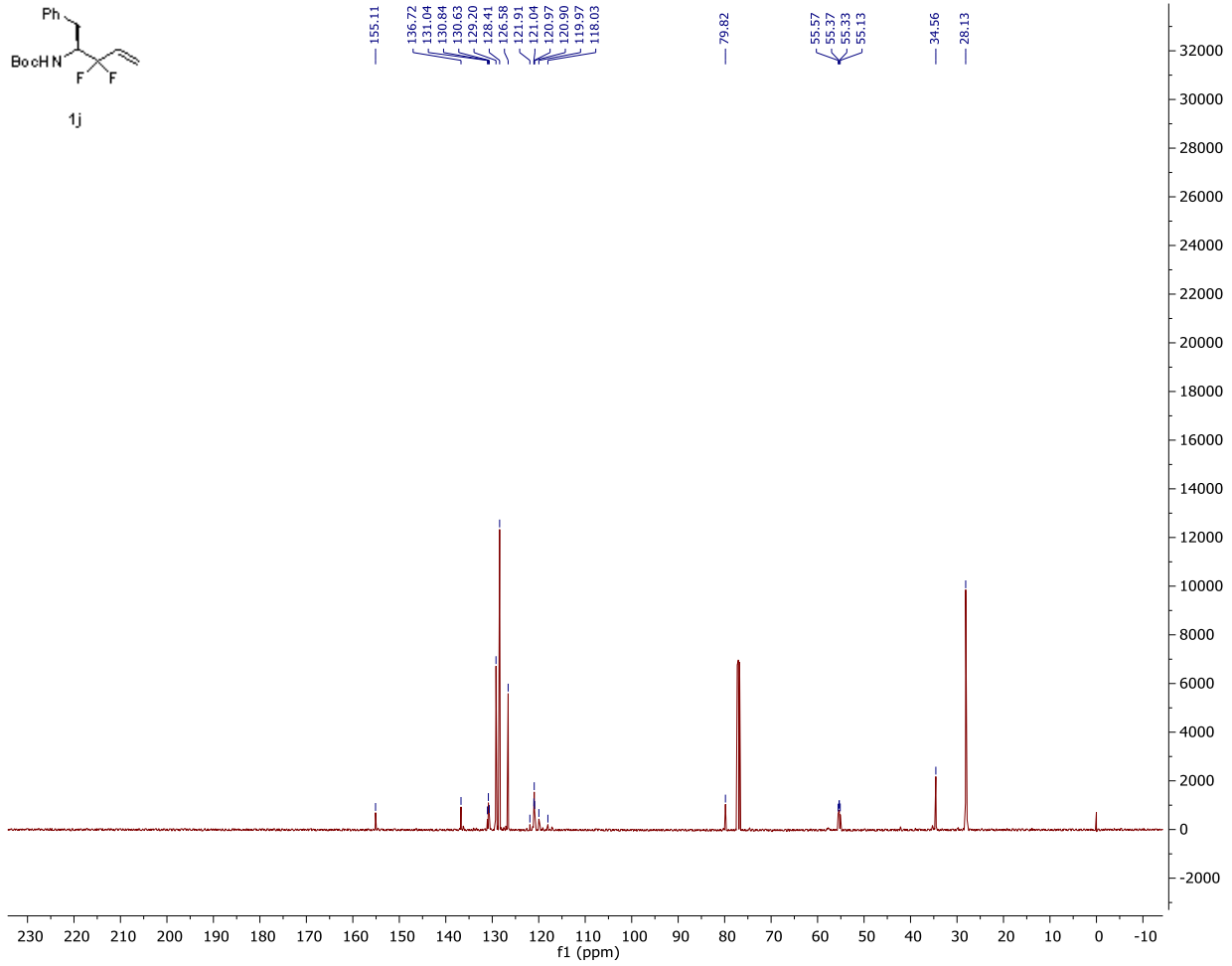
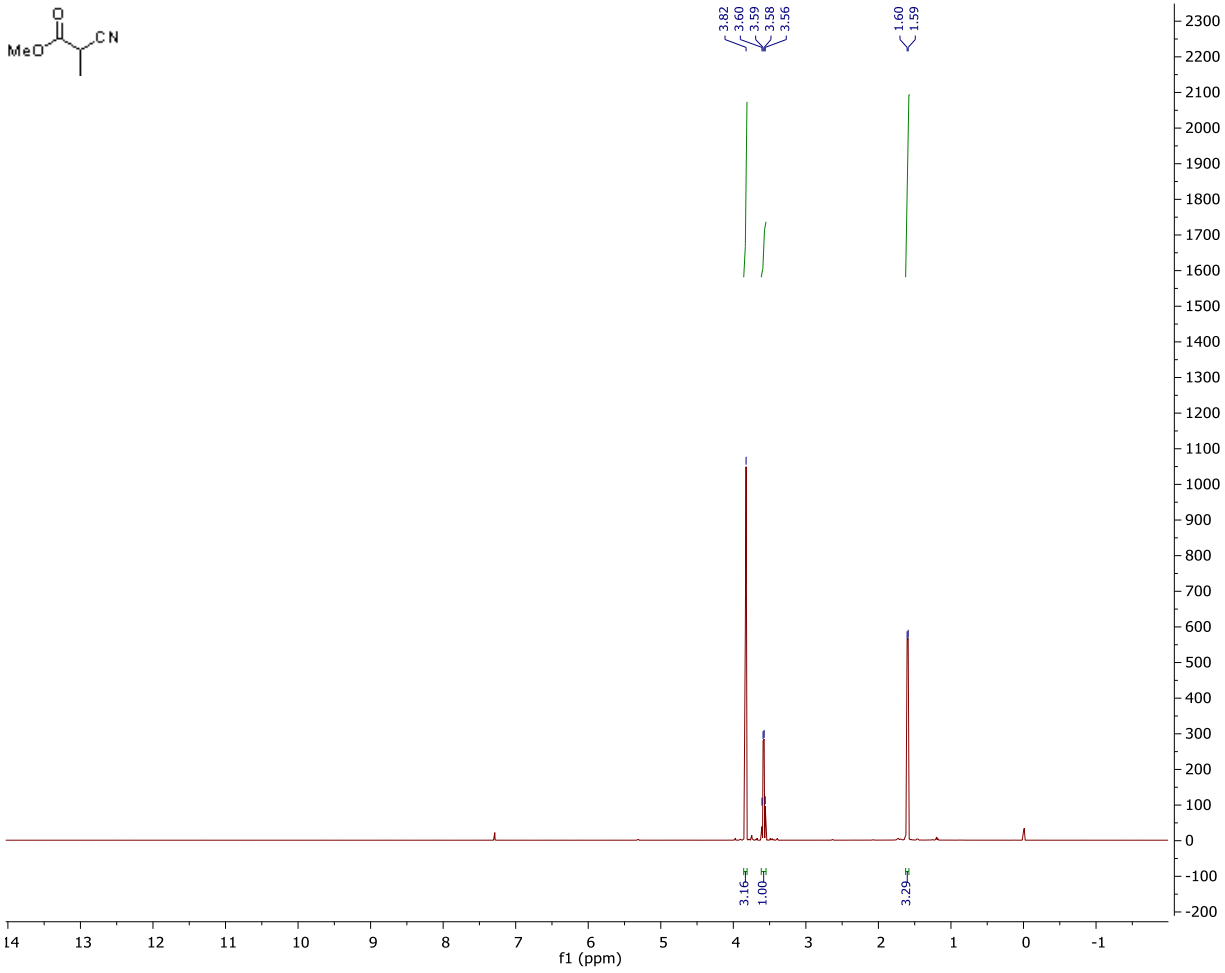
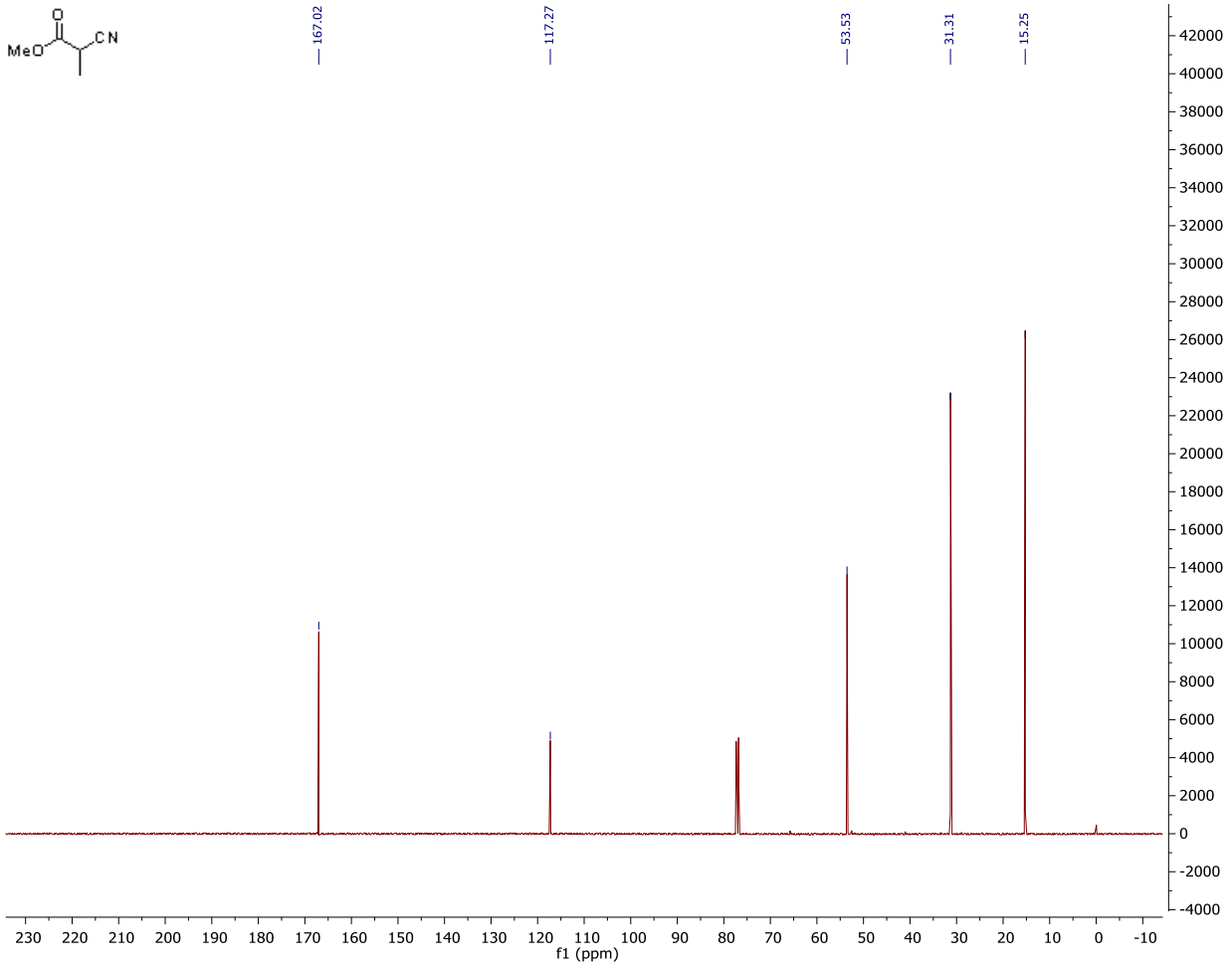


Methyl 2-cyanopropanoate

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

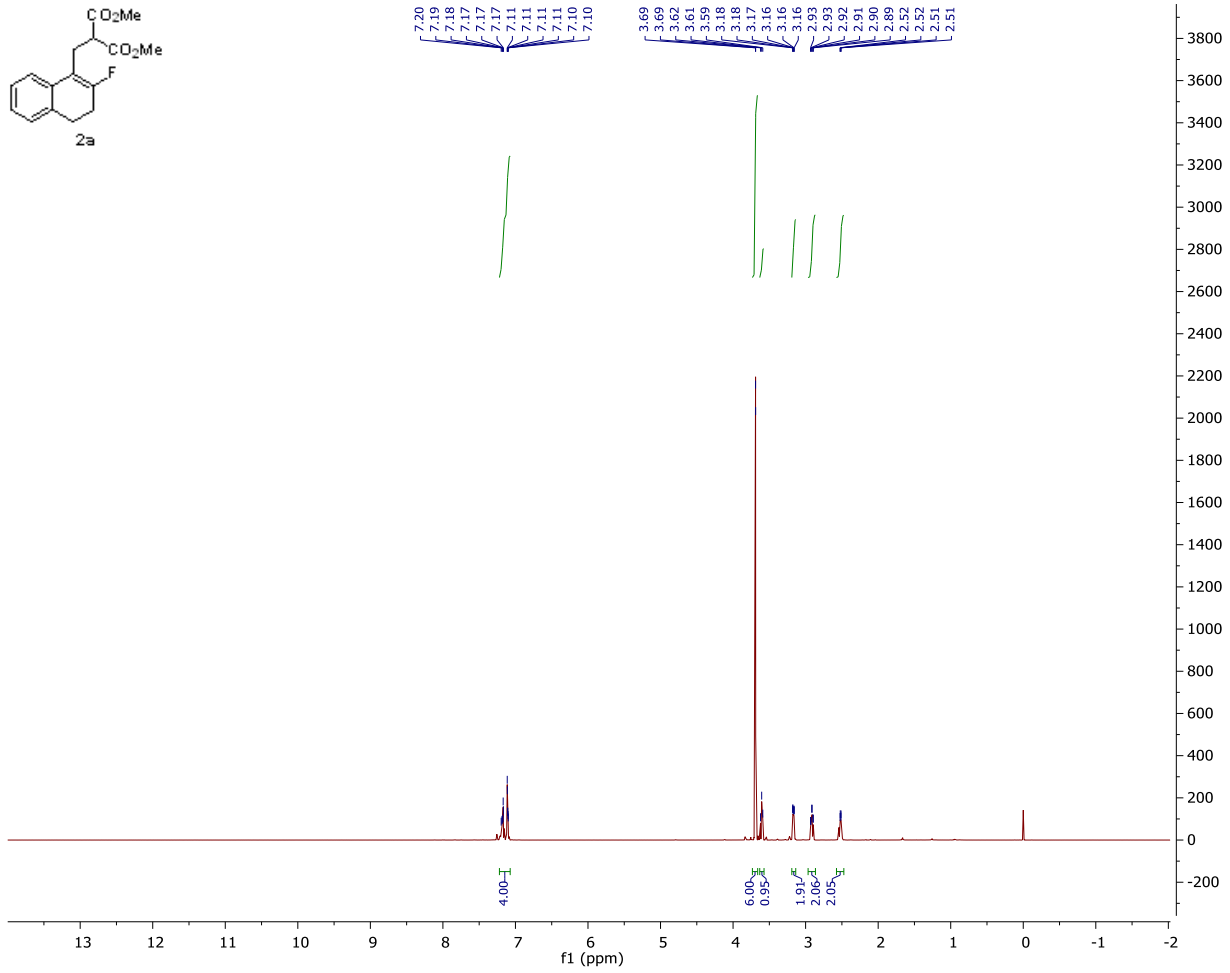


^{13}C (126 MHz, $CDCl_3$)



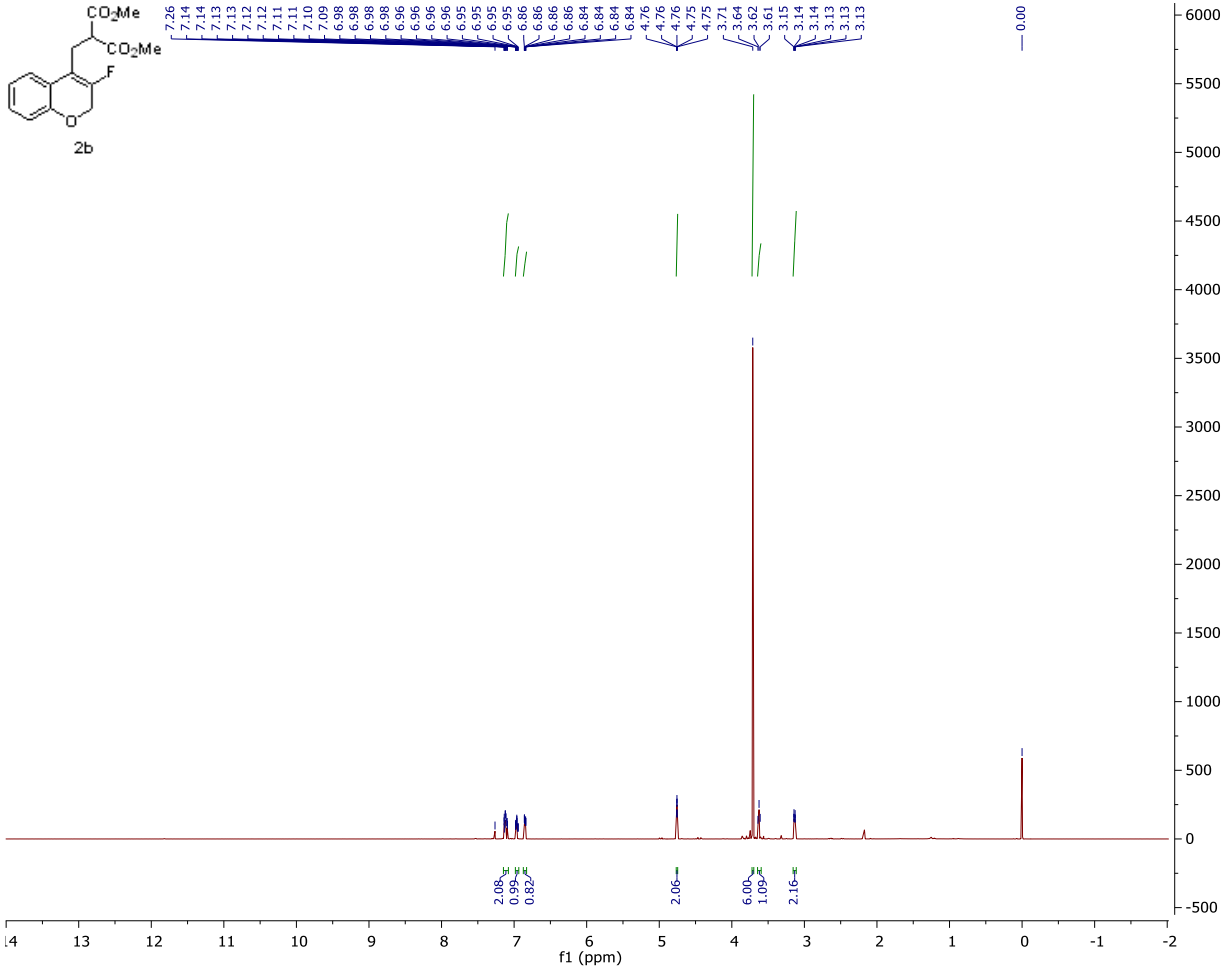
Dimethyl 2-((2-fluoro-3,4-dihydronaphthalen-1-yl)methyl)malonate (2a)

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

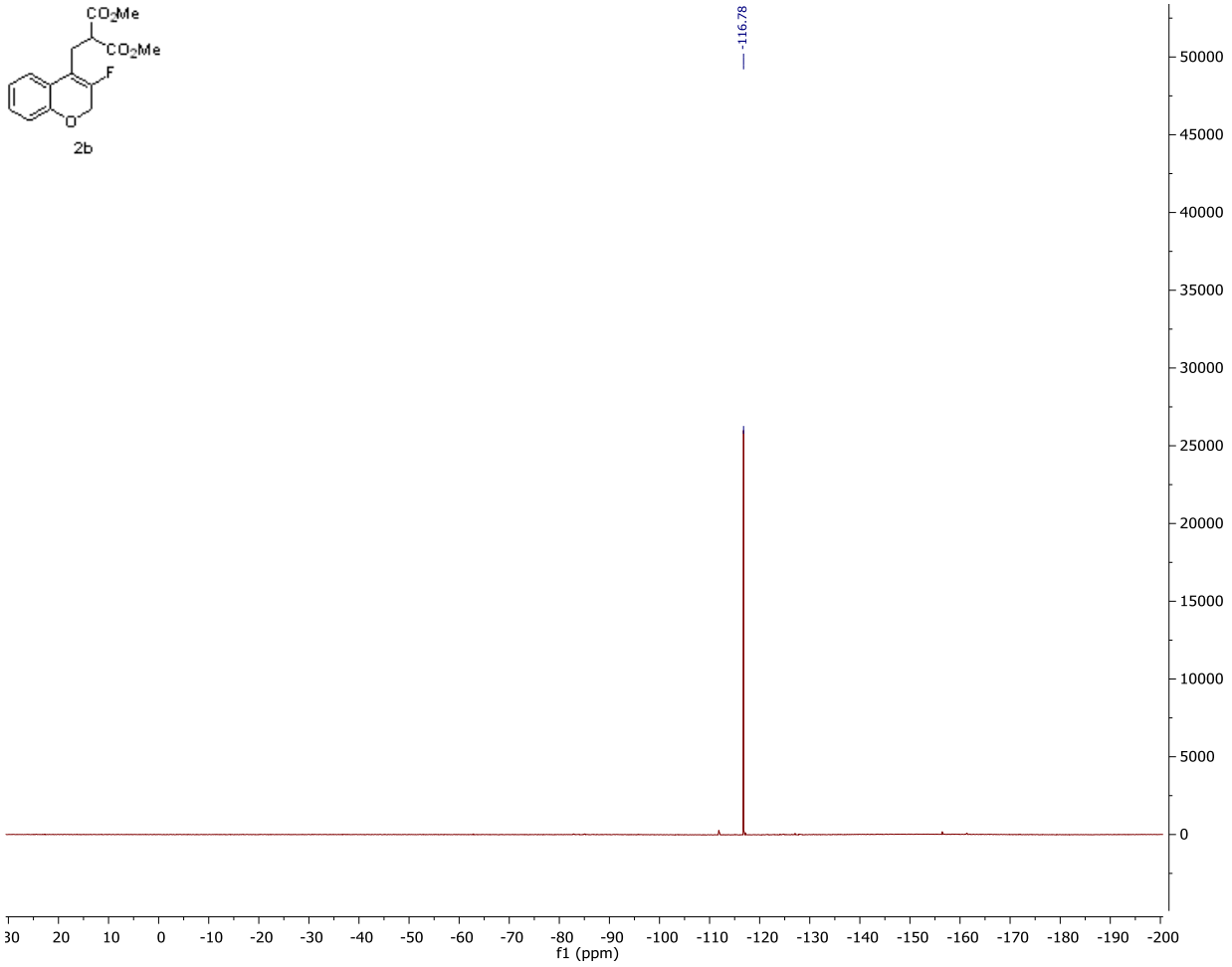


Dimethyl 2-((3-fluoro-2*H*-chromen-4-yl)methyl)malonate (2b)

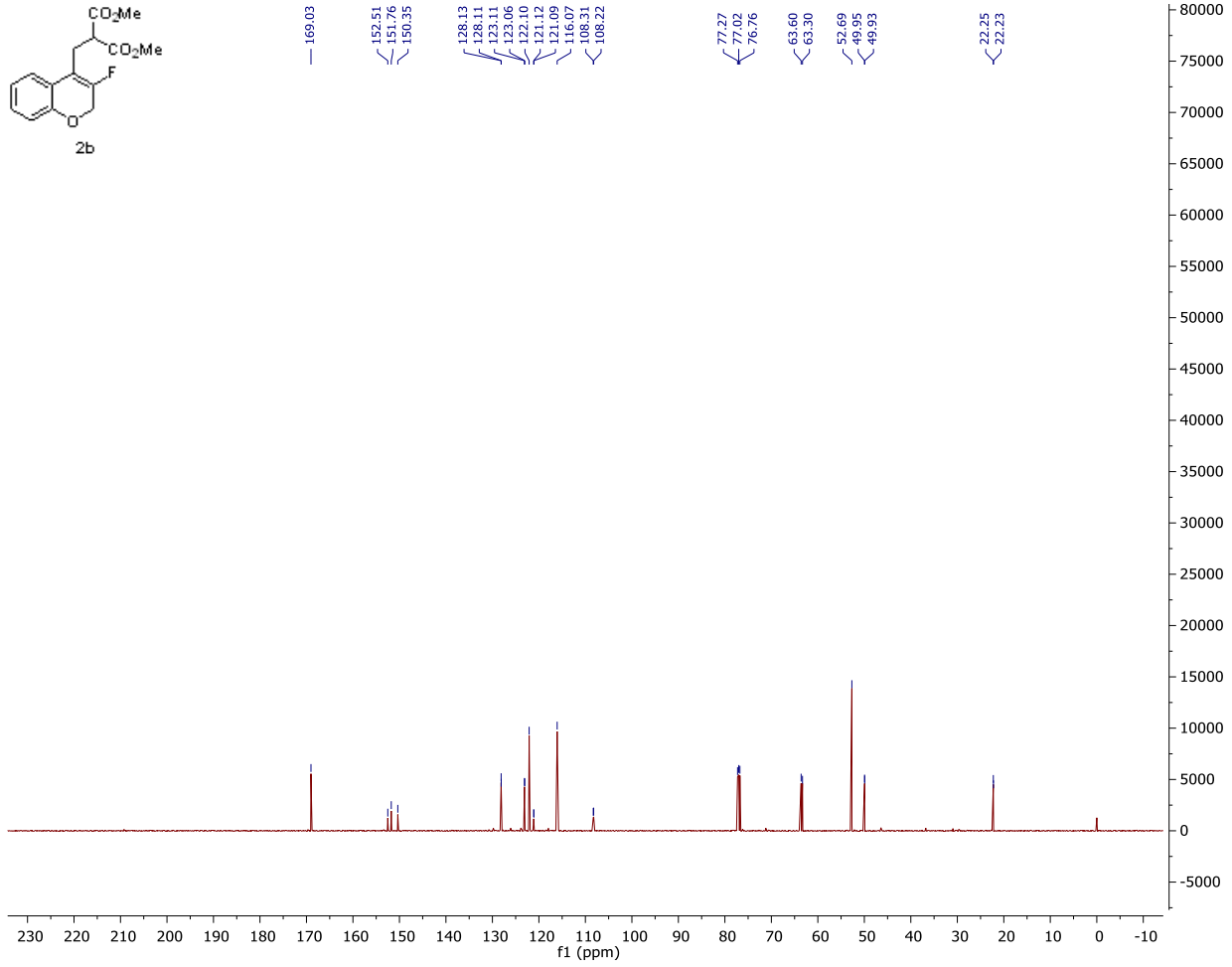
^{1}H (500 MHz, $CDCl_3$)



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

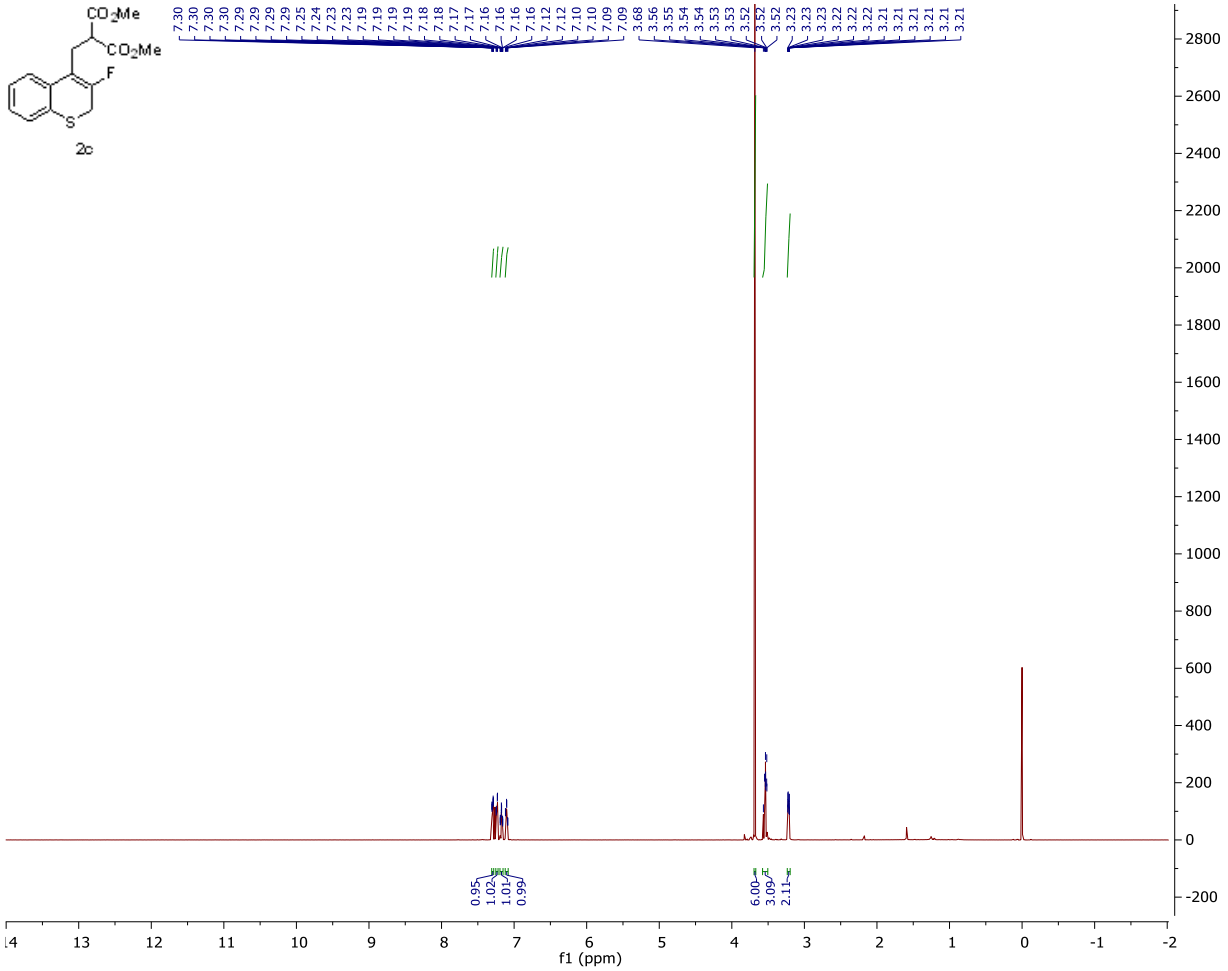


^{13}C (126 MHz, $CDCl_3$)

