SUPPORTING INFORMATION

Amide group directed protonolysis of cyclopropane. An approach to 2,2-disubstituted pyrrolidines

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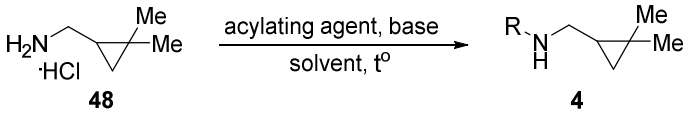
General considerations

All procedures were performed under argon atmosphere unless noted otherwise. Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. Flash column chromatography was carried out using silica gel (230−400 mesh). Thin layer chromatography (TLC) was performed on silica gel and was visualized by UV lamp or staining with $KMnO_4$. NMR spectra were recorded on 300, 400 and 600 MHz spectrometers with chemical shift values (δ) in parts per million using the residual chloroform, dimethylsulfoxide or methanol signal as an internal standard. Gas chromatographic (GC) analysis was performed on Agilent Technologies gas chromatographer with triple-axis detector, heating range 80-280 °C, column 30 m × 0.25 mm, 0.25 μm, 7 inch cage. HRMS analyses were performed on a hybrid quadrupole time-of-flight mass spectrometer equipped with an electrospray ion source.

Substrate synthesis

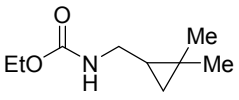
Amides **4** were obtained from commercially available (2,2-dimethylcyclopropyl)methanamine hydrochloride (**48**) after derivatization using various acylating agents (Scheme 1).



48 **4**

Scheme 1

Ethyl ((2,2-dimethylcyclopropyl)methyl)carbamate (4a)



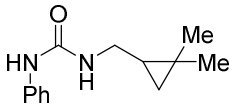
(2,2-Dimethylcyclopropyl)methanamine hydrochloride (**48**) (0.89 g, 6.55 mmol, 1.0 equiv) was dissolved in a mixture of saturated aq. $NaHCO_3$ (3 mL) and EtOAc (3 mL). Ethyl chloroformate (3.1 mL, 32.73 mmol, 5.0 equiv) was added to the resulting biphasic mixture and vigorous stirring was continued overnight. Organic phase was separated and washed with dist. water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. After column chromatography (eluent hexanes/EtOAc 6:1) 1.07 g (95 %) of a colorless oil was obtained.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.64 (bs, 1H), 4.11 (q, *J* = 7.3 Hz, 2H), 3.26 (ddd, *J* = 13.1, 7.2 and 5.8 Hz, 1H), 3.13 – 3.00 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 0.75 (tdd, *J* = 8.3, 7.1 and 5.2 Hz, 1H), 0.45 (dd, *J* = 8.6 and 4.5 Hz, 1H), 0.08 (t, *J* = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.4, 60.6, 41.9, 27.1, 23.9, 19.8, 18.5, 15.7, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_9H_{18}NO_2$ 172.1338; found: 172.1341 $[M+H]^+$.

1-((2,2-Dimethylcyclopropyl)methyl)-3-phenylurea (4b)



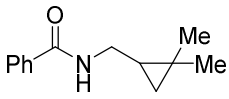
Phenyl isocyanate (36 μL, 0.33 mmol, 1.0 equiv) was added dropwise to a cooled (0 °C) solution of (2,2-dimethylcyclopropyl)methanamine hydrochloride (**48**) (44.70 mg, 0.33 mmol, 1.0 equiv) and Et_3N (55 μL, 0.40 mmol, 1.2 equiv) in DCM (5 mL) and reaction mixture was stirred at room temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 2:1) afforded 67.5 mg (94 %) of 1-((2,2-dimethylcyclopropyl)methyl)-3-phenylurea as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.38 – 7.23 (m, 4H), 7.15 (bs, 1H), 7.09 – 7.00 (m, 1H), 5.36 (bs, 1H), 3.32 (ddd, *J* = 12.1, 7.3 and 4.2 Hz, 1H), 3.25 – 3.14 (m, 1H), 1.07 (s, 3H), 1.03 (s, 3H), 0.77 (dtd, *J* = 8.6, 7.5 and 5.2 Hz, 1H), 0.45 (dd, *J* = 8.5 and 4.5 Hz, 1H), 0.09 (t, *J* = 4.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.2, 138.8, 129.1, 123.4, 120.6, 41.4, 27.1, 23.9, 19.8, 18.7, 15.7.

HR-MS (ESI-TOF) m/z: calcd. for $C_{13}H_{19}N_2O$ 219.1497; found: 219.1503 $[M+H]^+$.

***N*-((2,2-Dimethylcyclopropyl)methyl)benzamide (4c)**



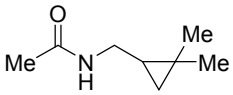
Benzoyl chloride (85 μL, 0.74 mmol, 1.0 equiv) was added dropwise to a cooled (0 °C) solution of (2,2-dimethylcyclopropyl)methanamine hydrochloride (**48**) (100.0 mg, 0.74 mmol, 1.0 equiv) and Et_3N (0.23 mL, 1.62 mmol, 2.2 equiv) in DCM (6 mL) and reaction mixture was stirred at room temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 2.5:1) afforded 135.0 mg (90%) of *N*-((2,2-dimethylcyclopropyl)methyl)benzamide as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.81 – 7.73 (m, 2H), 7.54 – 7.40 (m, 3H), 6.09 (bs, 1H), 3.57 – 3.33 (m, 2H), 1.15 (s, 3H), 1.09 (s, 3H), 0.88 (qd, *J* = 7.7 and 5.3 Hz, 1H), 0.53 (dd, *J* = 8.5 and 4.5 Hz, 1H), 0.19 (t, *J* = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.3, 134.8, 131.2, 128.5, 126.8, 41.1, 27.2, 23.6, 19.9, 18.8, 15.9.

HR-MS (ESI-TOF) m/z: calcd. for $C_{13}H_{18}NO$ 204.1388; found: 204.1393 $[M+H]^+$.

_N_-((2,2-Dimethylcyclopropyl)methyl)acetamide (4d)



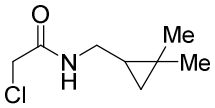
To a stirred solution of amine **48** (72.20 mg, 0.53 mmol) in DCM (6 mL) triethylamine (0.2 mL, 1.60 mmol, 3.0 equiv) was added followed by acetic acid anhydride (70 μL, 0.75 mmol). The mixture was stirred at ambient temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 1:1.5) afforded 64.1 mg (85 %) of *N*-((2,2-dimethylcyclopropyl)methyl)acetamide as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.49 (bs, 1H), 3.31 – 3.13 (m, 2H), 1.98 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.79 – 0.69 (m, 1H), 0.46 (dd, *J* = 8.5 and 4.5 Hz, 1H), 0.09 (t, *J* = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 169.8, 40.7, 27.2, 23.6, 23.4, 19.9, 18.7, 15.8.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{16}NO$ 142.1232; found: 142.1231 $[M+H]^+$.

2-Chloro-_N_-((2,2-dimethylcyclopropyl)methyl)acetamide (4e)



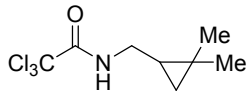
Chloroacetyl chloride (28 μL, 0.34 mmol, 1.0 equiv) was added dropwise to a cooled (0 °C) solution of (2,2-dimethylcyclopropyl)methanamine hydrochloride (**48**) (46.6 mg, 0.34 mmol, 1.0 equiv) and Et_3N (0.11 mL, 0.76 mmol, 2.2 equiv) in DCM (5 mL) and reaction mixture was stirred at room temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 2:1) afforded 51.1 mg (85 %) of 2-chloro-*N*-((2,2-dimethylcyclopropyl)methyl)acetamide as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.59 (s, 1H), 4.01 (s, 2H), 3.34 – 3.27 (m, 1H), 3.24 – 3.17 (m, 1H), 1.07 (s, 3H), 1.03 (s, 3H), 0.82 – 0.70 (m, 1H), 0.51 – 0.44 (m, 1H), 0.14 – 0.08 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 165.5, 42.5, 40.9, 27.0, 23.2, 19.8, 18.8, 15.8.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{15}NOCl$ 176.0842; found: 176.0845 $[M+H]^+$.

2,2,2-Trichloro-*N*-((2,2-dimethylcyclopropyl)methyl)acetamide (4f)



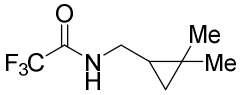
Trichloroacetic acid (132.5 mg, 0.81 mmol, 1.1 equiv), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (155.5 mg, 0.81 mmol, 1.1 equiv) and HOBt (124.2 mg, 0.81 mmol, 1.1 equiv) were added to a solution of (2,2-dimethylcyclopropyl)methanamine hydrochloride (**48**) (100.0 mg, 0.74 mmol, 1.0 equiv) and Et_3N (0.23 mL, 1.62 mmol, 2.2 equiv) in dry THF (6 mL) and reaction mixture was stirred at room temperature overnight. Reaction solvent was evaporated to dryness. The crude mixture was diluted with dist. water (5 mL) and extracted with DCM (2 x 5 mL). Combined organic phase was dried over $MgSO_4$ and filtered. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 2:1) afforded 45.4 mg (25 %) of 2,2,2-trichloro-*N*-((2,2-dimethylcyclopropyl)methyl)acetamide as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.65 (bs, 1H), 3.47 – 3.27 (m, 2H), 1.13 (s, 3H), 1.09 (s, 3H), 0.91 – 0.80 (m, 1H), 0.57 (dd, J = 8.5 and 4.6 Hz, 1H), 0.21 (t, J = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 161.6, 92.7, 42.8, 27.0, 22.9, 19.9, 18.9, 16.2.

HR-MS (ESI-TOF) m/z**:** calcd. for $C_8H_{13}NOCl_3$ 244.0063; found: 244.0029 $[M+H]^+$.

***N*-((2,2-Dimethylcyclopropyl)methyl)-2,2,2-trifluoroacetamide (4i)**



Trifluoroacetic anhydride (0.13 mL, 0.96 mmol, 1.4 equiv) was added dropwise to a cooled (0 °C) solution of (2,2-dimethylcyclopropyl)methanamine hydrochloride (**48**) (92.90 mg, 0.69 mmol, 1.0 equiv) and Et_3N (0.29 mL, 2.06 mmol, 3.0 equiv) in DCM (6 mL) and reaction mixture was stirred at room temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 10:1) afforded 123.1 mg (92 %) of *N*-((2,2-dimethylcyclopropyl)methyl)-2,2,2-trifluoroacetamide as a colorless oil.

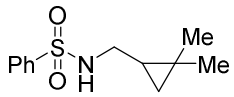
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.55 (bs, 1H), 3.43 – 3.25 (m, 2H), 1.09 (s, 3H), 1.06 (s, 3H), 0.86 – 0.75 (m, 1H), 0.53 (dd, J = 8.5 and 4.6 Hz, 1H), 0.16 (t, J = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.9 (q, J = 36.9 Hz), 115.9 (q, J = 288.9 Hz), 41.1, 26.9, 22.8, 19.8, 18.8, 16.2.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -76.1.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{13}NOF_3$ 196.0949; found: 196.0947 $[M+H]^+$.

***N*-((2,2-Dimethylcyclopropyl)methyl)benzenesulfonamide (4j)**



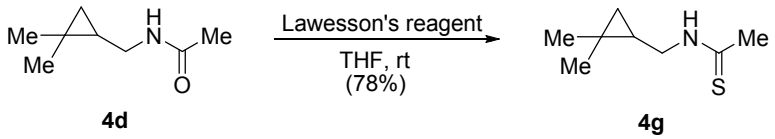
Benzenesulfonyl chloride (0.12 mL, 0.94 mmol, 1.05 equiv) was added dropwise to a cooled (0 °C) solution of (2,2-dimethylcyclopropyl)methanamine hydrochloride (**48**) (121.0 mg, 0.89 mmol, 1.0 equiv) and DIPEA (0.52 mL, 3.12 mmol, 3.5 equiv) in DCM (10 mL) and stirred at room temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 4:1) afforded 201.0 mg (94 %) of *N*-((2,2-dimethylcyclopropyl)methyl)benzenesulfonamide as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.91 – 7.87 (m, 2H), 7.61 – 7.45 (m, 3H), 4.90 (t, *J* = 5.7 Hz, 1H), 3.13 – 3.01 (m, 1H), 2.82 (ddd, *J* = 13.1, 8.4 and 5.0 Hz, 1H), 0.94 (s, 3H), (s, 3H), 0.65 (tdd, *J* = 8.4, 6.8 and 5.2 Hz, 1H), 0.38 (dd, *J* = 8.5 and 4.6 Hz, 1H), -0.03 (t, *J* = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 139.9, 132.5, 128.9, 127.0, 44.5, 26.8, 23.3, 19.5, 18.6, 15.9.

HR-MS (ESI-TOF) m/z: calcd. for $C_{12}H_{18}NO_2S$ 240.1058; found: 240.1064 $[M+H]^+$.

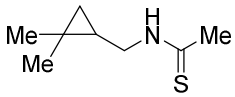
Thioamide **4g** was synthesized from previously described compound **4d** in the thionation reaction with Lawesson's reagent (Scheme 2).



4d **4g**

Scheme 2

***N*-((2,2-Dimethylcyclopropyl)methyl)ethanethioamide (4g)**



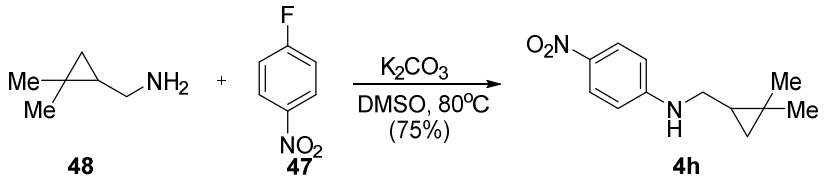
To a solution of acyl amide **4d** (171.9 mg, 1.22 mmol, 1.00 equiv) in THF (5 mL) at room temperature was added Lawesson's reagent (295.42 mg, 0.73 mmol, 0.6 equiv). The mixture was stirred at room temperature for 18 h, then filtered through a short pad of celite and concentrated under reduced pressure. Purification by column chromatography on silica gel (eluent: DCM) afforded 150 mg (78 %) of *N*-((2,2-dimethylcyclopropyl)methyl)ethanethio-amide as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40 (bs, 1H), 3.56 (dd, *J* = 7.9 and 4.7 Hz, 2H), 2.54 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.86 (qd, *J* = 7.9 and 5.2 Hz, 1H), 0.52 (dd, *J* = 8.5 and 4.5 Hz, 1H), 0.16 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 200.1, 47.7, 34.1, 26.9, 22.2, 19.9, 18.8, 16.1.

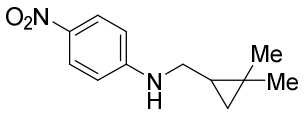
HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{16}NS$ 158.1003; found: 158.0996 $[M+H]^+$.

Amine **4h** was synthesized from commercially available (2,2-dimethylcyclopropyl)methanamine (**48**) and *p*-fluoro-nitrobenzene (**47**) in S_NAr reaction (Scheme 3).



Scheme 3

***N*-((2,2-Dimethylcyclopropyl)methyl)-4-nitroaniline (4h)**



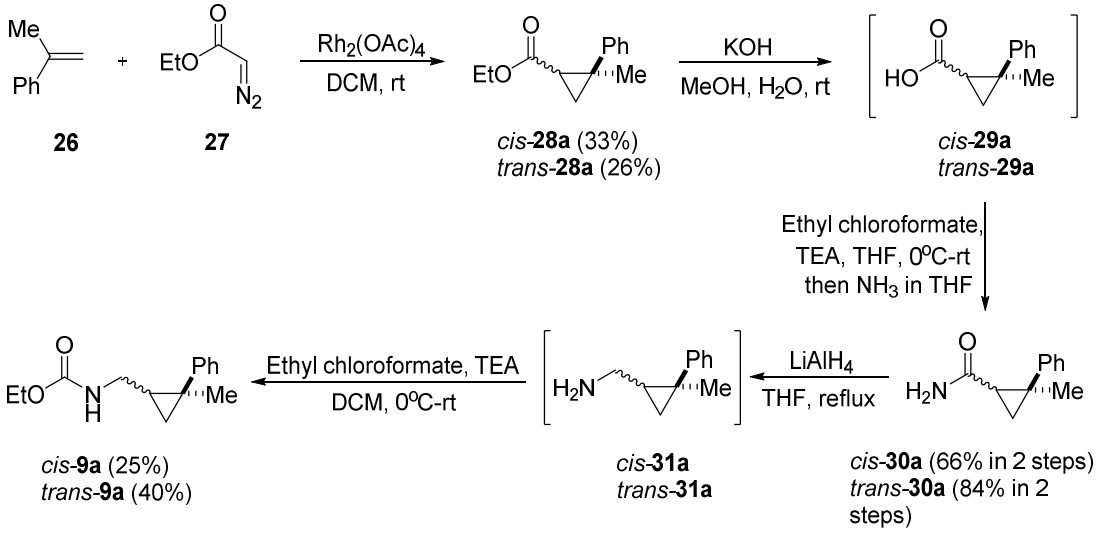
Amine **48** (294.1 mg, 2.97 mmol, 1.0 equiv) and *p*-fluoro-nitrobenzene (**47**) (0.3 mL, 2.97 mmol, 1.0 equiv) were dissolved in DMSO (5 mL) and after addition of anhydrous K_2CO_3 (450.83 mg, 3.26 mmol, 1.1 equiv), the mixture was allowed to react under gentle warming (80 °C) and stirring till completion (TLC). After cooling to room temperature, the reaction diluted with water and extracted with ethyl acetate (2 × 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (2 % ethyl acetate in toluene) to yield the title compound **4h** (487.0 mg, 75 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14 – 8.04 (m, 2H), 6.56 – 6.48 (m, 2H), 4.50 (bs, 1H), 3.17 (qd, *J* = 12.7 and 7.5 Hz, 2H), 1.14 (s, 3H), 1.11 (s, 3H), 0.98 – 0.82 (m, 1H), 0.58 (dd, *J* = 8.5 and 4.5 Hz, 1H), 0.20 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 153.3, 137.8, 126.4, 110.9, 44.4, 27.2, 23.4, 19.9, 18.9, 16.1.

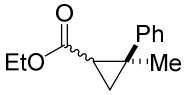
HR-MS (ESI-TOF) m/z: calcd. for $C_{12}H_{17}N_2O_2$ 221.1290; found: 221.1288 $[M+H]^+$.

Carbamates *cis/trans*-**9a** were synthesized in five steps from commercially available isopropenylbenzene **26** (Scheme 4). Separately racemic *trans*- and *cis*-isomers of **28** were obtained in cyclopropanation reaction from alkene **26** and ethyl diazoacetate (**27**) in the presence of Rh catalyst. After ester group hydrolysis corresponding acid *cis*/*trans*-**29** was converted to amide *cis*/*trans*-**30**. Reduction of amide gave amine, which *in situ* was acylated with ethyl chloroformate to afford carbamate *cis/trans*-**9a**.



Scheme 4

Ethyl 2-methyl-2-phenylcyclopropane-1-carboxylate (*cis*-28a)



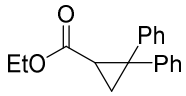
To a solution α-methylstyrene (**26**) (3.3 mL, 25.01 mmol, 2.63 equiv) and rhodium (II) acetate dimer (3.7 mg, 8.40 μmol, 2 mol-%) in DCM (10 mL) ethyl diazoacetate (1.0 mL, 9.51 mmol, 1.0 equiv) was added *via* syringe pump over 4 h. The resulting mixture was stirred at room temperature for 12 hours. Reaction mixture was concentrated under reduced pressure. A mixture of racemic *trans*- and *cis*-isomers *trans*-**28a** and *cis*-**28a** were obtained and their separation was done by column chromatography on silica gel (eluent hexanes/EtOAc 30:1). After purification 641 mg (44 %) of *cis*-**28a** and 512 mg (26 %) of *trans*-**28a** were obtained, both as colorless oils. Both diastereomers are known.[1]

<u>*Cis*-isomer:</u> ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.37 – 7.14 (m, 5H), 3.93 – 3.74 (m, 2H), 1.92 (dd, J = 7.7 and 5.4 Hz, 1H), 1.80 (t, J = 5.0 Hz, 1H), 1.48 (s, 3H), 1.16 (dd, J = 7.7 and 4.6 Hz, 1H), 0.96 (t, J = 7.1 Hz, 3H).

[1] Sanders, J. C.; Gillespie, K. M.; Scott, P. *Tetrahedron Asymm.* **2001**, 12, 1055.

Trans-isomer: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.55 – 7.45 (m, 1H), 7.43 – 7.17 (m, 4H), 4.22 (qd, *J* = 7.2 and 1.6 Hz, 2H), 1.99 (ddd, *J* = 8.3, 6.1 and 1.1 Hz, 1H), 1.55 (s, 3H), 1.52 – 1.38 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

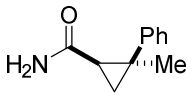
Ethyl 2,2-diphenylcyclopropane-1-carboxylate (28h)



Prepared by analogy to compound *cis*-**28a** from 1,1-diphenylethylene (1.84 mL, 10.4 mmol, 2.3 equiv), ethyl diazoacetate (1.42 mL, 3.95 mmol, 1.0 equiv), $Rh_2(OAc)_4$ (3.4 mg, 0.0077 mmol, 0.2 mol-%), and DCM (10 mL). Yield: 600 mg (57%). This compound is known.[2]

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.79 – 7.53 (m, 10H), 4.43 – 4.21 (m, 2H), 2.95 (dd, *J* = 8.1 and 6.0 Hz, 1H), 2.58 (dd, *J* = 5.9 and 4.8 Hz, 1H), 2.00 (dd, *J* = 8.1 and 4.8 Hz, 1H), 1.42 (t, *J* = 7.1 Hz, 3H).

(*1R*,2S)-2-Methyl-2-phenylcyclopropane-1-carboxamide (*cis*-30a)**



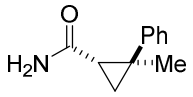
KOH (1.74 g, 31.01 mmol, 10.0 equiv) was added to a solution of ester *cis*-**28a** (633.35 mg, 3.10 mmol) in MeOH (25 mL) and was stirred at ambient temperature overnight. The reaction mixture was evaporated, quenched with 2 M HCl aq. and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Carboxylic acid *cis*-**29** was used for the next step without further purification.

At 0 ^{o}C Et_3N (0.48 mL, 3.41 mmol, 1.1 equiv) was added to a stirred solution of crude acid *cis*-**29a** (546.4 mg, 3.10 mmol, 1.0 equiv) in THF (10 mL). At the same temperature ethyl chloroformate (0.32 mL, 3.41 mmol, 1.1 equiv) was added dropwise. Reaction was allowed to proceed for 1 h, and then 5 M NH_3 in THF (15 mL) was added. Resulting mixture was stirred at room temperature for 12 hours. Then reaction mixture was evaporated, quenched with 5 % $NaHCO_3$ aq. and extracted with EtOAc. The organic layer was washed with water, 1 M HCl aq. and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Amide *cis*-**30a** was used for the next step without further purification. Reaction yield was 66 %. This compound is known.[3]

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.30 – 7.06 (m, 5H), 5.09 (bs, 2H), 1.74 – 1.59 (m, 2H), 1.39 (s, 3H), 1.10 (dd, *J* = 7.8 and 4.7 Hz, 1H).

[2] Gomes, L.; Veiros, L.; Maulide, N.; Afonso, C. *Chem. – Eur. J.* **2015**, 21 (4), 1449.
[3] Zhang, X. P. et al. *J. Am. Chem. Soc.* **2011**, 133, 15292.

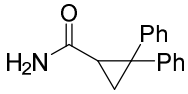
(*1S*,2S)-2-Methyl-2-phenylcyclopropane-1-carboxamide (*trans*-30a)**



Prepared by analogy to compound *cis*-**30a** from *trans*-**28a** (486.0 mg, 2.34 mmol), KOH (1.33 g, 23.79 mmol, 10.0 equiv), and MeOH (20 mL). Then ethyl chloroformate (0.25 mL, 2.62 mmol, 1.1 equiv), TEA (0.37 mL, 2.62 mmol, 1.1 equiv), and THF (5 mL). Yield was 84 %. This compound is known.[6]

^{1}H NMR (300 MHz, Methanol-d_4, ppm) δ 7.38 – 7.21 (m, 4H), 7.20 – 7.09 (m, 1H), 1.93 (dd, J = 8.3, 6.0 Hz, 1H), 1.46 (s, 3H), 1.42 – 1.21 (m, 2H).

2,2-Diphenylcyclopropane-1-carboxamide (30h)

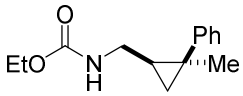


Prepared by analogy to compound *cis*-**30a** from **28h** (142.5 mg, 0.54 mmol), NaOH (214.0 mg, 5.35 mmol, 10.0 equiv), MeOH (3 mL) and H_2O (3 mL). Then ethyl chloroformate (73 µL, 0.77 mmol, 1.1 equiv), TEA (0.11 mL, 0.77 mmol, 1.1 equiv), and THF (5 mL). Yield was 55 %. This compound is known.[4]

^{1}H NMR (300 MHz, Methanol-d_4, ppm) δ 7.75 – 7.41 (m, 10H), 2.85 (dd, J = 8.2 and 6.0 Hz, 1H), 2.42 (t, J = 5.4 Hz, 1H), 1.83 (dd, J = 8.1 and 4.7 Hz, 1H).

Ethyl (((*1R*,2S)-2-methyl-2-phenylcyclopropyl)methyl)carbamate (*cis*-9a)**

A solution of amide *cis*-**30a** (346.2 mg, 1.98 mmol, 1.0 equiv) in THF (10 mL) was



cooled to 0 ºC and $LiAlH_4$ (150.0 mg, 3.95 mmol, 2.0 equiv) was added in several portions. After addition was complete, the mixture was allowed to warm to room temperature and then refluxed until the starting material disappeared (TLC). Reaction mixture was quenched with water (5.5 equiv) and filtered (to remove inorganic solids). Filtrate was concentrated under reduced pressure and was used to the next step without further purification.

Ethyl chloroformate (0.19 mL, 1.98 mmol, 1.0 equiv) was added dropwise to a cooled (0°C) solution of crude amine (*cis*-**31a**) and TEA (0.6 mL, 4.35 mmol, 2.2 equiv) in DCM (3 mL) and stirred at room temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 4:1)

[4] Dembkowski, L.; Rachon, J. *Phosphorus, Sulfur and Silicon and the Related Elements* **1994**, 91 (1-4), 251.

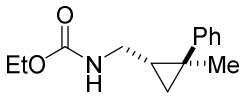
afforded 118 mg (25 %) of ethyl (((*1R*,2S**)-2-methyl-2-phenylcyclopropyl)methyl)carbamate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.33 – 7.15 (m, 5H), 4.54 (bs, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 2.92 – 2.79 (m, 1H), 2.76 – 2.64 (m, 1H), 1.38 (s, 3H), 1.30 – 1.17 (m, 4H), 0.88 – 0.84 m, 1H), 0.78 (dd, *J* = 8.4 and 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.4, 145.1, 128.97, 128.45, 126.37, 60.7, 41.6, 26.31, 23.0, 21.29, 19.4, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{14}H_{20}NO_2$ 234.1494; found: 234.1496 $[M+H]^+$.

Ethyl (((*1S*,2S)-2-methyl-2-phenylcyclopropyl)methyl)carbamate (*trans*-9a)**



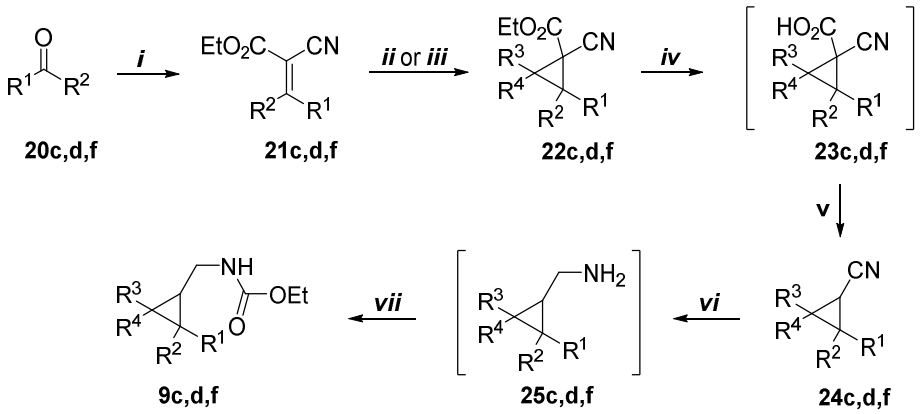
Prepared by analogy to compound *cis*-**9a** from *trans*-**30a** (329.5 mg, 1.88 mmol), $LiAlH_4$ (356.80 mg, 9.40 mmol, 5.0 equiv), and THF (10 mL). Then ethyl chloroformate (0.18 mL, 1.88 mmol, 1.0 equiv), TEA (0.58 mL, 4.14 mmol, 2.2 equiv), and DCM (6 mL). Yield: 168 mg (40 %).

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32 – 7.19 (m, 4H), 7.20 – 7.11 (m, 1H), 4.87 (bs, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.48 (s, 1H), 3.33 – 3.15 (m, 1H), 1.42 (s, 3H), 1.36 – 1.18 (m, 4H), 1.11 (dd, *J* = 8.9 and 4.8 Hz, 1H), 0.56 (t, *J* = 5.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.5, 147.3, 128.2, 126.9, 125.7, 60.6, 41.5, 25.4, 24.4, 20.4, 19.2, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{14}H_{20}NO_2$ 234.1494; found: 234.1496 $[M+H]^+$.

Carbamates **9c,d,f** were synthesized in four steps according to Scheme 5 from commercially available aldehydes/ketones **20c,d,f**. Cyclopropanes **22c,d,f** were synthesized from the corresponding carbonyl compounds **20c,d,f** through a standard synthetic sequence of *Knoevenagel condensation* and tandem *Michael addition*-nitrite displacement reactions. Nitriles **24c,d,f** were obtained by hydrolysis of the ester group and subsequential decarboxylation of corresponding acids **23c,d,f**. Further, nitriles **24c,d,f** were reduced to amines **25c,d,f** and acylated *in situ* to corresponding carbamates **9c,d,f**.



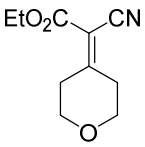
i) Ethyl cyanoacetate, piperidine, AcOH, toluene, reflux; *ii*) 2-Nitropropane, K_2CO_3, EtOH, reflux; *iii*) $MeNO_2$, DBU, MeCN, rt or 2-nitropropane, K_2CO_3, EtOH, reflux;; *iv*) 2M NaOH *aq.*, MeOH, rt; *v*) LiCl, $NaHCO_3$, DMSO, 160°C; *vi*) $LiAlH_4$, THF, reflux; *vii*) Ethyl chloroformate, sat. $NaHCO_3$ *aq.*, EtOAc, rt.

Scheme 5

General procedure for Knoevenagel condensation

A solution of ketone or aldehyde **20** (1.2 mmol), ethyl cyanoacetate (1.0 mmol), acetic acid (0.2 mmol), and piperidine (0.1 mmol) in toluene was refluxed overnight with a Dean-Stark apparatus. The reaction mixture was cooled to room temperature and reaction solvent was evaporated. Product **21** was purified by column chromatography on silica gel using appropriate eluent.

Ethyl 2-cyano-2-(tetrahydro-4*H*-pyran-4-ylidene)acetate (21c)

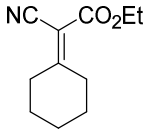


Tetrahydro-4*H*-pyran-4-one (**20c)** (1.0 mL, 10.83 mmol, 1.0 equiv), ethyl cyanoacetate (1.2 mL, 10.83 mmol, 1.0 equiv), AcOH (62 μL, 1.08 mmol, 0.1 equiv), piperidine (0.1 mL, 1.08 mmol, 0.1 equiv). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 3:1) afforded 1.89 g (89%) of ethyl 2-cyano-2-(tetrahydro-4*H*-pyran-4-ylidene)acetate as a colorless oil. This reaction was performed at 0 °C for 1 h. This compound is known.[5]

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 4.32 – 4.24 (m, 2H), 3.87 (t, *J* = 5.5 Hz, 2H), 3.79 (t, *J* = 5.6 Hz, 2H), 3.18 (t, *J* = 5.5 Hz, 2H), 2.79 (t, *J* = 5.6 Hz, 2H), 1.38 – 1.29 (m, 3H).

[5] Patel, N. C. *et al.* Synth. Comm. **2011**, 41 (15), 2209.

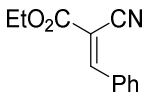
Ethyl 2-cyano-2-cyclohexylideneacetate (21f)



Ethyl cyanoacetate (1.7 mL, 15.96 mmol, 1.0 equiv), cyclohexanone (**20f**) (2.0 mL, 19.27 mmol, 1.2 equiv), piperidine (0.2 mL, 1.93 mmol, 0.1 equiv), AcOH (0.2 mL, 3.85 mmol, 0.2 equiv), and toluene (30 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 8:1) afforded 1.57 g (51 %) of ethyl 2-cyano-2-cyclohexylideneacetate as a colorless oil. This compound is known.[6]

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 4.27 (q, *J* = 7.2 Hz, 2H), 3.02 – 2.95 (m, 2H), 2.72 – 2.61 (m, 2H), 1.88 – 1.58 (m, 6H), 1.35 (t, *J* = 7.1 Hz, 3H).

Ethyl (*E*)-2-cyano-3-phenylacrylate (21d)



Ethyl cyanoacetate (1.7 mL, 15.98 mmol, 1.0 equiv), benzaldehyde (**20d**) (2.0 mL, 19.27 mmol, 1.2 equiv), piperidine (0.2 mL, 1.93 mmol, 0.1 equiv), AcOH (0.2 mL, 3.85 mmol, 0.2 equiv), and toluene (30 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 8:1) afforded 2.68 g (83 %) of ethyl (*E*)-2-cyano-3-phenylacrylate as a colorless oil. This compound is known.[3]

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.26 (s, 1H), 8.05 – 7.94 (m, 2H), 7.63 – 7.44 (m, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

General procedure for tandem Michael addition-nitrite displacement reactions

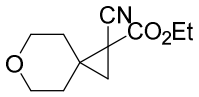
Method A[7]: A mixture of alkene **21**, 2-nitropropane and anhydrous potassium carbonate (equimolar ratio) in an absolute ethanol (0.8 mL/mmol) was under reflux until complete conversion (TLC). The reaction mixture was quenched with sat. $NaHCO_3$ aq. and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Product was isolated by column chromatography.

Method B[1]: Nitromethane (5.0 mmol) and DBU (1.0 mmol) were added to a solution of alkene **21** (1.0 mmol) in MeCN and the reaction mixture was stirred at ambient temperature for 16 h. The mixture was partitioned between EtOAc/1 N HCl aq. The

[6] Jia, Y.; Fang, Y.; Zhang, Y.; Miras, H. N.; Song, Y.-F. *Chem. Eur. J.* **2015**, 21, 14862.
[7] Takai, K.; Sone, T. et al. *Bioorg. Med. Chem. Lett.* **2015**, 25 (8), 1705.

phases were separated, the aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography.

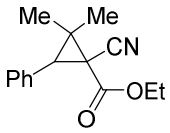
Ethyl 1-cyano-6-oxaspiro[2.5]octane-1-carboxylate (22c)



Alkene **21c** (1.01 g, 5.17 mmol, 1.0 equiv), $MeNO_2$ (1.4 mL, 25.87 mmol, 5.0 equiv), DBU (0.8 mL, 5.17 mmol, 1.0 equiv), and MeCN (20 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 1.05 g (97 %) of ethyl 1-cyano-6-oxaspiro[2.5]octane-1-carboxylate as a colorless oil. This compound is known.[1]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.28 (qd, J = 7.1, 0.5 Hz, 2H), 3.93 – 3.83 (m, 1H), 3.81 – 3.73 (m, 1H), 3.72 – 3.58 (m, 2H), 1.97 – 1.91 (m, 1H), 1.89 – 1.72 (m, 4H), 1.53 (d, J = 5.4 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H).

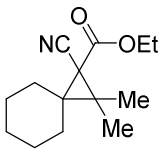
Ethyl 1-cyano-2,2-dimethyl-3-phenylcyclopropane-1-carboxylate (22d)



Alkene **21d** (1.29 g, 6.42 mmol, 1.0 equiv), 2-nitropropane (0.63 mL, 6.90 mmol, 1.07 equiv), K_2CO_3 (953.66 mg, 6.90 mmol, 1.07 equiv), and EtOH (5 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 6:1) afforded 1.35 g (86%) of ethyl 1-cyano-2,2-dimethyl-3-phenylcyclopropane-1-carboxylate as a colorless oil. This compound is known.[3]

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.54 – 7.21 (m, 5H), 4.33 (q, J = 7.1 Hz, 2H), 1.48 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.34 (s, 3H).

Ethyl 1-cyano-2,2-dimethylspiro[2.5]octane-1-carboxylate (22f)



Alkene **21f** (0.87 g, 4.50 mmol, 1.0 equiv), 2-nitropropane (0.41 mL, 4.50 mmol, 1.0 equiv), K_2CO_3 (622.49 mg, 4.50 mmol, 1.0 equiv), and EtOH (5 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 8:1) afforded 0.89 g (84 %) of ethyl 1-cyano-2,2-dimethylspiro[2.5]octane-1-carboxylate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.21 (q, J = 7.1 Hz, 2H), 2.00 – 1.89 (m, 1H), 1.86 – 1.20 (m, 18H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 165.8, 117.9, 61.8, 44.5, 38.8, 30.8, 26.4, 25.7, 25.5, 25.2, 20.4, 16.6, 14.2.

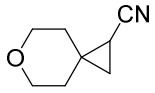
HR-MS (ESI-TOF) m/z: calcd. for $C_{14}H_{22}NO_2$ 236.1651; found: 236.1651 $[M+H]^+$.

*General procedure for hydrolysis and decarboxylation of ester **22***

2 M NaOH aq. (1.2 mmol) was added dropwise to a solution of ester **22** (1.0 mmol) in MeOH and was stirred at ambient temperature overnight. The reaction mixture was evaporated, quenched with 2 M HCl aq. and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Carboxylic acid **23** was used for the next reaction without purification.

To the solution of crude carboxylic acid **23** (1.0 mmol) in DMSO (5 mL), anhydrous LiCl (4.0 mmol) and $NaHCO_3$ (1.5 mmol) were added and stirred at 180 °C for 12 h. Reaction mixture was diluted with water and extracted with EtOAc. Organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Nitrile **24** was purified by column chromatography on silica gel using appropriate eluent.

6-Oxaspiro[2.5]octane-1-carbonitrile (24c)



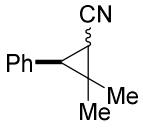
Ester **22c** (400.0 mg, 1.91 mmol), 2 M NaOH aq. (1.9 mL, 3.82 mmol, 2.0 equiv), and MeOH (5 mL). Then $NaHCO_3$ (240.89 mg, 2.87 mmol, 1.5 equiv), LiCl (324.17 mg, 7.65 mmol, 4.0 equiv), and DMSO (3 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 0.19 g (72 %) of 6-oxaspiro[2.5]octane-1-carbonitrile as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.87 – 3.65 (m, 4H), 1.83 – 1.66 (m, 2H), 1.64 – 1.55 (m, 1H), 1.42 – 1.31 (m, 1H), 1.29 (dd, *J* = 8.4 and 5.5 Hz, 1H), 1.12 – 1.01 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 120.1, 66.9, 66.8, 35.0, 32.2, 25.3, 20.2, 8.8.

Unstable under the conditions of HRMS.

***Cis*- and *trans*-2,2-dimethyl-3-phenylcyclopropane-1-carbonitrile (24d)**



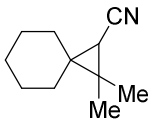
Ester **22d** (0.70 g, 2.88 mmol), 2 M NaOH aq. (1.7 mL, 3.46 mmol, 1.2 equiv), and MeOH (6 mL). Then $NaHCO_3$ (462.68 mg, 4.32 mmol, 1.5 equiv), LiCl (488.86 mg, 11.53 mmol, 4.0 equiv), and DMSO (6 mL). A mixture of racemic *trans*- and *cis*-isomers *trans*-**24d** and *cis*-**24d** were obtained and their separation was done by column chromatography on silica gel (eluent

hexanes/EtOAc 10:1). After separation 111 mg (26 %) of *cis*-**24d** and 270 mg (62%) of *trans*-**24d** were obtained, both as colorless oils. Both diastereomers are known.[3]

Cis isomer: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.42 – 7.18 (m, 5H), 2.40 (d, J = 8.7 Hz, 1H), 1.68 (d, J = 8.8 Hz, 1H), 1.36 (s, 3H), 1.16 (s, 3H).

Trans isomer: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.38 – 7.20 (m, 3H), 7.20 – 7.10 (m, 2H), 2.53 (d, J = 5.7 Hz, 1H), 1.64 (d, J = 5.6 Hz, 1H), 1.50 (s, 3H), 0.92 (s, 3H).

2,2-Dimethylspiro[2.5]octane-1-carbonitrile (24f)



Ester **22f** (221.6 mg, 0.94 mmol), 2 M NaOH aq. (0.6 mL, 1.13 mmol, 1.2 equiv), and MeOH (2 mL). Then $NaHCO_3$ (151.14 mg, 1.41 mmol, 1.5 equiv), LiCl (159.69 mg, 3.77 mmol, 4.0 equiv), and DMSO (5 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 10:1) afforded 124 mg (81 %) of 2,2-dimethylspiro[2.5]octane-1-carbonitrile as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.68 – 1.35 (m, 11H), 1.27 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 119.8, 34.4, 31.8, 28.9, 28.3, 25.8, 25.6, 25.1, 21.2, 20.1, 18.3.

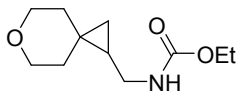
GC/MS m/z = 163.2 [M^+].

General procedure for reduction and acetylation

A solution of nitrile **24** (1.0 mmol) in THF (15 mL) was cooled to 0 °C and $LiAlH_4$ (5.0 mmol) was added in several portions. After addition was complete, the mixture was allowed to warm to room temperature and then refluxed until the starting material disappeared (TLC). The reaction mixture was quenched with water (5.5 mmol) and filtered (to remove inorganic solids). The filtrate was concentrated under reduced pressure and was used for the next reaction without further purification.

The crude amine **25** (1.0 mmol) was dissolved in a mixture of saturated aq. $NaHCO_3$ (3 mL) and EtOAc (3 mL). Ethyl chloroformate (5.0 mmol) was added to the resulting biphasic mixture and vigorous stirring was continued overnight. Organic phase was separated and washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The product **9** was purified by column chromatography on silica gel using appropriate eluent.

Ethyl ((6-oxaspiro[2.5]octan-1-yl)methyl)carbamate (9c)



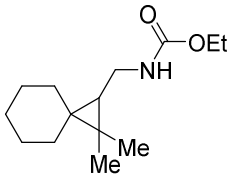
Nitrile **24c** (317.99 mg, 2.32 mmol, 1.0 equiv), $LiAlH_4$ (263.94 mg, 6.95 mmol, 3.0 equiv), and THF (34 mL). Then ethyl chloroformate (1.1 mL, 11.59 mmol, 5.0 equiv), sat. $NaHCO_3$ (7 mL) and EtOAc (7 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 1:1) afforded 467 mg (94 %) of ethyl ((6-oxaspiro[2.5]octan-1-yl)methyl)carbamate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.73 (bs, 1H), 4.09 (bs, 1H), 3.79 – 3.70 (m, 2H), 3.66 – 3.57 (m, 2H), 3.17 (bs, 2H), 1.73 – 1.57 (m, 2H), 1.35 – 1.11 (m, 5H), 0.87 – 0.79 (m, 1H), 0.57 – 0.52 (m, 1H), 0.20 (bs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.5, 67.5, 67.3, 60.7, 40.9, 37.2, 30.9, 23.3, 21.3, 16.5, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{11}H_{20}NO_3$ 214.1443; found: 214.1440 $[M+H]^+$.

((2,2-Dimethylspiro[2.5]octan-1-yl)methyl)carbamate (9f)



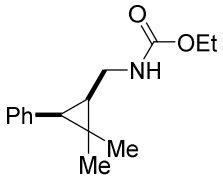
Nitrile **24f** (88.5 mg, 0.54 mmol), $LiAlH_4$ (102.87 mg, 2.71 mmol, 5.0 equiv), and THF (15 mL). Then ethyl chloroformate (0.26 mL, 2.71 mmol, 5.0 equiv), sat. $NaHCO_3$ (4 mL) and EtOAc (4 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 124 mg (78 %) of ((2,2-dimethylspiro[2.5]octan-1-yl)methyl)carbamate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.48 (bs, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.27 (dt, J = 12.7 and 6.2 Hz, 1H), 3.19 – 3.06 (m, 1H), 1.53 – 1.32 (m, 10H), 1.24 (t, J = 7.2 Hz, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.37 (t, J = 7.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.5, 60.6, 38.2, 34.9, 33.9, 32.5, 28.9, 27.6, 26.6, 26.3, 26.2, 23.1, 22.1, 21.9, 16.5, 14.7.

HR-MS (ESI-TOF) m/z: calcd. for $C_{14}H_{26}NO_2$ 240.1964; found: 240.1968 $[M+H]^+$.

Ethyl (((*1R*,3S)-2,2-dimethyl-3-phenylcyclopropyl)methyl)carbamate (*cis*-9d)**



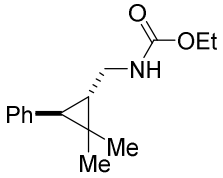
Nitrile *cis*-**24d** (111.0 mg, 0.65 mmol, 1.0 equiv), $LiAlH_4$ (123.01 mg, 3.24 mmol, 5.0 equiv), and THF (15 mL). Ethyl chloroformate (0.31 mL, 3.24 mmol, 5.0 equiv). sat. $NaHCO_3$ (4 mL) and EtOAc (4 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 147 mg (92 %) of ethyl (((*1R*,3S**)-2,2-dimethyl-3-phenylcyclopropyl)methyl)carbamate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.29 – 7.19 (m, 2H), 7.21 – 7.08 (m, 3H), 4.61 (bs, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.45 (dt, *J* = 12.8 and 6.0 Hz, 1H), 2.82 (ddd, *J* = 14.0, 9.3 and 4.7 Hz, 1H), 1.98 (d, *J* = 9.1 Hz, 1H), 1.28 – 1.19 (m, 6H), 1.18 – 1.05 (m, 1H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.4, 137.2, 130.5, 128.2, 126.1, 60.7, 39.4, 31.5, 29.0, 27.5, 19.4, 16.8, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{15}H_{22}NO_2$ 248.1651; found: 248.1651 $[M+H]^+$.

Ethyl (((*1S*,3S)-2,2-dimethyl-3-phenylcyclopropyl)methyl)carbamate (*trans*-9d)**



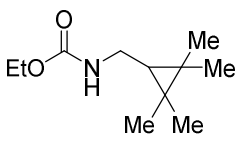
Nitrile *trans*-**24d** (187.20 mg, 1.09 mmol), $LiAlH_4$ (207.46 mg, 5.47 mmol, 5.0 equiv), and THF (15 mL). Then ethyl chloroformate (0.52 mL, 5.47 mmol, 5.0 equiv), sat. $NaHCO_3$ aq. (4 mL) and EtOAc (4 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 241 mg (89 %) of ethyl (((*1S*,3S**)-2,2-dimethyl-3-phenylcyclopropyl)methyl)carbamate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28 – 7.21 (m, 2H), 7.19 – 7.08 (m, 3H), 4.73 (bs, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.47 – 3.36 (m, 1H), 3.36 – 3.17 (m, 1H), 1.71 (d, *J* = 5.8 Hz, 1H), 1.36 – 1.18 (m, 7H), 0.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.5, 139.1, 128.7, 127.9, 125.8, 60.7, 41.6, 34.8, 28.7, 23.0, 22.0, 21.6, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{15}H_{22}NO_2$ 248.1651; found: 248.1651 $[M+H]^+$.

Ethyl ((2,2,3,3-tetramethylcyclopropyl)methyl)carbamate (9e)



Prepared by analogy to compound **4a** from (2,2-dimethylcyclopropyl)methanamine hydrochloride (**48e**) (202.20 mg, 1.24 mmol, 1.0 equiv), ethyl chloroformate (0.12 mL, 1.24 mol, 1.0 equiv), and Et_3N (0.52 mL, 3.71 mmol, 3.0 equiv) in DCM (5 mL).

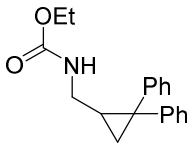
Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 5:1) afforded 118.0 mg (67 %) of ethyl ((2,2,3,3-tetramethylcyclopropyl)methyl)carbamate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.54 (bs, 1H), 4.11 – 4.05 (m, 2H), 3.15 (bs, 2H), 1.23 – 1.19 (m, 3H), 1.04 (s, 6H), 0.95 (s, 6H), 0.36 (t, *J* = 7.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.4, 60.5, 38.5, 32.6, 23.5, 21.4, 16.7, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{11}H_{22}NO_2$ 200.1651; found: 200.1647 $[M+H]^+$.

Ethyl ((2,2-diphenylcyclopropyl)methyl)carbamate (9h)



Prepared by analogy to compound *cis*-**9a** from **30h** (80.0 mg, 0.34 mmol), $LiAlH_4$ (76.76 mg, 2.02 mmol, 6.0 equiv), and THF (24 mL). Then ethyl chloroformate (32 µL, 0.34 mmol, 1.0 equiv), TEA (0.10 mL, 0.74 mmol, 2.2 equiv) and DCM (5 mL). Yield: 43 mg (43 %).

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.38 – 7.10 (m, 10H), 4.66 (bs, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.96 (dt, *J* = 13.7 and 6.6 Hz, 2H), 2.02 – 1.86 (m, 1H), 1.38 (t, *J* = 5.4 Hz, 1H), 1.30 – 1.18 (m, 4H).

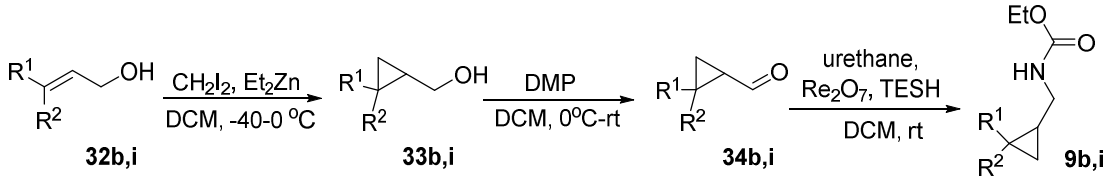
^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.5, 146.1, 140.8, 130.1, 1286, 128.3, 127.8, 126.7, 125.9, 60.7, 42.3, 35.4, 25.4, 18.8, 14.7.

HR-MS (ESI-TOF) m/z: calcd. for $C_{19}H_{22}NO_2$ 296.1651; found: 296.1653 $[M+H]^+$.

Carbamates *cis/trans*-**9i** and **9b** were obtained in three step sequence according to Scheme 6. Allylic alcohols **32b,i** under *Simmons-Smith* reaction conditions were transformed to the corresponding cyclopropane derivatives **33b,i**. Oxidation of alcohols **33b,i** to aldehydes **34b,i** was achieved using DMP. Finally, carbamates **9b,i** were obtained by reductive amination of electron defficient amine with aldehyde according to the literature procedure[8].

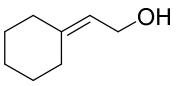
NOTE: 2-Cyclohexylideneethan-1-ol (**32b**) wasn't commercially available. It was synthesized in one step form ethyl cyclohexylideneacetate.

[8] Das, B. G.; Ghorai, P. *Chem. Commun.* **2012**, 48, 8276.



Scheme 6

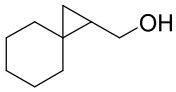
2-Cyclohexylideneethan-1-ol (32b)



1 M DIBALH in hexane (32.8 mL, 32.77 mmol, 2.1 equiv) was added dropwise to a cooled (0 °C) solution of ethyl cyclohexylideneacetate (2.5 mL, 15.60 mmol, 1.0 equiv) in THF (24 mL) and stirred at room temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 1:1) afforded 1.60 g (81 %) of 2-cyclohexylideneethan-1-ol as a colorless oil. This compound is known.[9]

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.36 (tt, *J* = 7.1 and 1.3 Hz, 1H), 4.19 – 4.10 (m, 2H), 2.27 – 2.04 (m, 4H), 1.60 – 1.48 (m, 6H), 1.09 (s, 1H).

Spiro[2.5]octan-1-ylmethanol (33b)



To a solution of alkene **32b** (1.59 g, 12.60 mmol, 1.0 equiv) in anh. DCM (20 mL) at -40 °C $ZnEt_2$ (1M in hexane, 31.5 mL, 31.5 mmol, 2.5 equiv) was added dropwise over 10 min. The reaction mixture was stirred for 5 min, and neat CH_2I_2 (2.0 mL, 25.20 mmol, 2.0 equiv) was added dropwise over 5 min. Reaction was allowed to gradually warm to rt and stirred for 12 h. The mixture was then quenched with sat. aq. NH_4Cl (20 mL). The phases were separated, aqueous layer was extracted with DCM (2 × 20 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (eluent hexanes/EtOAc 2:1) afforded 1.52 g (75 %) of spiro[2.5]octan-1-ylmethanol as a colorless oil. This compound is known.[12]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.66 – 3.56 (m, 2H), 1.58 – 1.13 (m, 11H), 0.87 (qd, *J* = 8.1, 5.2 Hz, 1H), 0.45 (dd, *J* = 8.5, 4.4 Hz, 1H), 0.11 (t, *J* = 4.8 Hz, 1H).

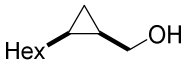
((1*R,2*S**)-2-Hexylcyclopropyl)methanol (*trans*-33i)**

[9] Comito, R. J.; Finelli, F. G.; MacMillan, D. *J. Am. Chem. Soc.* **2013**, 135 (25), 9358.

Prepared by analogy to compound **33b** from *trans*-**32i** (2.0 mL, 11.81 mmol, 1.0 equiv), $ZnEt_2$ (1 M in hexane, 29.5 mL, 29.5 mmol, 2.5 equiv), CH_2I_2 (1.9 mL, 23.6 mmol, 2.0 equiv), and DCM (24 mL). Yield: 1.72 g (93 %). This compound is known.[10]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.48 – 3.34 (m, 2H), 1.53 (bs, 1H), 1.42 – 1.15 (m, 10H), 0.91 – 0.75 (m, 4H), 0.63 – 0.52 (m, 1H), 0.34 (dtd, *J* = 8.6, 4.6 and 2.0 Hz, 1H), 0.28 (dtd, *J* = 7.0, 4.8 and 2.1 Hz, 1H).

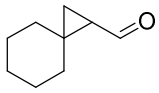
((1*R,2*S**)-2-Hexylcyclopropyl)methanol (*cis*-33i)**



Prepared by analogy to compound **33b** from *trans*-**32i** (2.0 mL, 11.88 mmol, 1.0 equiv), $ZnEt_2$ (1 M in hexane, 29.7 mL, 29.7 mmol, 2.5 equiv), CH_2I_2 (1.9 mL, 23.8 mmol, 2.0 equiv), and DCM (24 mL). Yield: 1.69 g (91 %). This compound is known.[11]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.68 – 3.50 (m, 2H), 1.54 (bs, 1H), 1.49 – 1.13 (m, 10H), 1.07 (tddd, *J* = 8.7, 7.1 and 5.3 and 1.8 Hz, 1H), 0.86 (tdd, *J* = 8.1, 4.1 and 2.1 Hz, 4H), 0.68 (tdd, *J* = 8.4, 4.6 and 2.0 Hz, 1H), -0.01 – -0.12 (m, 1H).

Spiro[2.5]octane-1-carbaldehyde (34b)



To a solution of alcohol **33b** (0.46 g, 3.27 mmol) in anh. DCM (24 mL) Dess-Martin periodinane (9.8 mL, 3.92 mmol, 1.2 equiv) was added at rt and reaction was stirred for 1 h. Then sat. Na_2SO_3 aq. (7 mL) was added and the mixture was vigorously stirred for 30 min. Phases were separated, and the aqueous layer was extracted with DCM (3 × 15 mL). Combined organic phase was washed with sat. $NaHCO_3$ aq. (10 mL), brine (10 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (eluent hexanes/EtOAc 10:1) afforded 0.34 g (75 %) of spiro[2.5]octane-1-carbaldehyde as a colorless oil. This compound is known.[12]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.37 (dd, *J* = 5.4 and 1.5 Hz, 1H), 1.71 – 1.25 (m, 12H), 1.05 (dd, *J* = 7.8 and 4.6 Hz, 1H).

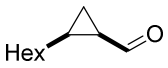
(1*S,2*S**)-2-Hexylcyclopropane-1-carbaldehyde (*trans*-34i)**

[10] Kumar, P.; Dubey, A.; Harbindu, A. *Org. Biomol. Chem*. **2012**, 10 (34), 6987.
[11] Cheng, D.; Huang, D.; Shi, Y. *Org. Biomol. Chem*. **2013**, 11 (34), 5588.
[12] Huang, H.; Forsyth, C. J. *Tetrahedron* **1997**, 53 (48), 16341.

Prepared by analogy to compound **34b** from *trans*-**33i** (398.2 mg, 2.55 mmol), Dess-Martin periodinane (7.6 mL, 3.06 mmol, 1.2 equiv), and DCM (22 mL). Yield: 300 mg (76 %). This compound is known.[13]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.98 (d, *J* = 5.6 Hz, 1H), 1.60 (ddt, *J* = 8.1, 5.7 and 4.2 Hz, 1H), 1.52 – 1.18 (m, 12H), 0.96 – 0.83 (m, 4H).

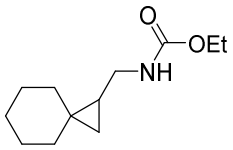
(1*R,2*S**)-2-Hexylcyclopropane-1-carbaldehyde (*cis*-34i)**



Prepared by analogy to compound **34b** from *cis*-**33i** (445.9 mg, 2.85 mmol), Dess-Martin periodinane (8.6 mL, 3.42 mmol, 1.2 equiv), and DCM (24 mL). Yield: 323 mg (73 %). This compound is known.[13]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.34 (d, *J* = 5.5 Hz, 1H), 1.84 (tt, *J* = 8.1 and 5.4 Hz, 1H), 1.66 – 1.11 (m, 13H), 0.86 (t, *J* = 6.9 Hz, 3H).

Ethyl (spiro[2.5]octan-1-ylmethyl)carbamate (9b)



To a stirred solution of aldehyde **34b** (290.9 mg, 2.10 mmol, 1.0 equiv) and urethane (225.03 mg, 2.53 mmol, 1.2 equiv) in DCM (9.0 mL) triethylsilane (4.0 mL, 25.26 mmol, 12.0 equiv) was added at room temperature, followed by the addition of Re_2O_7 (20.39 mg, 0.04 mmol, 0.02 equiv). After stirring for 16 h, the reaction mixture was quenched with brine (2 mL), followed by extraction with EtOAc (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 6:1) afforded 19.0 mg (4 %) of ethyl (spiro[2.5]octan-1-ylmethyl)carbamate as a colorless oil.

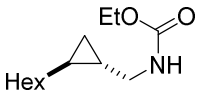
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.64 (bs, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.18 (t, *J* = 6.6 Hz, 2H), 2.03 – 1.83 (m, 1H), 1.74 – 1.07 (m, 12H), 0.79 – 0.66 (m, 1H), 0.42 (dd, *J* = 8.5 and 4.5 Hz, 1H), 0.07 (t, *J* = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.5, 60.6, 41.3, 37.6, 30.5, 26.4, 25.9, 25.6, 23.7, 23.6, 16.9, 14.7.

HR-MS (ESI-TOF) m/z: calcd. for $C_{12}H_{22}NO_2$ 212.1651; found: 212.1656.

[13] Roberts, I.; Baird, M.; Liu, Y. *Tetrahedron Lett.* **2004**, 45 (47), 8685.

Ethyl (((1*S,2*S**)-2-hexylcyclopropyl)methyl)carbamate (*trans*-9i)**



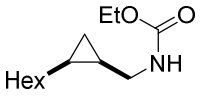
Prepared by analogy to compound **9b** from aldehyde *trans*-**34i** (58.4 mg, 0.38 mmol, 1.0 equiv), urethane (40.48 mg, 0.45 mmol, 1.2 equiv) triethylsilane (73 μL, 0.45 mmol, 1.2 equiv), Re_2O_7 (3.67 mg, 0.0076 mmol, 0.02 equiv), and DCM (5 mL). Yield: 71 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.69 (bs, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.02 (t, *J* = 6.4 Hz, 2H), 1.42 – 1.09 (m, 12H), 0.92 – 0.82 (m, 4H), 0.67 (qt, *J* = 7.3 and 4.2 Hz, 1H), 0.56 (tq, *J* = 7.2, 3.6 and 2.6 Hz, 1H), 0.32 (dt, *J* = 8.6 and 4.7 Hz, 1H), 0.28 – 0.21 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.6, 60.6, 45.4, 33.6, 31.9, 29.5, 29.1, 22.6, 18.5, 17.65, 14.7, 14.1, 10.4.

HR-MS (ESI-TOF) m/z: calcd. for $C_{13}H_{26}NO_2$ 228.1964; found: 228.1968 $[M+H]^+$.

Ethyl (((1*R,2*S**)-2-hexylcyclopropyl)methyl)carbamate (*cis*-9i)**



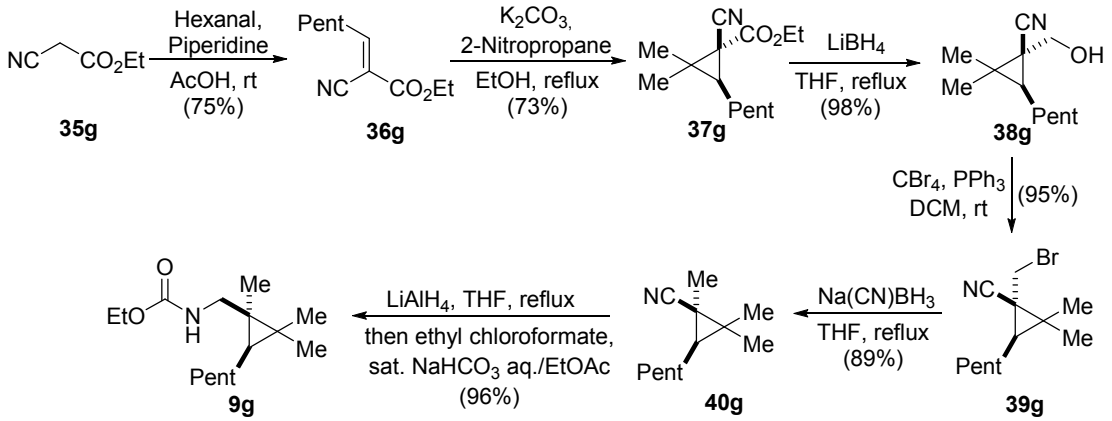
Prepared by analogy to compound **9b** from aldehyde *cis*-**34i** (288.1 mg, 1.87 mmol, 1.0 equiv), urethane (199.69 mg, 2.24 mmol, 1.2 equiv) triethylsilane (0.36 mL, 2.24 mmol, 1.2 equiv), Re_2O_7 (18.10 mg, 0.037 mmol, 0.02 equiv), and DCM (9 mL). Yield: 325 mg (77%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.66 (bs, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.26 – 3.05 (m, 2H), 1.47 – 1.10 (m, 13H), 1.01 – 0.81 (m, 4H), 0.78 (tt, *J* = 8.5 and 5.7 Hz, 1H), 0.66 (td, *J* = 8.4 and 4.6 Hz, 1H), -0.09 (q, *J* = 5.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.5, 60.6, 41.2, 31.8, 30.1, 29.2, 28.5, 22.6, 15.9, 15.5, 14.7, 14.1, 9.9.

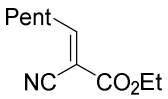
HR-MS (ESI-TOF) m/z: calcd. for $C_{13}H_{26}NO_2$ 228.1964; found: 228.1968 $[M+H]^+$.

Carbamate **9g** was synthesized in six steps according to Scheme 7. *α,β*-Unsaturated ester **36g** was obtained in *Knoevenagel condensation* reaction and further cyclopropanated with 2-nitropropane in the presence of base. Reduction of ester gave alcohol **38g**, which under *Appel* reaction conditions was transformed to bromide **39g**. After reduction of bromide **39g** and nitrile **40g** amine was obtained and *in situ* acylated to corresponding carbamate **9g**.



Scheme 7

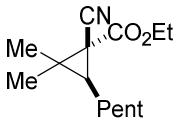
Ethyl (*E*)-2-cyanooct-2-enoate (36g)



Prepared by analogy to compound **21c** from ethyl cyanoacetate (**35g**) (1.73 mL, 16.27 mmol), hexanal (2 mL, 16.27 mmol, 1.0 equiv), piperidine (0.16 mL, 1.63 mmol, 0.1 equiv) in 5 mL AcOH at rt. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 6:1) afforded 2.38 g (75%) of ethyl (*E*)-2-cyanooct-2-enoate as a colorless oil. This compound is known.[14]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.64 (t, *J* = 8.0 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.60 – 2.49 (m, 2H), 1.61 – 1.48 (m, 2H), 1.40 – 1.20 (m, 7H), 0.97 – 0.82 (m, 3H).

Ethyl 1-cyano-2,2-dimethyl-3-pentylcyclopropane-1-carboxylate (37g)



Prepared by analogy to compound **22d** from ester **36g** (1.39 g, 7.10 mmol), 2-nitropropane (0.64 mL, 7.10 mmol, 1.0 equiv), K_2CO_3 (0.98 g, 7.10 mmol, 1.0 equiv), and EtOH (7 mL). Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 10:1) afforded 1.23 g (73 %) of ethyl 1-cyano-2,2-dimethyl-3-pentylcyclopropane-1-carboxylate as a colorless oil.

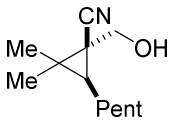
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.29 – 4.19 (m, 2H), 1.92 (t, *J* = 7.2 Hz, 1H), 1.62 – 1.26 (m, 17H), 0.94 – 0.84 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 166.6, 116.9, 62.4, 39.4, 36.9, 31.4, 29.8, 28.1, 25.5, 22.5, 20.8, 18.6, 14.2, 13.9.

HR-MS (ESI-TOF) m/z: calcd. for $C_{14}H_{24}NO_2$ 238.1807; found: 238.1802 $[M+H]^+$.

[14] Curini, M.; Epifano, F.; Marcotullio, M.; Rosati, O.; Tsadjout, A. *Synth. Comm.* **2002**, 32 (3), 355.

1-(Hydroxymethyl)-2,2-dimethyl-3-pentylcyclopropane-1-carbonitrile (38g)



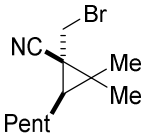
To a solution of ester **37g** (972.52 mg, 4.10 mmol) in 30 mL of THF was added lithium borohydride (4 M solution in THF, 2.2 mL, 8.61 mmol, 2.1 equiv) and the mixture was refluxed for 4 h. Hydrolysis with water (10 mL) and acidification with 1 N HCI was followed by extraction with ethyl ether (10 x 20 mL). The combined organic phase was dried over $MgSO_4$, filtered. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 1.5:1) afforded 785 mg (95 %) of 1-(hydroxymethyl)-2,2-dimethyl-3-pentylcyclopropane-1-carbonitrile as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.85 (d, *J* = 12.1 Hz, 1H), 3.63 (d, *J* = 12.1 Hz, 1H), 2.53 (bs, 1H), 1.58 – 1.17 (m, 14H), 0.97 – 0.78 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 120.7, 63.5, 35.3, 31.4, 28.6, 27.9, 27.5, 25.9, 22.5, 21.8, 18.8, 13.9.

HR-MS (ESI-TOF) m/z: calcd. for $C_{12}H_{22}NO$ 196.1701; found: 196.1706 $[M+H]^+$.

1-(Bromomethyl)-2,2-dimethyl-3-pentylcyclopropane-1-carbonitrile (39g)



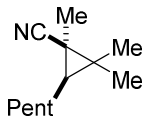
To a solution of alcohol **38g** (736.0 mg, 3.77 mmol) and carbon tetrabromide (1.87 g, 5.65 mmol, 1.5 equiv) in DCM (24 mL) triphenylphosphine (1.48 g, 5.65 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 16 h. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 6:1) afforded 926 mg (95 %) of 1-(bromomethyl)-2,2-dimethyl-3-pentylcyclopropane-1-carbonitrile as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.63 (d, *J* = 11.1 Hz, 1H), 3.44 (d, *J* = 11.2 Hz, 1H), 1.61 – 1.30 (m, 8H), 1.29 (s, 3H), 1.26 (s, 3H), 1.00 (t, *J* = 7.0 Hz, 1H), 0.95 – 0.85 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 119.4, 39.5, 33.8, 31.5, 31.3, 28.4, 28.0, 26.2, 22.5, 21.6, 18.8, 13.9.

HR-MS (ESI-TOF) m/z: calcd. for $C_{12}H_{21}NBr$ 258.0857; found: 258.0848 $[M+H]^+$.

1,2,2-Trimethyl-3-pentylcyclopropane-1-carbonitrile (40g)



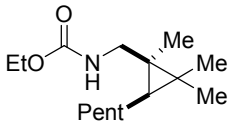
Prepared by analogy to literature procedure.[15] To a solution of bromide **39g** (0.55 g, 2.13 mmol) in THF (6 mL) sodium cyanoborohydride (0.54 g, 8.52 mmol, 4.0 equiv) was added and the resulting mixture was stirred at 70 ^{o}C for 8 h. Hydrolysis with brine (10 mL) was followed by extraction with EtOAc (2 x 10 mL). The combined organic phase was washed with brine and dried over $MgSO_4$, filtered. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 12:1) afforded 341 mg (89 %) of 1,2,2-trimethyl-3-pentylcyclopropane-1-carbonitrile as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.55 – 1.26 (m, 11H), 1.22 (s, 3H), 1.13 (s, 3H), 0.95 – 0.85 (m, 3H), 0.65 (t, J = 6.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 122.3, 37.6, 31.5, 28.7, 26.4, 26.2, 22.6, 21.9, 18.7, 18.5, 17.3, 14.0.

Unstable under the conditions of HRMS.

Ethyl ((1,2,2-trimethyl-3-pentylcyclopropyl)methyl)carbamate (9g)



Prepared by analogy to compound **9c** from nitrile **40g** (335.0 mg, 1.87 mmol), $LiAlH_4$ (354.56 mg, 9.34 mmol, 5.0 equiv), and THF (15 mL). Then ethylchloroformate (0.9 mL, 9.34 mmol, 5.0 equiv), EtOAc (5 mL) and sat. $NaHCO_3$ aq. (5 mL). Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 4:1) afforded 408 mg (96 %) of ethyl ((1,2,2-trimethyl-3-pentylcyclopropyl)methyl)carbamate as a colorless oil.

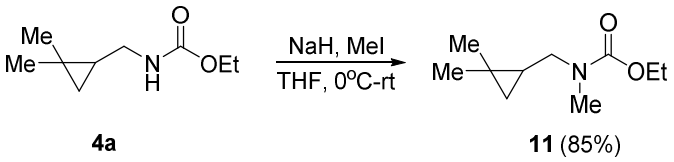
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.47 (bs, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.22 (dd, J = 13.6 and 5.7 Hz, 1H), 3.09 (dd, J = 13.6 and 5.0 Hz, 1H), 1.37 – 1.16 (m, 11H), 1.06 (s, 3H), 1.04 (s, 3H), 0.97 (s, 3H), 0.90 – 0.79 (m, 3H), 0.25 – 0.17 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.7, 60.5, 43.7, 34.9, 31.7, 29.9, 24.8, 24.6, 24.0, 22.6, 21.5, 19.5, 16.6, 14.6, 13.9.

Unstable under the conditions of HRMS.

[15] Saunders, M.; Kraus, N. *J. Am. Chem. Soc.* **1988**, 110 (24), 8050.

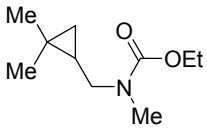
Carbamate **11** was synthesized from previously described compound **4a** by *N*-alkylation with MeI (Scheme 8).



4a **11** (85%)

Scheme 8

Ethyl ((2,2-dimethylcyclopropyl)methyl)(methyl)carbamate (11)



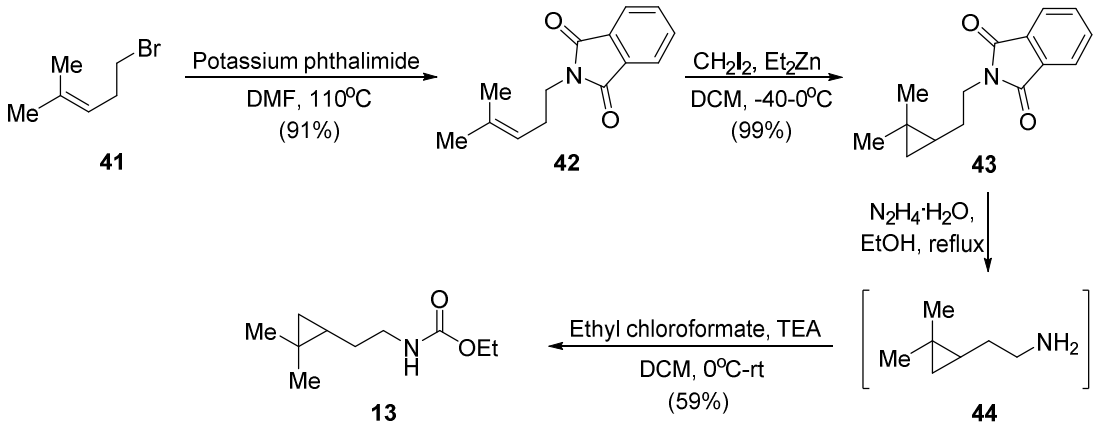
2 M solution of carbamate **4a** in THF (0.35 g, 2.04 mmol, 1.0 equiv) was added dropwise to a cooled (0 °C) solution of NaH (408.76 g, 10.22 mmol, 5.0 equiv; 60 % dispersion in mineral oil) in THF (20 mL). Reaction mixture was stirred at room temperature for 1 h. Methyl iodide (0.64 mL, 10.22 mmol, 5.0 equiv) was added dropwise to the previous solution at 0 °C and then stirred at room temperature for 20 h. The reaction was quenched with sat. NH_4Cl aq. (15 mL), extracted with diethyl ether (3 x 10 mL), washed with brine (3x10 mL), dried over $MgSO_4$, filtered. Concentration under reduced pressure gave crude product. After purification by column chromatography on silica gel (eluting with hexanes/EtOAc 6:1) 0.32 g (85 %) of the desired compound was obtained as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.12 (q, *J* = 7.1, 0.9 Hz, 2H), 3.35 – 3.24 (m, 2H), 2.92 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 0.74 (dtd, *J* = 8.6, 7.1 and 5.4 Hz, 1H), 0.47 (dd, *J* = 8.7 and 4.4 Hz, 1H), 0.10 (bs, 1H).

^{13}C NMR (101 MHz, $cdcl_3$) δ 156.5, 61.1, 48.7, 33.7, 27.1, 22.9, 20.1, 18.6, 14.8.

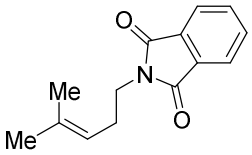
HR-MS (ESI-TOF) m/z: calcd. for $C_{10}H_{20}NO_2$ 186.1494; found: 186.1494 $[M+H]^+$.

Carbamate **13** was synthesized in four steps according to Scheme 9. Alkylation of potassium phtalimide with 5-bromo-2-methyl-2-pentene (**41**) gave alkene **42**, which under *Simmons-Smith* reaction conditions was transformed to the corresponding cyclopropane derivative **43**. Removal of protecting group gave amine **44**, which *in situ* was acylated to corresponding carbamate **13**.