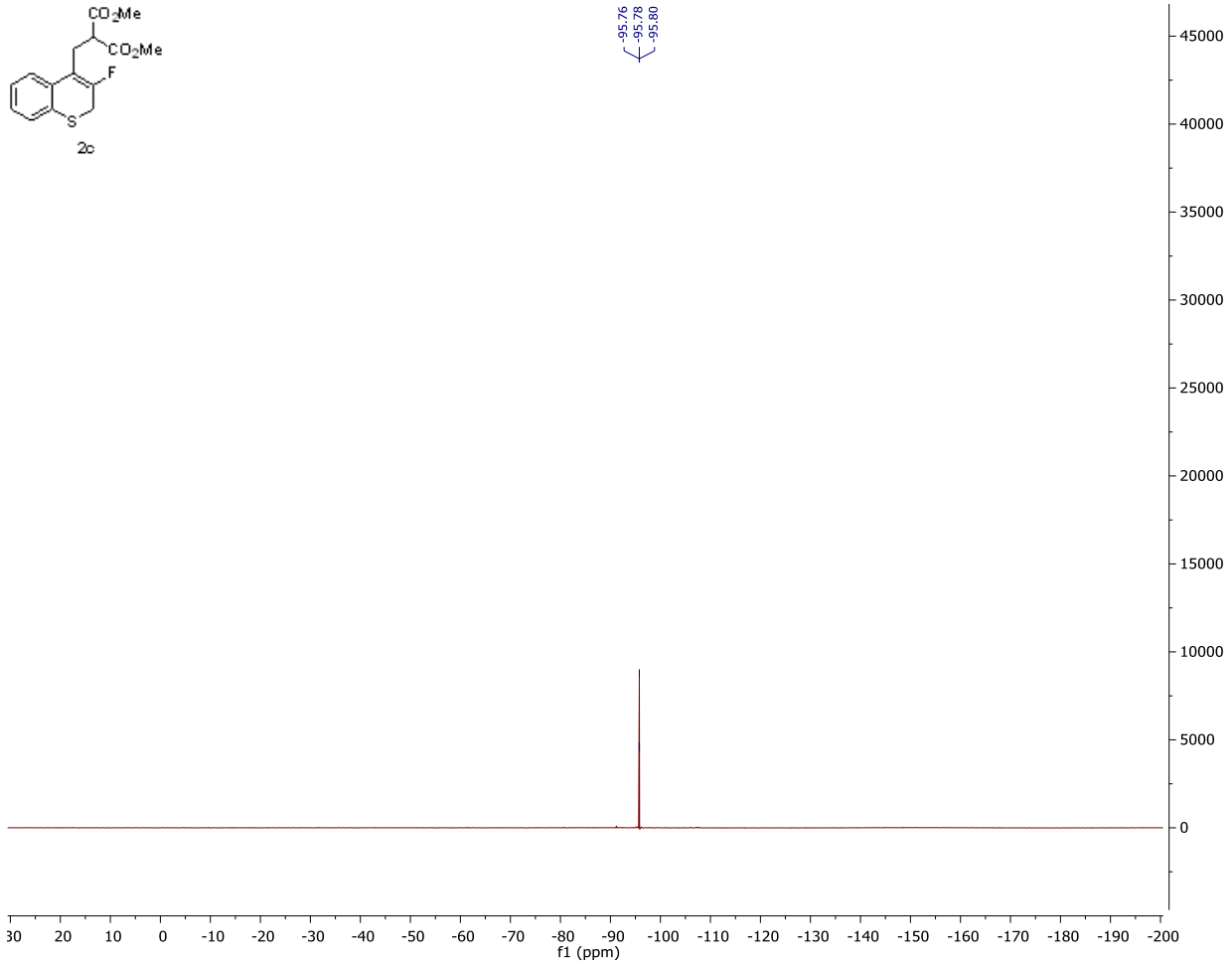


Dimethyl 2-((3-fluoro-2*H*-thiochromen-4-yl)methyl)malonate (2c)

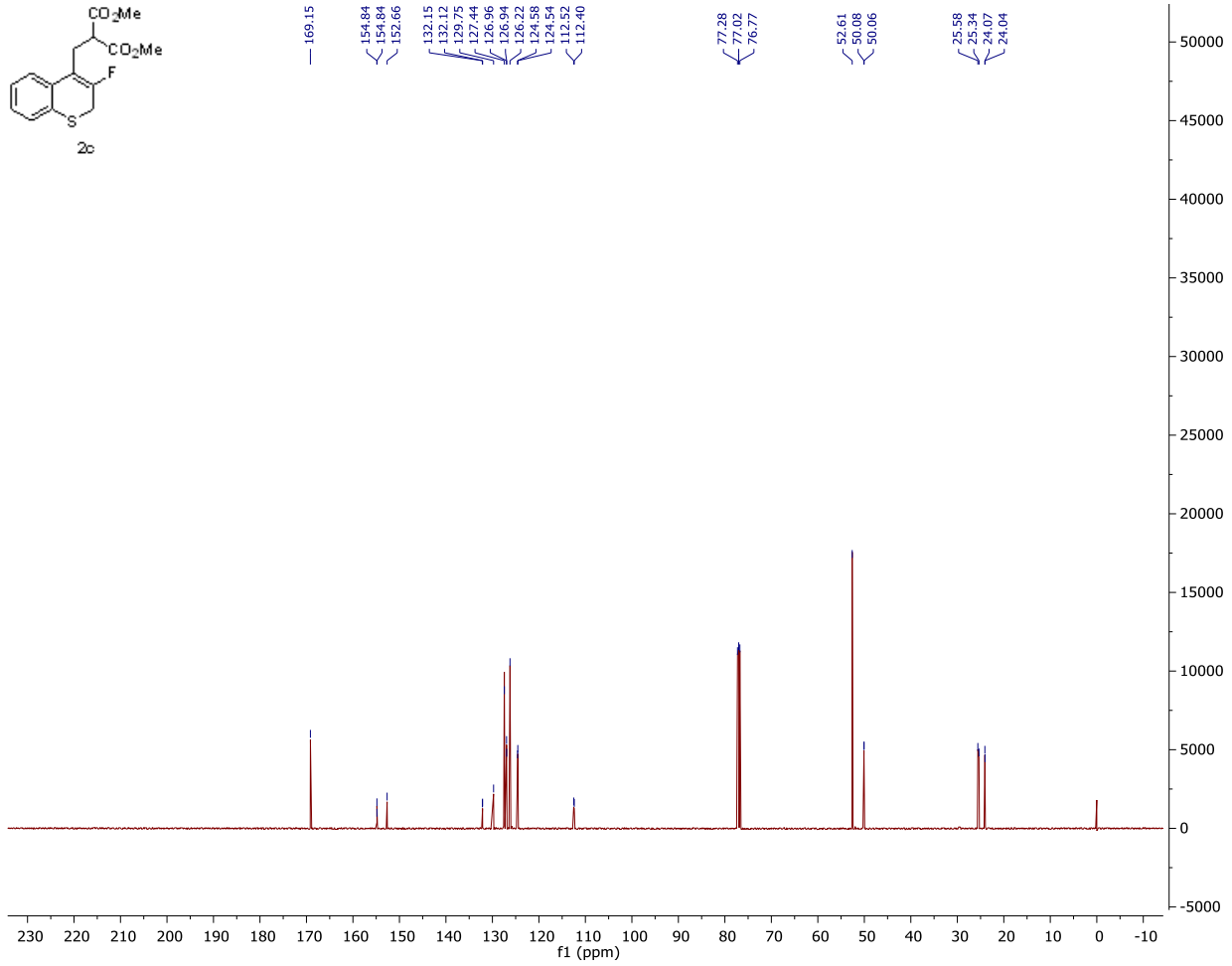
^{1}H (500 MHz, $CDCl_3$)



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

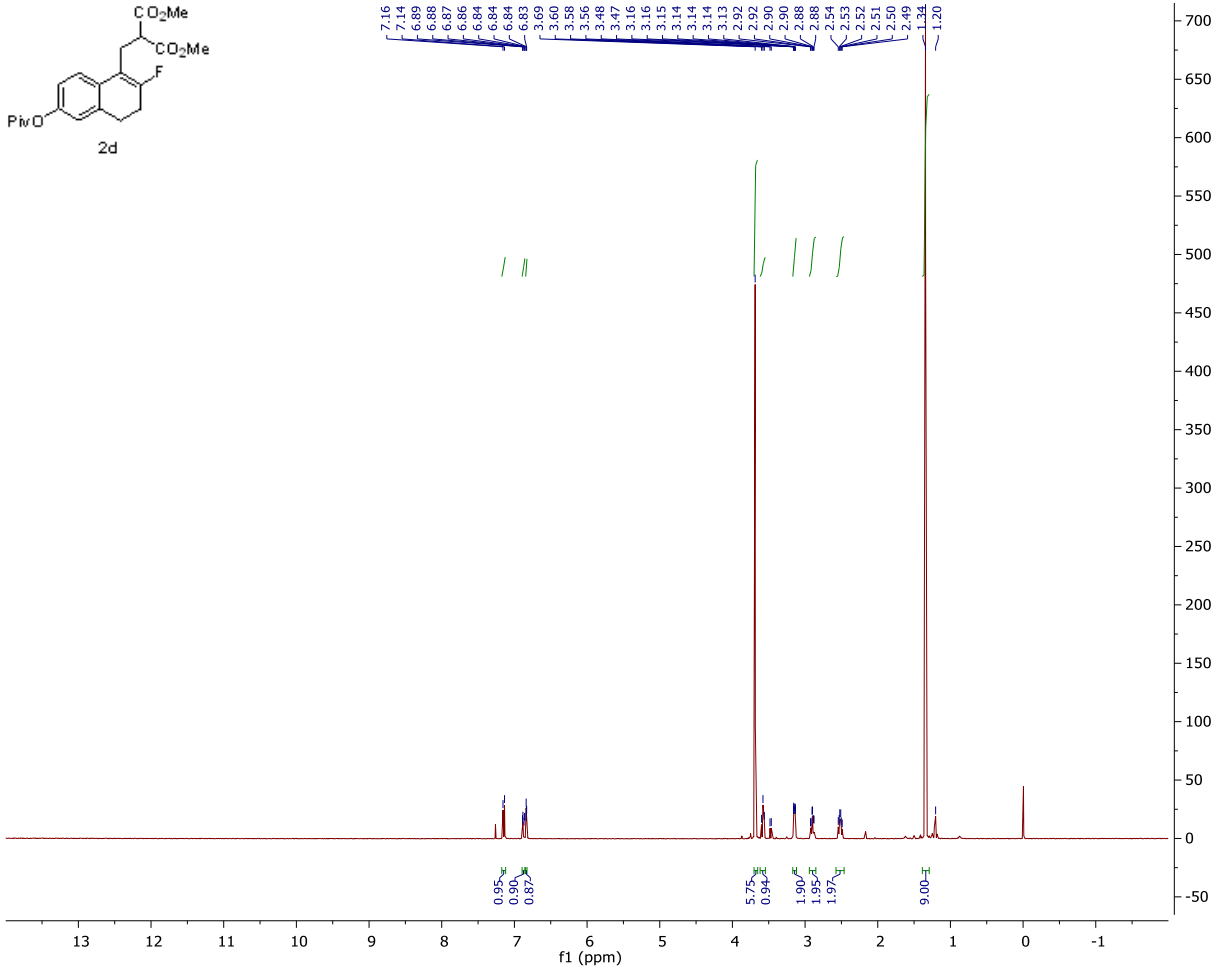


^{13}C (126 MHz, $CDCl_3$)

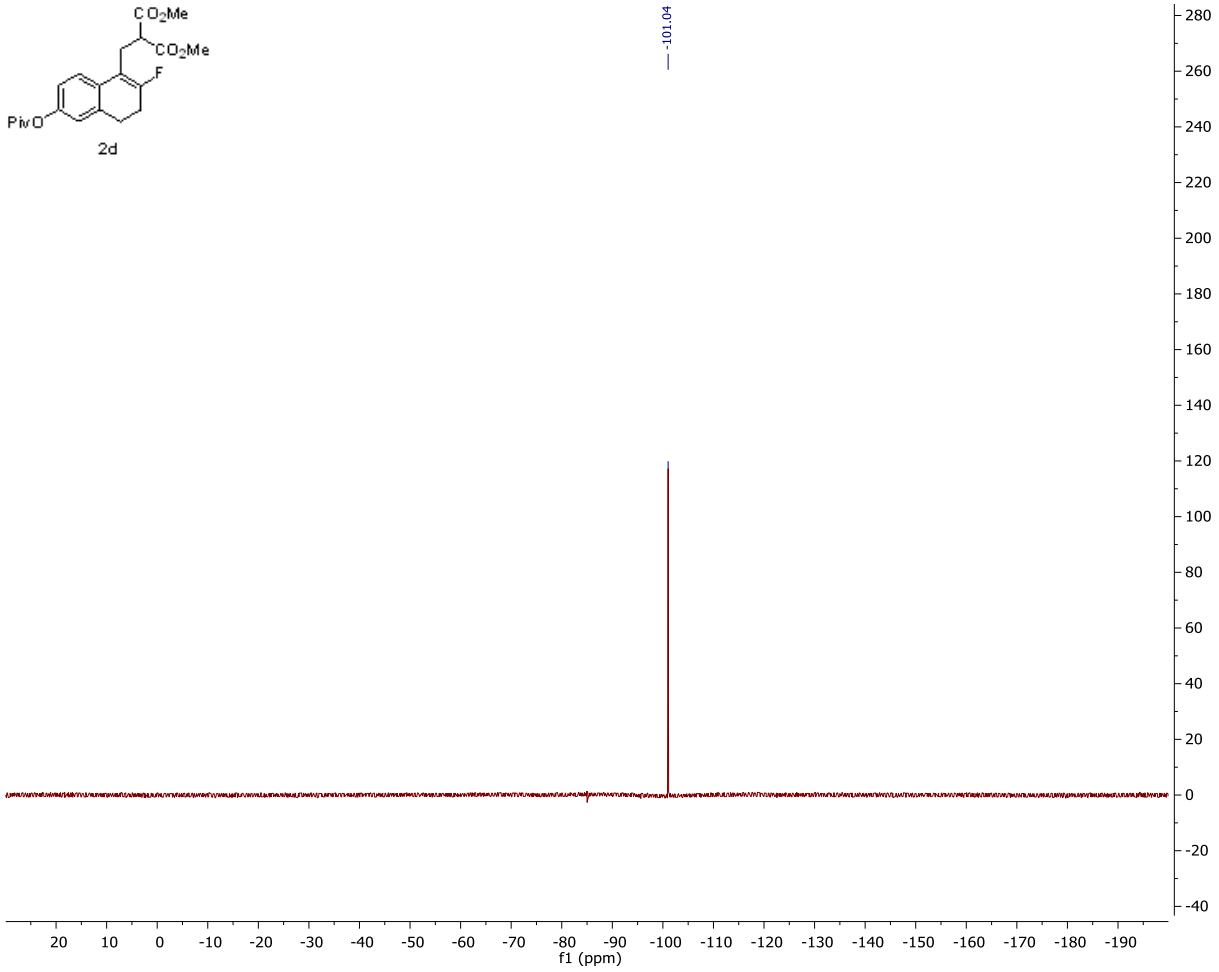


Dimethyl-2-((2-fluoro-6-(pivaloyloxy)-3,4-dihydronaphthalen-1-yl)methyl)malonate (2d)

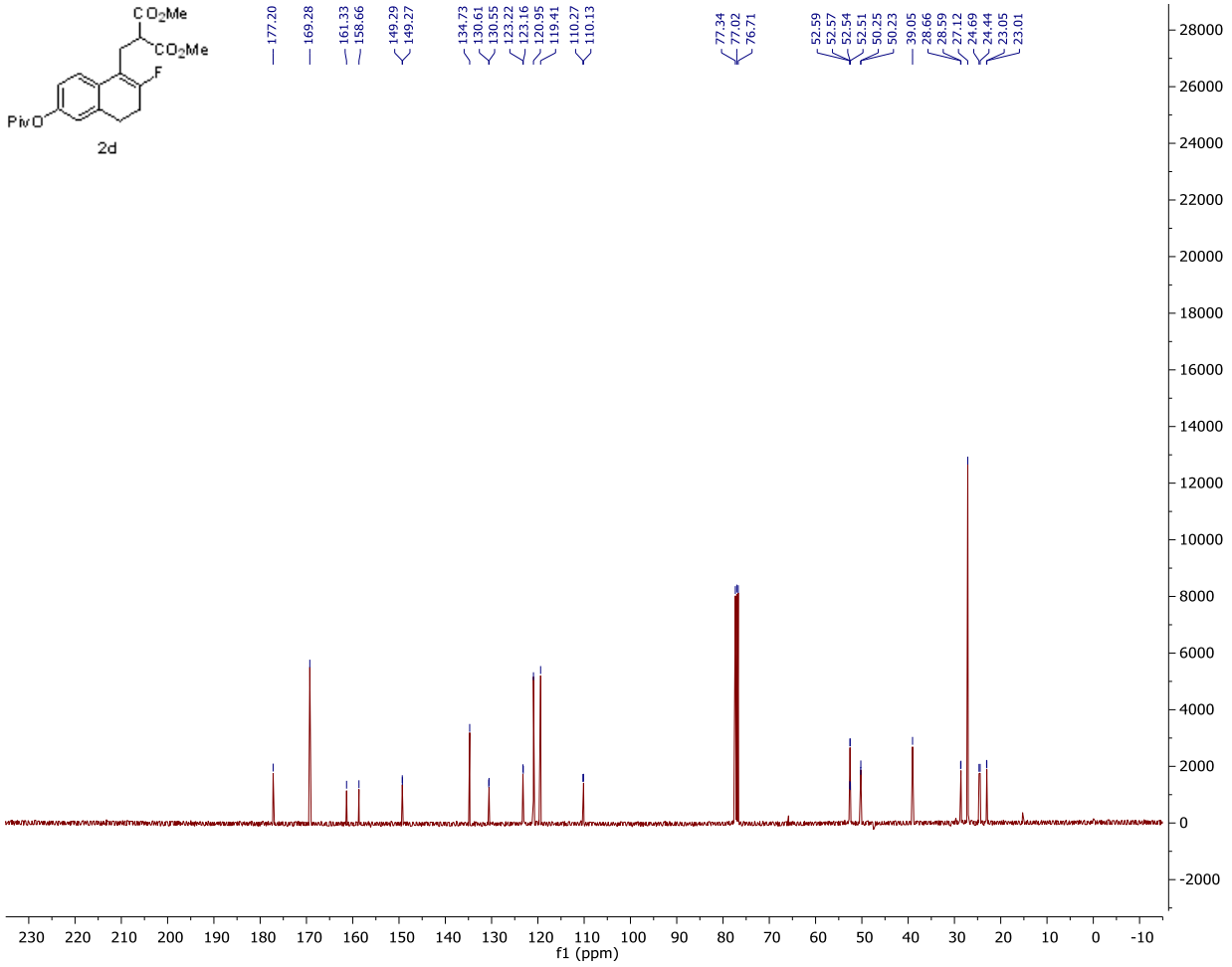
^{1}H (400 MHz, $CDCl_3$)



^{19}F (376 MHz, $CDCl_3$)

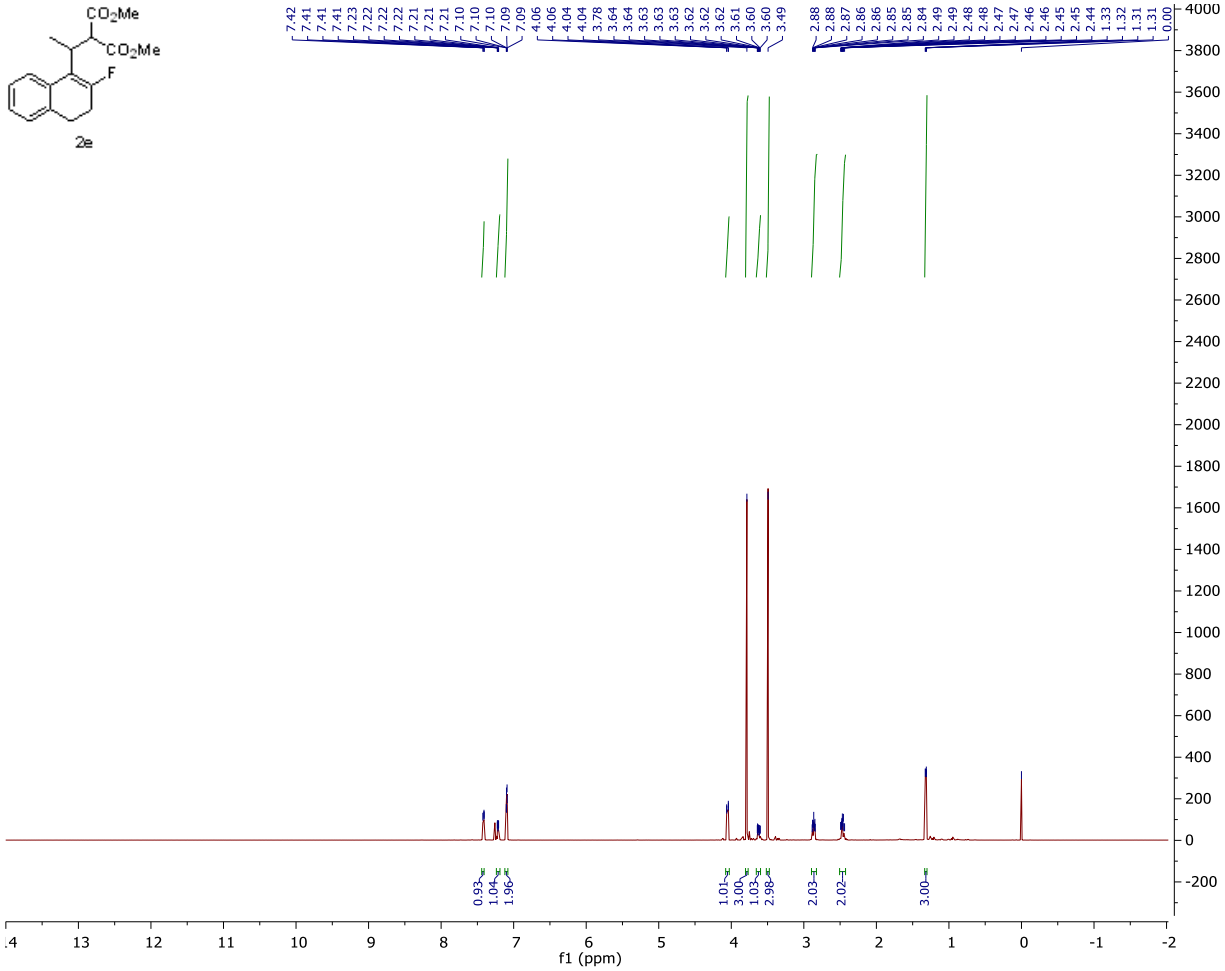


^{13}C (75 MHz, $CDCl_3$)

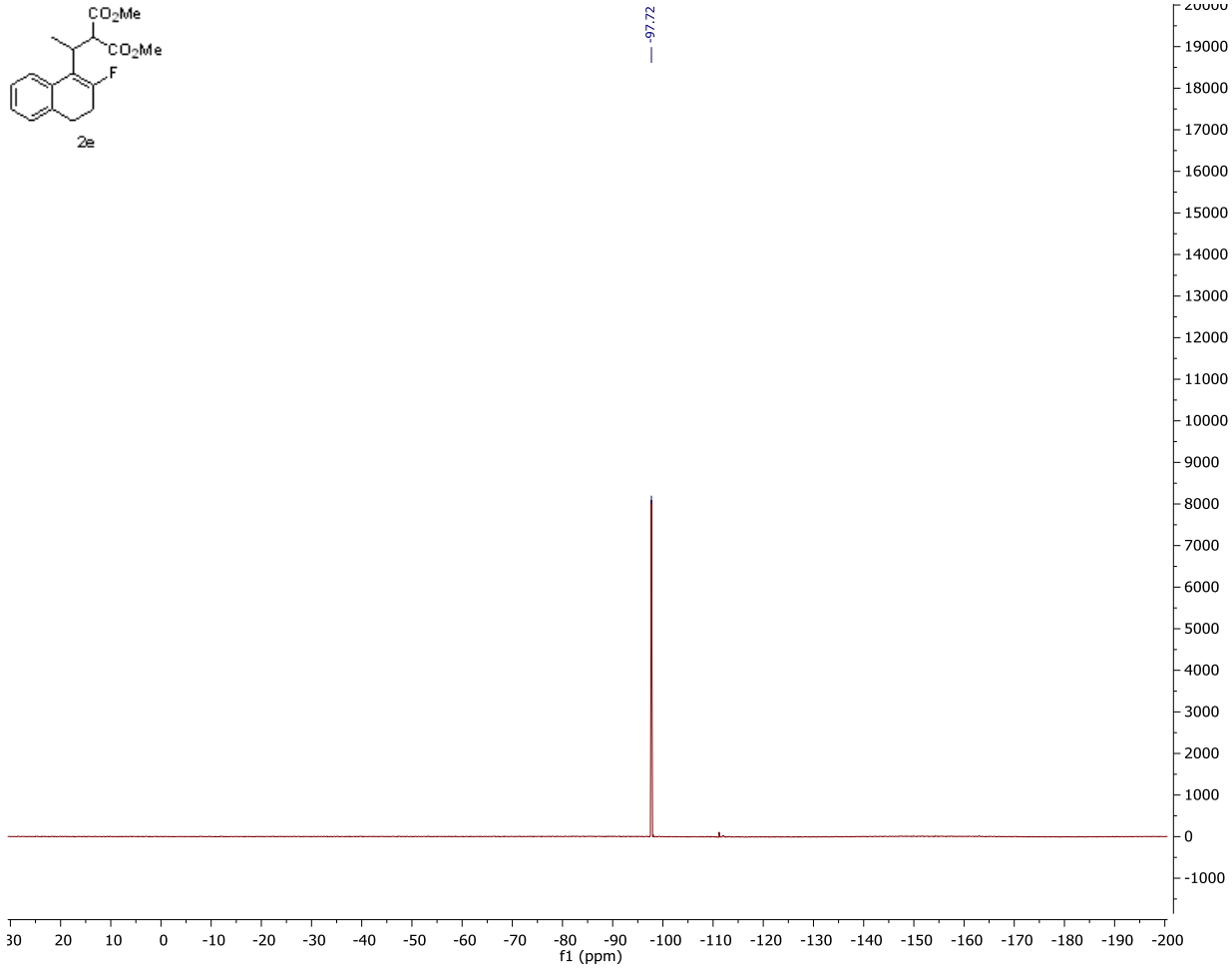


Dimethyl 2-(1-(2-fluoro-3,4-dihydronaphthalen-1-yl)ethyl)malonate (2e)

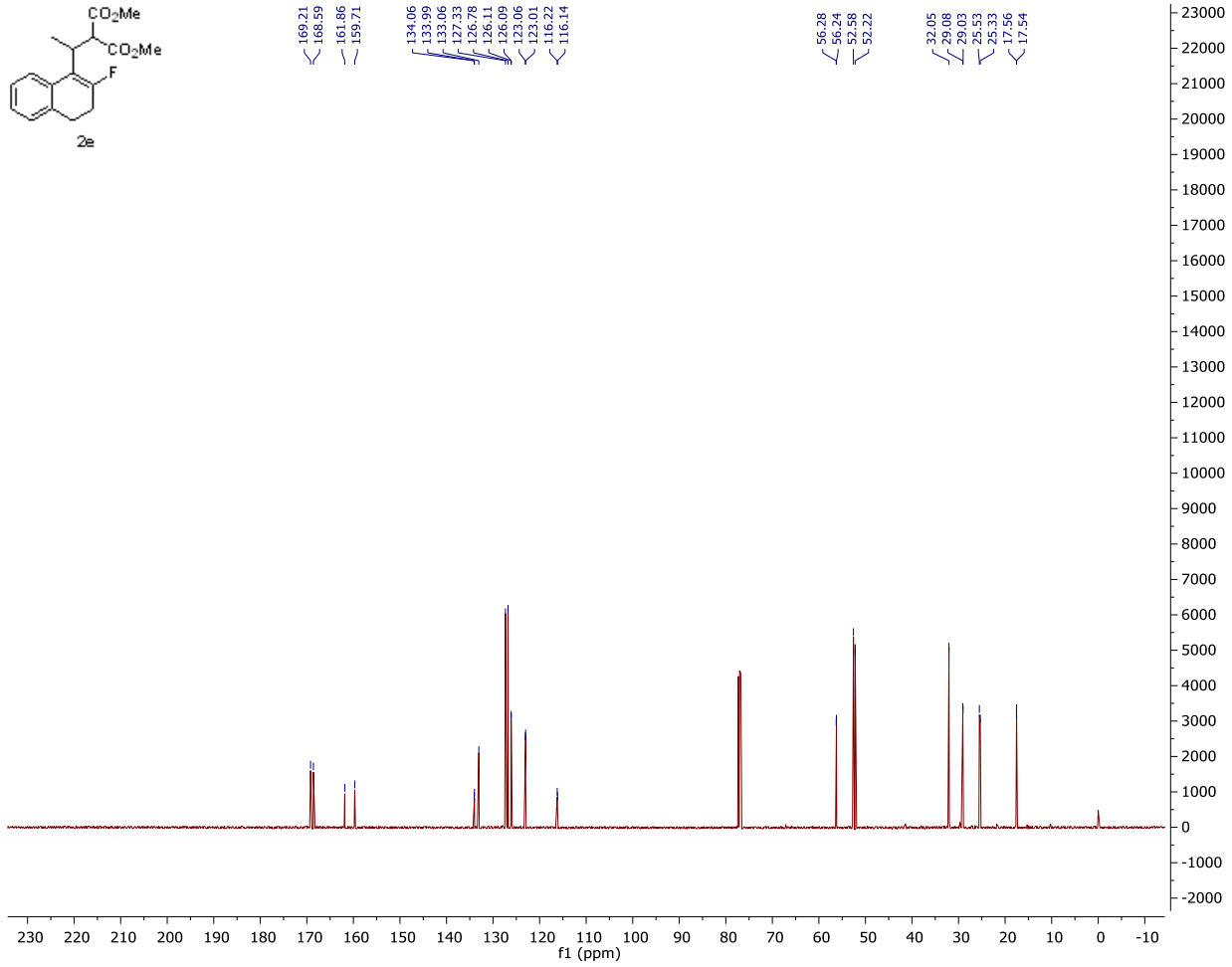
^{1}H (500 MHz, $CDCl_3$)



^{19}F (376 MHz, $CDCl_3$)

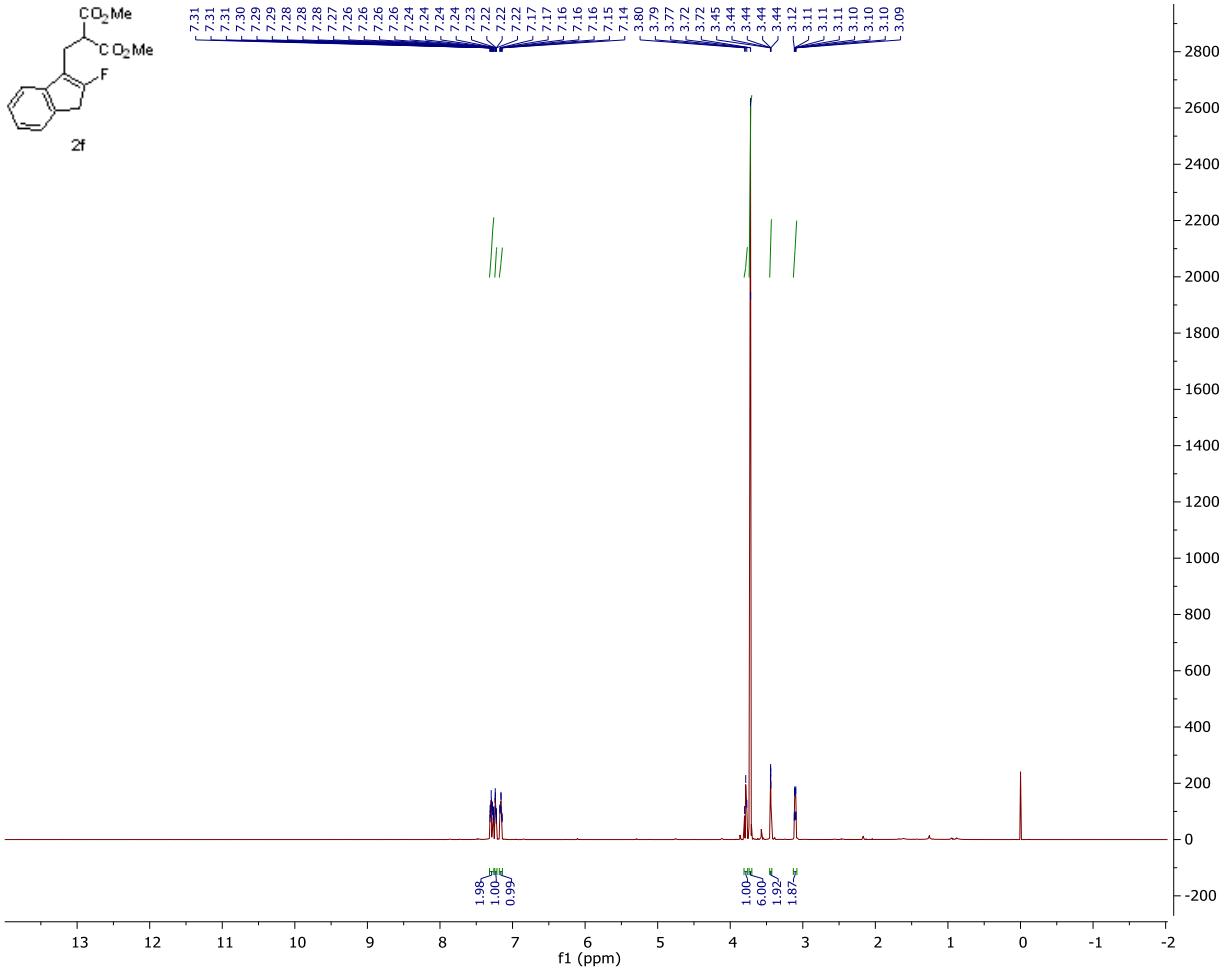


^{13}C (75 MHz, $CDCl_3$)

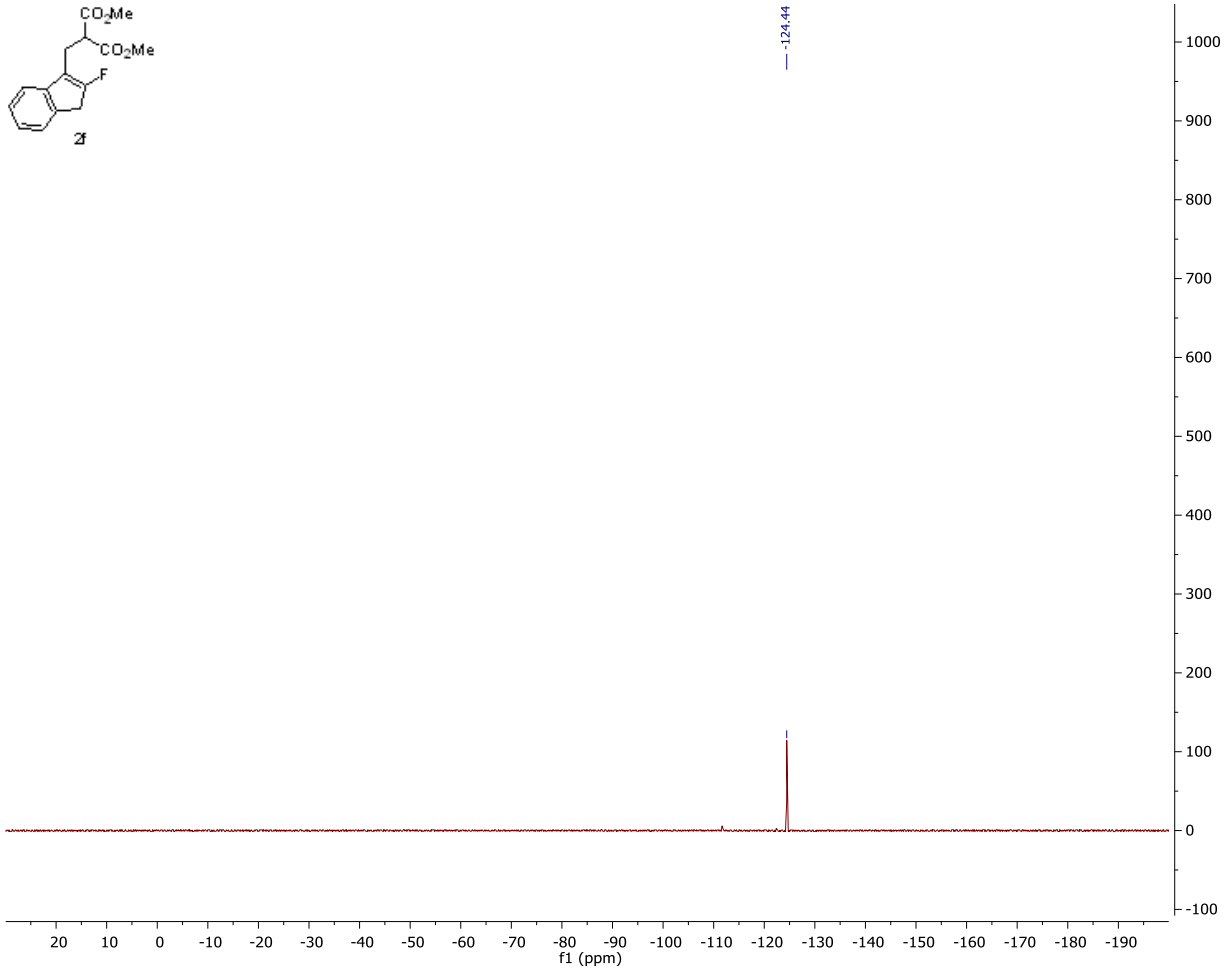


Dimethyl-2-((2-fluoro-1*H*-inden-3-yl)methyl)malonate (2f)

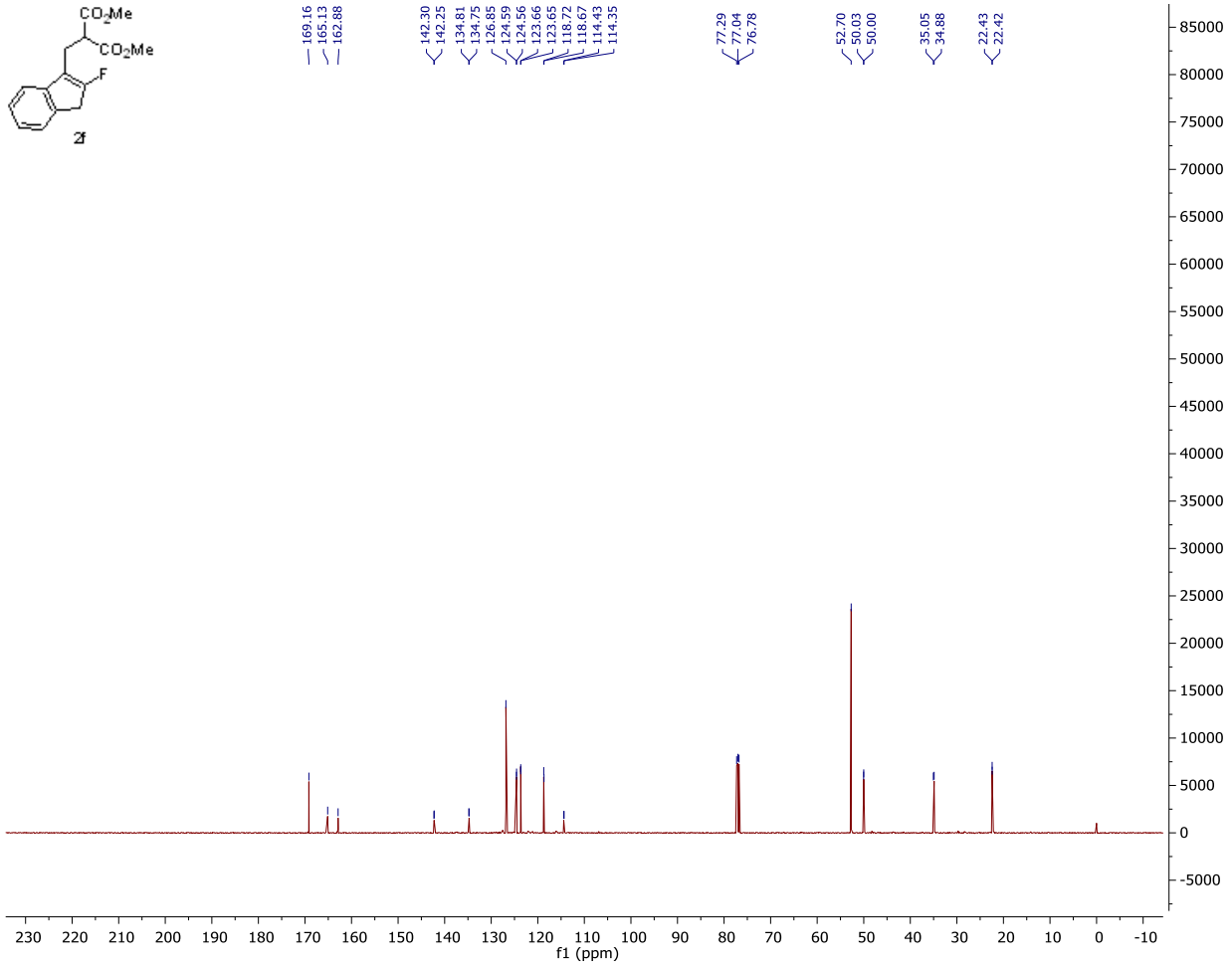
^{1}H (500 MHz, $CDCl_3$)



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

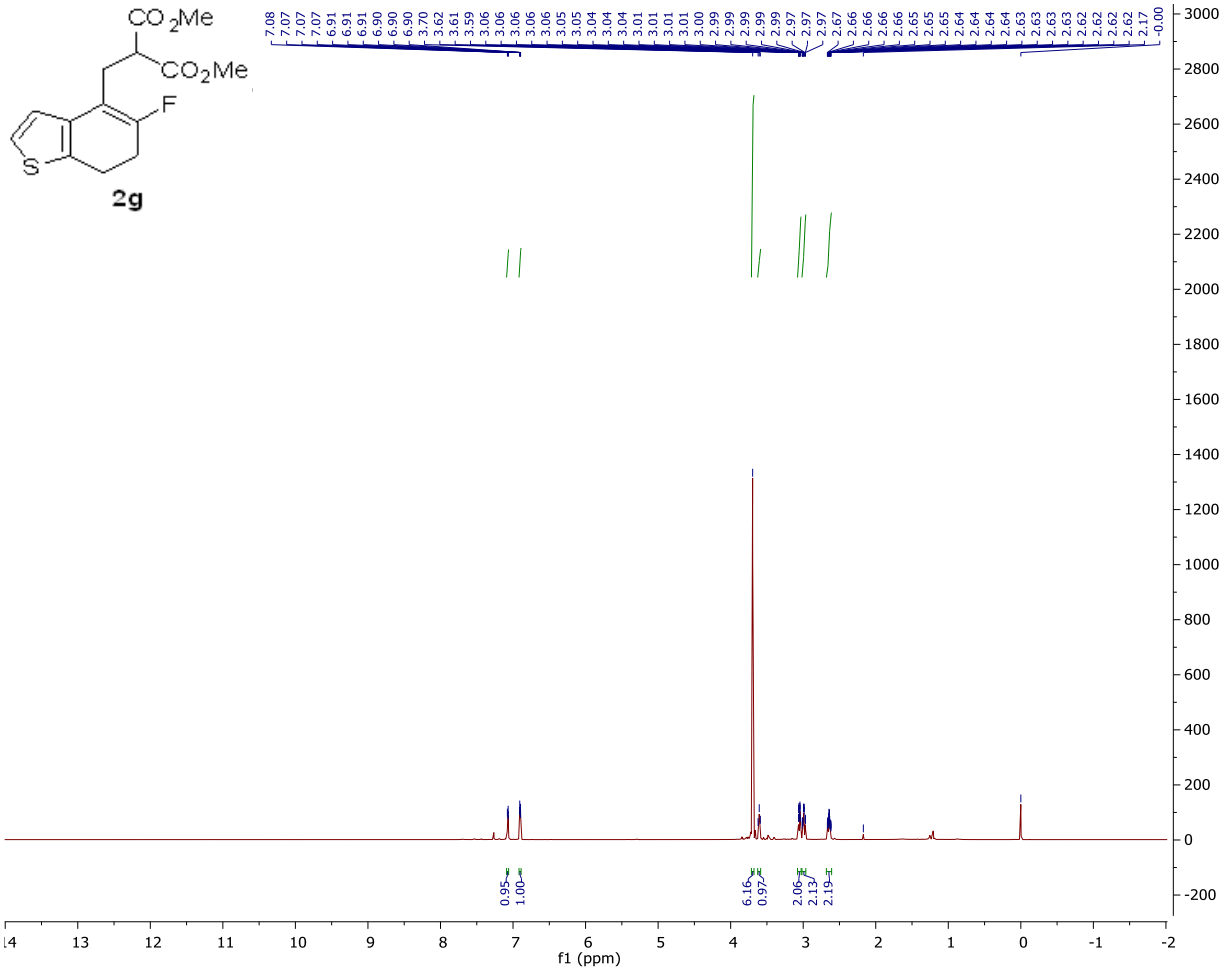


^{13}C (126 MHz, $CDCl_3$)

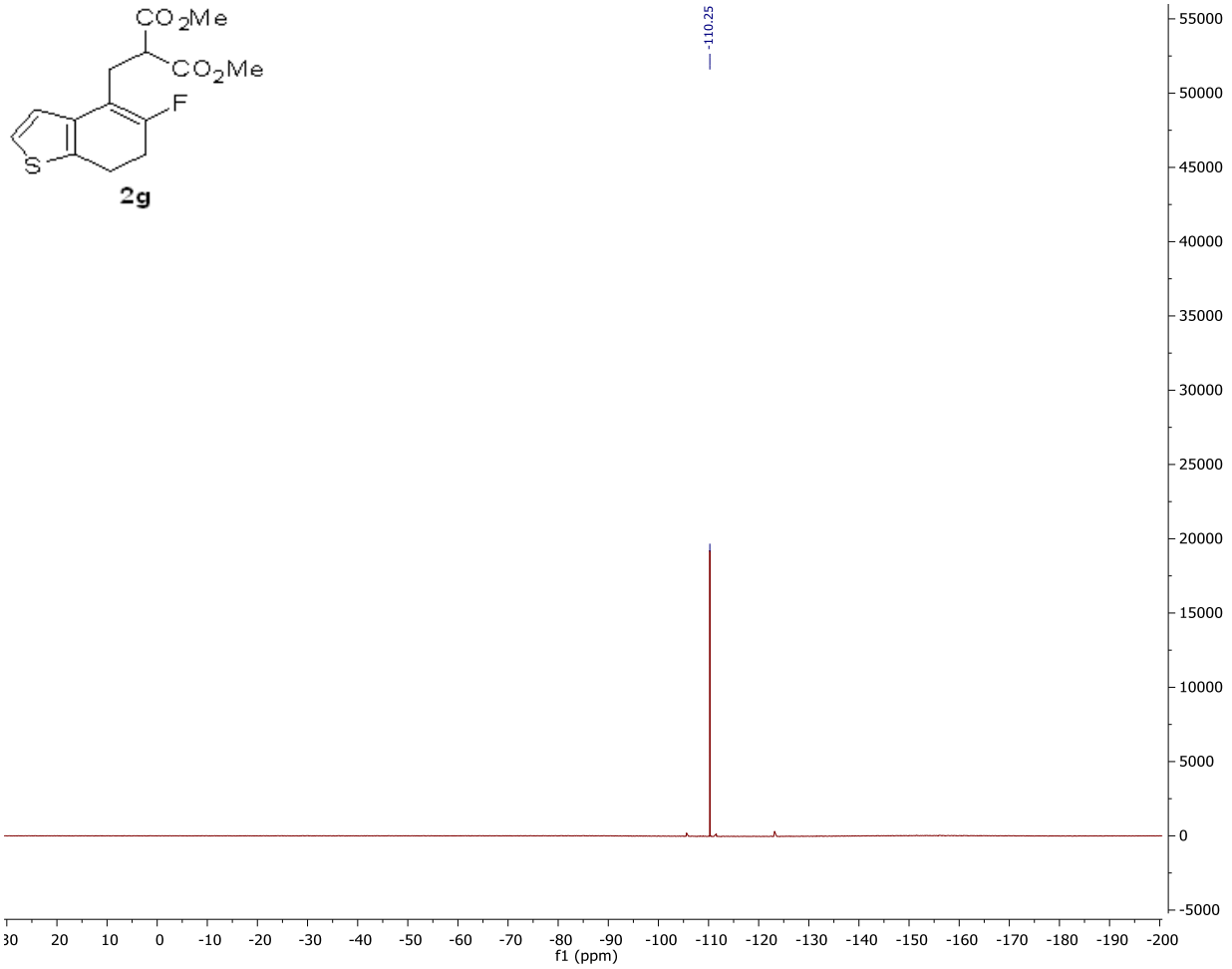


Dimethyl 2-((5-fluoro-6,7-dihydrobenzo[*b*]thiophen-4-yl)methyl)malonate (2g)

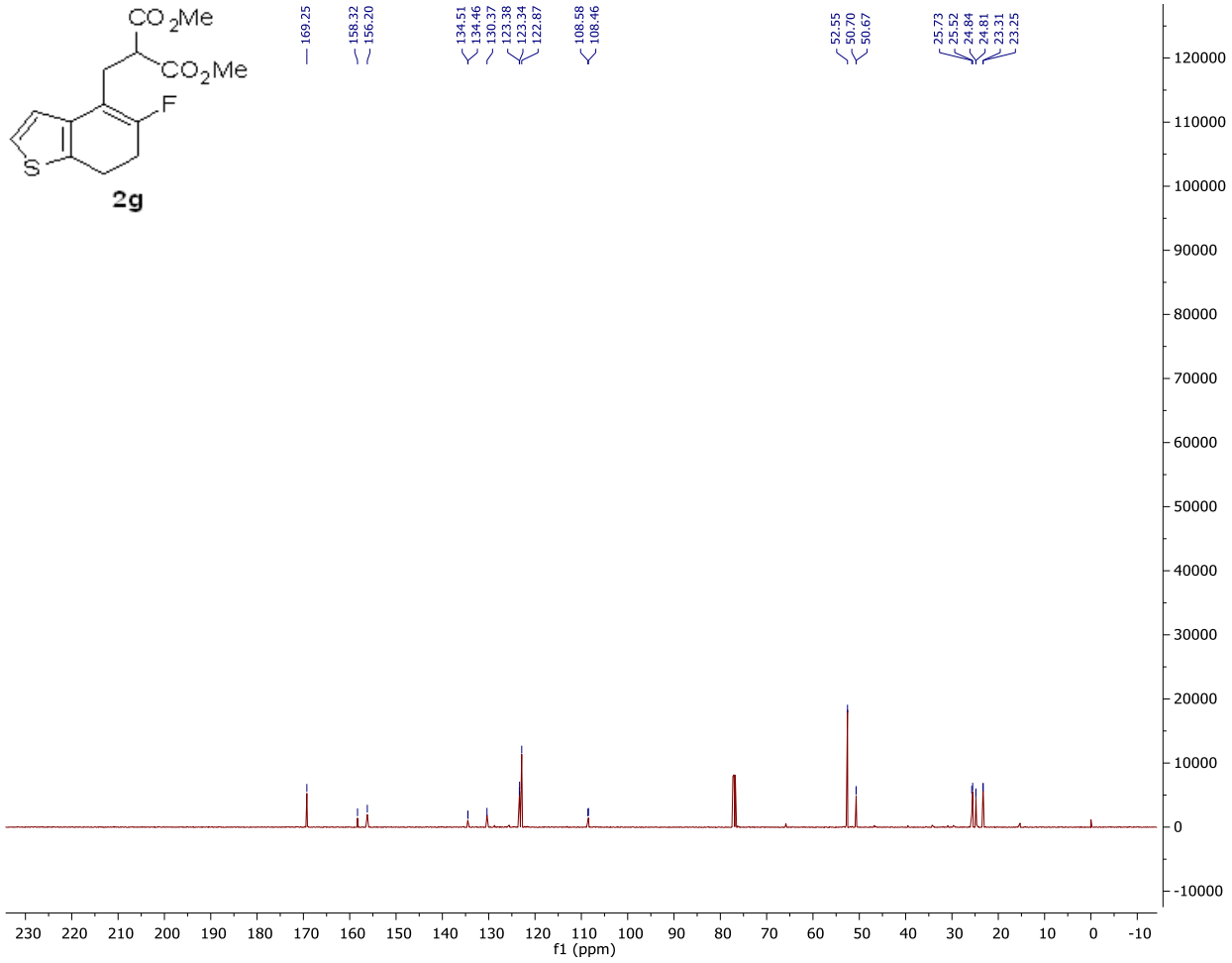
^{1}H (500 MHz, $CDCl_3$)



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

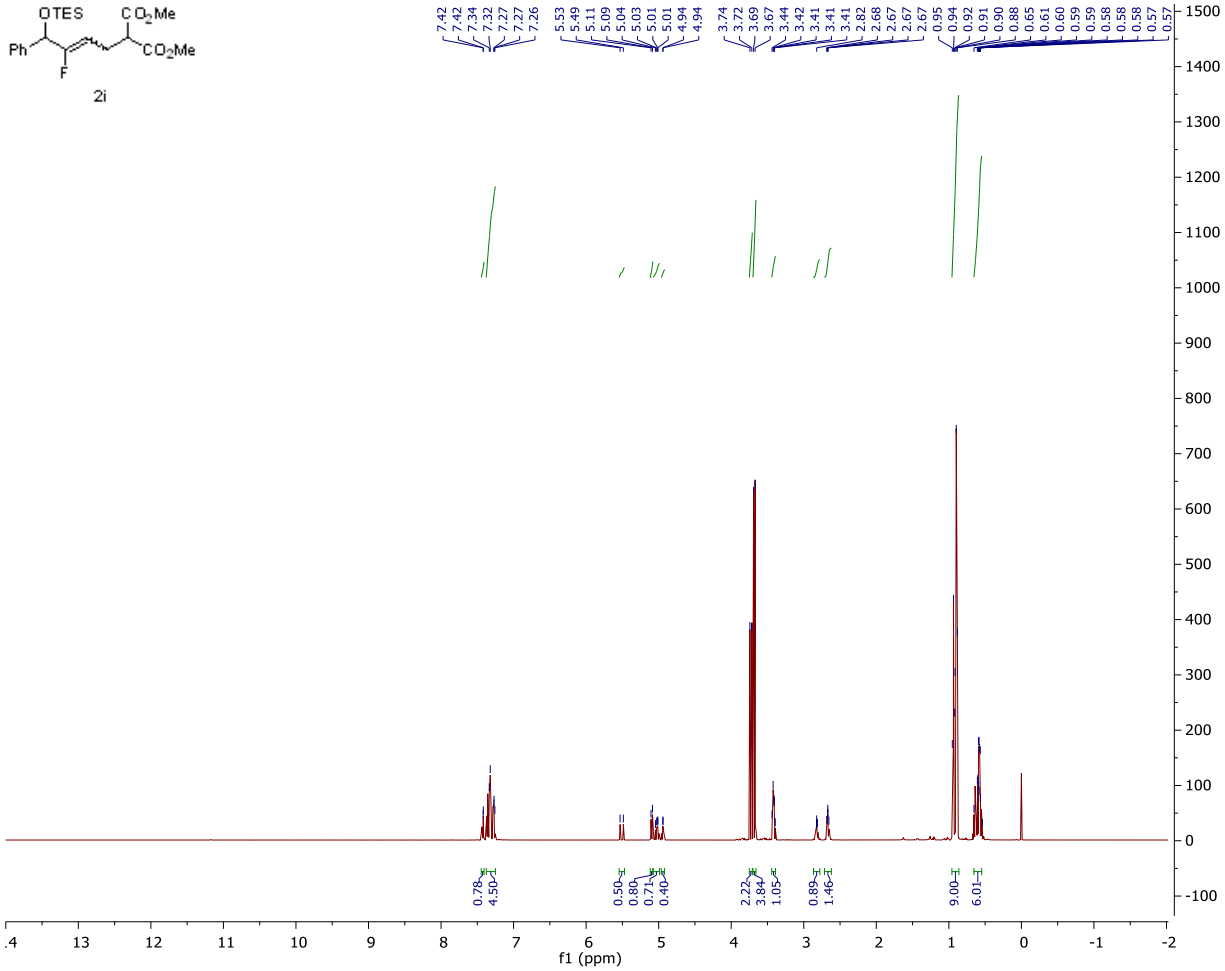


^{13}C (126 MHz, $CDCl_3$)