Scheme 9

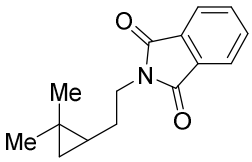
2-(4-Methylpent-3-en-1-yl)isoindoline-1,3-dione (42)



5-Bromo-2-methylpent-2-ene (**41**) (2.0 mL, 14.93 mmol) was added to a mixture of potassium phtalimide (4.15 g, 22.39 mmol, 1.5 equiv) in DMF (15 mL). After heating at 110 °C overnight, the mixture was then diluted with ethyl acetate (15 mL), washed with water and dried with $MgSO_4$. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 5:1) afforded 3.1 g (91 %) of 2-(4-methylpent-3-en-1-yl)isoindoline-1,3-dione as a colorless oil. This compound is known.[16]

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.87 – 7.80 (m, 2H), 7.73 – 7.67 (m, 2H), 5.13 (tp, J = 7.4 and 1.5 Hz, 1H), 3.68 (t, J = 7.3 Hz, 2H), 2.37 (q, J = 7.4 Hz, 2H), 1.66 (s, 3H), 1.58 (s, 3H).

2-(2-(2,2-Dimethylcyclopropyl)ethyl)isoindoline-1,3-dione (43)



Prepared by analogy to compound **33b** from alkene **42** (436.3 mg, 1.90 mmol), CH_2I_2 (0.6 mL, 7.61 mmol, 4.0 equiv), Et_2Zn (1 M in hexane, 3.8 mL, 3.81 mmol, 2.0 equiv), and DCM (15 mL). Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 6:1) afforded 458 mg (99 %) of 2-(2-(2,2-dimethylcyclopropyl)ethyl)isoindoline-1,3-dione as a colorless oil.

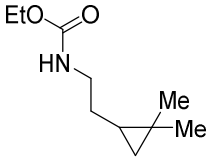
[16] Zhao, C.; Jia, X.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2014**, 136, 17645.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.88 – 7.78 (m, 2H), 7.72 – 7.68 (m, 2H), 3.82 – 3.67 (m, 2H), 1.79 – 1.54 (m, 2H), 1.00 (s, 3H), 0.98 (s, 3H), 0.56 – 0.44 (m, 1H), 0.37 (dd, *J* = 8.5, 4.2 Hz, 1H), -0.06 – -0.11 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.4, 133.8, 132.2, 123.1, 38.3, 28.7, 27.3, 22.0, 19.9, 19.3, 15.3.

HR-MS (ESI-TOF) m/z: calcd. for $C_{15}H_{18}NO_2$ 244.1338; found: 244.1338 $[M+H]^+$.

Ethyl (2-(2,2-dimethylcyclopropyl)ethyl)carbamate (13)



Phthalimide intermediate **43** (425.0 mg, 1.75 mmol) and hydrazine monohydrate (0.9 mL, 17.47 mmol, 10.0 equiv) in EtOH (8 mL) were refluxed for 3 h. Suspension was cooled to rt, acidified with 1 M HCl aq., and extracted with EtOAc (5 mL). The pH of the water phase was then adjusted to ~11 by adding 2 M NaOH aq. and extracted with diethylether (4 x 10 mL). The combined organic phase was dried over NaOH, filtered and concentrated under reduced pressure. The amine **44** was used for the next step without further purification.

Ethyl chloroformate (0.22 mL, 2.31 mmol, 1.0 equiv) was added dropwise to a cooled (0 °C) solution of crude amine **44** (261.4 mg, 2.31 mmol) and TEA (0.7 mL, 5.08 mmol, 2.2 equiv) in DCM (3 mL) and stirred at room temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (gradient hexanes/EtOAc 2:1 to EtOAc) afforded 154.2 mg (59 %) of ethyl (2-(2,2-dimethylcyclopropyl)ethyl)carbamate as a colorless oil.

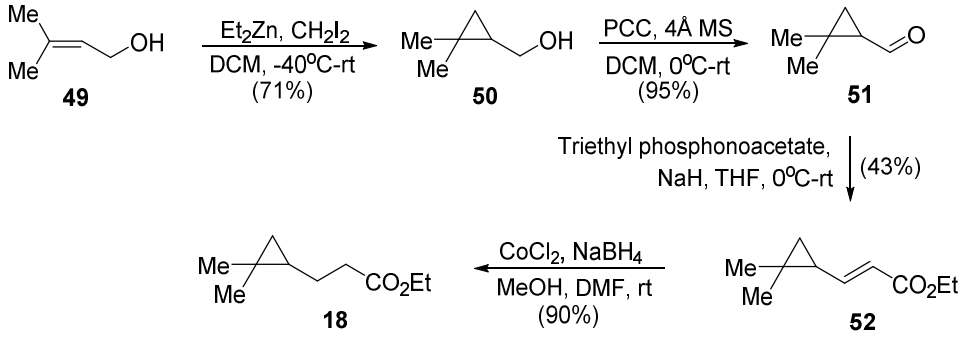
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.71 (bs, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.22 (q, *J* = 6.7 Hz, 2H), 1.57 (dq, *J* = 13.8, 6.7 Hz, 1H), 1.40 (dq, *J* = 14.1 and 7.1 Hz, 1H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.52 – 0.35 (m, 2H), -0.08 (t, *J* = 4.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.6, 60.6, 41.4, 30.0, 27.4, 21.9, 19.9, 19.4, 15.1, 14.7.

HR-MS (ESI-TOF) m/z: calcd. for $C_{10}H_{20}NO_2$ 186.1494; found: 186.1494 $[M+H]^+$.

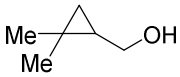
Ester **18** was obtained in four step sequence according to Scheme 10. Allylic alcohol **49** under *Simmons-Smith* reaction conditions was transformed to the corresponding cyclopropane derivative **50**. Oxidation of alcohol **50** to aldehyde **51** was achieved using

PCC. The (*E*)-alkene **52** was obtained in *HWE* reaction from triethyl phosphonoacetate and aldehyde **51**. Finally, unsaturated ester **52** was obtained by reduction of double bond with $CoCl_2$ and $NaBH_4$ according to the literature procedure.



Scheme 10

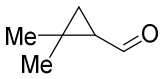
(2,2-Dimethylcyclopropyl)methanol (50)



Prepared by analogy to compound **33b** from alkene **49** (3.0 mL, 29.26 mmol, 1.0 equiv), $ZnEt_2$ (1M in hexane, 81.3 mL, 73.14 mmol, 2.5 equiv), CH_2I_2 (4.7 mL, 58.52 mmol, 2.0 equiv) and DCM (100 mL). Concentration in vacuum followed by purification by flash column chromatography (eluent 5 % methanol in methylene chloride) afforded 2.09 g (71 %) of (2,2-dimethylcyclopropyl)methanol as a colorless oil. This compound is known.[17]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.70 (dd, J = 11.4 and 6.7 Hz, 1H), 3.53 (dd, J = 11.4 and 8.5 Hz, 1H), 1.28 (bs, 1H), 1.12 (s, 3H), 1.08 (s, 3H), 0.91 (tdd, J = 8.5, 6.7 and 5.3 Hz, 1H), 0.49 (dd, J = 8.6 and 4.4 Hz, 1H), 0.13 (t, J = 4.8 Hz, 1H).

2,2-Dimethylcyclopropane-1-carbaldehyde (51)



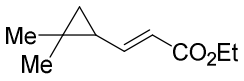
To an ice-cooled solution of alcohol **50** (999.0 mg, 9.974 mmol) in dry CH_2C1_2 (30 mL) was added PCC (2.15 g, 9.974 mmol, 1.0 equiv). The mixture was stirred at ambient temperature overnight. Ether (5 ml) was added to the reaction mixture and filtered through celite bed, the black residue washed with ether (2 × 10 mL). The total filtrate was concentrated under reduced pressure (30 °C, 300 mBar). The crude product was purified by silica gel chromatography (eluent: CH_2Cl_2)

[17] Charette, A. B. et al. *J. Am. Chem. Soc.* **2001**, 123(49), 12160.

to yield the title compound **51** (969.0 mg, 95 %) as a colorless oil. This compound is known.[18]

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.30 (dd, *J* = 5.5 and 1.0 Hz, 1H), 1.67 (dtd, *J* = 8.0, 5.3 and 1.0 Hz, 1H), 1.31 (t, *J* = 4.9 Hz, 1H), 1.25 (s, 1H), 1.16 (s, 3H), 1.04 (dd, *J* = 8.1 and 4.5 Hz, 1H).

Ethyl (*E*)-3-(2,2-dimethylcyclopropyl)acrylate (52)



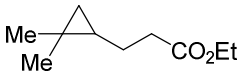
Triethyl phosphonoacetate (2.63 mL, 13.25 mmol, 1.3 equiv) was added dropwise to a suspension of NaH (529.79 mg, 13.25 mmol, 1.3 equiv; 60 wt% in mineral oil) in THF (100 mL) at 0 °C, and the mixture was stirred for 30 min at 0 °C. A solution of 2,2-dimethylcyclopropane-1-carbaldehyde (**51**) (1.0 g, 10.19 mmol, 1.0 equiv) obtained above was added to it with the aid of THF (5 mL) at 0 °C, and the resulting mixture was stirred for 20 h at room temperature. The mixture was then quenched with sat. aq. NH_4Cl (10 mL) and diethyl ether (10 mL) was added. The phases were separated, aqueous layer was extracted with diethyl ether (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (eluent hexanes/EtOAc 6:1) afforded 740.0 mg (43 %) of ethyl (*E*)-3-(2,2-dimethylcyclopropyl)acrylate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.72 – 6.59 (m, 1H), 5.89 – 5.78 (m, 1H), 4.20 – 4.05 (m, 2H), 1.44 – 1.32 (m, 1H), 1.29 – 1.19 (m, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 0.88 (dd, *J* = 8.3 and 4.5 Hz, 1H), 0.62 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 166.6, 151.2, 119.6, 59.9, 28.3, 26.9, 24.2, 22.2, 20.8, 14.3.

HR-MS (ESI-TOF) m/z: calcd. for $C_{10}H_{17}O_2$ 169.1229; found: 169.1222 $[M+H]^+$.

Ethyl 3-(2,2-dimethylcyclopropyl)propanoate (18)



Prepared by analogy to literature procedure.[19] A solution of **52** (483.9 mg, 2.88 mmol, 1.0 equiv) in MeOH (8 mL) and anhydrous $CoCl_2$ (74.69 mg, 0.58 mmol, 0.2 equiv) was stirred for 30 min under argon atmosphere. Then, $NaBH_4$ (435.29 mg, 11.51 mmol) in DMF (3 mL) was added at room temperature

[18] Cheeseman, M.; Davies, I. R.; Axe, P.; Johnson, A. L.; Bull, S. D. *Org. Biomol. Chem.* **2009**, 7, 3537.
[19] He, R.; Deng, M. Z. *Tetrahedron* **2002**, 58, 7613.

and stirred for additional 0.5 h. Then the reaction was quenched by water (10 mL) and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was washed with water (3 × 15 mL) to remove DMF, dried over $MgSO_4$ and concentrated. The residues were chromatographed on silica gel (elution with hexanes/ethyl acetate 20:1) to afford the ester **18** (442.0 mg, 90 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.11 (qd, *J* = 7.1 and 1.0 Hz, 2H), 2.35 (td, *J* = 7.6 and 1.0 Hz, 2H), 1.68 (dq, *J* = 14.2 and 7.2 Hz, 1H), 1.55 (dq, *J* = 14.1 and 7.7 Hz, 1H), 1.24 (td, *J* = 7.1 and 1.0 Hz, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.54 – 0.42 (m, 1H), 0.37 (dd, *J* = 8.5 and 4.2 Hz, 1H), -0.10 (t, *J* = 4.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 173.8, 60.1, 34.9, 27.4, 25.4, 23.9, 19.8, 19.5, 15.6, 14.2.

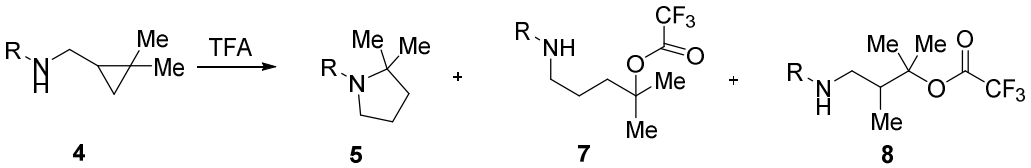
HR-MS (ESI-TOF) m/z: calcd. for $C_{10}H_{19}O_2$ 171.1385; found: 171.1384 $[M+H]^+$.

Optimization of the reaction conditions and characterization of byproducts

Directing group

NOTE: All reactions were performed in 10 mL RBF. Carbamate (0.1 mmol) was dissolved in TFA (1 mL) and stirred at room temperature for 24 h. Reaction solvent was evaporated to dryness. The crude mixture was dissolved in diethyl ether and evaporated to dryness (2 × 3 mL). Internal standard (1,4-*b*is(trichloromethyl)benzene) was added and crude reaction mixture was analyzed by ^{1}H-NMR. Then products and byproducts were purified by column chromatography on silica gel using appropriate eluent.

Table S1. Scope of *N*-substituents for the synthesis of pyrrolidine 5



4 **5** **7** **8**

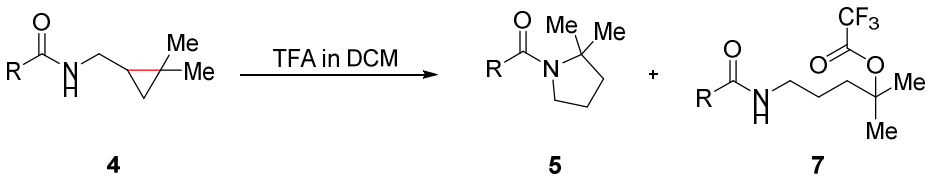
entry	**4**, R	product (yield %)
1	**4a**, EtOCO	**5a** (92)
2	**4b**, PhNHCO	**5b** (99)
3	**4c**, PhCO	**5c** (99)
4	**4d**, MeCO	**5d** (74)[b,c]
5	**4e**,$ClCH_2CO$	**5e** (99)[b]
6	**4f**, Cl_3CCO	**5f** : **7f**, ratio 1 : 1 (97)[d,e]
7	**4g**, MeCS	**5g** (17)[e] and unidentified by-products

8	**4h**, 4-$NO_2C_6H_4$	no conversion of **4h**[a,d]
9	**4i**, CF_3CO	mixture of **5i**, **7i** and **8i**
10	**4j**, $PhSO_2$	mixture of **5j**, **8j** and $PhSO_2NH_2$

[a]Reaction conditions: a solution of **4** (c = 0.1 M) in 25 vol % TFA in CH_2Cl_2, rt, 24 h, if not otherwise stated. Isolated yields are given. [b]50 vol % TFA in CH_2Cl_2, rt; [c]volatile compound; [d]neat TFA; [e]NMR yield using 1,4-*b*is(trichloromethyl)benzene as an internal standard.

Concentration of TFA

Table S2. Concentration of TFA



4 **5** **7**

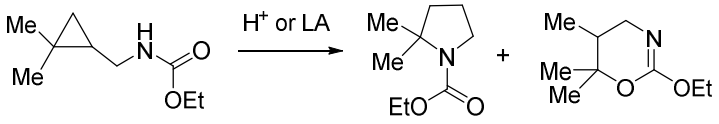
R	50% TFA	25% TFA	10% TFA	5% TFA	1% TFA
Ph					
Me					
$ClCH_2$					
EtO					
PhNH					

*Green – only product **5** is formed;Yellow – mixture of **5** and **7**; Orange – partial conversion; Red – no reaction; White – no data.*

Other acids

Other acids - CSA, TsOH, $BF_3{\cdot}OEt_2$, MsOH, TfOH and $Fe(OTf)_3$ were tried for the reaction. In the case of CSA, TsOH, $BF_3{\cdot}OEt_2$ no product formation was observed. In the presence of MsOH and TfOH unselective protonation of cyclopropane ring took place (products **5a** and **6a** was obtained). $Fe(OTf)_3$ was suitable acid for this transformation (**5a** formed as a major product) (see Table S3).

Table S3. Acid promoted cleavage of cyclopropane 4a



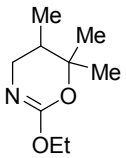
4a **5a** **6a**

entry	acid	product (yield %)[a]
1	TFA (neat)	**5a** (93)
2	$(CuOTf)_2{\cdot}C_6H_6$ (1.0 equiv)	no reaction
3	$Fe(OTf)_3$ (1.0 equiv)	**5a** (61), **6a** (17)
4	1vol% MsOH in DCM	**5a** (70), **6a** (17)
5	1vol% TfOH in DCM	**5a** (47), **6a** (25)
6	$BF_3{\cdot}OEt_2$ (1.0 equiv)	no reaction
7	*p*-$TsOH{\cdot}H_2O$ (1.0 equiv)	no reaction
8	CSA (1.0 equiv)	no reaction

[a] NMR yield using 1,4-*bis*(trichloromethyl)benzene as internal standard

Characterization of byproducts

2-Ethoxy-5,6,6-trimethyl-5,6-dihydro-4*H*-1,3-oxazine (6a)



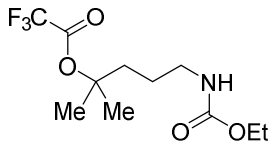
Isolated as byproduct.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.01 (q, *J* = 7.1 Hz, 2H), 3.29 (dd, *J* = 15.6 and 5.3 Hz, 1H), 2.97 (dd, *J* = 15.6 and 10.4 Hz, 1H), 1.73 (dqd, *J* = 10.3, 6.9 and 5.3 Hz, 1H), 1.30 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.14 (s, 3H), 0.86 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 152.6, 80.8, 62.7, 47.9, 35.7, 27.3, 20.5, 14.4, 13.5.

HR-MS (ESI-TOF) m/z: calcd. for $C_9H_{18}NO_2$ 172.1338; found: 172.1340 $[M+H]^+$.

5-((Ethoxycarbonyl)amino)-2-methylpentan-2-yl 2,2,2-trifluoroacetate (7a)



Isolated as a byproduct.

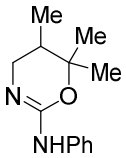
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.75 (bs, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.17 (q, *J* = 6.8 Hz, 2H), 1.87 – 1.78 (m, 2H), 1.59 – 1.51 (m, *J* = 0.6 Hz, 8H), 1.22 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.7, 156.1 (q, *J* = 41.2 Hz), 114.3 (q, *J* = 287.1 Hz), 88.63, 60.72, 40.74, 37.59, 25.42, 24.39, 14.55.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -75.9.

HR-MS (ESI-TOF) m/z: calcd. for $C_9H_{18}NO_2$ 172.1338; found: 172.1341 $[M-CF_3CO_2H+H]^+$.

5,6,6-Trimethyl-*N*-phenyl-5,6-dihydro-4*H*-1,3-oxazin-2-amine (6d)



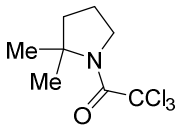
Isolated as a byproduct (when MsOH was used instead of TFA).

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.37 – 7.27 (m, 2H), 7.30 – 7.21 (m, 2H), 7.23 – 7.13 (m, 1H), 3.55 (dd, *J* = 13.1, 5.4 Hz, 1H), 3.22 – 3.05 (m, 1H), 2.25 – 2.11 (m, 1H), 1.56 (s, 3H), 1.41 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.2, 134.5, 129.1, 125.8, 121.9, 88.3, 42.0, 34.6, 26.7, 20.5, 13.4.

HR-MS (ESI-TOF) m/z: calcd. for $C_{13}H_{19}N_2O$ 219.1497; found: 219.1503 $[M+H]^+$.

2,2,2-Trichloro-1-(2,2-dimethylpyrrolidin-1-yl)ethan-1-one (5f)

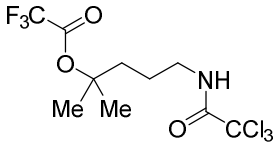


^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.94 (t, *J* = 6.2 Hz, 2H), 1.95 – 1.79 (m, 4H), 1.50 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 157.8, 94.9, 66.0, 51.0, 41.0, 25.1, 23.8.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{13}NOCl_3$ 244.0063; found: 244.0067 $[M+H]^+$.

2-Methyl-5-(2,2,2-trichloroacetamido)pentan-2-yl 2,2,2-trifluoroacetate (7f)



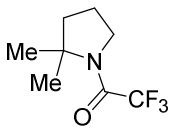
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.78 (s, 1H), 3.46 – 3.35 (m, 2H), 1.93 – 1.84 (m, 2H), 1.74 – 1.64 (m, 2H), 1.57 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 162.1, 156.1 (q, *J* = 40.9 Hz), 114.3 (q, *J* = 287.4 Hz), 92.5, 88.3, 41.2, 37.5, 25.5, 23.4.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -75.7.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{13}NOCl_3$ 244.0063; found: 244.0063 $[M-CF_3CO_2H+H]^+$.

1-(2,2-Dimethylpyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (5i)



Isolated as a byproduct.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.69 – 3.65 (m, 2H), 1.98 – 1.86 (m, 2H), 1.87 – 1.79 (m, 2H), 1.48 (s, 6H).

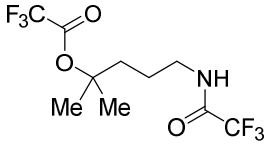
^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 154.7 (q, *J* = 40.9 Hz), 116.3 (q, *J* = 287.1 Hz), 64.6, 48.0, 41.0, 25.1, 23.2.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -72.9.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{13}NOF_3$ 196.0949; found: 196.0944 $[M+H]^+$.

2-Methyl-5-(2,2,2-trifluoroacetamido)pentan-2-yl 2,2,2-trifluoroacetate (7i)

Isolated as a byproduct.



^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.54 (s, 1H), 3.38 (q, *J* = 6.8 Hz, 2H), 1.89 – 1.82 (m, 2H), 1.73 – 1.61 (m, 2H), 1.56 (s, 6H).

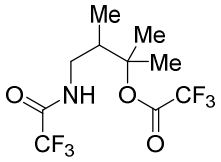
^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 157.4 (q, *J* = 37.1 Hz), 156.2 (q, *J* = 41.2 Hz), 115.8 (q, *J* = 287.4 Hz), 114.3 (q, *J* = 286.2 Hz), 88.3, 39.7, 37.5, 25.4, 23.3.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -75.8 and -76.1.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{13}NOF_3$ 196.0949; found: 196.0940 [M-CF_3CO_2H+H]$^+$.

2,3-Dimethyl-4-(2,2,2-trifluoroacetamido)butan-2-yl 2,2,2-trifluoroacetate (8i)

Isolated as a byproduct.



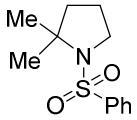
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.49 (bs, 1H), 3.53 (dt, *J* = 13.8, 5.2 Hz, 1H), 3.44 – 3.31 (m, 1H), 2.23 (pd, *J* = 6.9, 4.9 Hz, 1H), 1.65 (s, 3H), 1.60 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 157.5 (q, *J* = 37.2 Hz), 155.8 (q, *J* = 41.6 Hz), 115.8 (q, *J* = 286.0 Hz), 114.3 (q, *J* = 286.0 Hz), 90.9, 42.1, 41.3, 23.9, 21.9, 12.9.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -75.8 and -76.1.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{13}NOF_3$ 196.0949; found: 196.0952 [M-CF_3CO_2H+H]$^+$.

2,2-Dimethyl-1-(phenylsulfonyl)pyrrolidine (5j)



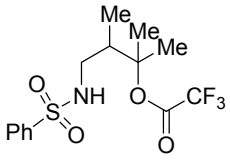
Isolated as a byproduct.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.87 – 7.84 (m, 2H), 7.55 – 7.45 (m, 3H), 3.41 (t, *J* = 6.6 Hz, 2H), 1.86 – 1.75 (m, 4H), 1.45 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 141.6, 131.9, 128.7, 127.0, 65.2, 49.4, 42.9, 28.2, 22.5.

HR-MS (ESI-TOF) m/z: calcd. for $C_{12}H_{18}NO_2S$ 240.1058; found: 240.1064 [M+H]$^+$.

2,3-Dimethyl-4-(phenylsulfonamido)butan-2-yl 2,2,2-trifluoroacetate (8j)



Isolated as a byproduct.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.87 – 7.84 (m, 2H), 7.63 – 7.58 (m, 1H), 7.56 – 7.51 (m, 2H), 4.54 (t, *J* = 6.2 Hz, 1H), 3.13 (ddd, *J* = 13.0, 9.8 and 4.1 Hz, 1H) 2.85 – 2.77 (m, 1H), 2.22 – 2.11 (m, 1H), 1.54 (s, 3H), 1.49 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H).

Fluorine decoupled ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 155.9, 139.6, 132.8, 129.2, 126.9, 90.7, 44.6, 42.3, 23.7, 22.0, 12.8.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -78.3.

Unstable under the conditions of HRMS.

Protonation/cyclization reaction and characterization of products

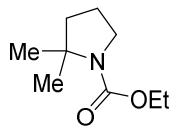
General procedure for protonation/cyclization

Method A: Carbamate (1 mmol) was dissolved in 25 % solution of TFA in DCM (10 mL) and stirred at room temperature for 24 h. Reaction solvent was evaporated to dryness. The crude mixture was dissolved in diethyl ether and evaporated to dryness (2 × 3 mL). Product was purified by column chromatography on silica gel using appropriate eluent.

Method B: Carbamate (1 mmol) was dissolved in TFA (10 mL) and stirred at room temperature for 24 h. Reaction solvent was evaporated to dryness. The crude mixture was dissolved in diethyl ether and evaporated to dryness (2 × 3 mL). Product was purified by column chromatography on silica gel using appropriate eluent.

Method C: Carbamate (1 mmol) was dissolved in TFA (10 mL) and stirred at 70 ^{o}C for 24 h. Reaction was cooled to room temperature. Reaction solvent was evaporated to dryness. The crude mixture was dissolved in diethyl ether and evaporated to dryness (2 × 3 mL). Product was purified using column chromatography on silica gel using appropriate eluent.

Ethyl 2,2-dimethylpyrrolidine-1-carboxylate (5a)



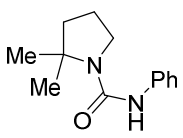
Prepared according to method A: From carbamate **4a** (113.9 mg, 0.67 mmol) and 25 % TFA in DCM (6 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 105 mg (92 %) of ethyl 2,2-dimethylpyrrolidine-1-carboxylate as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 4.09 (bs, 2H), 3.43 (bs, 2H), 1.78 – 1.71 (m, 4H), 1.36 (s, 6H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 155.6, 154.3, 60.9, 60.3, 48.5, 47.7, 42.8, 41.8, 26.9, 26.0, 22.1, 21.8, 14.7.

HR-MS (ESI-TOF) m/z: calcd. for $C_9H_{18}NO_2$ 172.1338; found: 172.1341 $[M+H]^+$.

2,2-Dimethyl-1-(phenylaminocarbonyl)pyrrolidine (5b)



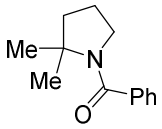
Prepared according to method B: From amide **4b** (26.7 mg, 0.122 mmol) in neat TFA (1.2 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 2:1) afforded 26.5 mg (99 %) of 2,2-dimethyl-1-(phenylaminocarbonyl)pyrrolidine as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.38 (dd, *J* = 8.7, 1.2 Hz, 2H), 7.29 – 7.23 (m, 2H), 7.04 – 6.95 (m, 1H), 6.07 (bs, 1H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.00 – 1.87 (m, 2H), 1.88 – 1.79 (m, 2H), 1.50 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 153.3, 139.3, 128.8, 122.6, 119.6, 61.4, 47.6, 42.1, 26.6, 22.3.

HR-MS (ESI-TOF) m/z: calcd. for $C_{13}H_{19}N_2O$ 219.1497; found: 219.1495 $[M+H]^+$.

(2,2-Dimethylpyrrolidin-1-yl)(phenyl)methanone (5c)



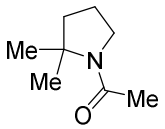
Prepared according to method B: From amide **4c** (48.2 mg, 0.237 mmol) in neat TFA (2 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 2:1) afforded 48.1 mg (99 %) of (2,2-dimethylpyrrolidin-1-yl)(phenyl)methanone as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.42 – 7.37 (m, 2H), 7.39 – 7.30 (m, 3H), 3.37 (t, *J* = 6.6 Hz, 2H), 1.90 – 1.80 (m, 2H), 1.77 (p, *J* = 6.6 Hz, 2H), 1.58 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 169.3, 139.0, 128.9, 128.1, 126.3, 62.1, 51.6, 42.2, 25.8, 23.2.

HR-MS (ESI-TOF) m/z: calcd. for $C_{13}H_{18}NO$ 204.1388; found: 204.1392 $[M+H]^+$.

1-(2,2-Dimethylpyrrolidin-1-yl)ethan-1-one (5d)



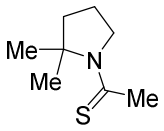
Prepared according to method B: From amide **4d** (78.0 mg, 0.552 mmol) in neat TFA (5.5 mL). Purification by column chromatography on silica gel (eluent EtOAc) afforded 57.1 mg (73 %) of 2-chloro-1-(2,2-dimethylpyrrolidin-1-yl)ethan-1-one as a yellowish oil. This compound is known.[20]

^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 3.55 and 3.43 (both t, *J* = 6.7 Hz, total 2H, rotamers), 2.19 and 1.98 (both s, total 3H, rotamers), 1.87 -1.73 (m, 4H), 1.40 and 1.38 (both s, 6H, rotamers).

^{13}C NMR (201 MHz, $CDCl_3$, ppm) δ 169.3, 168.8, 61.7, 59.6, 49.5, 48.8, 44.1, 41.9, 27.9, 25.8, 24.4, 22.8, 22.5, 20.7.

1-(2,2-Dimethylpyrrolidin-1-yl)ethane-1-thione (5g)

[20] Yuan, X.; Liu, K.; Li, C. *J. Org. Chem.* **2008**, 73(*16*), 6166.



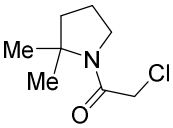
Prepared according to method A: From thioamide **4g** (50.2 mg, 0.319 mmol) and 25 % TFA in DCM (3.0 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 8.7 mg (17 %) of 1-(2,2-dimethylpyrrolidin-1-yl)ethane-1-thione as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.03 and 3.66 (both t, *J* = 6.7 Hz, total 2H, rotamers), 2.77 and 2.58 (both s, total 3H, rotamers), 2.04 -1.83 (m, 4H), 1.73 and 1.50 (both s, total 6H, rotamers).

^{13}C NMR (101 MHz, $cdcl_3$) δ 196.9 and 196.5, 67.3 and 65.9, 57.9 and 54.7, 44.8 and 43.2, 37.4 and 32.1, 27.31 and 24.28, 21.45 and 20.76.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{16}NS$ 158.1003; found: 158.1003 $[M+H]^+$.

2-Chloro-1-(2,2-dimethylpyrrolidin-1-yl)ethan-1-one (5e)



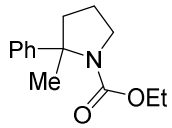
Prepared according to method B: From amide **4e** (40.8 mg, 0.232 mmol) in neat TFA (2.3 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 40.5 mg (99 %) of 2-chloro-1-(2,2-dimethylpyrrolidin-1-yl)ethan-1-one as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.94 (s, 2H), 3.52 (t, *J* = 6.7 Hz, 2H), 1.93 – 1.81 (m, 2H), 1.82 – 1.73 (m, 2H), 1.43 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 164.1 62.8, 48.4, 43.8, 41.5, 29.6, 25.5, 22.8.

HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{15}NOCl$ 176.0842; found: 176.0845 $[M+H]^+$.

Ethyl 2-methyl-2-phenylpyrrolidine-1-carboxylate (10a)



Prepared according to method B: From *cis*-**9a** (66.3 mg, 0.28 mmol) in TFA (2.8 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 61.3 mg (92 %) of ethyl 2-methyl-2-phenylpyrrolidine-1-carboxylate as a colorless oil.

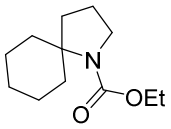
Prepared according to method A: From *trans*-**9a** (83.7 mg, 0.36 mmol) and 25 % TFA in DCM (3.6 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 4:1) afforded 83.6 mg (99 %) of product as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.34 – 7.17 (m, 5H), 4.15 – 4.04 and 3.93 (m and q, *J* = 7.1 Hz, total 2H, rotamers), 3.79 – 3.61 (m, 2H), 2.11 – 2.03 (m, 2H), 1.87 – 1.67 (m, 5H), 1.26 and 0.87 (both t, *J* = 7.1 Hz, total 3H, rotamers).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 155.3, 154.1, 147.7, 146.7, 128.1, 127.9, 126.2, 126.0, 124.8, 65.9, 65.3, 60.5, 60.4, 49.0, 48.3, 45.7, 44.6, 25.9, 25.6, 22.0, 21.8, 14.8, 14.2.

HR-MS (ESI-TOF) m/z: calcd. for $C_{14}H_{20}NO_2$ 234.1494; found: 234.1492 $[M+H]^+$.

Ethyl 1-azaspiro[4.5]decane-1-carboxylate (10b)



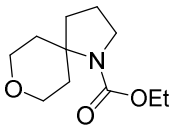
Prepared according to method A: From carbamate **9b** (16.02 mg, 0.08 mmol) and 25 % TFA in DCM (0.8 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 8:1) afforded 15.5 mg (97 %) of product as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.19 – 4.13 and 4.06 (m and q, J = 7.1 Hz, total 2H, rotamers), 3.51 – 3.46 and 3.41 (both t, J = 6.6 Hz, total 2H, rotamers), 2.47 and 2.22 (both m, total 2H, rotamers), 1.87 – 1.82 (m, 2H), 1.75 – 1.59 (m, 5H), 1.35 – 1.22 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 153.9, 64.4, 63.9, 60.5, 59.9, 48.4, 47.6, 36.9, 35.9, 34.5, 33.5, 25.4, 25.2, 24.3, 22.3, 21.9, 14.8.

HR-MS (ESI-TOF) m/z: calcd. for $C_{12}H_{22}NO_2$ 212.1651; found: 212.1656 $[M+H]^+$.

Ethyl 8-oxa-1-azaspiro[4.5]decane-1-carboxylate (10c)



Prepared according to method C: From carbamate **9c** (80.0 mg, 0.38 mmol) in neat TFA (1.0 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 1:1) afforded 62.0 mg (77 %) of ethyl 8-oxa-1-azaspiro[4.5]decane-1-carboxylate as a colorless oil.

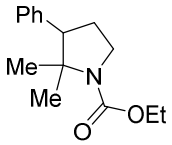
^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, ppm) δ 4.19 and 4.09 (both bs, total 2H, rotamers), 3.93 (dd, J = 11.6 and 5.1 Hz, 2H), 3.51 (m, 4H), 2.88 and 2.64 (both bs, total 2H, rotamers), 1.97 (bs, 2H), 1.77 (p, J = 6.8, 2H), 1.25 (bs, 5H).

^{1}H NMR (400 MHz, 58 °C, $CDCl_3$, ppm) δ 4.17 – 4.10 (m, 2H), 3.94 (dd, J = 11.6 and 5.1 Hz, 2H), 3.49 (t, J = 6.8 Hz, 2H), 3.48 – 3.40 (m, 2H), 2.83 (bs, 2H), 1.99 (t, J = 7.0 Hz, 2H), 1.78 (p, J = 6.9 Hz, 2H), 1.29 – 1.21 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 155.1, 153.9, 65.9, 61.5, 61.1, 60.8, 60.1, 48.3, 47.4, 36.4, 35.4, 35.1, 33.9, 29.6, 22.1, 21.6, 14.7.

HR-MS (ESI-TOF) m/z: calcd. for $C_{11}H_{20}NO_3$ 214.1443; found: 214.1444 $[M+H]^+$.

Ethyl 2,2-dimethyl-3-phenylpyrrolidine-1-carboxylate (10d)



Prepared according to method A: From *trans*-**9d** (17.6 mg, 0.07 mmol) and 25 % TFA in DCM (0.7 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 2:1) afforded 16.9 mg (96 %) of product as colorless oil.

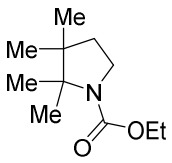
Prepared according to method B: From *cis*-**9d** (25.6 mg, 0.10 mmol) in TFA (1.0 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 2:1) afforded 24.3 mg (95 %) of ethyl 2,2-dimethyl-3-phenylpyrrolidine-1-carboxylate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.27 – 7.15 (m, 5H), 4.13 – 4.01 (m, 2H), 3.69 and 3.62 (both t, J = 9.6 Hz, total 1H, rotamers), 3.38 – 3.27 (m, 1H), 3.02 – 2.94 (m, 1H), 2.25 – 2.16 (m, 1H), 1.94 – 1.88 (m, 1H), 1.45 and 1.36 (both s, total 3H, rotamers), 1.20 (t, J = 7.1 Hz, 3H), 0.89 and 0.85 (both s, total 3H, rotamers).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 154.2, 138.4, 129.1, 128.9, 128.1, 127.1, 62.9, 62.4, 60.7, 60.2, 56.8, 56.0, 46.2, 45.6, 27.1, 26.8, 26.7, 25.9, 21.7, 20.7, 14.8, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{15}H_{22}NO_2$ 248.1651; found: 248.1651 $[M+H]^+$.

Ethyl 2,2,3,3-tetramethylpyrrolidine-1-carboxylate (10e)



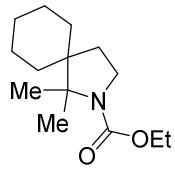
Prepared according to method A: From carbamate **9e** (77.6 mg, 0.39 mmol) and 25 % TFA in DCM (3.9 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 6:1) afforded 75.0 mg (97%) of ethyl 2,2,3,3-tetramethylpyrrolidine-1-carboxylate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.14 and 4.06 (both q, J = 7.1 Hz, total 2H, rotamers), 3.41 and 3.35 (both t, J = 7.3 Hz, total 2H, rotamers), 1.64 – 1.59 (m, 2H), 1.28 – 1.17 (m, 9H), 0.92 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 155.9, 154.6, 64.7, 64.2, 60.5, 59.9, 45.1, 44.5, 44.2, 43.3, 36.0, 35.4, 23.3, 23.2, 22.9, 21.9, 14.8, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{11}H_{22}NO_2$ 200.1651; found: 200.1648 $[M+H]^+$.

Ethyl 1,1-dimethyl-2-azaspiro[4.5]decane-2-carboxylate (10f')



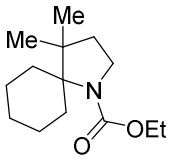
Prepared according to method A: From carbamate **9f** (90.0 mg, 0.38 mmol) and 25 % TFA in DCM (3.8 mL). Two regioisomers **10f** and **10f'** were obtained and their separation was done by column chromatography on silica gel (eluent hexanes/EtOAc 8:1). After purification 71.0 mg (79 %) of **10f'** and 15.0 mg (17 %) of **10f** were obtained both as colorless oils.

Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.14 and 4.05 (q, J = 7.1 Hz, total 2H, rotamers), 3.38 and 3.32 (t, J = 7.3 Hz, total 2H, rotamers), 1.75 (t, J = 7.3 Hz, 2H), 1.68 – 1.6 (m, 3H), 1.40 – 1.04 (m, 16H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 155.9, 154.6, 65.6, 65.1, 60.5, 59.9, 47.8, 46.9, 45.1, 44.4, 30.2, 28.4, 27.8, 26.3, 22.9, 22.7, 21.7, 14.8, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{14}H_{26}NO_2$ 240.1964; found: 240.1970 $[M+H]^+$.

Ethyl 4,4-dimethyl-1-azaspiro[4.5]decane-1-carboxylate (10f)

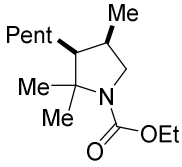


Isolated as a minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.07 (q, J = 7.0 Hz, 2H), 3.35 (t, J = 7.2 Hz, 2H), 2.42 (bs, 2H), 1.68 – 1.33 (m, 10H), 1.24 (t, J = 7.1 Hz, 3H), 1.11 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 155.6, 66.9, 60.1, 44.7, 37.8, 29.8, 25.9, 25.3, 23.4, 14.8.

HR-MS (ESI-TOF) m/z: calcd. for $C_{14}H_{26}NO_2$ 240.1964; found: 240.1968 $[M+H]^+$.

Ethyl 2,2,4-trimethyl-3-pentylpyrrolidine-1-carboxylate (10g)



Prepared according to method A: From carbamate **9g** (201.3 mg, 0.79 mmol) and 25 % TFA in DCM (7.5 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 6:1) afforded 195.0 mg (97 %) of ethyl 2,2,4-trimethyl-3-pentylpyrrolidine-1-carboxylate as a colorless oil.

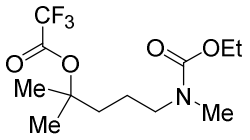
^{1}H NMR (400 MHz, 25 °C, DMSO-d_6, ppm) δ 4.08 – 4.02 and 3.96 (m and q, J = 7.0 Hz, total 2H, rotamers), 3.34 (dd, J = 10.7 and 6.2 Hz, 1H), 3.22 (d, J = 10.7 Hz, 1H), 2.17 – 2.09 (m, 1H), 1.91 – 1.79 (m, 1H), 1.48 – 1.04 (m, 17H), 0.96 – 0.82 (m, 6H).

^{1}H NMR (400 MHz, 70 °C, DMSO-d_6, ppm) δ 4.06 – 3.97 (m, 2H), 3.36 (dd, J = 10.9 and 6.3 Hz, 1H), 3.23 (dd, J = 10.9 and 1.3 Hz, 1H), 2.21 – 2.12 (m, 1H), 1.88 – 1.83 (m, 1H), 1.44 – 1.11 (m, 17H), 0.98 – 0.87 (m, 6H).

^{13}C NMR (101 MHz, 25 ºC, DMSO-d_6, ppm) δ 154.4, 153.2, 61.4, 60.8, 59.8, 59.4, 53.7, 53.0, 52.7, 51.8, 31.9, 31.6, 31.5, 30.9, 28.3, 27.2, 25.2, 25.0, 22.8, 22.02, 21.9, 21.6, 14.6, 14.4, 14.3, 14.2, 13.8.

Unstable under the conditions of HRMS.

5-((Ethoxycarbonyl)(methyl)amino)-2-methylpentan-2-yl 2,2,2-trifluoroacetate (12)



Prepared according to method A: From amide **11** (40.9 mg, 0.221 mmol) and 25 % TFA in DCM (2.2 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 3:1) afforded 64.0 mg (97 %) of 5-((ethoxycarbonyl)(methyl)amino)-2-methylpentan-2-yl 2,2,2-trifluoroacetate as a colorless oil.

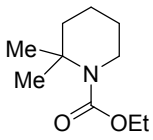
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.12 (q, J = 7.1 Hz, 2H), 3.27 (bs, 2H), 2.88 (s, 3H), 1.86 – 1.73 (m, 2H), 1.64 – 1.50 (m, 8H), 1.25 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.6, 156.1 (q, J = 41.4 Hz), 114.36 (q, J = 285.6 Hz), 88.6, 61.3, 48.5, 37.4, 34.4, 33.7, 25.5, 22.1, 21.7, 14.7.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -75.8.

HR-MS (ESI-TOF) m/z: calcd. for $C_{10}H_{20}NO_2$ 186.1494; found: 186.1494 [M-CF_3CO_2H+H]$^+$.

Ethyl 2,2-dimethylpiperidine-1-carboxylate (15)



Prepared according to method A: From carbamate **13** (20.9 mg, 0.11 mmol) and 25 % TFA in DCM (1.1 mL). Two products **14** and **15** were obtained in ratio 1:1 (yield: 97 %). They were separated by column chromatography on silica gel (gradient hexanes/EtOAc 8:1 – EtOAc). After purification both products were obtained as colorless oils.

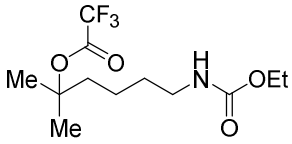
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.09 (qd, J = 7.1 and 0.5 Hz, 2H), 3.45 (t, J = 5.8 Hz, 2H), 1.62 – 1.51 (m, 6H), 1.41 (s, 6H), 1.25 (td, J = 7.1 and 0.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.8, 60.6, 54.8, 41.4, 39.5, 26.6, 23.9, 18.7, 14.6.

HR-MS (ESI-TOF) m/z: calcd. for $C_{10}H_{20}NO_2$ 186.1494; found: 186.1494 [M+H]$^+$.

6-((Ethoxycarbonyl)amino)-2-methylhexan-2-yl 2,2,2-trifluoroacetate (14)

Isolated as a byproduct.



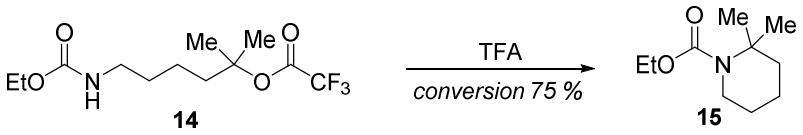
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.64 (bs, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.17 (q, J = 6.7 Hz, 2H), 1.85 – 1.81 (m, 2H), 1.56 – 1.47 (m, 8H), 1.41 – 1.32 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 156.8, 156.2 (q, J = 41.2 Hz), 114.4 (q, J = 286.8 Hz), 88.9, 60.7, 40.6, 40.0, 30.1, 25.5, 20.8, 14.6.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -75.8.

HR-MS (ESI-TOF) m/z: calcd. for $C_{10}H_{20}NO_2$ 186.1494; found: 186.1494 [M-CF_3CO_2H+H]$^+$.

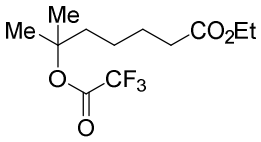
NOTE:



Scheme 11

Trifluoracetate **14** (16.2 mg, 0.054 mmol) in neat TFA (0.5 mL) was stirred at room temperature for 24 h (Scheme 11). Reaction solvent was evaporated to dryness. The crude mixture was dissolved in diethyl ether and evaporated to dryness (2 × 3 mL). Internal standard (1,4-bis(trichloromethyl)benzene) was added and was analyzed by ^{1}H-NMR: after 24 h incomplete conversion of product **14** to **15** (75 %) was observed.

Ethyl 6-methyl-6-(2,2,2-trifluoroacetoxy)heptanoate (19)



Prepared according to method A: From ester **18** (30.9 mg, 0.18 mmol) and 25 % TFA in DCM (1.8 mL). Purification by column chromatography on silica gel (eluent hexanes/EtOAc 10:1) afforded 50 mg (97 %) of ethyl 6-methyl-6-(2,2,2-trifluoroacetoxy)heptanoate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.12 (q, J = 7.1 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.87 – 1.78 (m, 2H), 1.64 (p, J = 7.3 Hz, 2H), 1.53 (s, 6H), 1.44 – 1.31 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H).

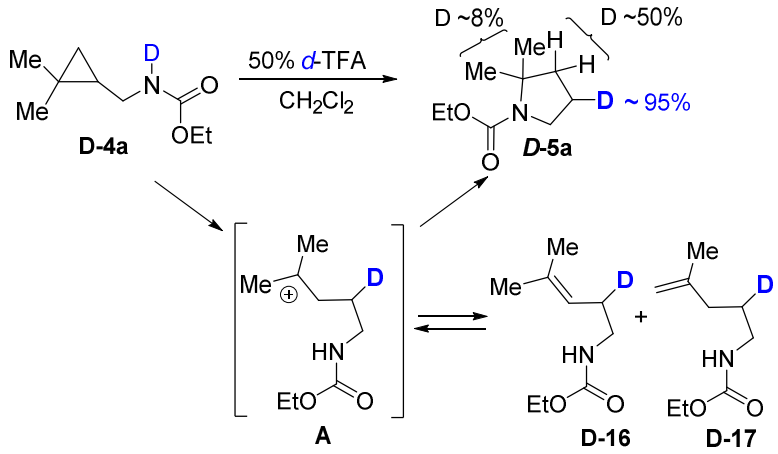
^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 173.4, 156.1 (q, J = 41.0 Hz), 114.4 (q, J = 290.1 Hz), 88.9, 60.3, 40.0, 34.0, 25.5, 24.9, 23.1, 14.2.

^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -75.9.

HR-MS (ESI-TOF) m/z: calcd. for $C_{10}H_{19}O_2$ 171.1385; found: 171.1386 [M-CF_3CO_2H+H]$^+$.

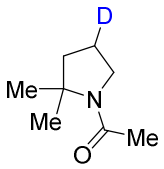
Deuterium labelling experiments

In order to determine the selectivity of the protonation step reaction of carbamate **4** under the standard reaction conditions using *d*-TFA was performed (Scheme 12). As it was expected, significant (D = 95 %) deuterium incorporation in pyrrolidine 3rd position was observed. Deuterium incorporation on smaller extent in 2nd position (D = 50%) and in pyrrolidine methyl groups (D = 8 %) was observed. Most likely, formation of *syn*/*anti*-**D-5a** could be explained by proton elimination and alkene formation, and subsequent double bond protonation.



Scheme 12

1-(2,2-Dimethylpyrrolidin-1-yl)ethan-1-one-*d (*d*-5a)**



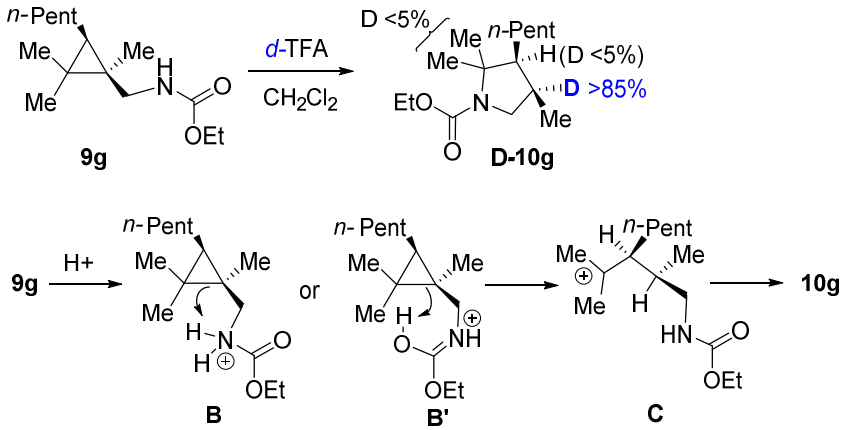
To a solution of deuterated amide *d*-**4a** (93.7 mg, 0.659 mmol) in dry DCM (1.5 mL) trifluoroacetic acid-*d* (1.5 mL) was added and the reaction mixture was stirred at room temperature for 24 h. Concentration in vacuum followed by purification by flash column chromatography (eluent EtOAc) afforded 89.0 mg (96 %) of 1-(2,2-dimethylpyrrolidin-1-yl)ethan-1-one-*d** as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 3.55 and 3.41 (both d, *J* = 6.7 Hz, total 2H, rotamers), 2.11 and 1.96 (both s, total 3H*, rotamers), 1.86 -1.70 (m, 2H), 1.40 and 1.38 (both s, 6H*, rotamers).

^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 169.2 and 168.7, 61.6 – 61.3 and 59.6 – 59.3 (both m), 49.5 – 49.4 and 48.7 (both m), 41.9 – 41.3 (m), 27.9 – 27.8 and 25.8 – 25.7 (m), 24.5, 22.8, 22.5 – 21.8 (m).

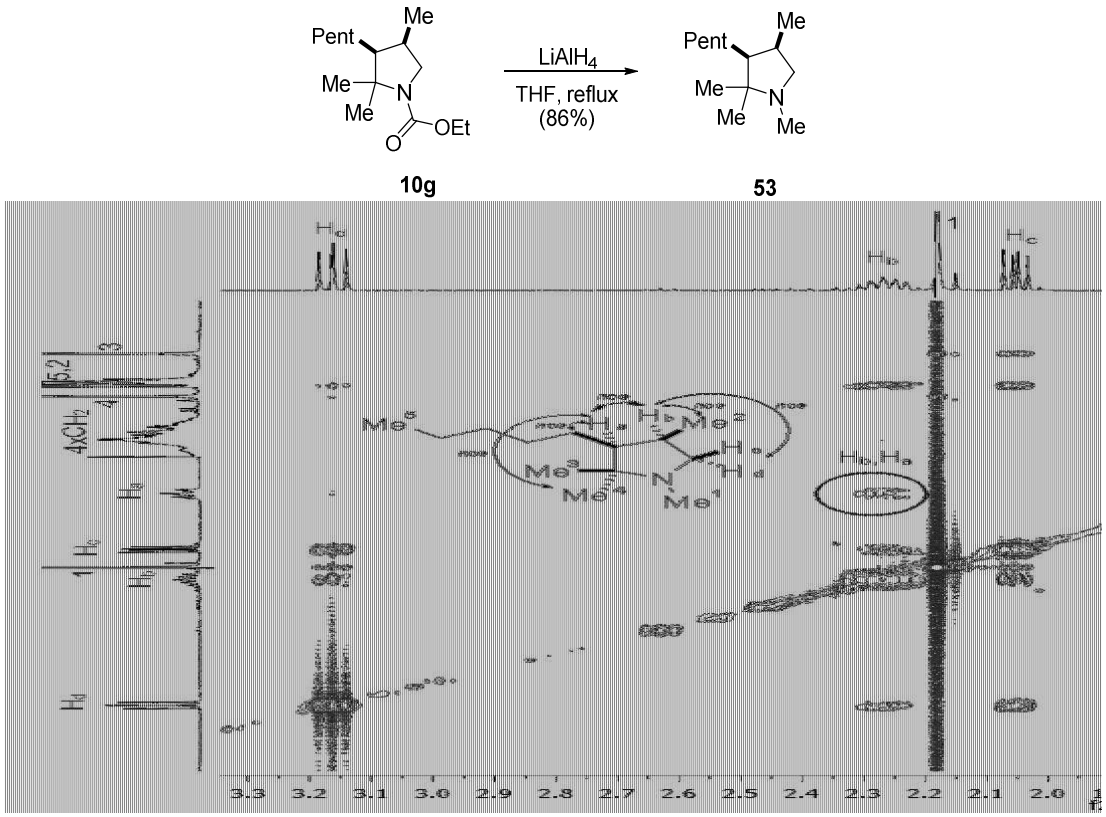
HR-MS (ESI-TOF) m/z: calcd. for $C_8H_{14}D_2NO$ 144.1357; found: 144.1358 $[M+H]^+$.

In the case of penta-substituted carbamate **9g** selective protonation of cyclopropane was observed, only one diastereomer was formed (Scheme 13). *Cis*-configuration of **D-10g** could be explained by the *edge* protonation of cyclopropane.



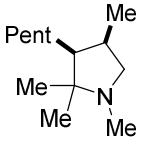
Scheme 13

To establish the relative configuration of carbamate **10g**, it was transformed to pyrrolidine derivative **53** by reduction of carbamate function with $LiAlH_4$ and analyzed by 2D NMR spectra (Scheme 14).



Scheme 14

(3*S,4*S**)-1,2,2,4-Tetramethyl-3-pentylpyrrolidine (53)**



A solution of pyrrolidine **10g** (81.0 mg, 0.31 mmol) in THF (12 mL) was cooled to 0 ºC and $LiAlH_4$ (26.48 mg, 0.70 mmol, 2.2 equiv) was added in several portions. After addition was complete, the mixture was allowed to warm to room temperature and then refluxed until the starting material disappeared (TLC). The reaction mixture was quenched with water (5 drops) and filtered (to remove inorganic solids). The filtrate was concentrated under reduced pressure. The crude amine was dissolved in a mixture of 1 M HCl (3 mL) and diethyl ether (3 mL). Organic phase was separated and the pH of the water phase was then adjusted to ~11 by adding 2 M NaOH aq. and extracted with diethyl ether (3 x 10 mL). The combined organic phase was dried over NaOH, filtered and concentrated under reduced pressure. (3*S**,4*S**)-1,2,2,4-tetramethyl-3-pentylpyrrolidine was obtained as a colorless oil. Yield was 54 mg (86%).

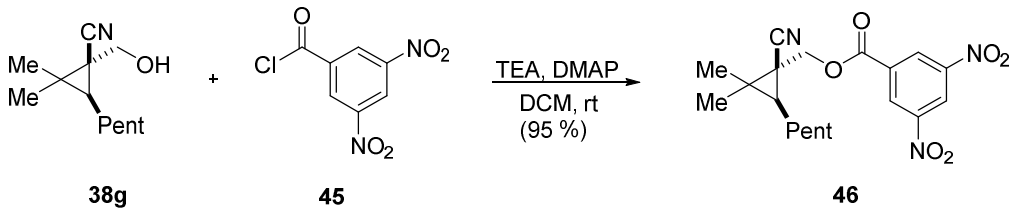
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 3.18 (dd, *J* = 9.5 and 8.2 Hz, 1H), 2.38 – 2.23 (m, 1H), 2.20 (s, 3H), 2.07 (dd, *J* = 9.5 and 6.2 Hz, 1H), 1.68 (td, *J* = 10.1 and 3.4 Hz, 1H), 1.42 – 1.11 (m, 8H), 0.98 (s, 3H), 0.95 – 0.80 (m, 6H), 0.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 61.9, 61.7, 51.6, 34.1, 32.3, 30.8, 28.7, 26.2, 26.0, 22.6, 16.3, 14.5, 14.1.

HR-MS (ESI-TOF) m/z: calcd. for $C_{13}H_{28}N$ 198.2222; found: 198.2227 $[M+H]^+$.

Structure determination of intermediate 38g by X-ray of dinitrobenzoyl derivative 46

To establish the configuration of carbamate **9g** intermediate **38g** was acylated with acyl chloride **45** in the presence of TEA and DMAP (Scheme 15). Product **46** was obtained as a white crystalline compound. Product configuration was determined by X-ray diffraction. Crystal of **46** was grown in system hexane/diethyl ether 1/1.

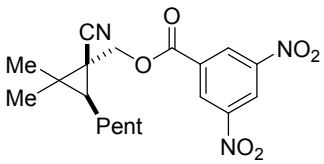


38g **45** **46**

Scheme 15

*Derivatization procedure of **38g** and characterization of product **46***

(1-Cyano-2,2-dimethyl-3-pentylcyclopropyl)methyl 3,5-dinitrobenzoate (46)



3,5-Dinitrobenzoyl chloride (148.7 mg, 0.64 mmol, 2.0 equiv) was added portionwise to a cooled (0 °C) solution of alcohol **38g** (67.5 mg, 0.32 mmol, 1.0 equiv), Et_3N (90 μL, 0.65 mmol, 2.0 equiv) and DMAP (3.94 mg, 0.03 mmol, 0.1 equiv) in DCM (10 mL) and reaction mixture was stirred at room temperature overnight. Concentration in vacuum followed by purification by flash column chromatography (eluent hexanes/EtOAc 4:1) afforded 124.0 mg (95%) of (1-cyano-2,2-dimethyl-3-pentylcyclopropyl)methyl 3,5-dinitrobenzoate as a white crystalline compound.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.25 – 9.23 (m, 1H), 9.16 (ddd, J = 2.2 and 0.6 Hz, 2H), 4.65 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 1.69 – 1.55 (m, 1H), 1.58 – 1.35 (m, 1H), 1.33 (d, J = 14.6 Hz, 13H), 1.19 (dd, J = 7.6 and 5.9 Hz, 1H), 0.86 (t, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 162.1, 148.7, 133.1, 129.4, 122.7, 119.1, 67.2, 36.9, 31.4, 28.9, 28.4, 25.8, 24.4, 22.4, 22.4, 18.6, 13.9.

EA: Calcd for $C_{19}H_{23}N_3O_6$: C, 58.60%; H, 5.95%; N, 10.79%; O, 24.65%; found: C, 58.64%; H, 5.94%; N, 10.64%.

Mp (Hexane): 61 – 64ºC.

X-ray structure of dinitrobenzoyl derivative ***46***

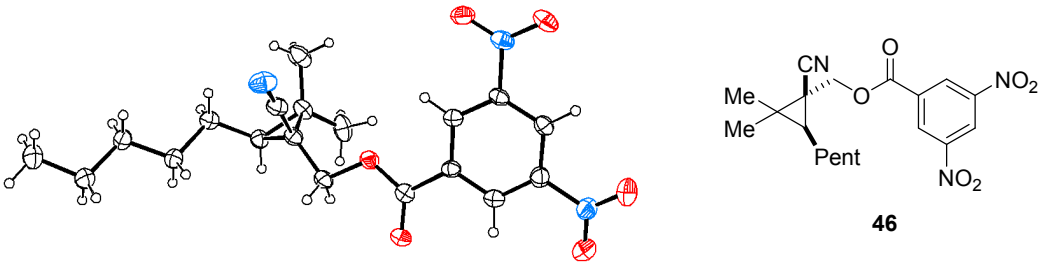
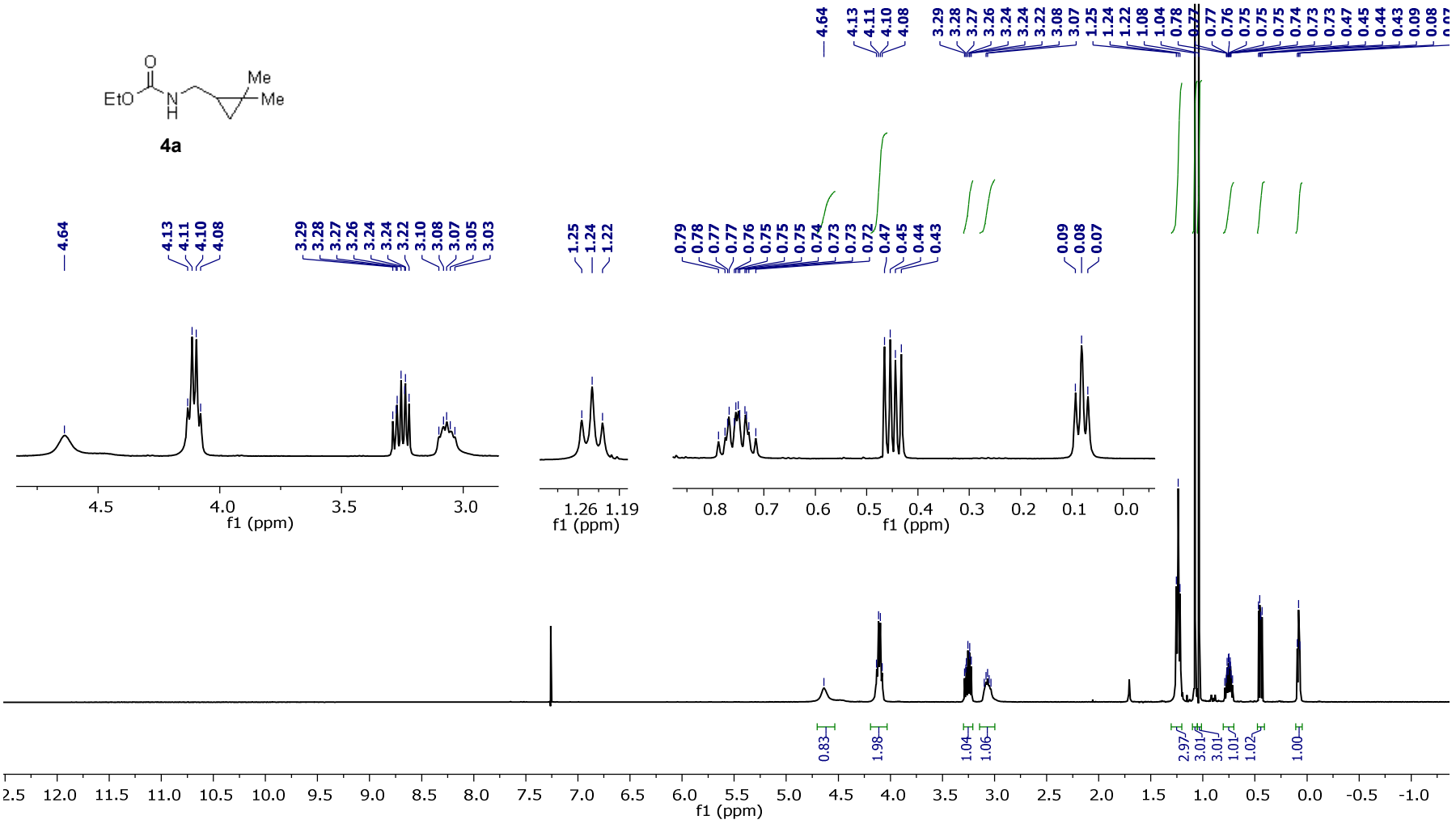
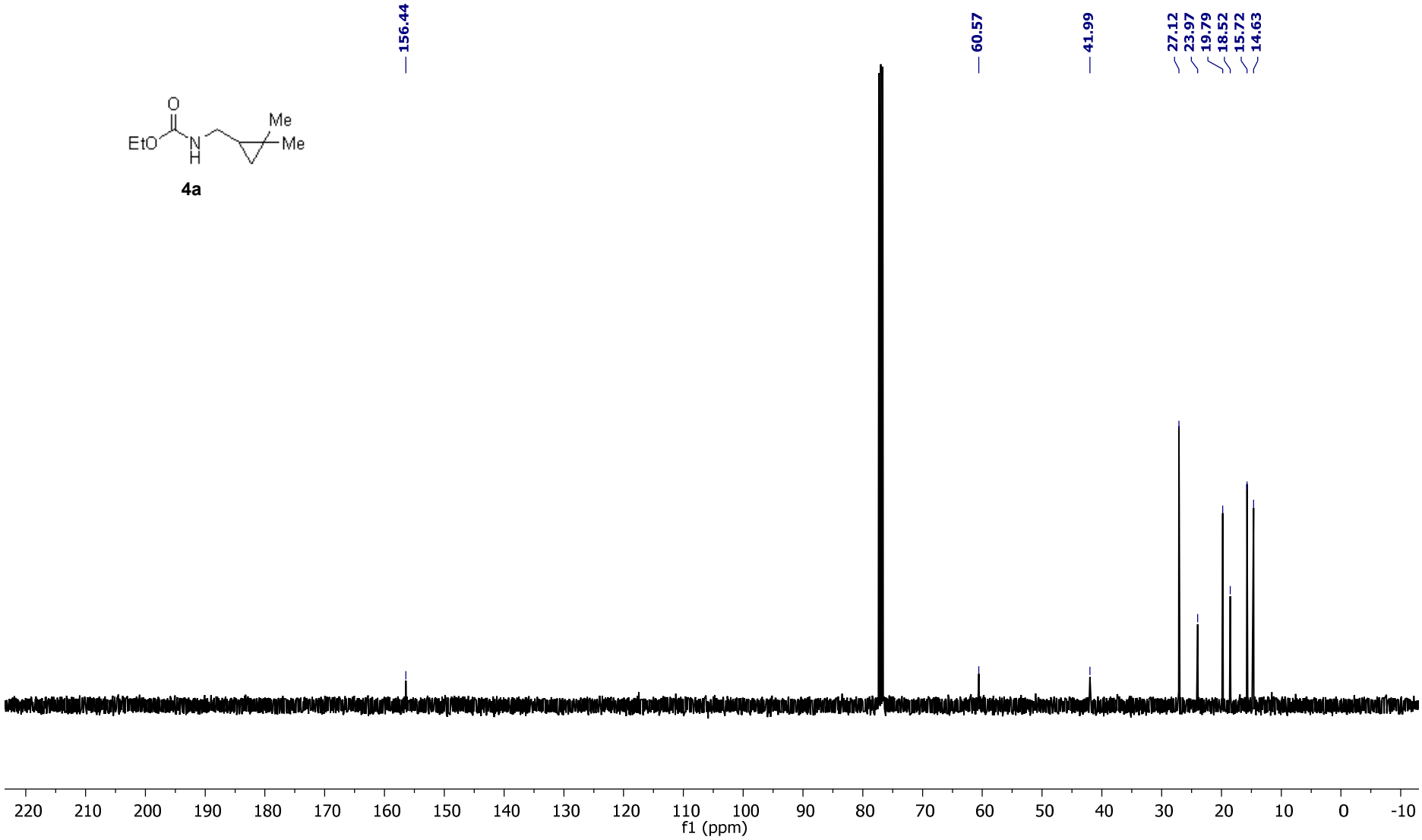


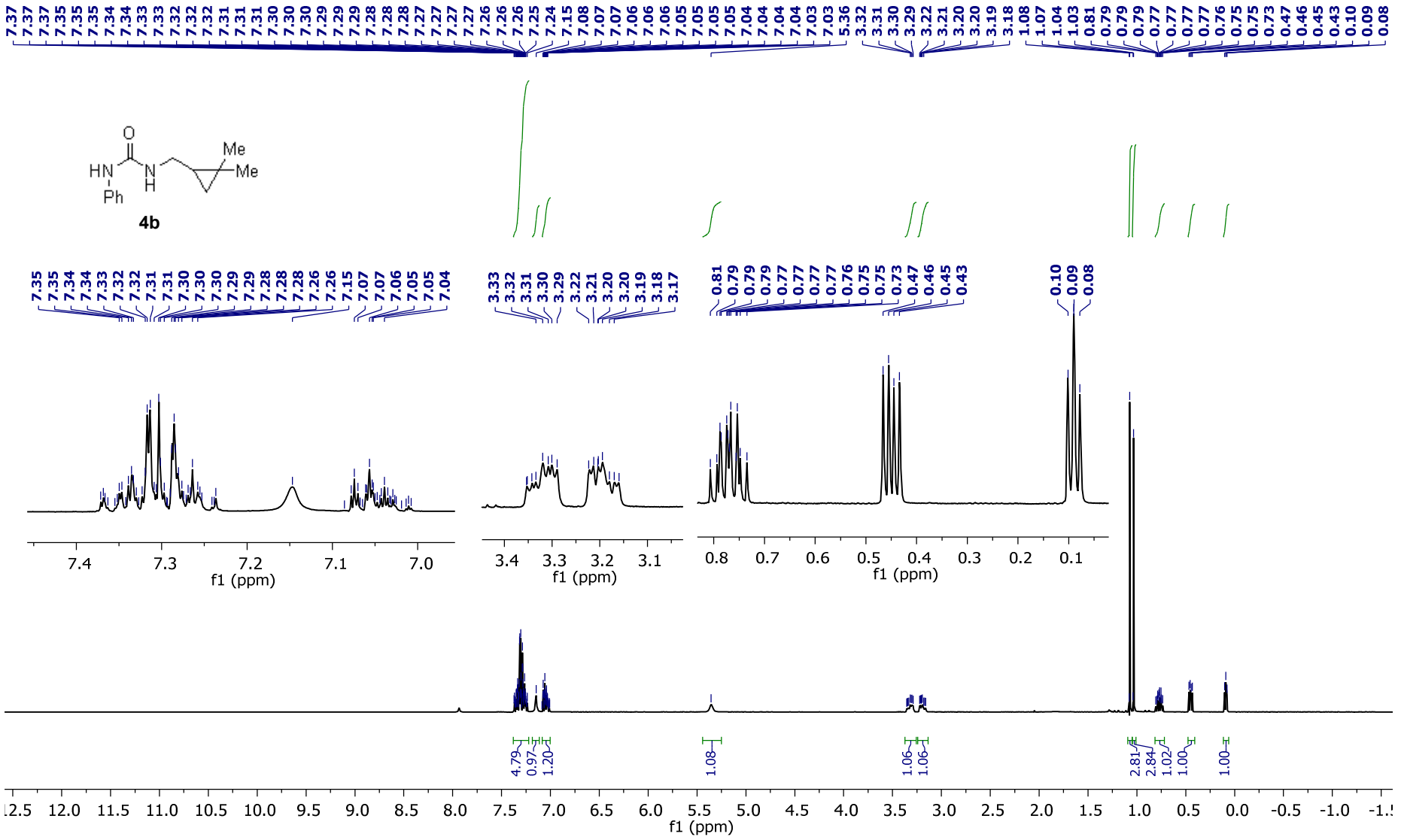
Figure S1 ORTEP diagram of derivatization product **46** (Displacement ellipsoid are drawn at 50% probability level)

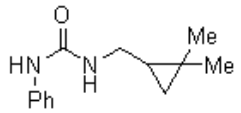
NMR data


4.64
4.13
4.11
4.10
4.08
3.29
3.28
3.27
3.26
3.24
3.24
3.22
3.08
3.07
1.25
1.24
1.22
1.08
1.04
0.78
0.77
0.76
0.75
0.75
0.74
0.73
0.73
0.47
0.45
0.44
0.43
0.09
0.08
0.07
f1 (ppm)

4a

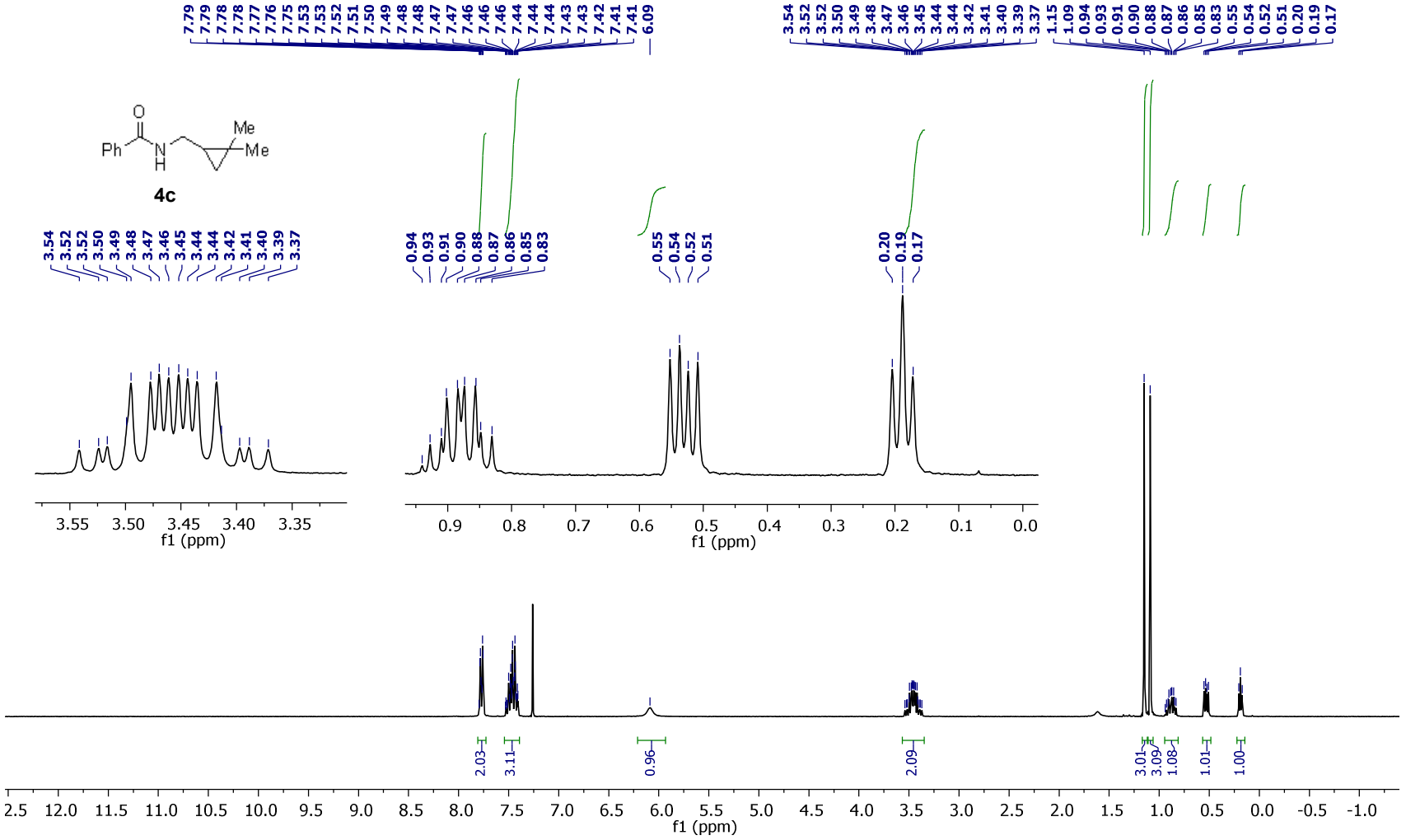

156.44
60.57
41.99
27.12
23.97
19.79
18.52
15.72
14.63
O
EtO
N
H
Me
Me
4a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