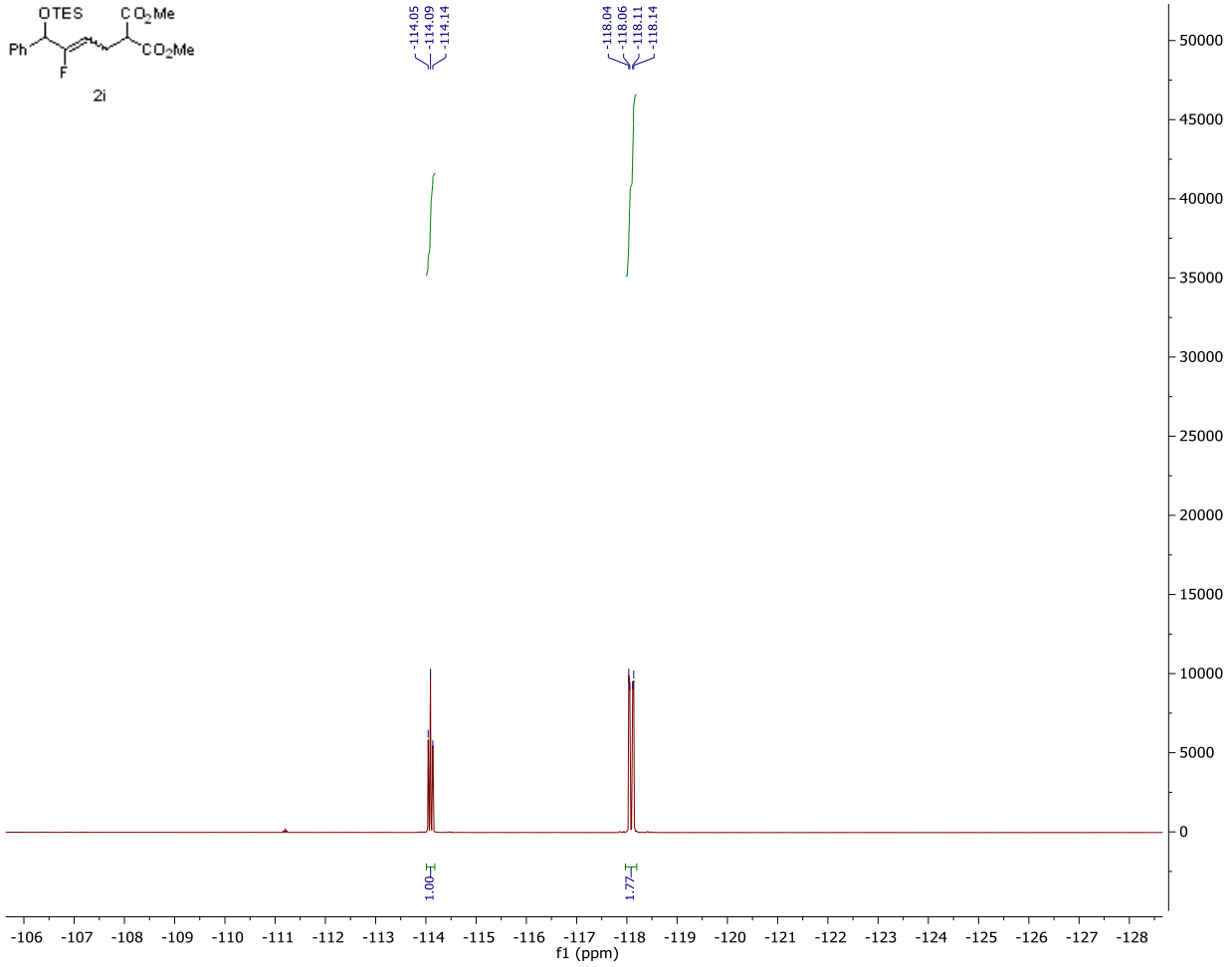


Triethylsilyl dimethyl 2-(3-fluoro-4-hydroxy-4-phenylbut-2-en-1-yl)malonate (2i)

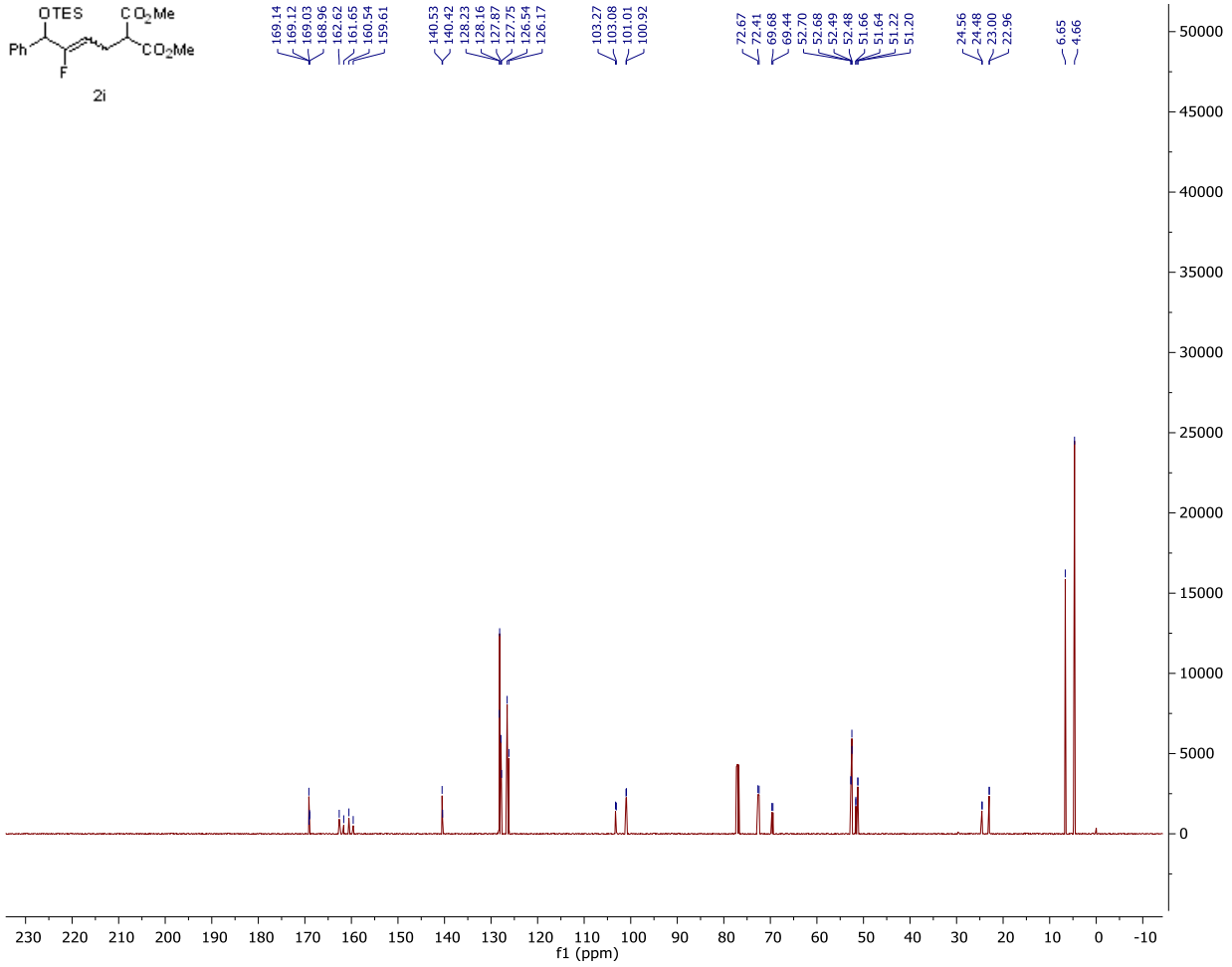
^{1}H (500 MHz, $CDCl_3$)



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

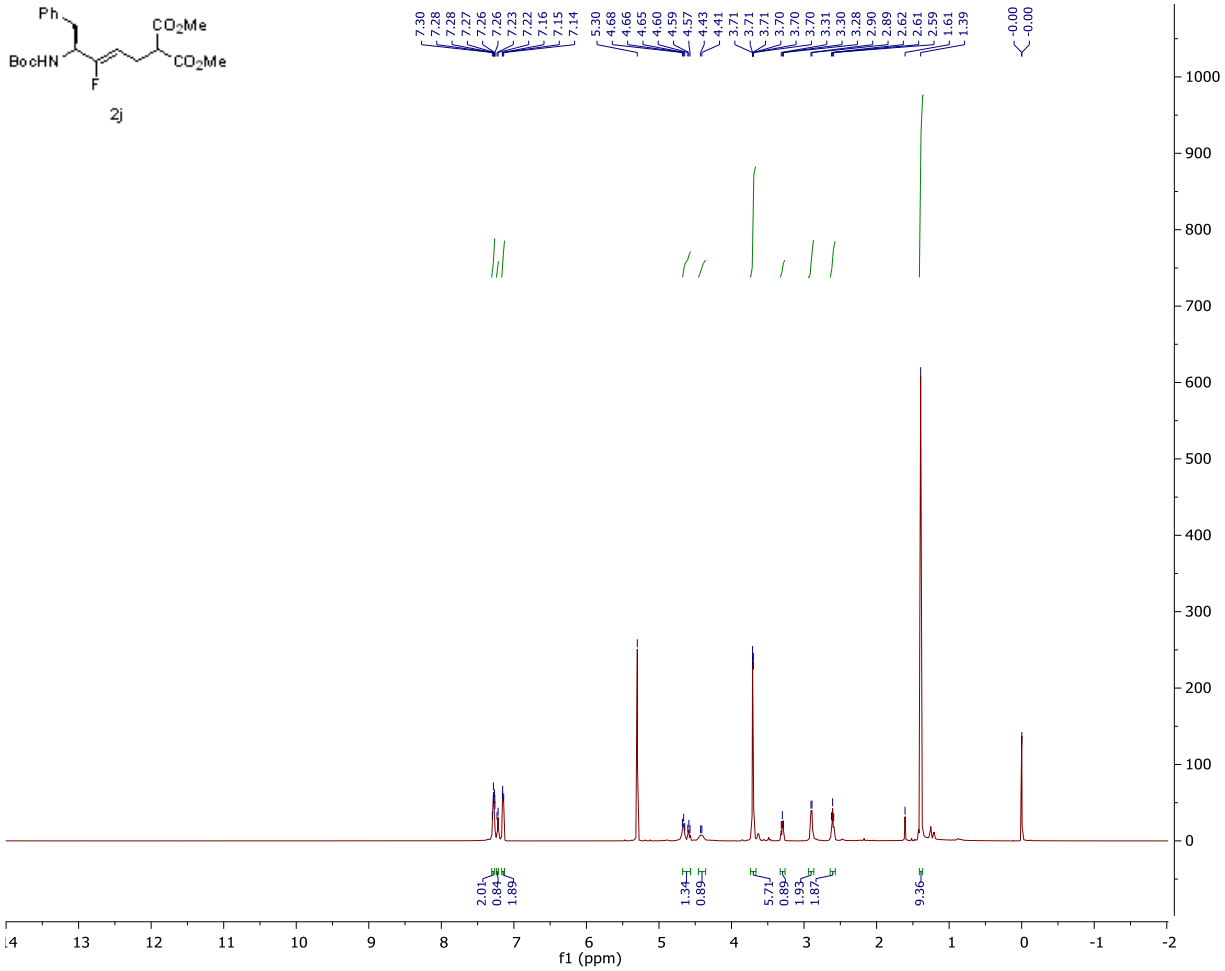


^{13}C (126 MHz, $CDCl_3$)

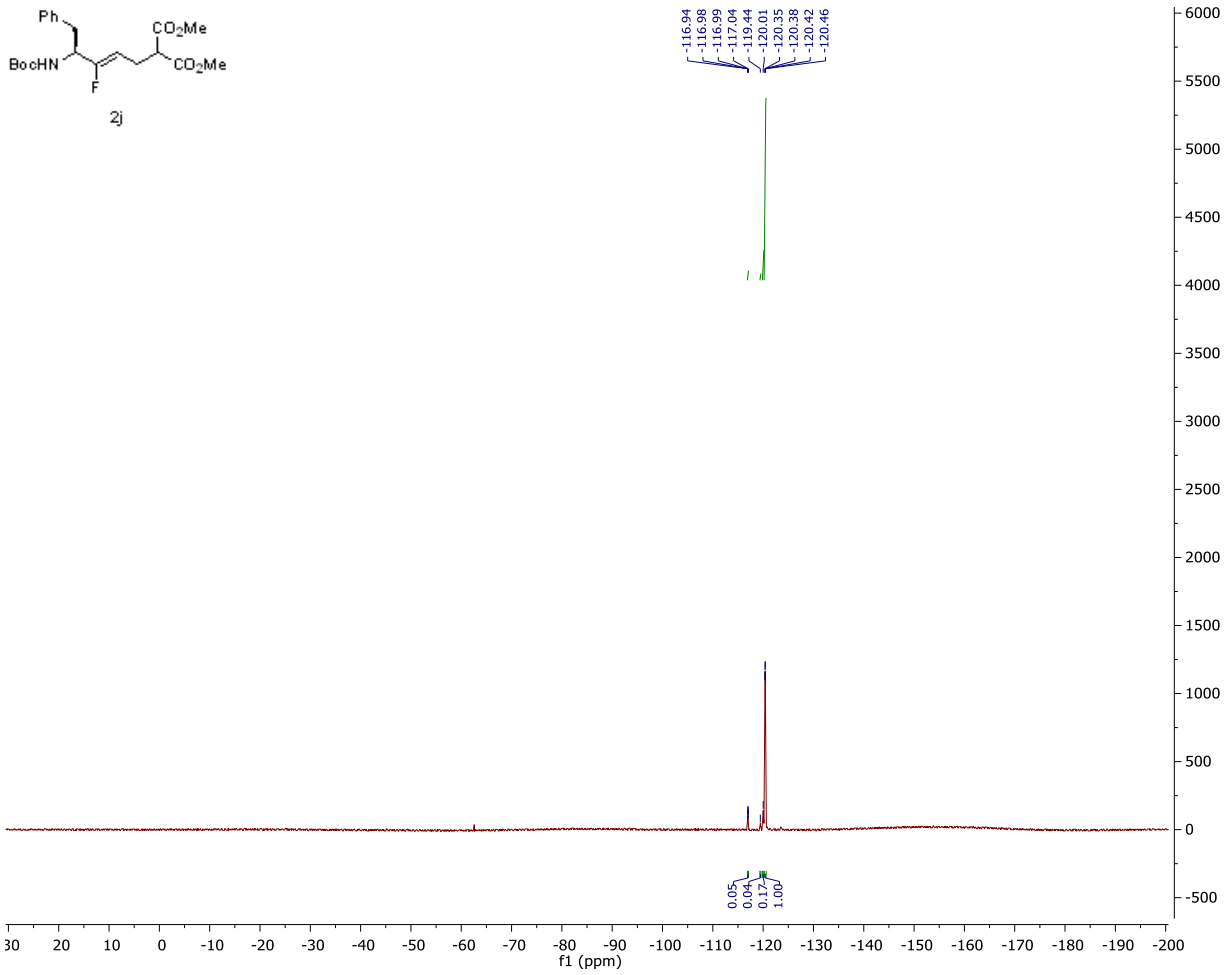


(*S*)-Dimethyl-2-(4-((*tert*-butoxycarbonyl)amino)-3-fluoro-5-phenylpent-2-en-1-yl)malonate (2j)

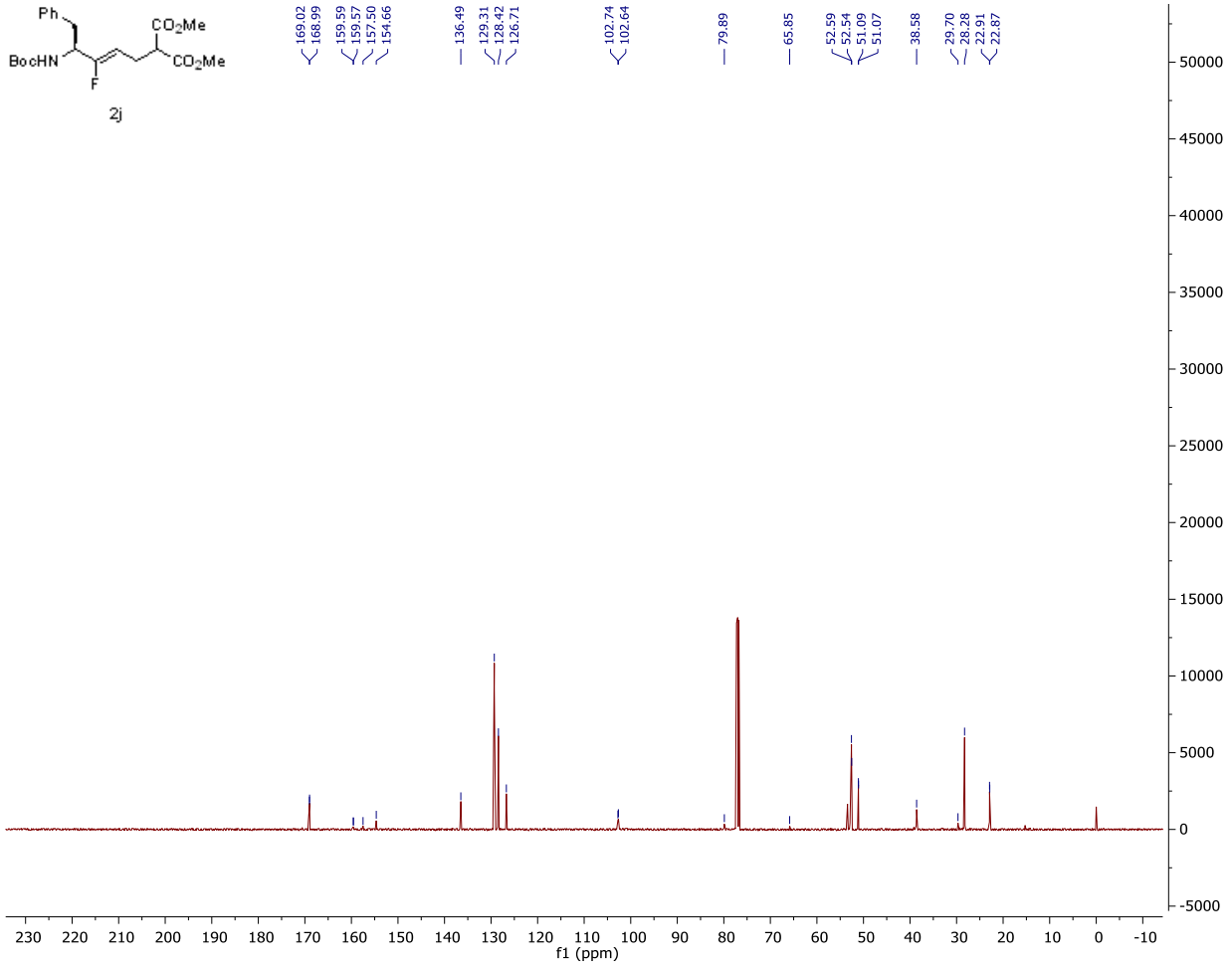
^{1}H (500 MHz, $CDCl_3$)



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

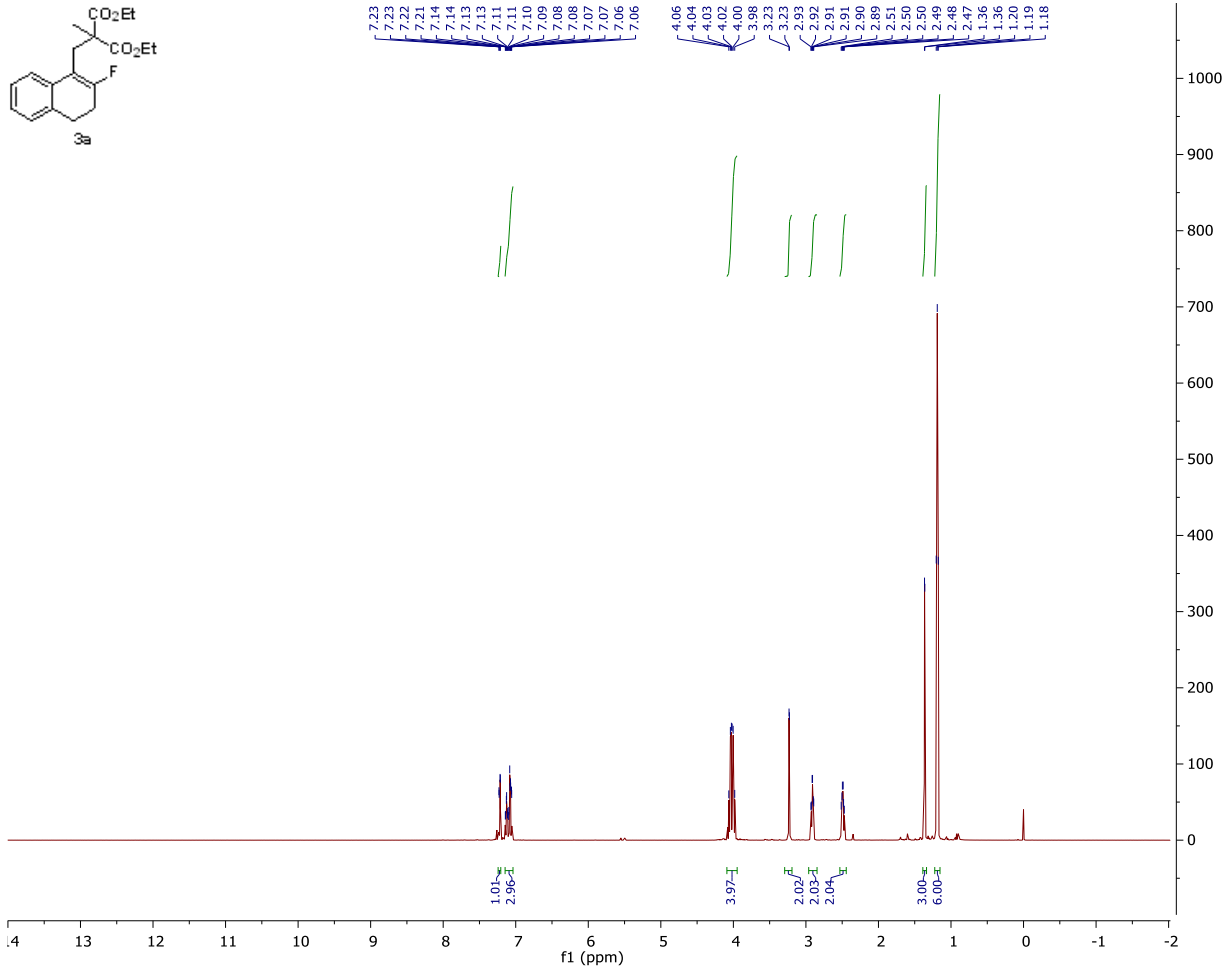


^{13}C (126 MHz, $CDCl_3$)

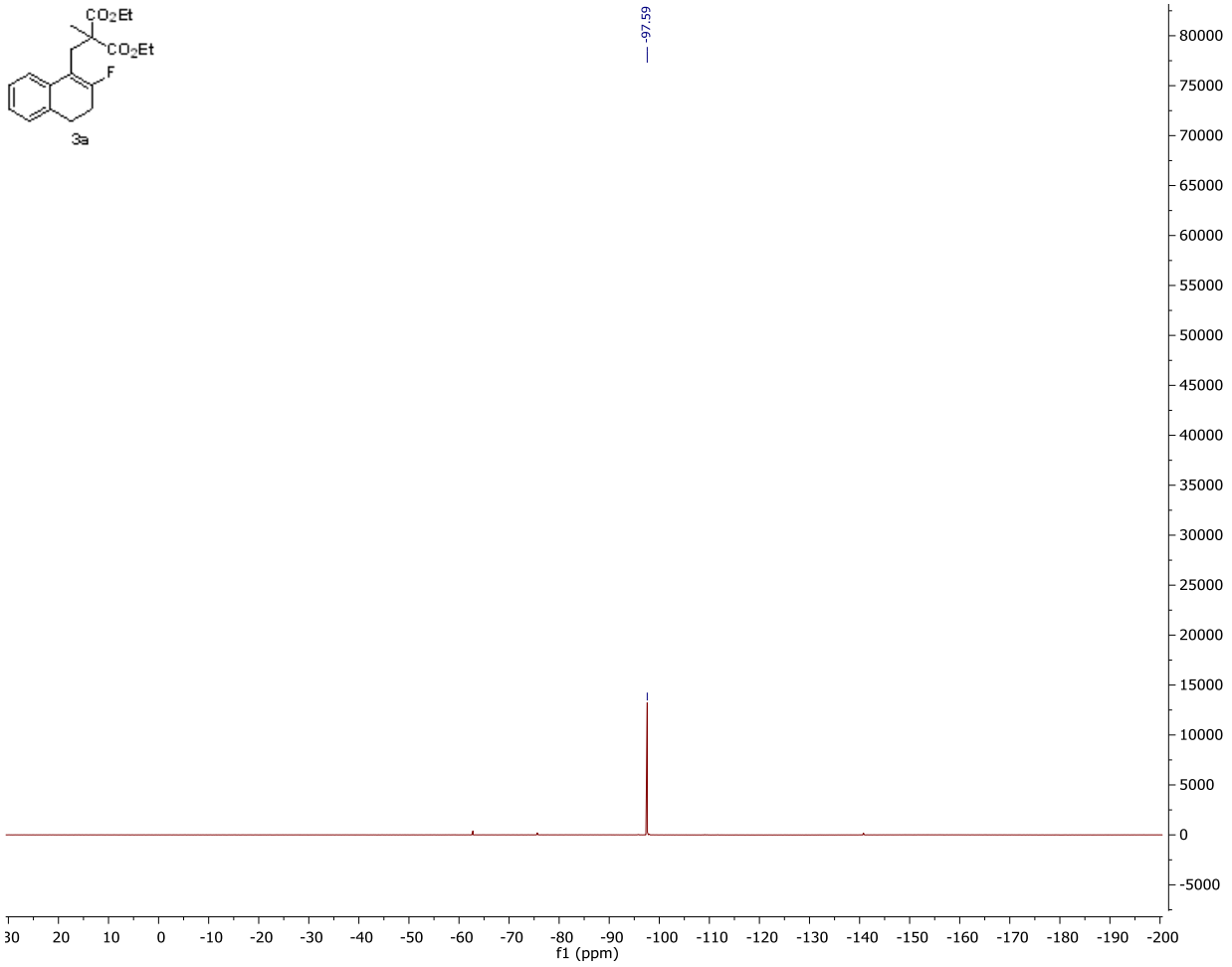


Diethyl 2-((2-fluoro-3,4-dihydronaphthalen-1-yl)methyl)-2-methylmalonate (3a)

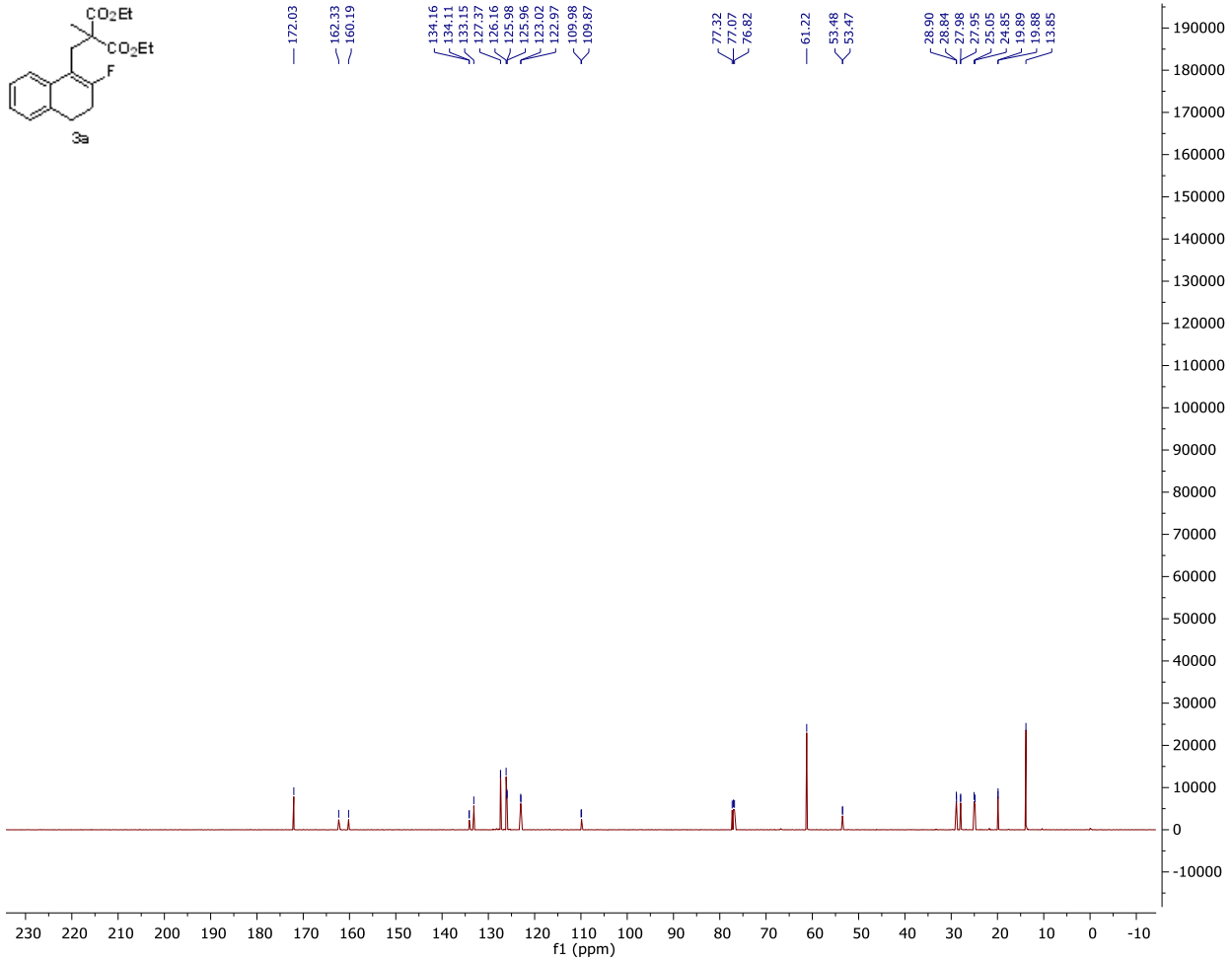
^{1}H (500 MHz, $CDCl_3$)



^{19}F (370 MHz, $CDCl_3$)