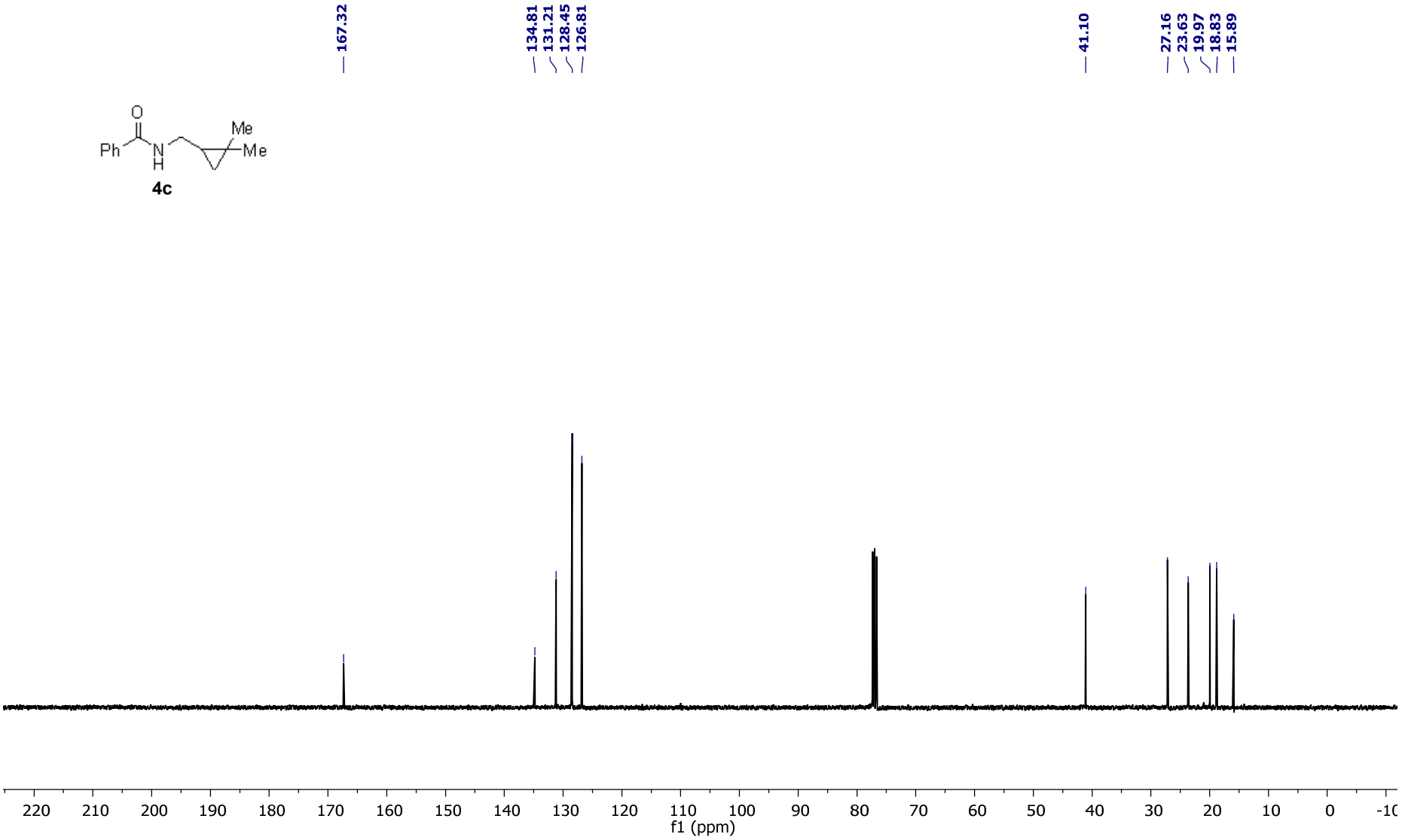

4b
f1 (ppm)

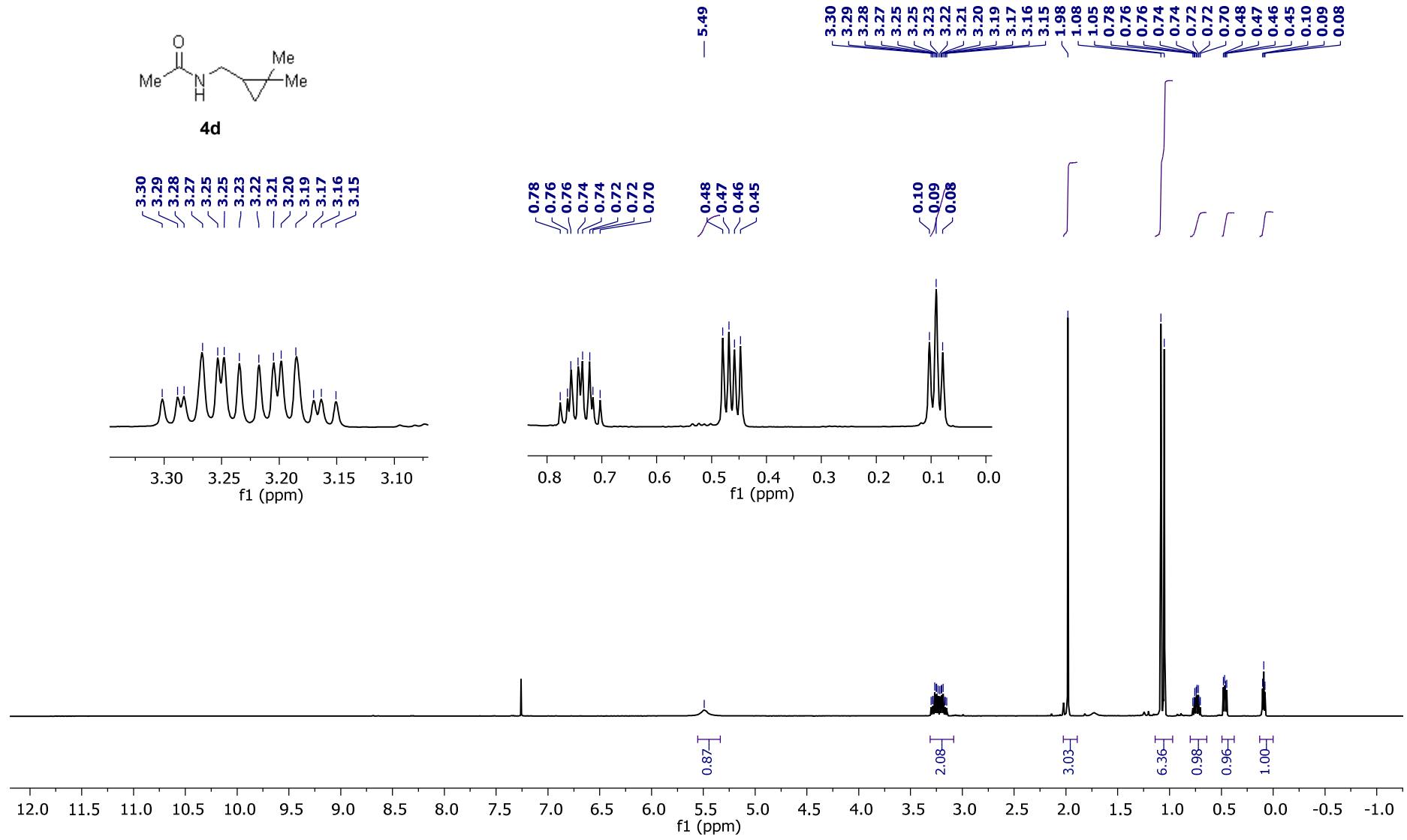

O
HN
Ph
N
H
Me
Me

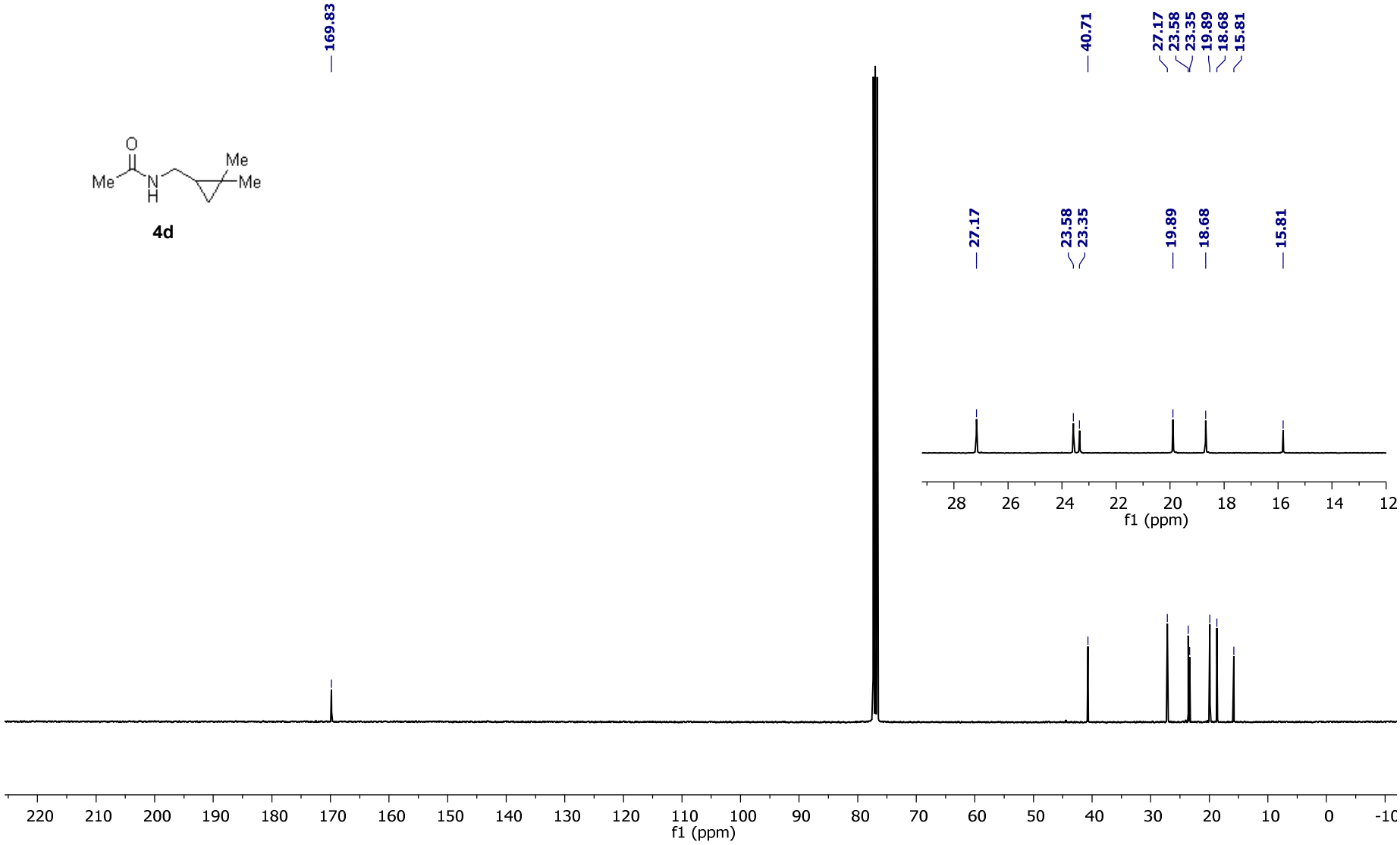
4b

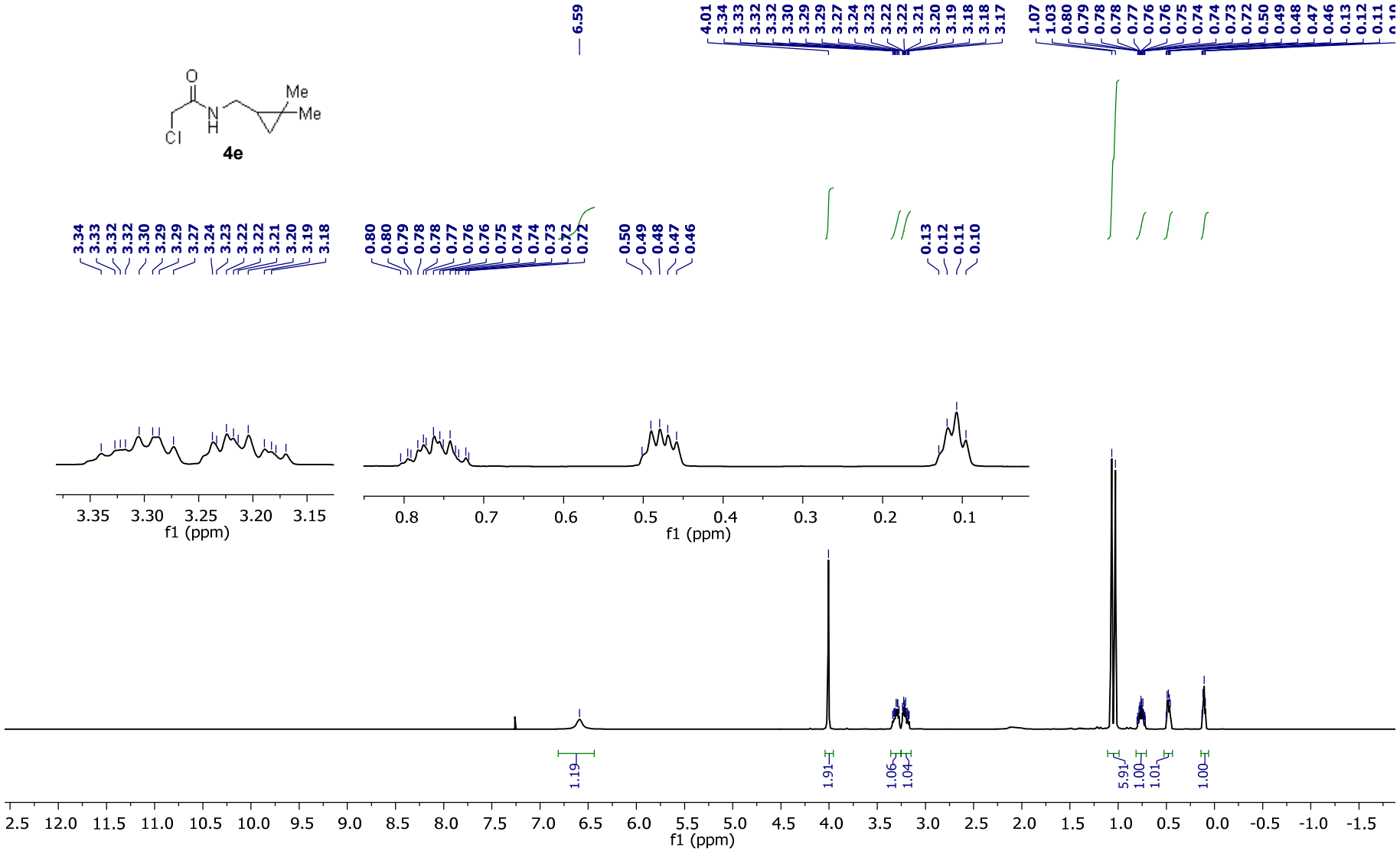
156.17
138.84
129.12
123.37
120.58
41.36
27.13
23.99
19.82
18.70
15.72
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

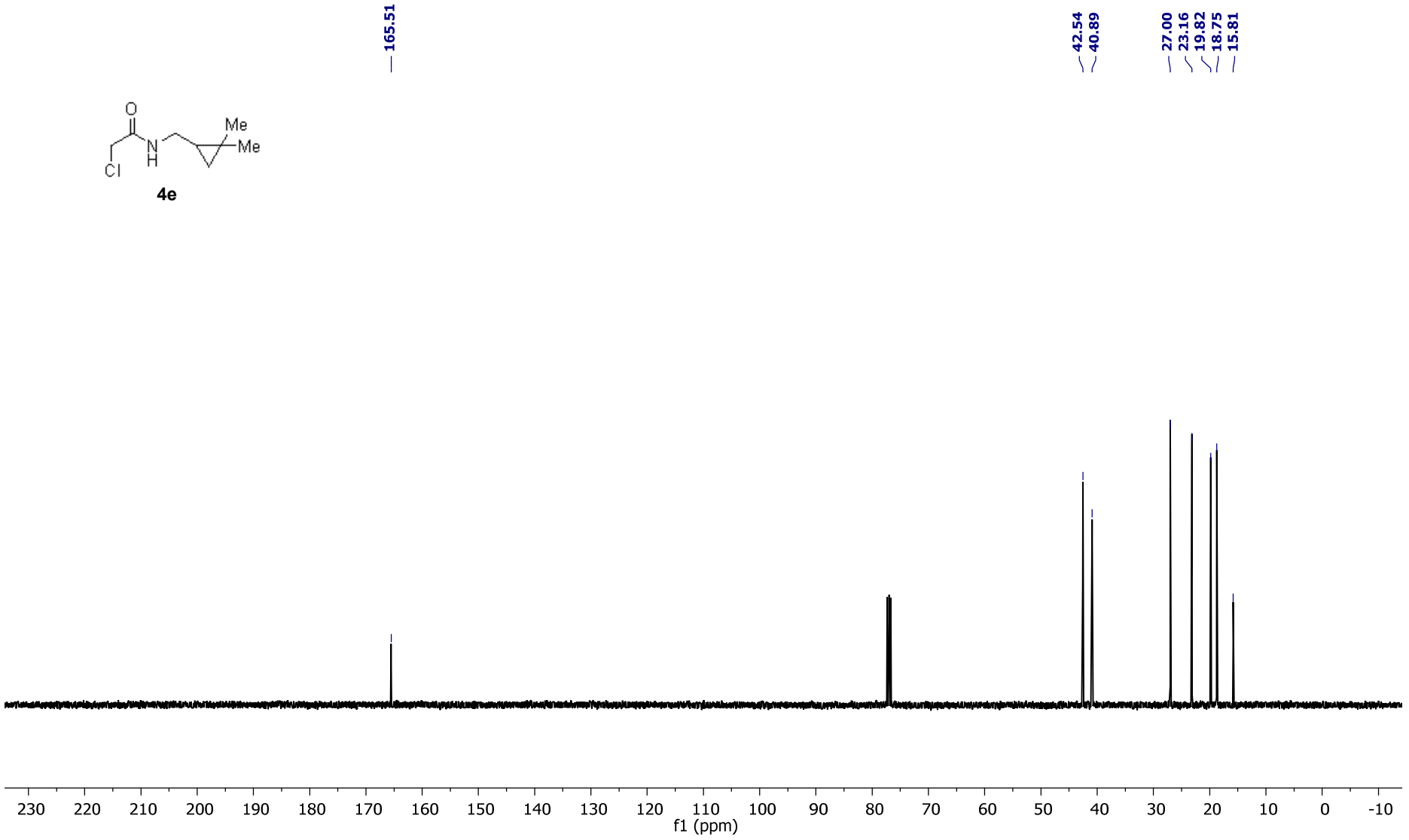

7.79 7.79 7.78 7.78 7.77 7.76 7.75 7.53 7.53 7.52 7.51 7.50 7.49 7.48 7.48 7.47 7.47 7.46 7.46 7.46 7.44 7.44 7.44 7.43 7.43 7.42 7.41 7.41 6.09
3.54 3.52 3.52 3.50 3.49 3.48 3.47 3.46 3.45 3.44 3.44 3.42 3.41 3.40 3.39 3.37
1.15 1.09 0.94 0.93 0.91 0.90 0.88 0.87 0.86 0.85 0.83 0.55 0.54 0.52 0.51 0.20 0.19 0.17
O
Ph
N
H
Me
Me
4c
f1 (ppm)
2.03
3.11
0.96
2.09
3.01
3.09
1.08
1.01
1.00


167.32
134.81
131.21
128.45
126.81
41.10
27.16
23.63
19.97
18.83
15.89
O
Ph
N
H
Me
Me
4c
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
Me
N
H
Me
Me
4d
5.49
3.30
3.29
3.28
3.27
3.25
3.25
3.23
3.22
3.21
3.20
3.19
3.17
3.16
3.15
1.98
1.08
1.05
0.78
0.76
0.76
0.74
0.74
0.72
0.72
0.70
0.48
0.47
0.46
0.45
0.10
0.09
0.08
3.30 3.25 3.20 3.15 3.10
f1 (ppm)
0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
f1 (ppm)
0.87
2.08
3.03
6.36
0.98
0.96
1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


169.83
40.71
27.17
23.58
23.35
19.89
18.68
15.81
O
Me
N
H
Me
Me
4d
f1 (ppm)
f1 (ppm)


4e
Me
Me
Cl
f1 (ppm)
f1 (ppm)
f1 (ppm)


165.51
42.54
40.89
27.00
23.16
19.82
18.75
15.81
O
N
H
Cl
Me
Me
4e
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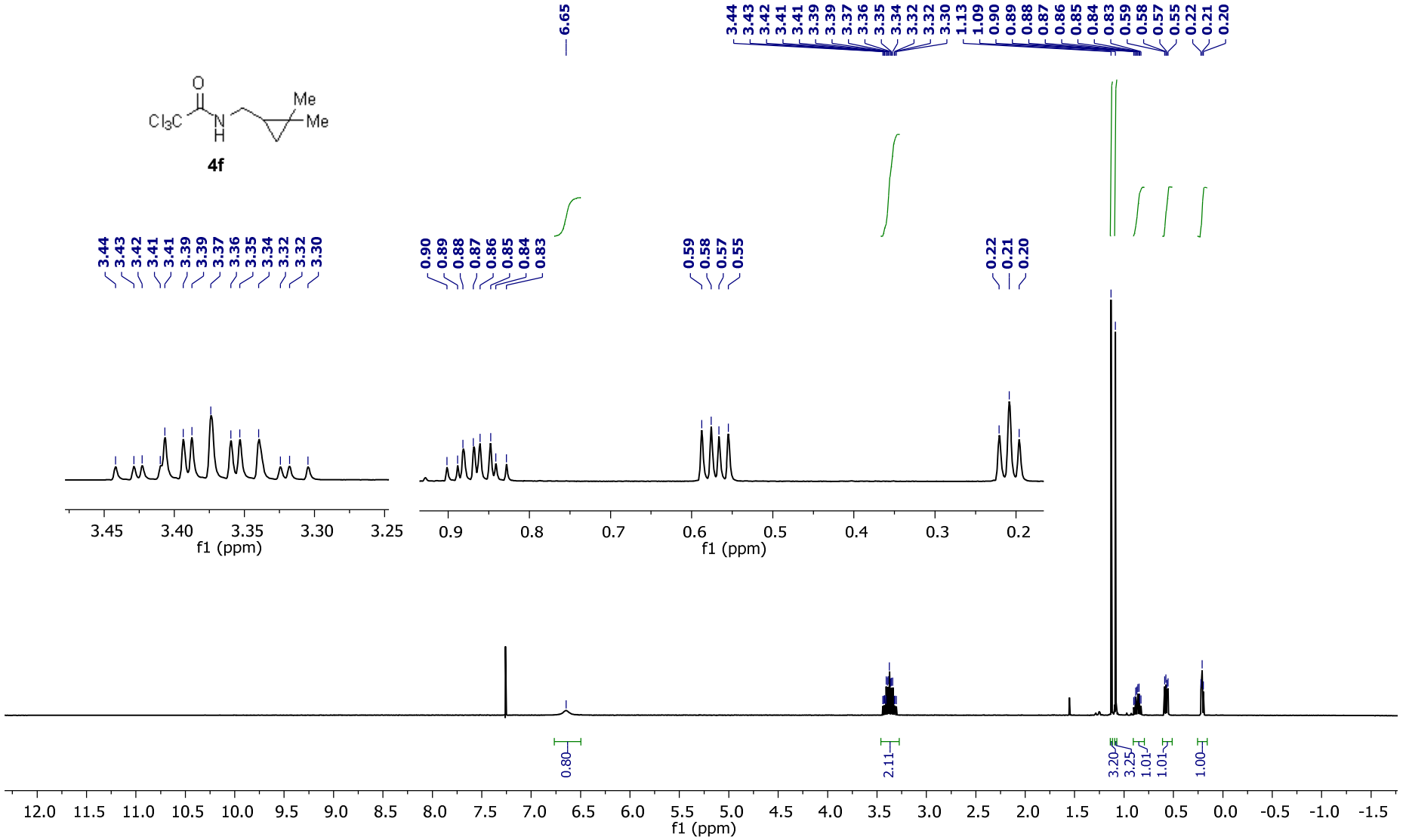
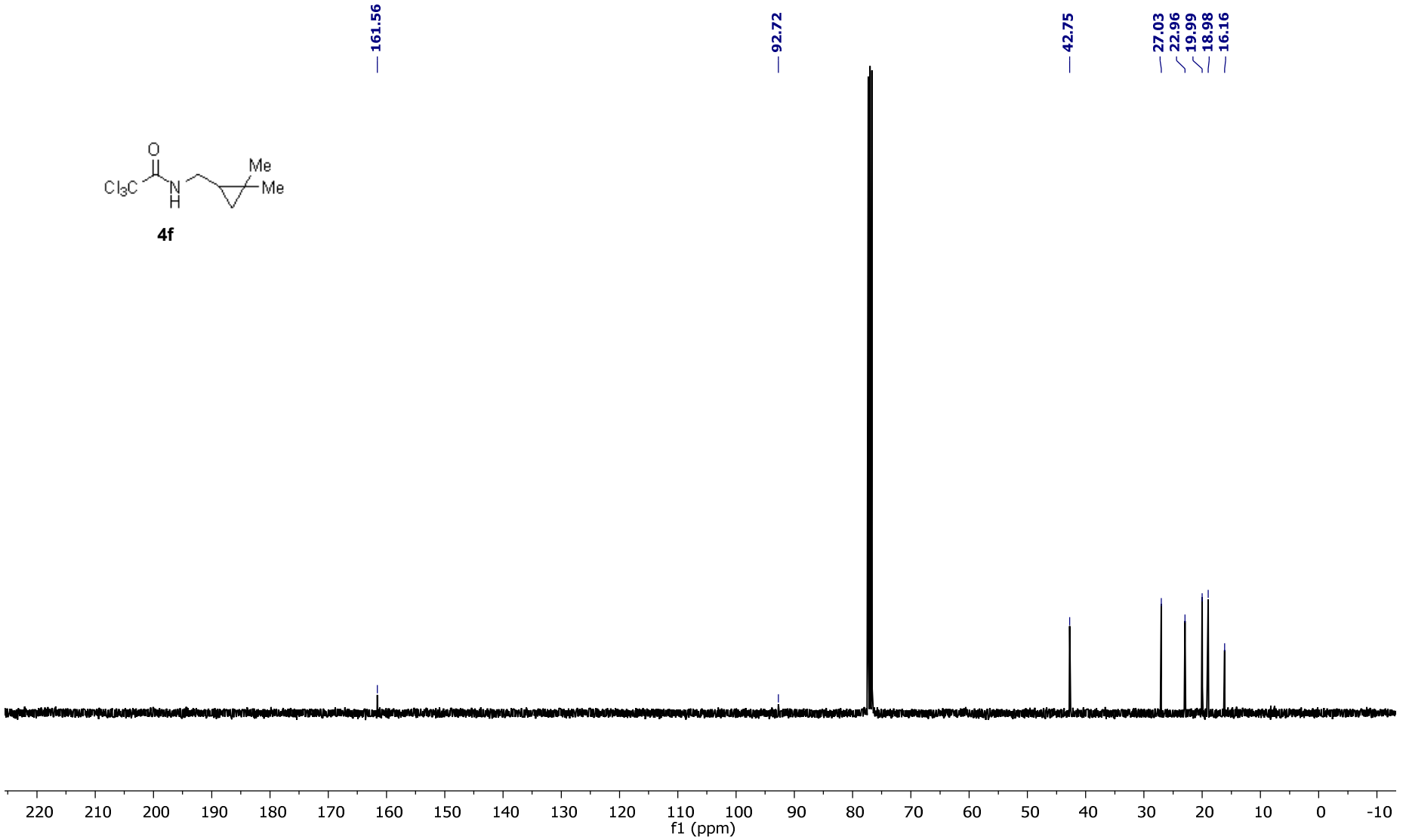
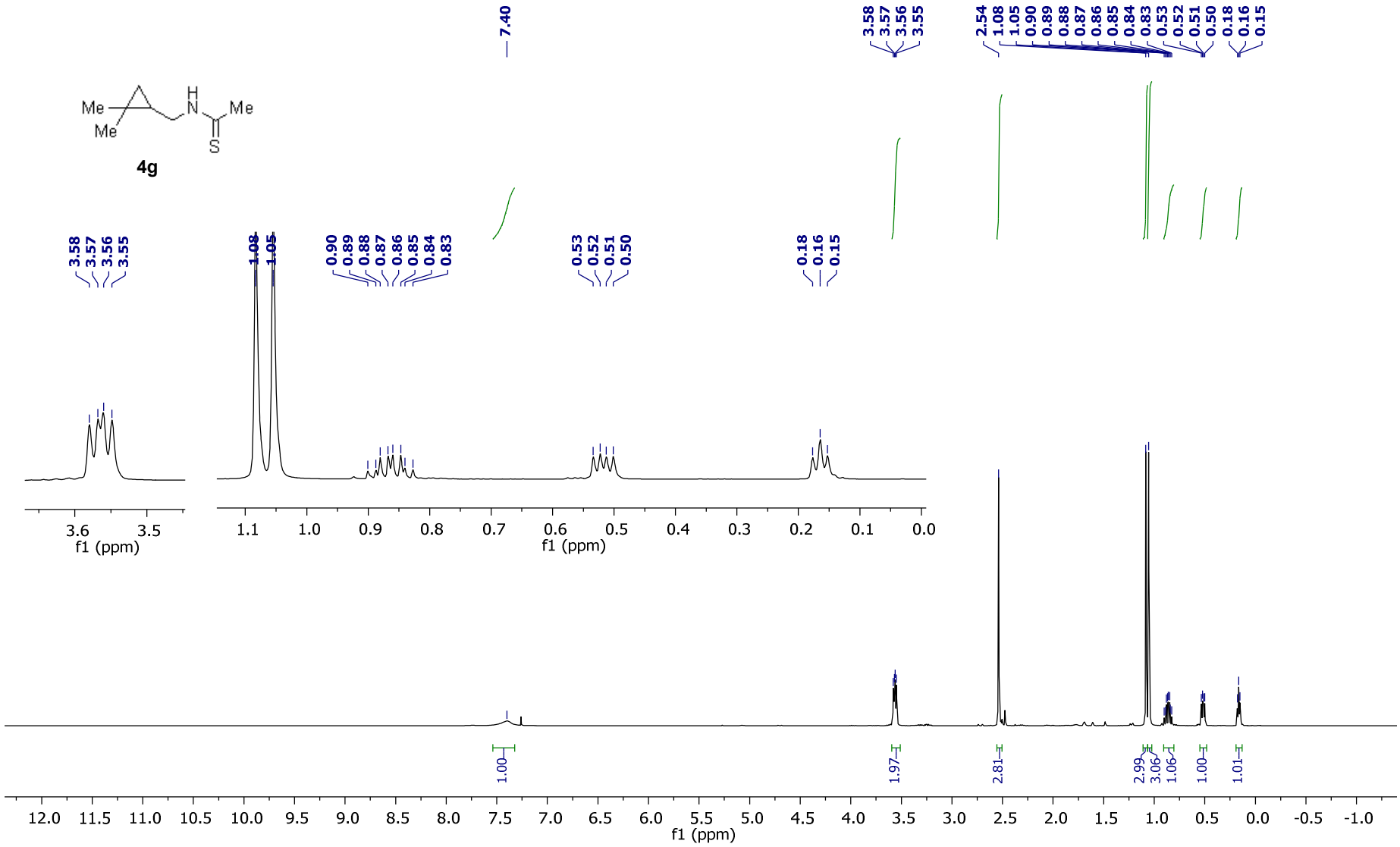
f1 (ppm)


6.65
3.44 3.43 3.42 3.41 3.41 3.39 3.39 3.37 3.36 3.35 3.34 3.32 3.32 3.30
1.13 1.09 0.90 0.89 0.88 0.87 0.86 0.85 0.84 0.83 0.59 0.58 0.57 0.55 0.22 0.21 0.20
O
Cl3C
N
H
Me
Me
4f
f1 (ppm)
0.80
2.11
3.20
3.25
1.01
1.01
1.00


161.56
92.72
42.75
27.03
22.96
19.99
18.98
16.16
O
Cl3C
N
H
Me
Me
4f
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
Me
H
N
Me
S
4g
7.40
3.58
3.57
3.56
3.55
2.54
1.08
1.05
0.90
0.89
0.88
0.87
0.86
0.85
0.84
0.83
0.53
0.52
0.51
0.50
0.18
0.16
0.15
f1 (ppm)
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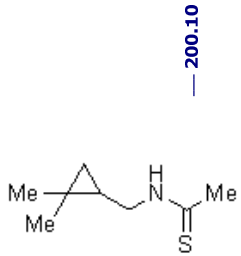
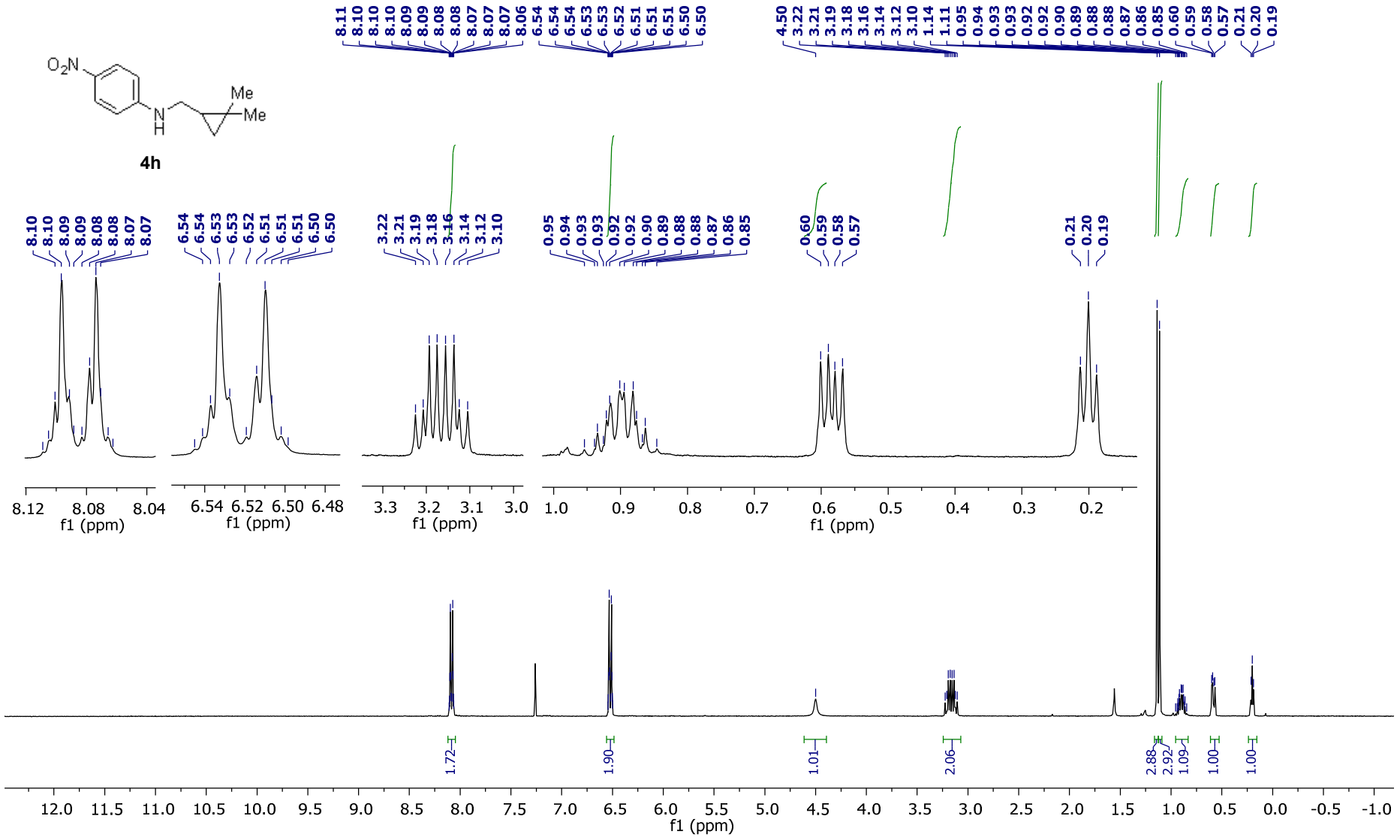
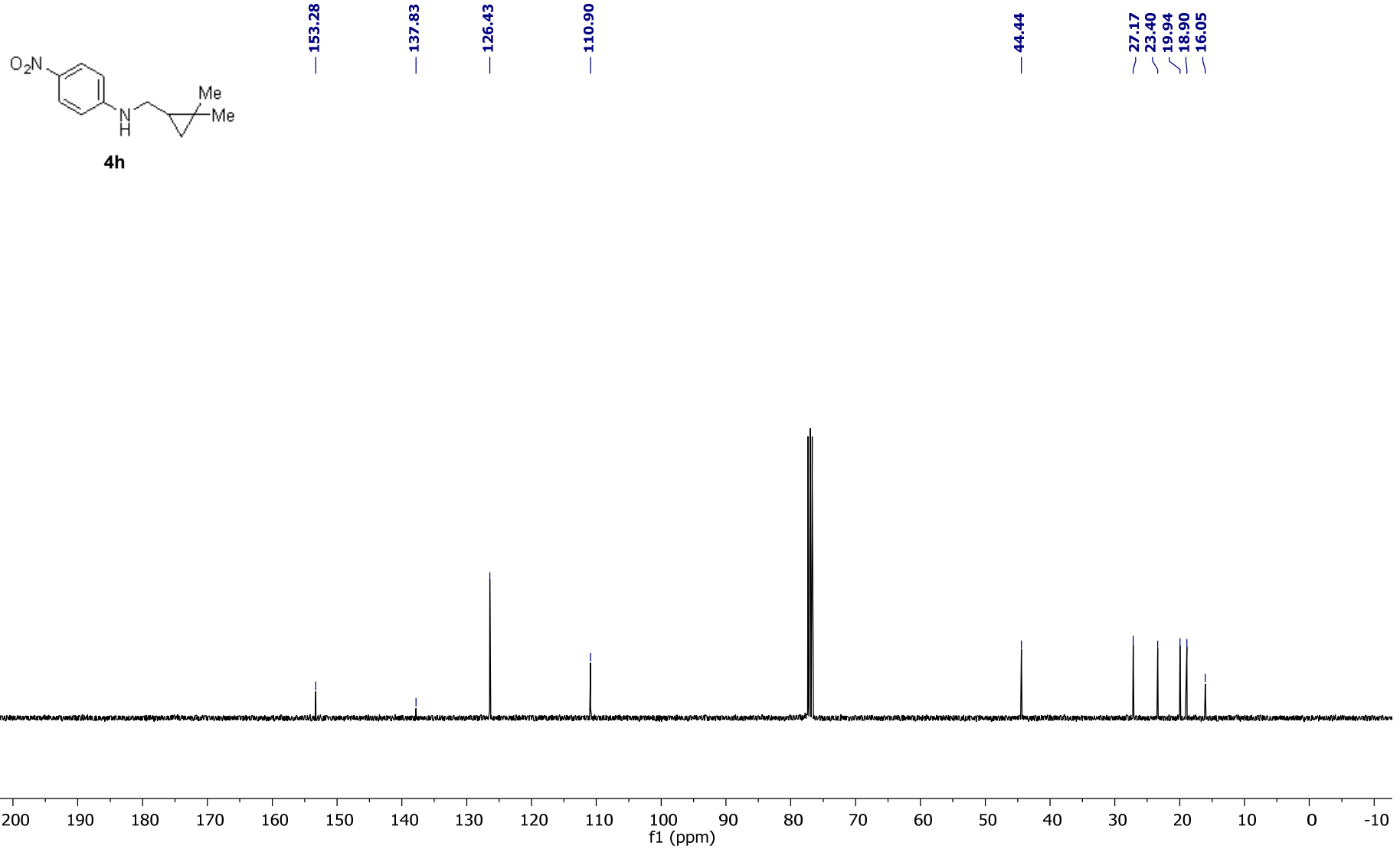
1.97
2.81
2.99
3.06
1.06
1.00
1.01

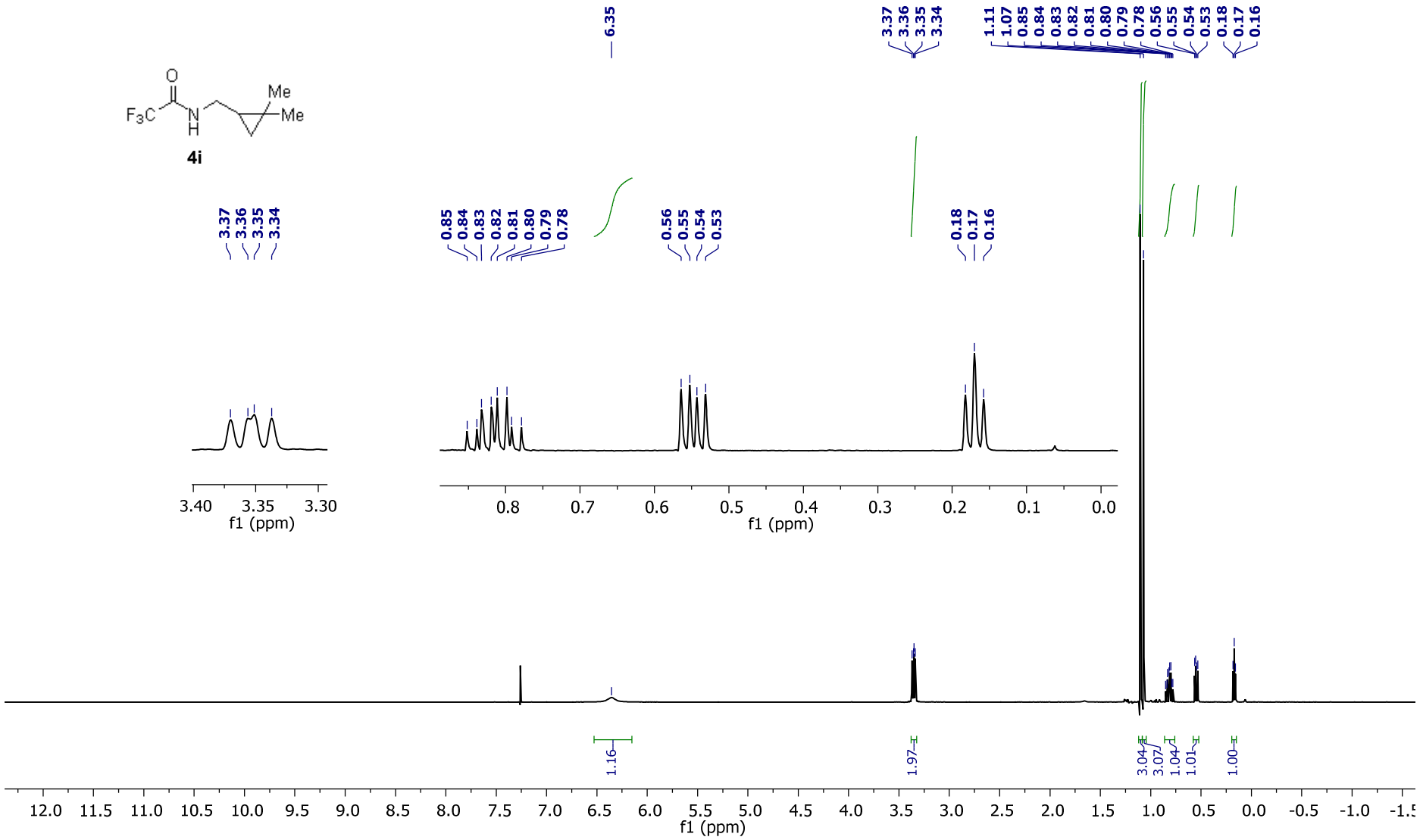

Me
Me
H
N
Me
S

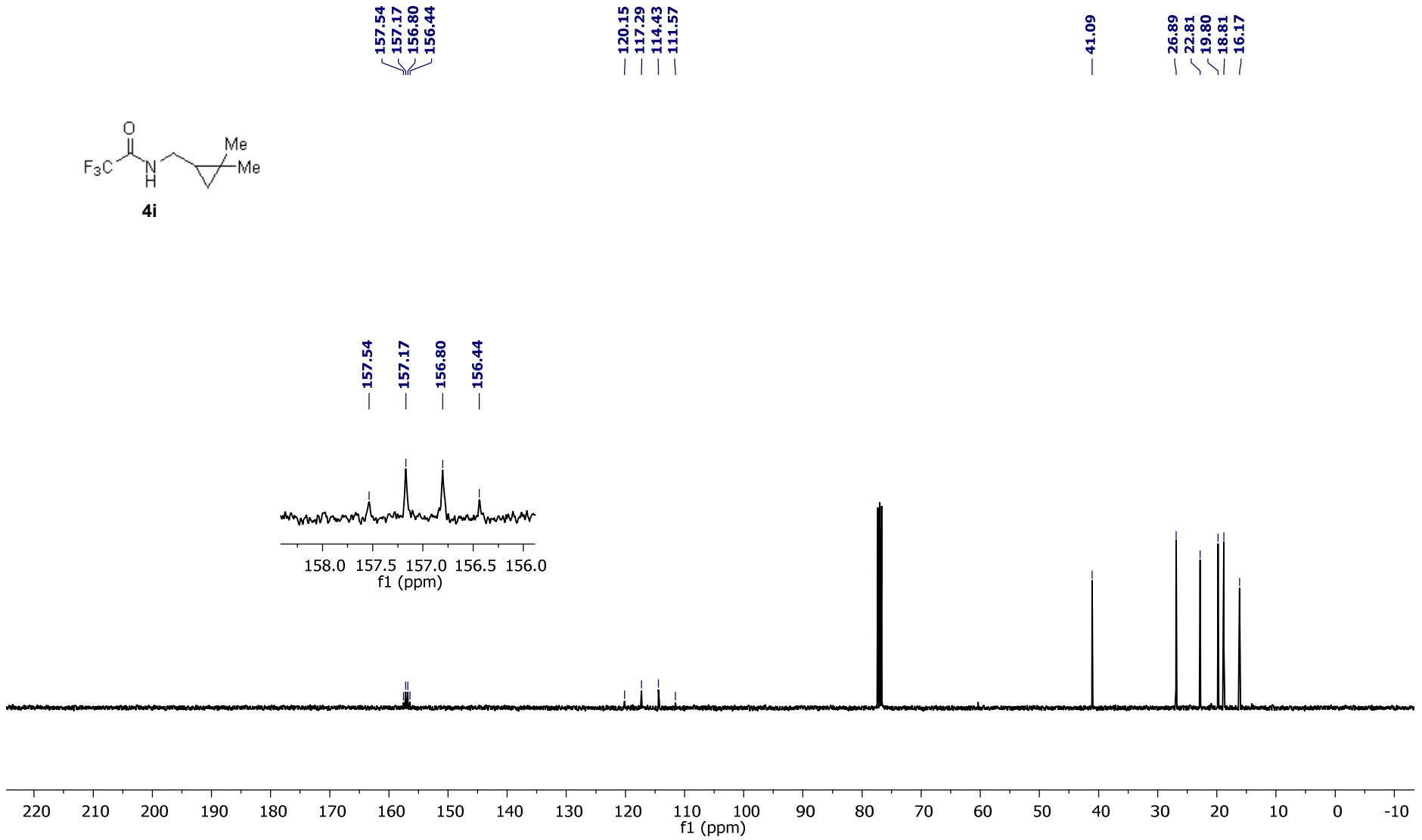
4g

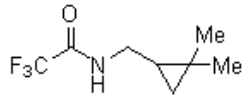
200.10
47.72
34.08
26.94
22.17
19.94
18.78
16.12
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O2N
N
H
Me
Me
4h
f1 (ppm)


O2N
N
H
Me
Me
4h
153.28
137.83
126.43
110.90
44.44
27.17
23.40
19.94
18.90
16.05
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

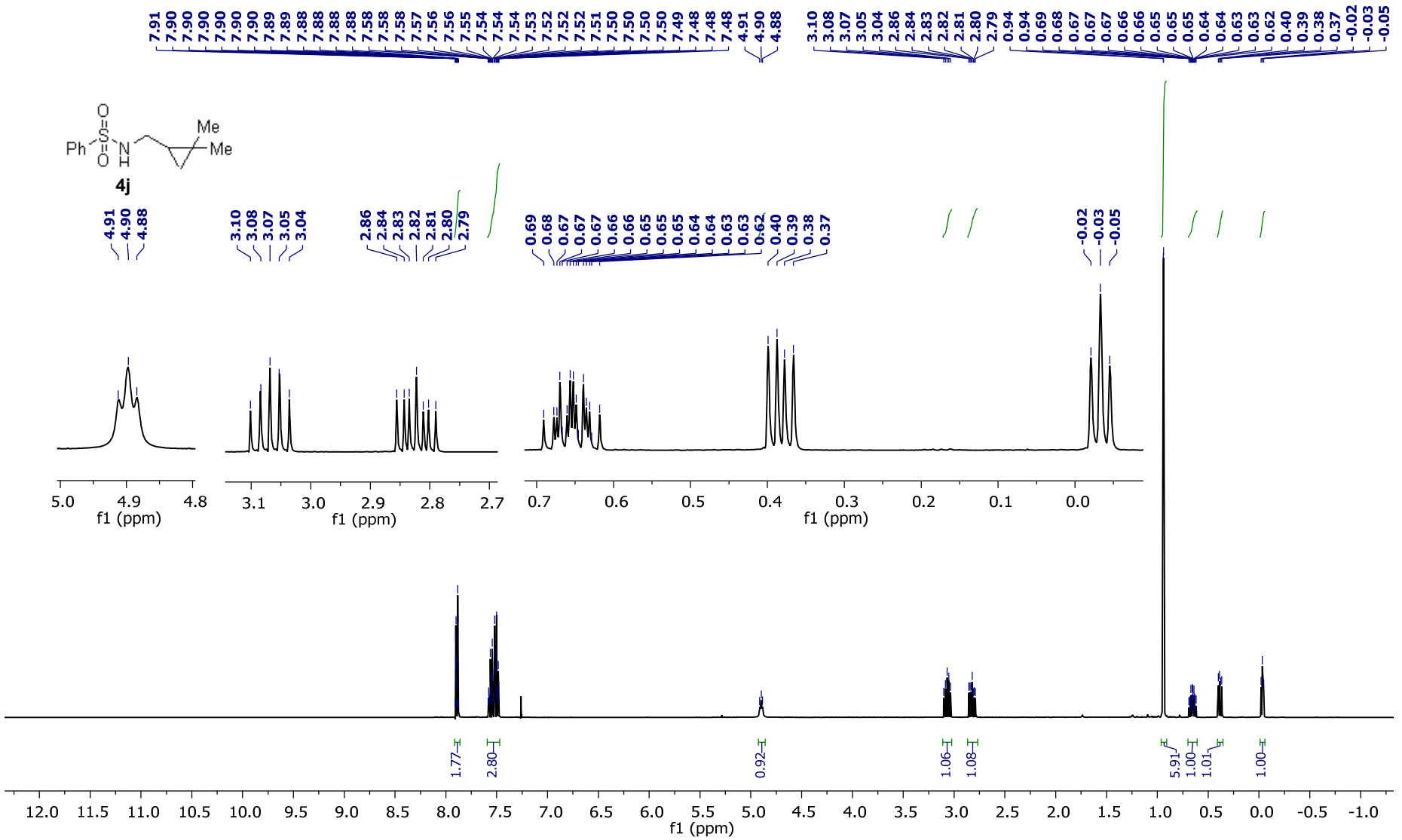

O
F3C
N
H
Me
Me
4i
6.35
3.37
3.36
3.35
3.34
1.11
1.07
0.85
0.84
0.83
0.82
0.81
0.80
0.79
0.78
0.56
0.55
0.54
0.53
0.18
0.17
0.16
3.40 3.35 3.30
f1 (ppm)
0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
f1 (ppm)
1.16
1.97
3.04
3.07
1.04
1.01
1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

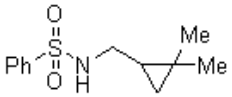

157.54
157.17
156.80
156.44
120.15
117.29
114.43
111.57
41.09
26.89
22.81
19.80
18.81
16.17
O
F3C
N
H
Me
Me
4i
158.0 157.5 157.0 156.5 156.0
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
F3C
N
H
Me
Me

4i

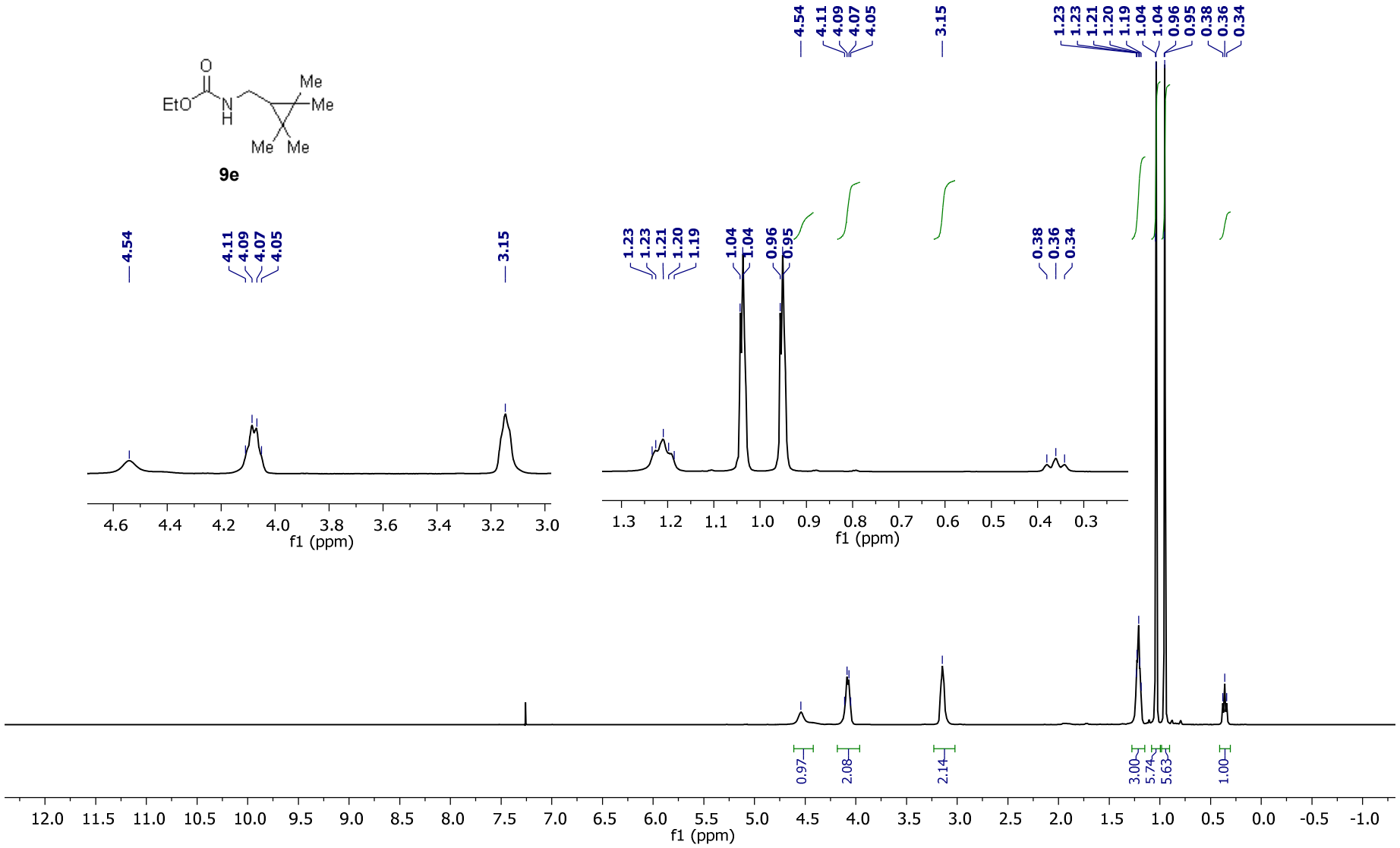
-76.08
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
f1 (ppm)

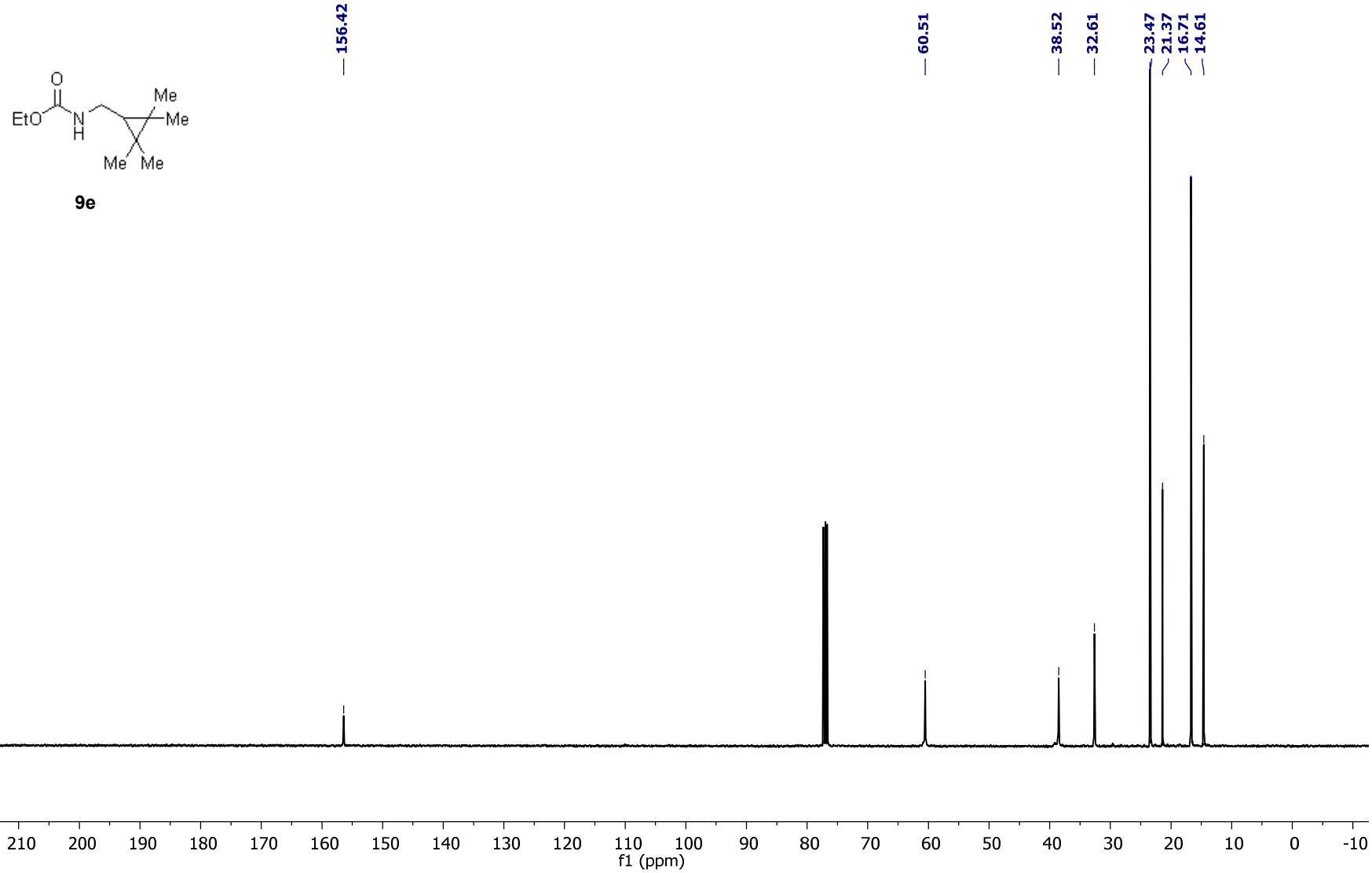

4j
f1 (ppm)


O
Ph
S
O
N
H
Me
Me

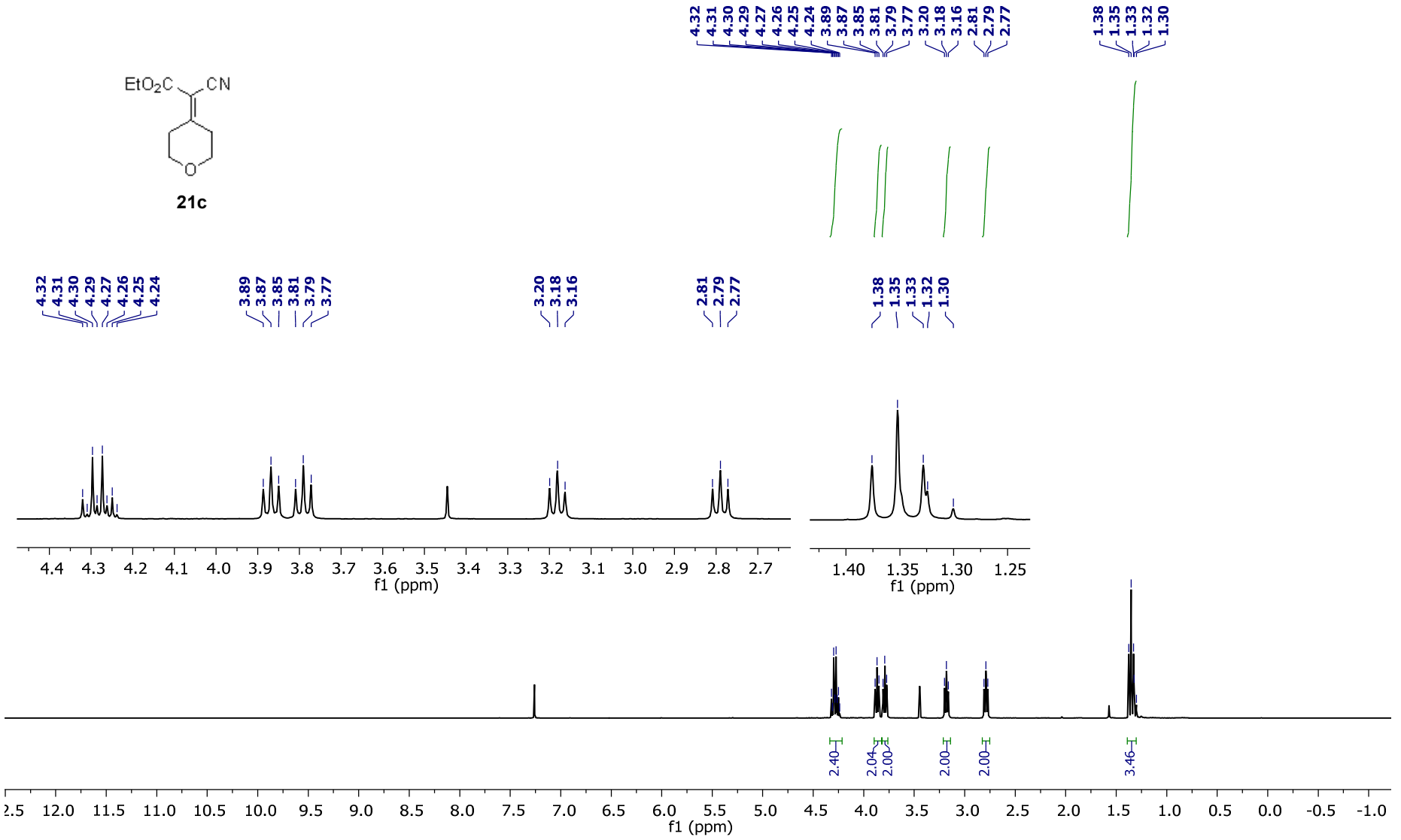
4j

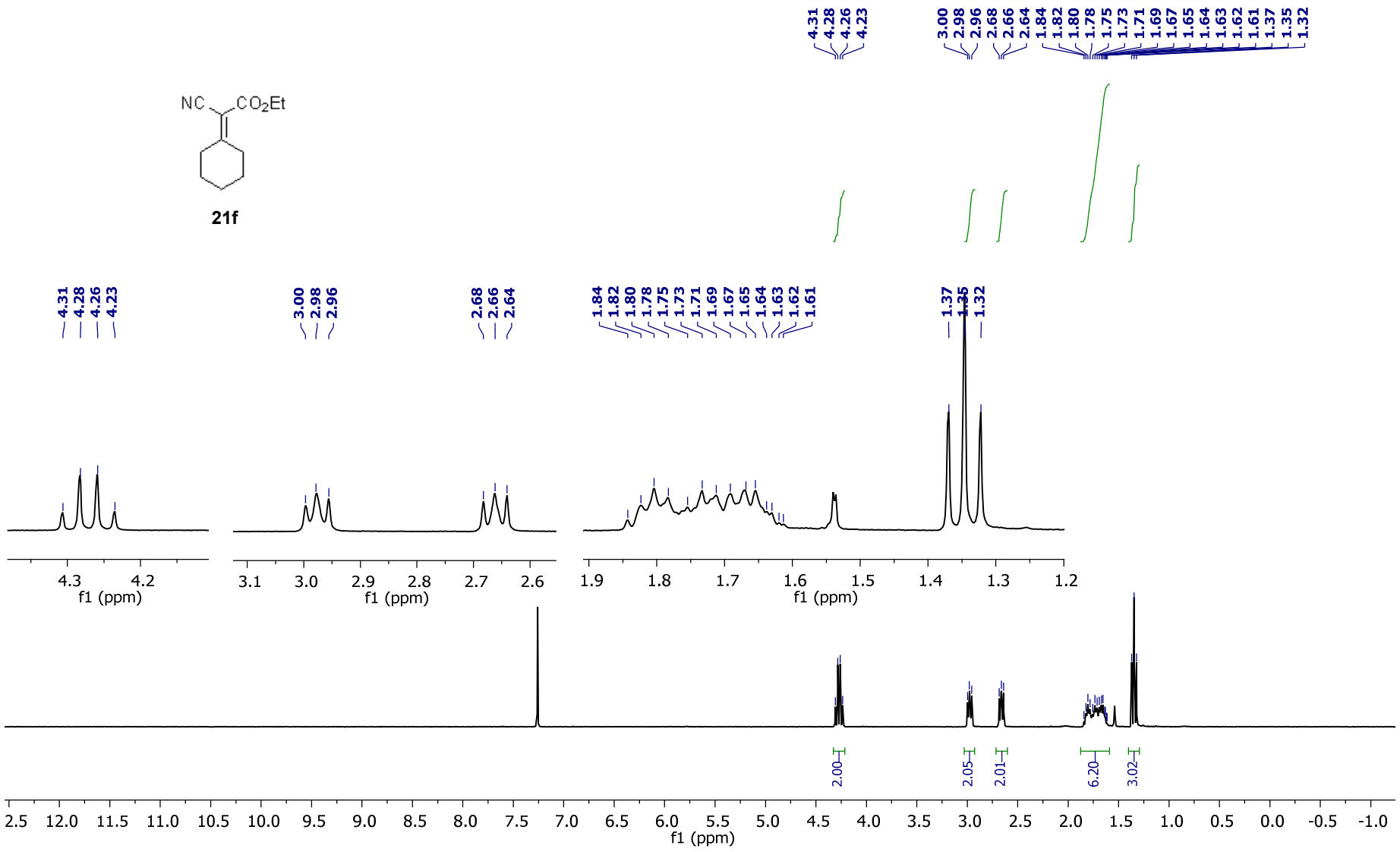
139.97
132.47
128.99
127.01
44.47
26.78
23.32
19.47
18.58
15.98
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

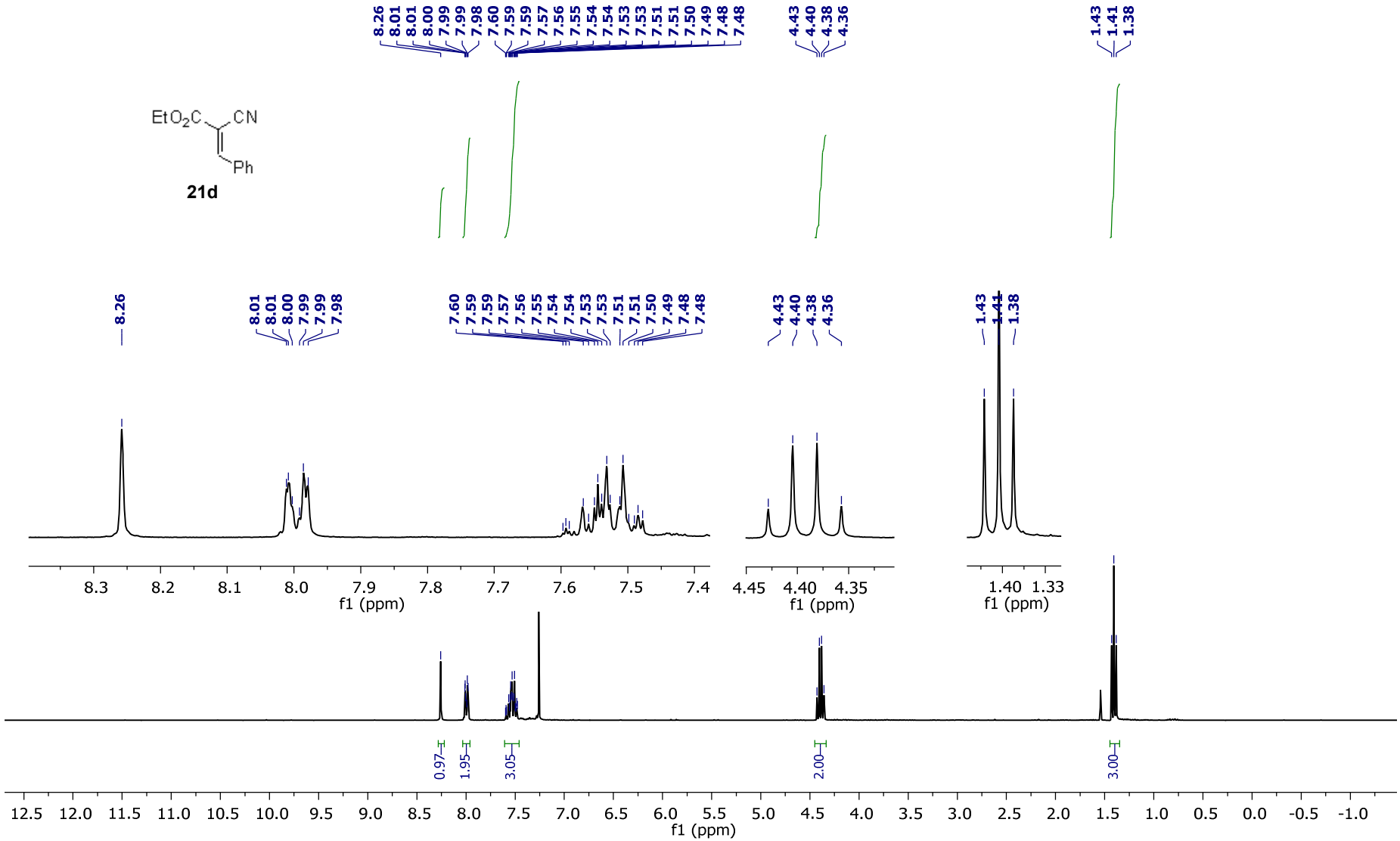

O
EtO
N
H
Me
Me
Me
Me
9e
4.54
4.11
4.09
4.07
4.05
3.15
1.23
1.23
1.21
1.20
1.19
1.04
1.04
0.96
0.95
0.38
0.36
0.34
f1 (ppm)
0.97
2.08
2.14
3.00
5.74
5.63
1.00

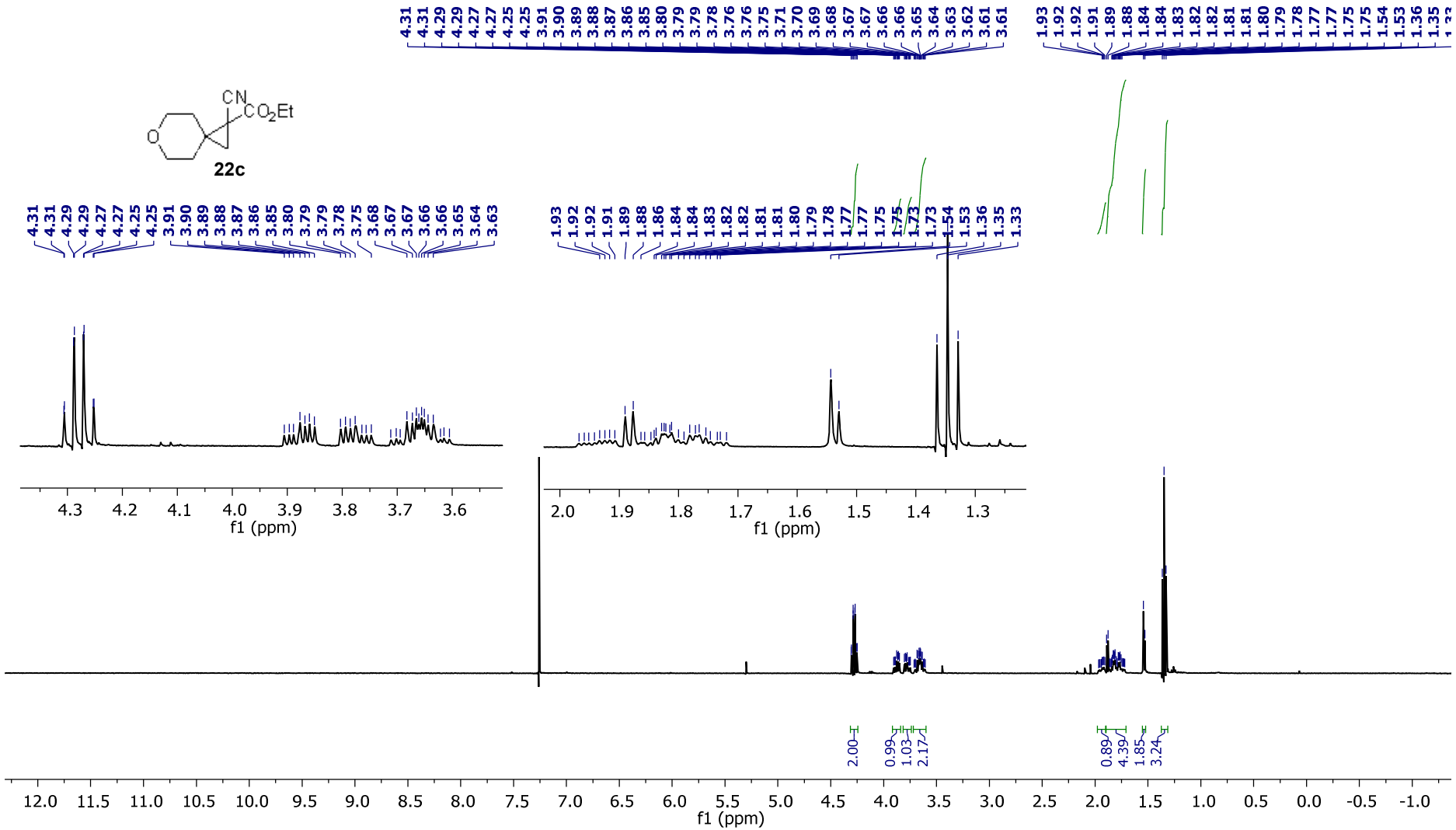

156.42
60.51
38.52
32.61
23.47
21.37
16.71
14.61
O
EtO
N
H
Me
Me
Me
Me
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

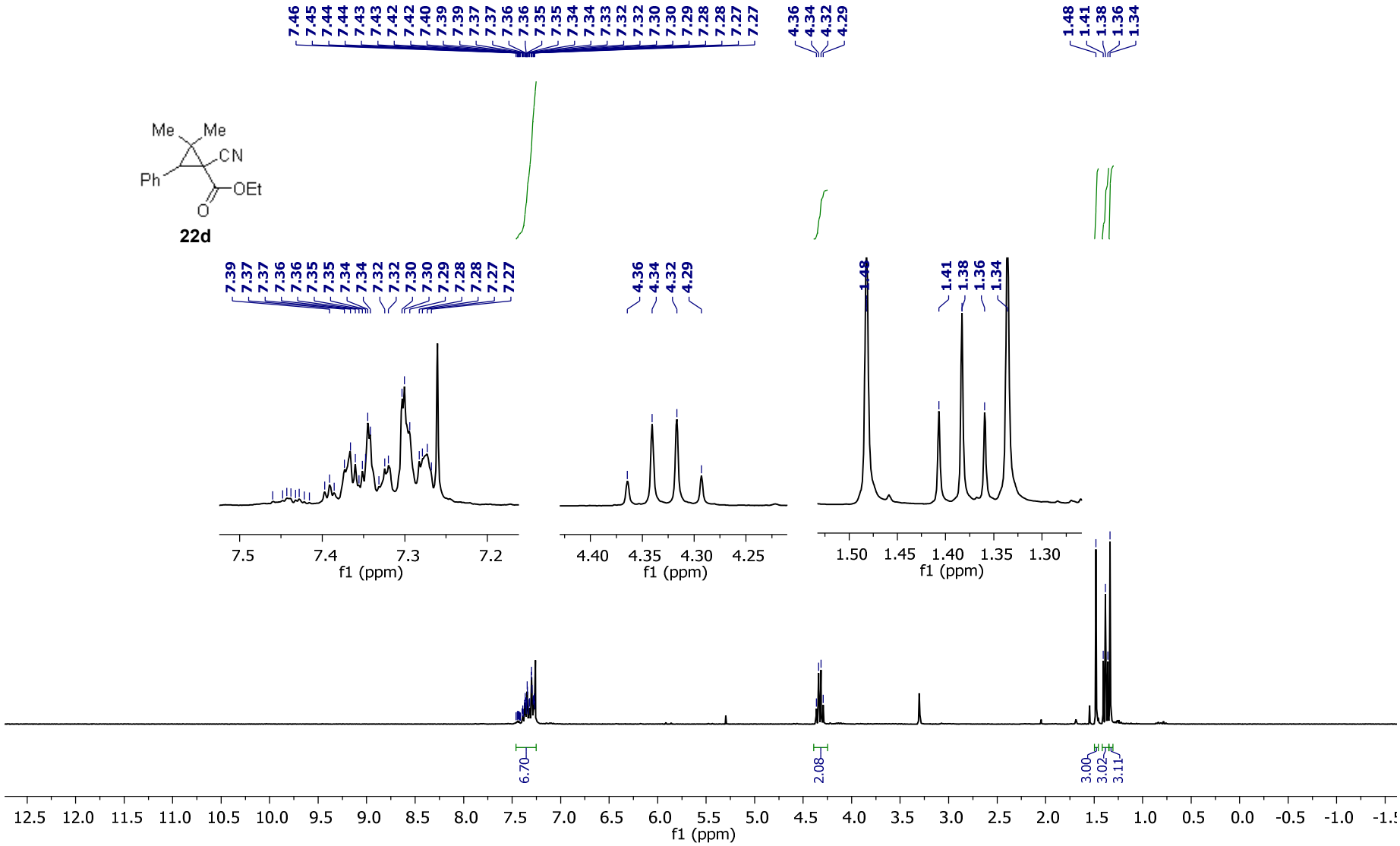
9e

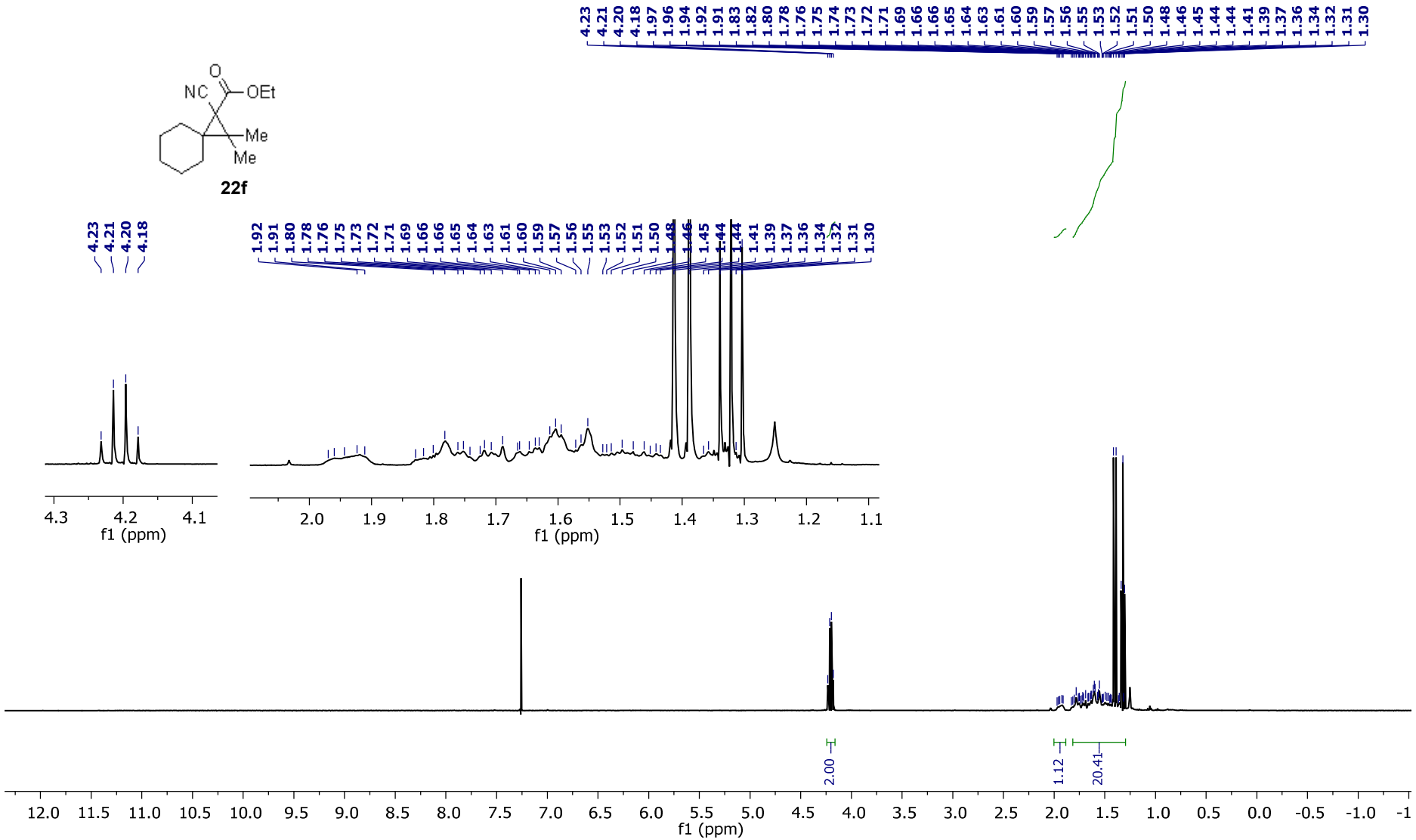

EtO2C
CN
O
21c
4.32
4.31
4.30
4.29
4.27
4.26
4.25
4.24
3.89
3.87
3.85
3.81
3.79
3.77
3.20
3.18
3.16
2.81
2.79
2.77
1.38
1.35
1.33
1.32
1.30
f1 (ppm)
2.40
2.04
2.00
2.00
2.00
3.46

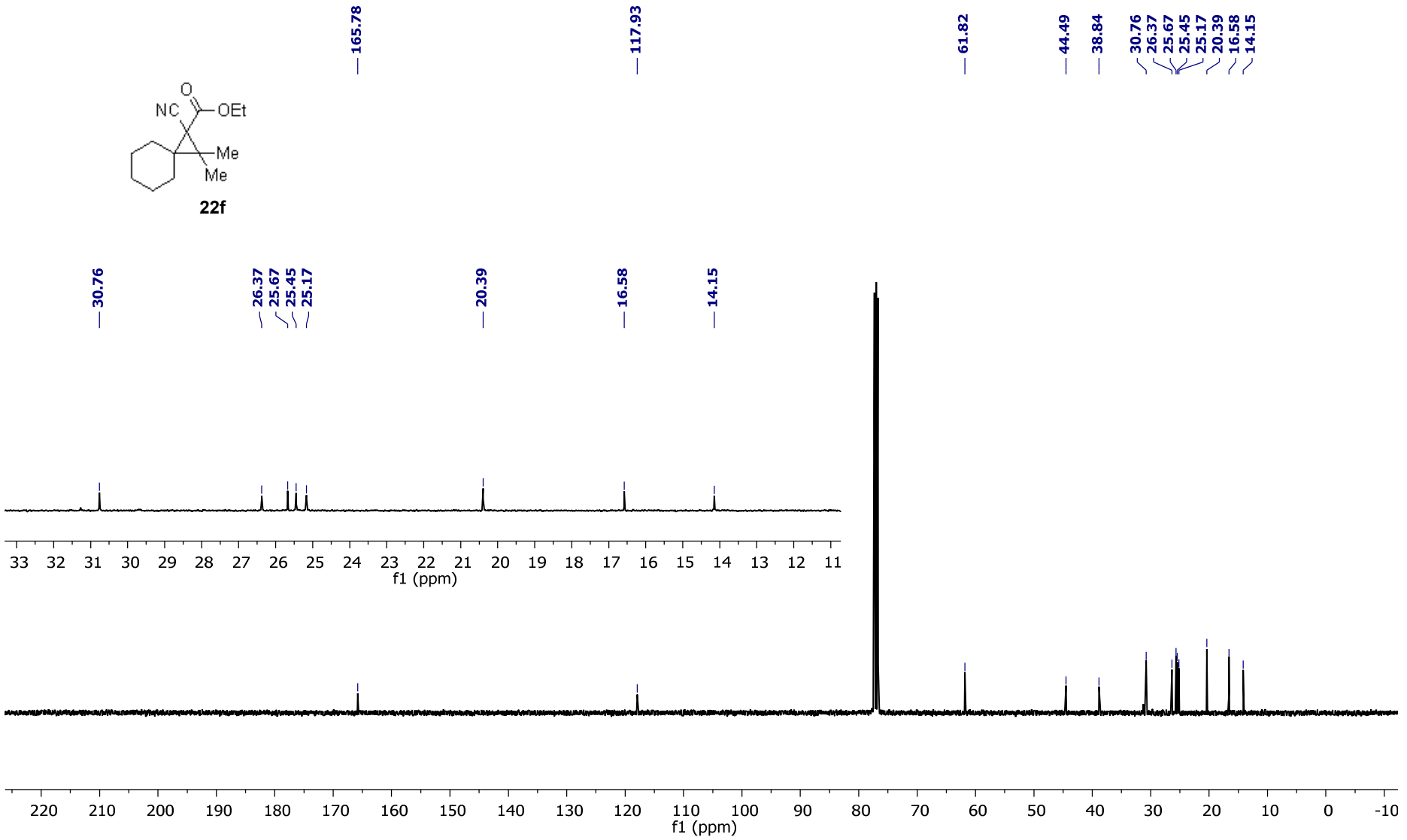

NC
CO2Et
21f
4.31
4.28
4.26
4.23
3.00
2.98
2.96
2.68
2.66
2.64
1.84
1.82
1.80
1.78
1.75
1.73
1.71
1.69
1.67
1.65
1.64
1.63
1.62
1.61
1.37
1.35
1.32
f1 (ppm)
2.00
2.05
2.01
6.20
3.02

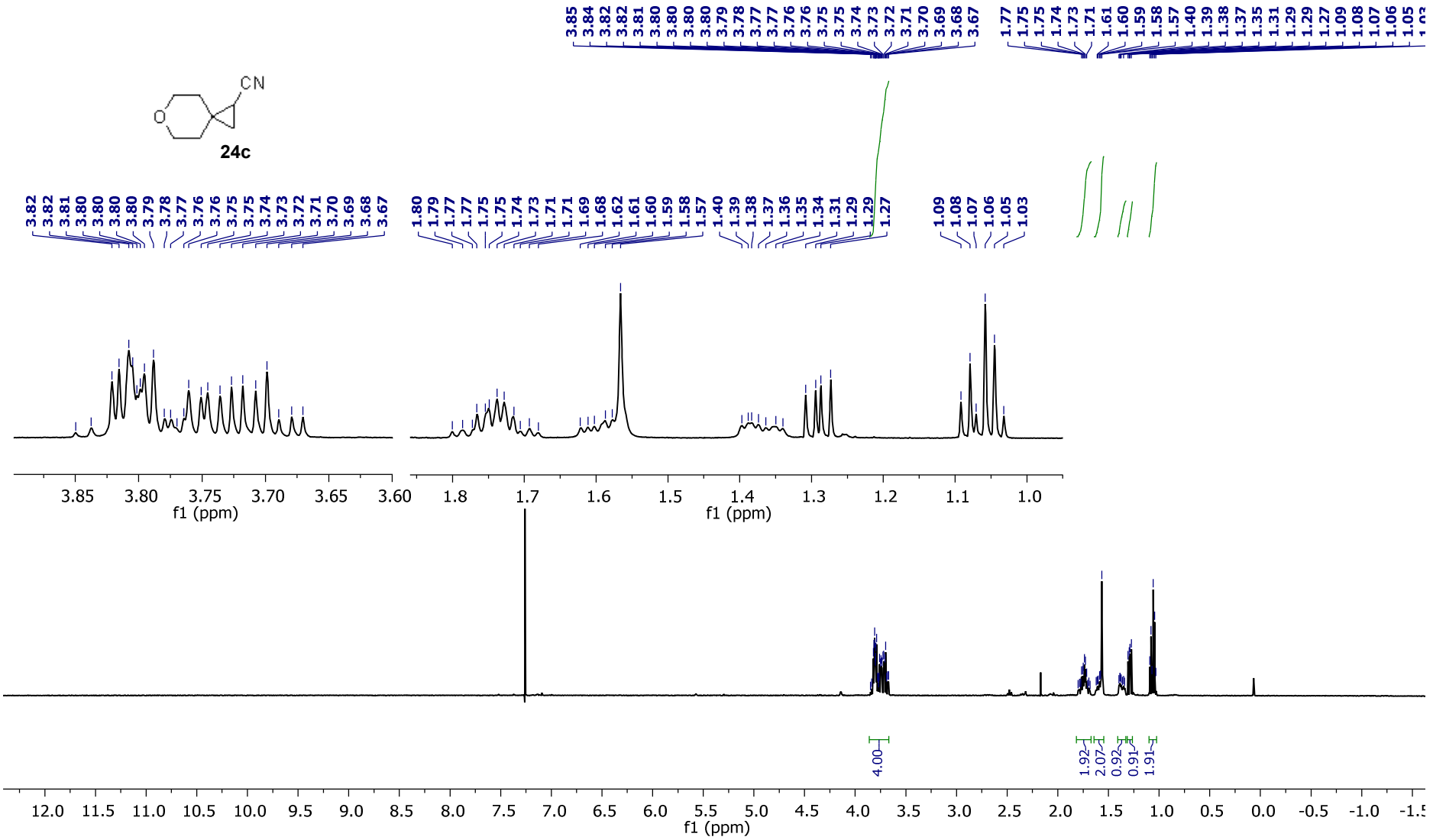

8.26
8.01
8.01
8.00
7.99
7.99
7.98
7.60
7.59
7.59
7.57
7.56
7.55
7.54
7.54
7.53
7.53
7.51
7.51
7.50
7.49
7.48
7.48
4.43
4.40
4.38
4.36
1.43
1.41
1.38
EtO2C
CN
Ph
21d
f1 (ppm)
0.97
1.95
3.05
2.00
3.00

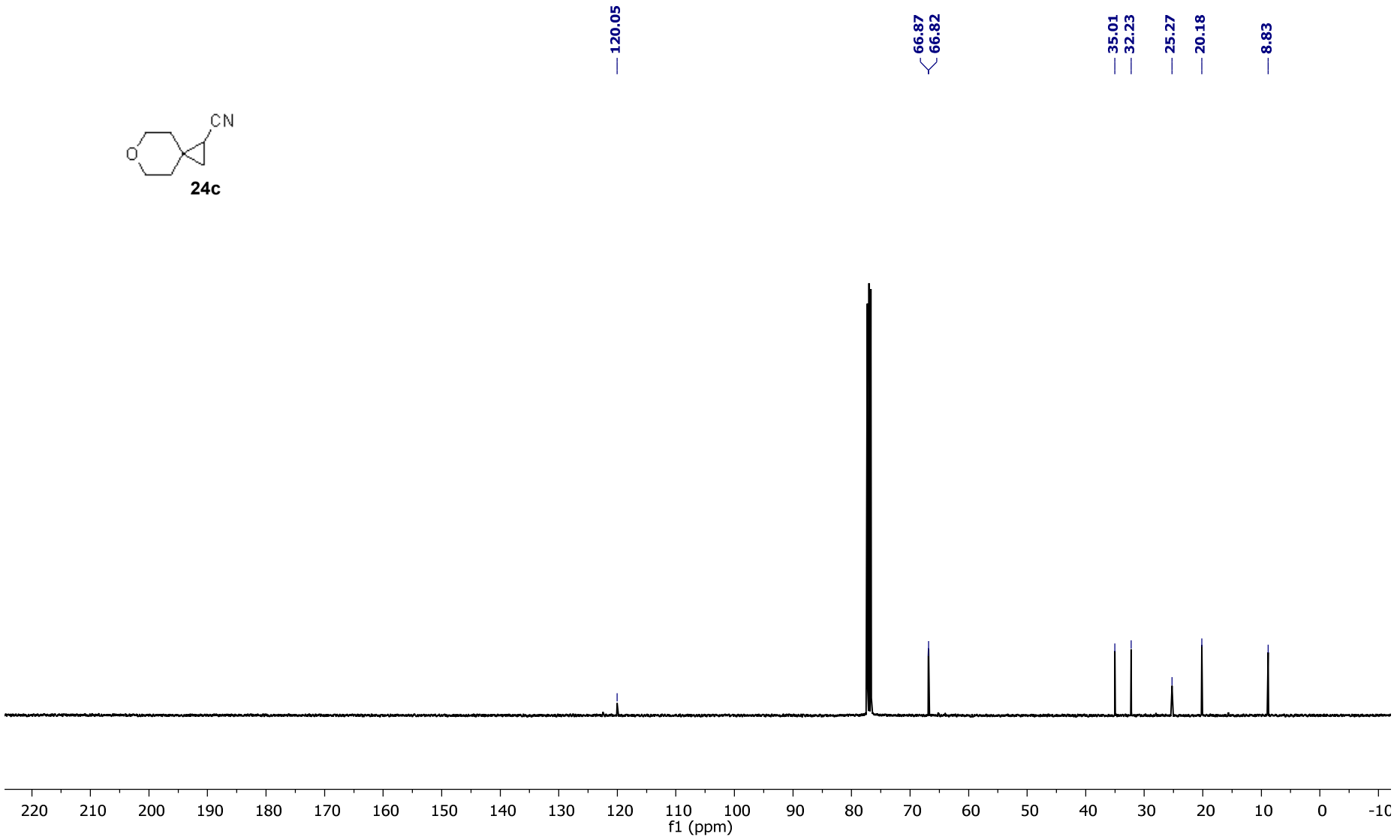

CN
CO2Et
O
22c
f1 (ppm)

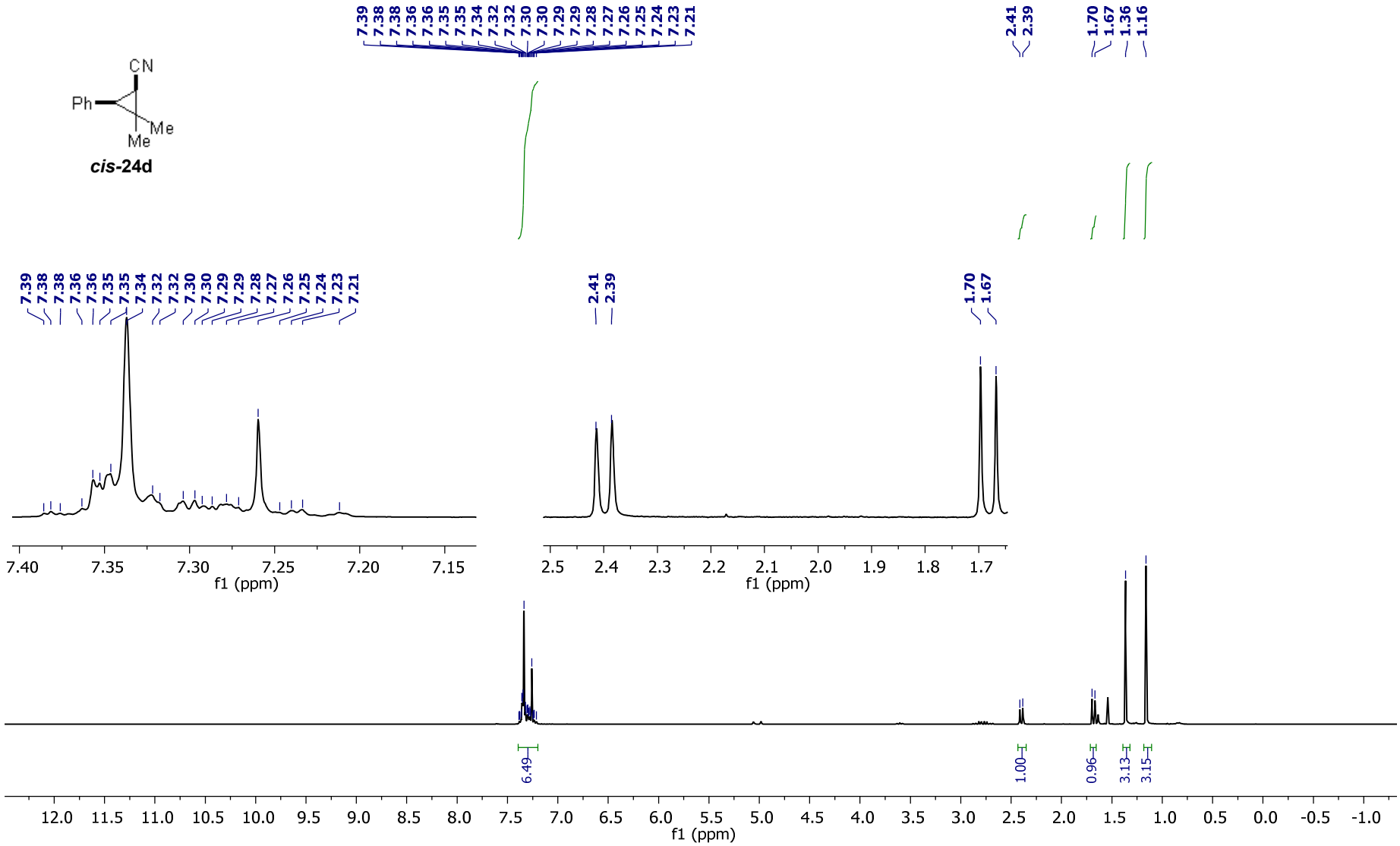

Me
Me
CN
Ph
OEt
O
22d
f1 (ppm)

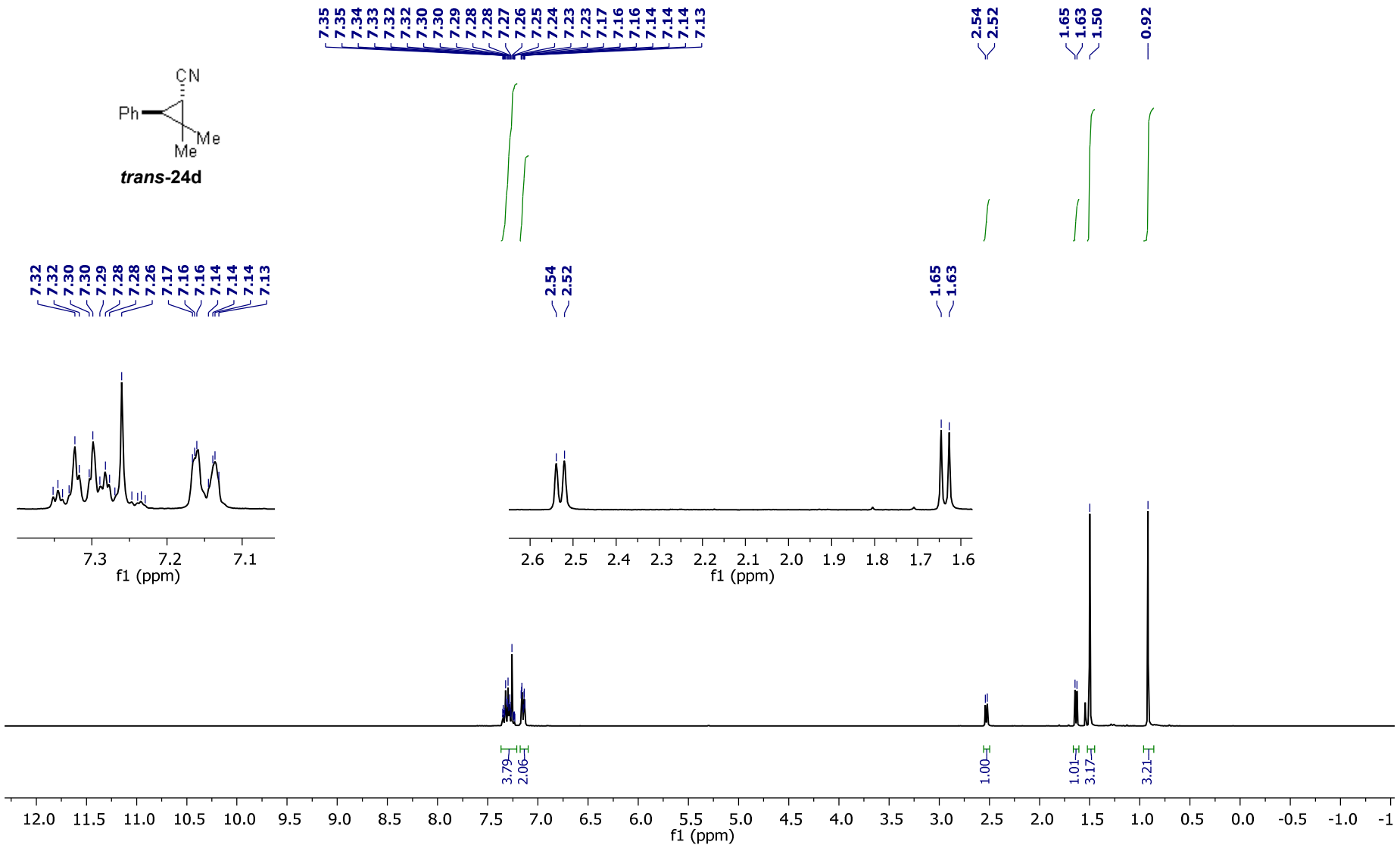

4.23 4.21 4.20 4.18 1.97 1.96 1.94 1.92 1.91 1.83 1.82 1.80 1.78 1.76 1.75 1.74 1.73 1.72 1.71 1.69 1.66 1.66 1.65 1.64 1.63 1.61 1.60 1.59 1.57 1.56 1.55 1.53 1.52 1.51 1.50 1.48 1.46 1.45 1.44 1.44 1.41 1.39 1.37 1.36 1.34 1.32 1.31 1.30
O
NC
OEt
Me
Me
22f
4.23 4.21 4.20 4.18
1.92 1.91 1.80 1.78 1.76 1.75 1.73 1.72 1.71 1.69 1.66 1.66 1.65 1.64 1.63 1.61 1.60 1.59 1.57 1.56 1.55 1.53 1.52 1.51 1.50 1.48 1.46 1.45 1.44 1.44 1.41 1.39 1.37 1.36 1.34 1.32 1.31 1.30
4.3 4.2 4.1
f1 (ppm)
2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1
f1 (ppm)
2.00
1.12
20.41
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1
f1 (ppm)

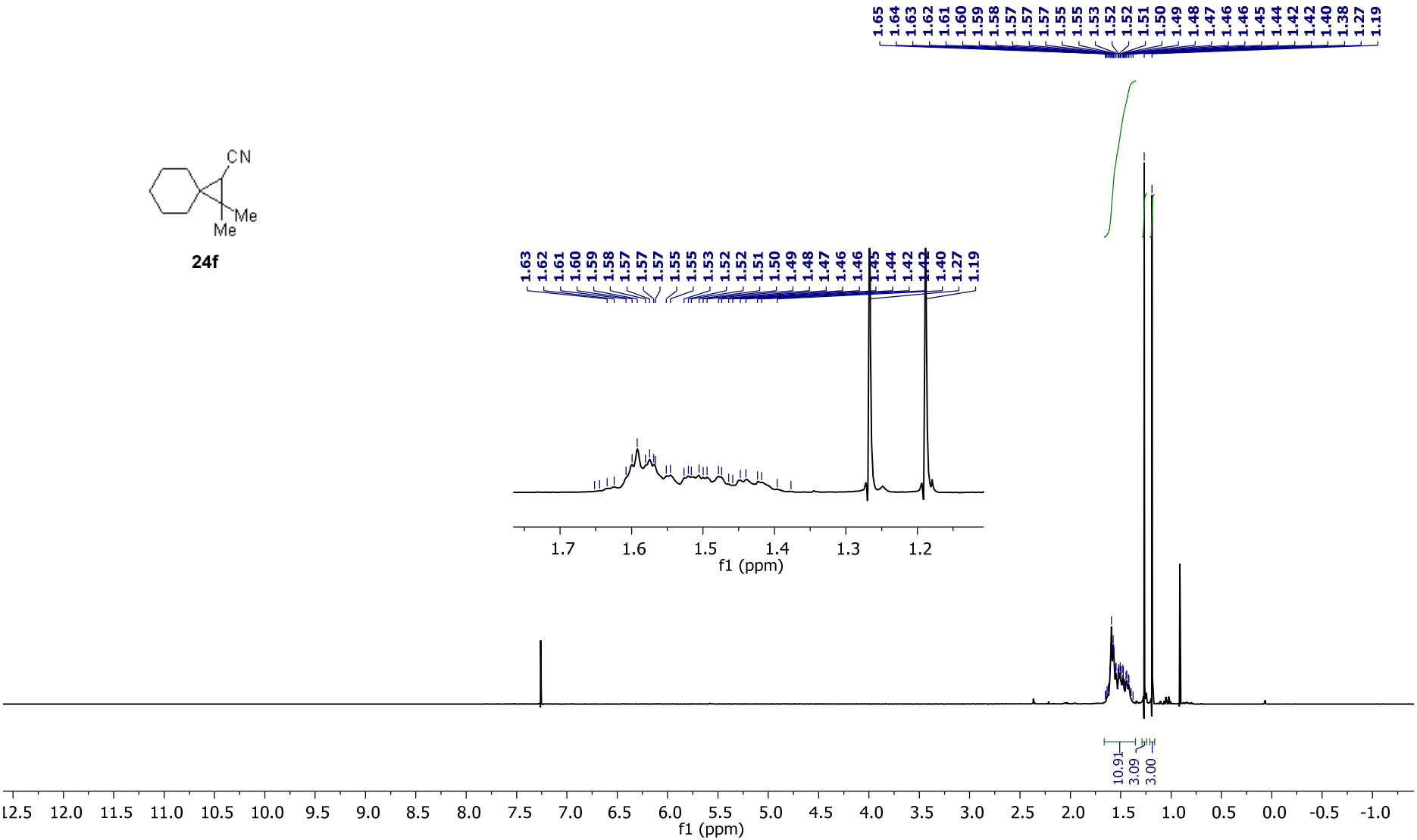

165.78
117.93
61.82
44.49
38.84
30.76
26.37
25.67
25.45
25.17
20.39
16.58
14.15
O
NC
OEt
Me
Me
22f
f1 (ppm)
f1 (ppm)

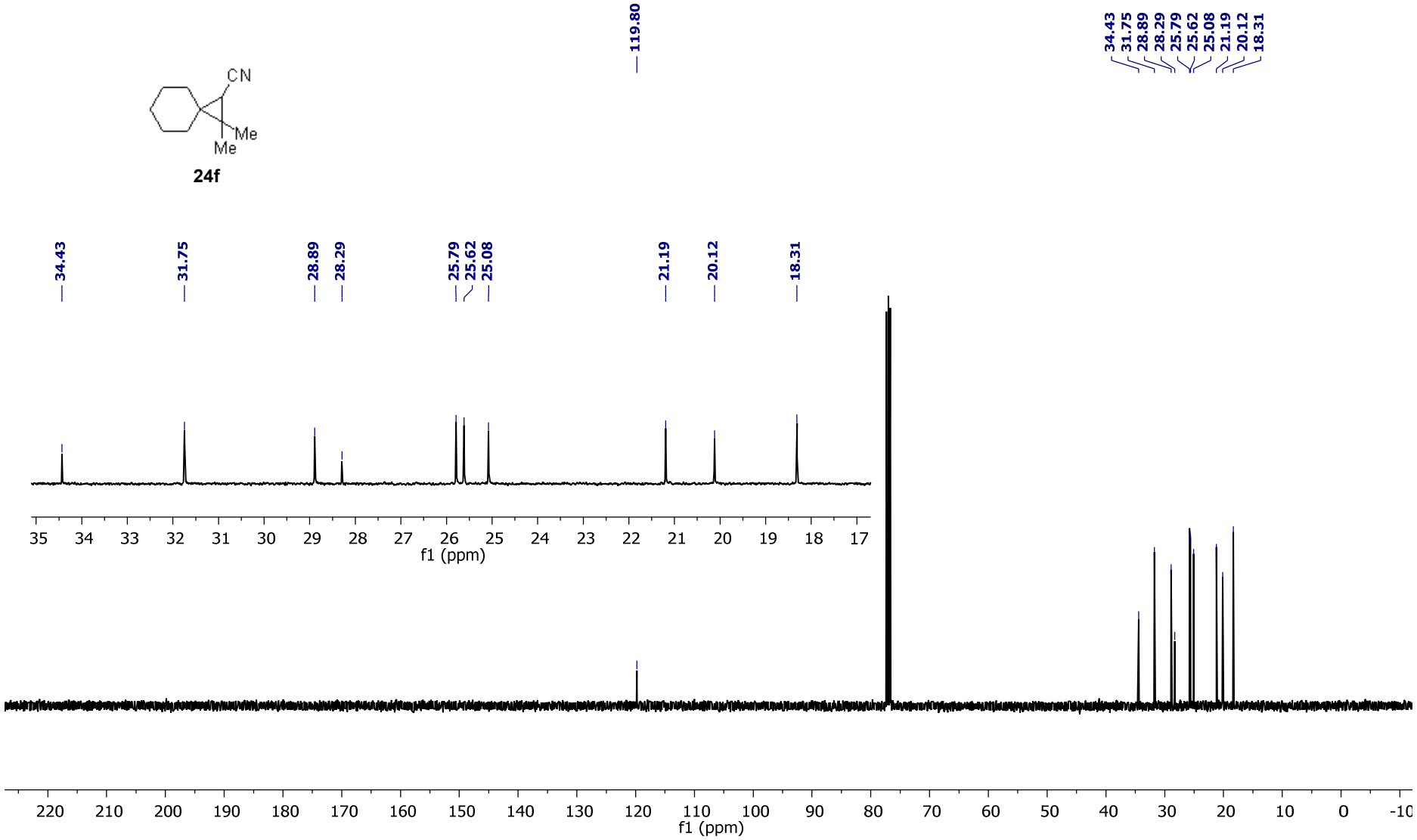

CN
O
24c
f1 (ppm)
4.00
1.92
2.07
0.92
0.91
1.91

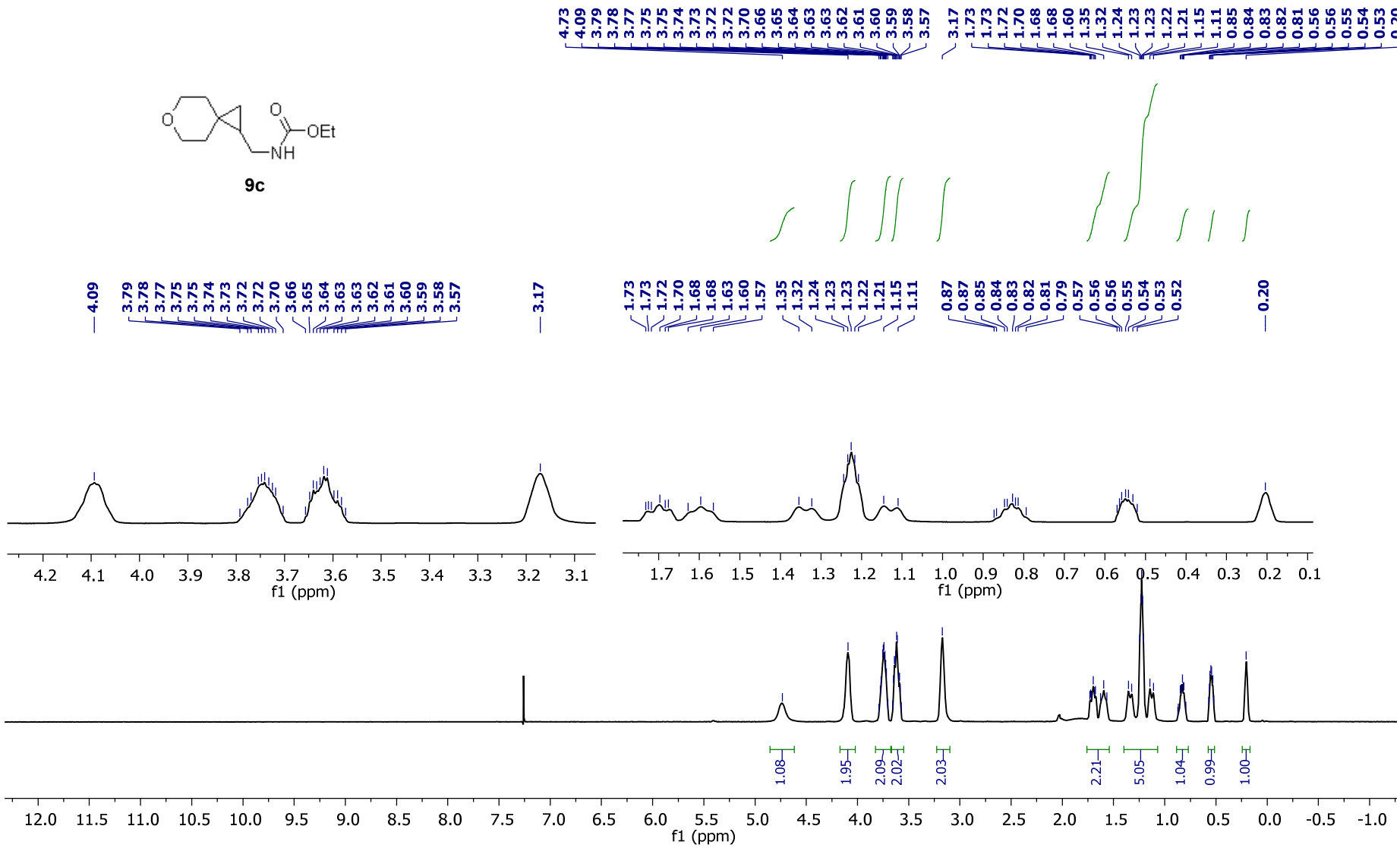

120.05
66.87
66.82
35.01
32.23
25.27
20.18
8.83
CN
O
24c
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

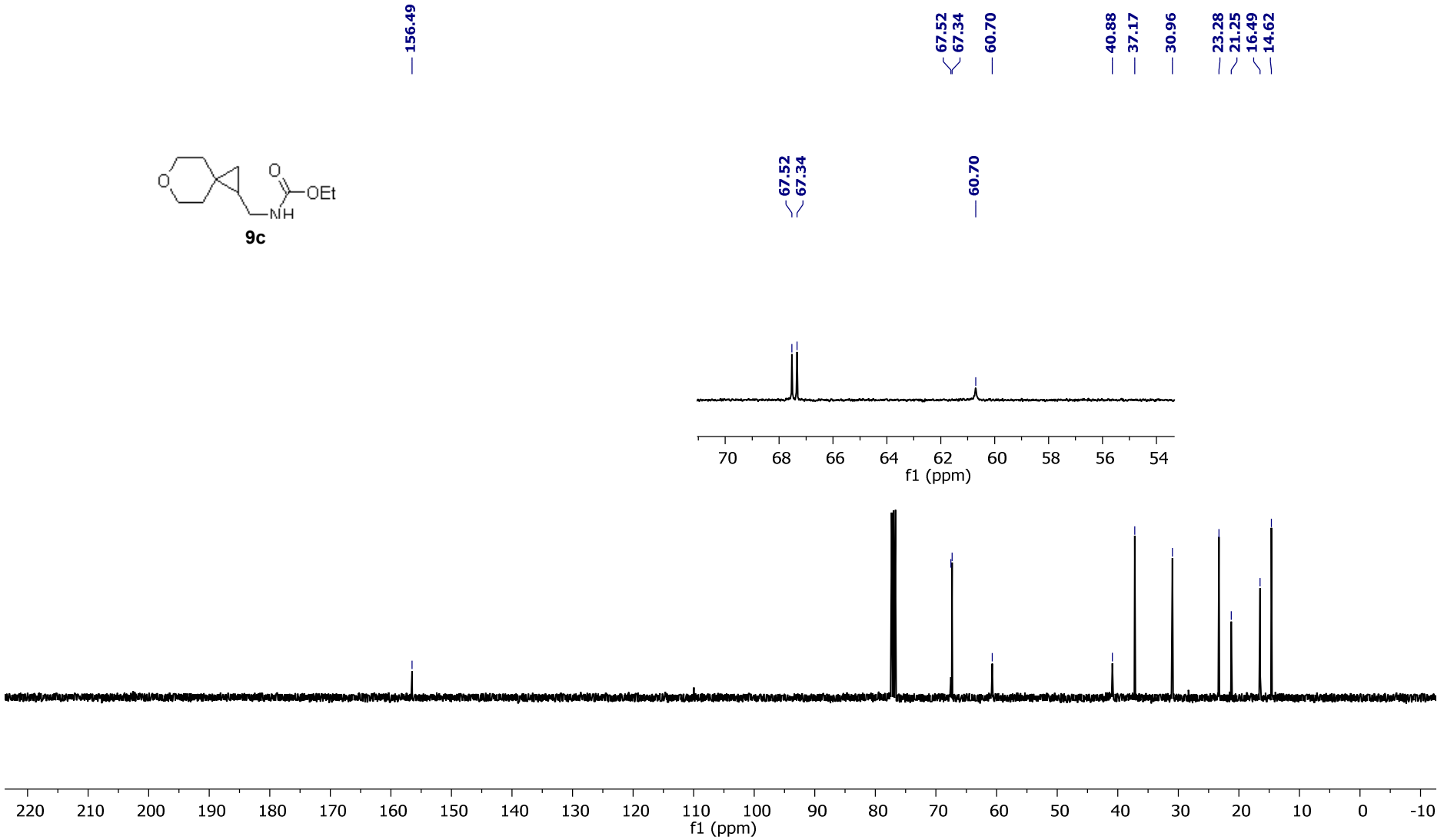

CN
Ph
Me
Me
cis-24d
7.39 7.38 7.38 7.36 7.36 7.35 7.35 7.34 7.32 7.32 7.30 7.30 7.29 7.29 7.28 7.27 7.26 7.25 7.24 7.23 7.21
2.41 2.39
1.70 1.67
1.36
1.16
f1 (ppm)
6.49
1.00
0.96
3.13
3.15

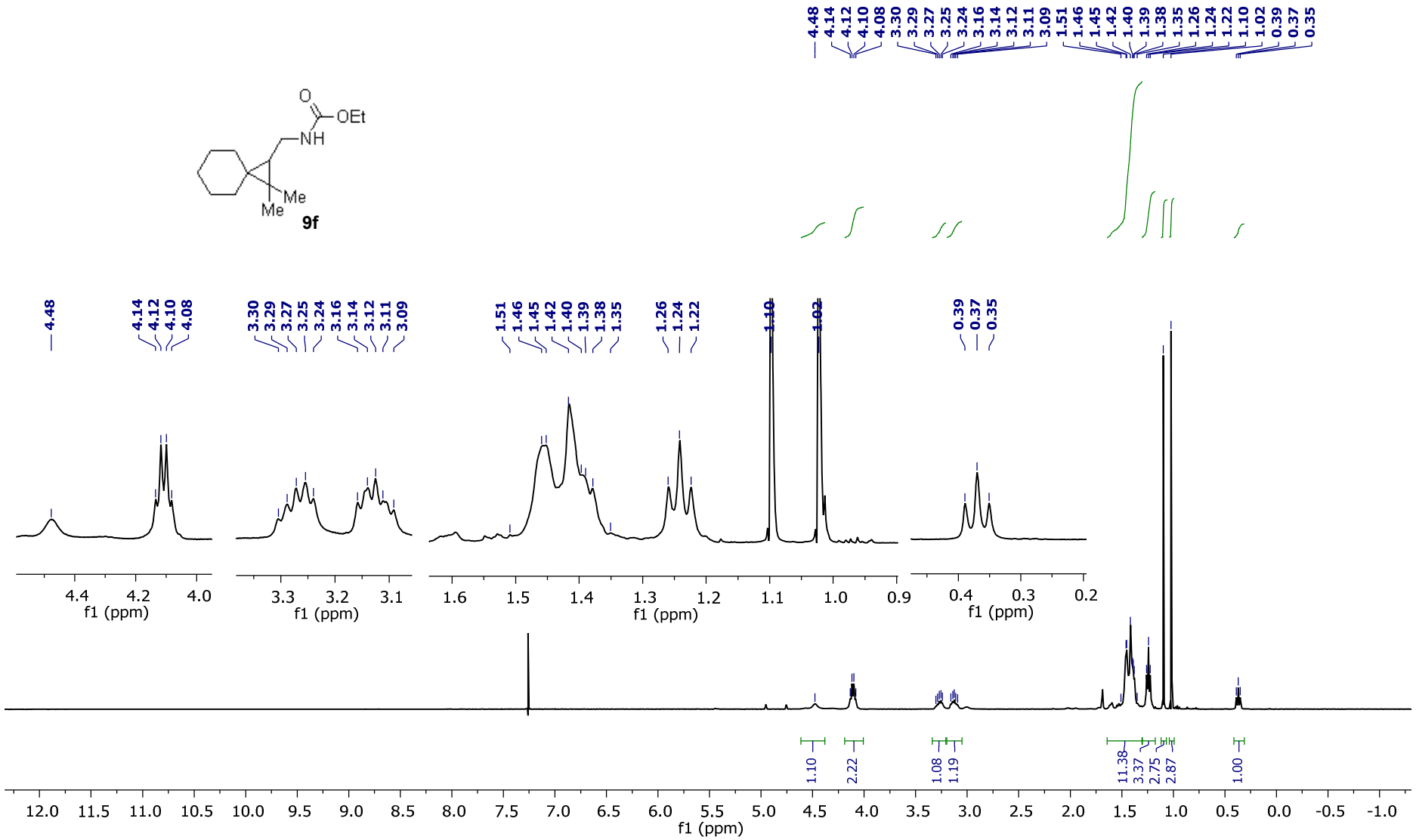

7.35 7.35 7.34 7.33 7.32 7.32 7.30 7.30 7.29 7.28 7.28 7.27 7.26 7.25 7.24 7.23 7.17 7.16 7.16 7.14 7.14 7.14 7.13
2.54 2.52
1.65 1.63 1.50
0.92
CN
Ph
Me
Me
trans-24d
7.32 7.32 7.30 7.30 7.29 7.28 7.28 7.26 7.17 7.16 7.16 7.14 7.14 7.14 7.13
2.54 2.52
1.65 1.63
7.3 7.2 7.1
f1 (ppm)
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6
f1 (ppm)
3.79 2.06 1.00 1.01 3.17 3.21
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1
f1 (ppm)

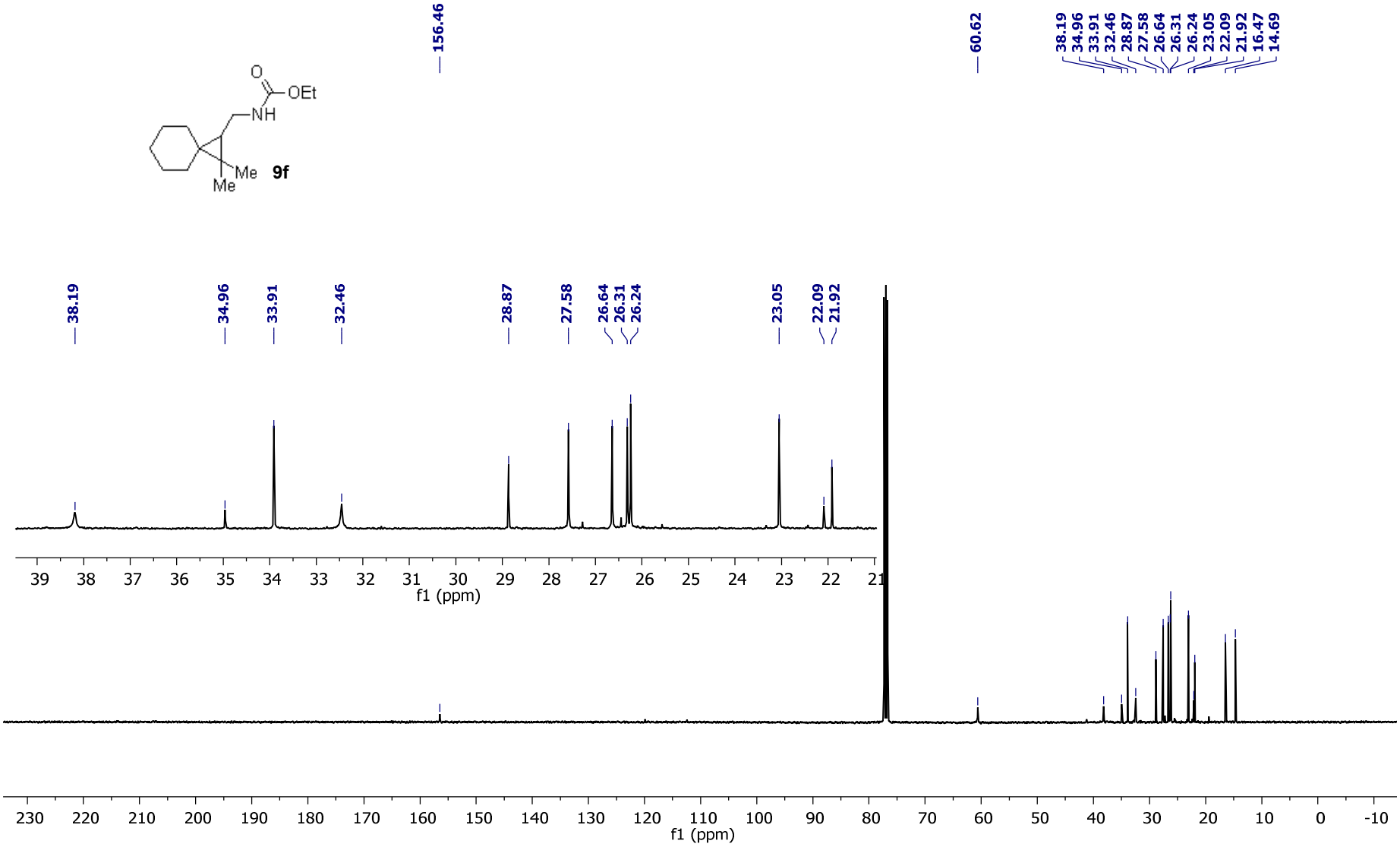

CN
Me
Me
24f
1.65 1.64 1.63 1.62 1.61 1.60 1.59 1.58 1.57 1.57 1.57 1.55 1.55 1.53 1.52 1.52 1.51 1.50 1.49 1.48 1.47 1.46 1.46 1.45 1.44 1.42 1.42 1.40 1.38 1.27 1.19
1.63 1.62 1.61 1.60 1.59 1.58 1.57 1.57 1.57 1.55 1.55 1.53 1.52 1.52 1.51 1.50 1.49 1.48 1.47 1.46 1.46 1.45 1.44 1.42 1.42 1.40 1.27 1.19
1.7 1.6 1.5 1.4 1.3 1.2
f1 (ppm)
10.91
3.09
3.00
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

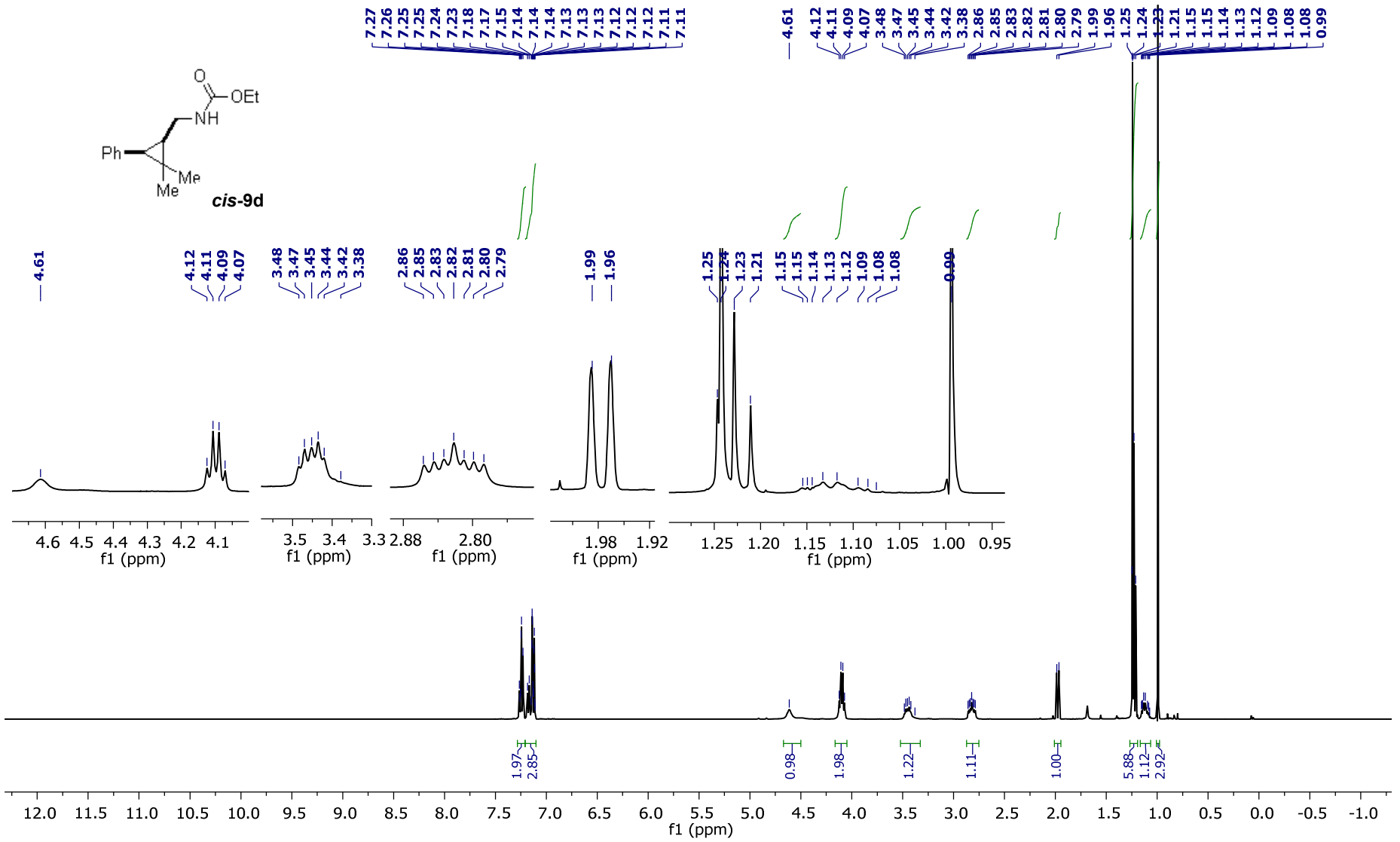

CN
Me
Me
24f
119.80
34.43
31.75
28.89
28.29
25.79
25.62
25.08
21.19
20.12
18.31
f1 (ppm)
f1 (ppm)

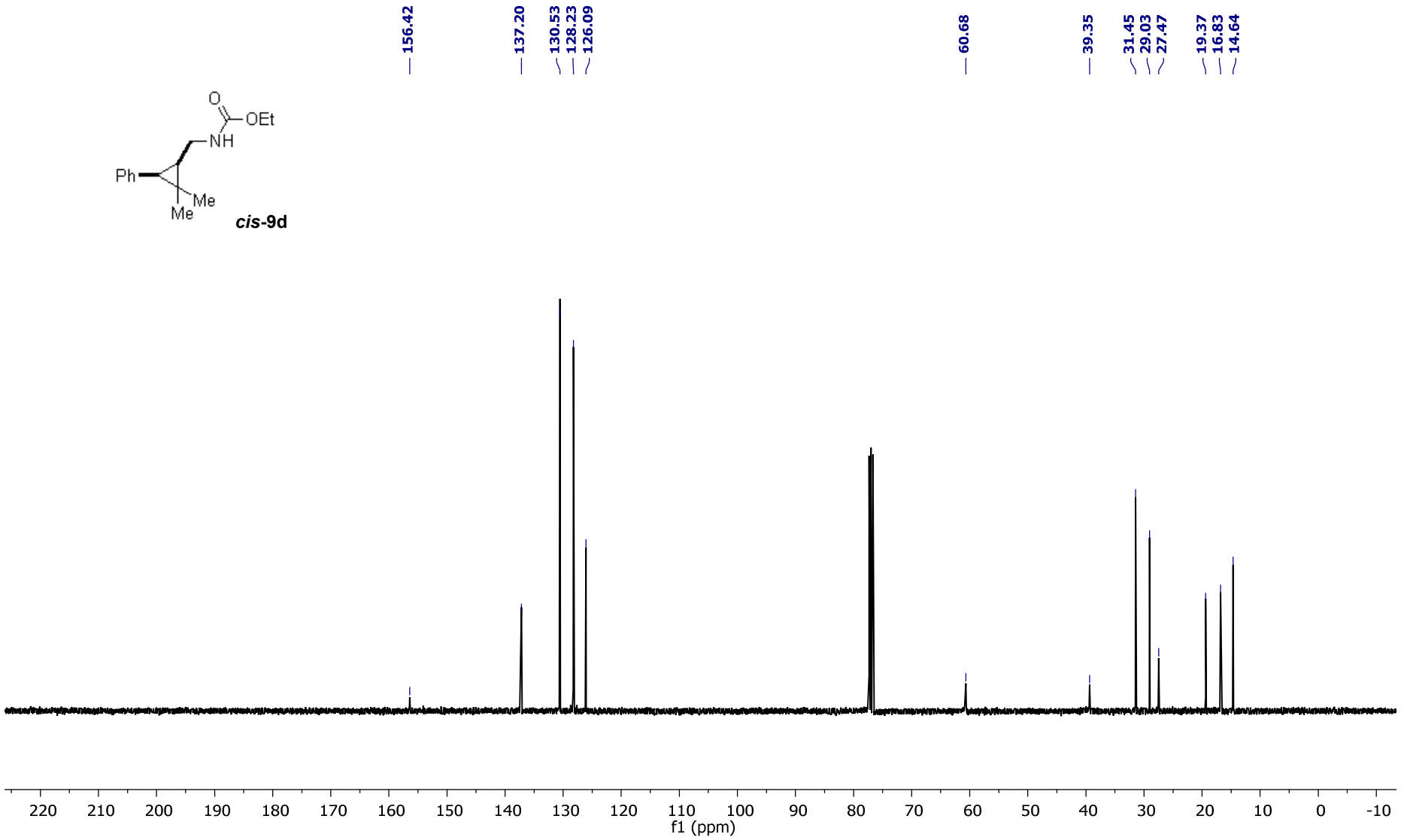

9c
f1 (ppm)
f1 (ppm)
f1 (ppm)

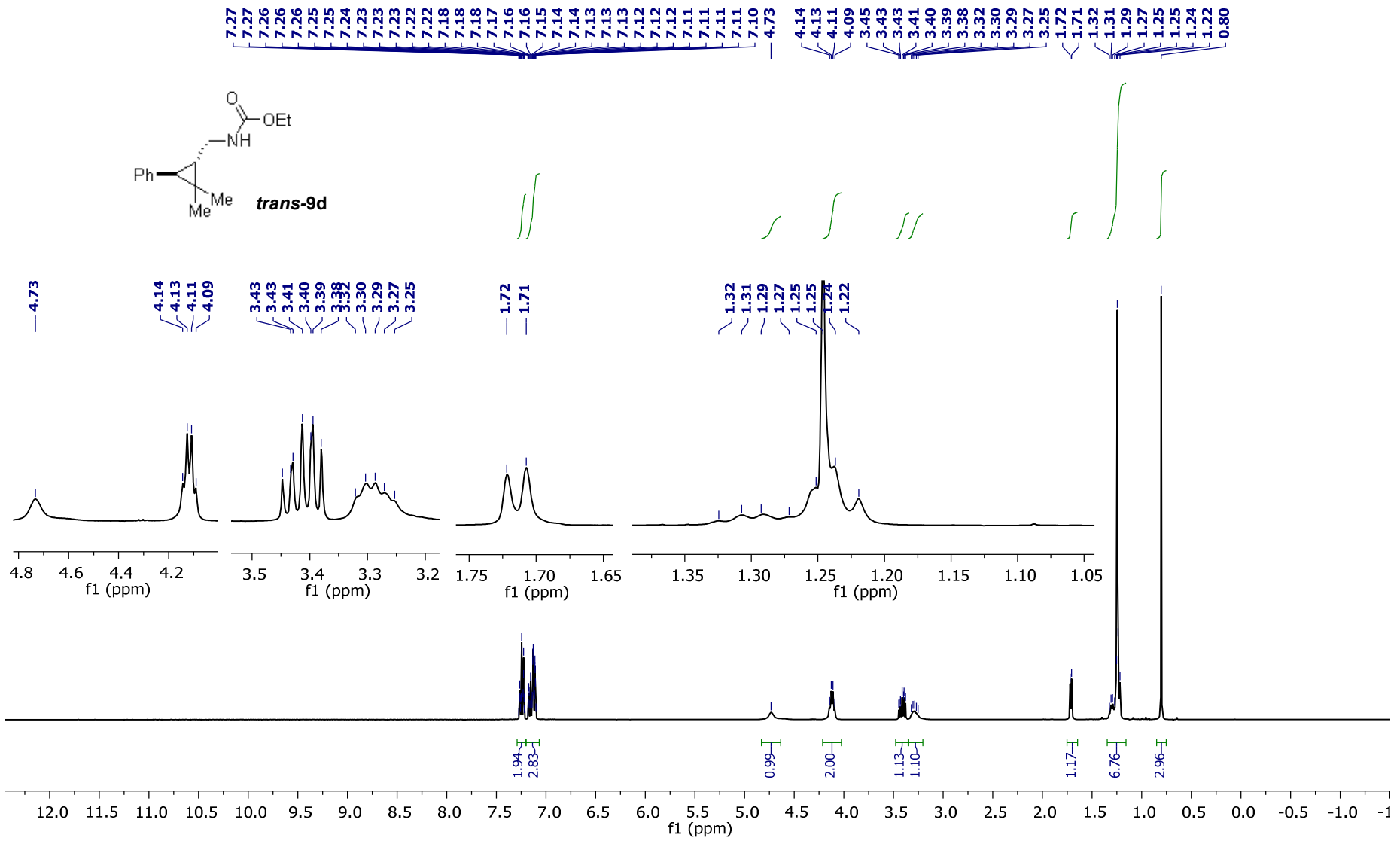

156.49
67.52
67.34
60.70
40.88
37.17
30.96
23.28
21.25
16.49
14.62
O
O
OEt
NH
9c
67.52
67.34
60.70
70
68
66
64
62
60
58
56
54
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

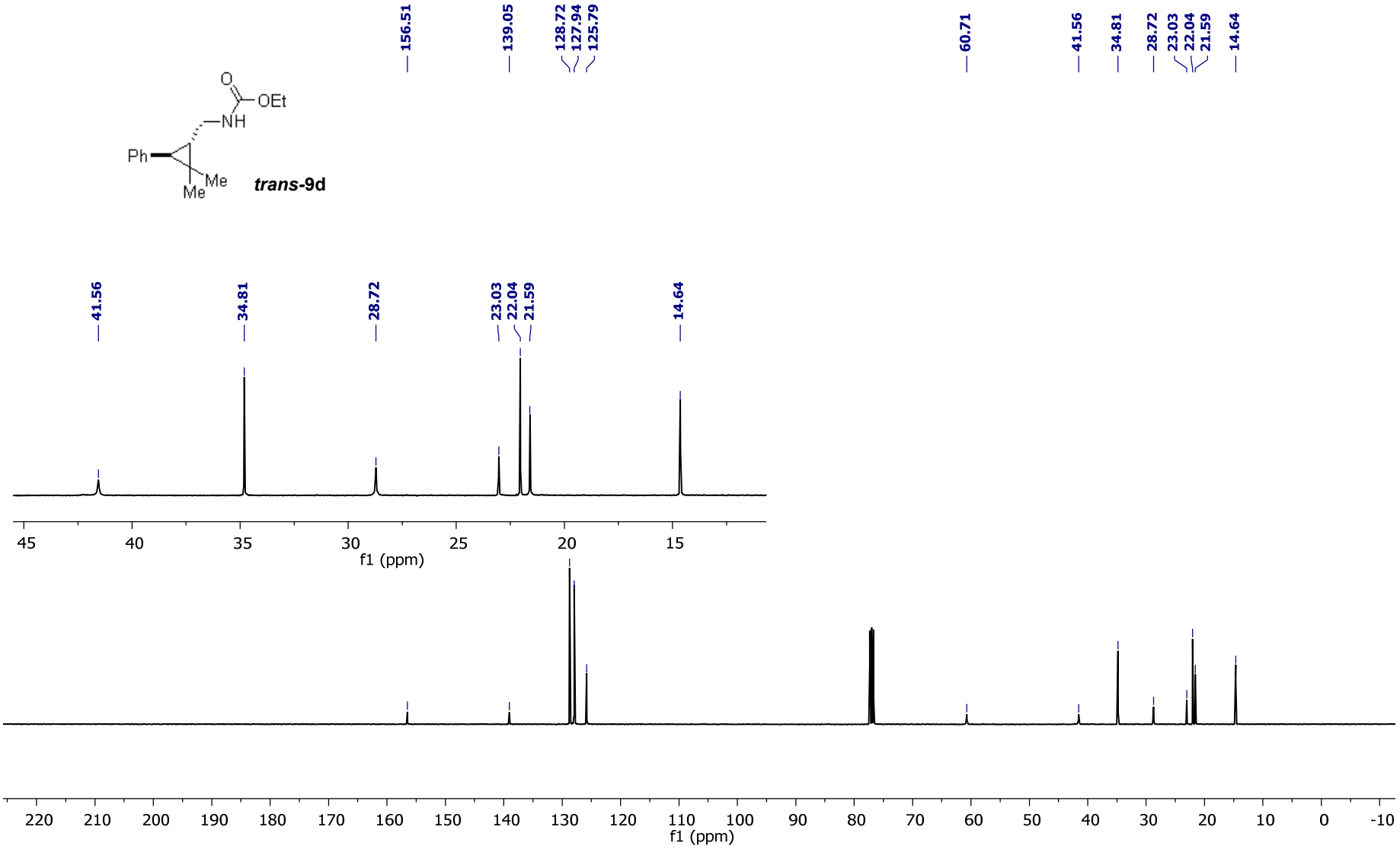

4.48
4.14
4.12
4.10
4.08
3.30
3.29
3.27
3.25
3.24
3.16
3.14
3.12
3.11
3.09
1.51
1.46
1.45
1.42
1.40
1.39
1.38
1.35
1.26
1.24
1.22
1.10
1.02
0.39
0.37
0.35
O
OEt
NH
Me
Me
9f
f1 (ppm)
1.10
2.22
1.08
1.19
11.38
3.37
2.75
2.87
1.00

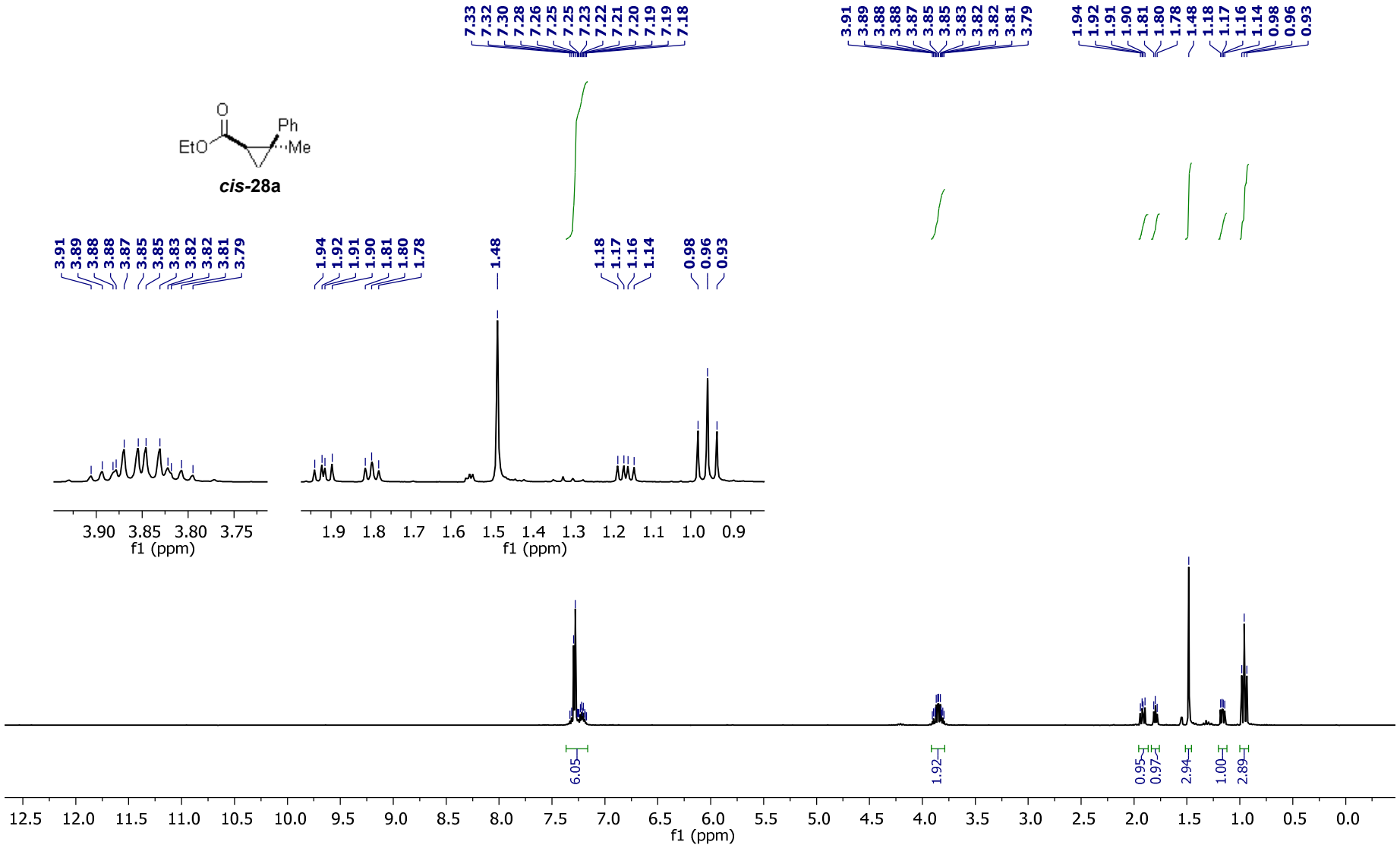

156.46
60.62
38.19
34.96
33.91
32.46
28.87
27.58
26.64
26.31
26.24
23.05
22.09
21.92
16.47
14.69
O
OEt
NH
Me
Me
9f
f1 (ppm)
f1 (ppm)

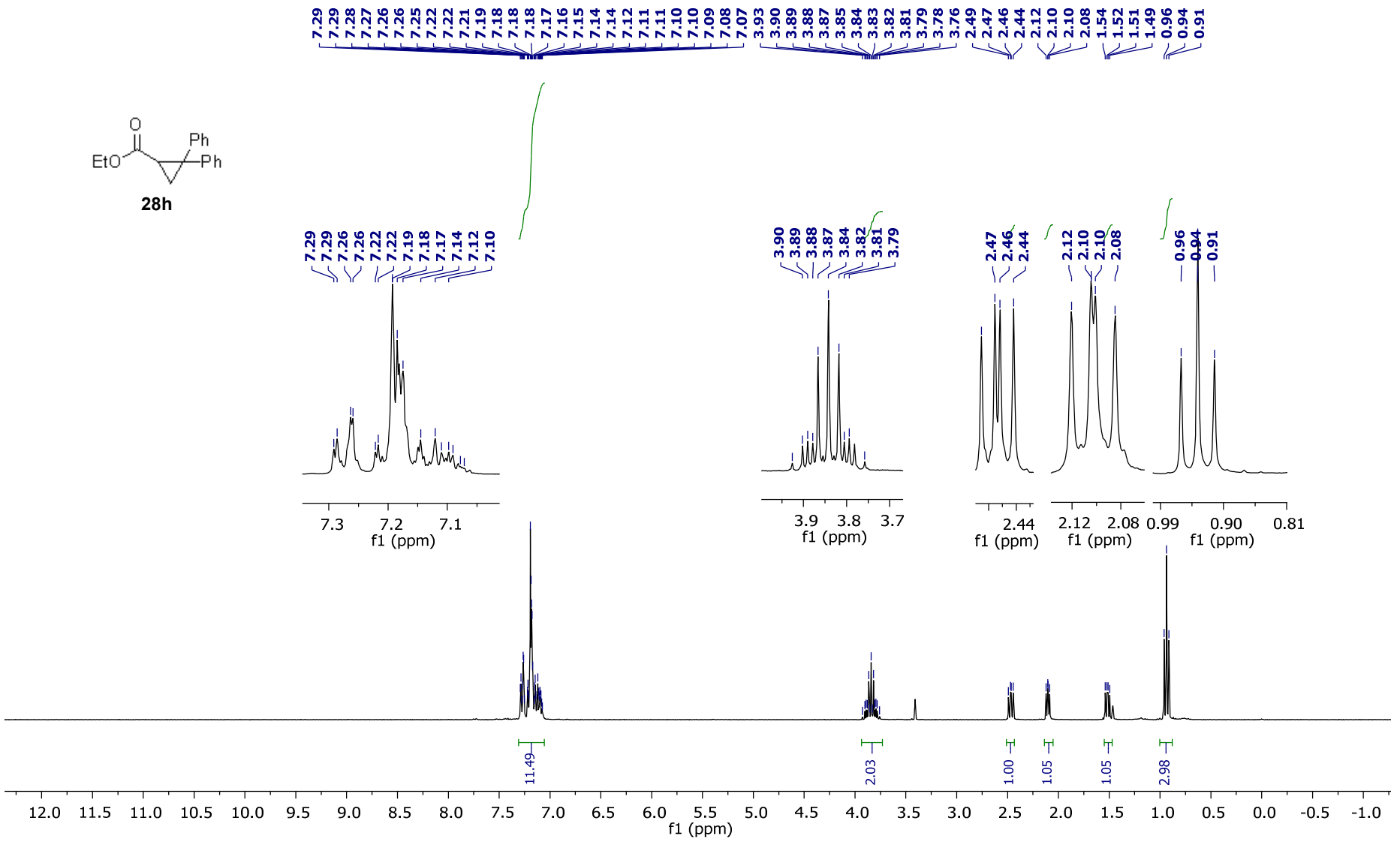

cis-9d
f1 (ppm)