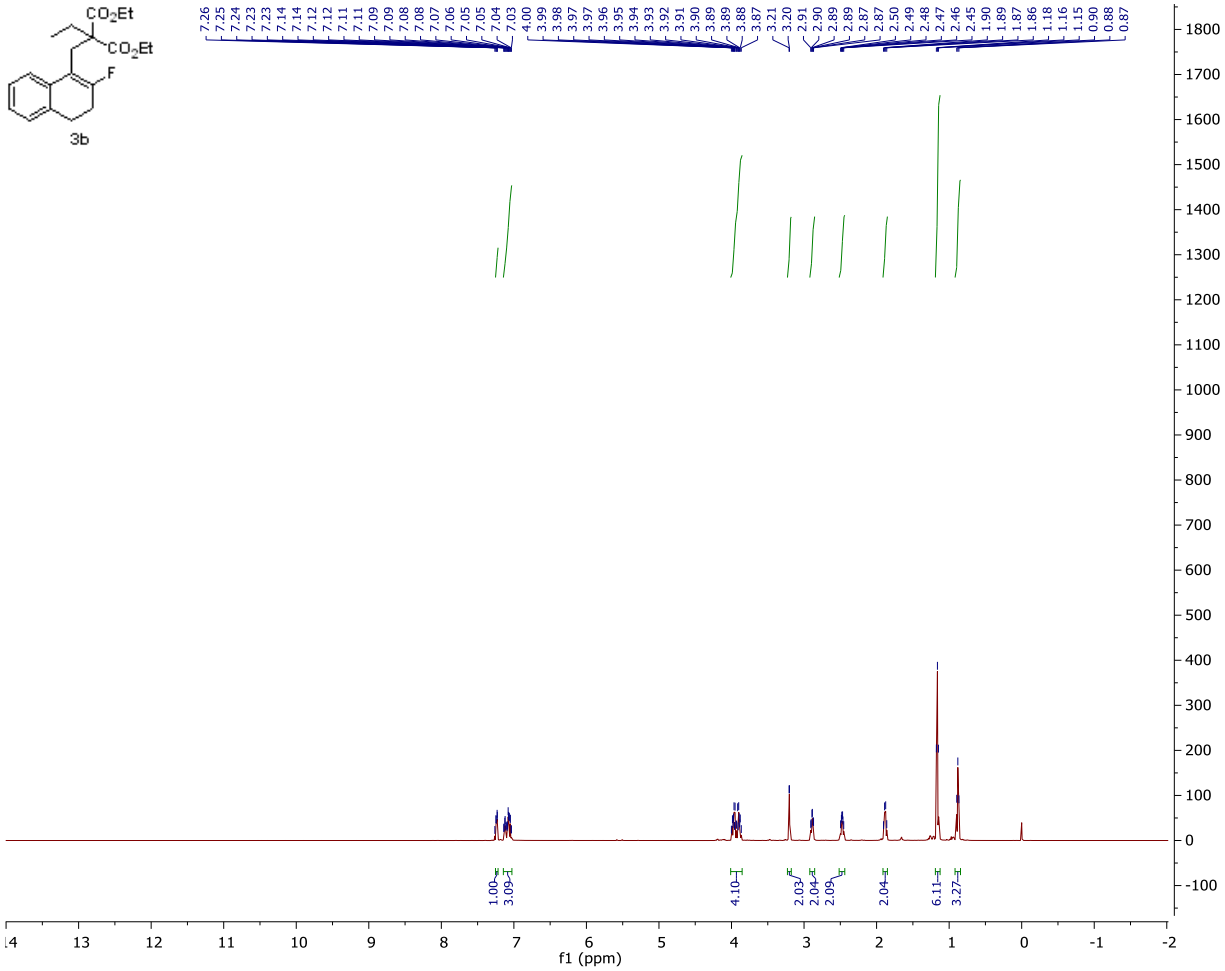


^{13}C (126 MHz, $CDCl_3$)

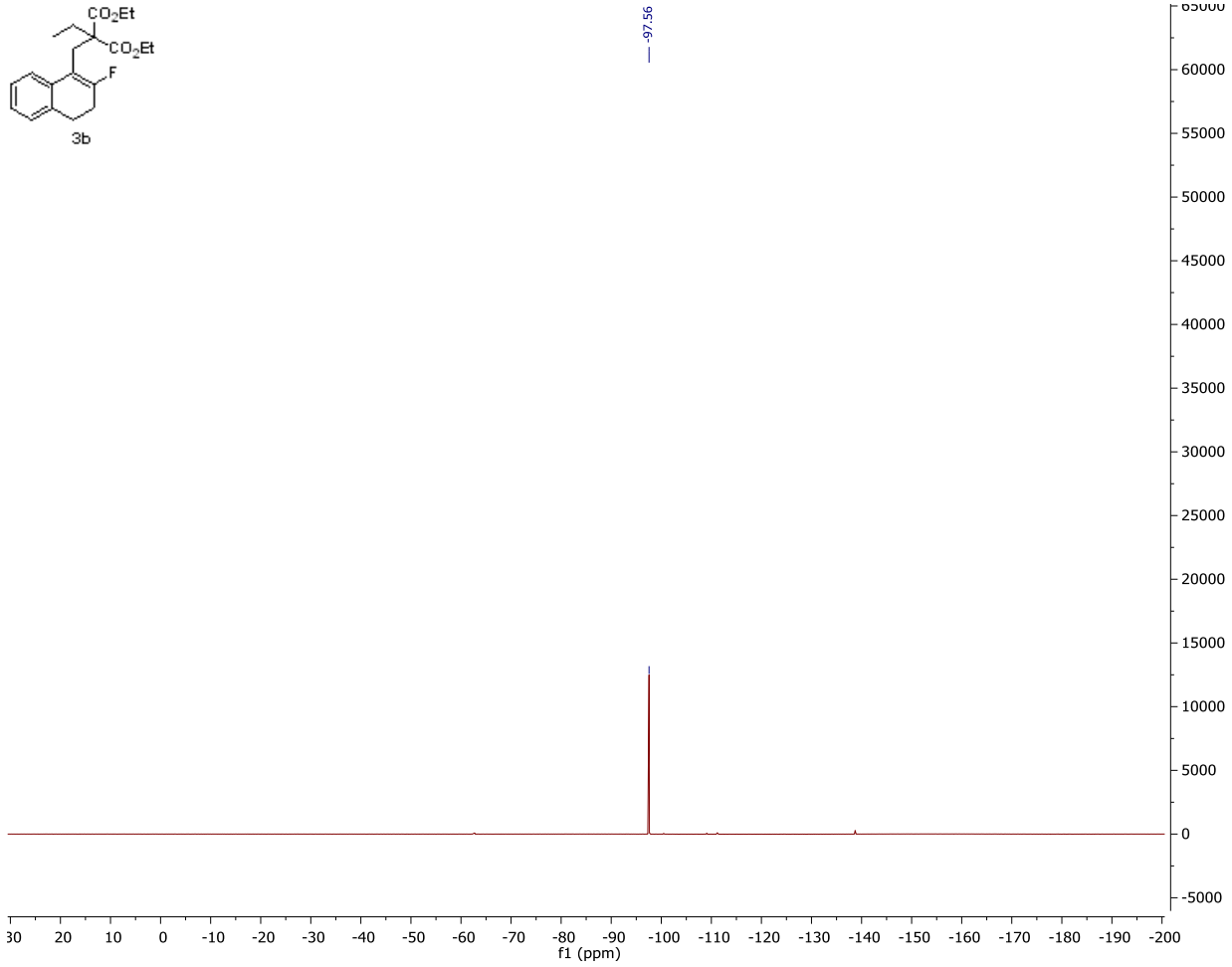


Diethyl 2-ethyl-2-((2-fluoro-3,4-dihydronaphthalen-1-1yl)methyl)malonate (3b)

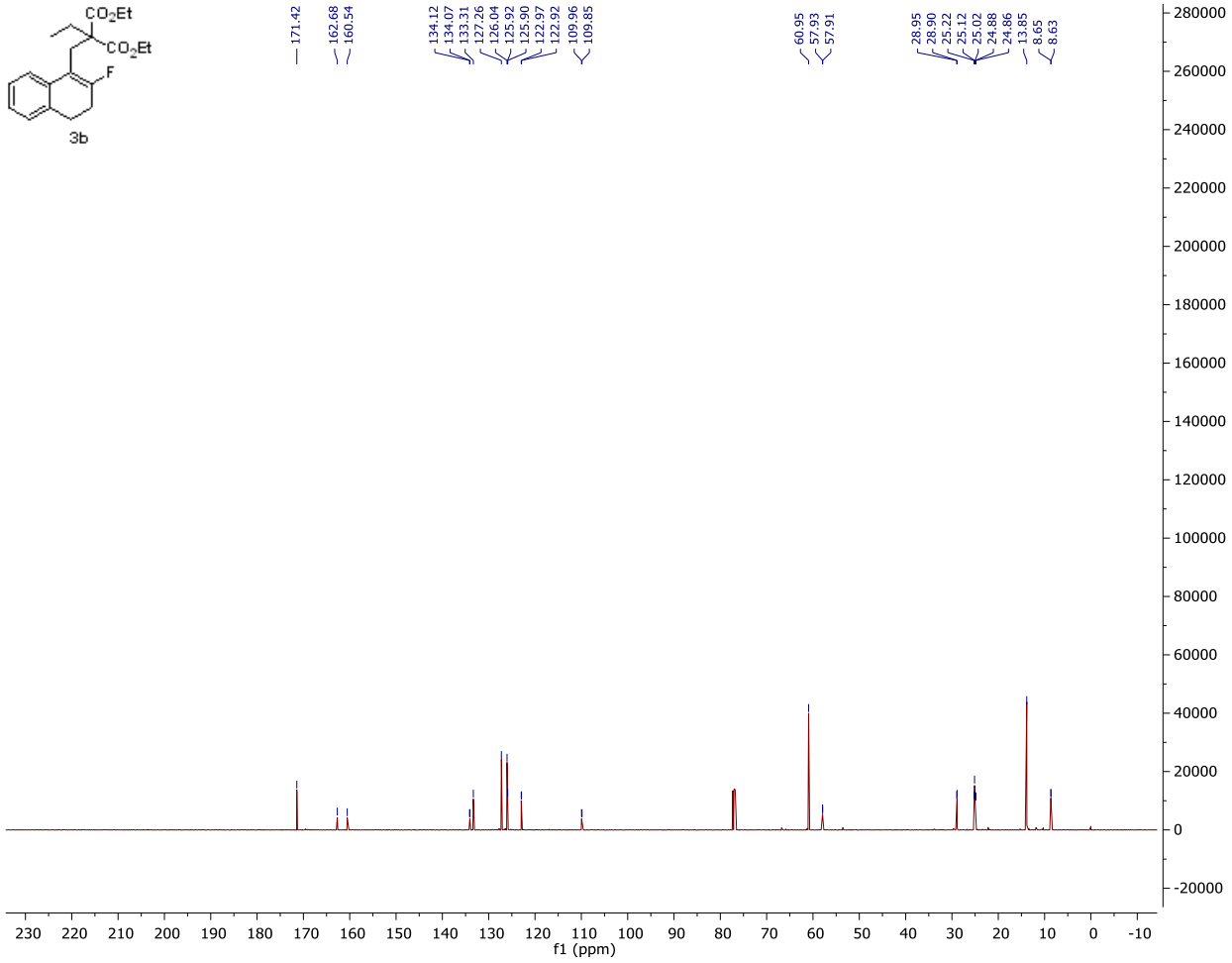
^{1}H (500 MHz, $CDCl_3$)



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

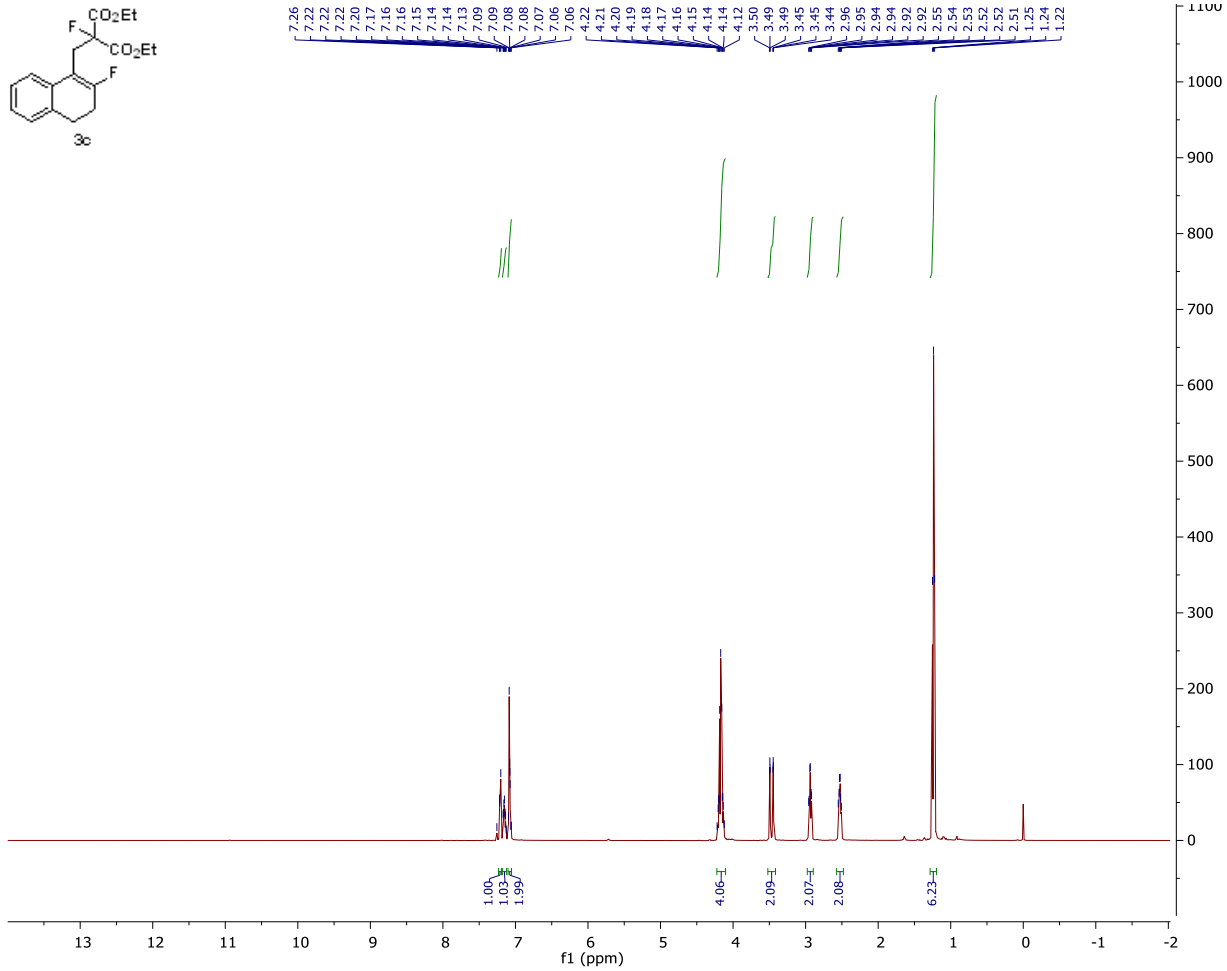


^{13}C (126 MHz, $CDCl_3$)

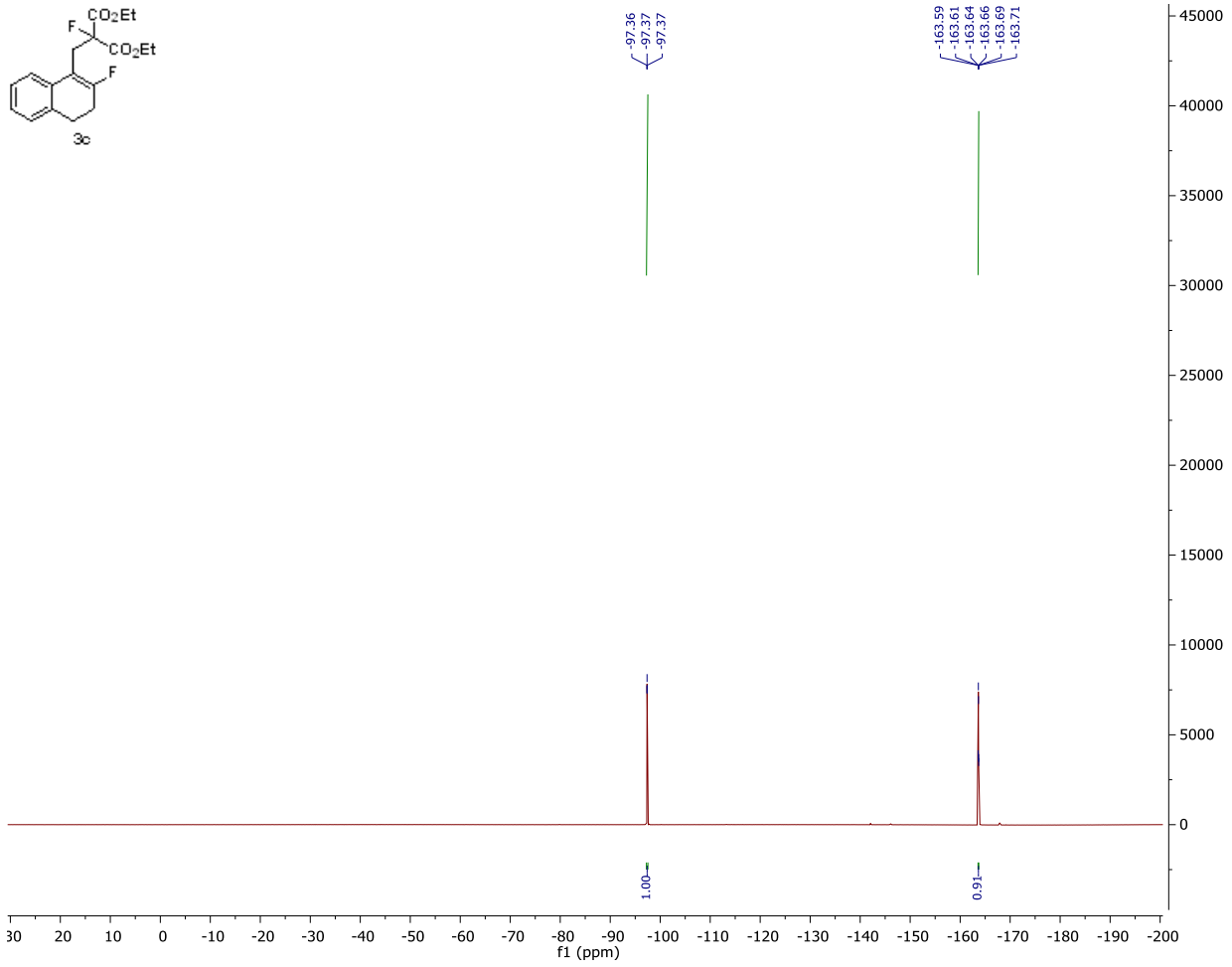


Diethyl 2-fluoro-2-((2-fluoro-3,4-dihydronaphthalen-1-yl)methyl)malonate (3c)

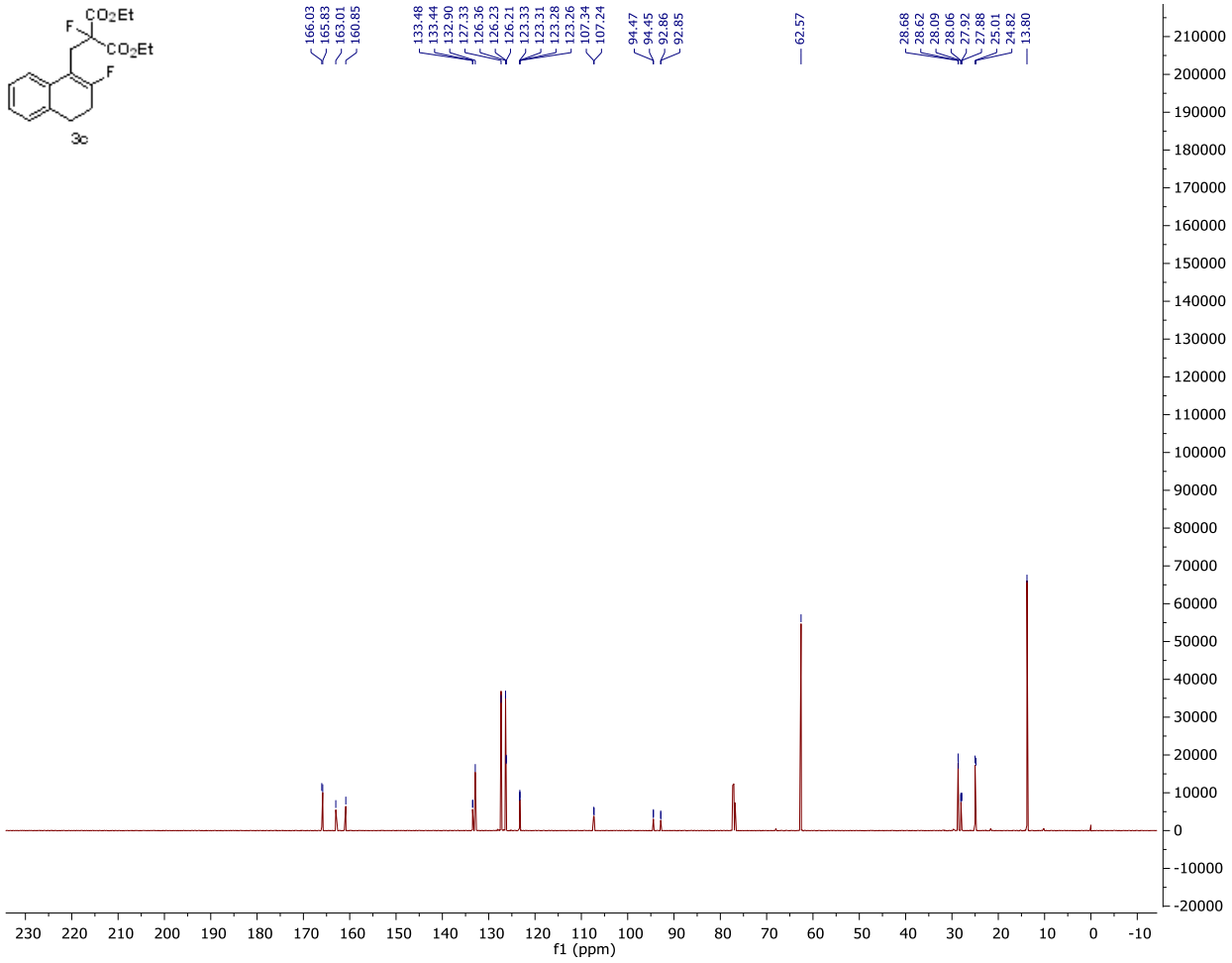
^{1}H (500 MHz, $CDCl_3$)



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

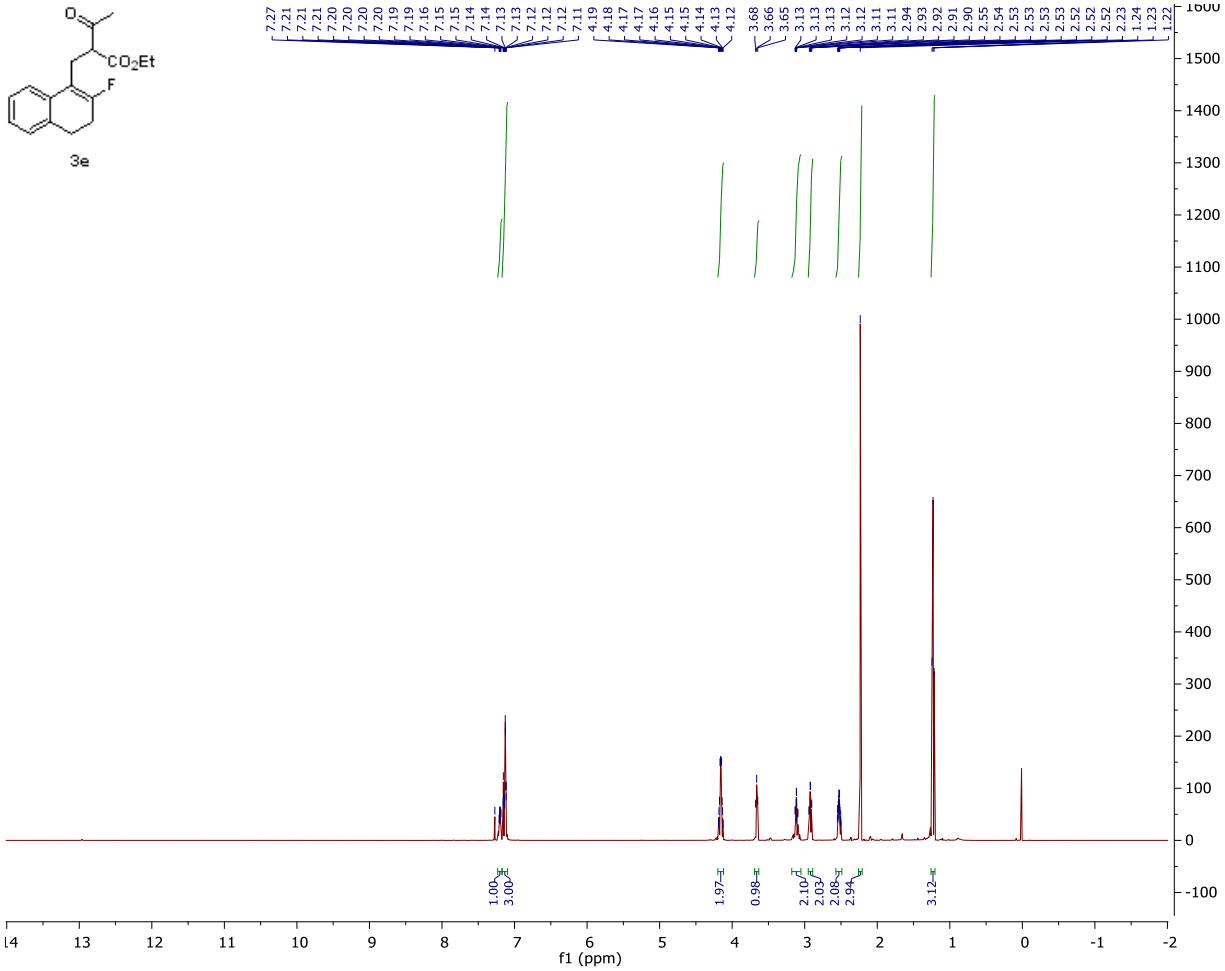


^{13}C (126 MHz, $CDCl_3$)

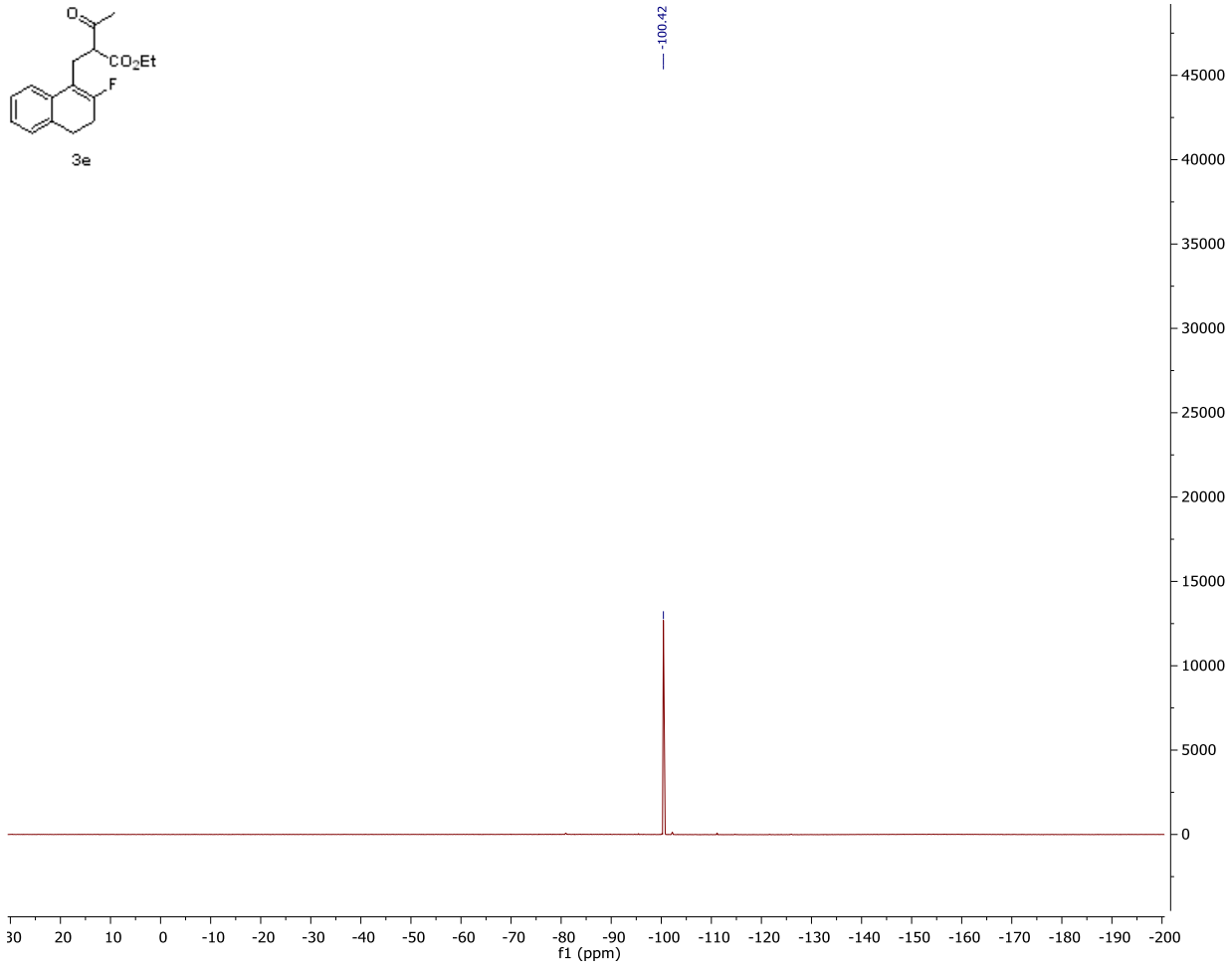


Ethyl 2-((2-fluoro-3,4-dihydronaphthalen-1-yl)methyl)-3-oxobutanoate (3e)