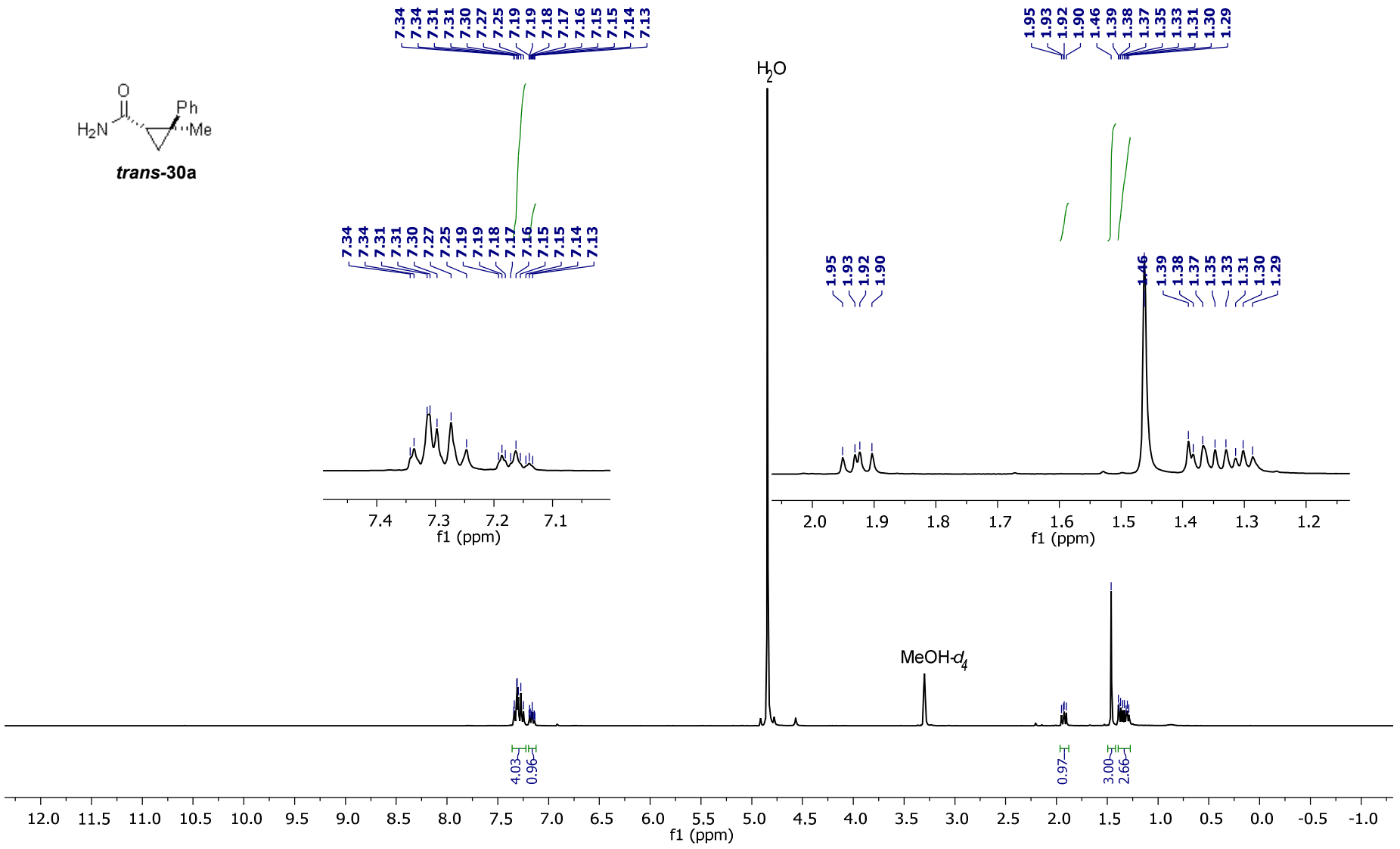

156.42
137.20
130.53
128.23
126.09
60.68
39.35
31.45
29.03
27.47
19.37
16.83
14.64
O
OEt
NH
Ph
Me
Me
cis-9d
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

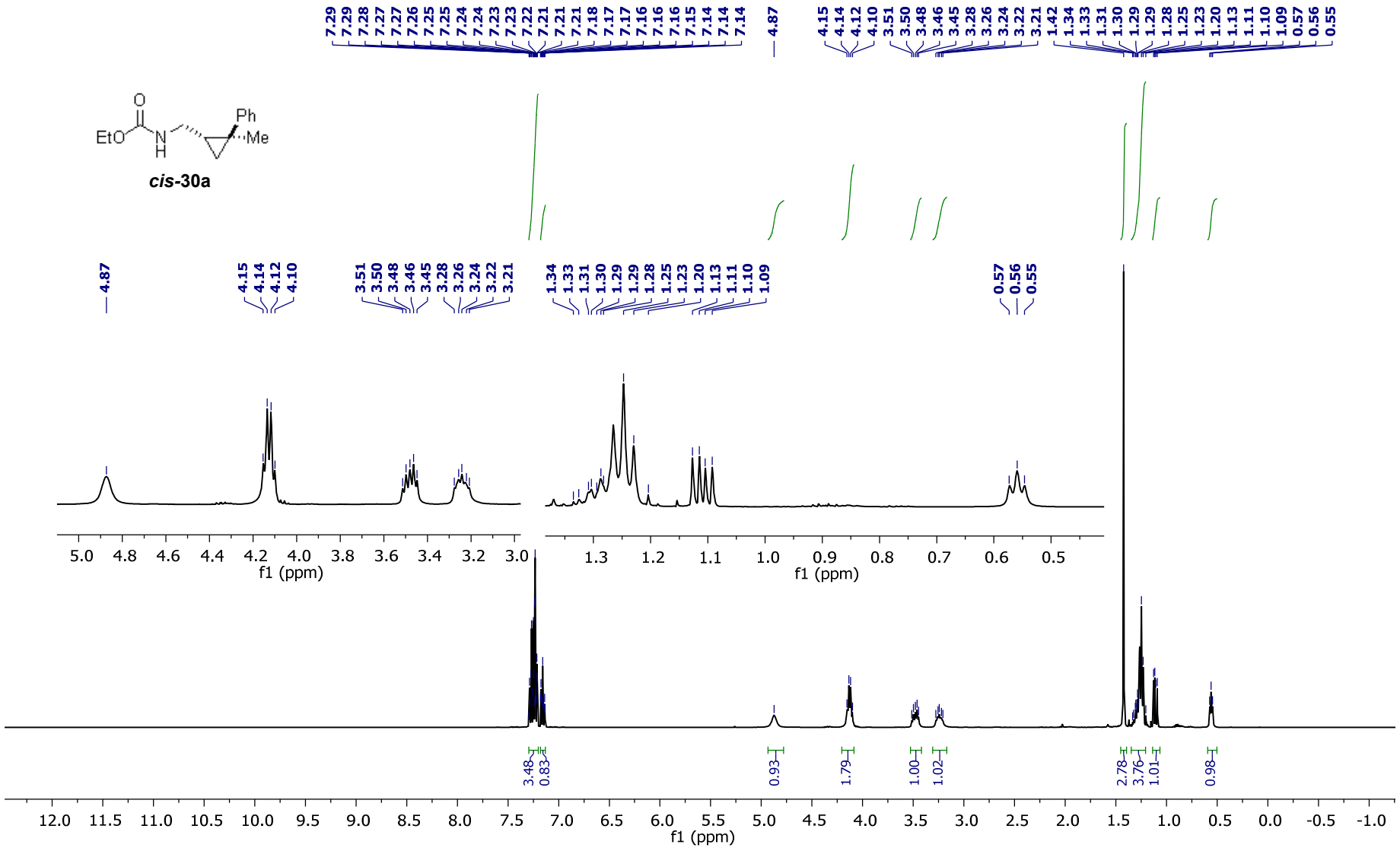

7.27 7.27 7.26 7.26 7.26 7.25 7.25 7.24 7.23 7.23 7.23 7.22 7.22 7.18 7.18 7.17 7.16 7.16 7.15 7.14 7.14 7.13 7.13 7.13 7.12 7.12 7.12 7.11 7.11 7.11 7.10 4.73
4.14 4.13 4.11 4.09 3.45 3.43 3.43 3.41 3.40 3.39 3.38 3.32 3.30 3.29 3.27 3.25 1.72 1.71 1.32 1.31 1.29 1.27 1.25 1.25 1.24 1.22 0.80
O
OEt
NH
Ph
Me
Me
trans-9d
4.73
4.14 4.13 4.11 4.09
3.43 3.43 3.41 3.40 3.39 3.38 3.32 3.30 3.29 3.27 3.25
1.72 1.71
1.32 1.31 1.29 1.27 1.25 1.25 1.24 1.22
4.8 4.6 4.4 4.2
f1 (ppm)
3.5 3.4 3.3 3.2
f1 (ppm)
1.75 1.70 1.65
f1 (ppm)
1.35 1.30 1.25 1.20 1.15 1.10 1.05
f1 (ppm)
1.94 2.83 0.99 2.00 1.13 1.10 1.17 6.76 2.96
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1
f1 (ppm)

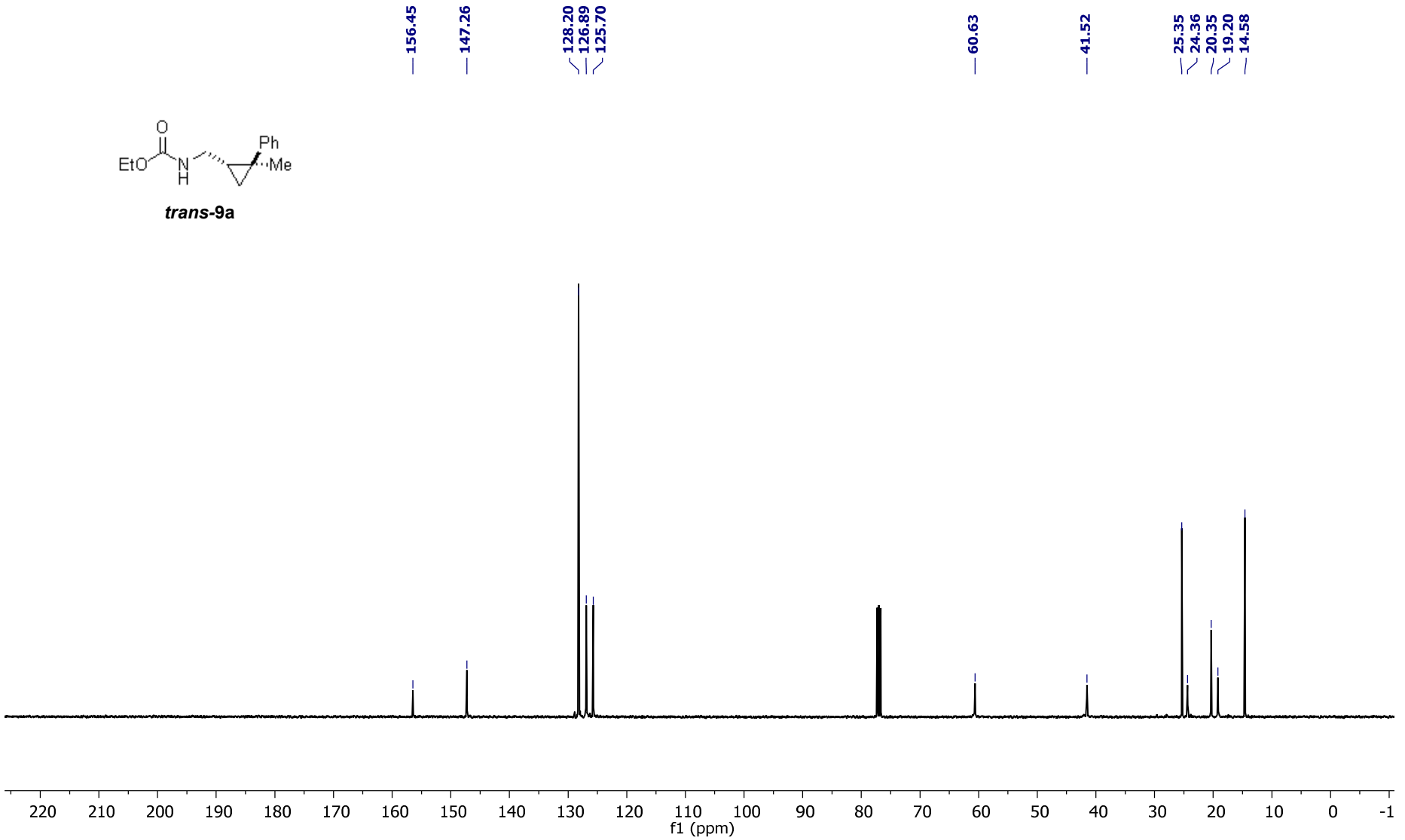

156.51
139.05
128.72
127.94
125.79
60.71
41.56
34.81
28.72
23.03
22.04
21.59
14.64
O
OEt
NH
Ph
Me
Me
trans-9d
f1 (ppm)
f1 (ppm)

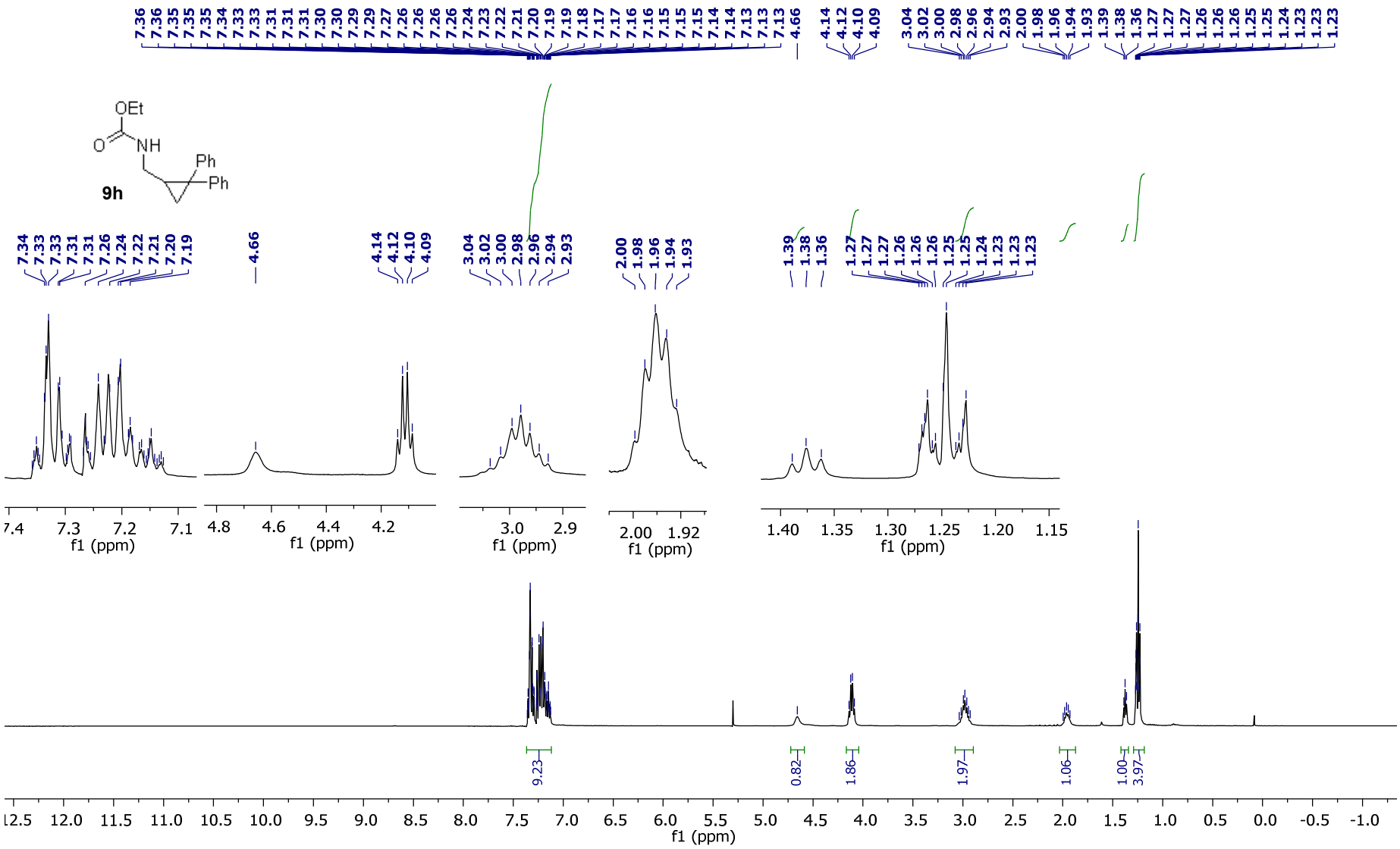

7.33 7.32 7.30 7.28 7.26 7.25 7.25 7.23 7.22 7.21 7.20 7.19 7.19 7.18
3.91 3.89 3.88 3.88 3.87 3.85 3.85 3.83 3.82 3.82 3.81 3.79
1.94 1.92 1.91 1.90 1.81 1.80 1.78 1.48 1.18 1.17 1.16 1.14 0.98 0.96 0.93
O
Ph
EtO
Me
cis-28a
3.90 3.85 3.80 3.75
f1 (ppm)
1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9
f1 (ppm)
6.05
1.92
0.95
0.97
2.94
1.00
2.89
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

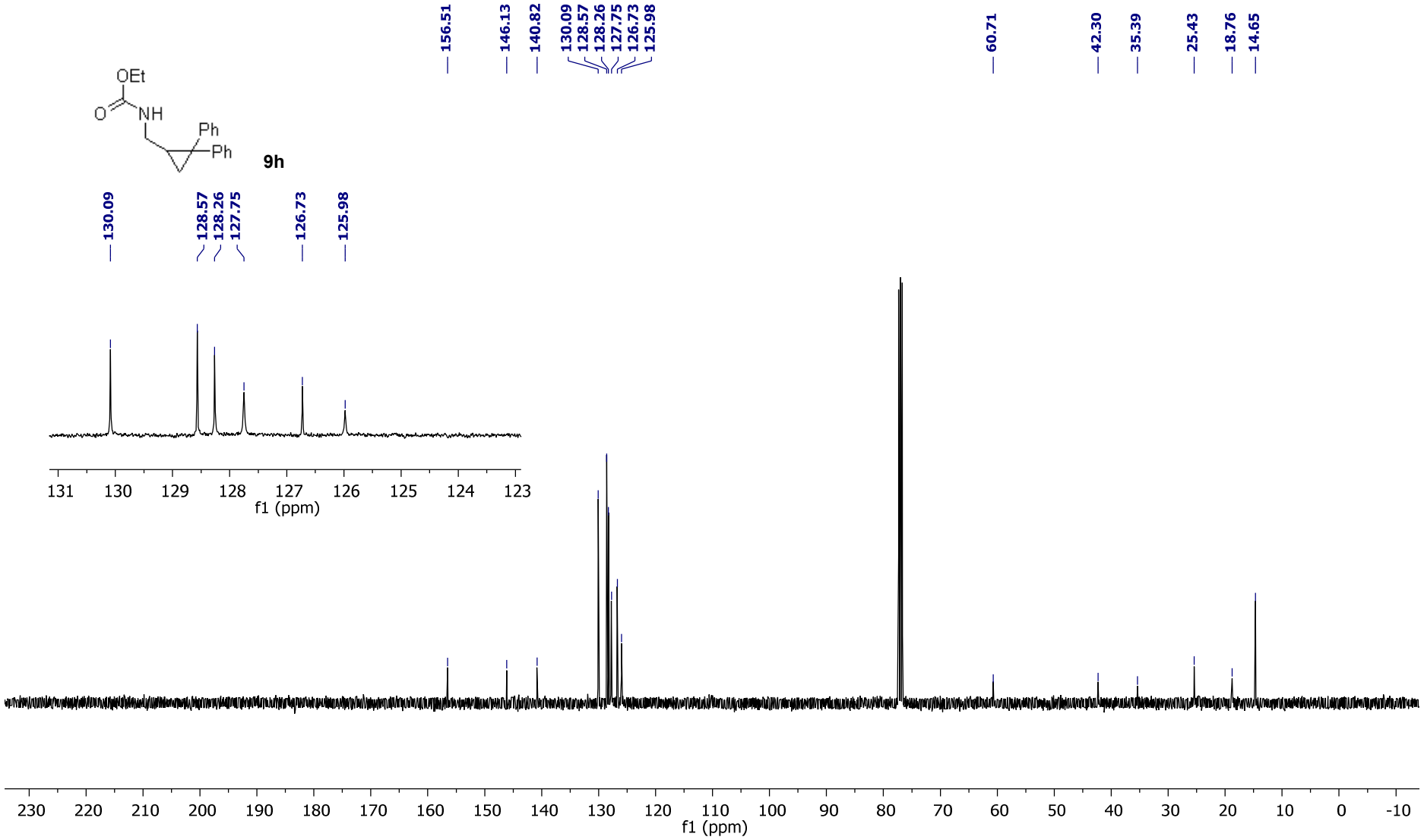

O
EtO
Ph
Ph
28h
f1 (ppm)

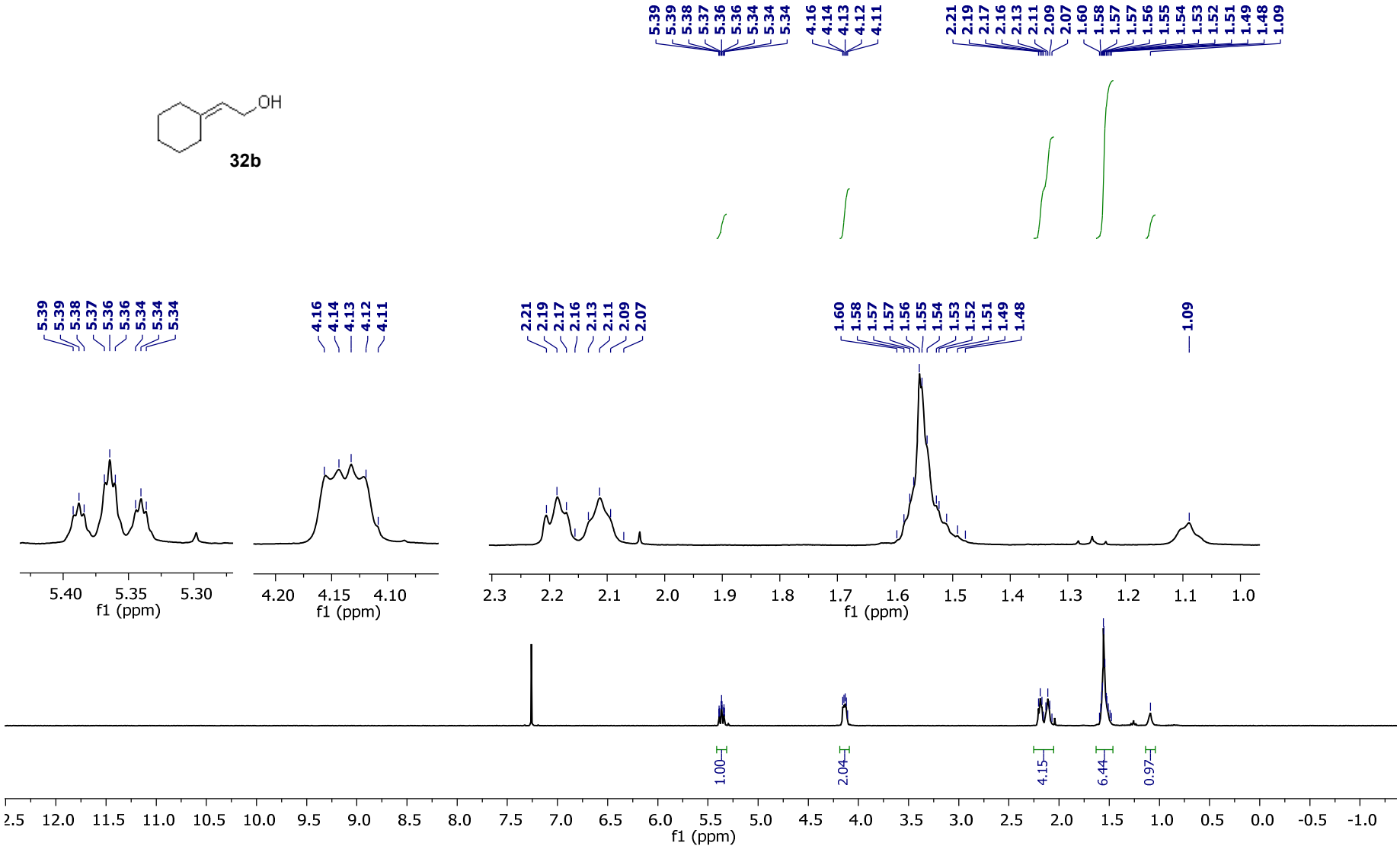

O
Ph
H2N
Me
trans-30a
7.34
7.34
7.31
7.31
7.30
7.27
7.25
7.19
7.19
7.18
7.17
7.16
7.15
7.15
7.14
7.13
1.95
1.93
1.92
1.90
1.46
1.39
1.38
1.37
1.35
1.33
1.31
1.30
1.29
H2O
MeOH-d4
4.03
0.96
0.97
3.00
2.66
f1 (ppm)

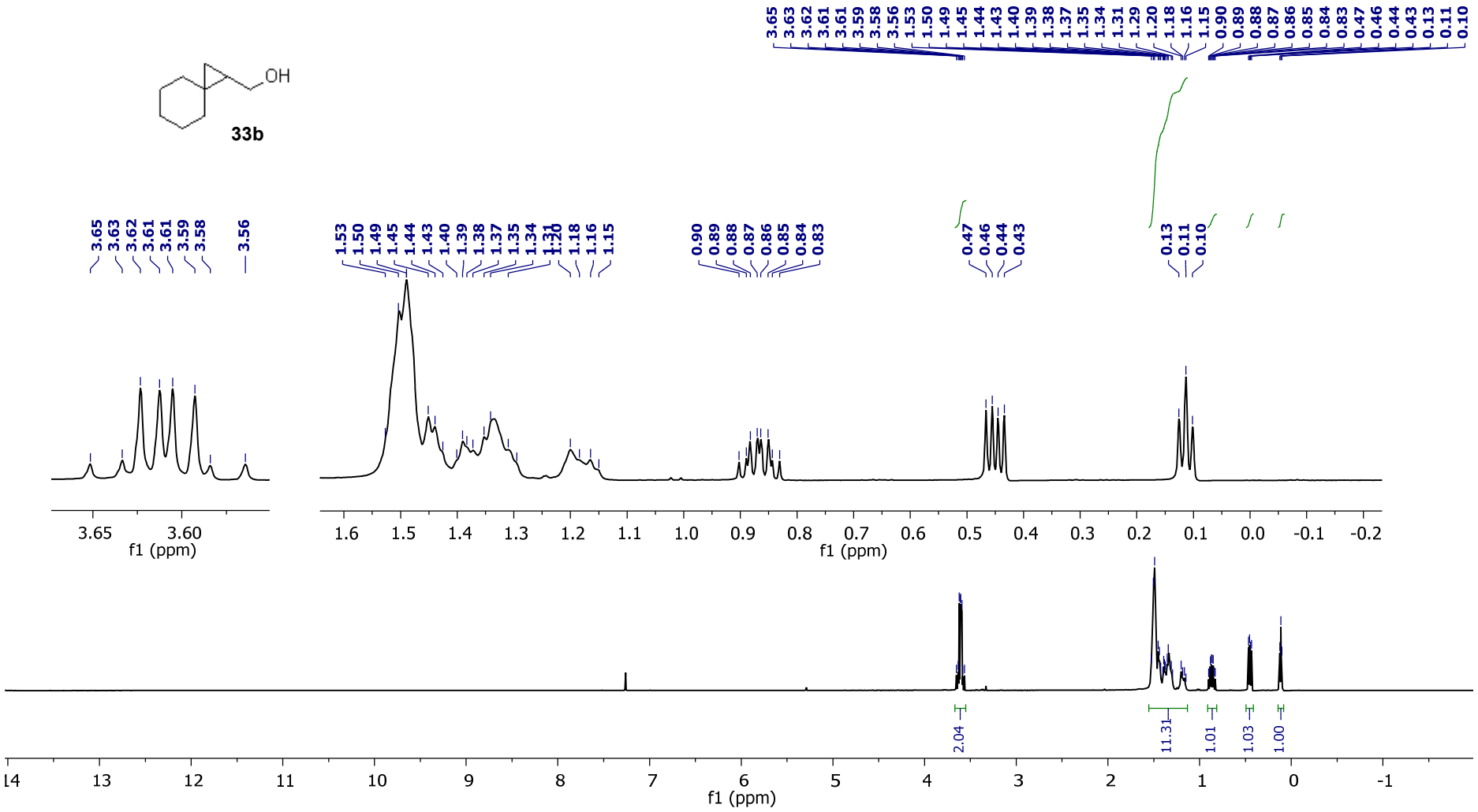

7.29 7.29 7.28 7.27 7.27 7.26 7.25 7.25 7.24 7.24 7.23 7.23 7.22 7.21 7.21 7.21 7.18 7.17 7.17 7.16 7.16 7.16 7.15 7.14 7.14 7.14
4.87
4.15 4.14 4.12 4.10 3.51 3.50 3.48 3.46 3.45 3.28 3.26 3.24 3.22 3.21 1.42 1.34 1.33 1.31 1.30 1.29 1.29 1.28 1.25 1.23 1.20 1.13 1.11 1.10 1.09 0.57 0.56 0.55
O
EtO
N
H
Ph
Me
cis-30a
f1 (ppm)
3.48
0.83
0.93
1.79
1.00
1.02
2.78
3.76
1.01
0.98

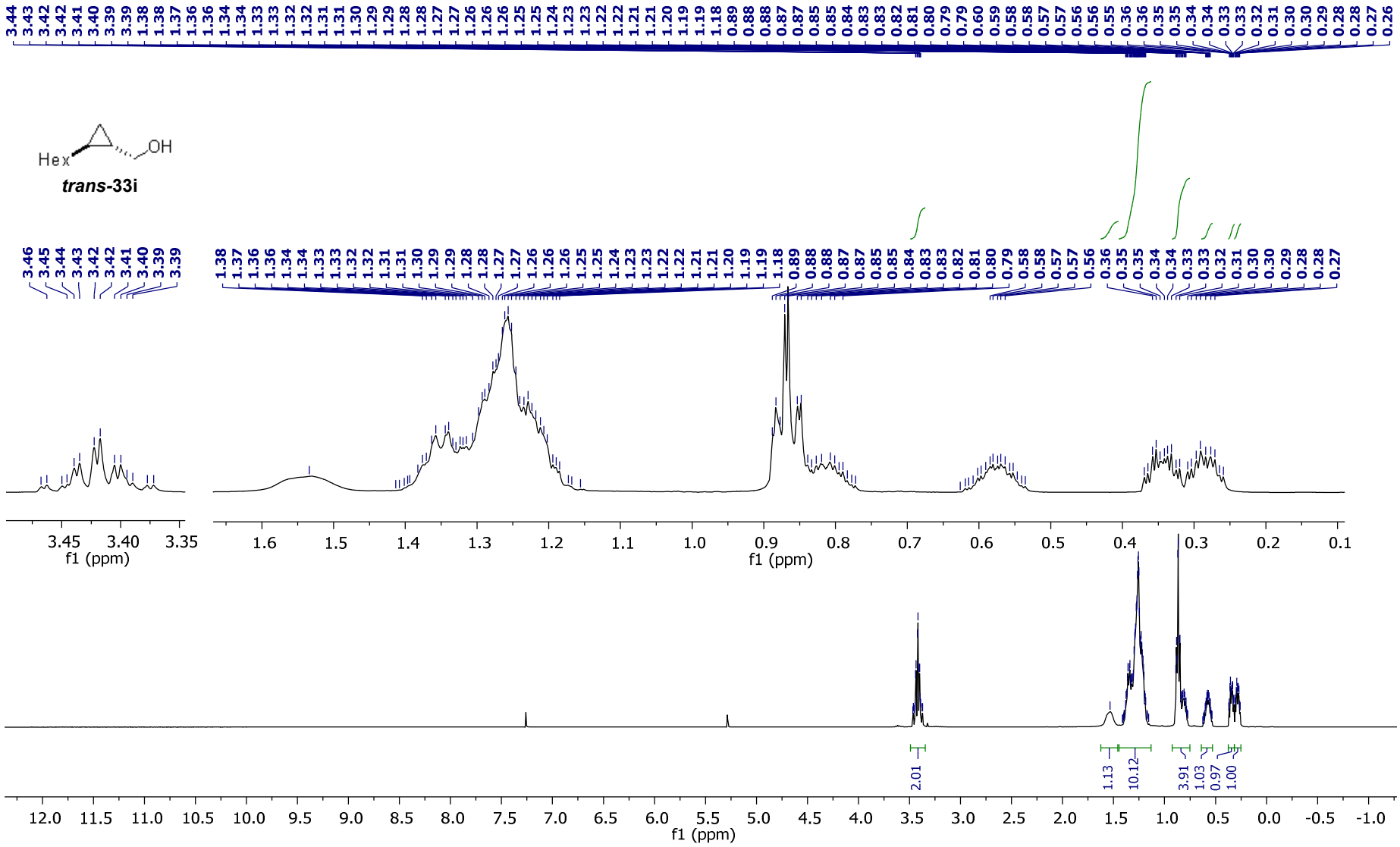

156.45
147.26
128.20
126.89
125.70
60.63
41.52
25.35
24.36
20.35
19.20
14.58
O
EtO
N
H
Ph
Me
trans-9a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

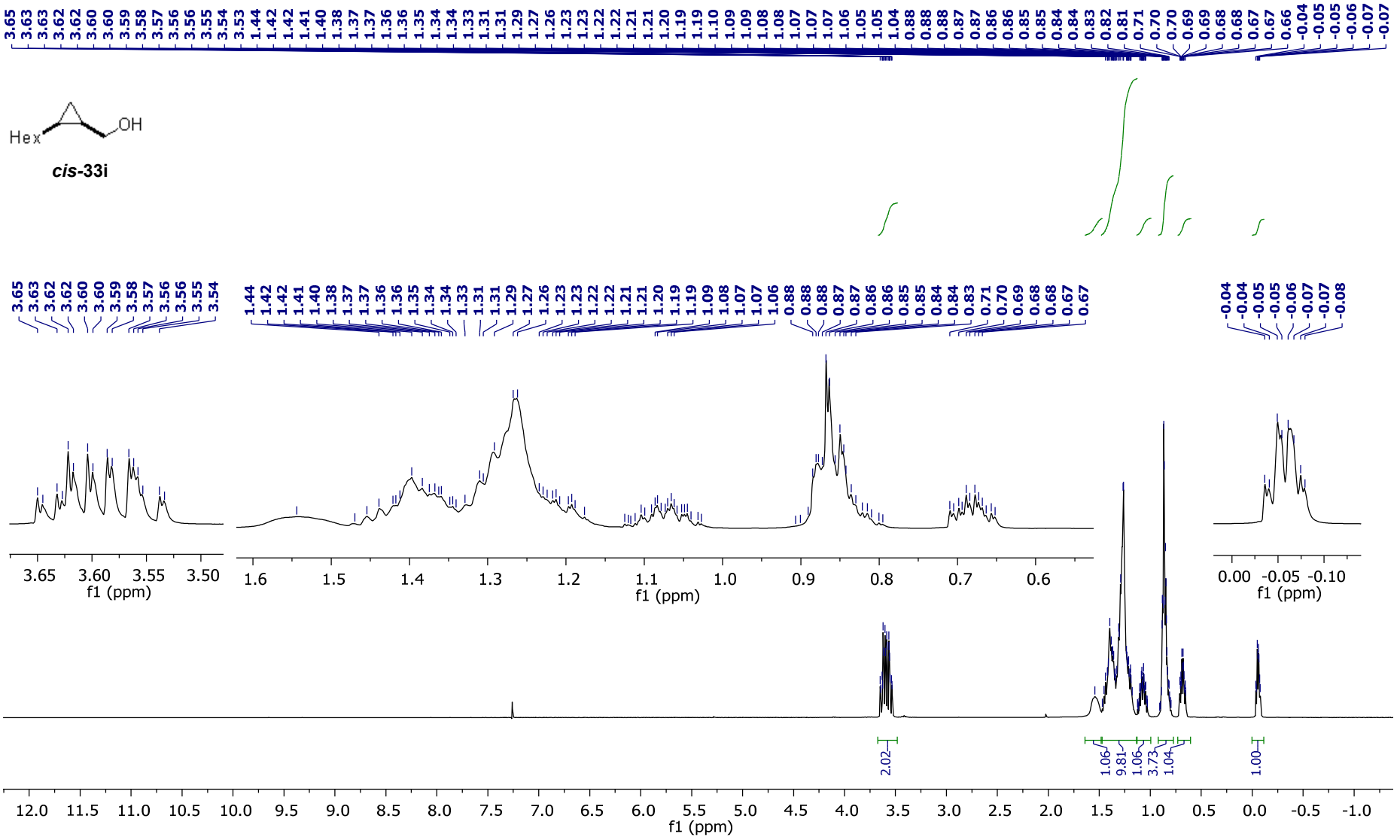

OEt
O
NH
Ph
Ph
9h
f1 (ppm)

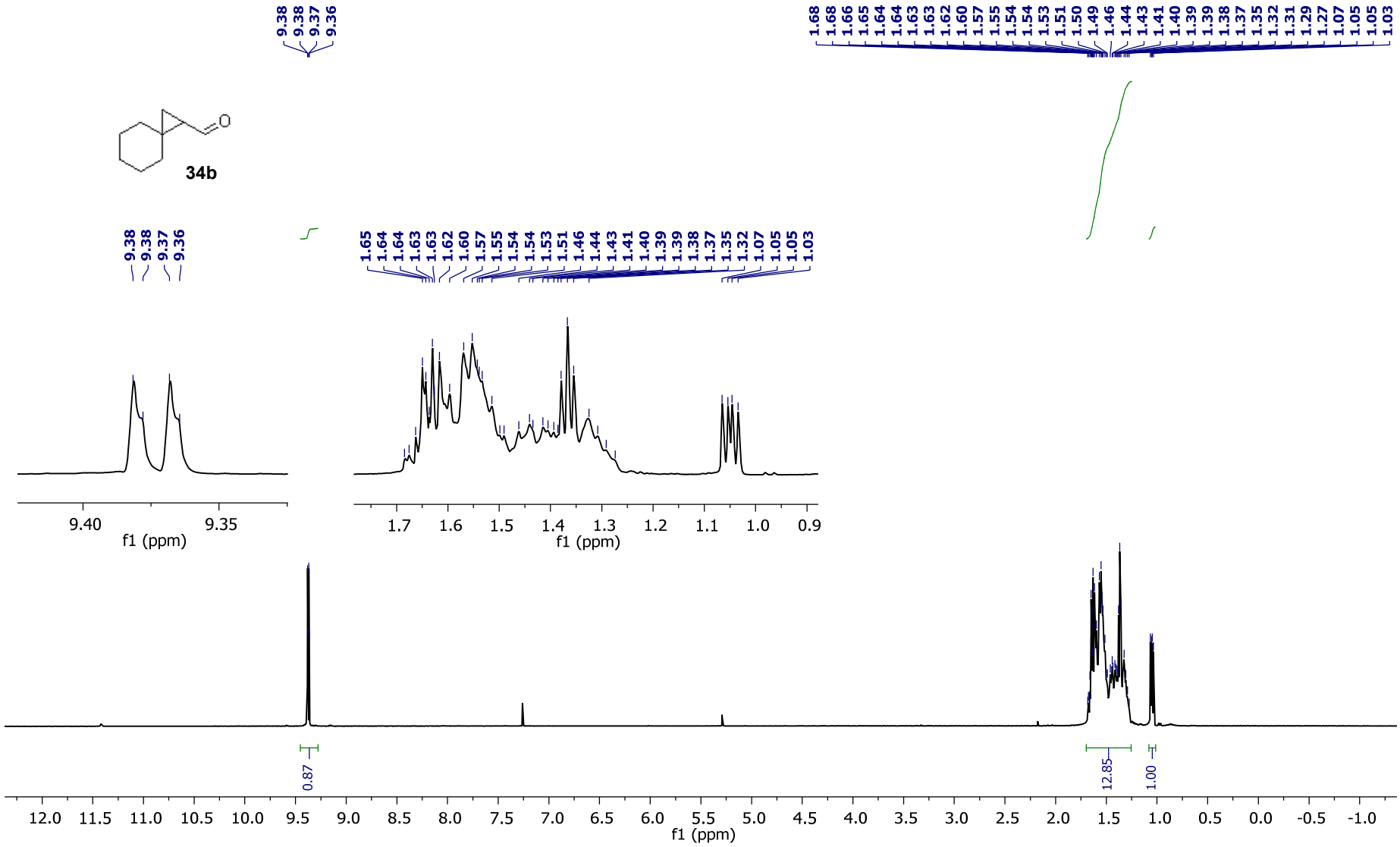

OEt
O
NH
Ph
Ph
9h
156.51
146.13
140.82
130.09
128.57
128.26
127.75
126.73
125.98
60.71
42.30
35.39
25.43
18.76
14.65
f1 (ppm)

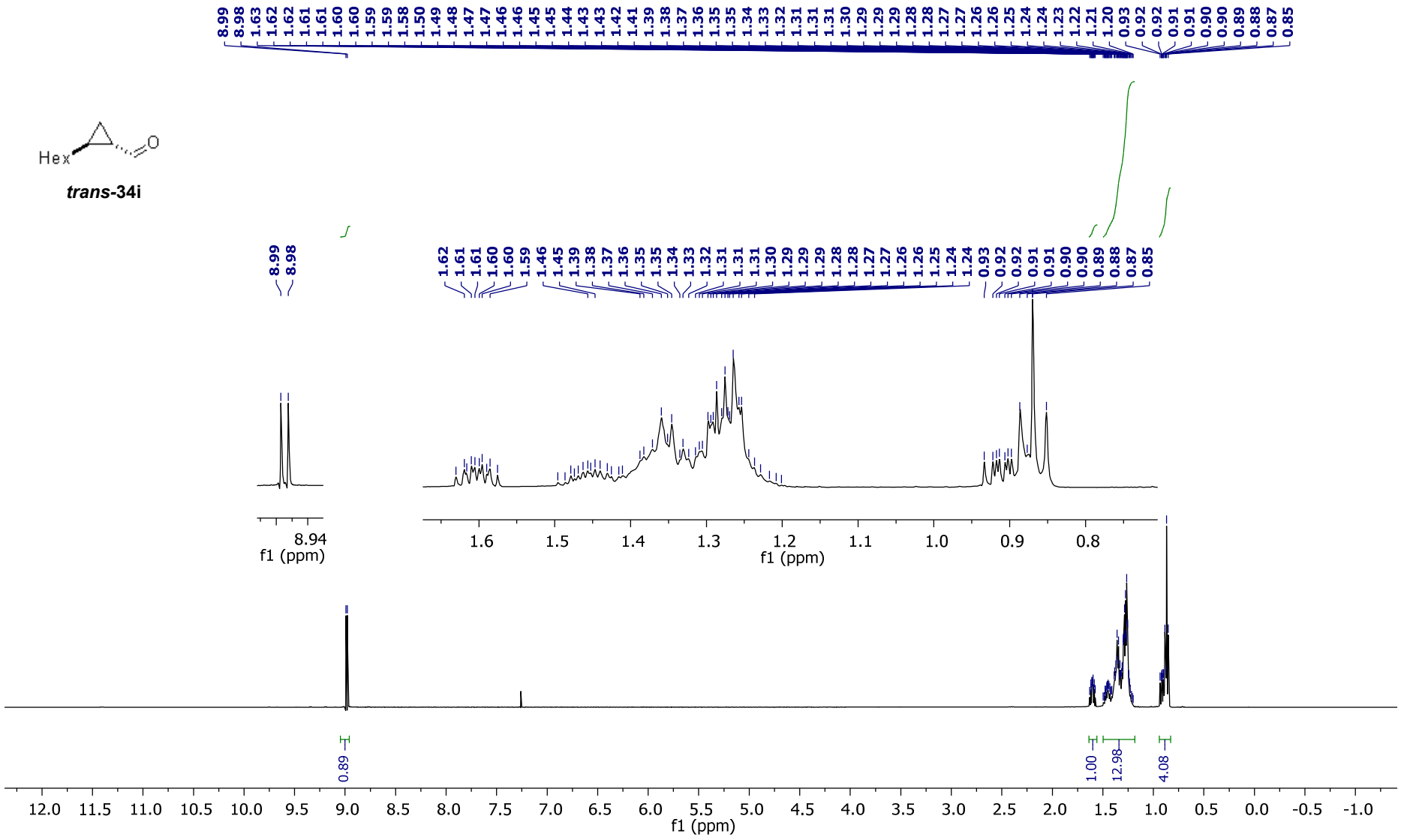

OH
32b
5.39 5.39 5.38 5.37 5.36 5.36 5.34 5.34 5.34
4.16 4.14 4.13 4.12 4.11
2.21 2.19 2.17 2.16 2.13 2.11 2.09 2.07
1.60 1.58 1.57 1.57 1.56 1.55 1.54 1.53 1.52 1.51 1.49 1.48
1.09
f1 (ppm)
1.00
2.04
4.15
6.44
0.97


OH
33b
3.65 3.63 3.62 3.61 3.61 3.59 3.58 3.56
1.53 1.50 1.49 1.45 1.44 1.43 1.40 1.39 1.38 1.37 1.35 1.34 1.31 1.20 1.18 1.16 1.15
0.90 0.89 0.88 0.87 0.86 0.85 0.84 0.83
0.47 0.46 0.44 0.43
0.13 0.11 0.10
f1 (ppm)
2.04
11.31
1.01
1.03
1.00

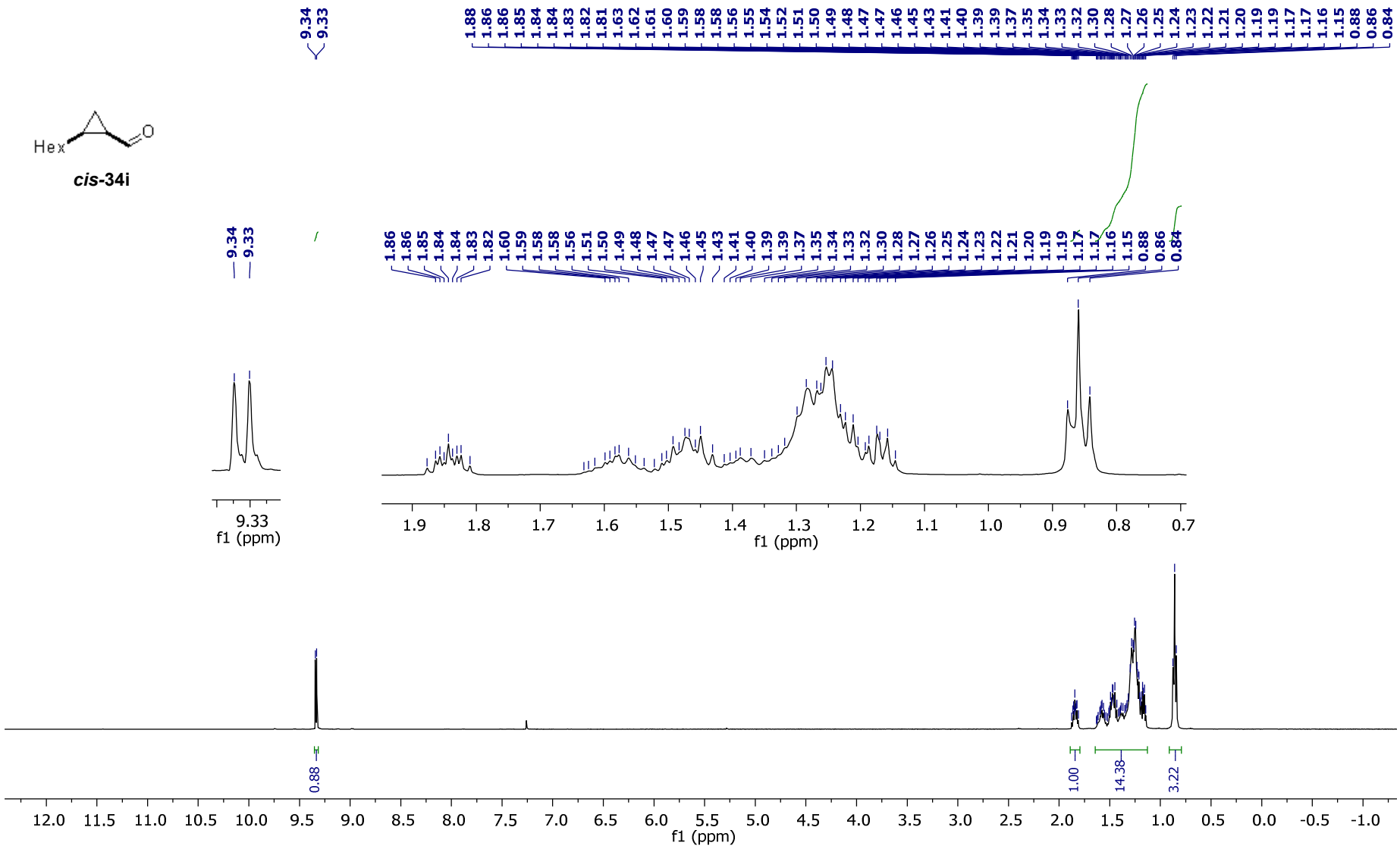

Hex
OH
trans-33i
f1 (ppm)
f1 (ppm)
f1 (ppm)
2.01
1.13
10.12
3.91
1.03
0.97
1.00

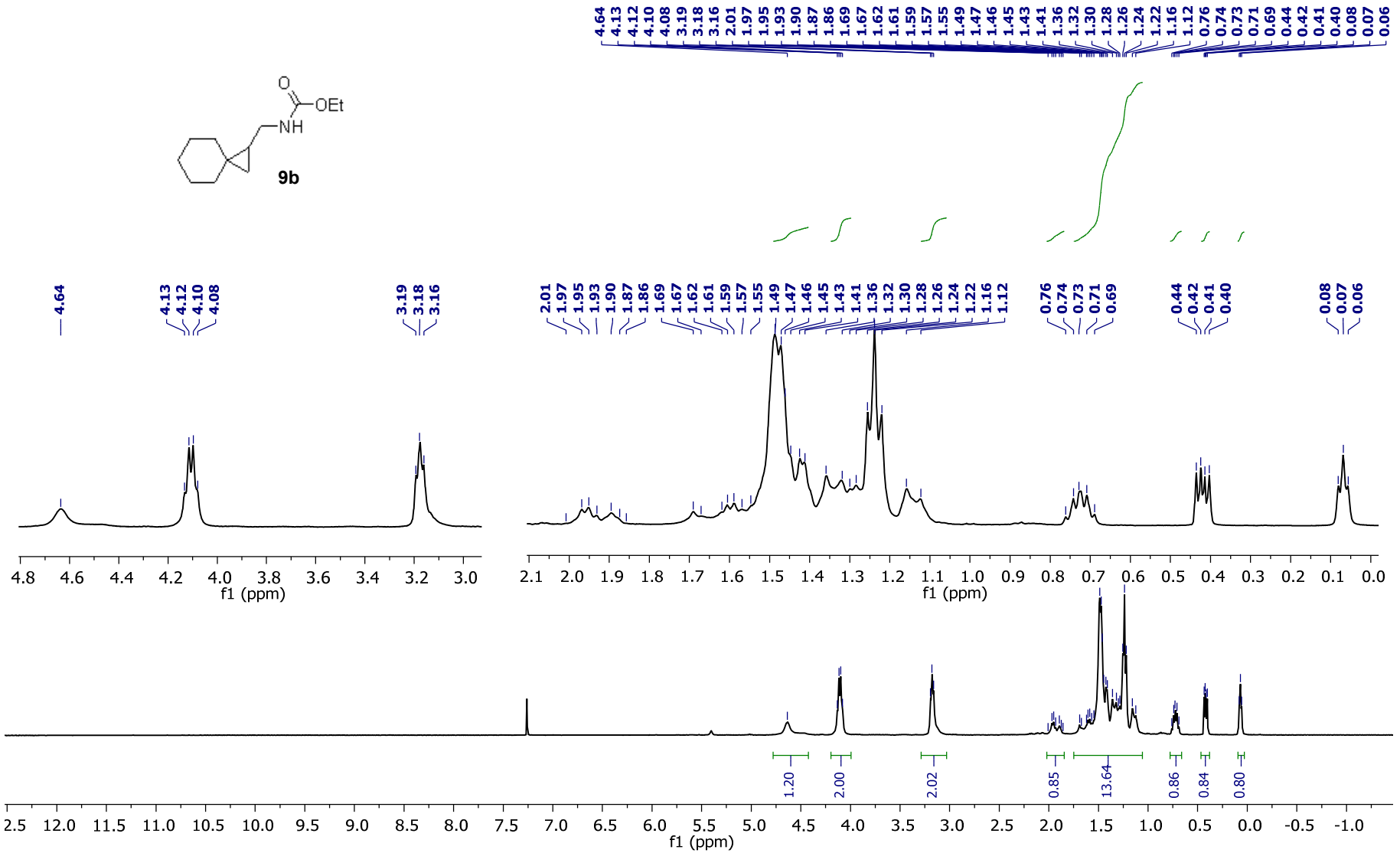

Hex
OH
cis-33i
f1 (ppm)

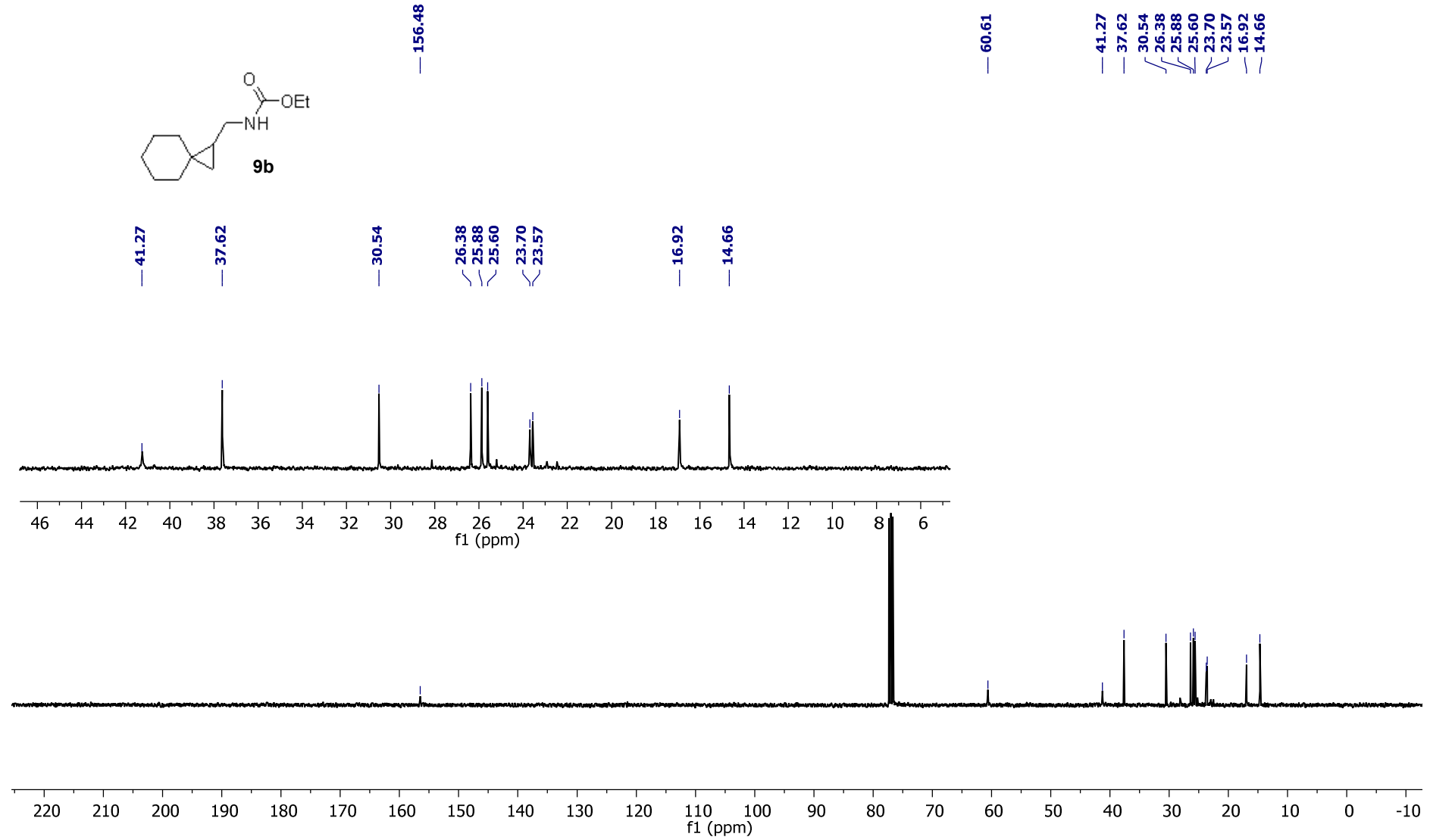

9.38
9.38
9.37
9.36
1.68
1.68
1.66
1.65
1.64
1.64
1.63
1.63
1.62
1.60
1.57
1.55
1.54
1.54
1.53
1.51
1.50
1.49
1.46
1.44
1.43
1.41
1.40
1.39
1.39
1.38
1.37
1.35
1.32
1.31
1.29
1.27
1.07
1.05
1.05
1.03
O
34b
9.40
9.35
f1 (ppm)
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
f1 (ppm)
0.87
12.85
1.00
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

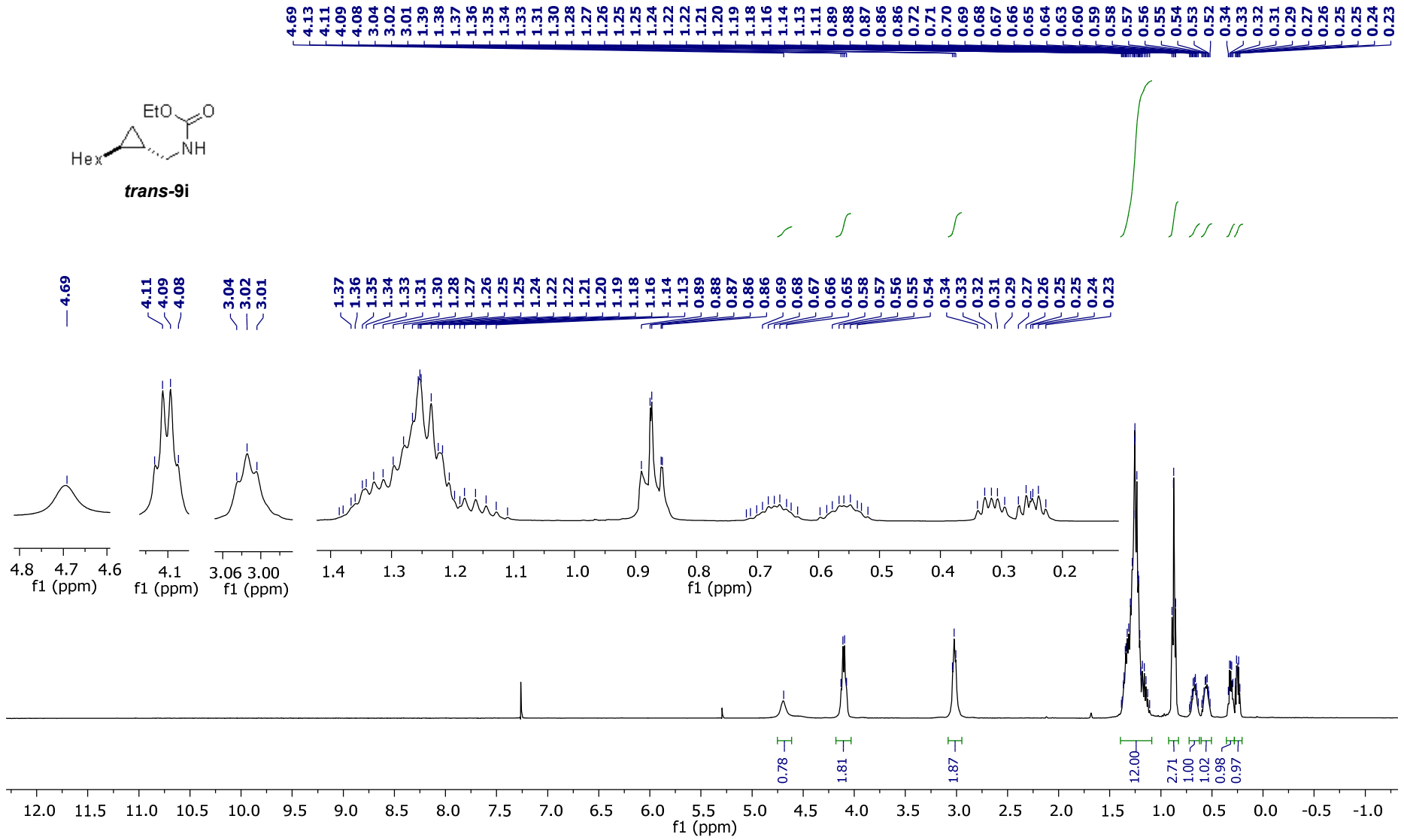

Hex
O
8.99 8.98 1.63 1.62 1.62 1.61 1.61 1.60 1.60 1.59 1.59 1.58 1.50 1.49 1.48 1.47 1.47 1.46 1.46 1.45 1.45 1.44 1.43 1.43 1.42 1.41 1.39 1.38 1.37 1.36 1.35 1.35 1.34 1.33 1.32 1.31 1.31 1.31 1.30 1.29 1.29 1.28 1.28 1.27 1.27 1.26 1.26 1.25 1.24 1.24 1.23 1.22 1.21 1.20 0.93 0.92 0.92 0.91 0.91 0.90 0.90 0.89 0.88 0.87 0.85
8.99 8.98
1.62 1.61 1.61 1.60 1.60 1.59 1.46 1.45 1.39 1.38 1.37 1.36 1.35 1.35 1.34 1.33 1.32 1.31 1.31 1.31 1.30 1.29 1.29 1.29 1.28 1.28 1.27 1.27 1.26 1.26 1.25 1.24 1.24 0.93 0.92 0.92 0.91 0.91 0.90 0.90 0.89 0.88 0.87 0.85
8.94
f1 (ppm)
1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8
f1 (ppm)
0.89
1.00
12.98
4.08
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

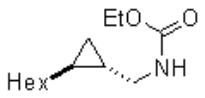
***trans*-34i**


Hex
O
cis-34i
9.34
9.33
1.88
1.86
1.86
1.85
1.84
1.84
1.83
1.82
1.81
1.63
1.62
1.61
1.60
1.59
1.58
1.58
1.56
1.55
1.54
1.52
1.51
1.50
1.49
1.48
1.47
1.47
1.46
1.45
1.43
1.41
1.40
1.39
1.39
1.37
1.35
1.34
1.33
1.32
1.30
1.28
1.27
1.26
1.25
1.24
1.23
1.22
1.21
1.20
1.19
1.19
1.17
1.17
1.16
1.15
0.88
0.86
0.84
9.33
f1 (ppm)
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
f1 (ppm)
0.88
1.00
14.38
3.22
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


4.64 4.13 4.12 4.10 4.08 3.19 3.18 3.16 2.01 1.97 1.95 1.93 1.90 1.87 1.86 1.69 1.67 1.62 1.61 1.59 1.57 1.55 1.49 1.47 1.46 1.45 1.43 1.41 1.36 1.32 1.30 1.28 1.26 1.24 1.22 1.16 1.12 0.76 0.74 0.73 0.71 0.69 0.44 0.42 0.41 0.40 0.08 0.07 0.06
O
OEt
NH
9b
f1 (ppm)
1.20 2.00 2.02 0.85 13.64 0.86 0.84 0.80

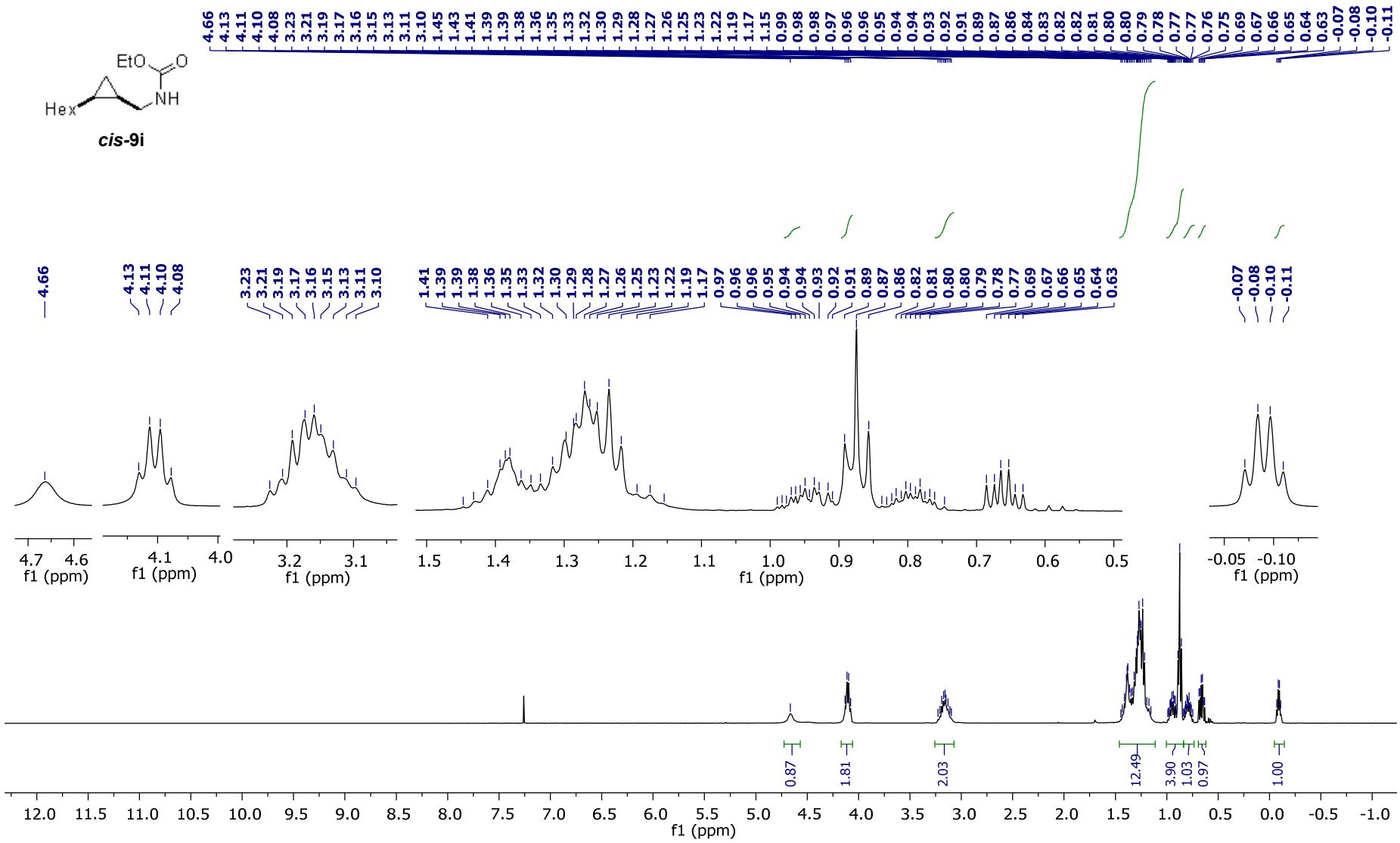

156.48
60.61
41.27
37.62
30.54
26.38
25.88
25.60
23.70
23.57
16.92
14.66
O
OEt
NH
9b
f1 (ppm)
f1 (ppm)

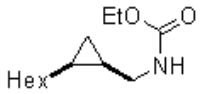

EtO
O
NH
Hex
trans-9i
4.69
4.11
4.09
4.08
3.04
3.02
3.01
f1 (ppm)
0.78
1.81
1.87
12.00
2.71
1.00
1.02
0.98
0.97


EtO
O
NH
Hex

***trans*-9i**

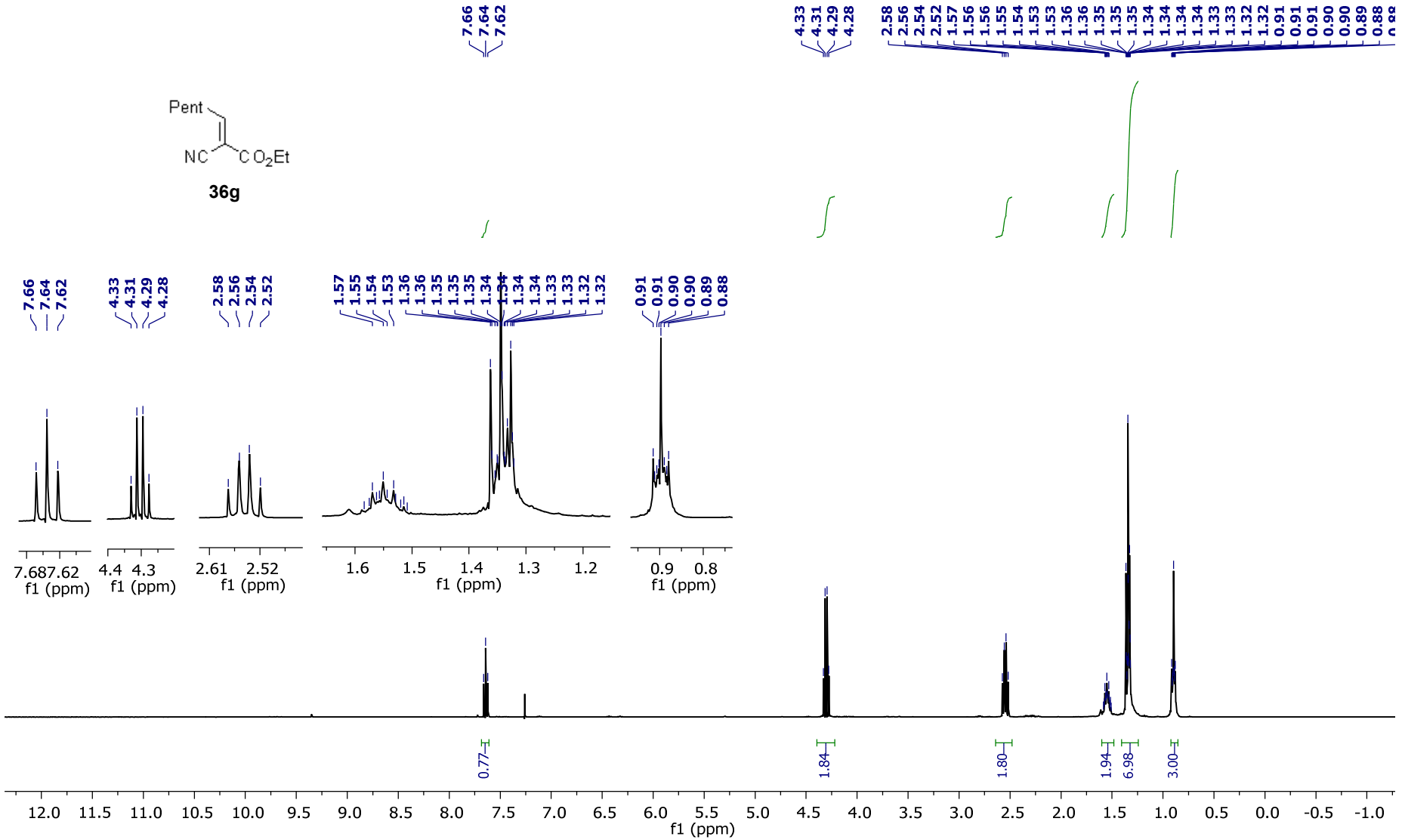
156.55
60.59
45.39
33.60
31.86
29.49
29.07
22.63
18.50
17.65
14.65
14.07
10.38
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

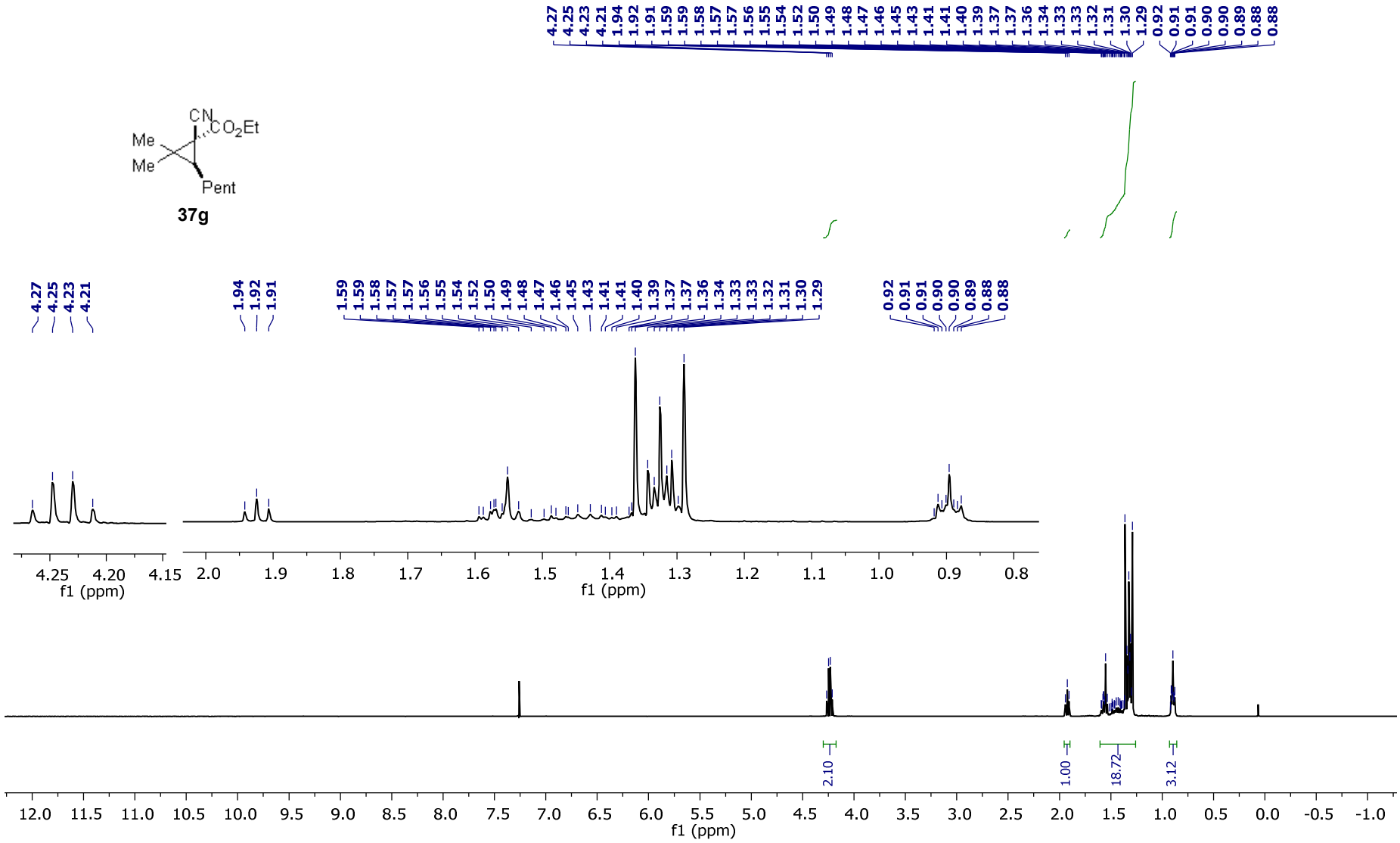

EtO
O
NH
Hex
cis-9i
f1 (ppm)
0.87
1.81
2.03
12.49
3.90
1.03
0.97
1.00

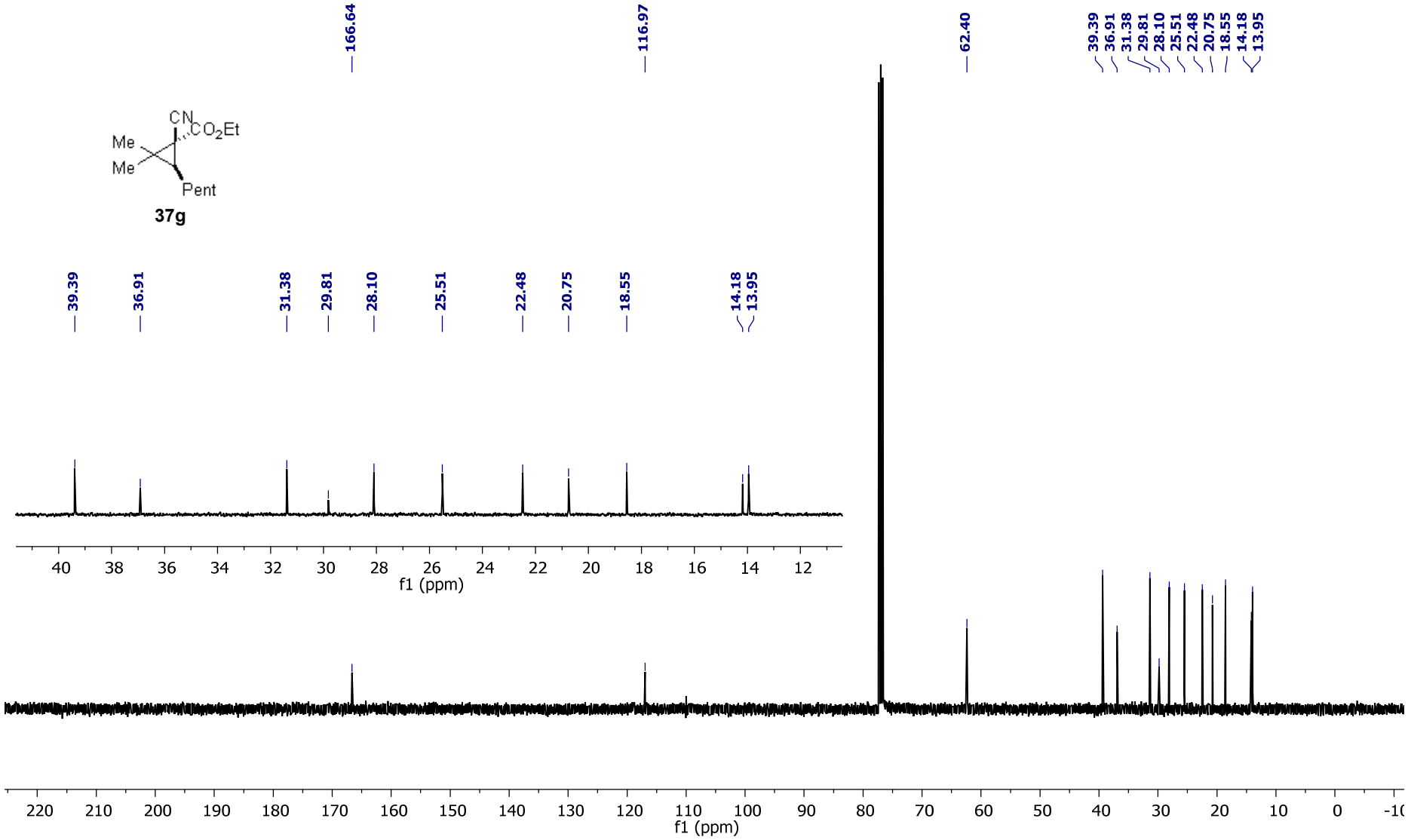

EtO
O
NH
Hex

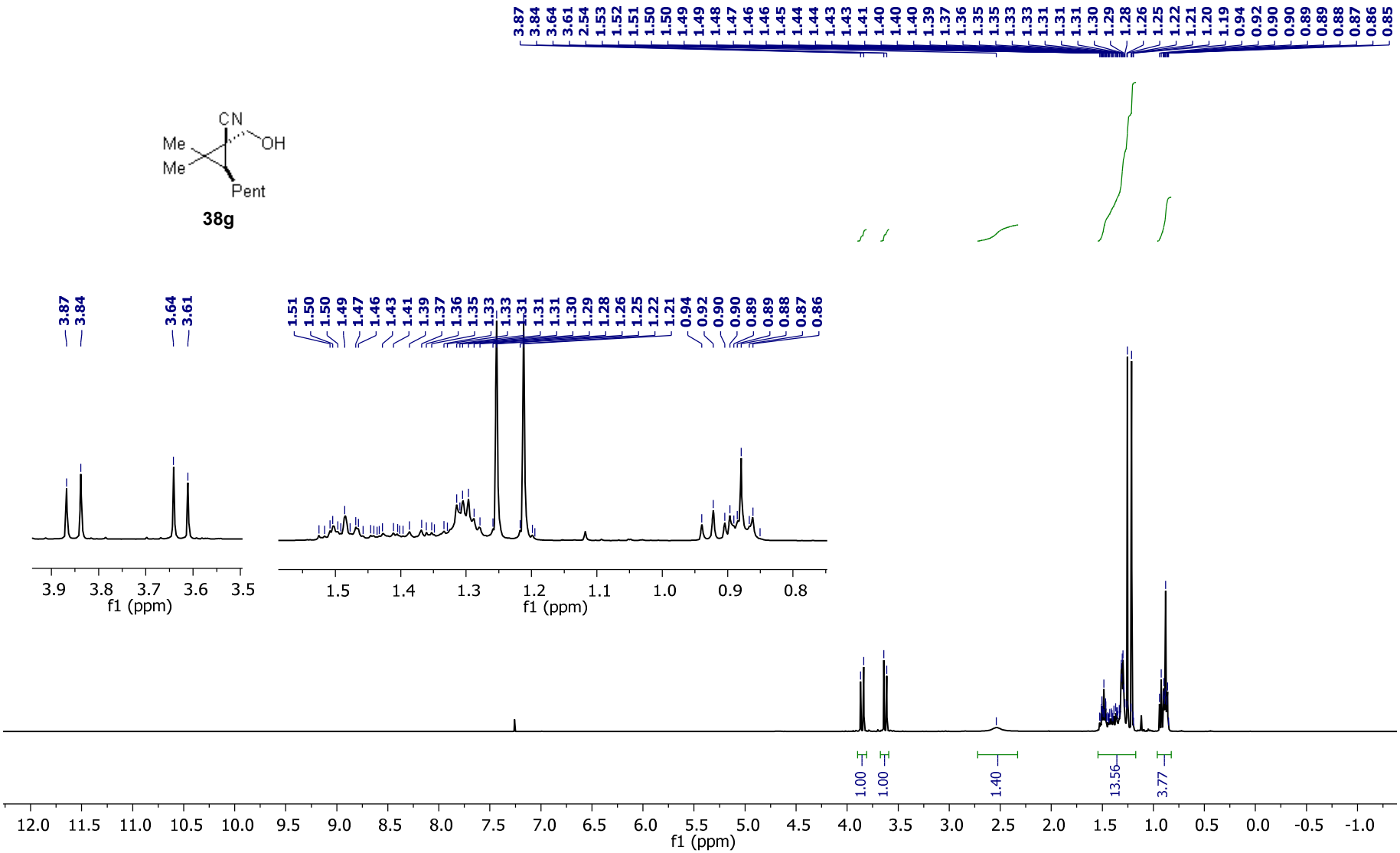
***cis*-9i**

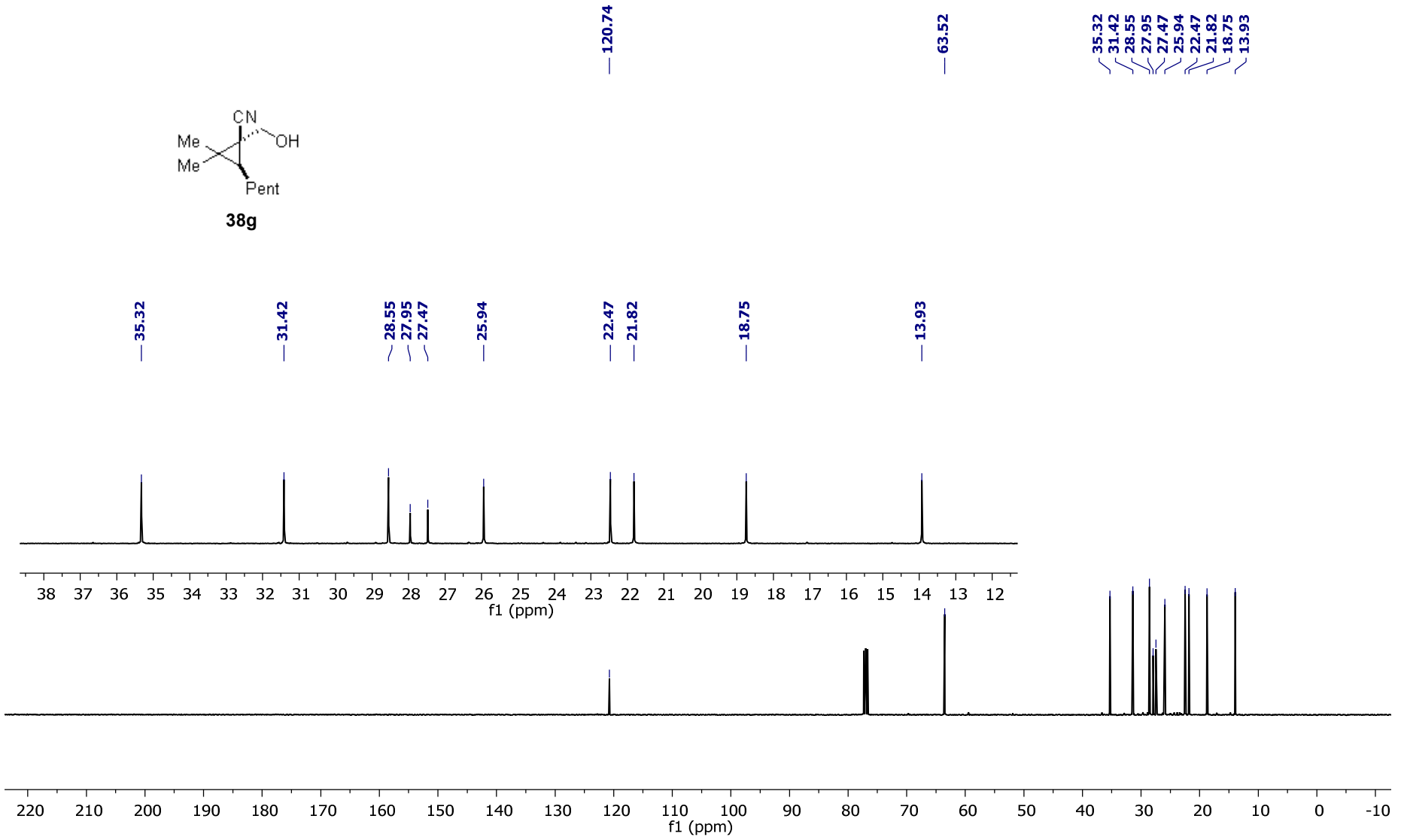
156.49
60.61
41.20
31.83
30.07
29.18
28.54
22.63
15.87
15.50
14.66
14.06
9.88
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

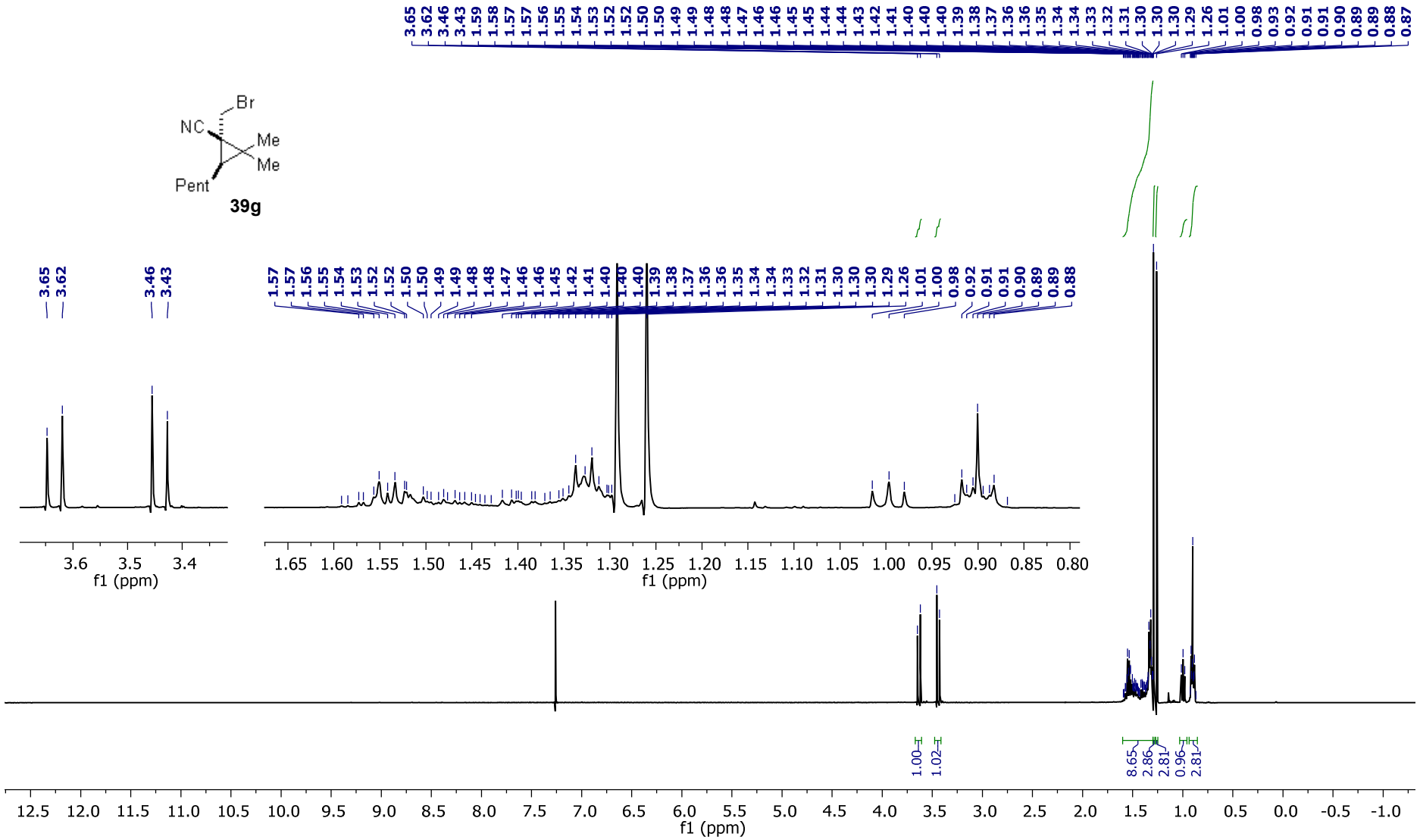

Pent
NC
CO2Et
36g
7.66
7.64
7.62
4.33
4.31
4.29
4.28
2.58
2.56
2.54
2.52
1.57
1.55
1.54
1.53
1.36
1.35
1.34
1.33
1.32
0.91
0.90
0.89
0.88
f1 (ppm)
0.77
1.84
1.80
1.94
6.98
3.00

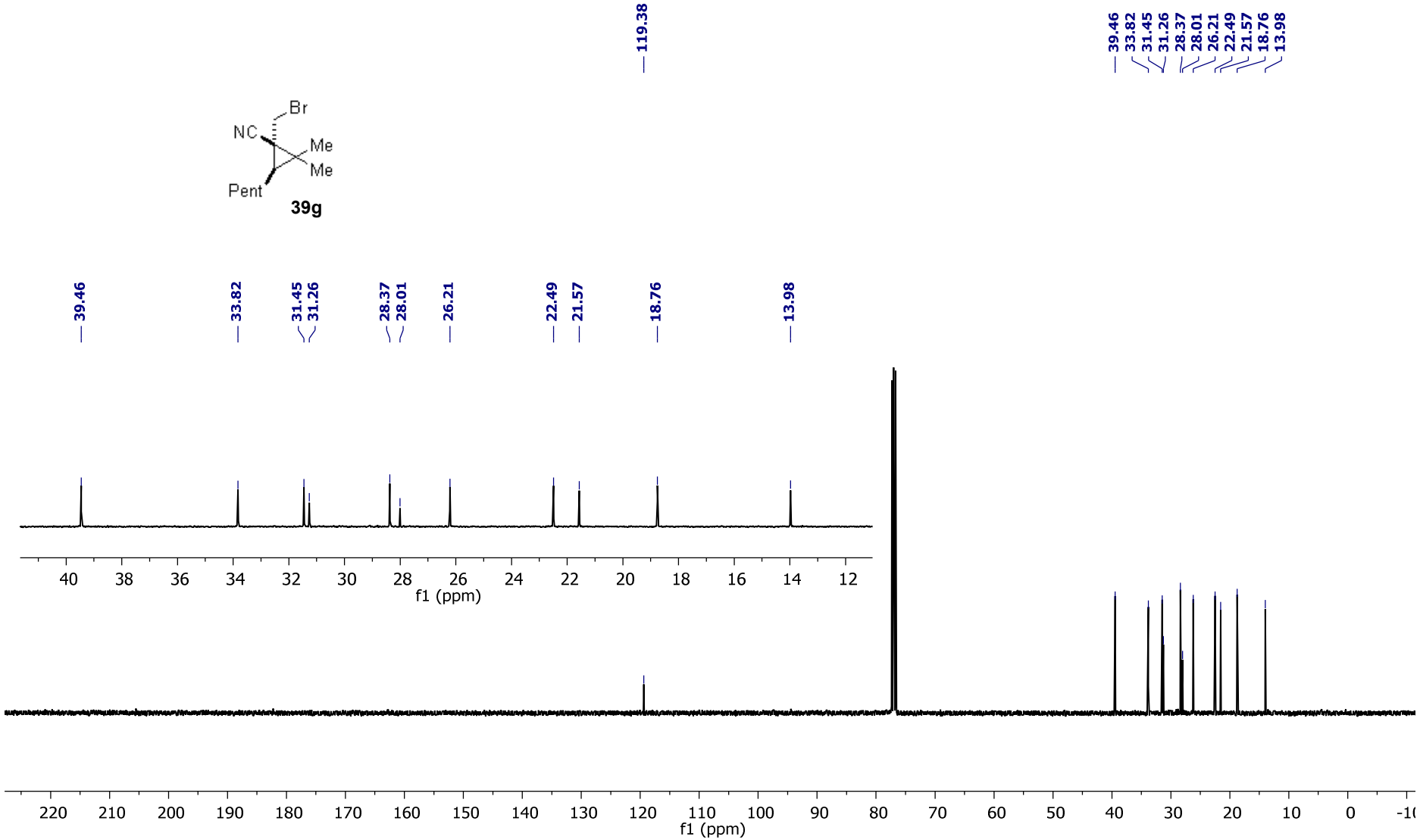

4.27 4.25 4.23 4.21 1.94 1.92 1.91 1.59 1.59 1.58 1.57 1.57 1.56 1.55 1.54 1.52 1.50 1.49 1.48 1.47 1.46 1.45 1.43 1.41 1.41 1.40 1.39 1.37 1.37 1.36 1.34 1.33 1.33 1.32 1.31 1.30 1.29 0.92 0.91 0.91 0.90 0.90 0.89 0.88 0.88
CN
CO2Et
Me
Me
Pent
37g
f1 (ppm)
2.10
1.00
18.72
3.12

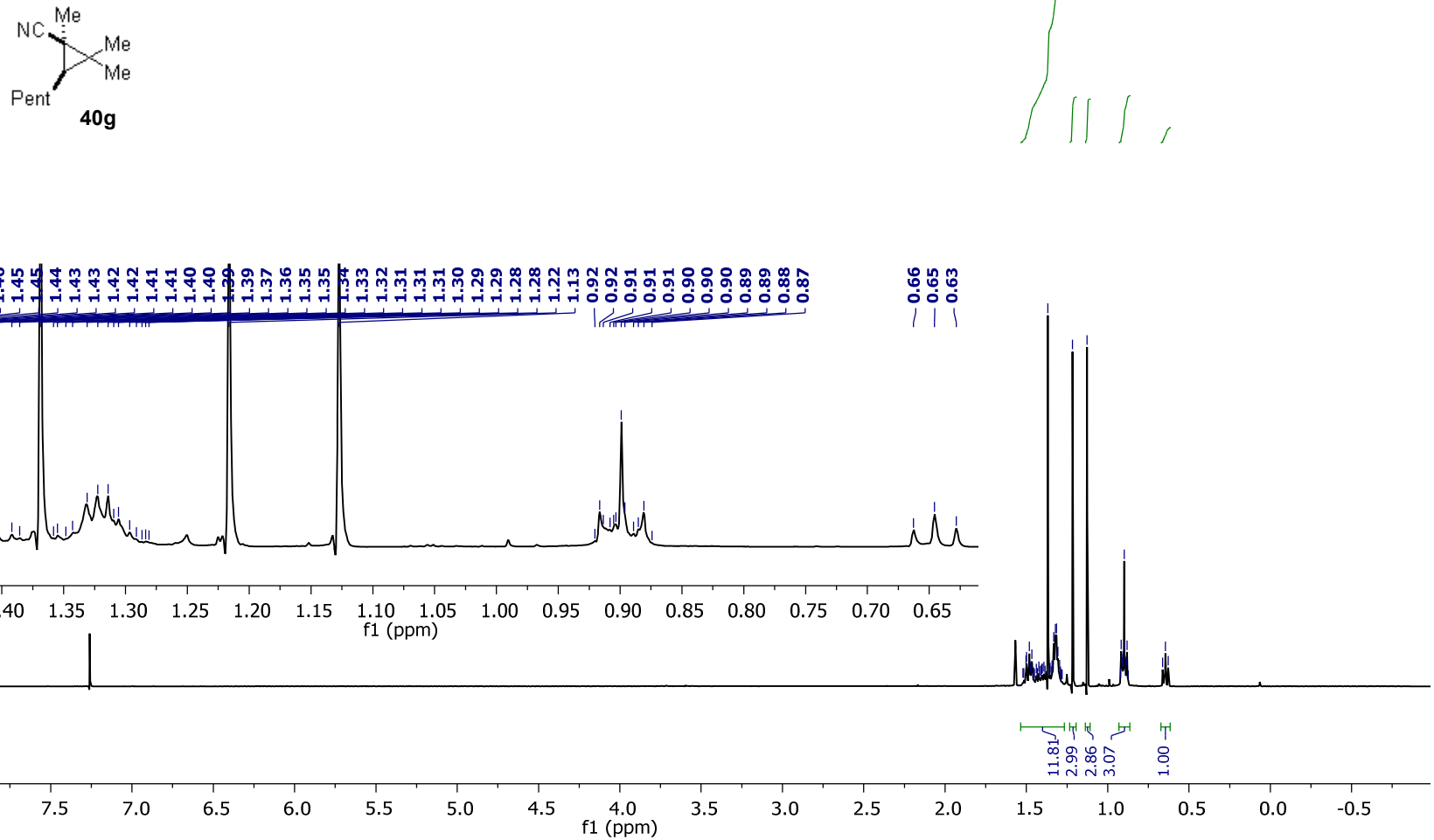

166.64
116.97
62.40
39.39
36.91
31.38
29.81
28.10
25.51
22.48
20.75
18.55
14.18
13.95
CN
CO2Et
Me
Me
Pent
37g
f1 (ppm)
f1 (ppm)

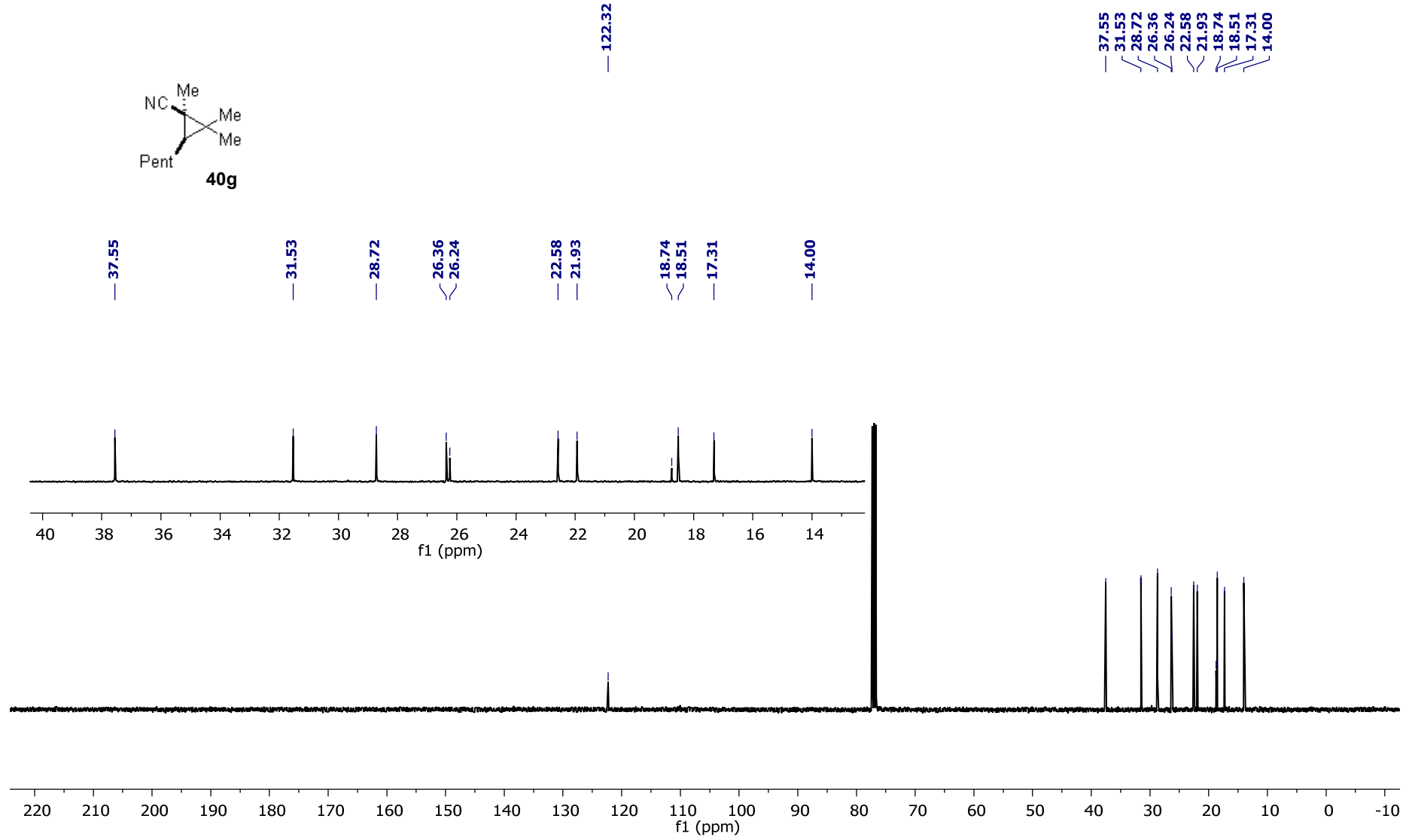

CN
OH
Me
Me
Pent
38g
3.87 3.84 3.64 3.61 2.54 1.53 1.52 1.51 1.50 1.50 1.49 1.49 1.48 1.47 1.46 1.46 1.45 1.44 1.44 1.43 1.43 1.41 1.40 1.40 1.40 1.39 1.37 1.36 1.35 1.35 1.33 1.33 1.31 1.31 1.31 1.30 1.29 1.28 1.26 1.25 1.22 1.21 1.20 1.19 0.94 0.92 0.90 0.90 0.89 0.89 0.88 0.87 0.86 0.85
f1 (ppm)
1.00
1.00
1.40
13.56
3.77

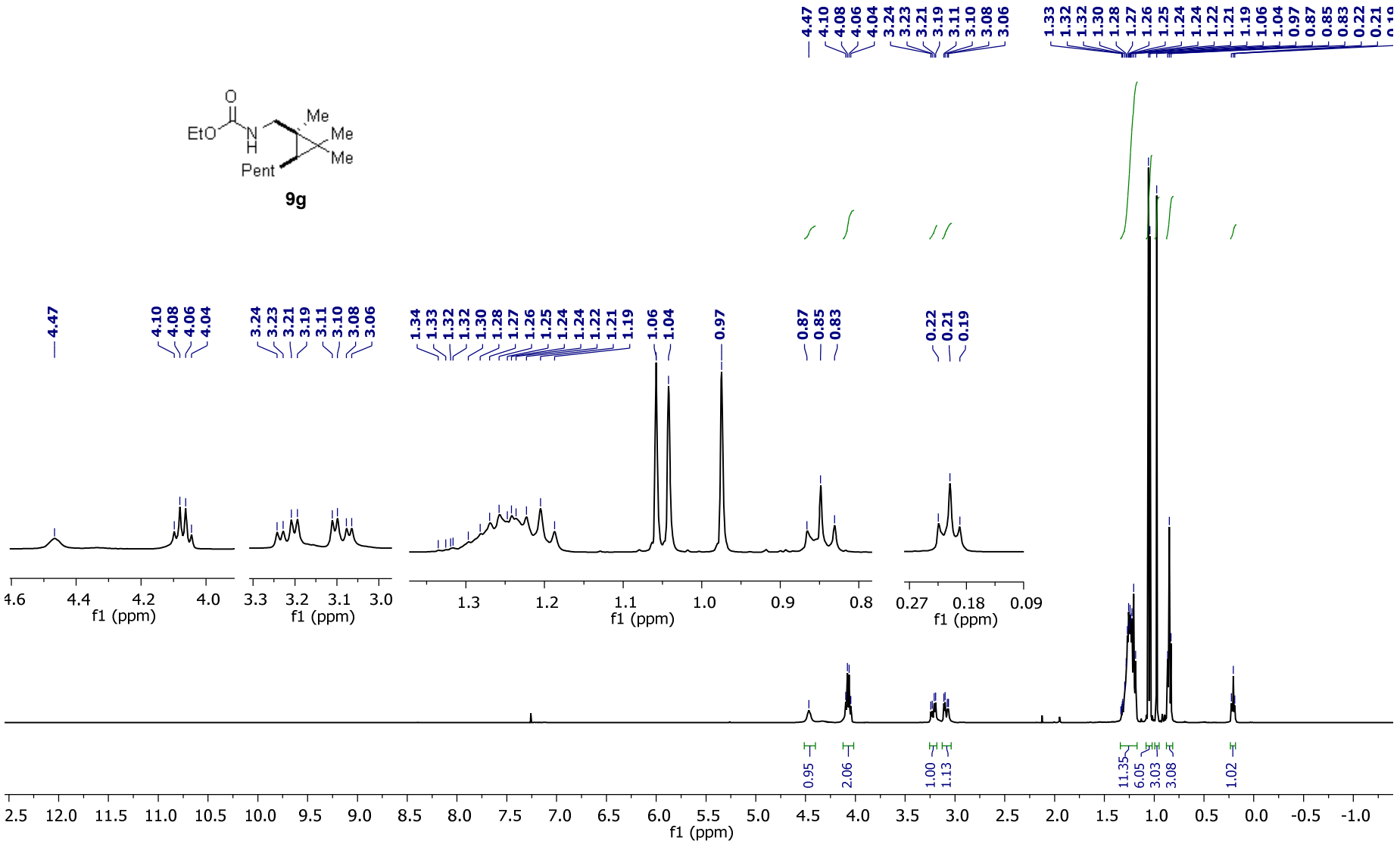

CN
OH
Me
Me
Pent
38g
120.74
63.52
35.32
31.42
28.55
27.95
27.47
25.94
22.47
21.82
18.75
13.93
f1 (ppm)
f1 (ppm)

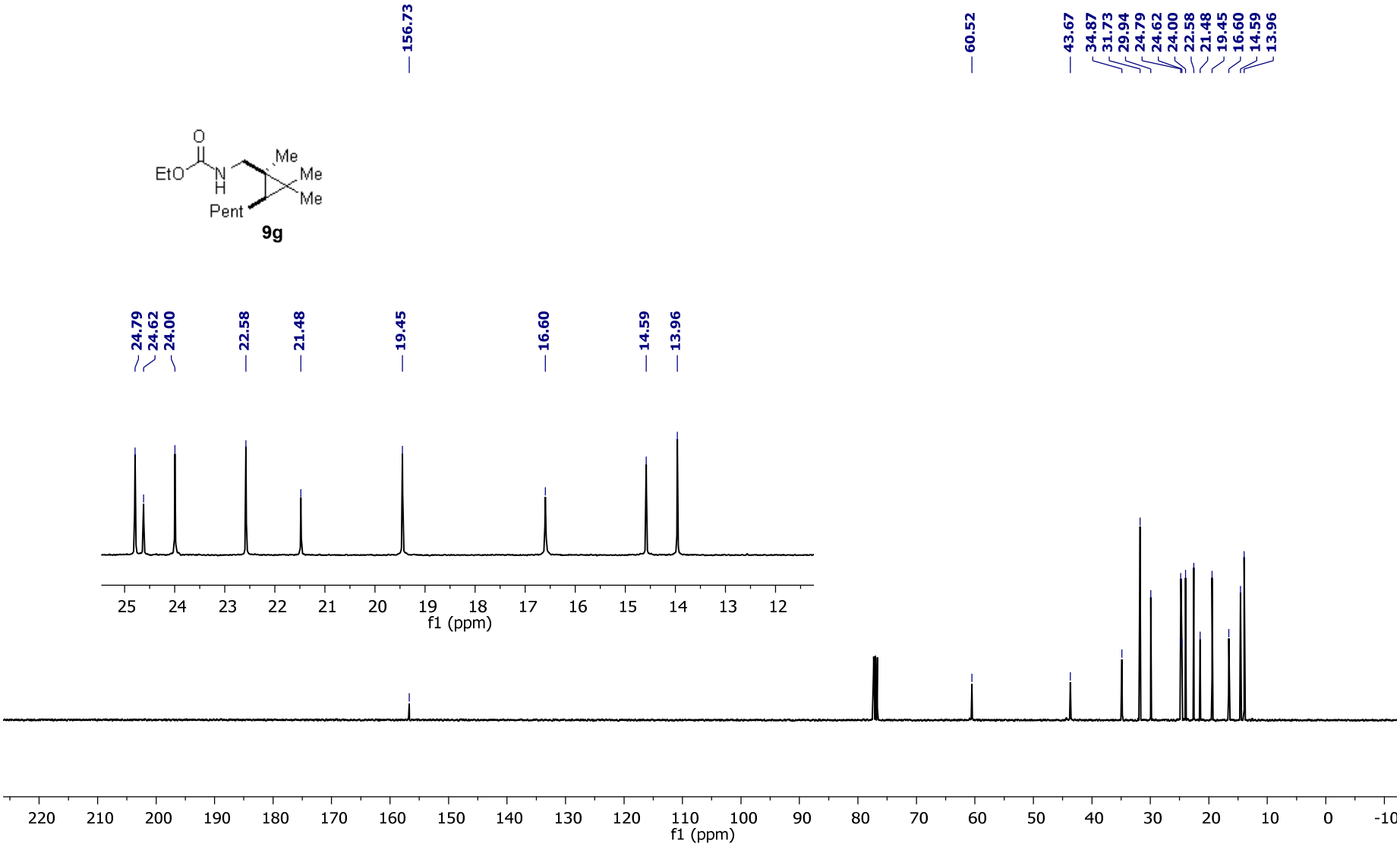

Br
NC
Me
Me
Pent
39g
f1 (ppm)

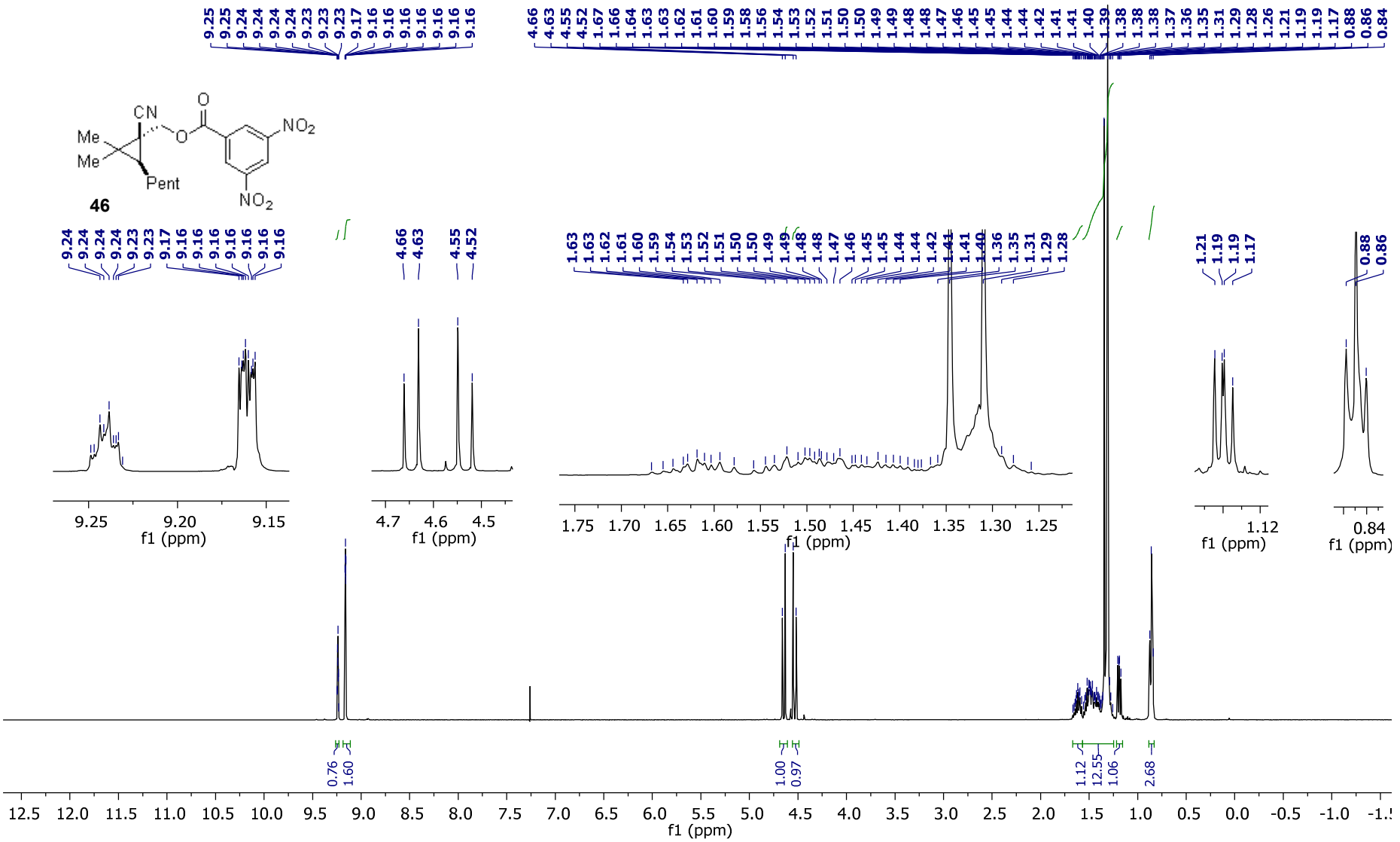

119.38
39.46
33.82
31.45
31.26
28.37
28.01
26.21
22.49
21.57
18.76
13.98
Br
NC
Me
Me
Pent
39g
f1 (ppm)
f1 (ppm)

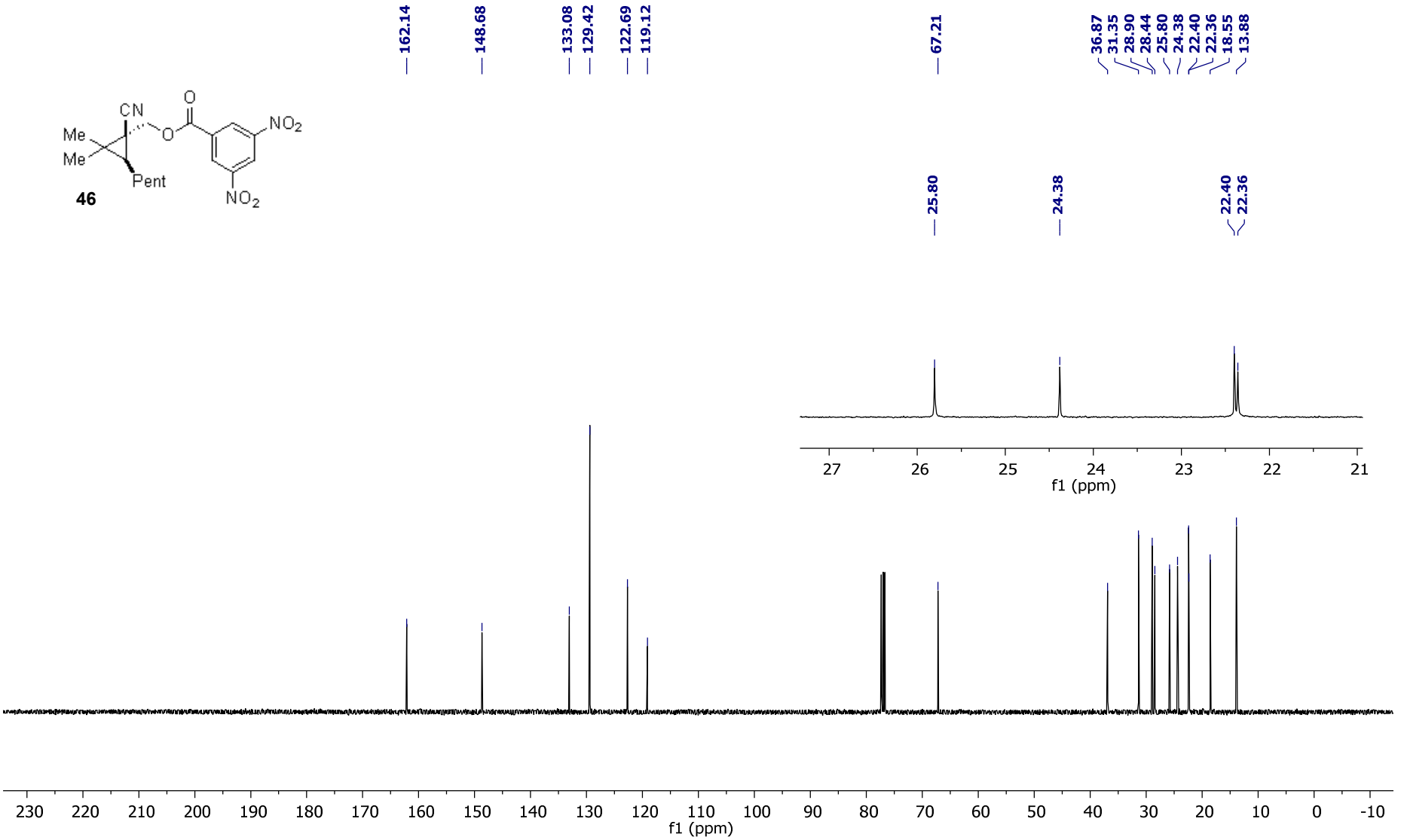

Me
NC
Me
Me
Pent
40g
1.52 1.52 1.50 1.50 1.48 1.47 1.47 1.47 1.46 1.46 1.45 1.45 1.44 1.43 1.43 1.42 1.42 1.41 1.41 1.40 1.40 1.39 1.39 1.37 1.36 1.35 1.35 1.34 1.33 1.32 1.31 1.31 1.31 1.30 1.29 1.29 1.28 1.28 1.22 1.13 0.92 0.92 0.91 0.91 0.90 0.90 0.90 0.89 0.89 0.88 0.87 0.66 0.65 0.63
1.50 1.45 1.40 1.35 1.30 1.25 1.20 1.15 1.10 1.05 1.00 0.95 0.90 0.85 0.80 0.75 0.70 0.65
f1 (ppm)
11.81
2.99
2.86
3.07
1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

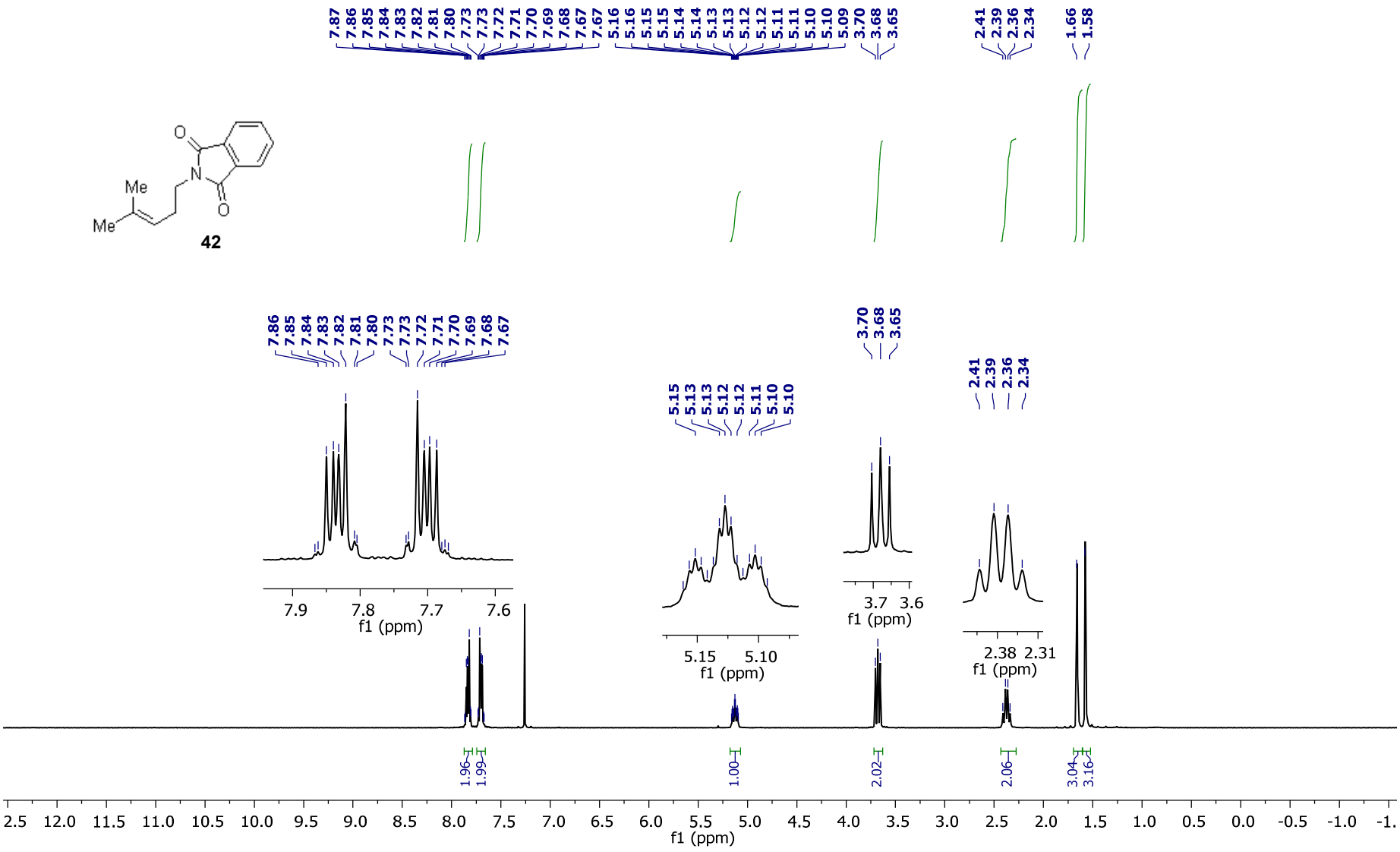

Me
NC
Me
Me
Pent
40g
122.32
37.55
31.53
28.72
26.36
26.24
22.58
21.93
18.74
18.51
17.31
14.00
f1 (ppm)
f1 (ppm)

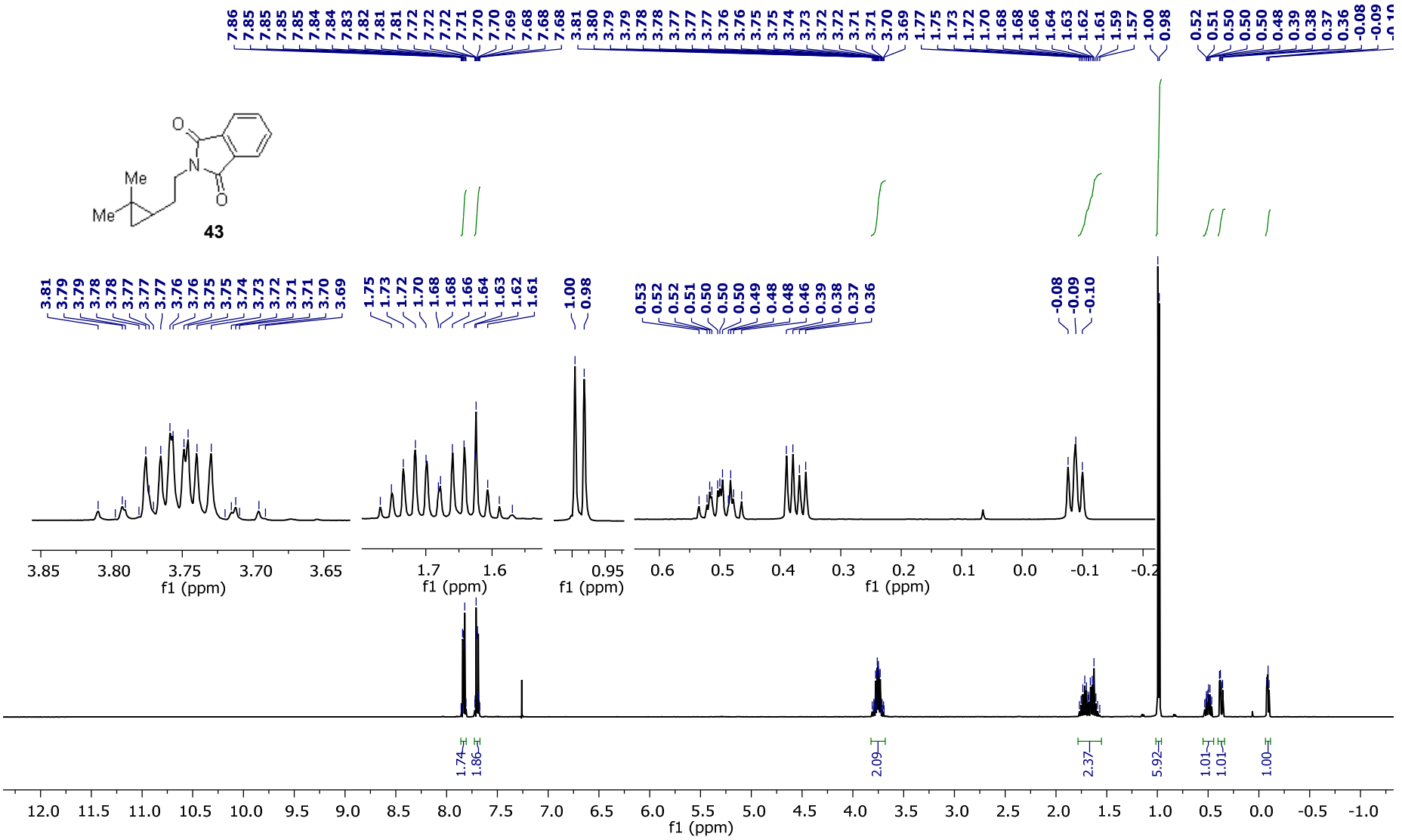

O
EtO
N
H
Me
Me
Me
Pent
9g
4.47
4.10
4.08
4.06
4.04
3.24
3.23
3.21
3.19
3.11
3.10
3.08
3.06
1.34
1.33
1.32
1.32
1.30
1.28
1.27
1.26
1.25
1.24
1.24
1.22
1.21
1.19
1.06
1.04
0.97
0.87
0.85
0.83
0.22
0.21
0.19
f1 (ppm)
0.95
2.06
1.00
1.13
11.35
6.05
3.03
3.08
1.02

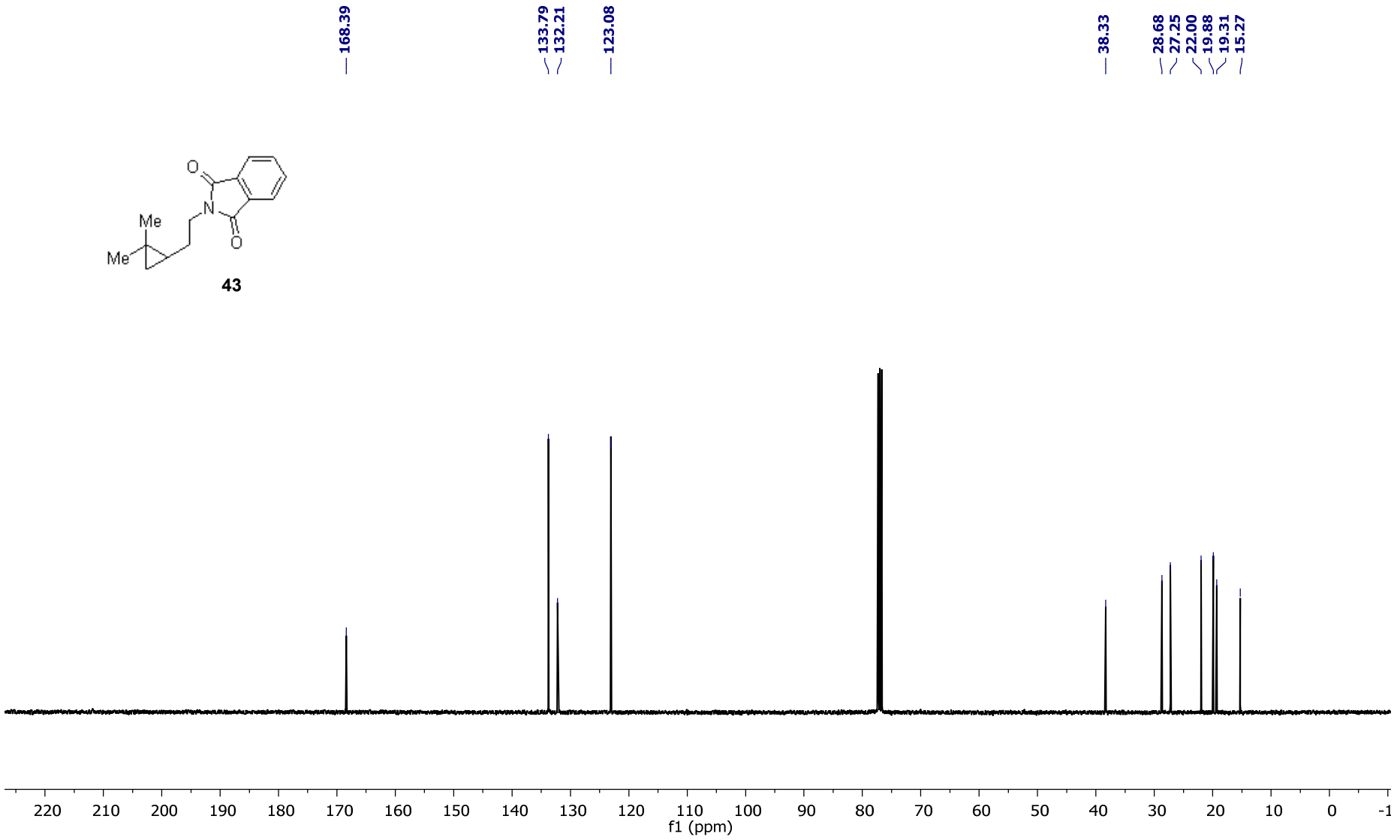

156.73
60.52
43.67
34.87
31.73
29.94
24.79
24.62
24.00
22.58
21.48
19.45
16.60
14.59
13.96
O
EtO
N
H
Me
Me
Me
Pent
9g
f1 (ppm)
f1 (ppm)

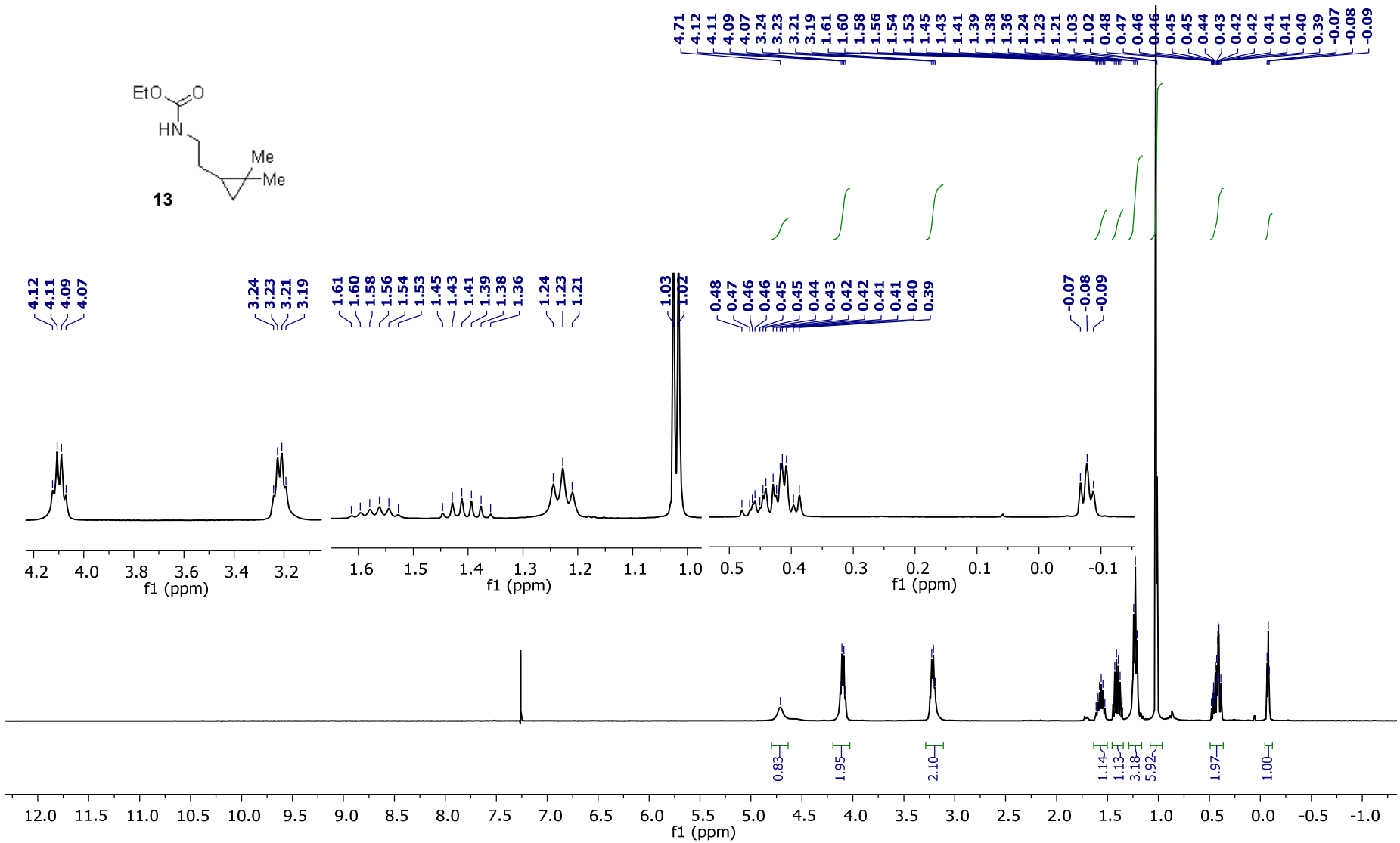

CN
O
Me
Me
Pent
O
NO2
NO2
46
f1 (ppm)
0.76
1.60
1.00
0.97
1.12
12.55
1.06
2.68

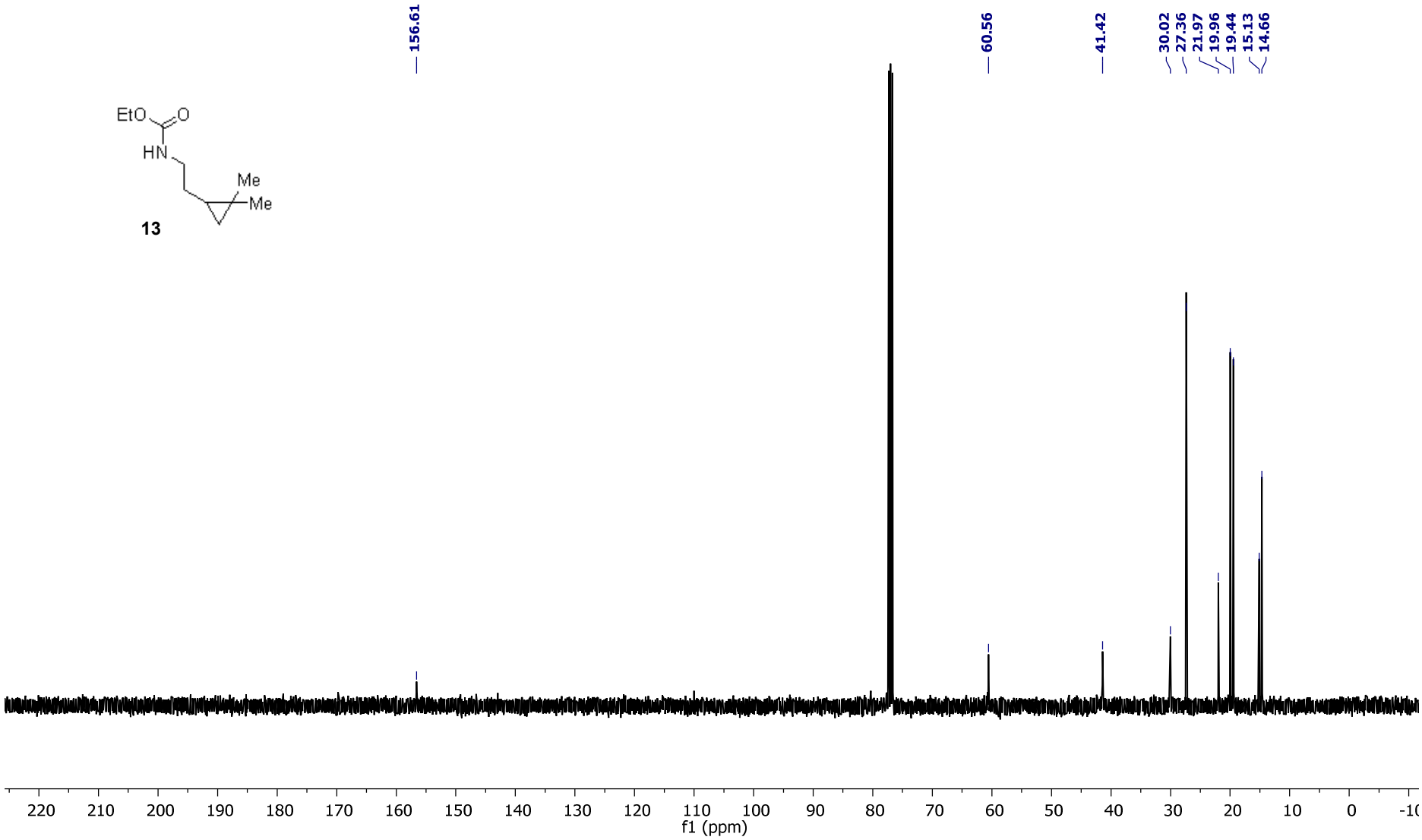

162.14
148.68
133.08
129.42
122.69
119.12
67.21
36.87
31.35
28.90
28.44
25.80
24.38
22.40
22.36
18.55
13.88
CN
O
O
NO2
Me
Me
Pent
NO2
46
25.80
24.38
22.40
22.36
27
26
25
24
23
22
21
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

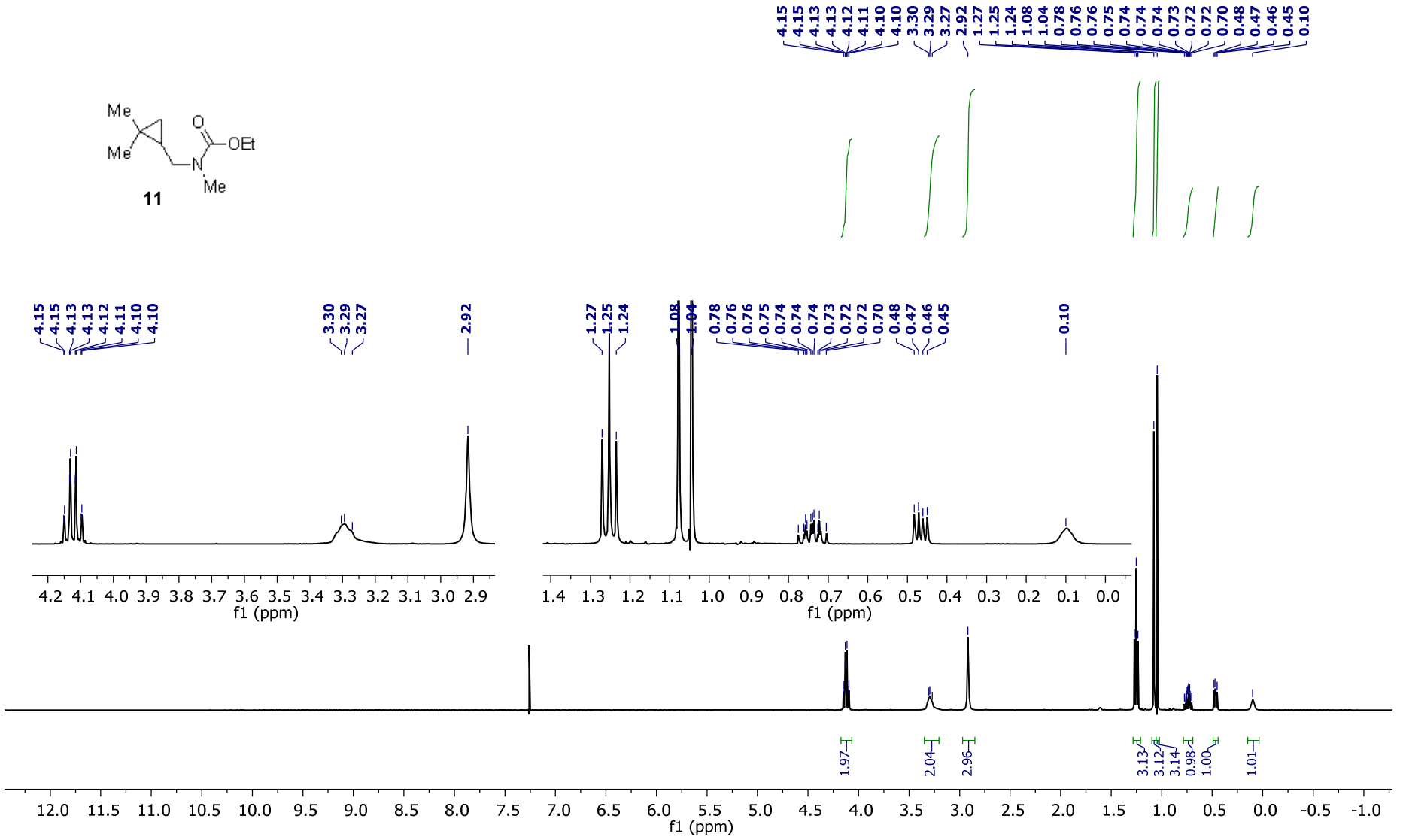

7.87 7.86 7.85 7.84 7.83 7.82 7.81 7.80 7.73 7.73 7.72 7.71 7.70 7.69 7.68 7.67 7.67
5.16 5.16 5.15 5.15 5.14 5.14 5.13 5.13 5.12 5.12 5.11 5.11 5.10 5.10 5.09
3.70 3.68 3.65
2.41 2.39 2.36 2.34
1.66 1.58
O
N
O
Me
Me
42
7.9 7.8 7.7 7.6
f1 (ppm)
5.15 5.10
f1 (ppm)
3.7 3.6
f1 (ppm)
2.38 2.31
f1 (ppm)
1.96 1.99 1.00 2.02 2.06 3.04 3.16
f1 (ppm)

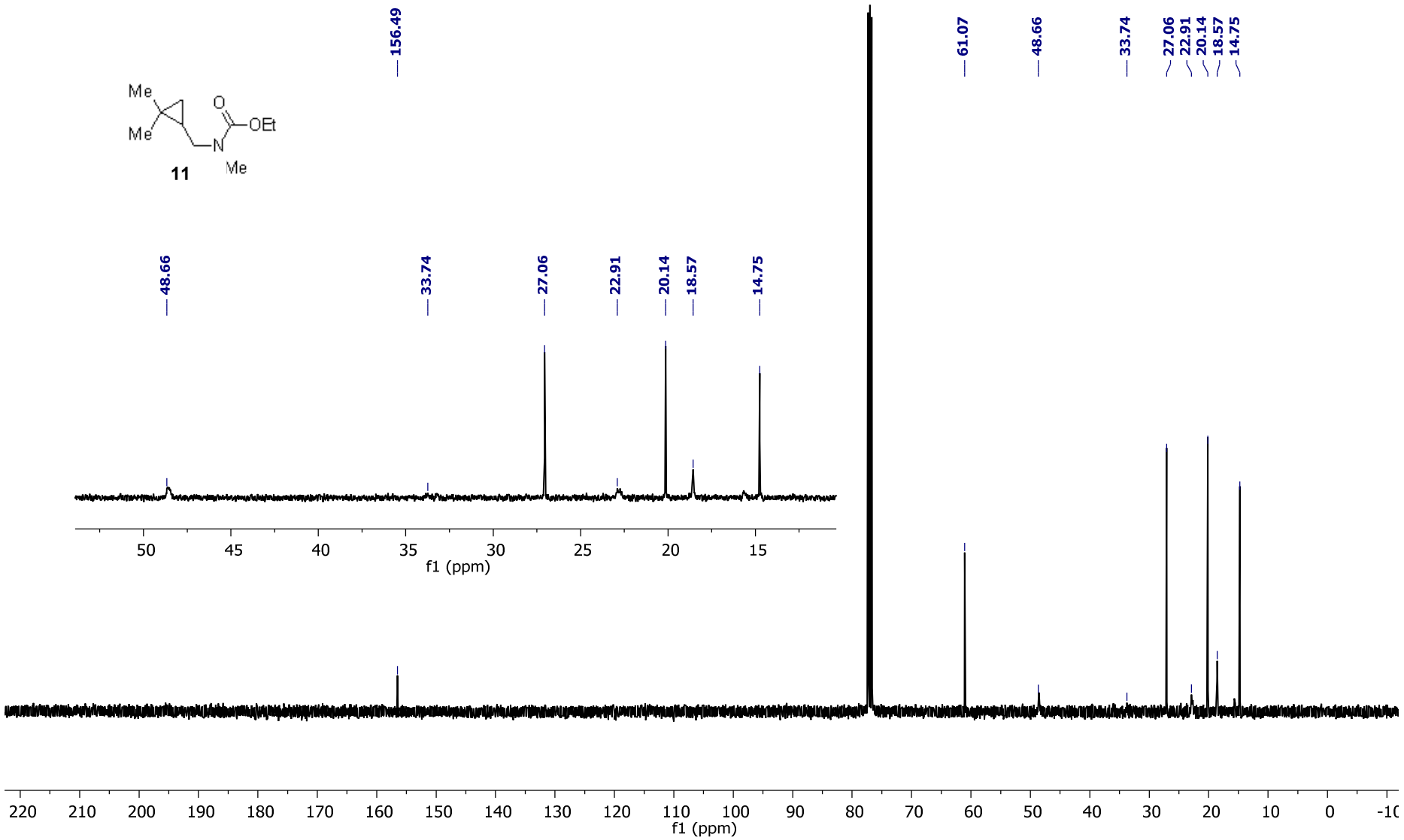

7.86 7.85 7.85 7.85 7.85 7.84 7.84 7.83 7.82 7.81 7.81 7.72 7.72 7.72 7.71 7.70 7.70 7.69 7.68 7.68 7.68
3.81 3.80 3.79 3.79 3.78 3.78 3.77 3.77 3.77 3.76 3.76 3.75 3.75 3.74 3.73 3.72 3.72 3.71 3.71 3.70 3.69
1.77 1.75 1.73 1.72 1.70 1.68 1.68 1.66 1.64 1.63 1.62 1.61 1.59 1.57 1.00 0.98
0.52 0.51 0.50 0.50 0.50 0.48 0.39 0.38 0.37 0.36 -0.08 -0.09
O
N
O
Me
Me
43
f1 (ppm)
1.74
1.86
2.09
2.37
5.92
1.01
1.01
1.00

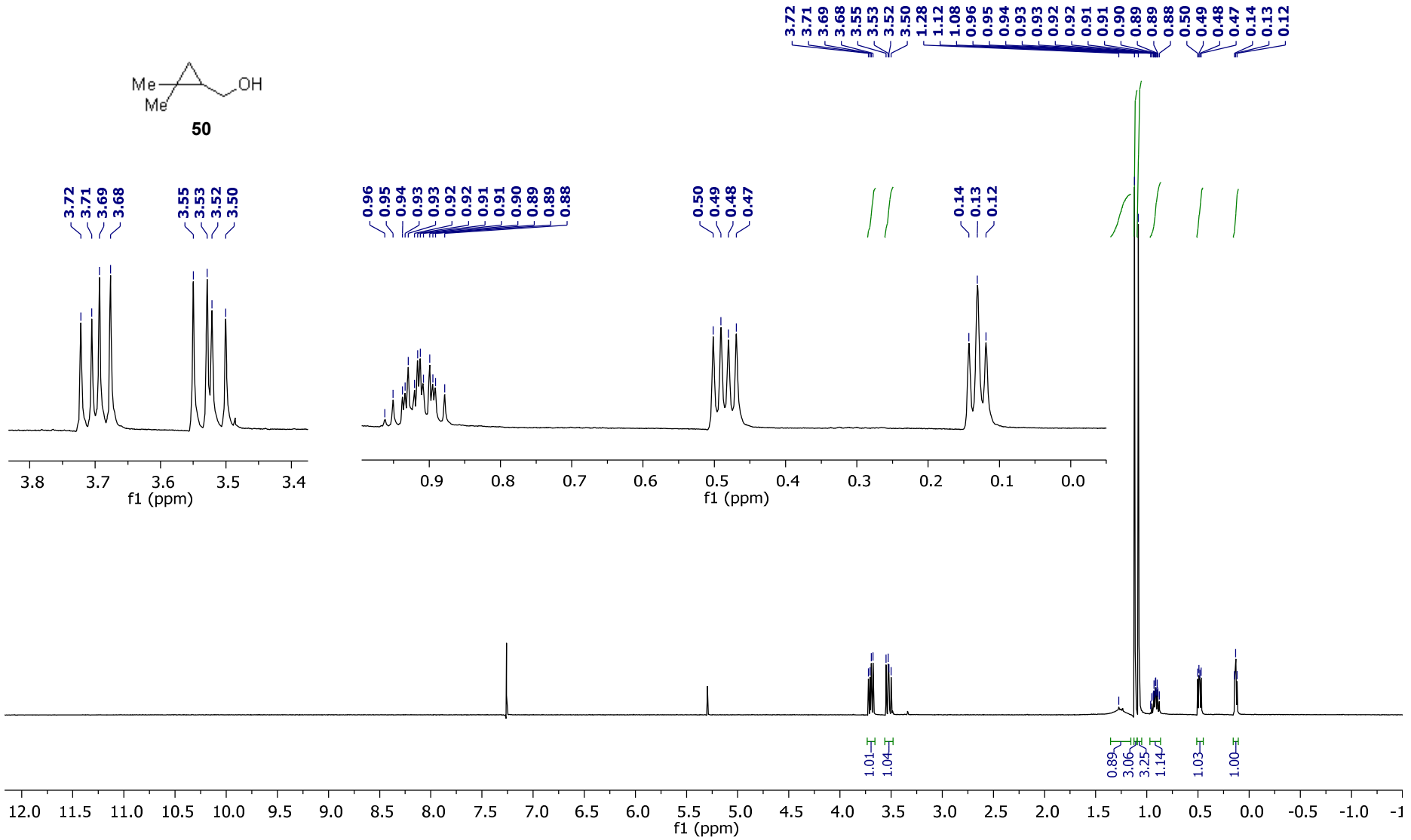

168.39
133.79
132.21
123.08
38.33
28.68
27.25
22.00
19.88
19.31
15.27
O
N
O
Me
Me
43
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