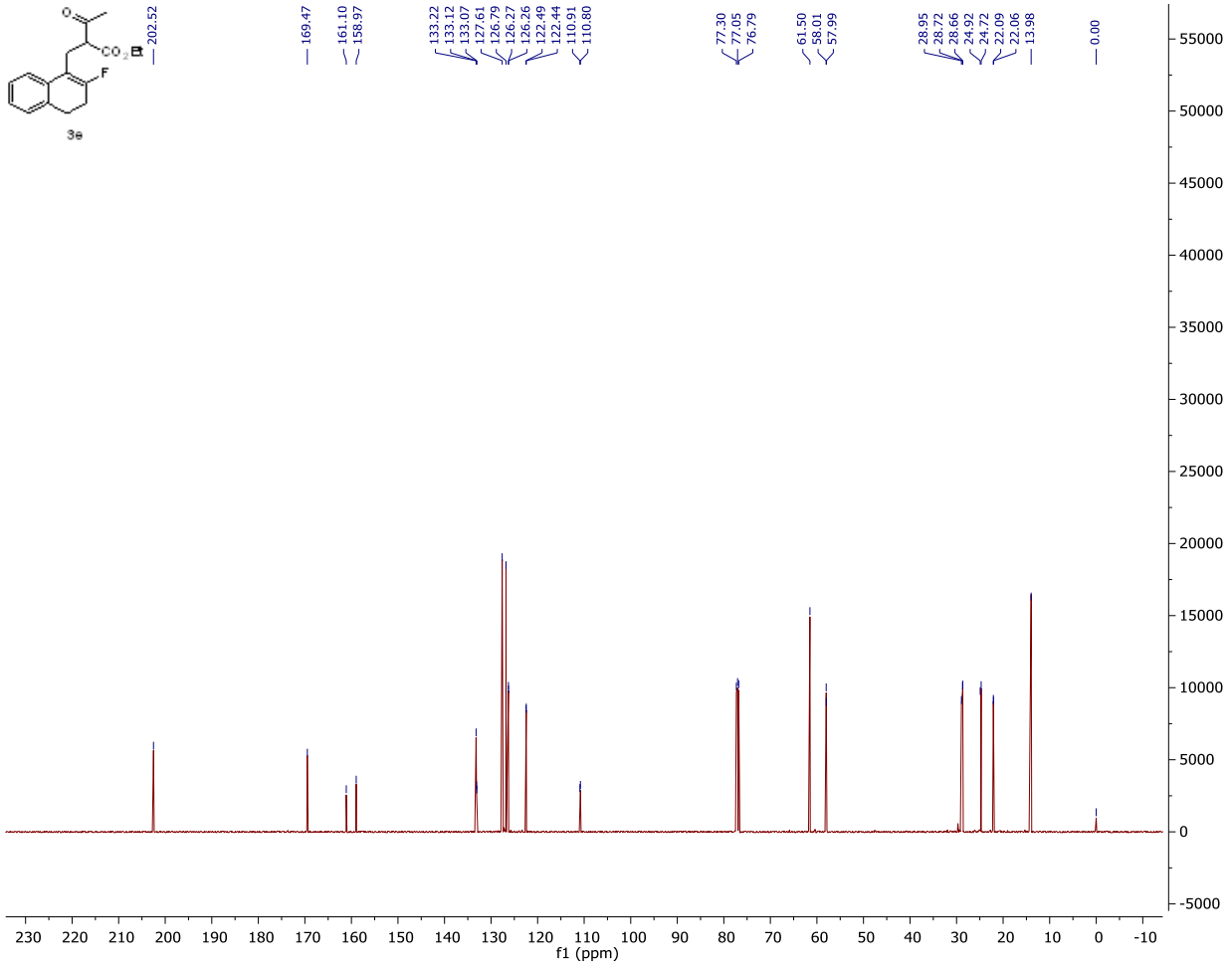
^{1}H (500 MHz, $CDCl_3$)



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

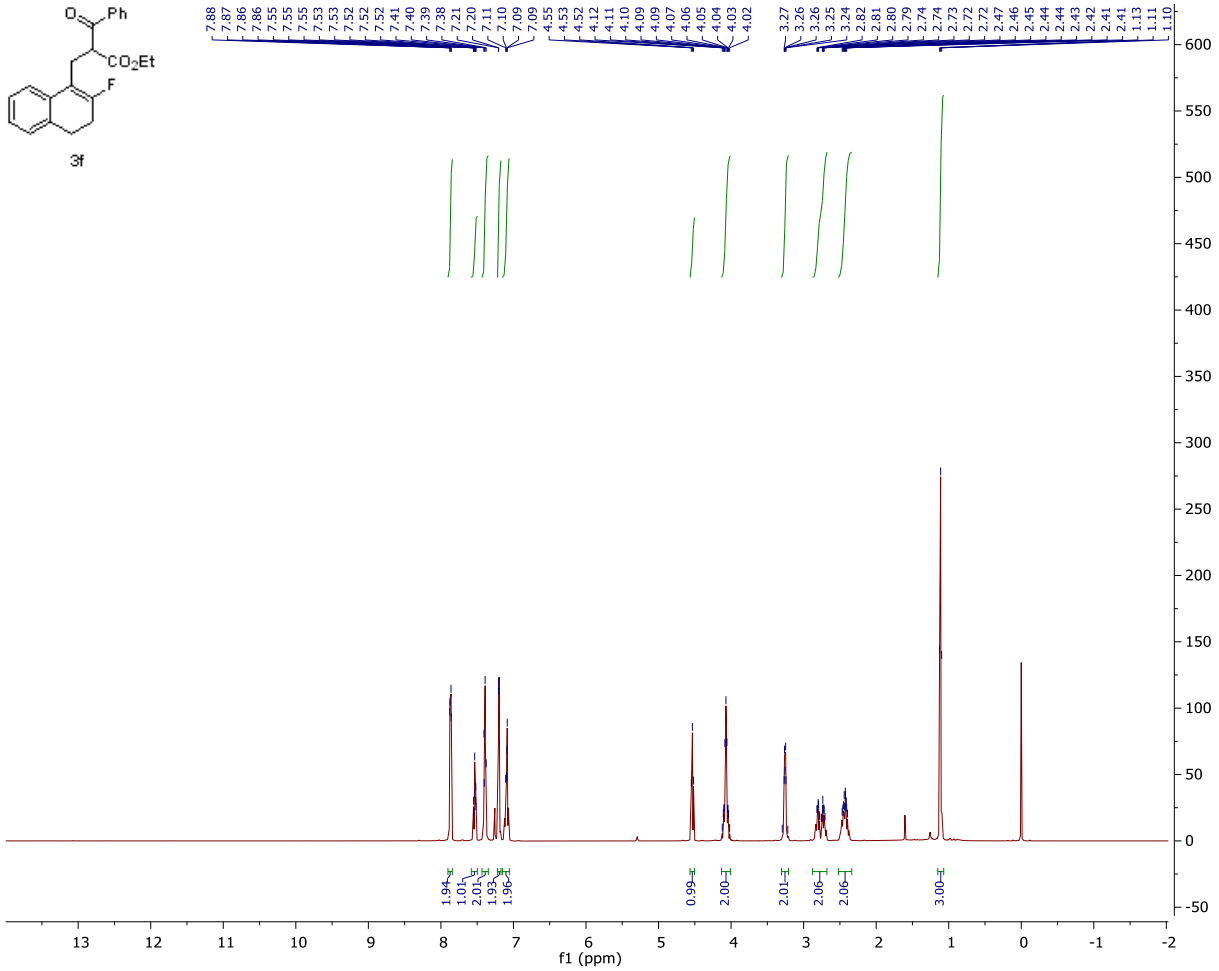


^{13}C (126 MHz, $CDCl_3$)

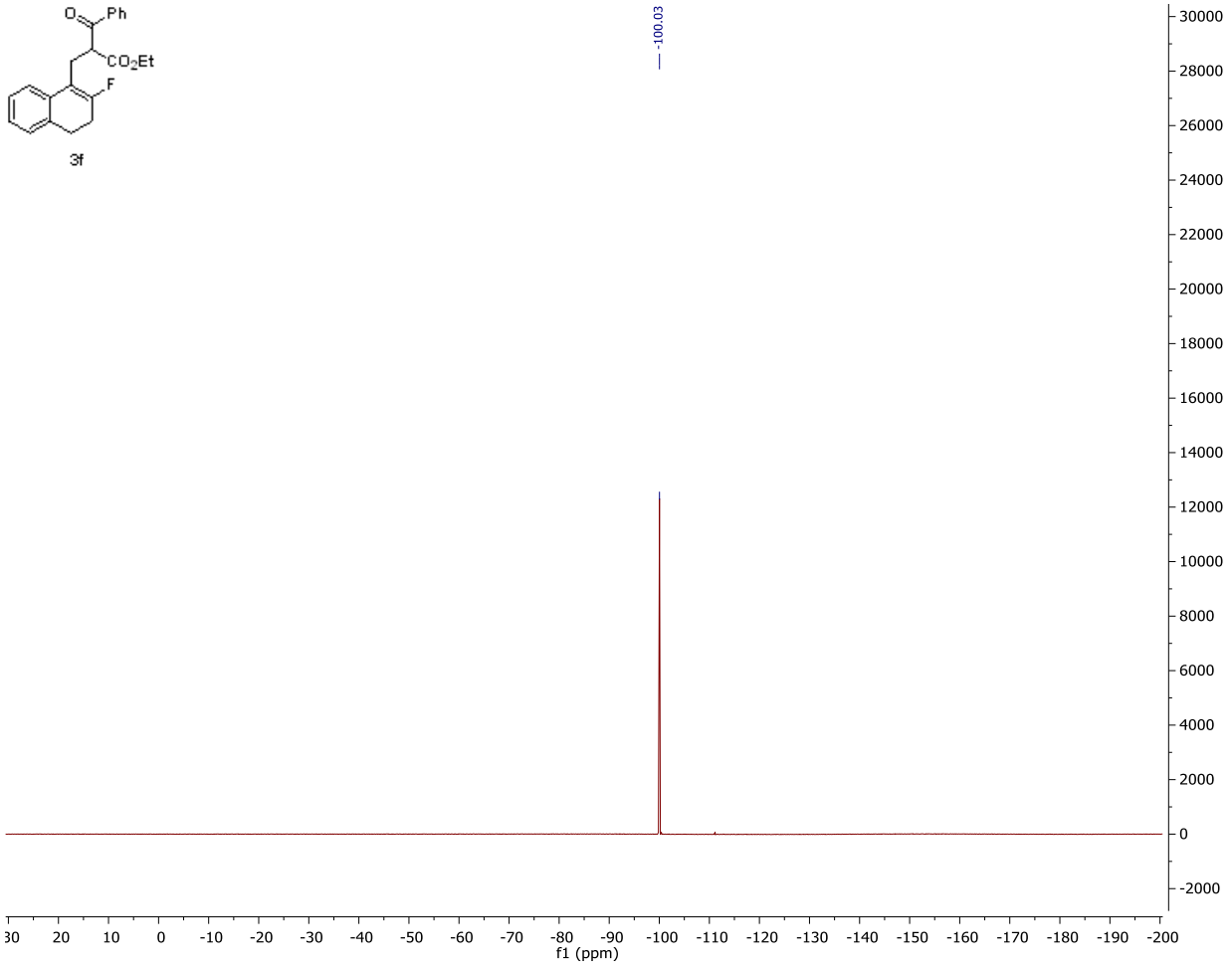


Ethyl 2-((2-fluoro-3,4-dihydronaphthalen-1-yl)methyl)-3-oxo-3-phenylpropanoate (3f)

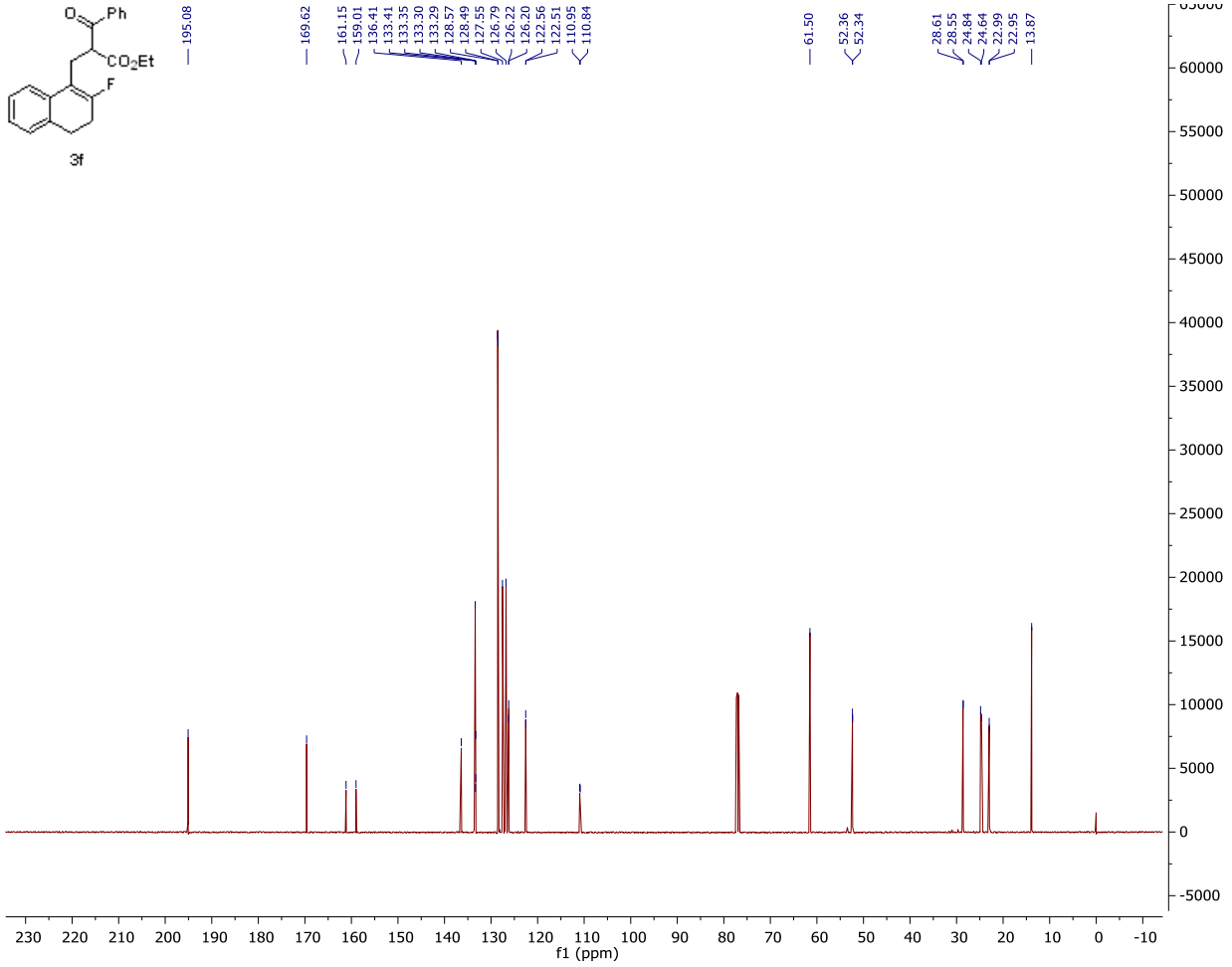
^{1}H (500 MHz, $CDCl_3$)



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

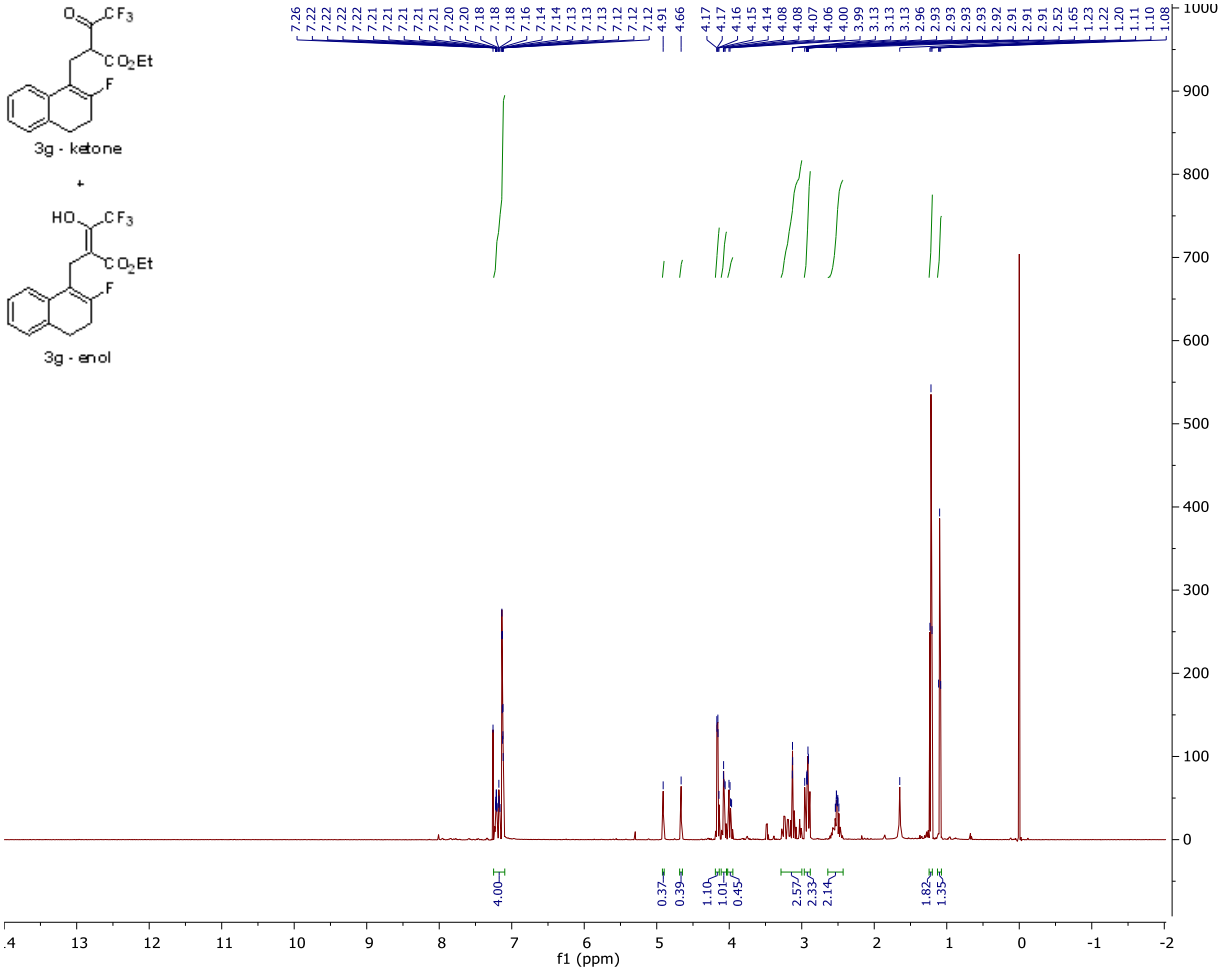


^{13}C (126 MHz, $CDCl_3$)

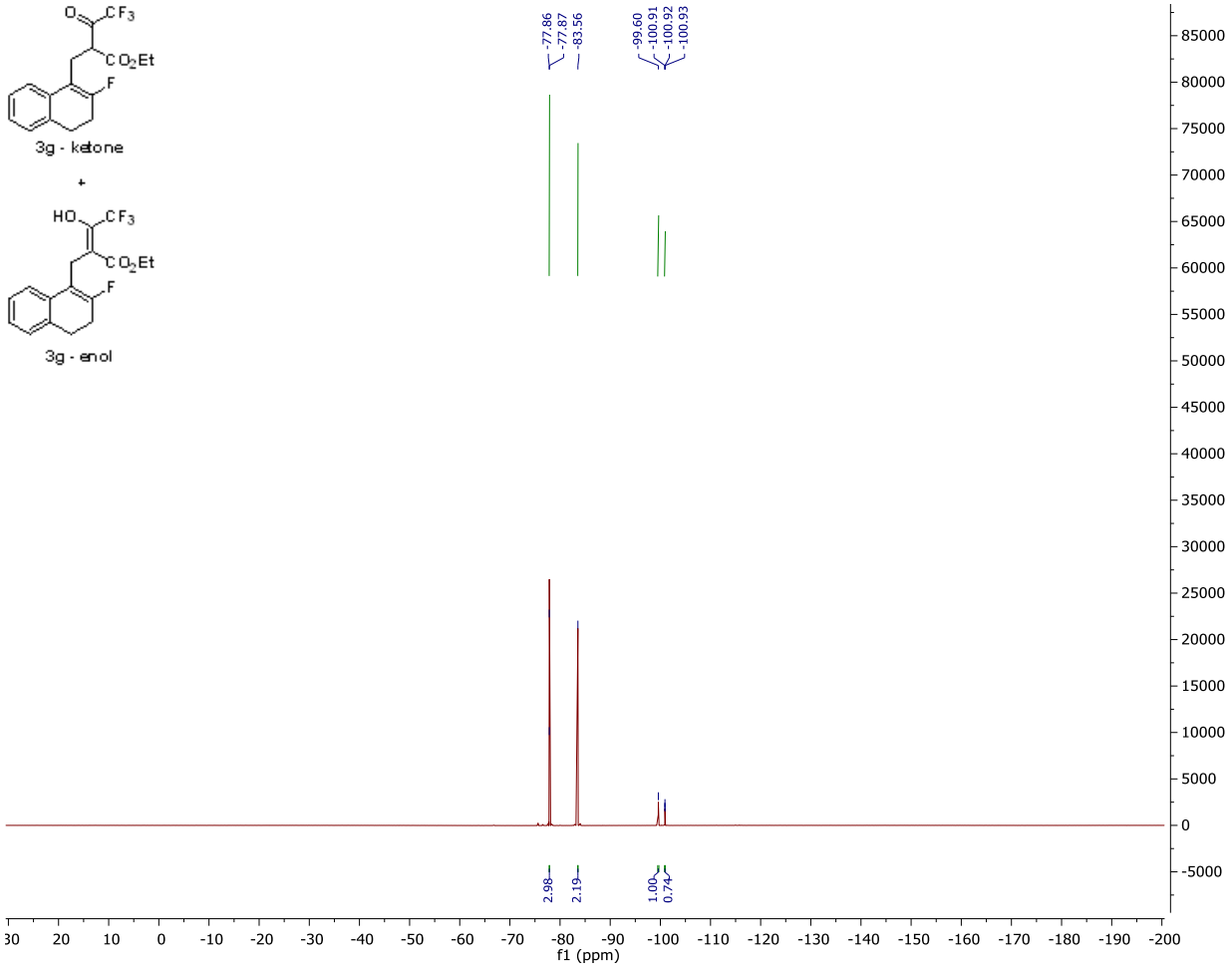


Ethyl 4,4,4-trifluoro-2-((2-fluoro-3,4-dihydronaphthalen-1-yl)methyl)-3-oxobutanoate (3g)

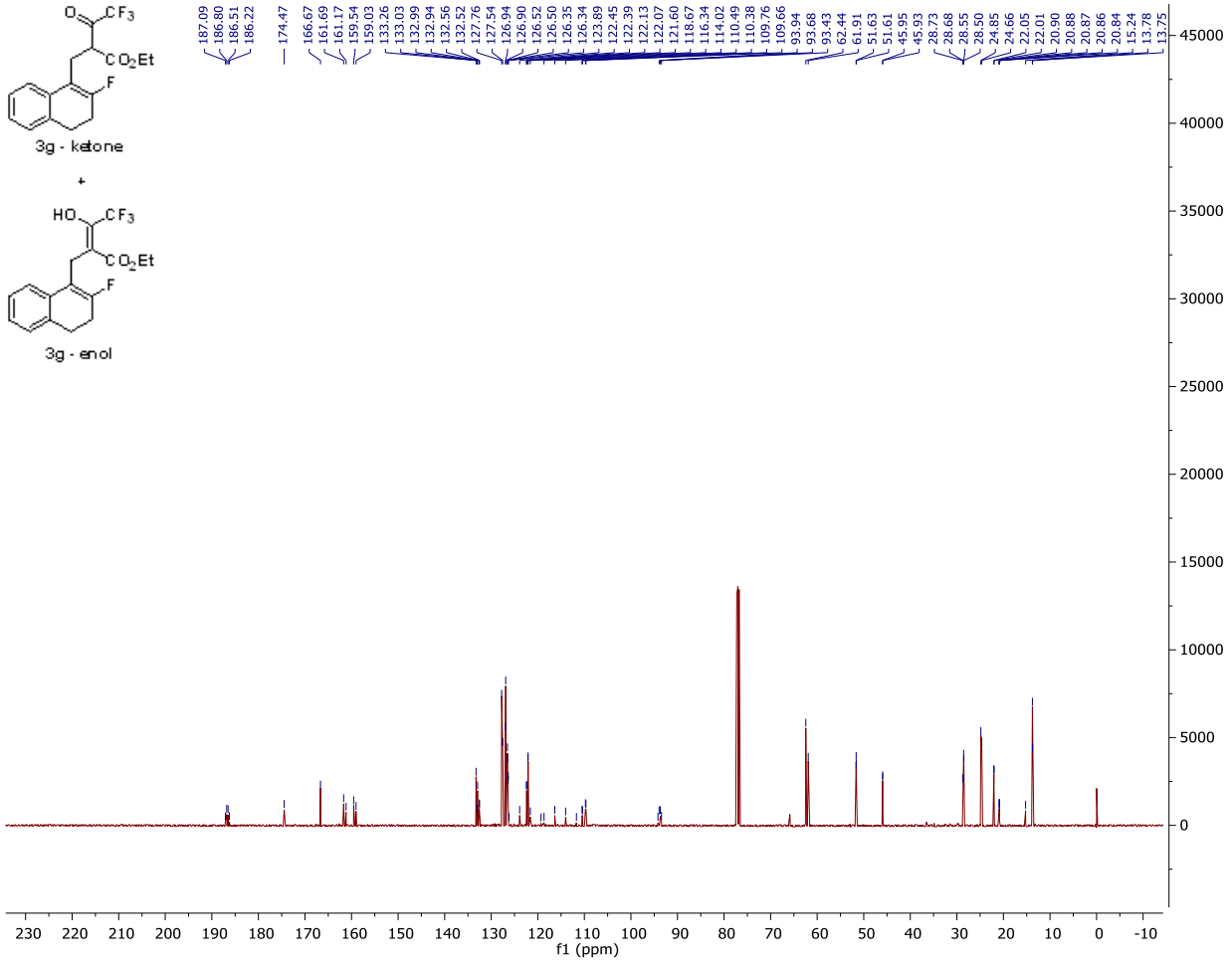
^{1}H (500 MHz, $CDCl_3$)



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

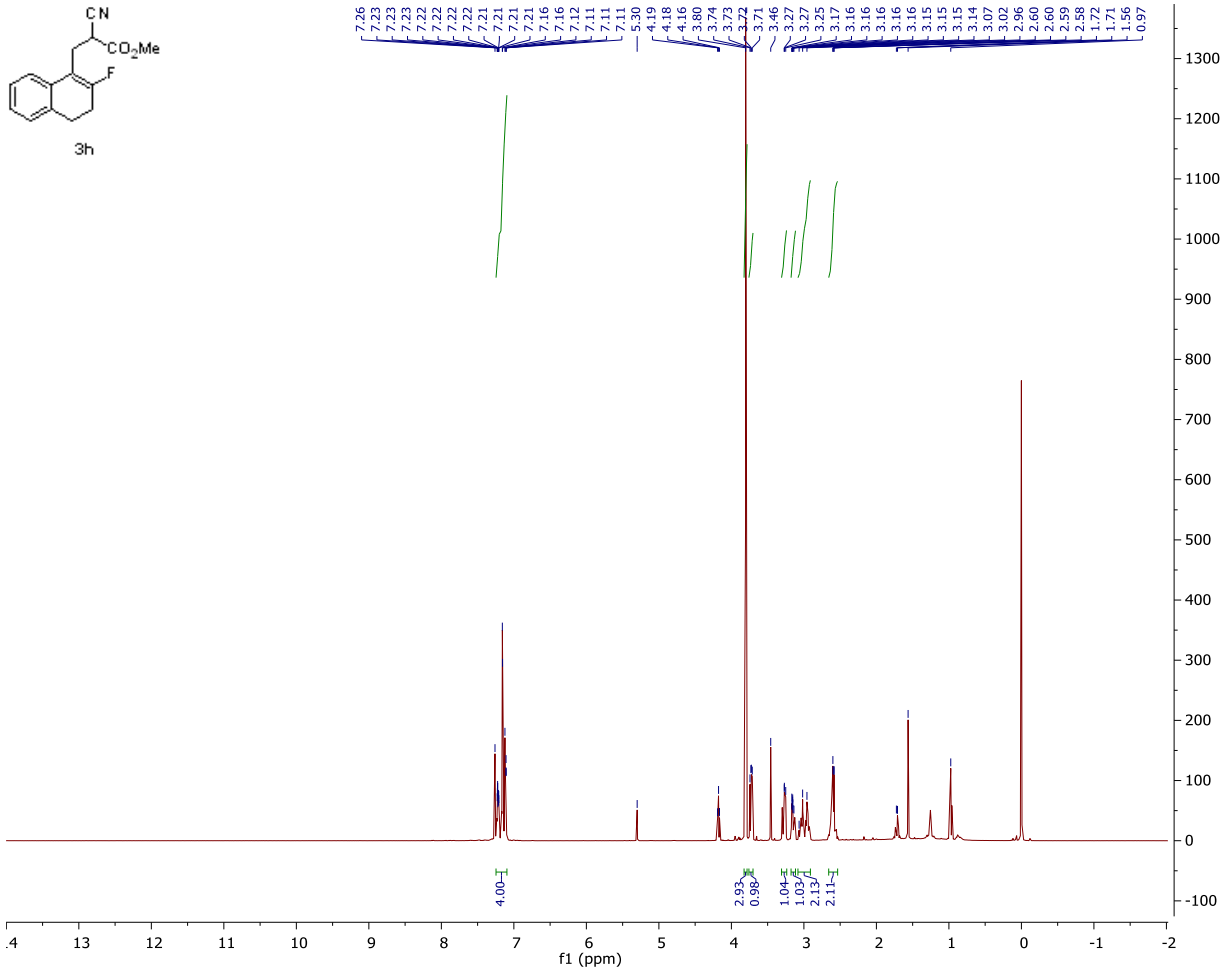


^{13}C (126 MHz, $CDCl_3$)