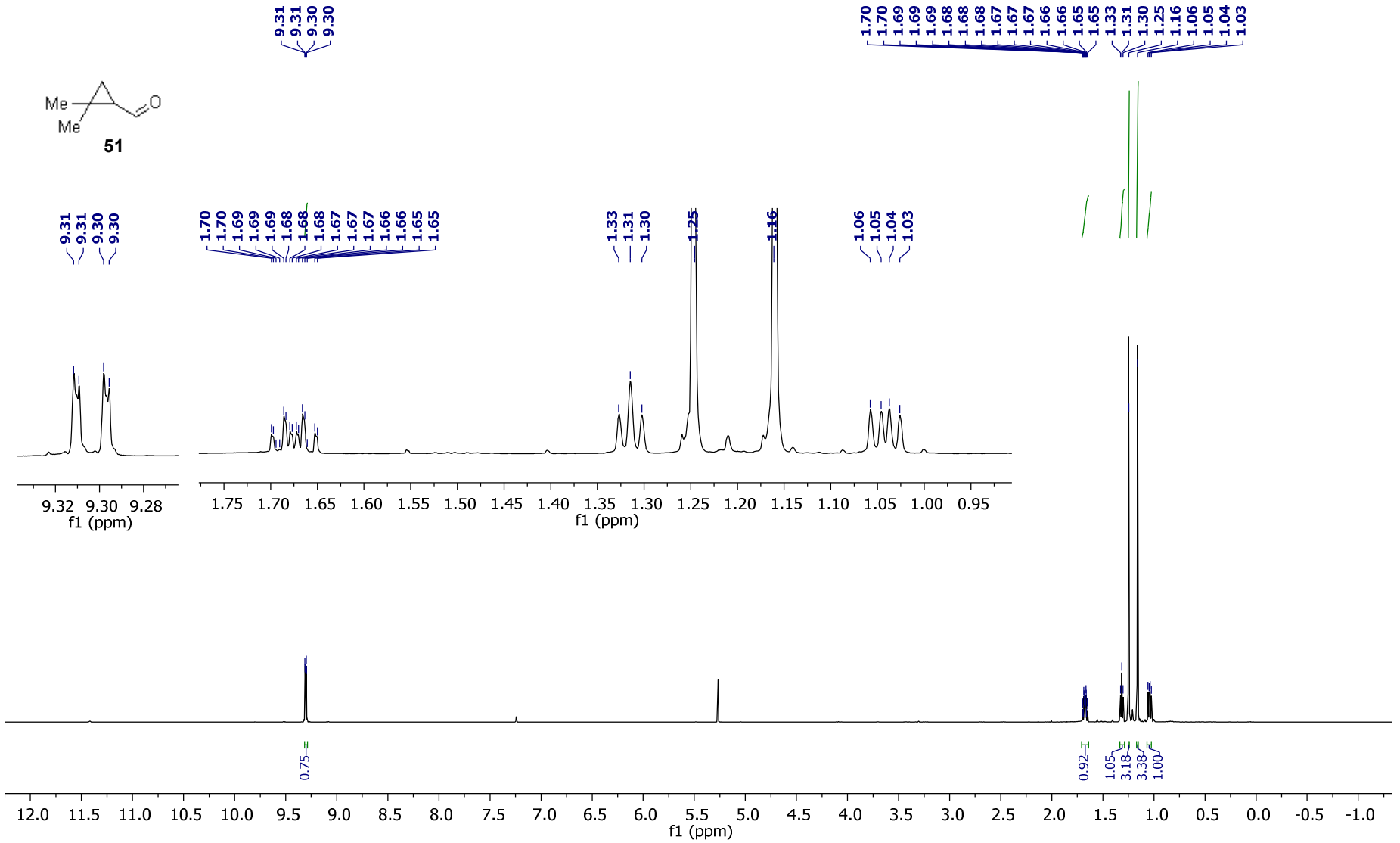

EtO
O
HN
Me
Me
13
4.71 4.12 4.11 4.09 4.07 3.24 3.23 3.21 3.19 1.61 1.60 1.58 1.56 1.54 1.53 1.45 1.43 1.41 1.39 1.38 1.36 1.24 1.23 1.21 1.03 1.02 0.48 0.47 0.46 0.46 0.45 0.45 0.44 0.43 0.42 0.42 0.41 0.41 0.40 0.39 -0.07 -0.08 -0.09
f1 (ppm)
0.83 1.95 2.10 1.14 1.13 3.18 5.92 1.97 1.00

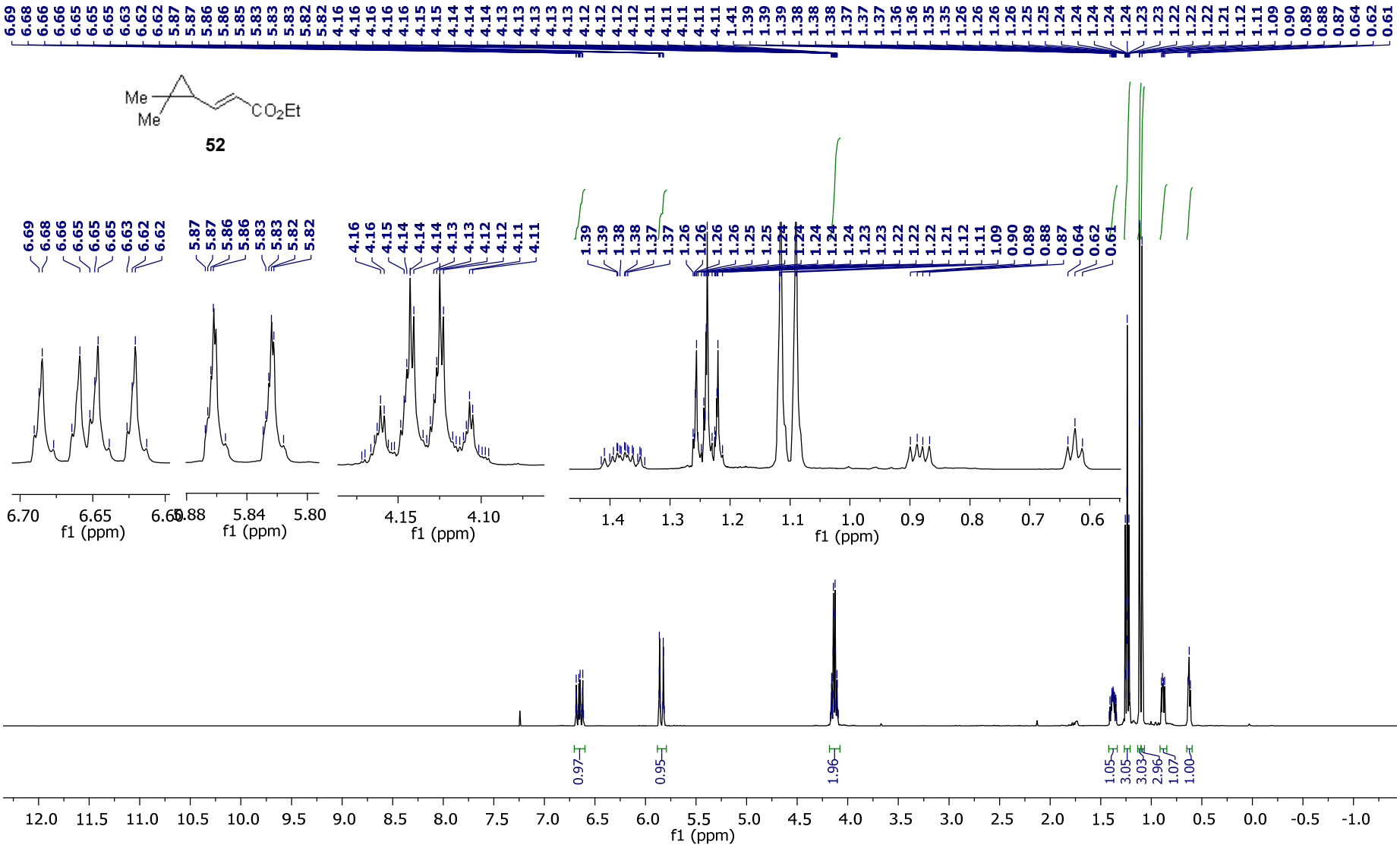

156.61
60.56
41.42
30.02
27.36
21.97
19.96
19.44
15.13
14.66
EtO
O
HN
Me
Me
13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

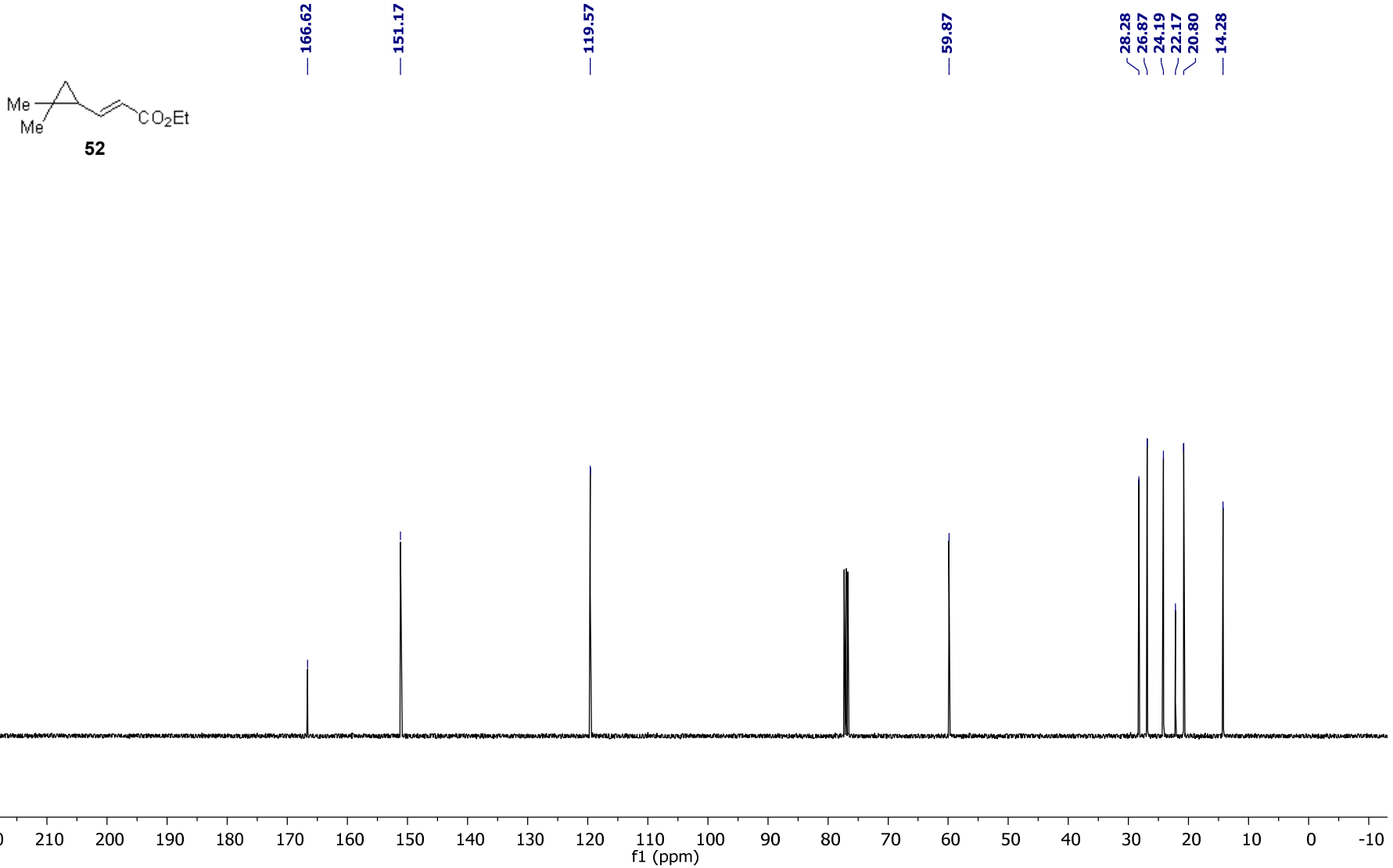

Me
Me
O
OEt
N
Me
11
4.15 4.15 4.13 4.13 4.12 4.11 4.10 4.10
3.30 3.29 3.27
2.92
1.27 1.25 1.24
1.08 1.04
0.78 0.76 0.76 0.75 0.74 0.74 0.74 0.73 0.72 0.72 0.70 0.48 0.47 0.46 0.45
0.10
f1 (ppm)
1.97
2.04
2.96
3.13
3.12
3.14
0.98
1.00
1.01

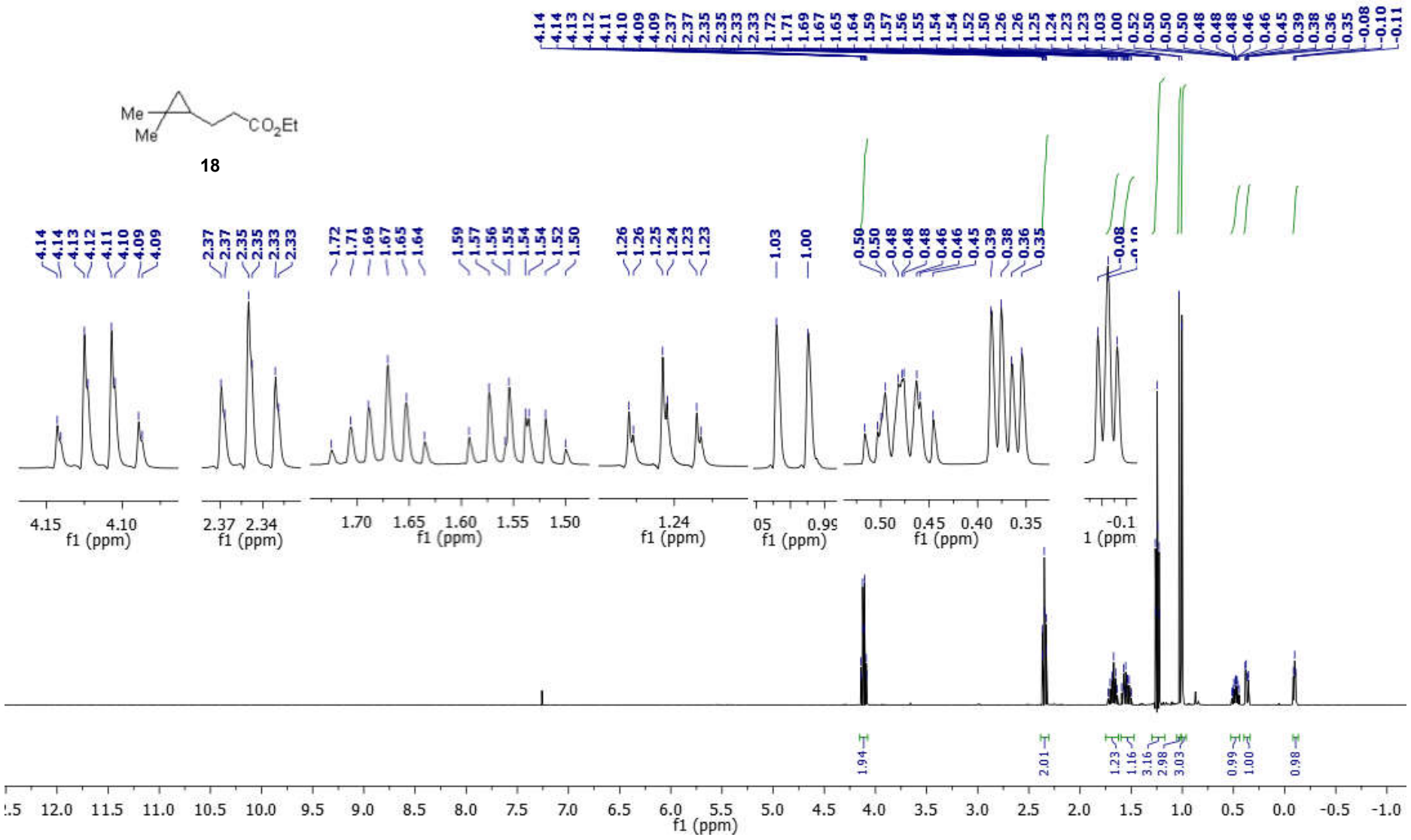

156.49
61.07
48.66
33.74
27.06
22.91
20.14
18.57
14.75
Me
Me
O
OEt
N
Me
11
f1 (ppm)
f1 (ppm)

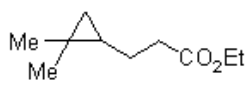

Me
Me
OH
50
3.72 3.71 3.69 3.68 3.55 3.53 3.52 3.50 1.28 1.12 1.08 0.96 0.95 0.94 0.93 0.93 0.92 0.92 0.91 0.91 0.90 0.89 0.89 0.88 0.50 0.49 0.48 0.47 0.14 0.13 0.12
f1 (ppm)
1.01 1.04 0.89 3.06 3.25 1.14 1.03 1.00


Me
Me
O
51
9.31
9.31
9.30
9.30
1.70
1.70
1.69
1.69
1.69
1.68
1.68
1.67
1.67
1.66
1.66
1.65
1.65
1.33
1.31
1.30
1.25
1.16
1.06
1.05
1.04
1.03
9.32 9.30 9.28
f1 (ppm)
1.75 1.70 1.65 1.60 1.55 1.50 1.45 1.40 1.35 1.30 1.25 1.20 1.15 1.10 1.05 1.00 0.95
f1 (ppm)
0.75
0.92
1.05
3.18
3.38
1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


Me
Me
CO2Et
52
f1 (ppm)

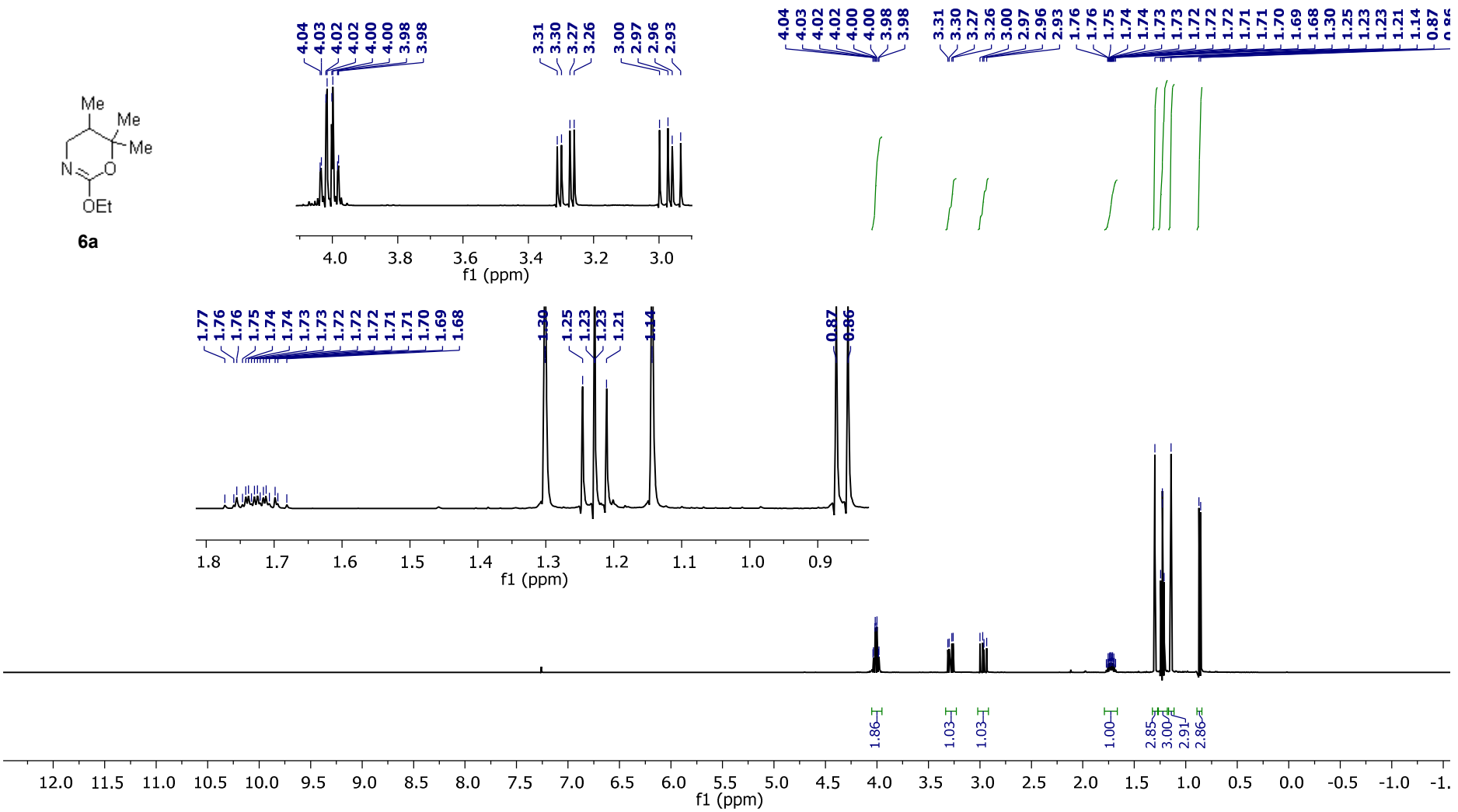

166.62
151.17
119.57
59.87
28.28
26.87
24.19
22.17
20.80
14.28
Me
Me
CO2Et
52
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

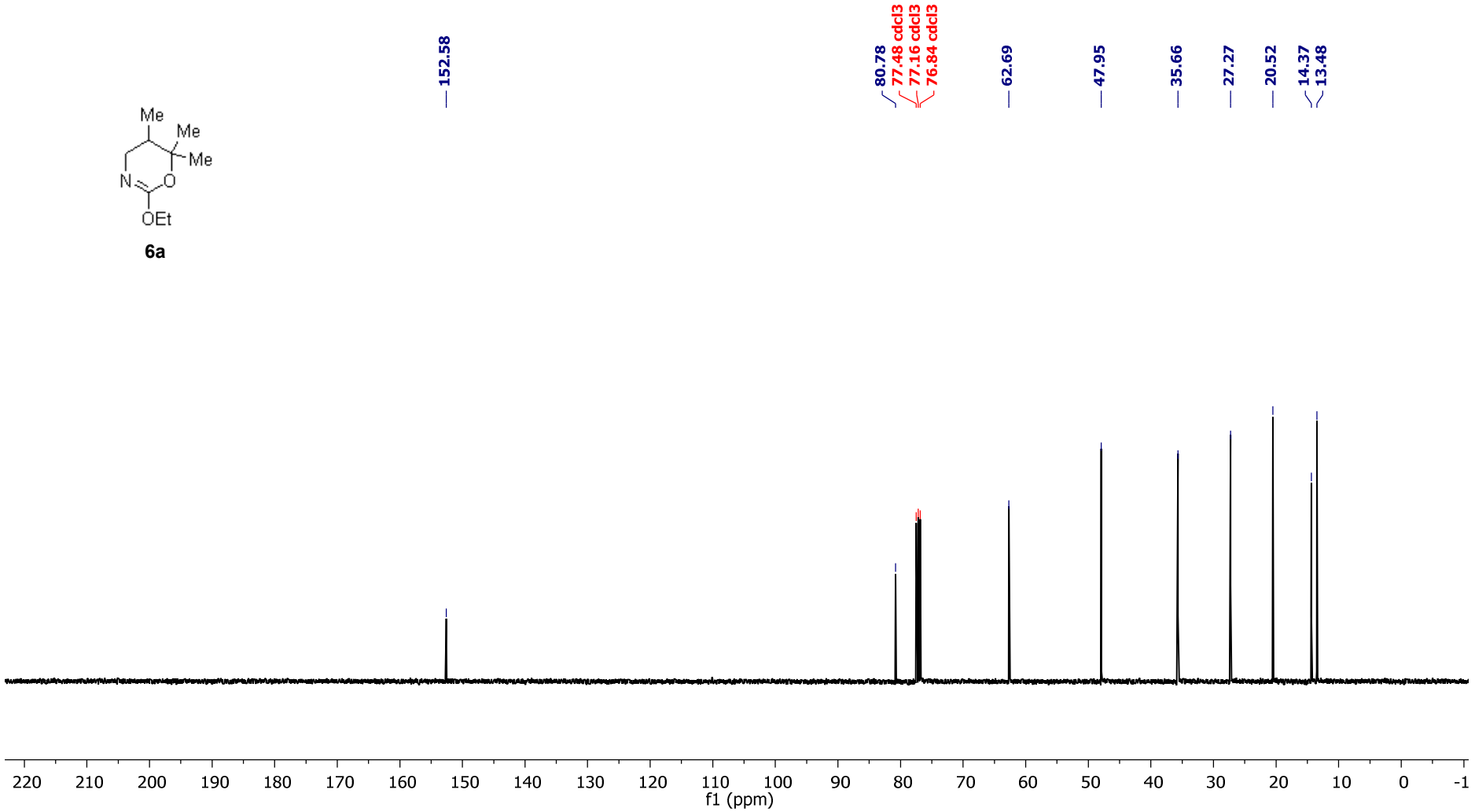

Me
Me
CO2Et
18
f1 (ppm)

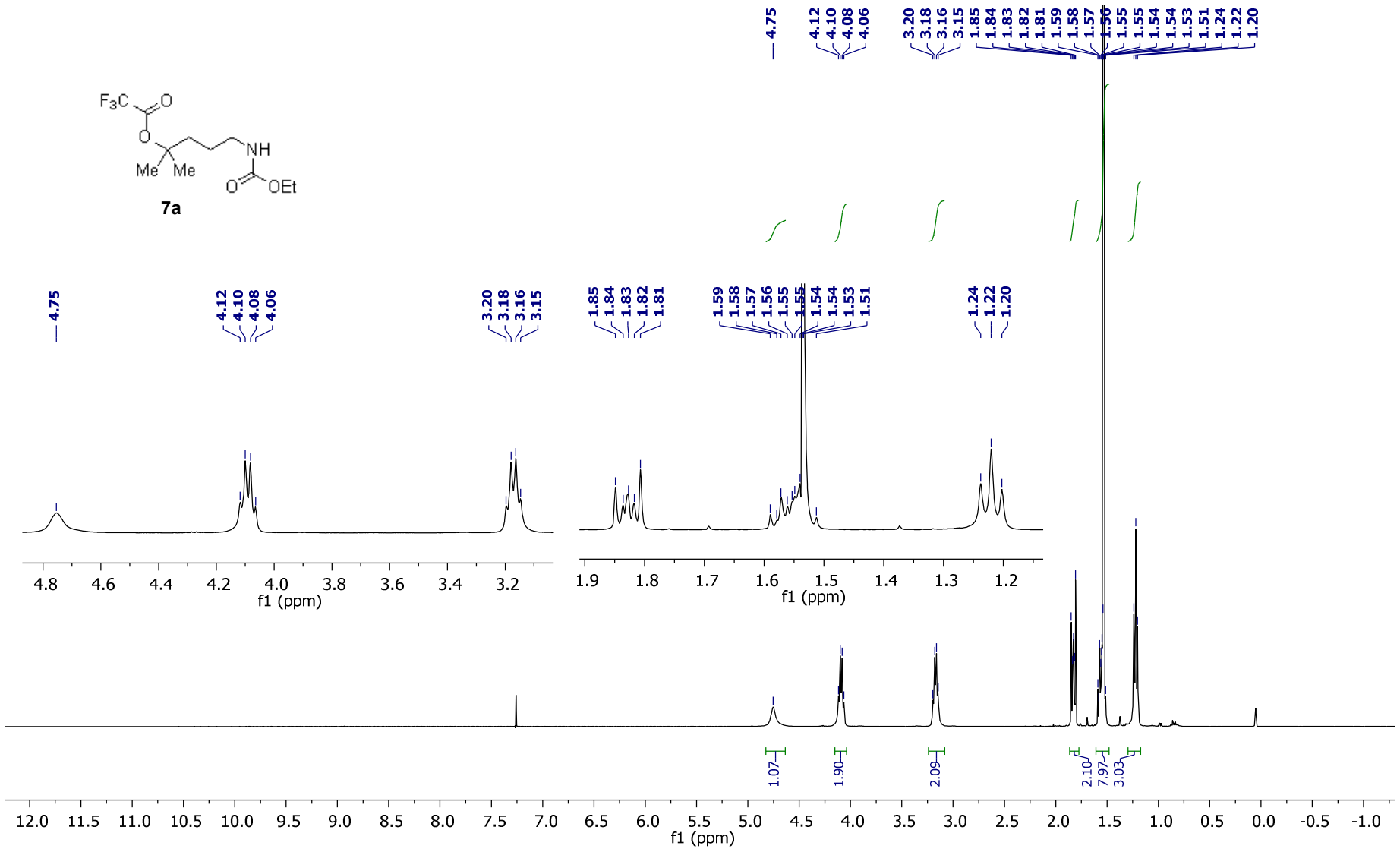

Me
Me
CO2Et

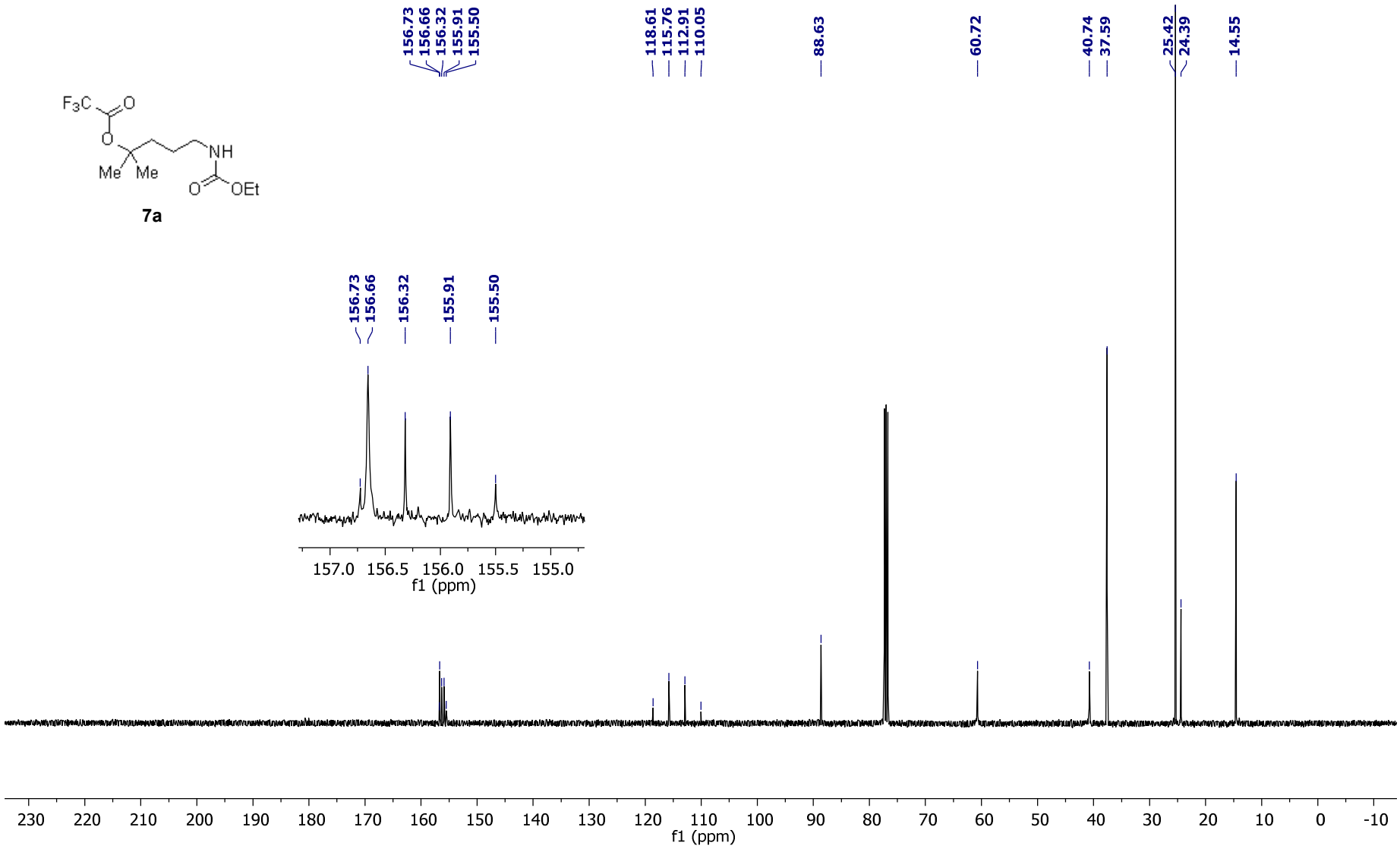
18

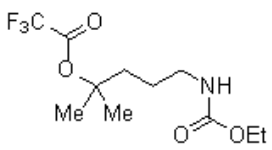
173.75
60.12
34.88
27.41
25.36
23.96
19.78
19.54
15.55
14.23
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
Me
Me
N
O
OEt
6a
4.04 4.03 4.02 4.02 4.00 4.00 3.98 3.98
3.31 3.30 3.27 3.26
3.00 2.97 2.96 2.93
4.0 3.8 3.6 3.4 3.2 3.0
f1 (ppm)
1.77 1.76 1.76 1.75 1.74 1.74 1.73 1.73 1.72 1.72 1.72 1.71 1.71 1.70 1.69 1.68
1.30 1.25 1.23 1.23 1.21 1.14
0.87 0.86
1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9
f1 (ppm)
1.86 1.03 1.03 1.00 2.85 3.00 2.91 2.86
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


Me
Me
Me
N
O
OEt
6a
152.58
80.78
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
62.69
47.95
35.66
27.27
20.52
14.37
13.48
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

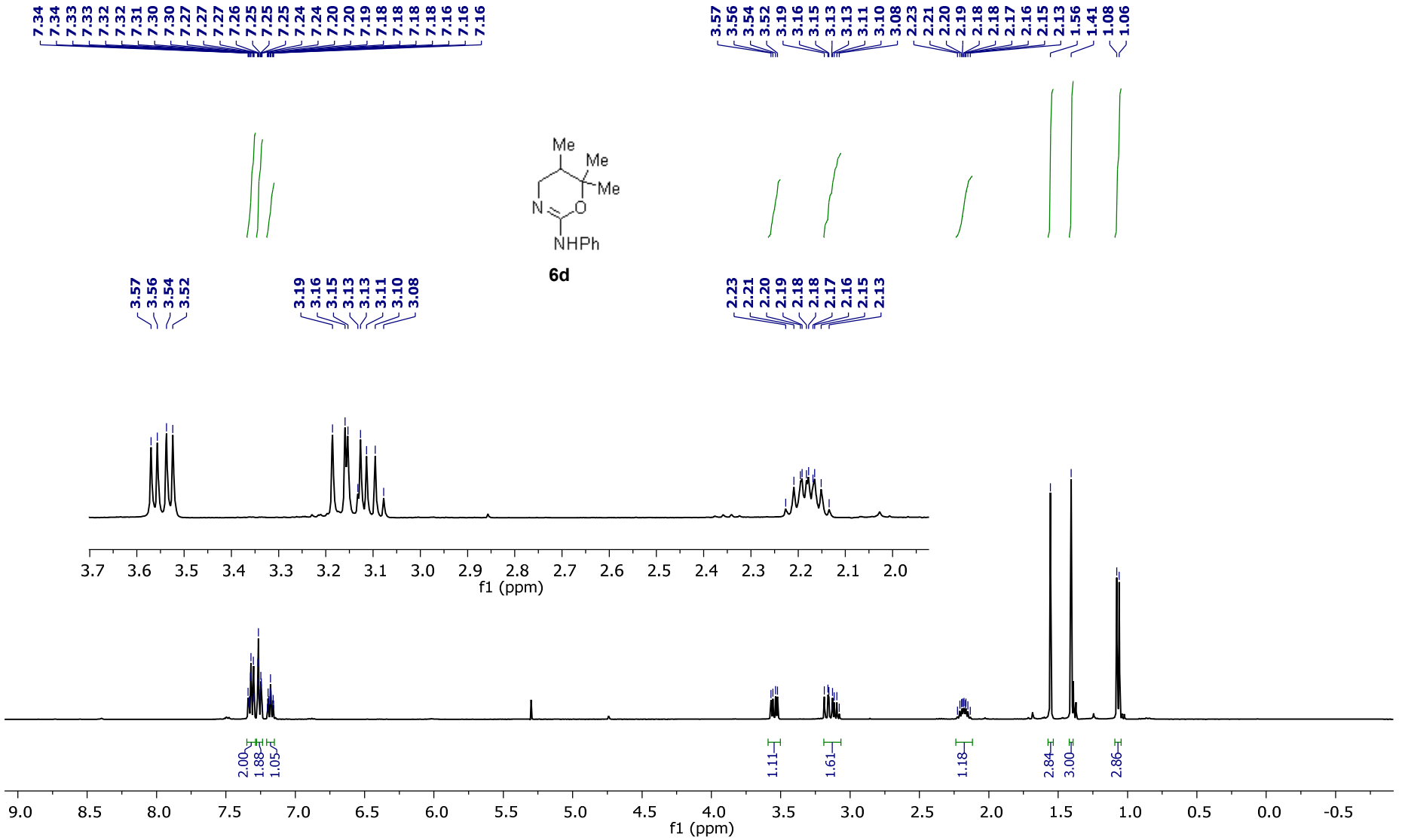

F3C
O
O
Me
Me
NH
O
OEt
7a
4.75
4.12
4.10
4.08
4.06
3.20
3.18
3.16
3.15
1.85
1.84
1.83
1.82
1.81
1.59
1.58
1.57
1.56
1.55
1.54
1.54
1.53
1.51
1.24
1.22
1.20
f1 (ppm)
1.07
1.90
2.09
2.10
7.97
3.03

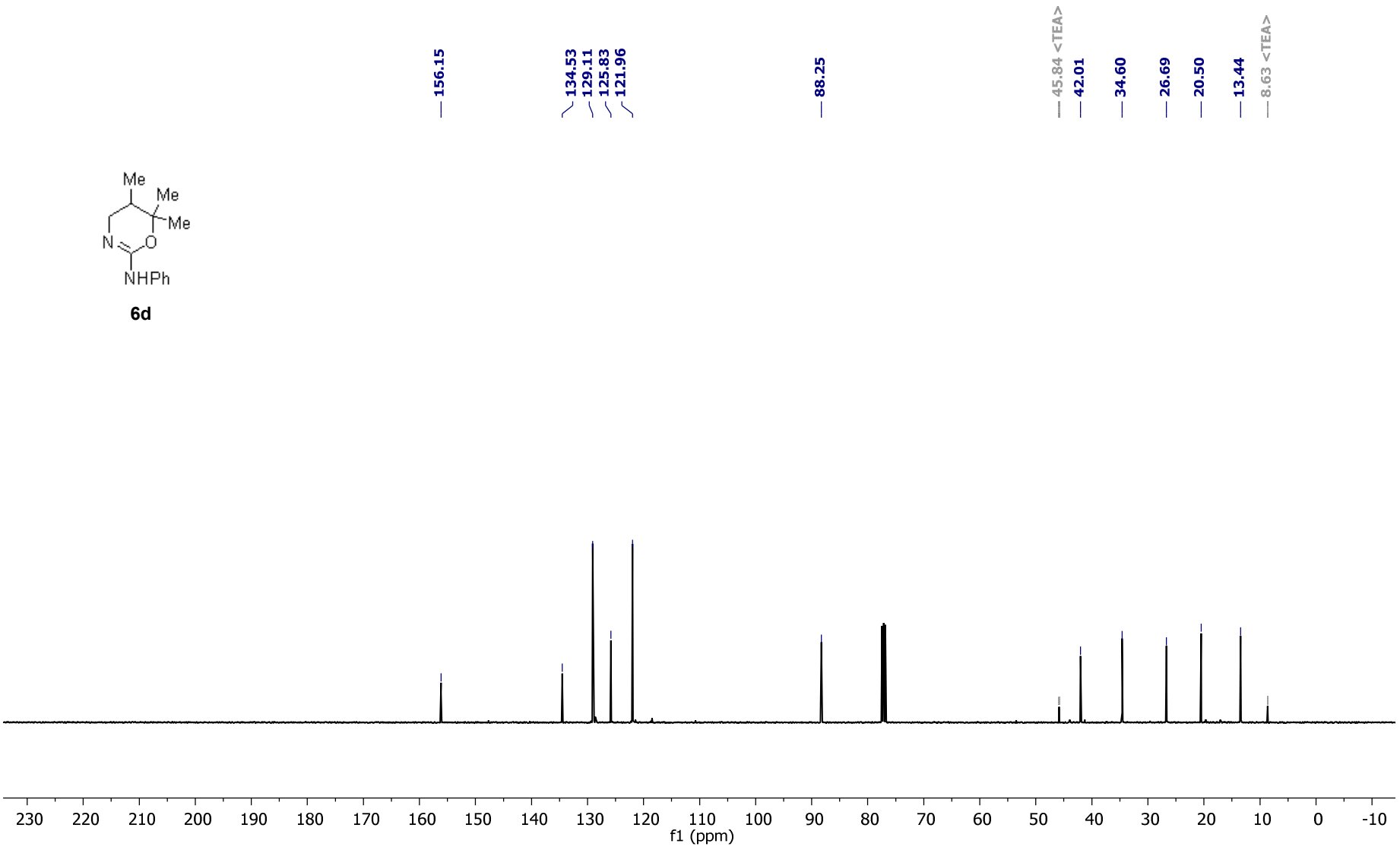

156.73
156.66
156.32
155.91
155.50
118.61
115.76
112.91
110.05
88.63
60.72
40.74
37.59
25.42
24.39
14.55
F3C
O
O
NH
Me
Me
O
OEt
7a
157.0 156.5 156.0 155.5 155.0
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

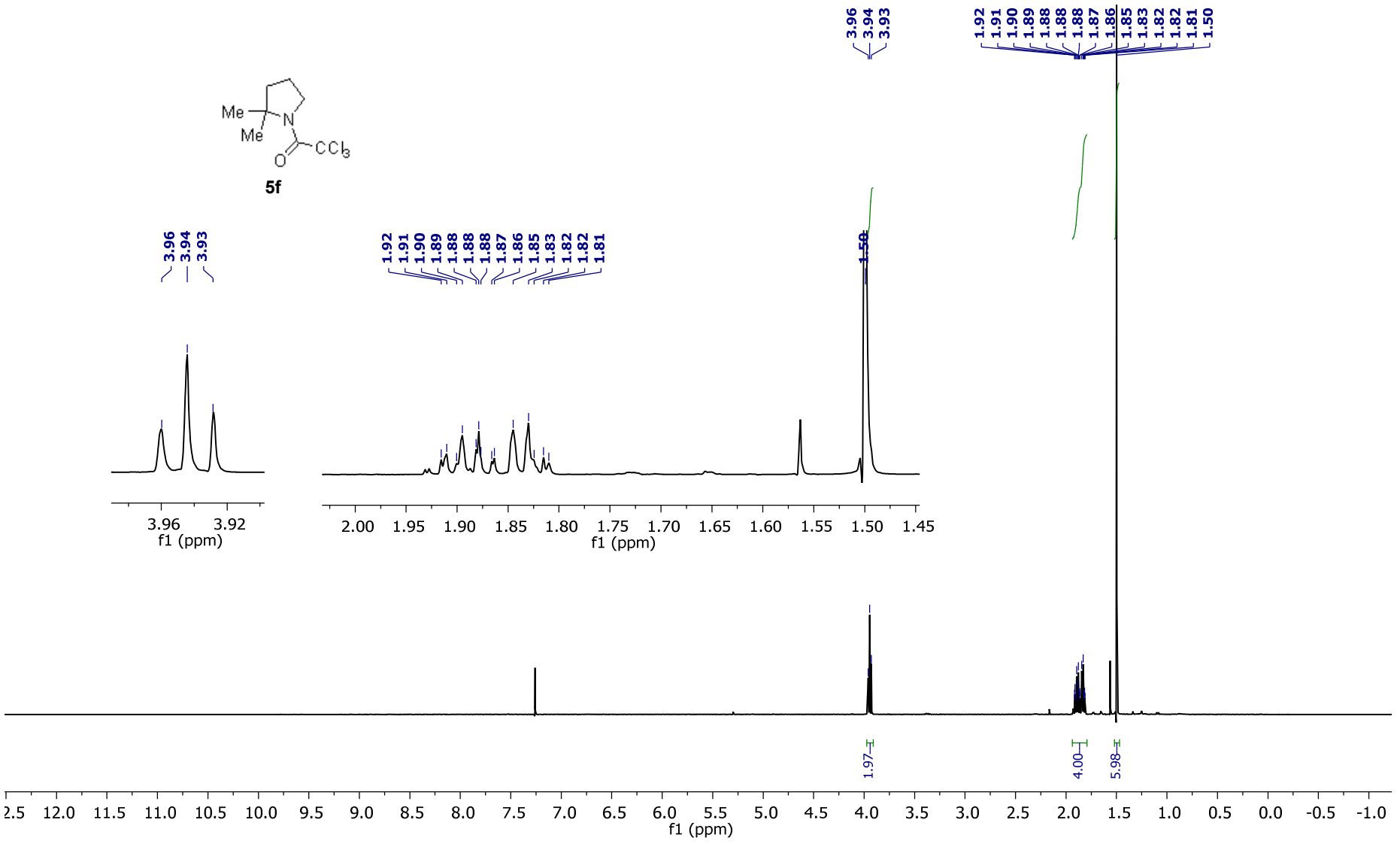

F3C
O
O
Me
Me
NH
O
OEt

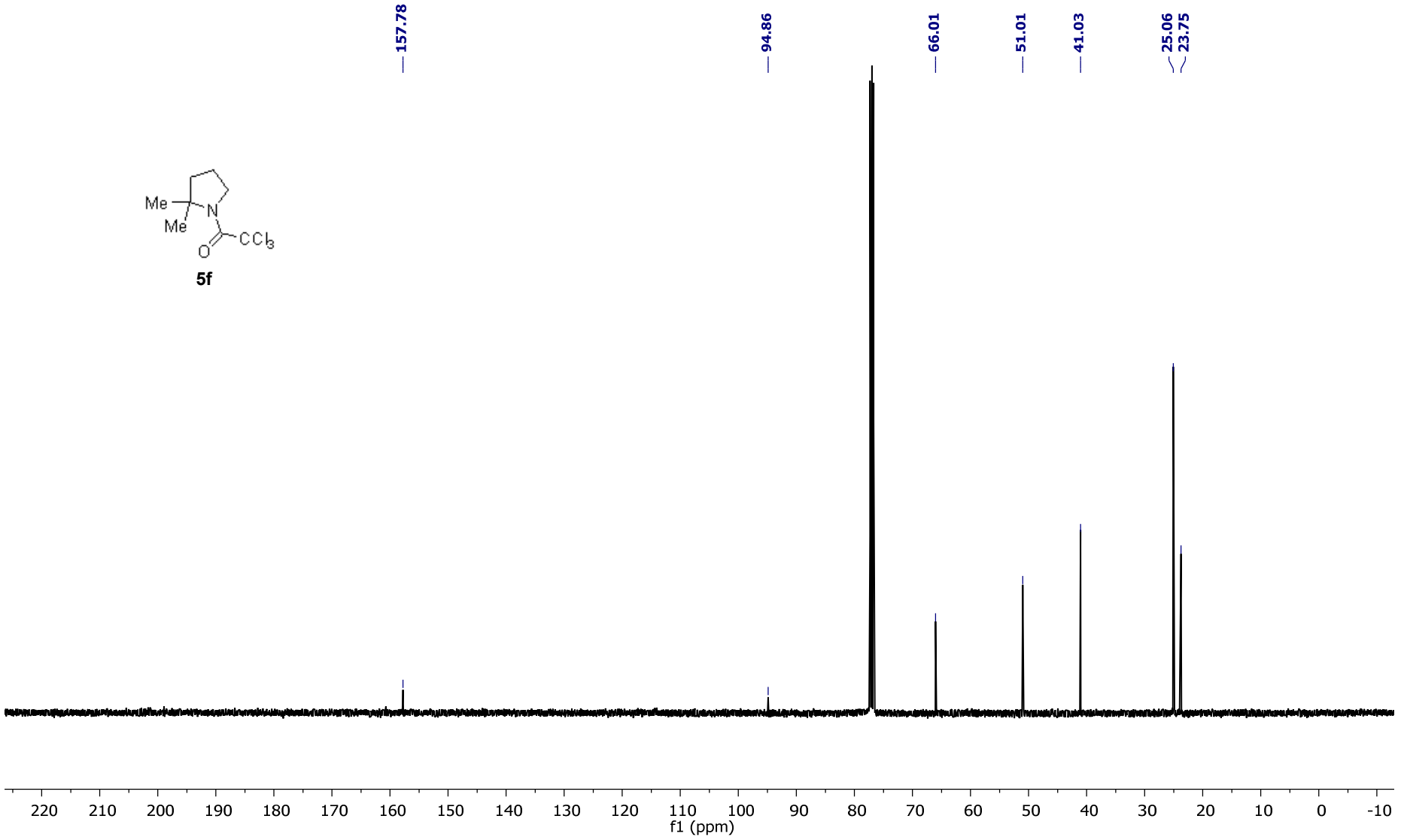
7a

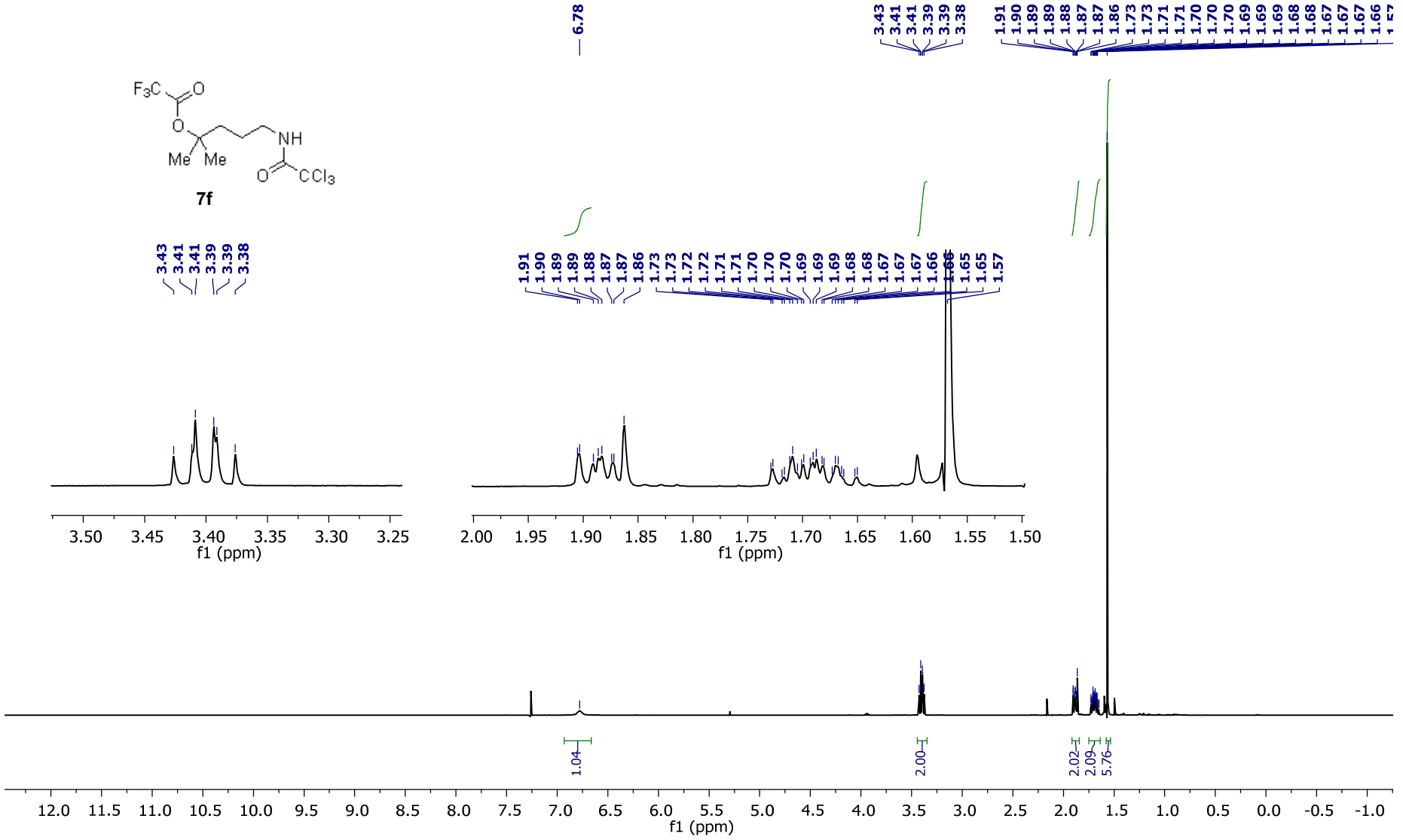
-75.85
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

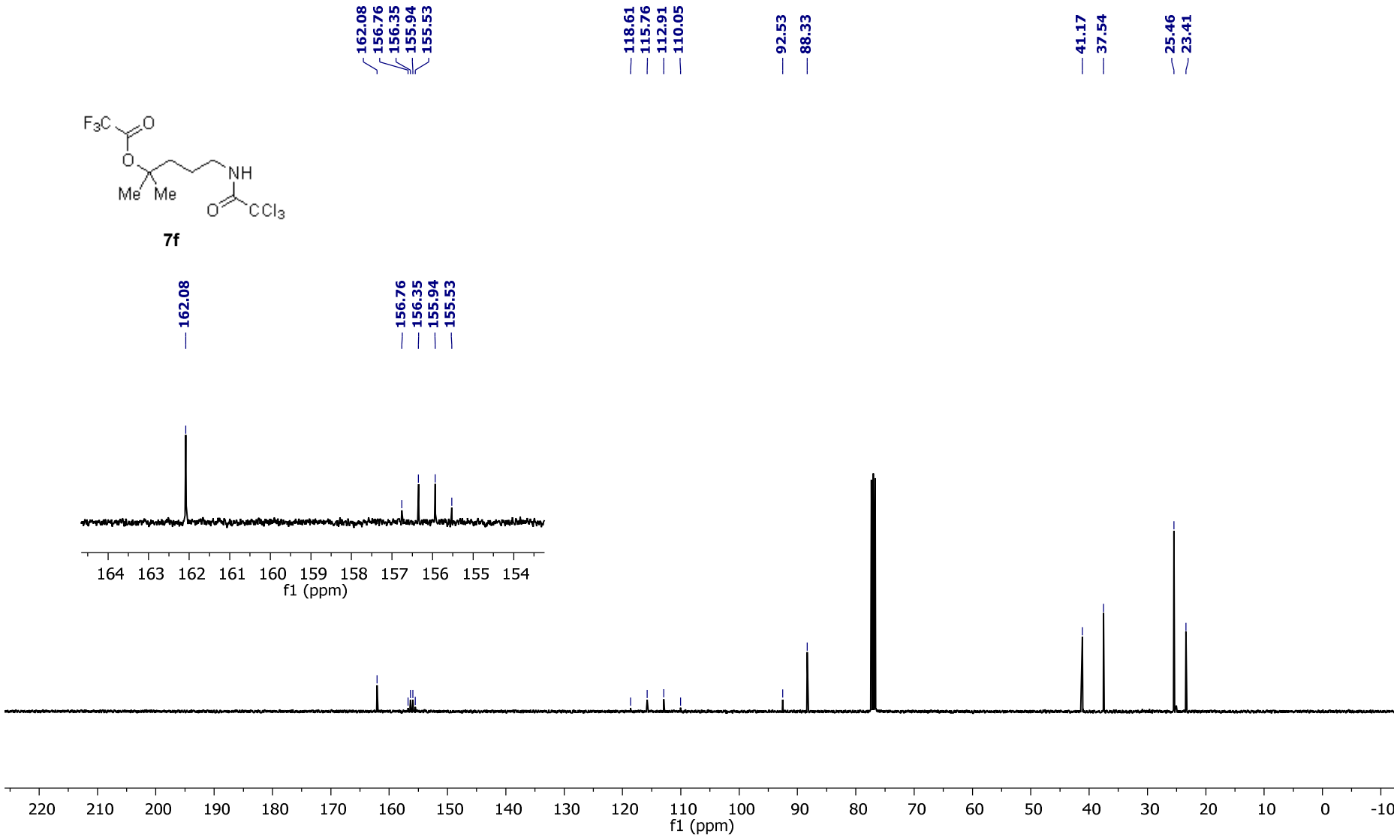

7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.30 7.30 7.27 7.27 7.27 7.26 7.25 7.25 7.25 7.24 7.24 7.20 7.20 7.19 7.18 7.18 7.18 7.16 7.16 7.16
3.57 3.56 3.54 3.52 3.19 3.16 3.15 3.13 3.13 3.11 3.10 3.08 2.23 2.21 2.20 2.19 2.18 2.18 2.17 2.16 2.15 2.13 1.56 1.41 1.08 1.06
Me
Me
Me
N
O
NHPh
6d
f1 (ppm)
2.00
1.88
1.05
1.11
1.61
1.18
2.84
3.00
2.86

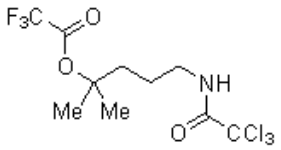

156.15
134.53
129.11
125.83
121.96
88.25
45.84 <TEA>
42.01
34.60
26.69
20.50
13.44
8.63 <TEA>
Me
Me
Me
N
O
NHPh
6d
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
Me
N
O
CCl3
5f
3.96
3.94
3.93
1.92
1.91
1.90
1.89
1.88
1.88
1.88
1.87
1.86
1.85
1.83
1.82
1.82
1.81
1.50
3.96 3.92
f1 (ppm)
2.00 1.95 1.90 1.85 1.80 1.75 1.70 1.65 1.60 1.55 1.50 1.45
f1 (ppm)
1.97
4.00
5.98
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


157.78
94.86
66.01
51.01
41.03
25.06
23.75
Me
Me
N
O
CCl3
5f
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

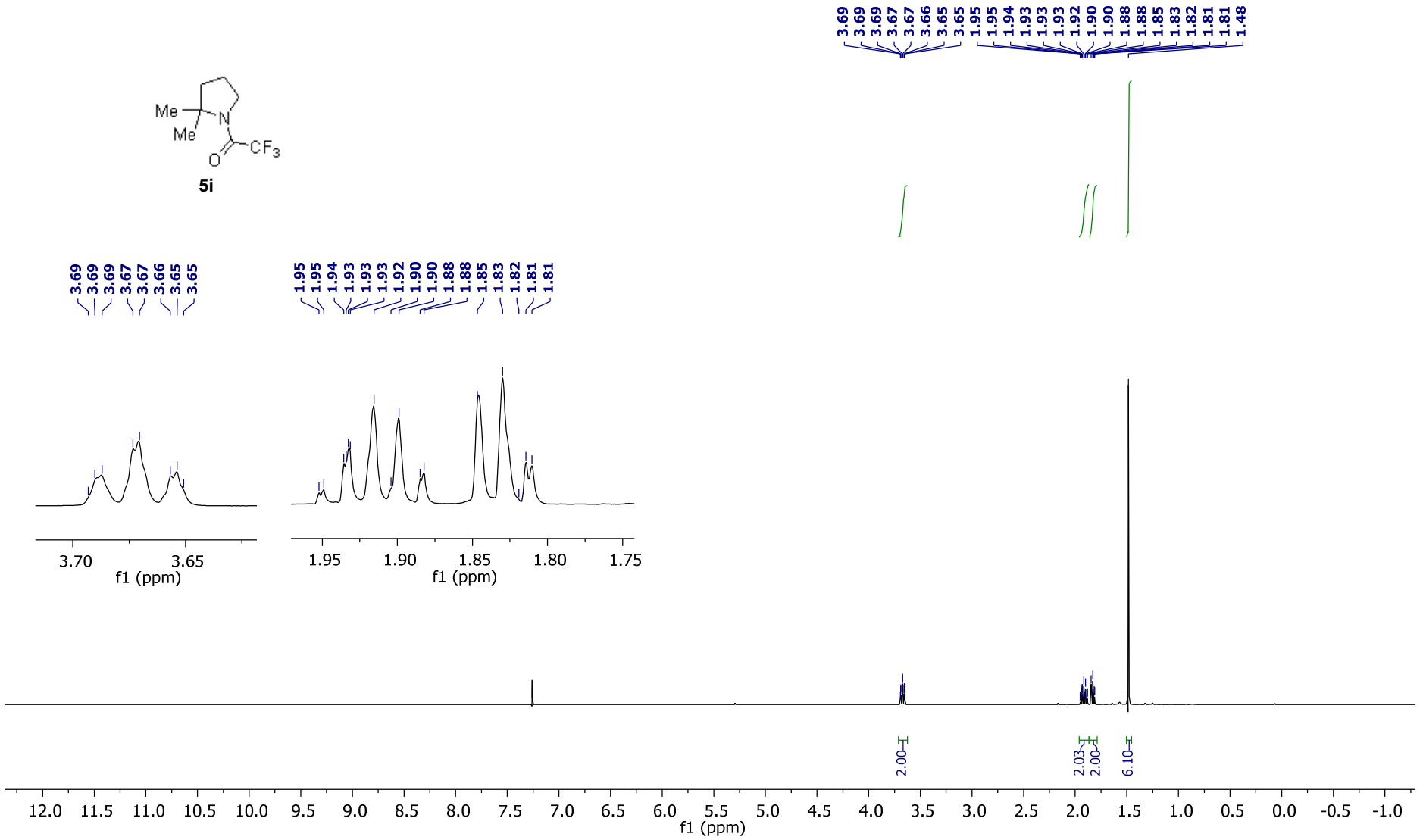

F3C
O
O
NH
Me
Me
O
CCl3
7f
6.78
3.43
3.41
3.41
3.39
3.39
3.38
1.91
1.90
1.89
1.89
1.88
1.87
1.87
1.86
1.73
1.73
1.72
1.72
1.71
1.71
1.70
1.70
1.70
1.69
1.69
1.69
1.68
1.68
1.67
1.67
1.67
1.66
1.65
1.65
1.57
3.50 3.45 3.40 3.35 3.30 3.25
f1 (ppm)
2.00 1.95 1.90 1.85 1.80 1.75 1.70 1.65 1.60 1.55 1.50
f1 (ppm)
1.04
2.00
2.02
2.09
5.76
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

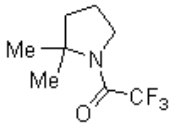

162.08
156.76
156.35
155.94
155.53
118.61
115.76
112.91
110.05
92.53
88.33
41.17
37.54
25.46
23.41
F3C
O
O
NH
Me
Me
O
CCl3
7f
162.08
156.76
156.35
155.94
155.53
164 163 162 161 160 159 158 157 156 155 154
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


F3C
O
O
Me
Me
NH
O
CCl3

7f

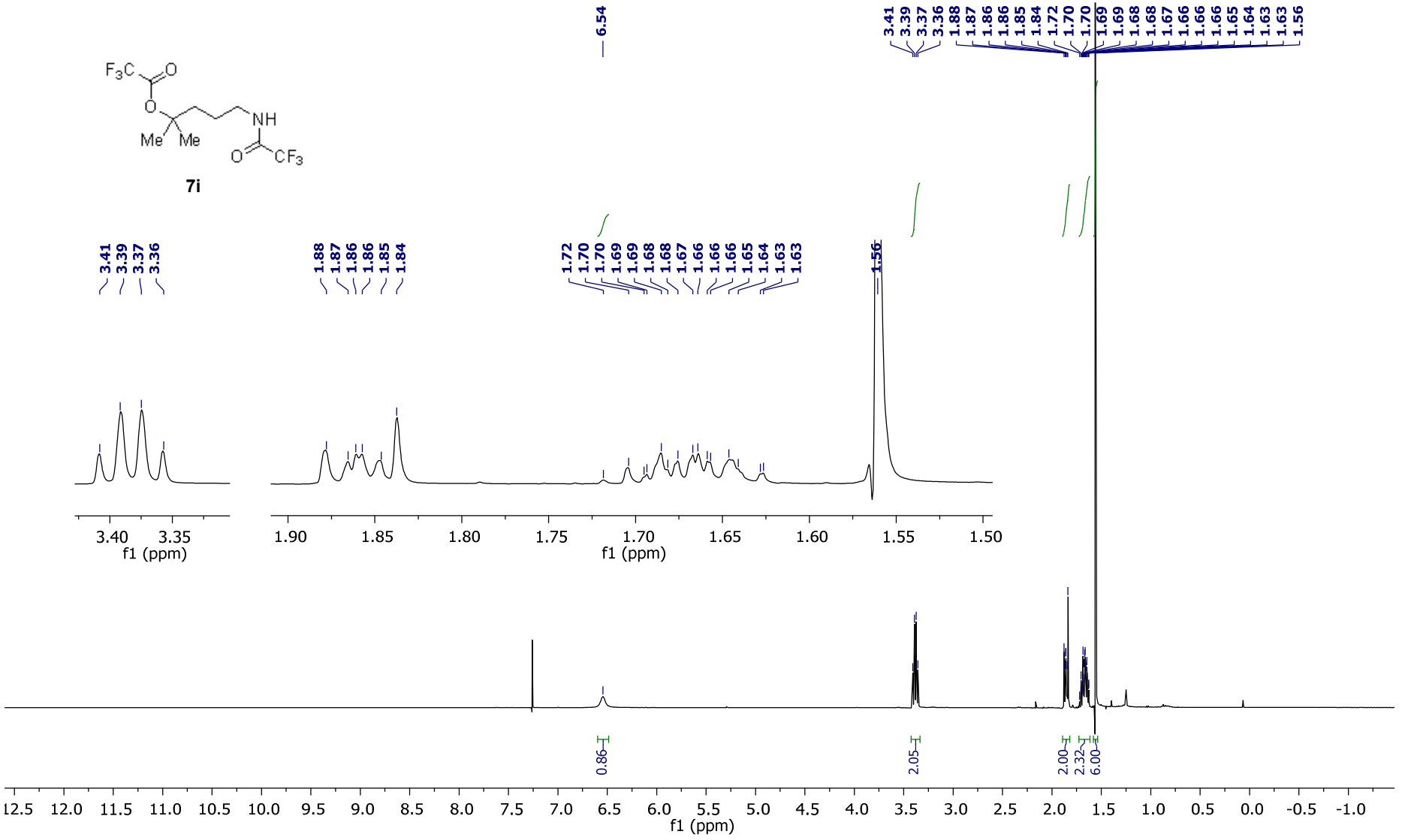
-75.73
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
f1 (ppm)

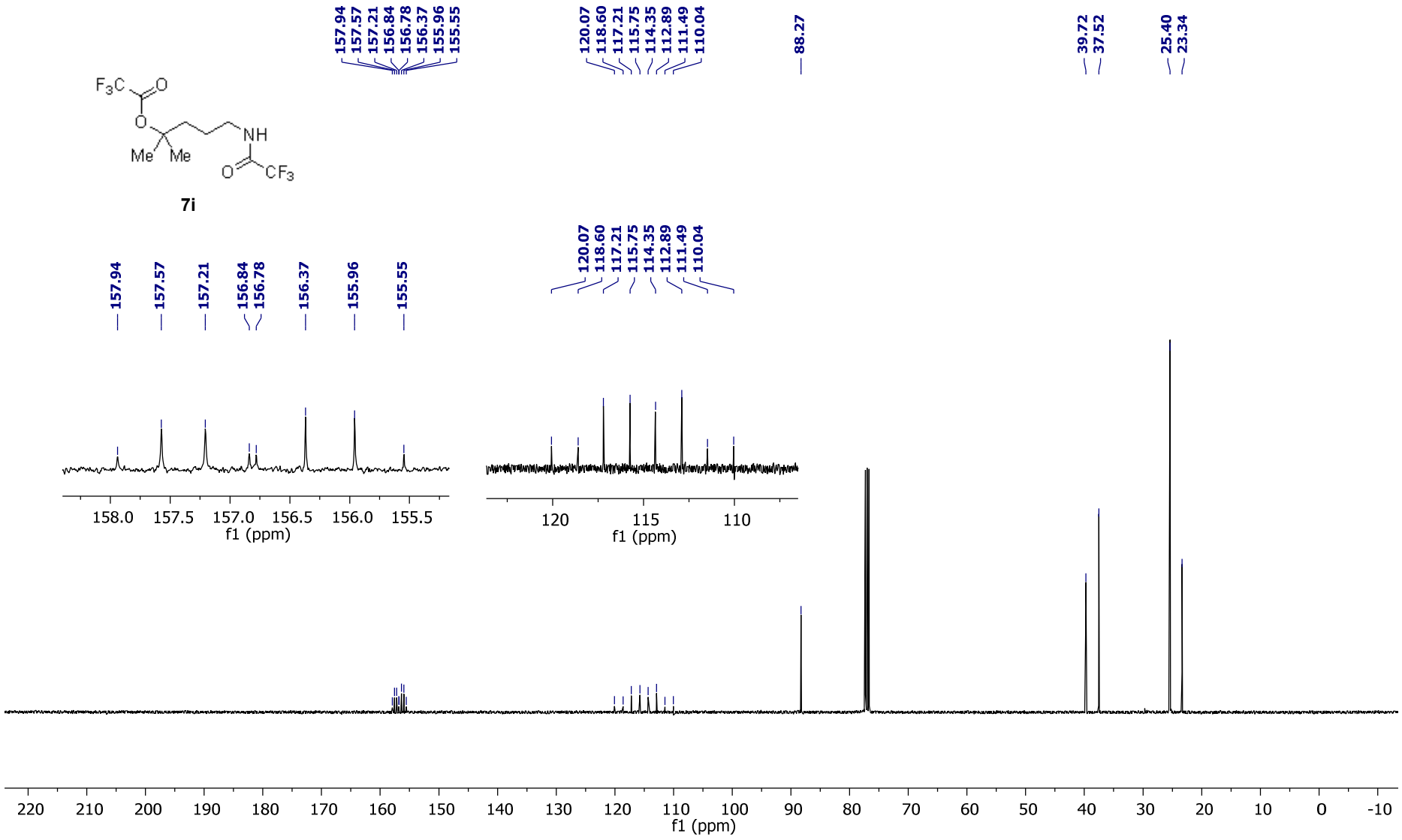

Me
Me
N
O
CF3
5i
3.69 3.69 3.69 3.67 3.67 3.66 3.65 3.65
1.95 1.95 1.94 1.93 1.93 1.93 1.92 1.90 1.90 1.88 1.88 1.85 1.83 1.82 1.81 1.81 1.48
3.70 3.65
f1 (ppm)
1.95 1.90 1.85 1.80 1.75
f1 (ppm)
2.00
2.03
2.00
6.10
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

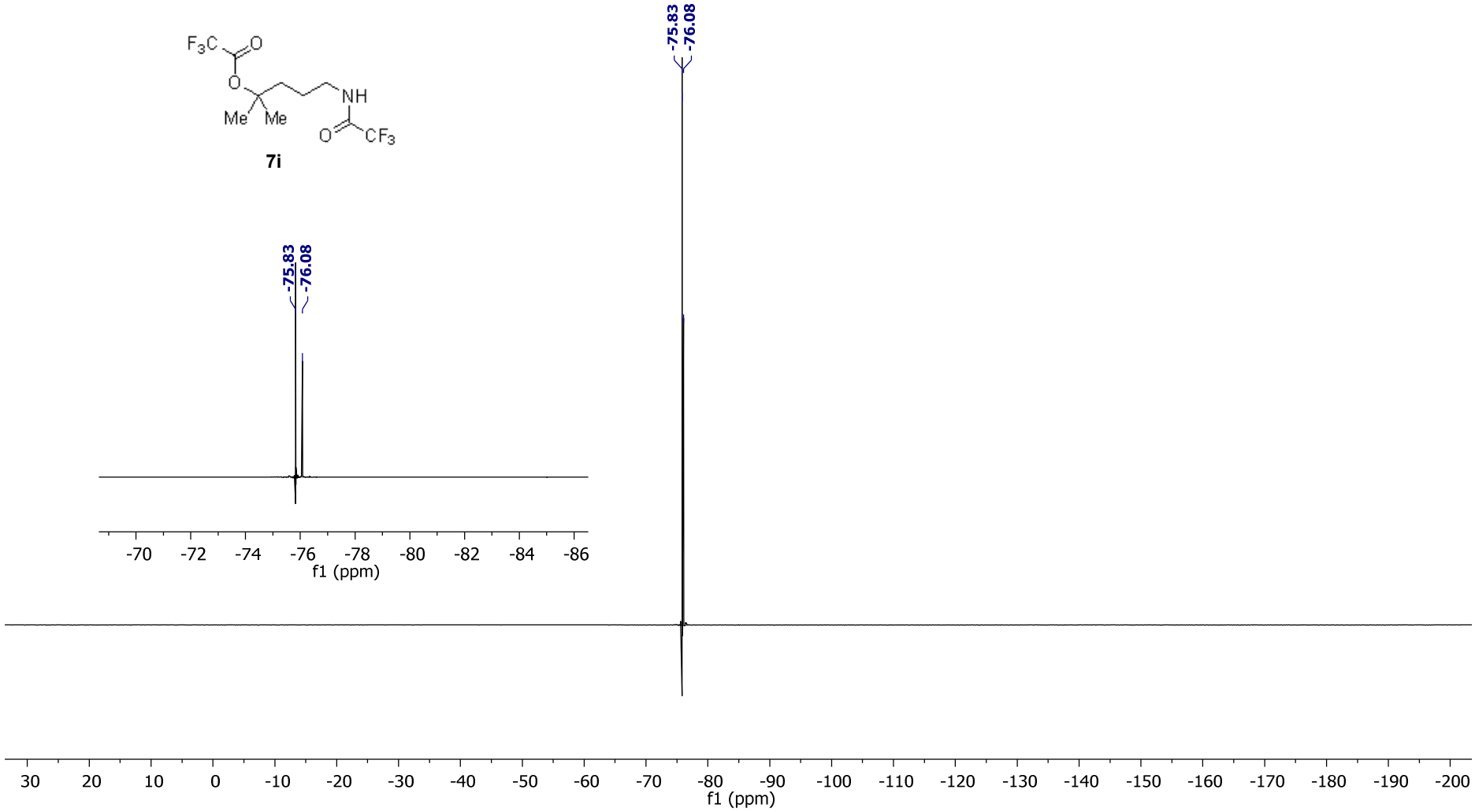

Me
Me
N
O
CF3

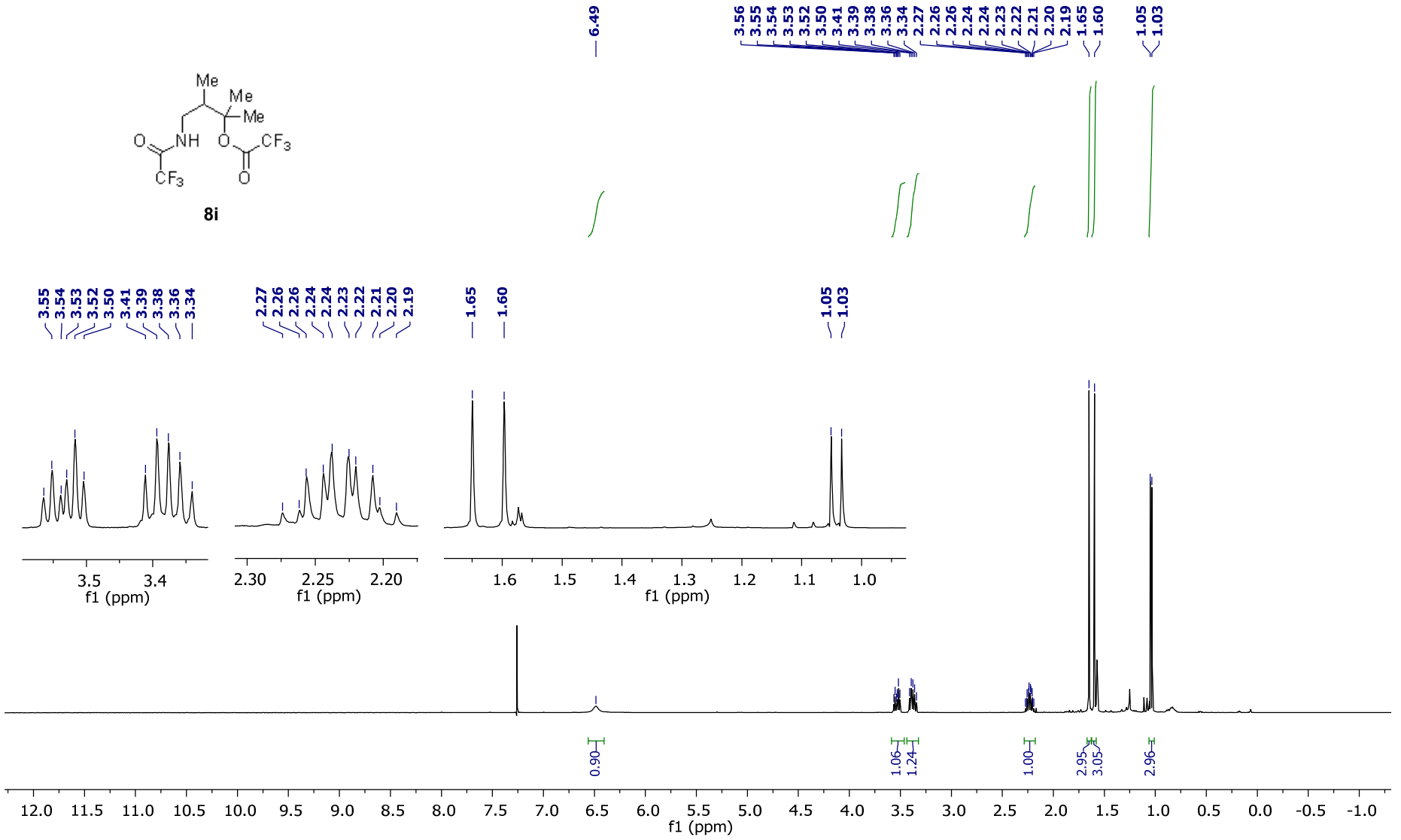
5i

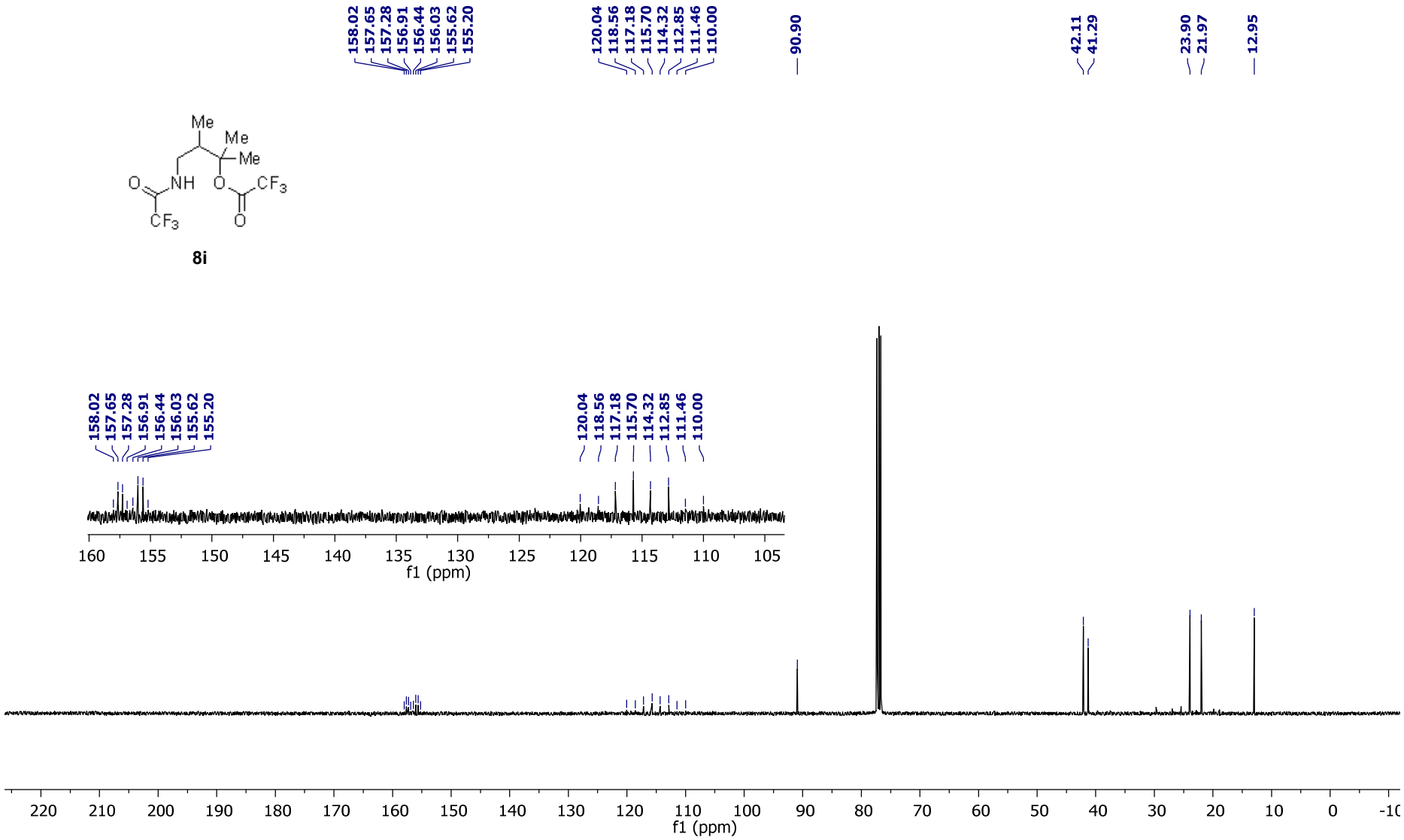
-72.85
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