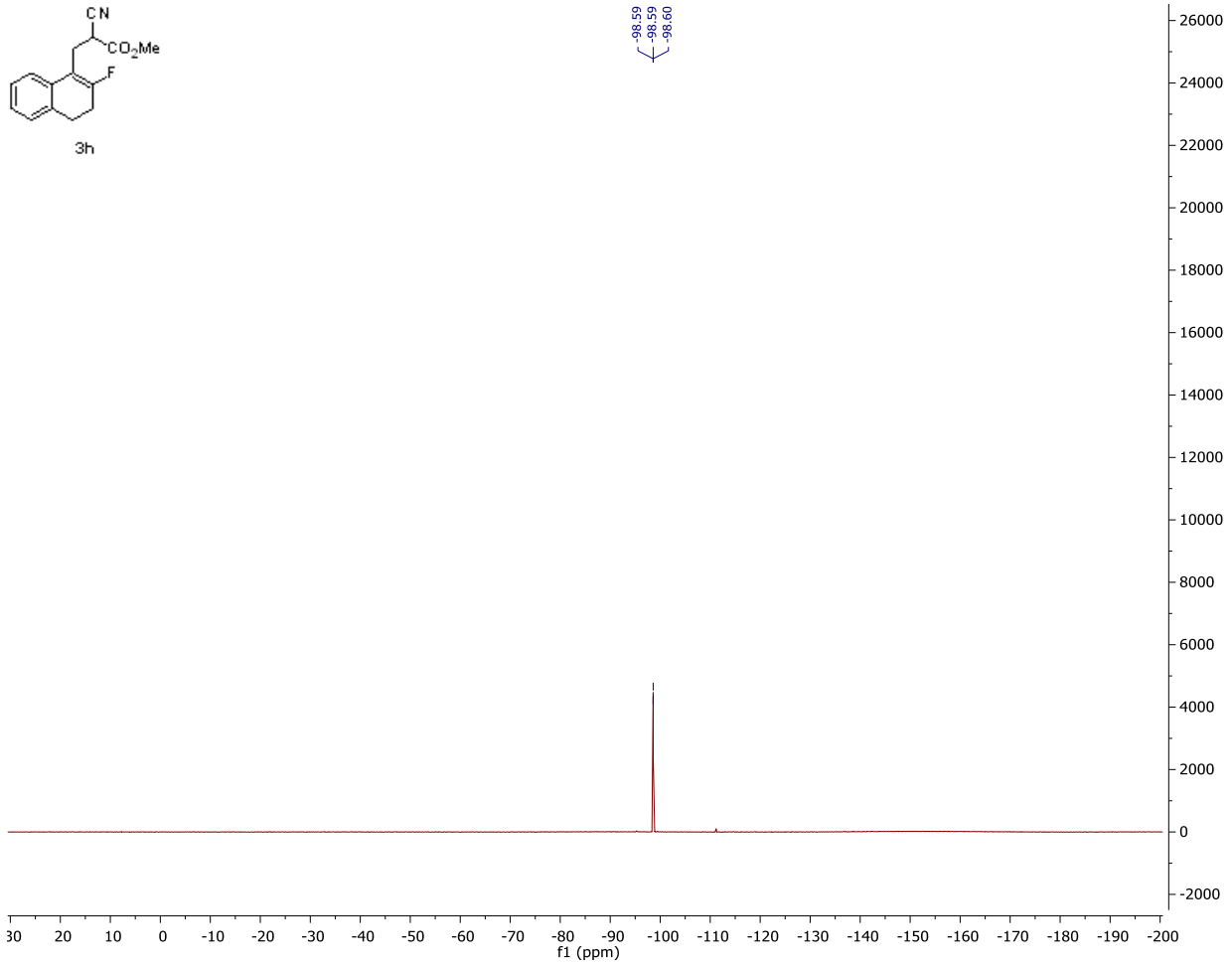


Methyl 2-cyano-3-(2-fluoro-3,4-dihydronaphthalen-1-yl)propanoate (3h)

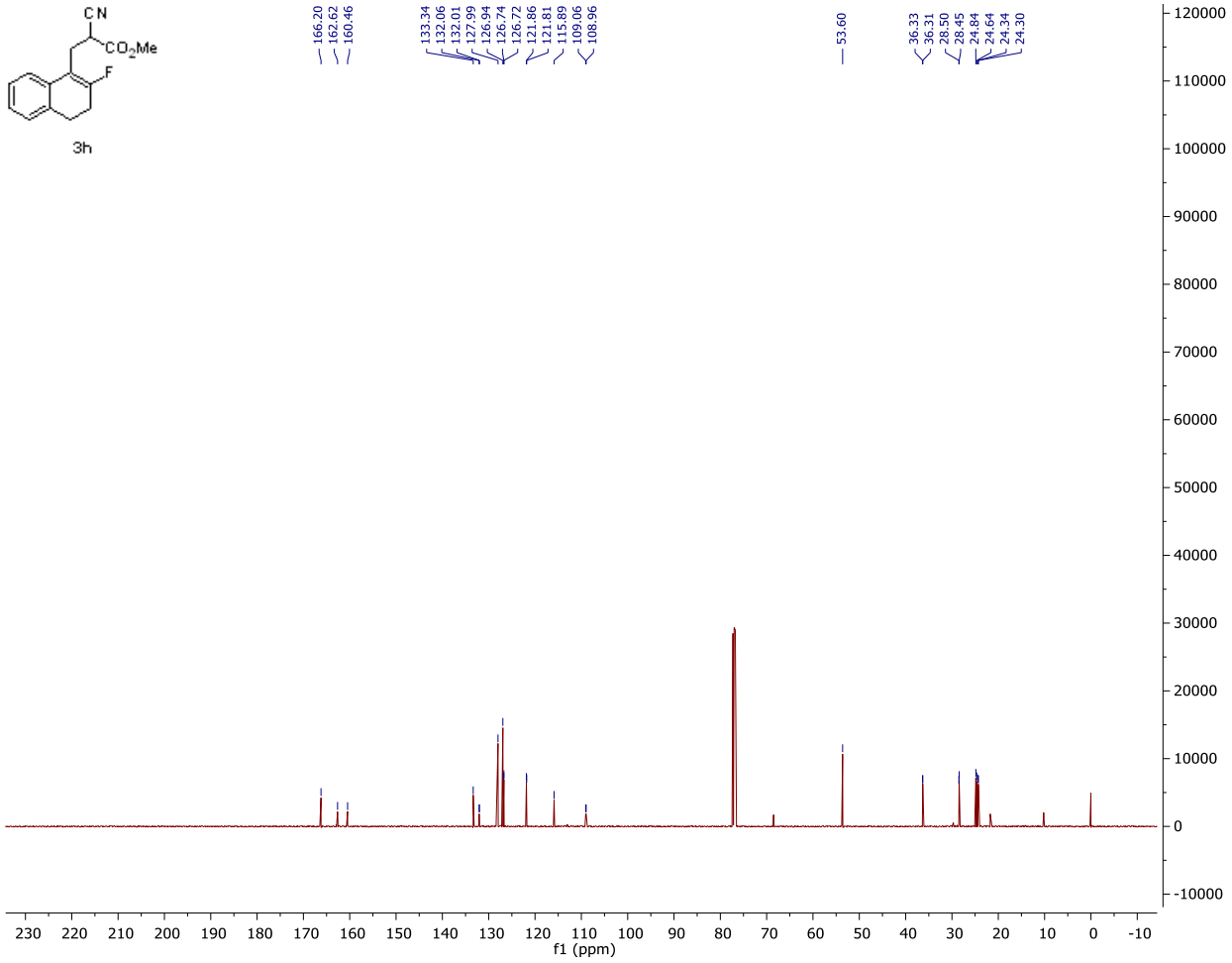
^{1}H (500 MHz, $CDCl_3$)



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

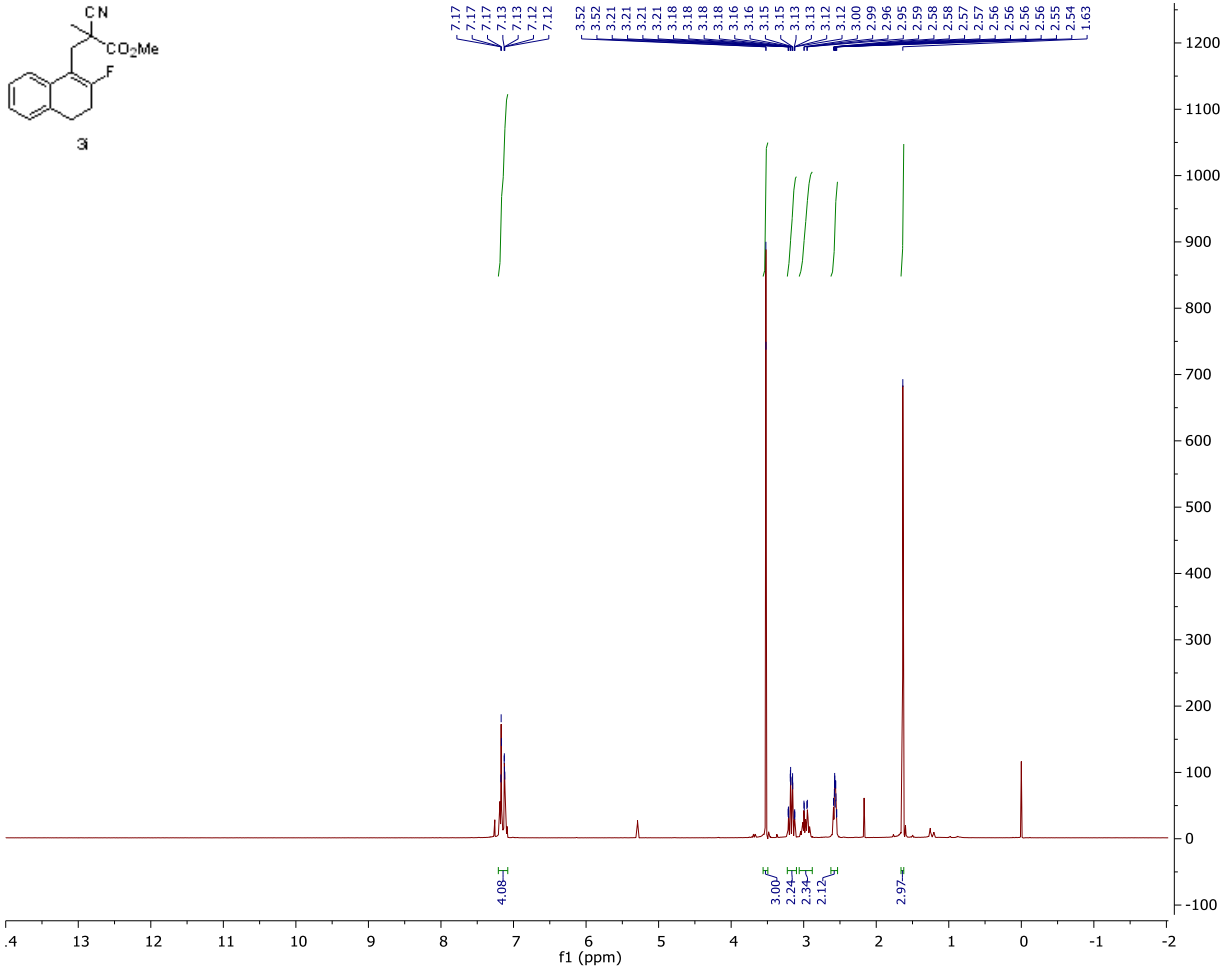


^{13}C (126 MHz, $CDCl_3$)

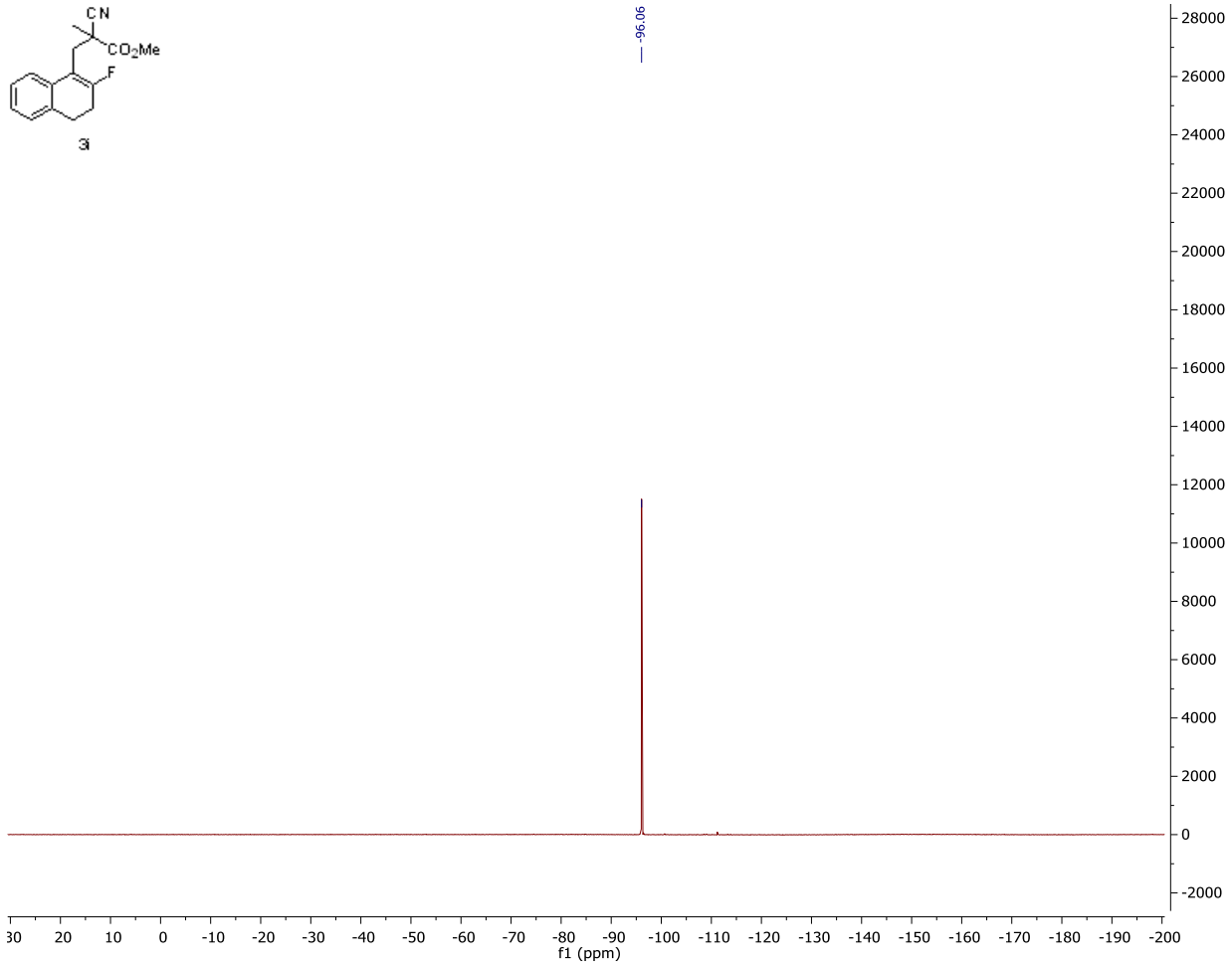


Methyl 2-cyano-3-(2-fluoro-3.4-dihydronaphthalen-1-yl)-2-methylpropanoate (3i)

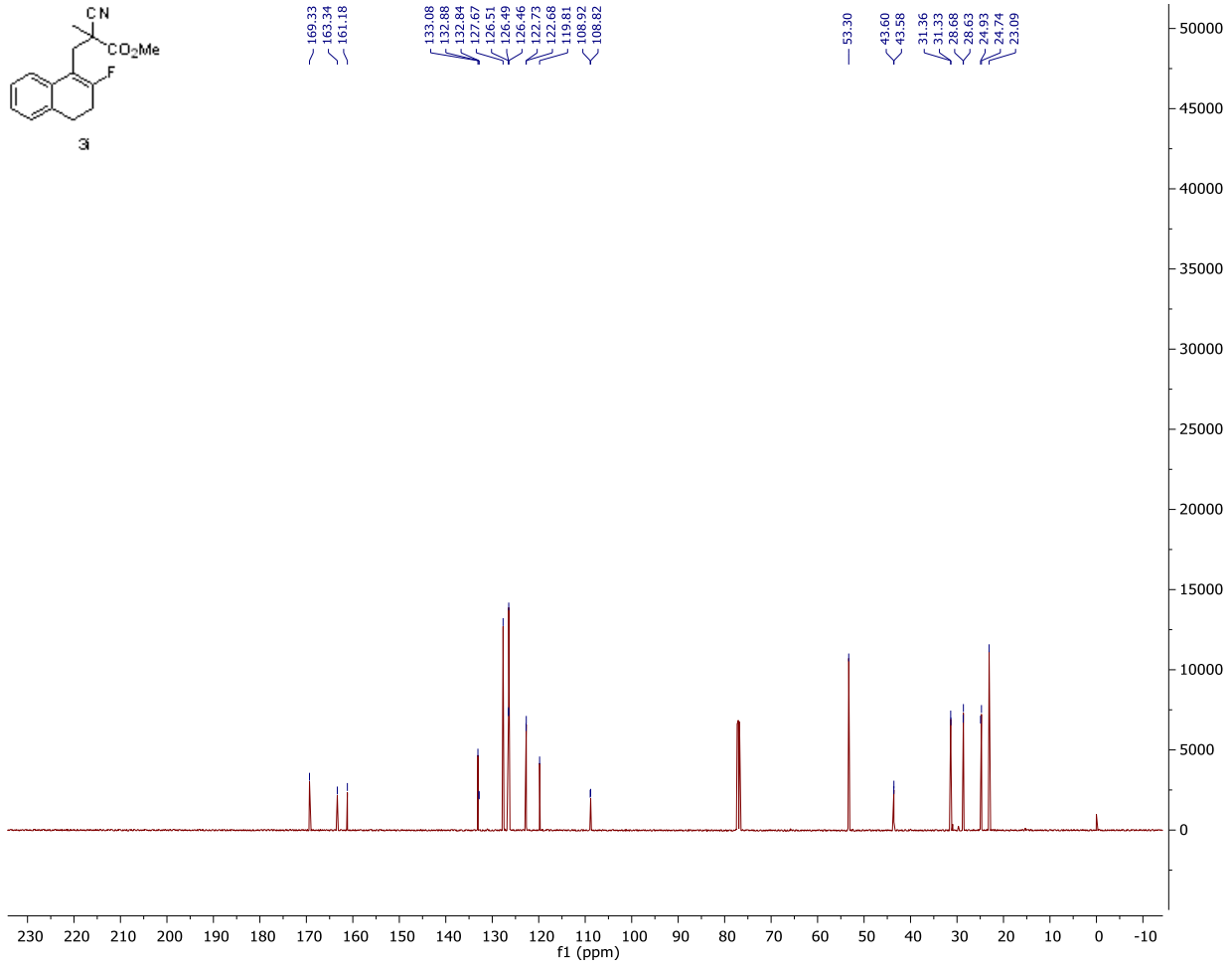
^{1}H (500 MHz, $CDCl_3$)



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

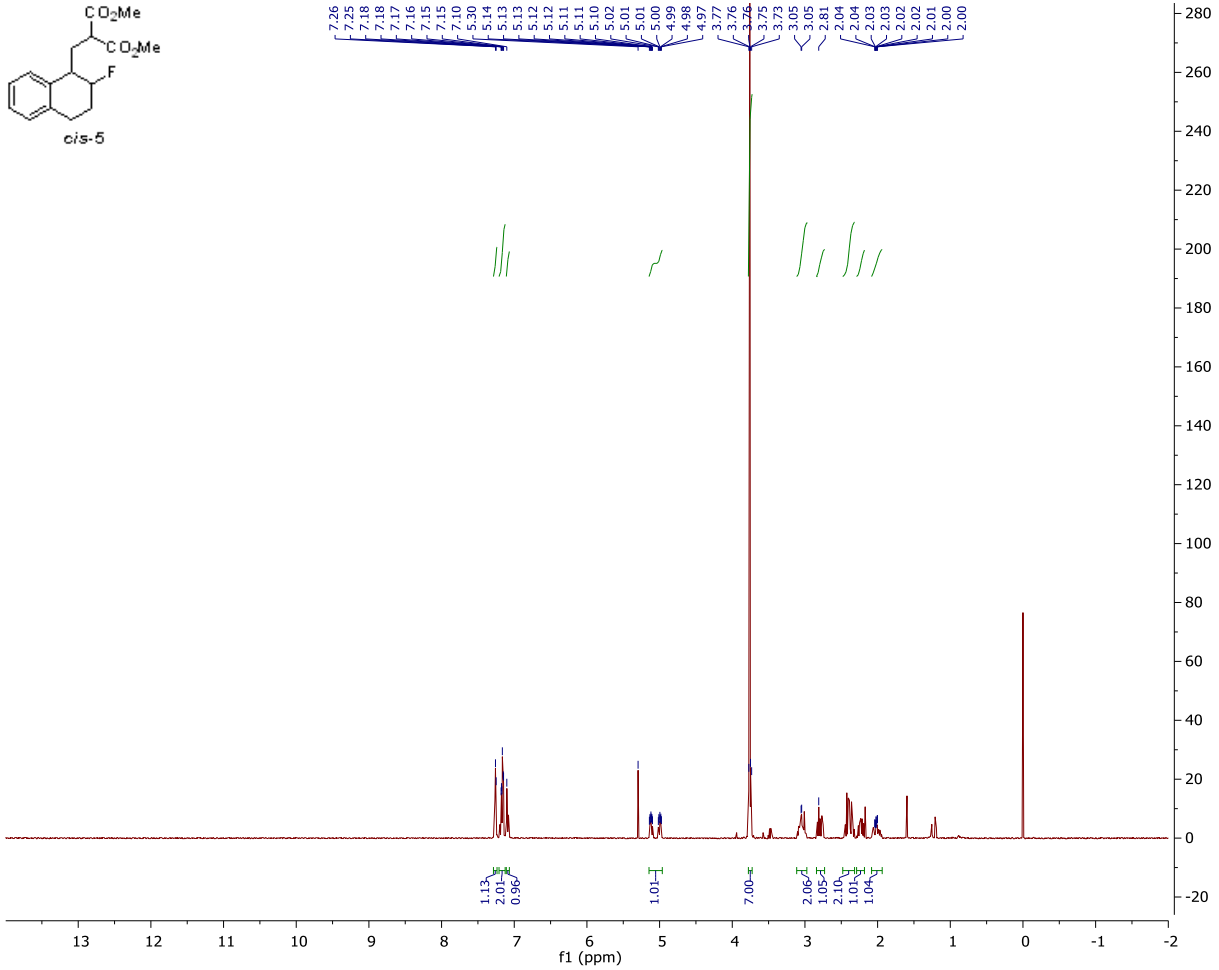


^{13}C (126 MHz, $CDCl_3$)

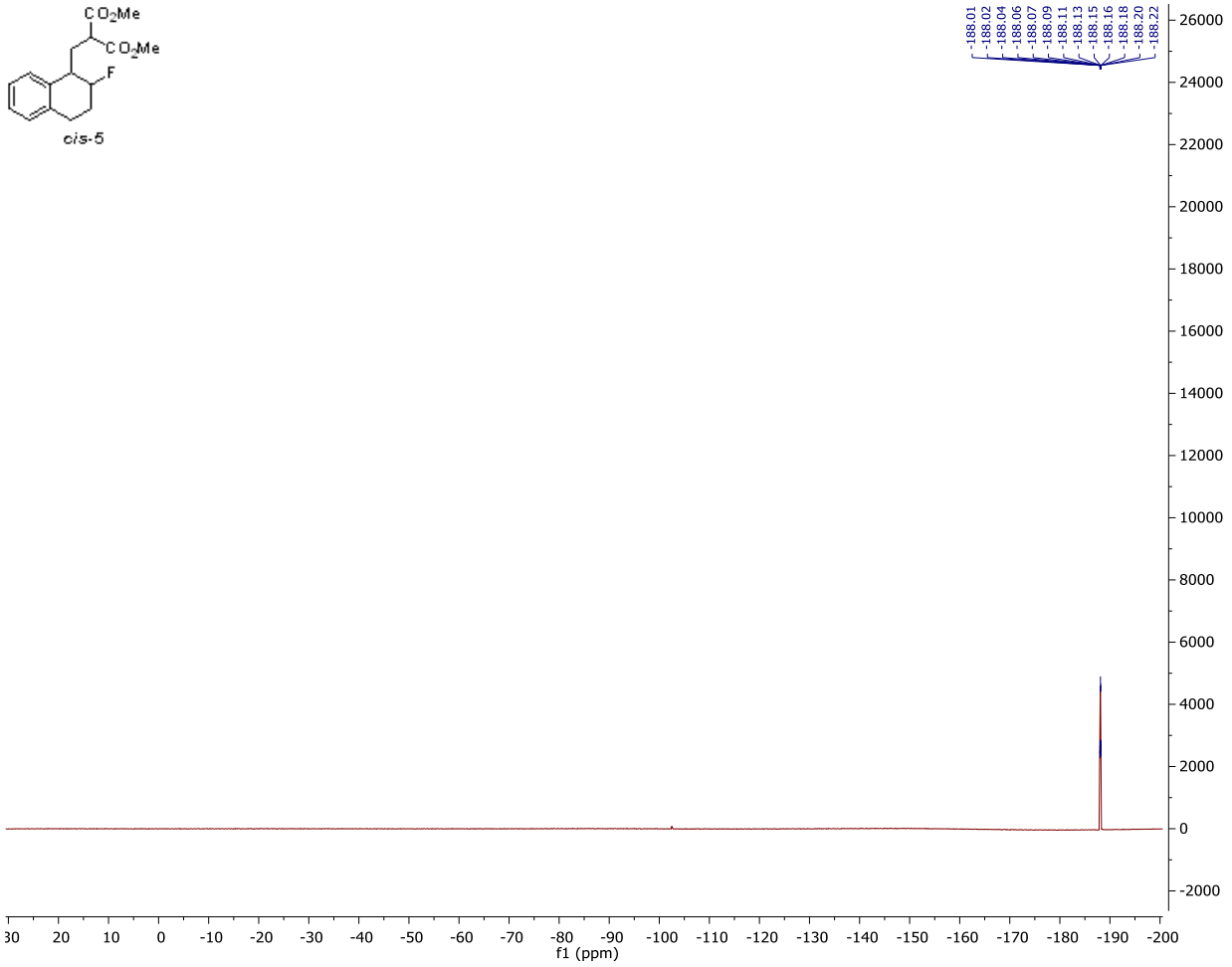


Dimethyl 2-((2-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)malonate (*cis*-5)

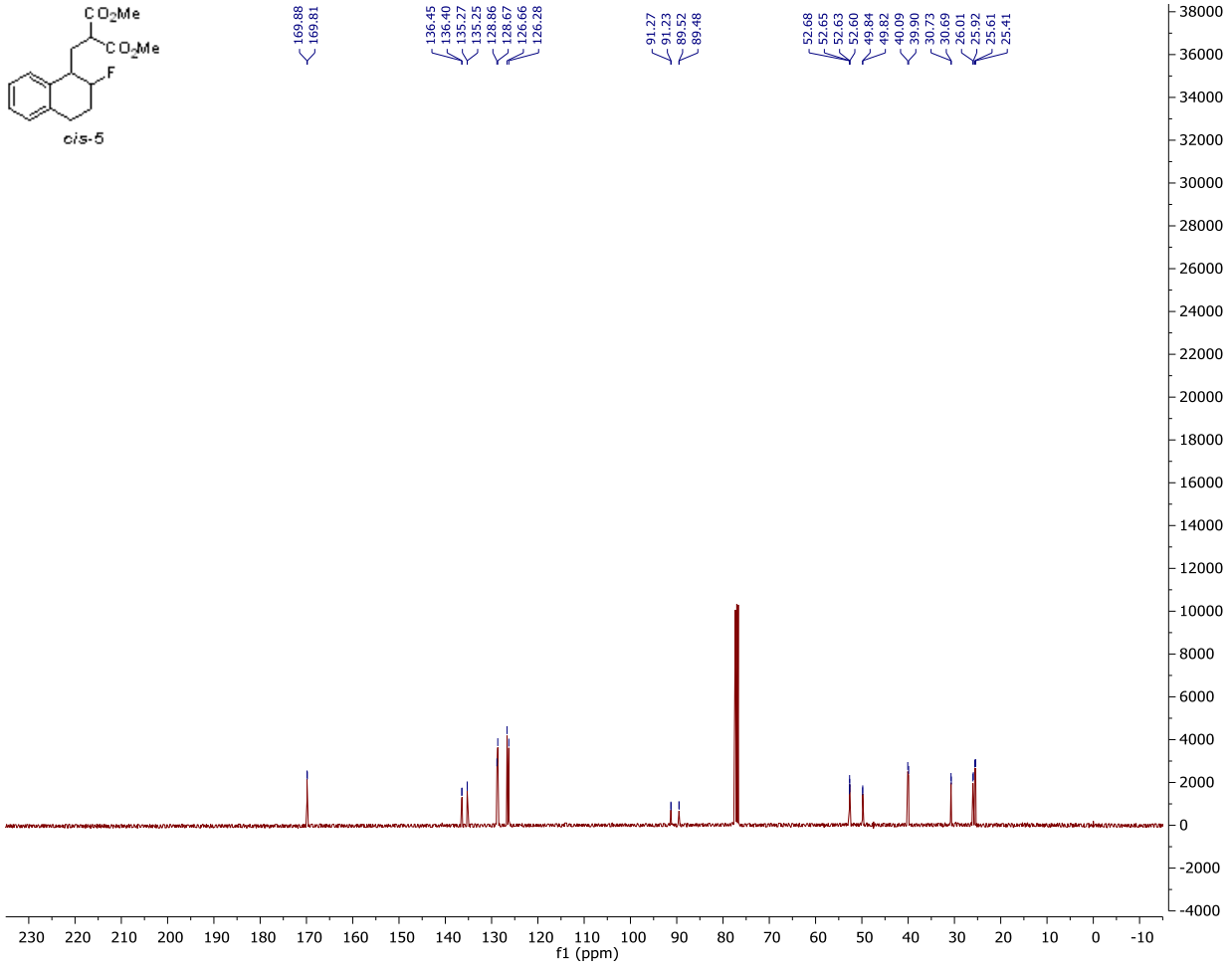
^{1}H (400 MHz, $CDCl_3$)



^{19}F (376 MHz, $CDCl_3$)

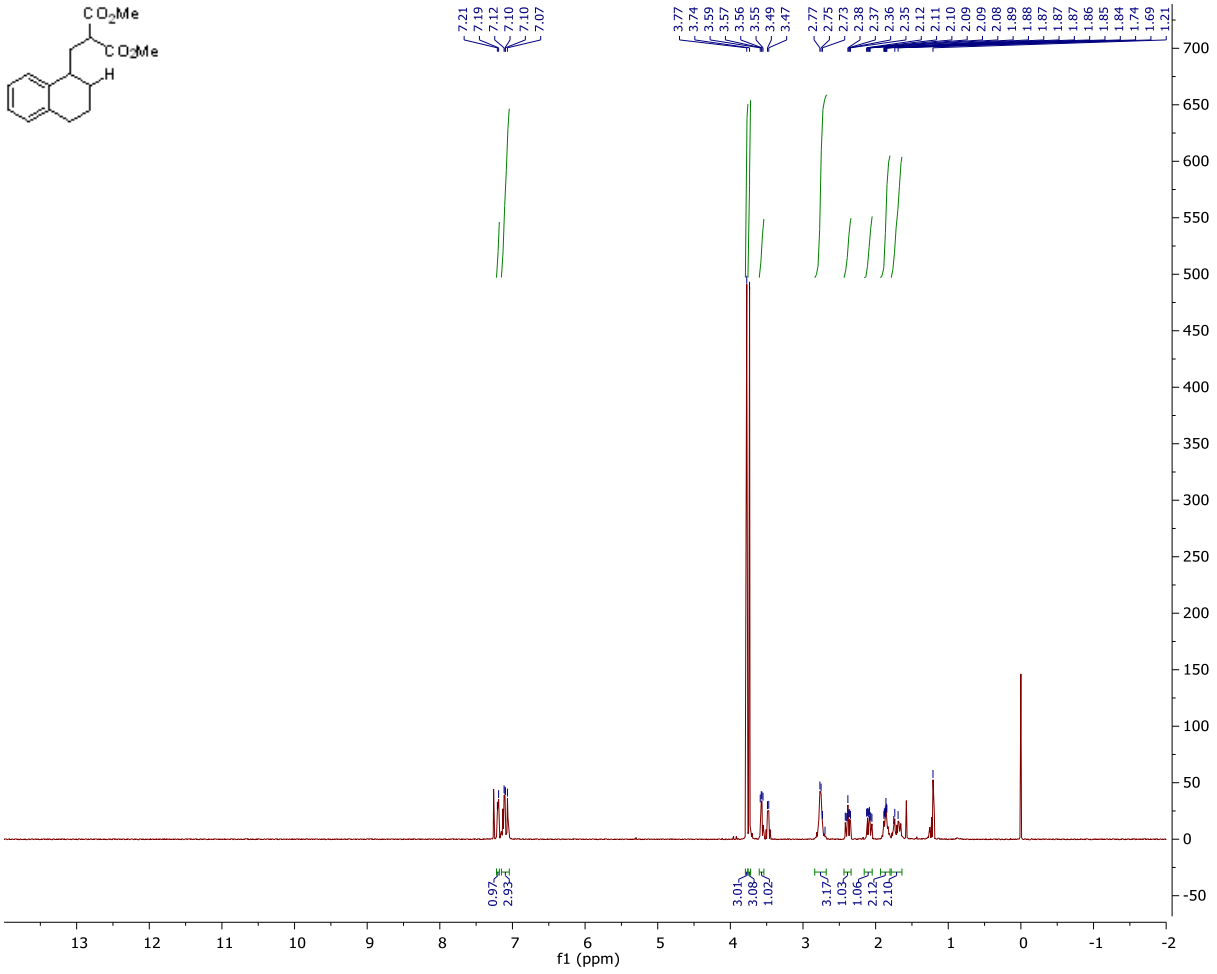


^{19}F (75 MHz, $CDCl_3$)

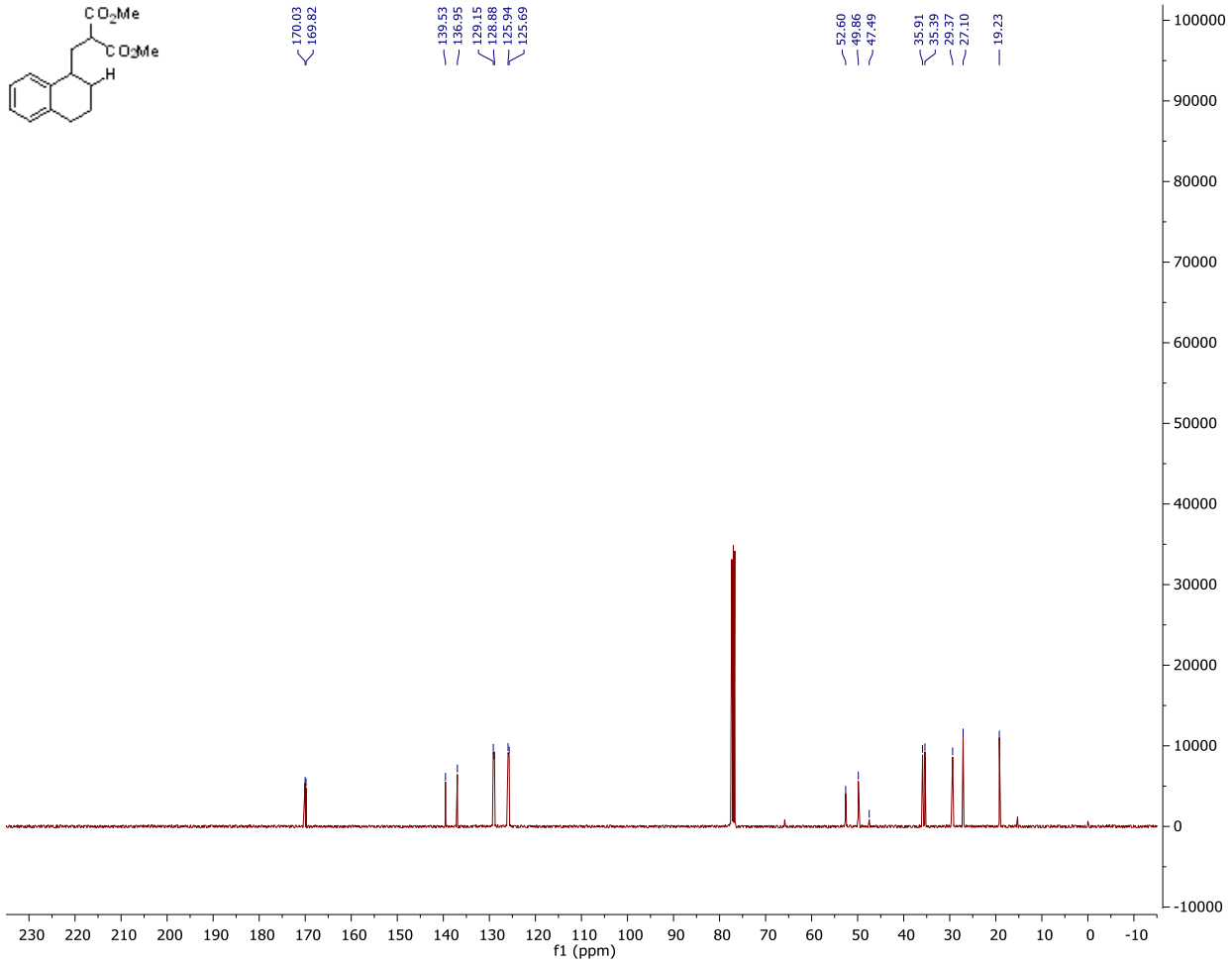


Dimethyl 2-((1,2,3,4-tetrahydronaphthalen-1-yl)methyl)malonate (*rac*-5)

^{1}H (400 MHz, $CDCl_3$)

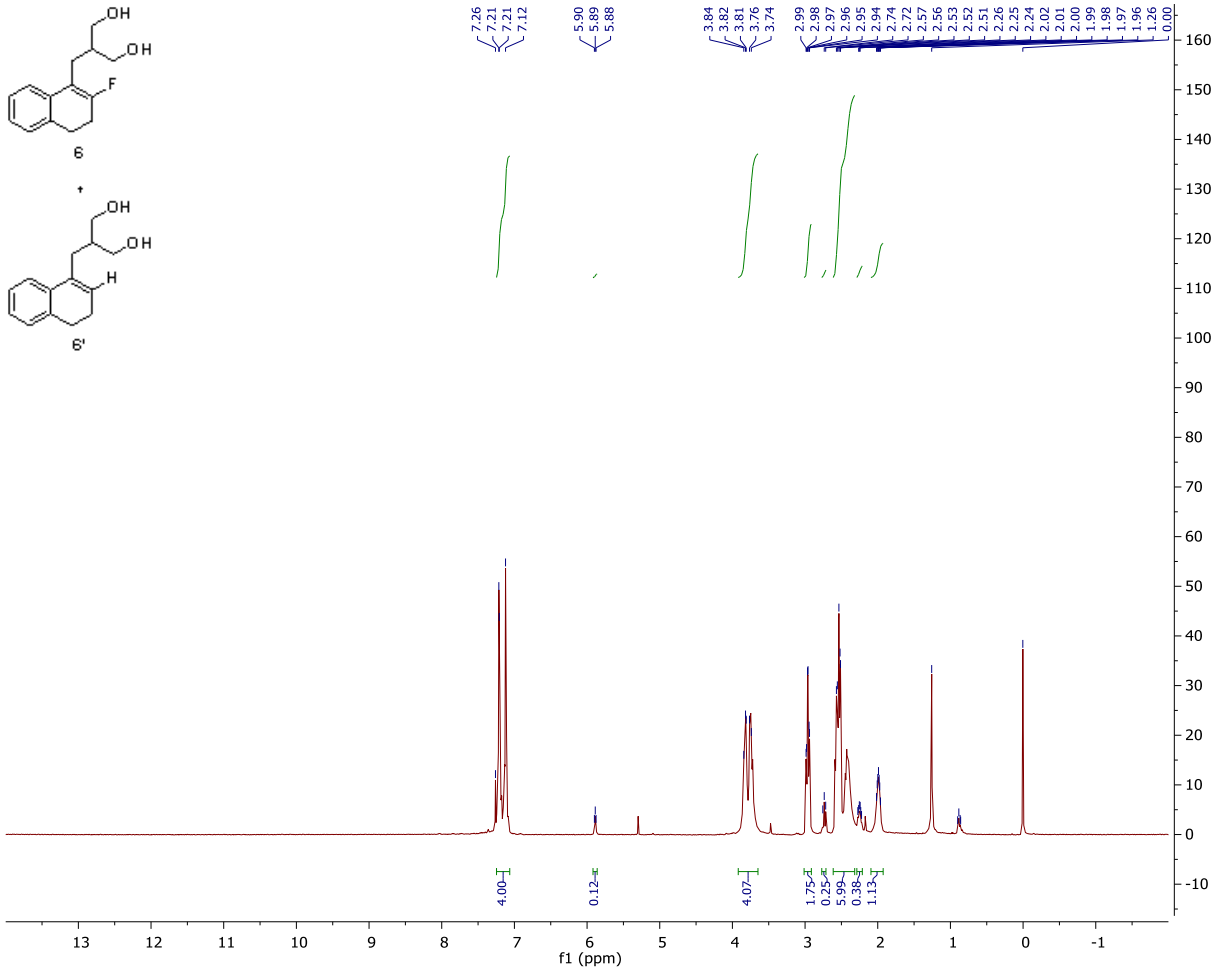


^{13}C (75 MHz, $CDCl_3$)

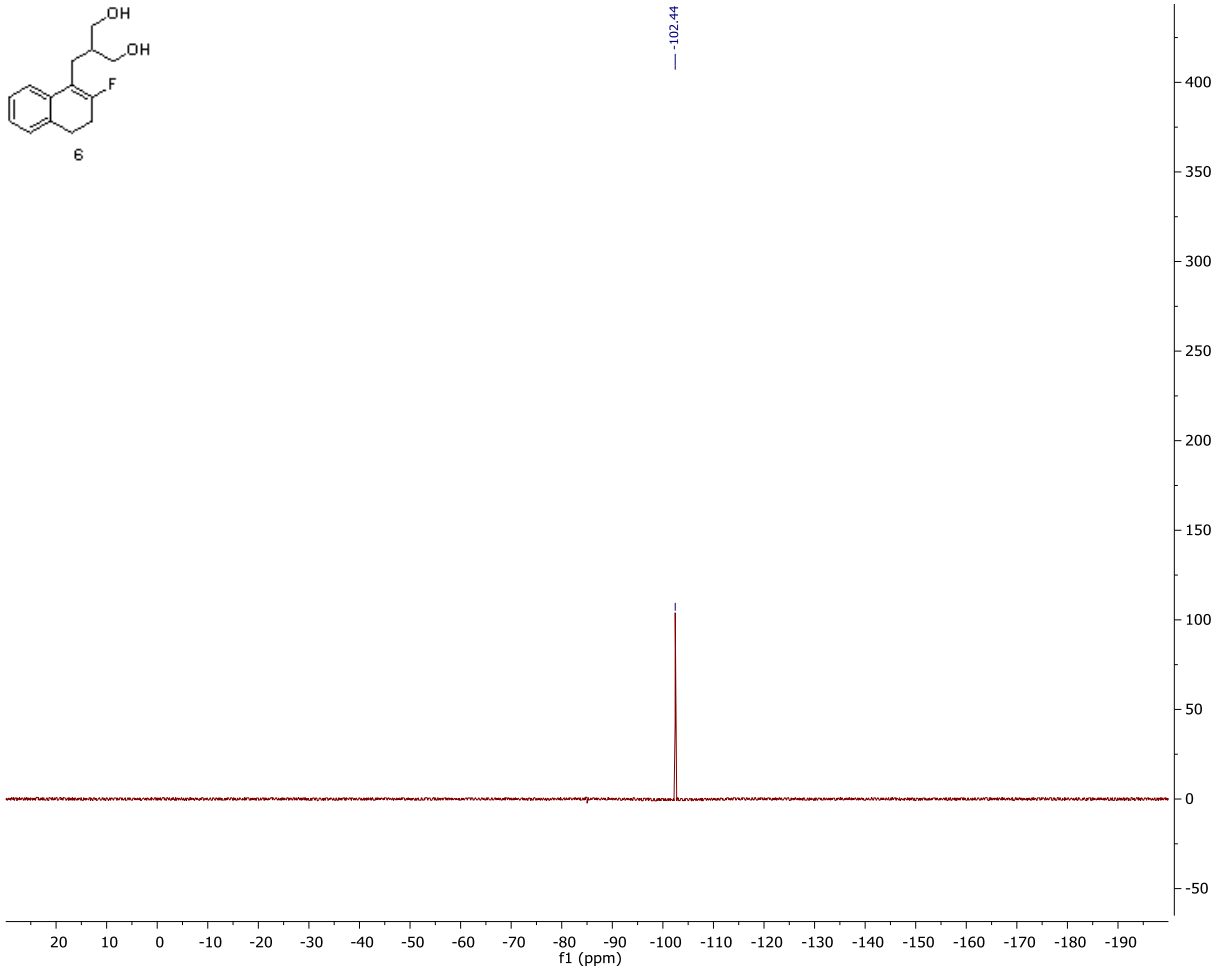


2-((2-Fluoro-3,4-dihydromaphthalen-1-yl)methyl)propane-1,3-diol (6)

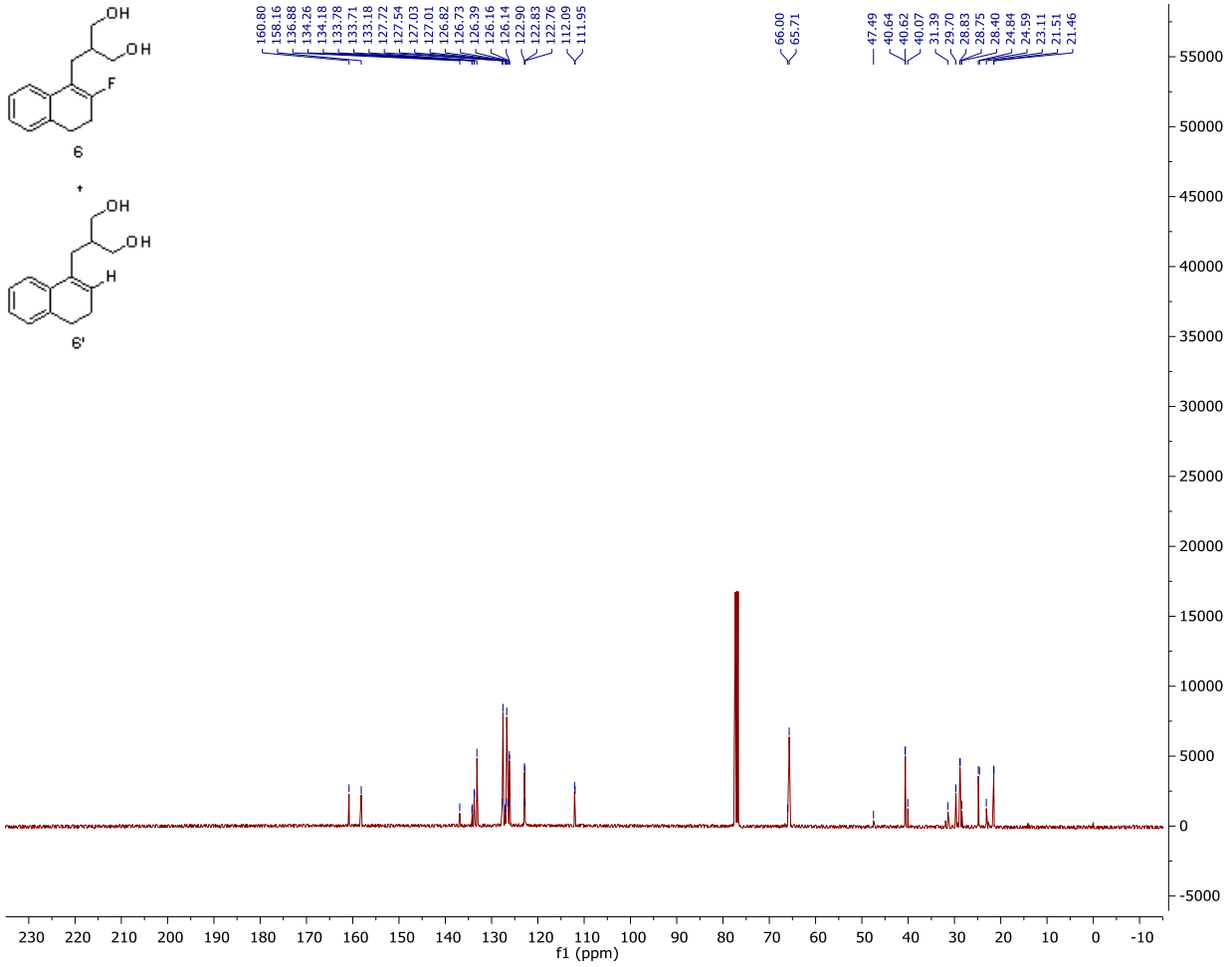
^{1}H (400 MHz, $CDCl_3$)



^{19}F (376 MHz, $CDCl_3$)

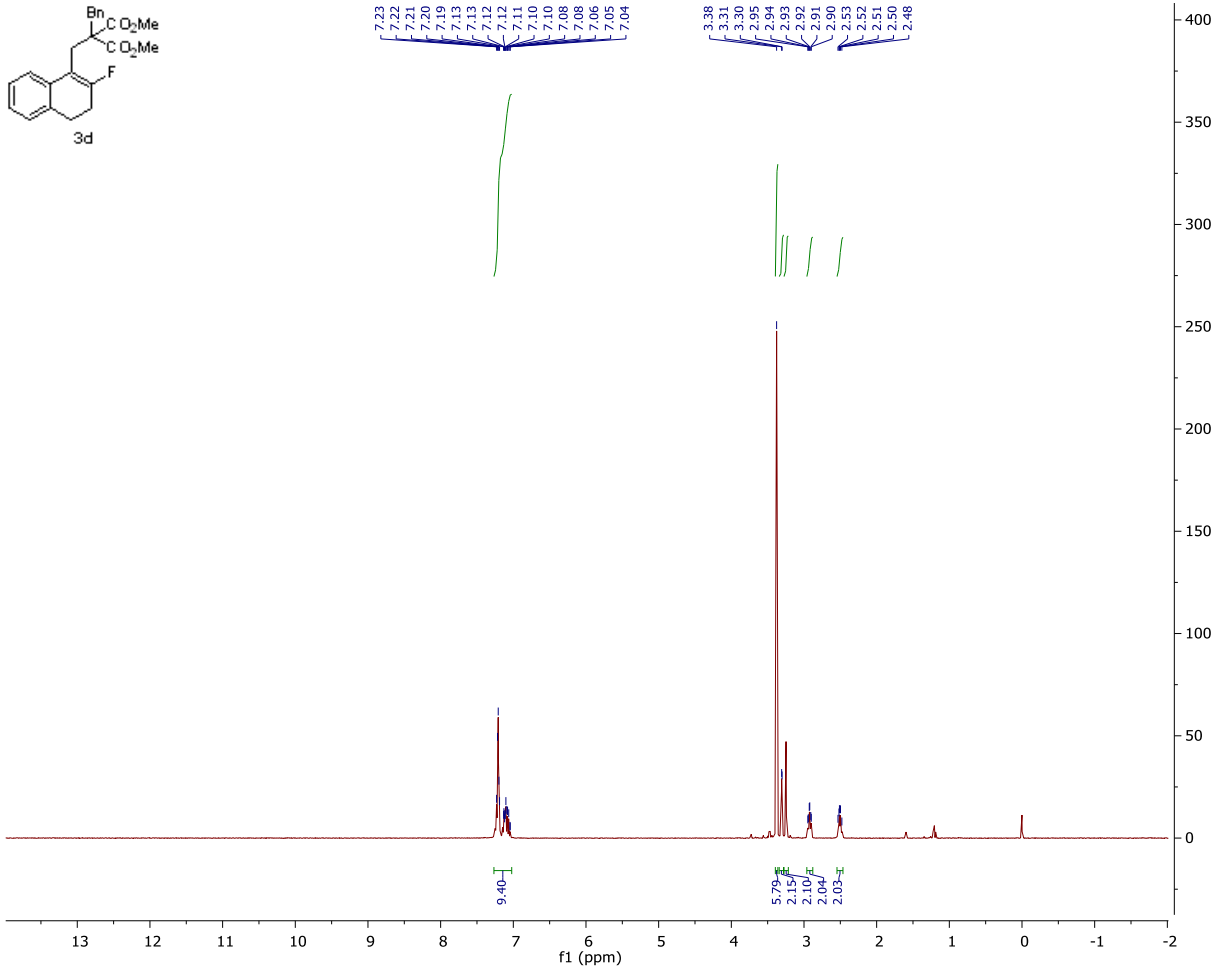


^{13}C (75 MHz, $CDCl_3$)

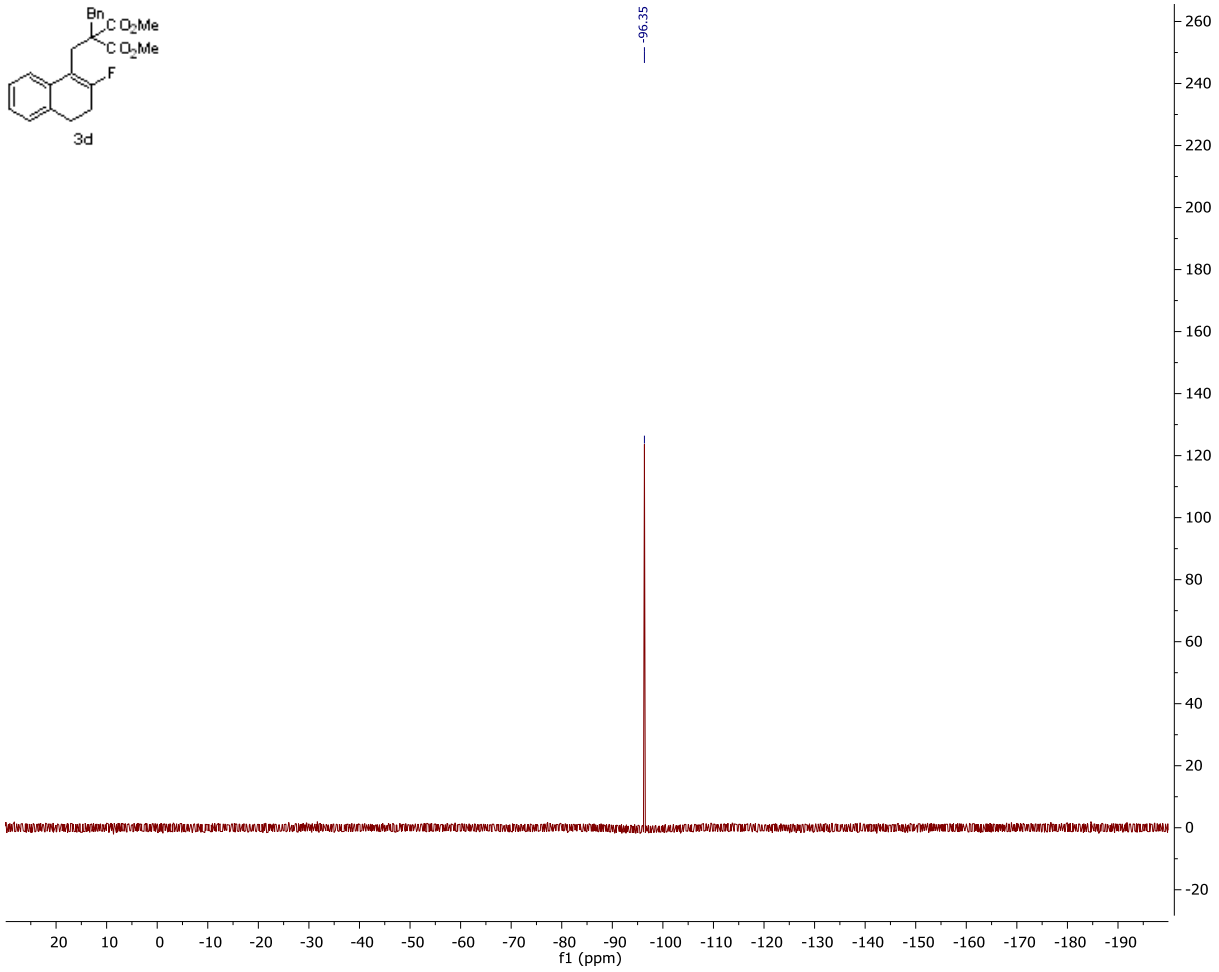


Dimethyl 2-benzyl-2-((2-fluoro-3.4-dihydronaphthalen-1-yl)methyl)malonate (3d)

^{1}H (400 MHz, $CDCl_3$)



^{19}F (376 MHz, $CDCl_3$)



^{13}C (75 MHz, $CDCl_3$)