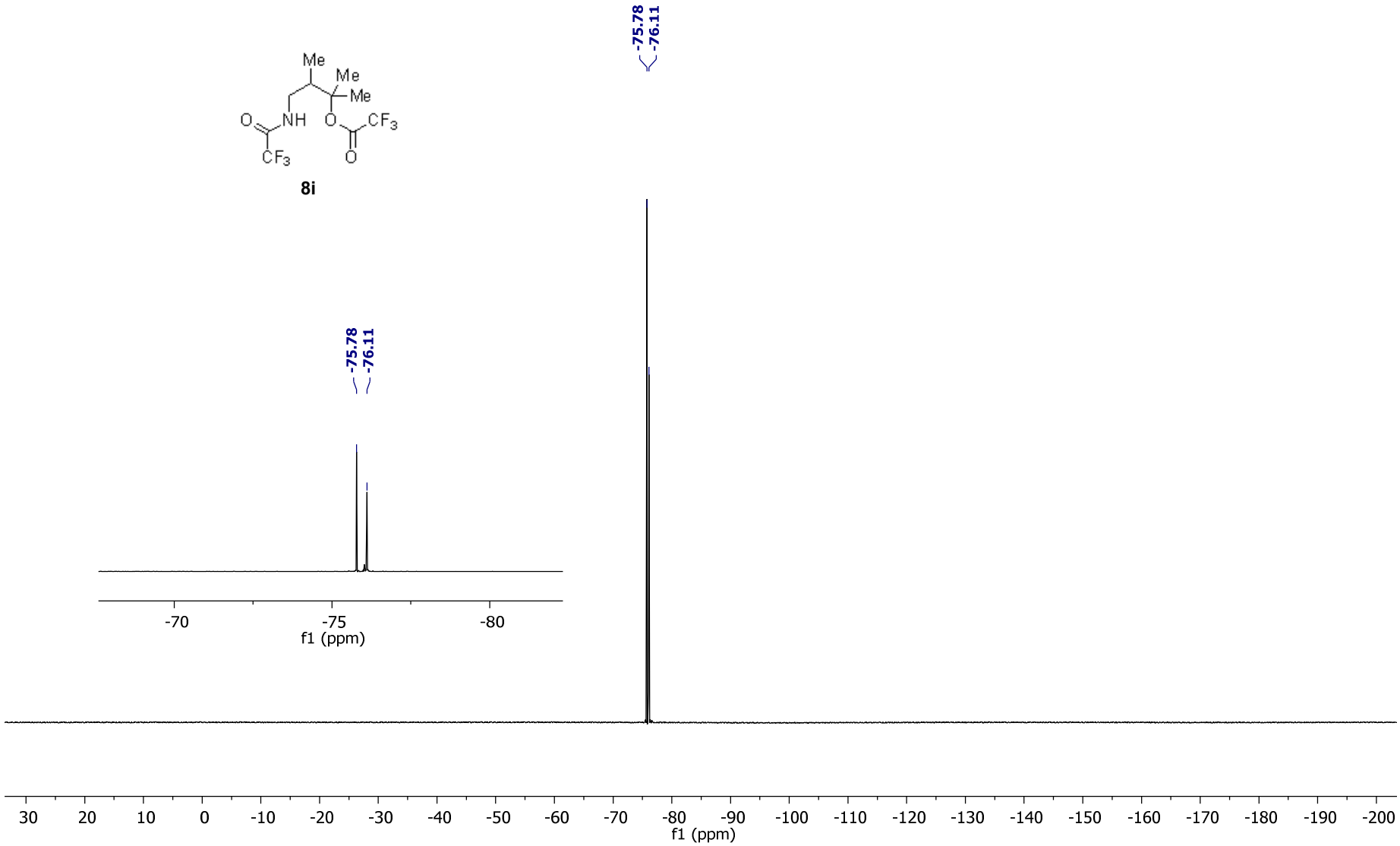

F3C
O
O
NH
Me
Me
O
CF3
7i
6.54
3.41
3.39
3.37
3.36
1.88
1.87
1.86
1.86
1.85
1.84
1.72
1.70
1.70
1.69
1.69
1.68
1.68
1.67
1.66
1.66
1.66
1.65
1.64
1.63
1.63
1.56
3.40
3.35
f1 (ppm)
1.90
1.85
1.80
1.75
1.70
1.65
1.60
1.55
1.50
f1 (ppm)
0.86
2.05
2.00
2.32
6.00
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

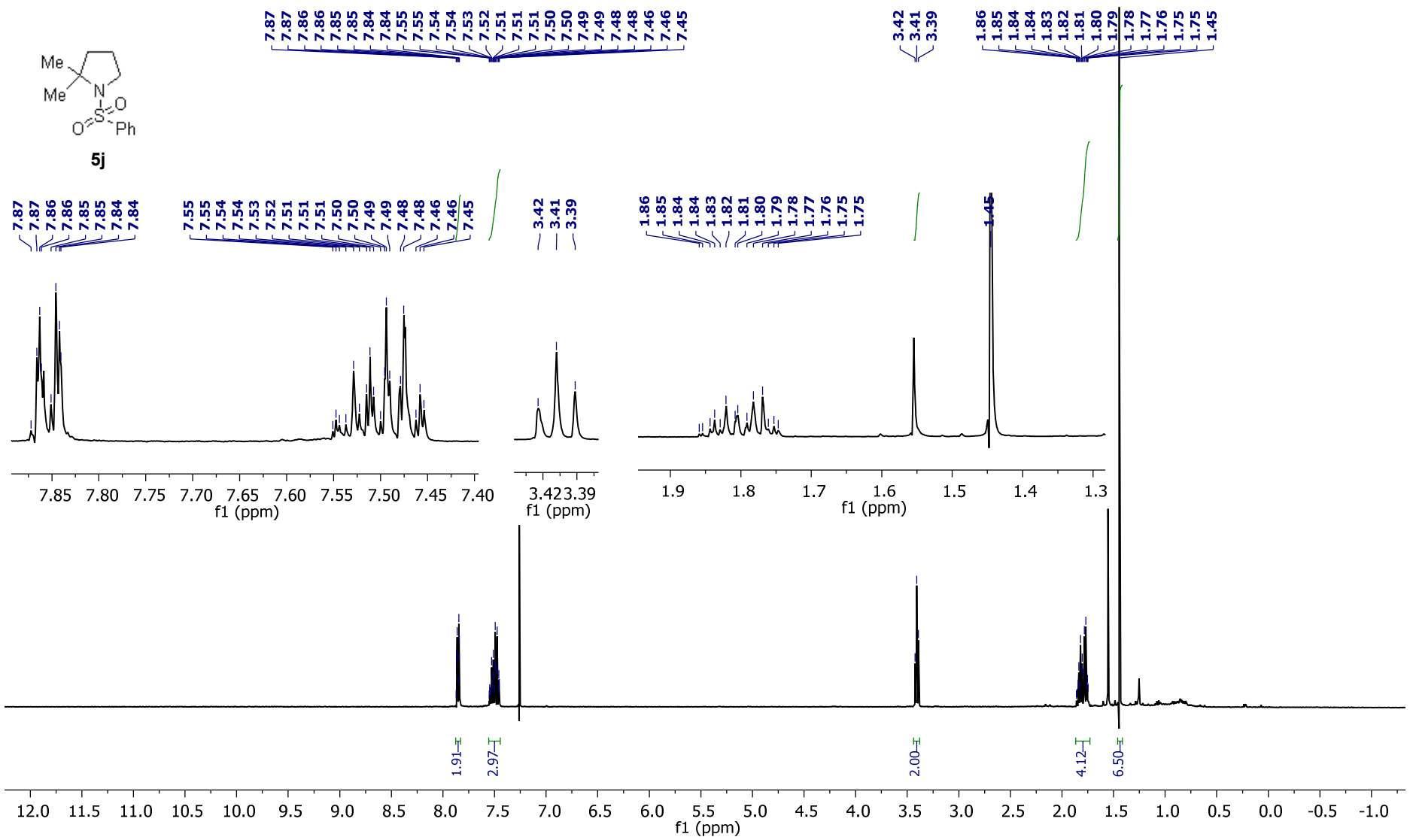

157.94
157.57
157.21
156.84
156.78
156.37
155.96
155.55
120.07
118.60
117.21
115.75
114.35
112.89
111.49
110.04
88.27
39.72
37.52
25.40
23.34
F3C
O
O
NH
Me
Me
O
CF3
7i
158.0
157.5
157.0
156.5
156.0
155.5
f1 (ppm)
120
115
110
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

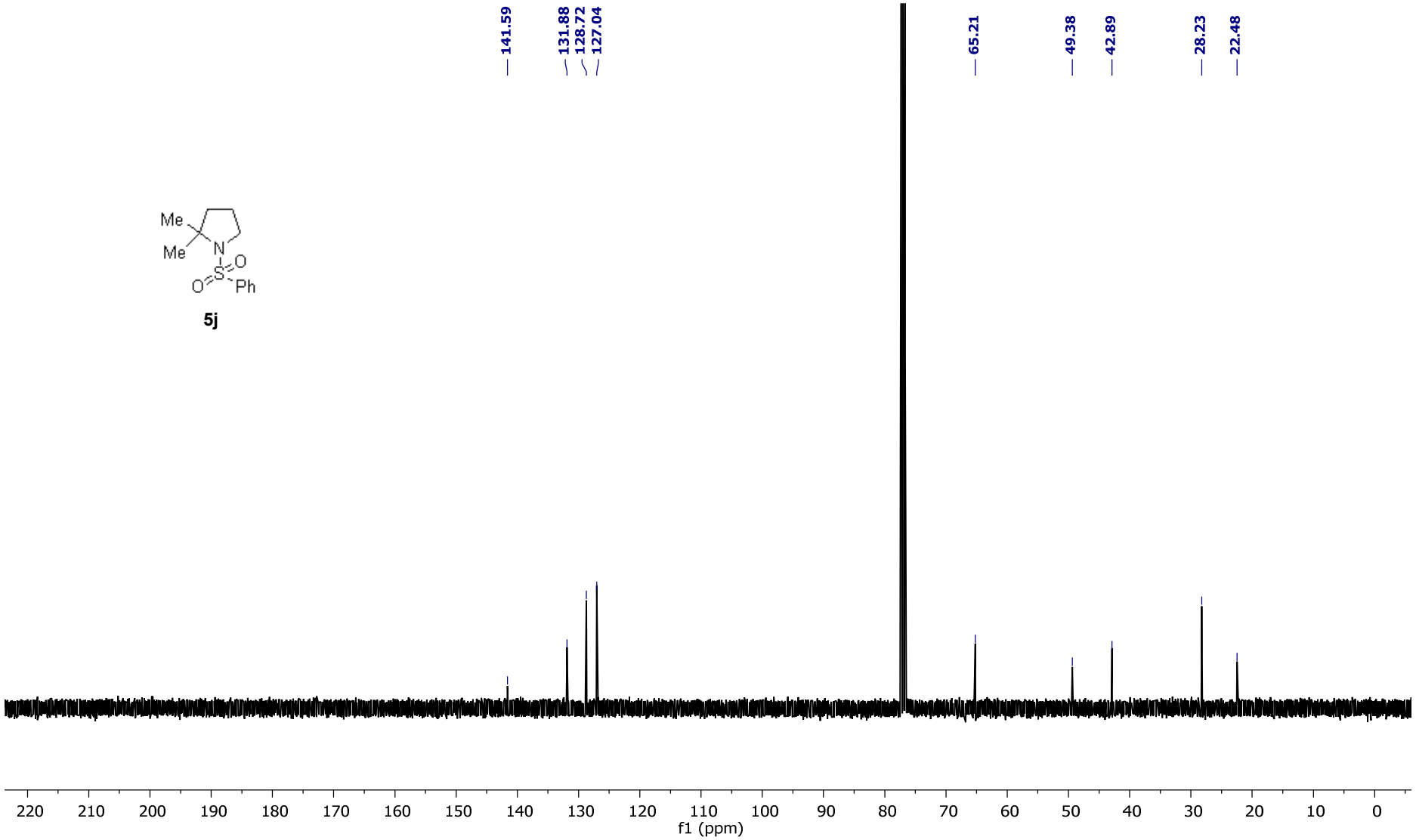

F3C
O
O
Me
Me
NH
O
CF3
7i
-75.83
-76.08
-75.83
-76.08
-70
-72
-74
-76
-78
-80
-82
-84
-86
f1 (ppm)
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

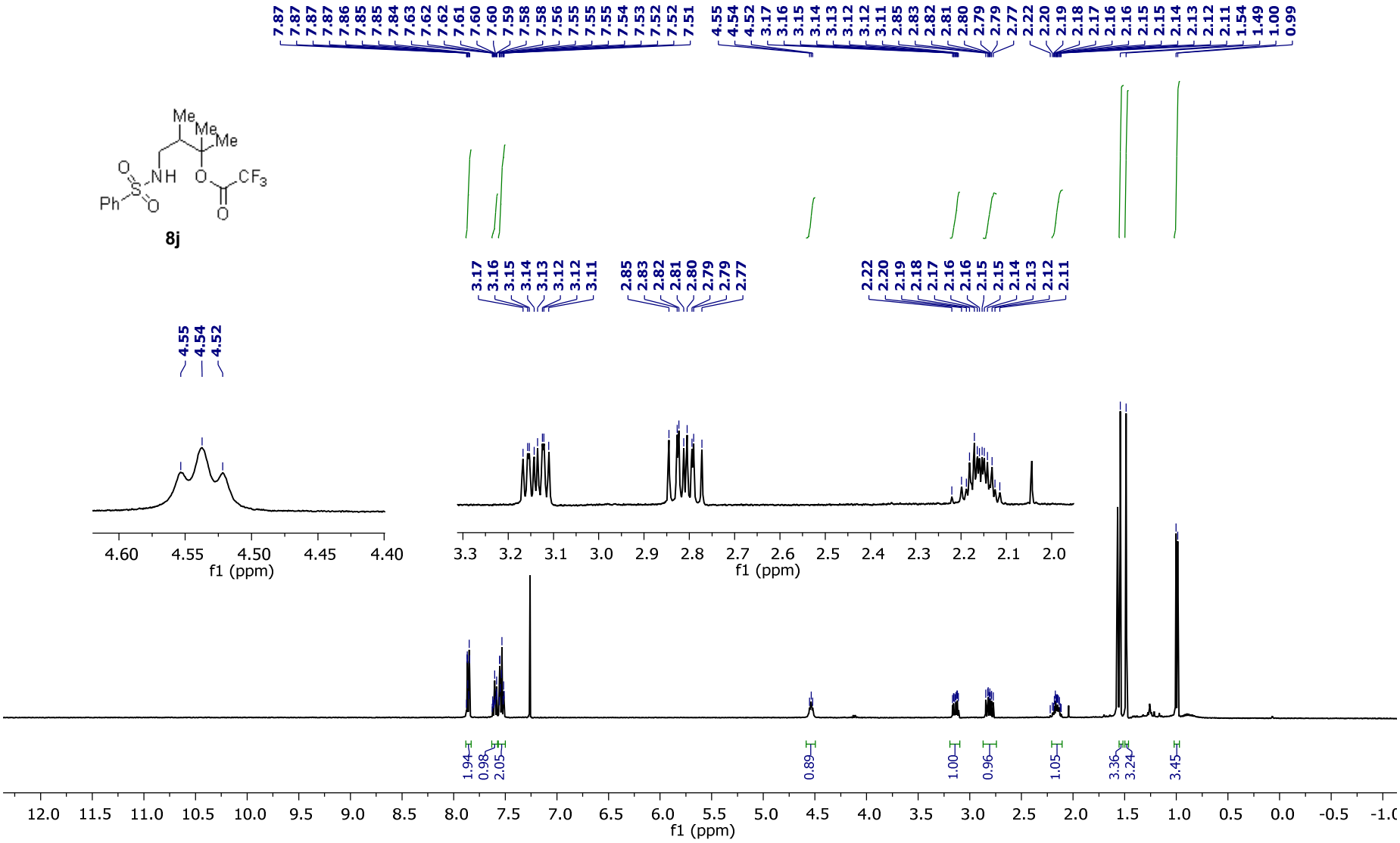

Me
Me
Me
O
NH
O
CF3
CF3
O
8i
6.49
3.56
3.55
3.54
3.53
3.52
3.50
3.41
3.39
3.38
3.36
3.34
2.27
2.26
2.26
2.24
2.24
2.23
2.22
2.21
2.20
2.19
1.65
1.60
1.05
1.03
f1 (ppm)
0.90
1.06
1.24
1.00
2.95
3.05
2.96

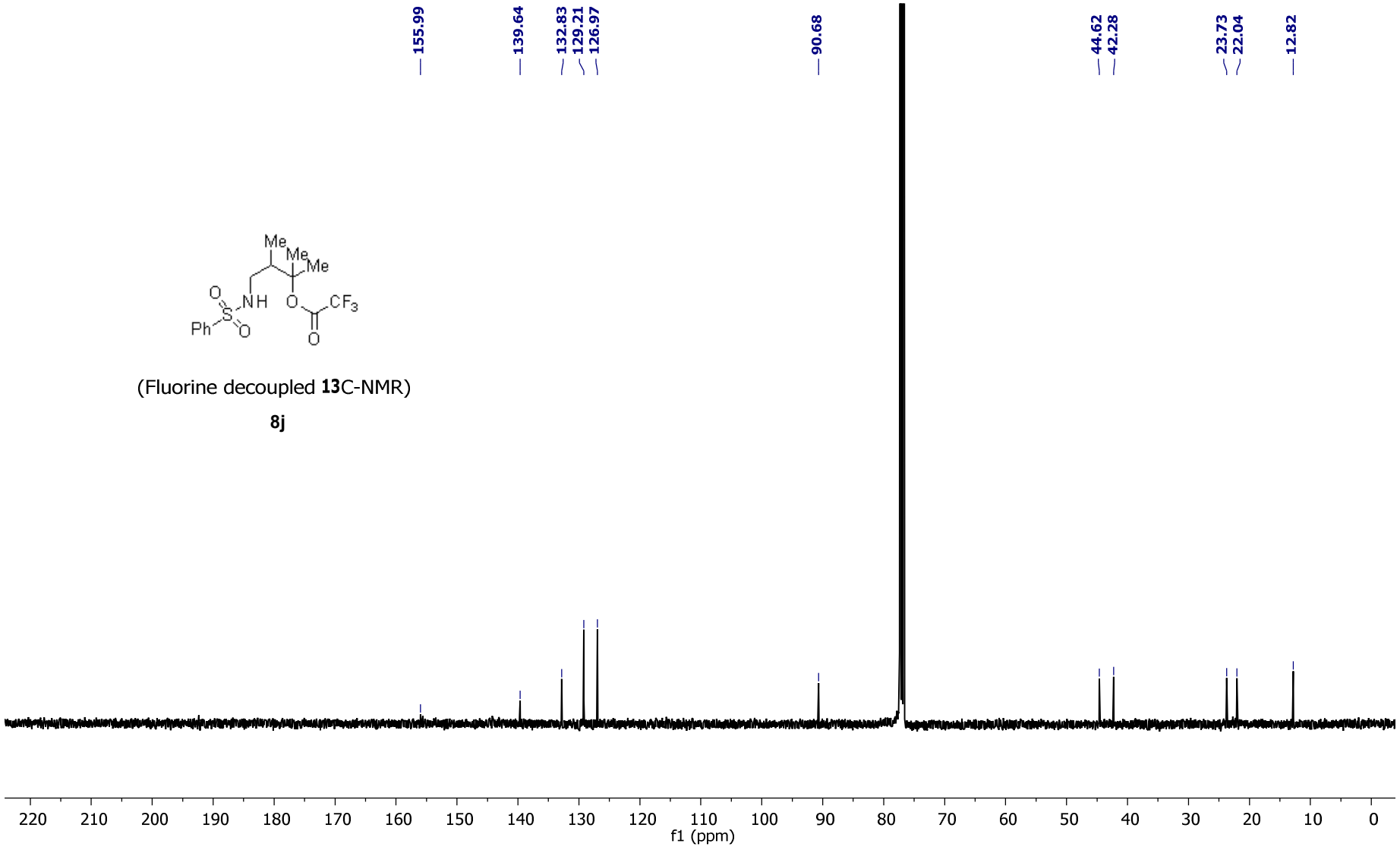

158.02
157.65
157.28
156.91
156.44
156.03
155.62
155.20
120.04
118.56
117.18
115.70
114.32
112.85
111.46
110.00
90.90
42.11
41.29
23.90
21.97
12.95
Me
Me
Me
NH
O
CF3
CF3
O
8i
f1 (ppm)
f1 (ppm)


Me
Me
Me
O
NH
O
CF3
CF3
O
8i
-75.78
-76.11
-75.78
-76.11
-70
-75
-80
f1 (ppm)
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


Me
Me
N
O
S
O
Ph
5j
7.87 7.87 7.86 7.86 7.85 7.85 7.84 7.84 7.55 7.55 7.54 7.54 7.53 7.52 7.51 7.51 7.51 7.50 7.50 7.49 7.49 7.48 7.48 7.46 7.46 7.45
3.42 3.41 3.39
1.86 1.85 1.84 1.84 1.83 1.82 1.81 1.80 1.79 1.78 1.77 1.76 1.75 1.75 1.45
7.85 7.80 7.75 7.70 7.65 7.60 7.55 7.50 7.45 7.40
f1 (ppm)
3.42 3.39
f1 (ppm)
1.9 1.8 1.7 1.6 1.5 1.4 1.3
f1 (ppm)
1.91 2.97 2.00 4.12 6.50
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

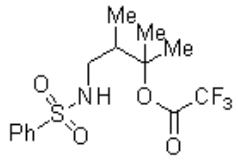

141.59
131.88
128.72
127.04
65.21
49.38
42.89
28.23
22.48
Me
Me
N
O
S
O
Ph
5j
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8j
f1 (ppm)



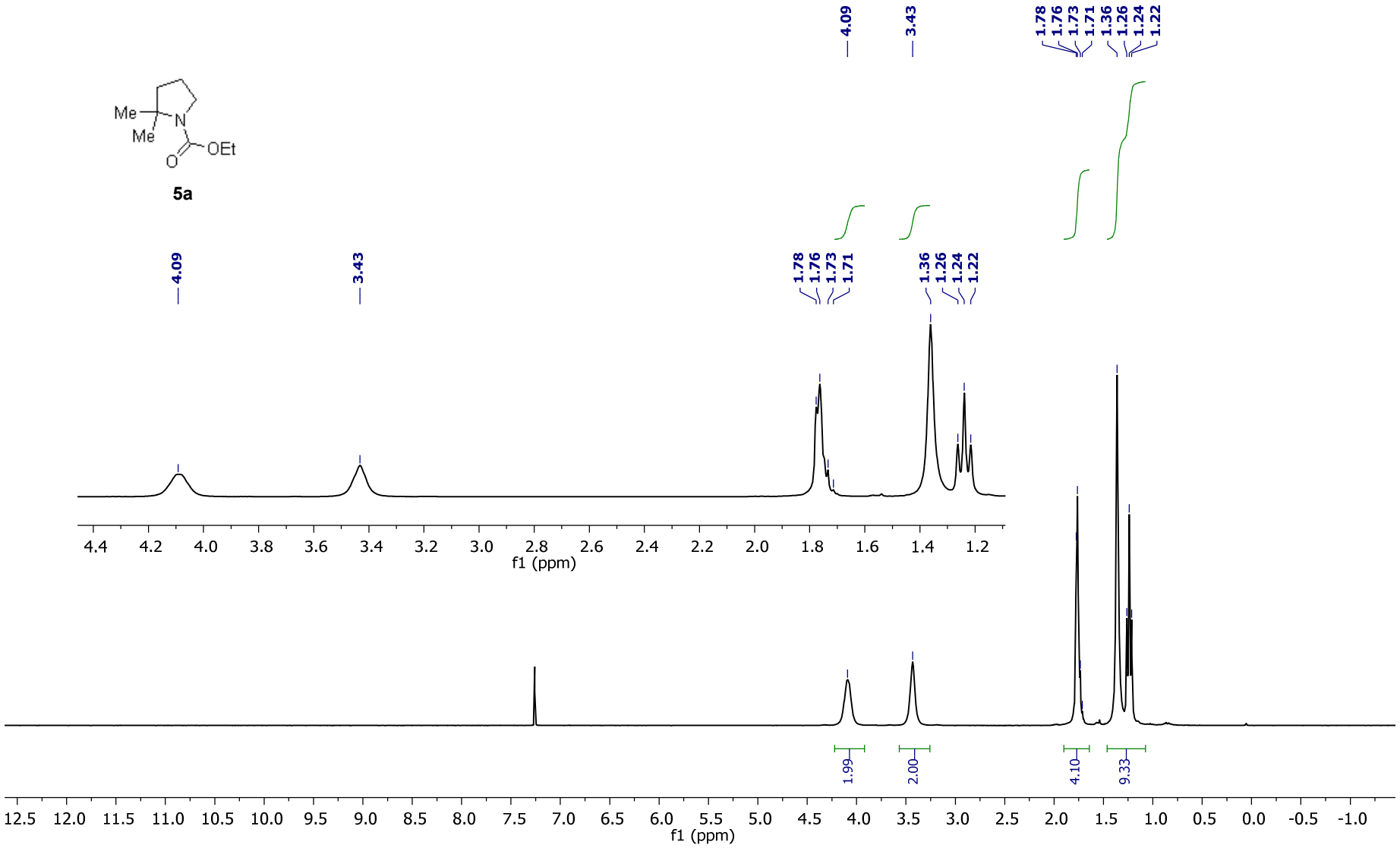
(Fluorine decoupled **13**C-NMR)

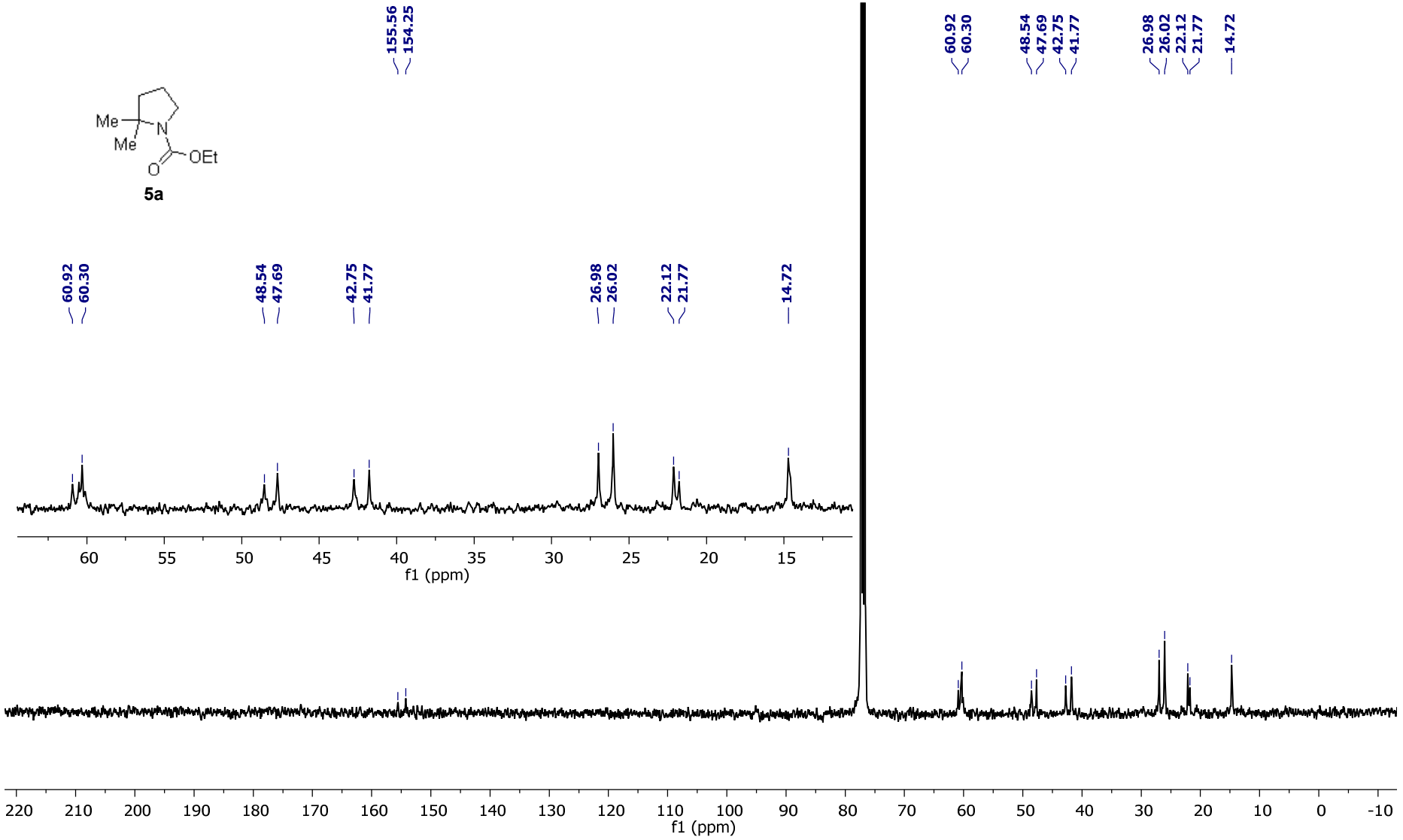
8j

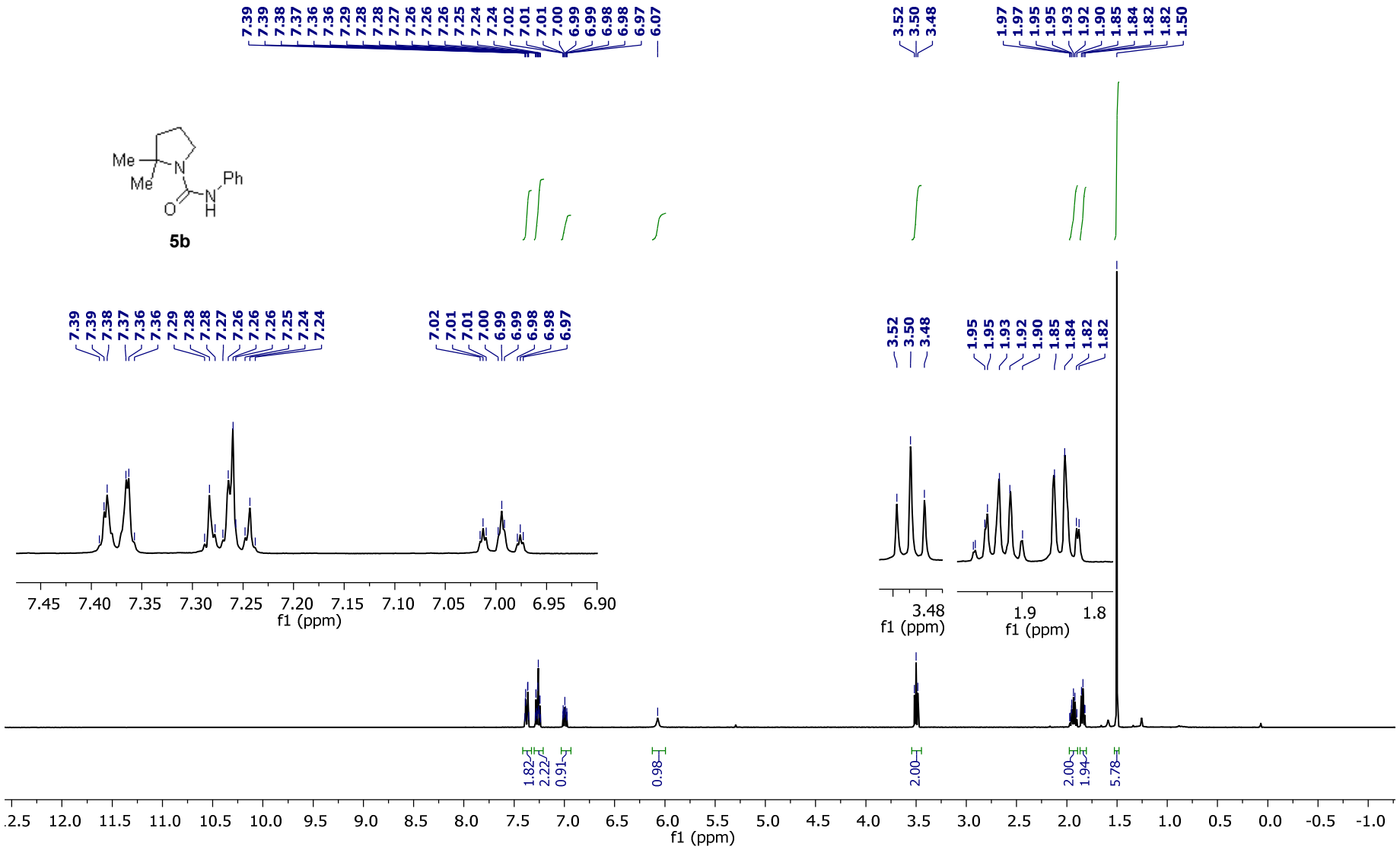

Me
Me
Me
O
NH
O
CF3
Ph
S
O
O

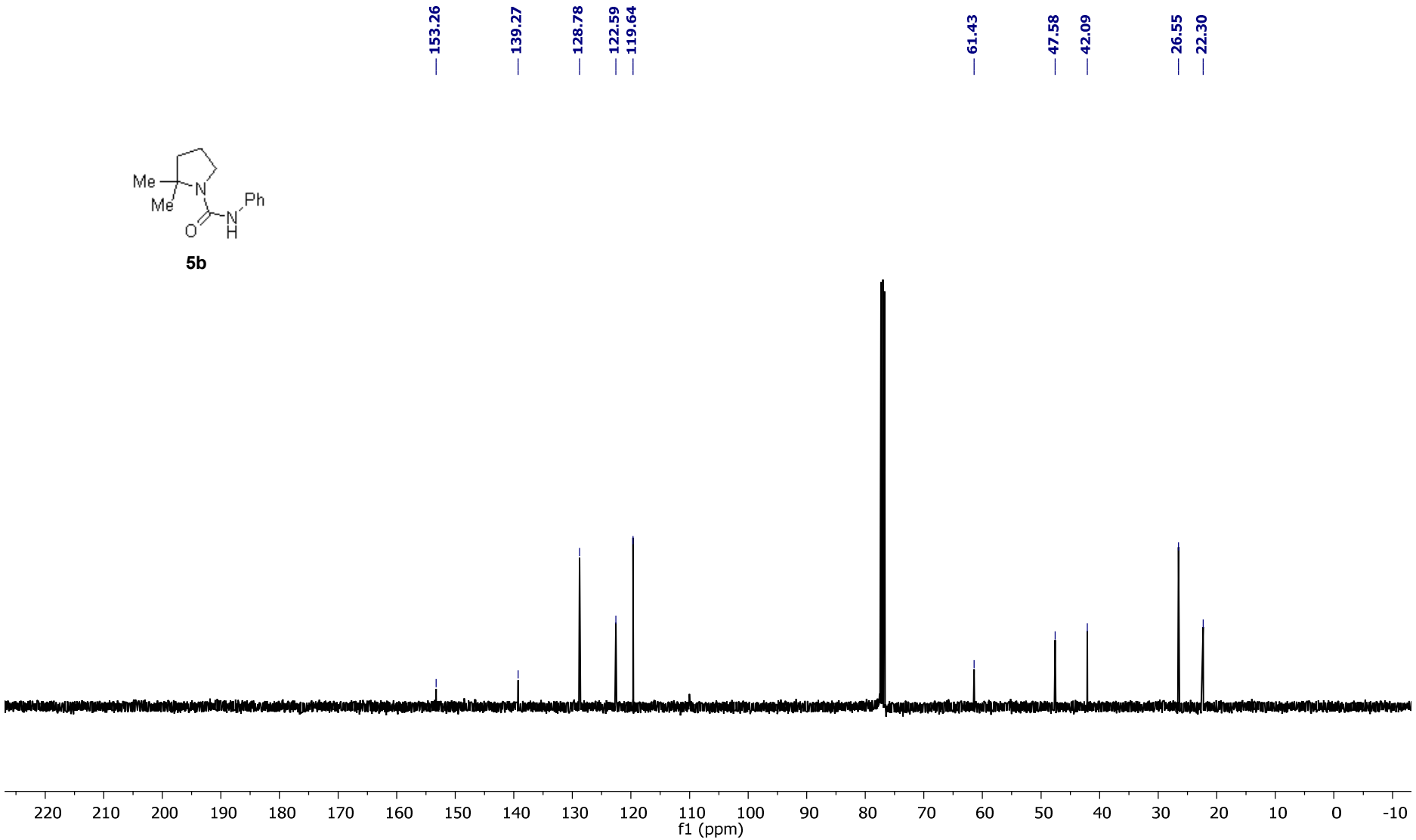
8j

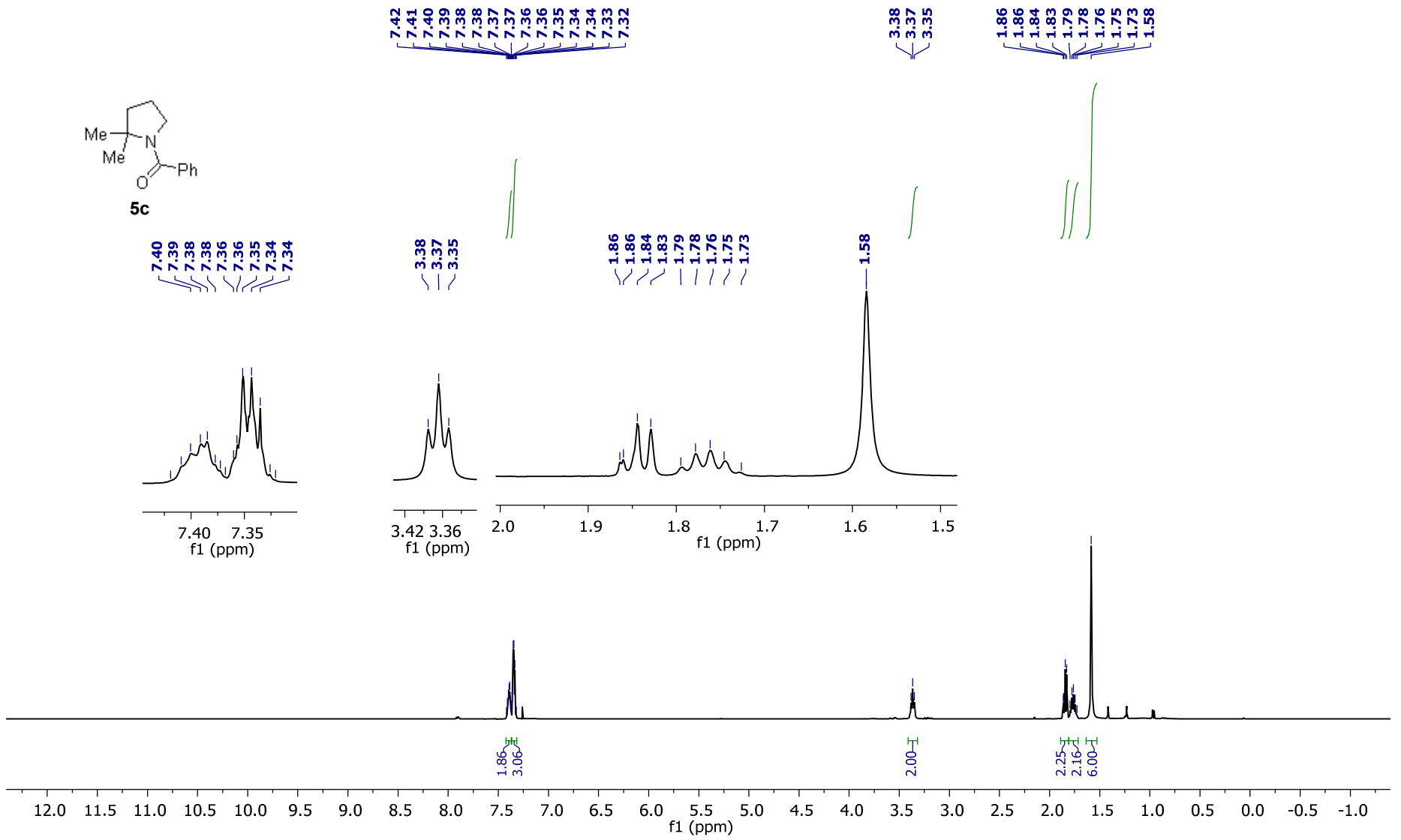
-78.29
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
f1 (ppm)

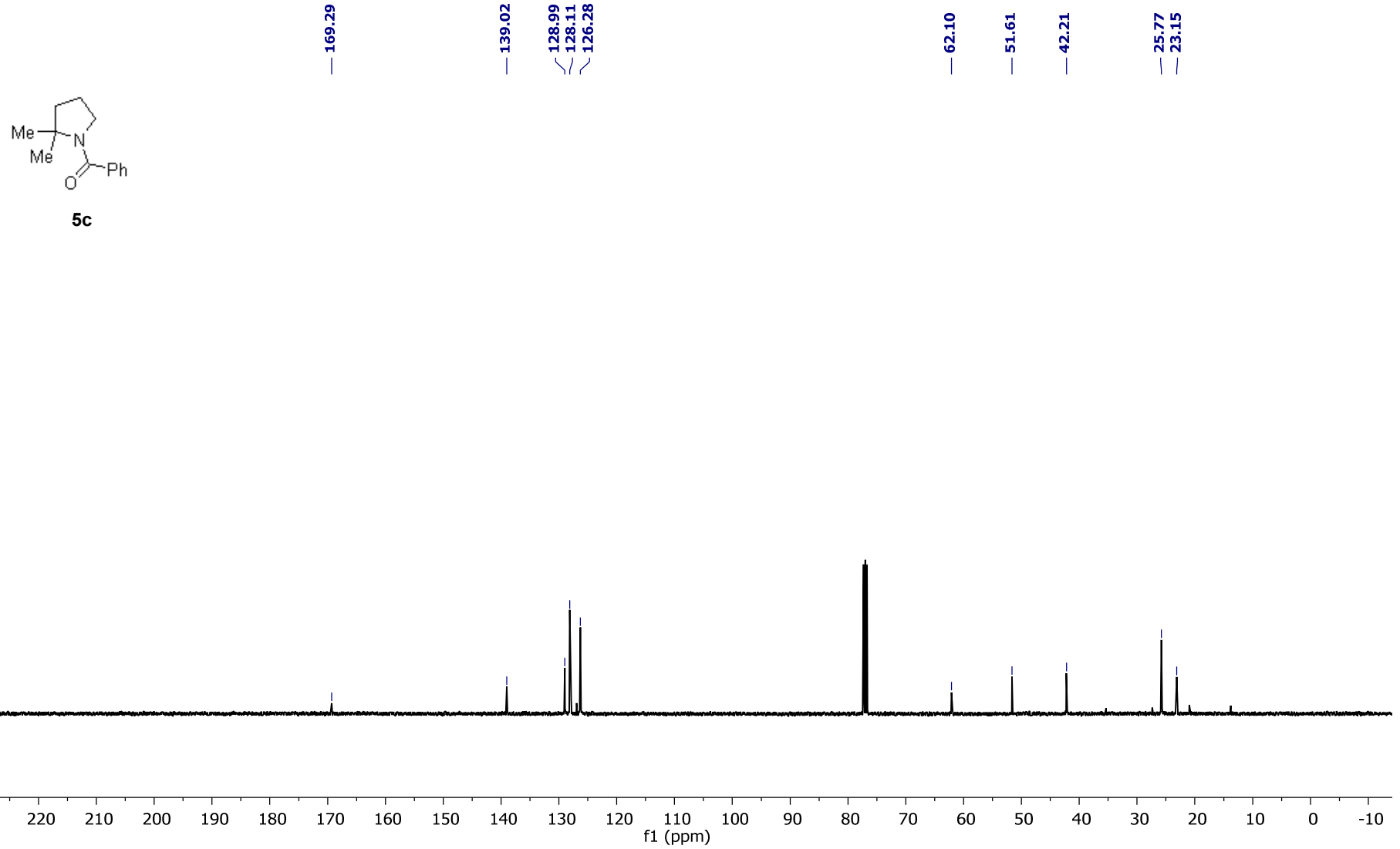

Me
Me
N
O
OEt
5a
4.09
3.43
1.78
1.76
1.73
1.71
1.36
1.26
1.24
1.22
f1 (ppm)
1.99
2.00
4.10
9.33

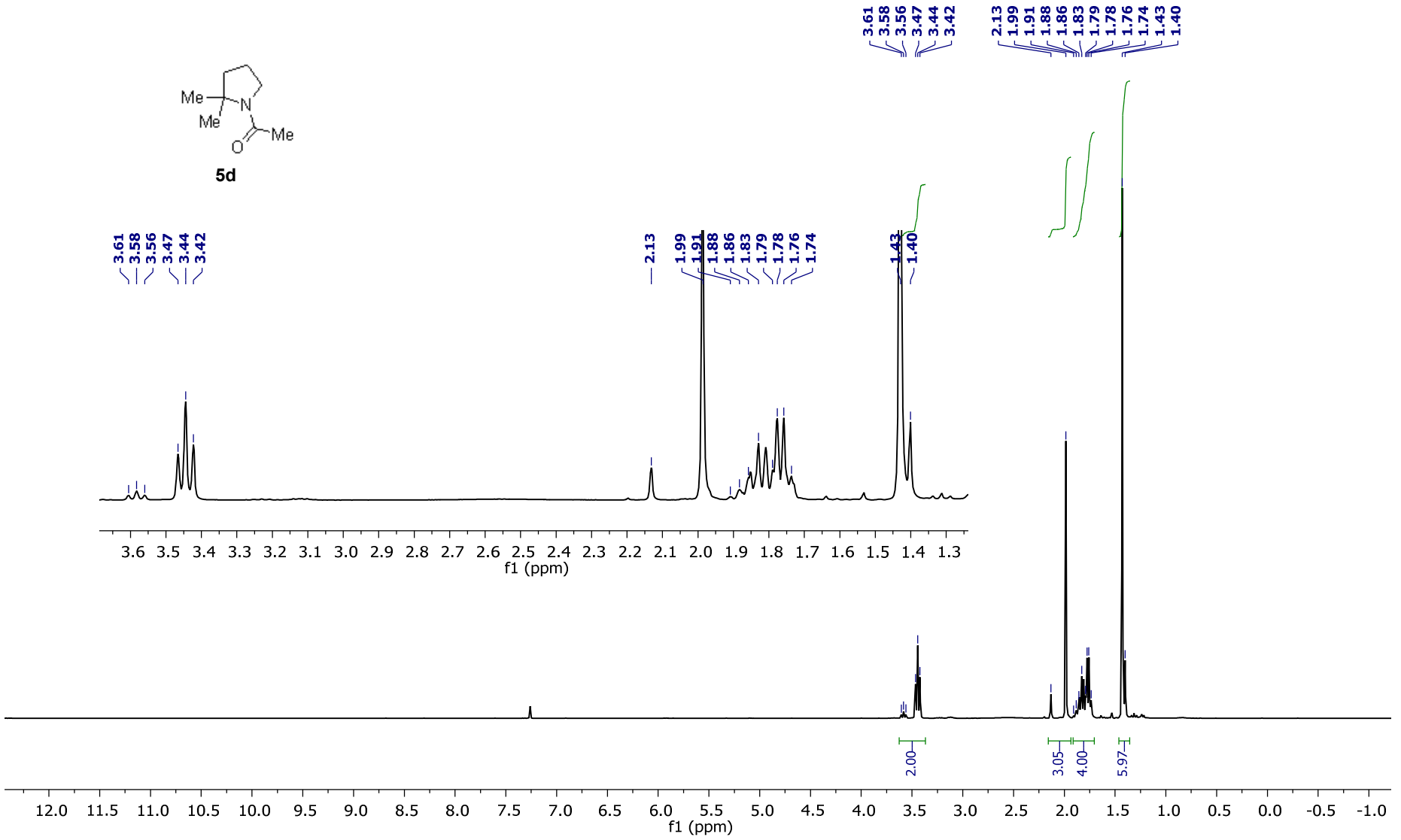

155.56
154.25
60.92
60.30
48.54
47.69
42.75
41.77
26.98
26.02
22.12
21.77
14.72
Me
Me
N
O
OEt
5a
f1 (ppm)
f1 (ppm)

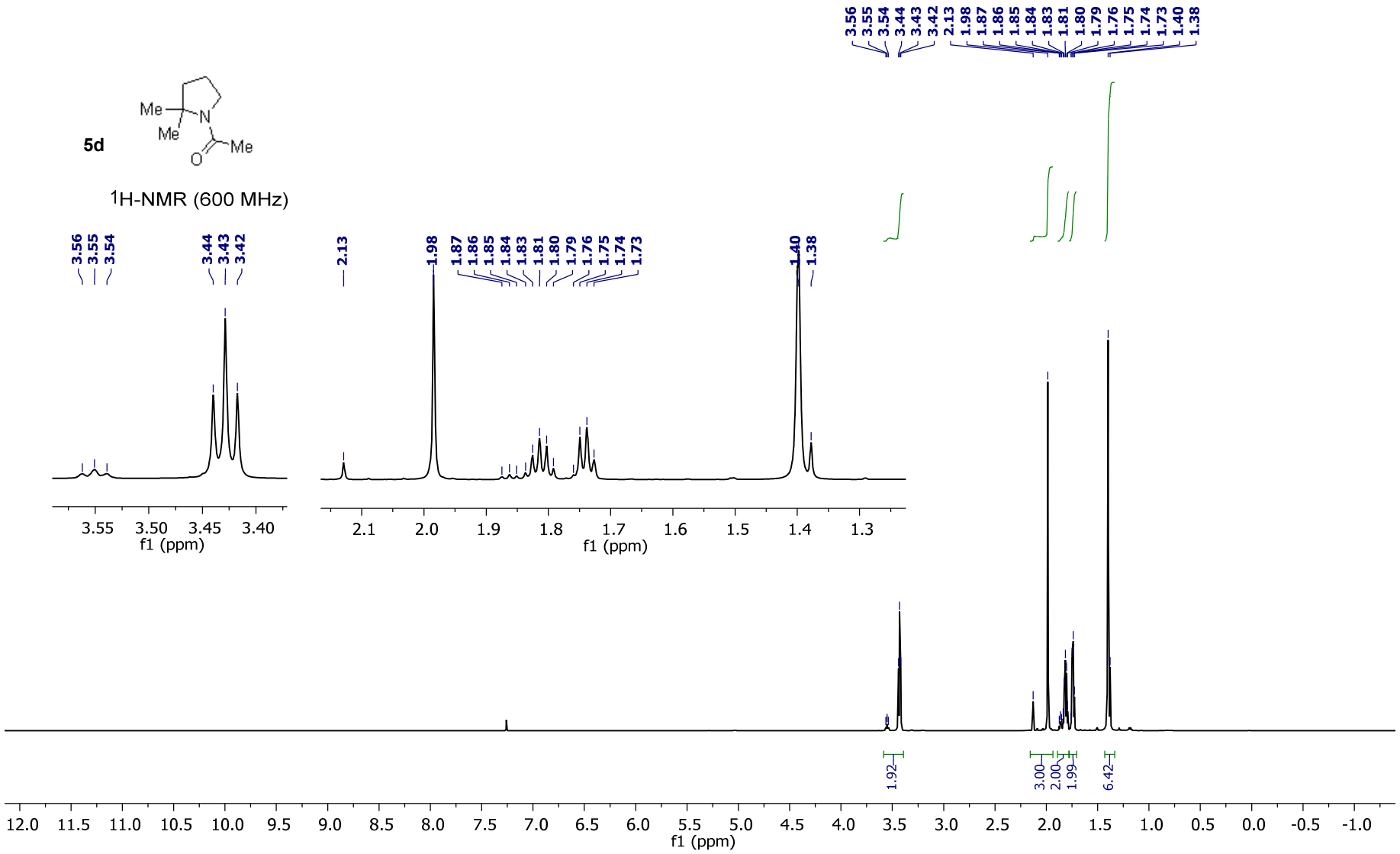

7.39 7.39 7.38 7.37 7.36 7.36 7.29 7.28 7.28 7.27 7.26 7.26 7.26 7.25 7.24 7.24 7.02 7.01 7.01 7.00 6.99 6.99 6.98 6.98 6.97 6.07
3.52 3.50 3.48
1.97 1.97 1.95 1.95 1.93 1.92 1.90 1.85 1.84 1.82 1.82 1.50
Me
Me
N
O
N
H
Ph
5b
7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90
f1 (ppm)
3.48
f1 (ppm)
1.9 1.8
f1 (ppm)
1.82 2.22 0.91 0.98 2.00 2.00 1.94 5.78
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

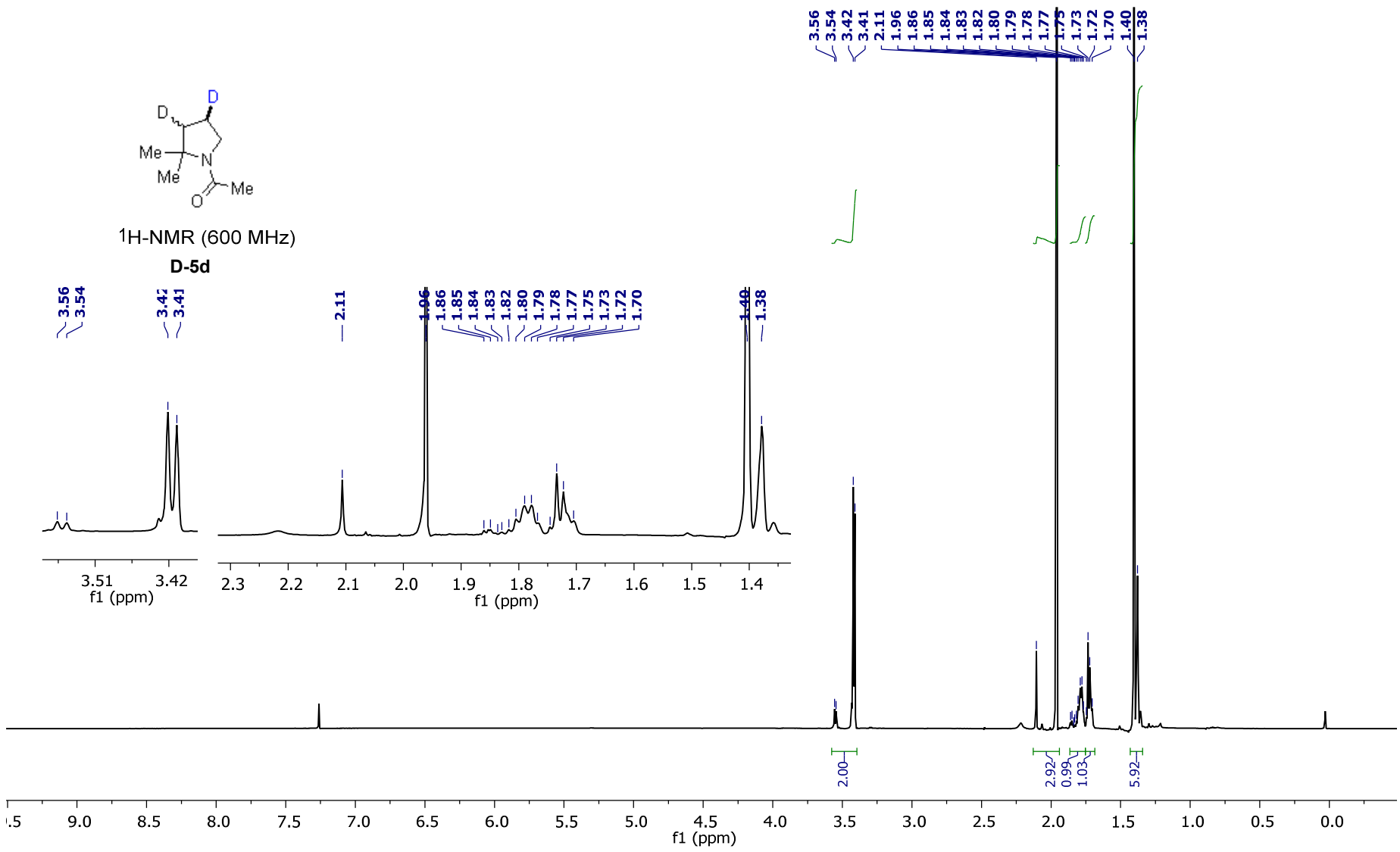

153.26
139.27
128.78
122.59
119.64
61.43
47.58
42.09
26.55
22.30
Me
Me
N
O
N
H
Ph
5b
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

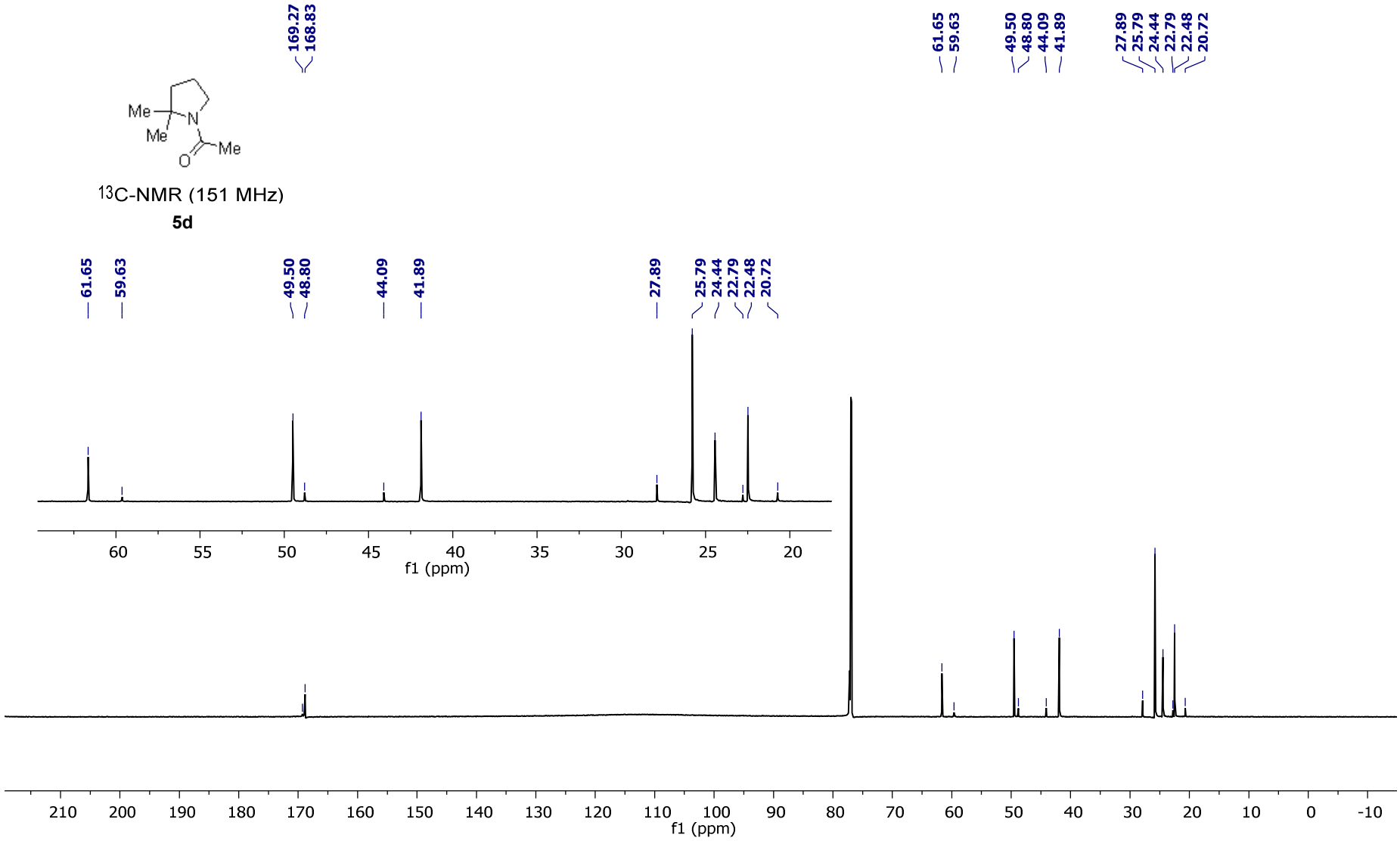

Me
Me
N
O
Ph
5c
7.42 7.41 7.40 7.39 7.38 7.38 7.37 7.37 7.36 7.36 7.35 7.34 7.34 7.33 7.32
3.38 3.37 3.35
1.86 1.86 1.84 1.83 1.79 1.78 1.76 1.75 1.73 1.58
7.40 7.39 7.38 7.38 7.36 7.36 7.35 7.34 7.34
7.40 7.35
f1 (ppm)
3.38 3.37 3.35
3.42 3.36
f1 (ppm)
1.86 1.86 1.84 1.83 1.79 1.78 1.76 1.75 1.73 1.58
2.0 1.9 1.8 1.7 1.6 1.5
f1 (ppm)
1.86
3.06
2.00
2.25
2.16
6.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

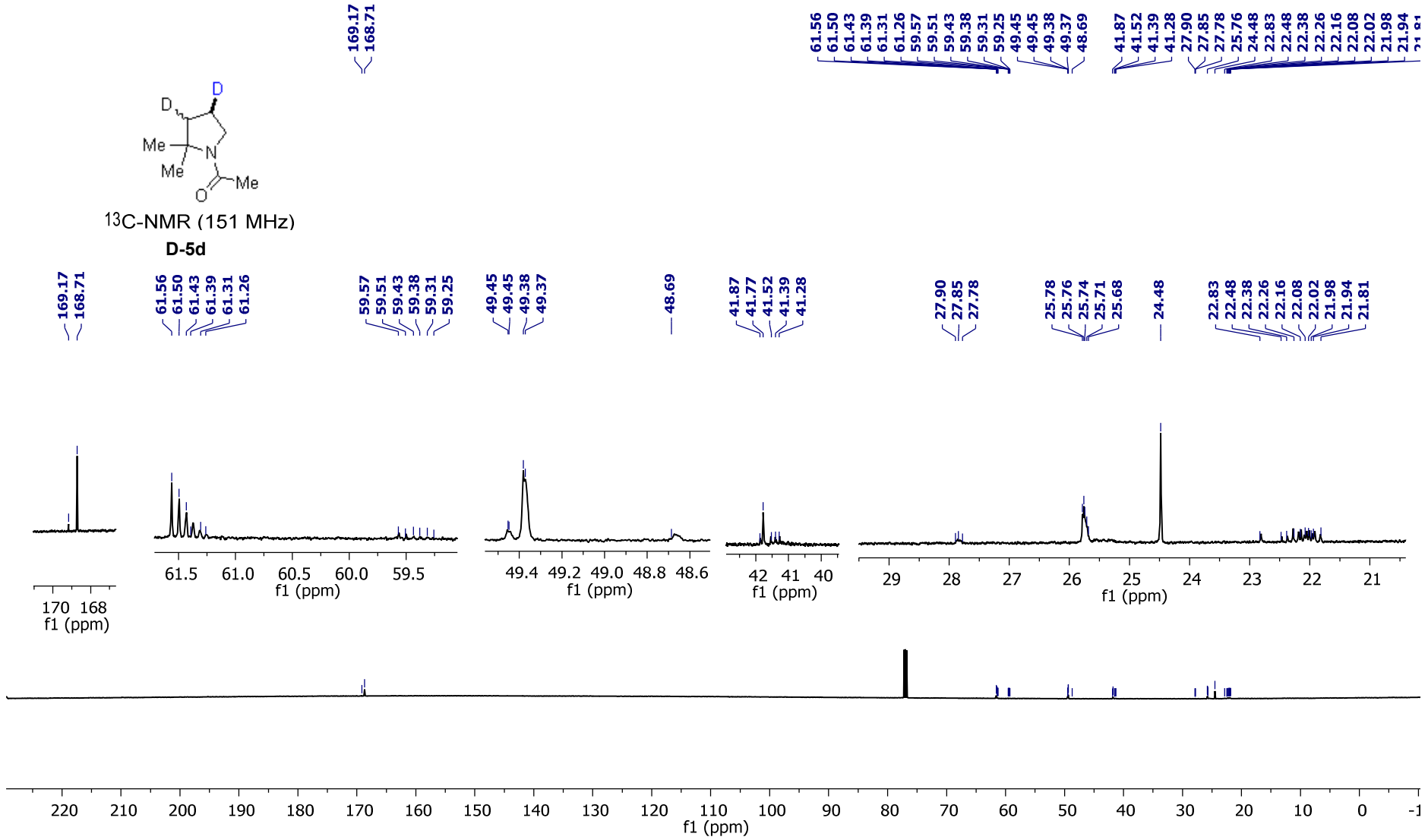

169.29
139.02
128.99
128.11
126.28
62.10
51.61
42.21
25.77
23.15
Me
Me
N
O
Ph
5c
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

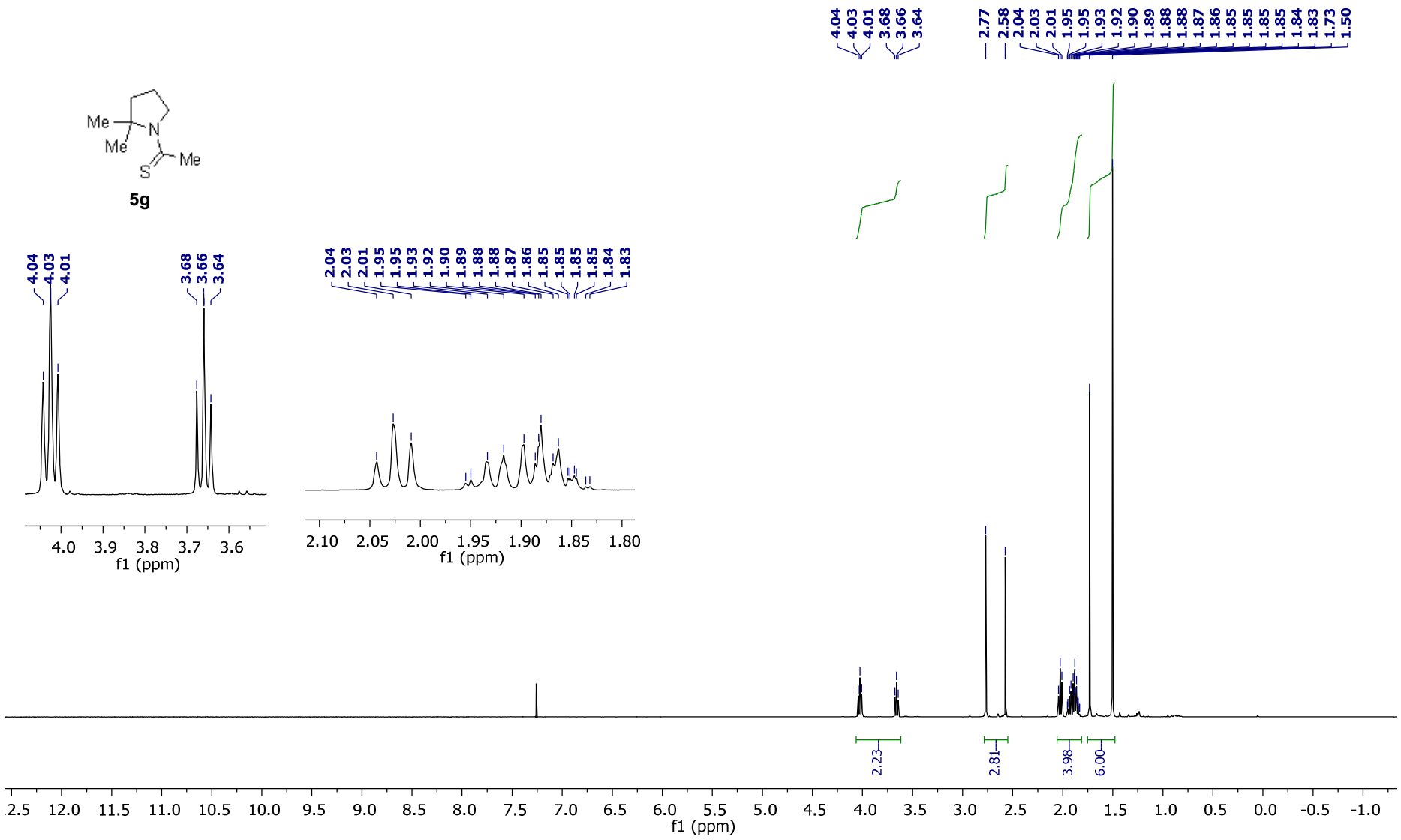

Me
Me
N
O
Me
5d
3.61
3.58
3.56
3.47
3.44
3.42
2.13
1.99
1.91
1.88
1.86
1.83
1.79
1.78
1.76
1.74
1.43
1.40
3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3
f1 (ppm)
2.00
3.05
4.00
5.97
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

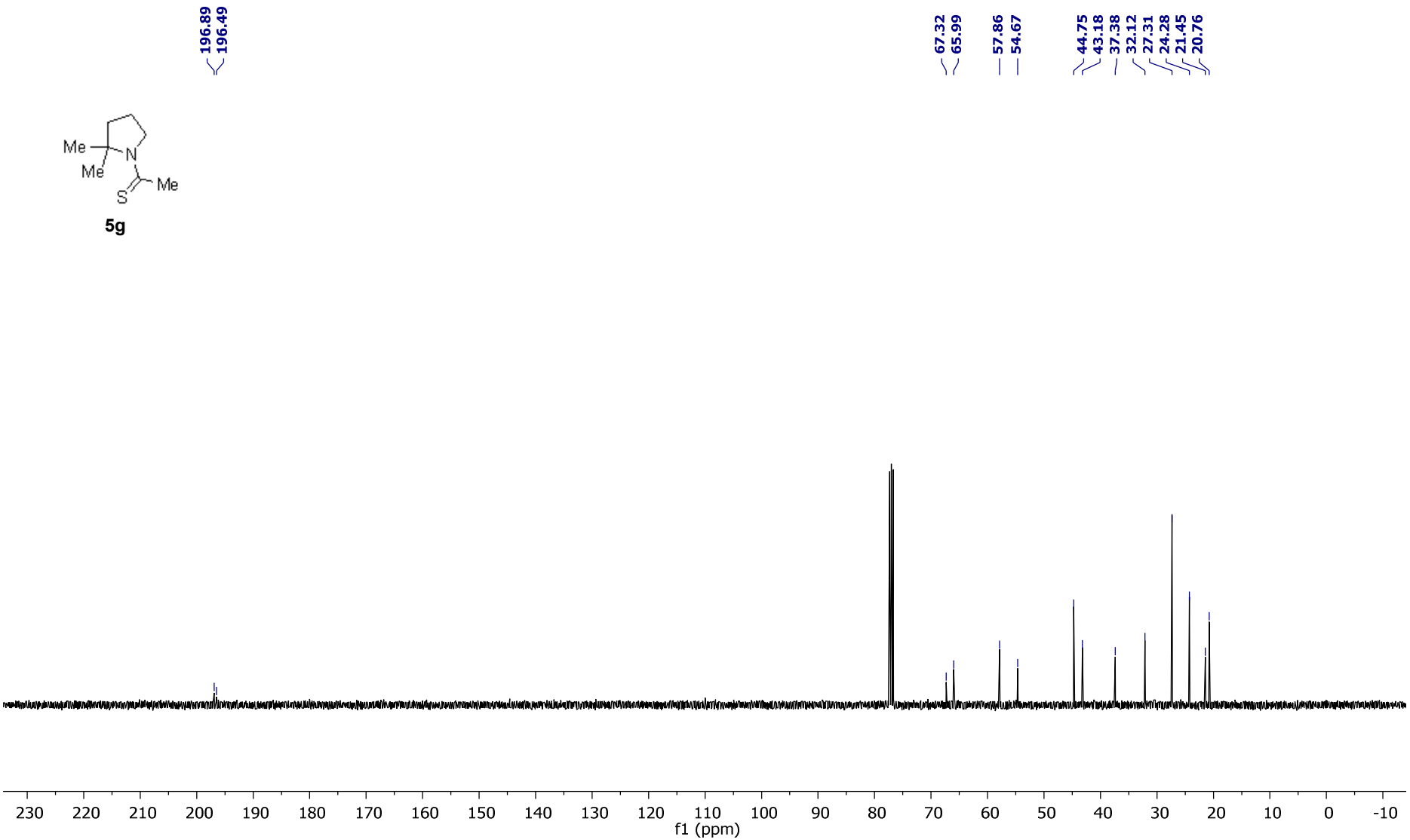

5d
Me
Me
N
O
Me
1H-NMR (600 MHz)
3.56 3.55 3.54 3.44 3.43 3.42 2.13 1.98 1.87 1.86 1.85 1.84 1.83 1.81 1.80 1.79 1.76 1.75 1.74 1.73 1.40 1.38
3.55 3.50 3.45 3.40
f1 (ppm)
2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3
f1 (ppm)
1.92 3.00 2.00 1.99 6.42
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


D
D
Me
Me
N
Me
O
1H-NMR (600 MHz)
D-5d
3.56
3.54
3.42
3.41
2.11
1.96
1.86
1.85
1.84
1.83
1.82
1.80
1.79
1.78
1.77
1.75
1.73
1.72
1.70
1.40
1.38
3.51
3.42
f1 (ppm)
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
f1 (ppm)
2.00
2.92
0.99
1.03
5.92
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

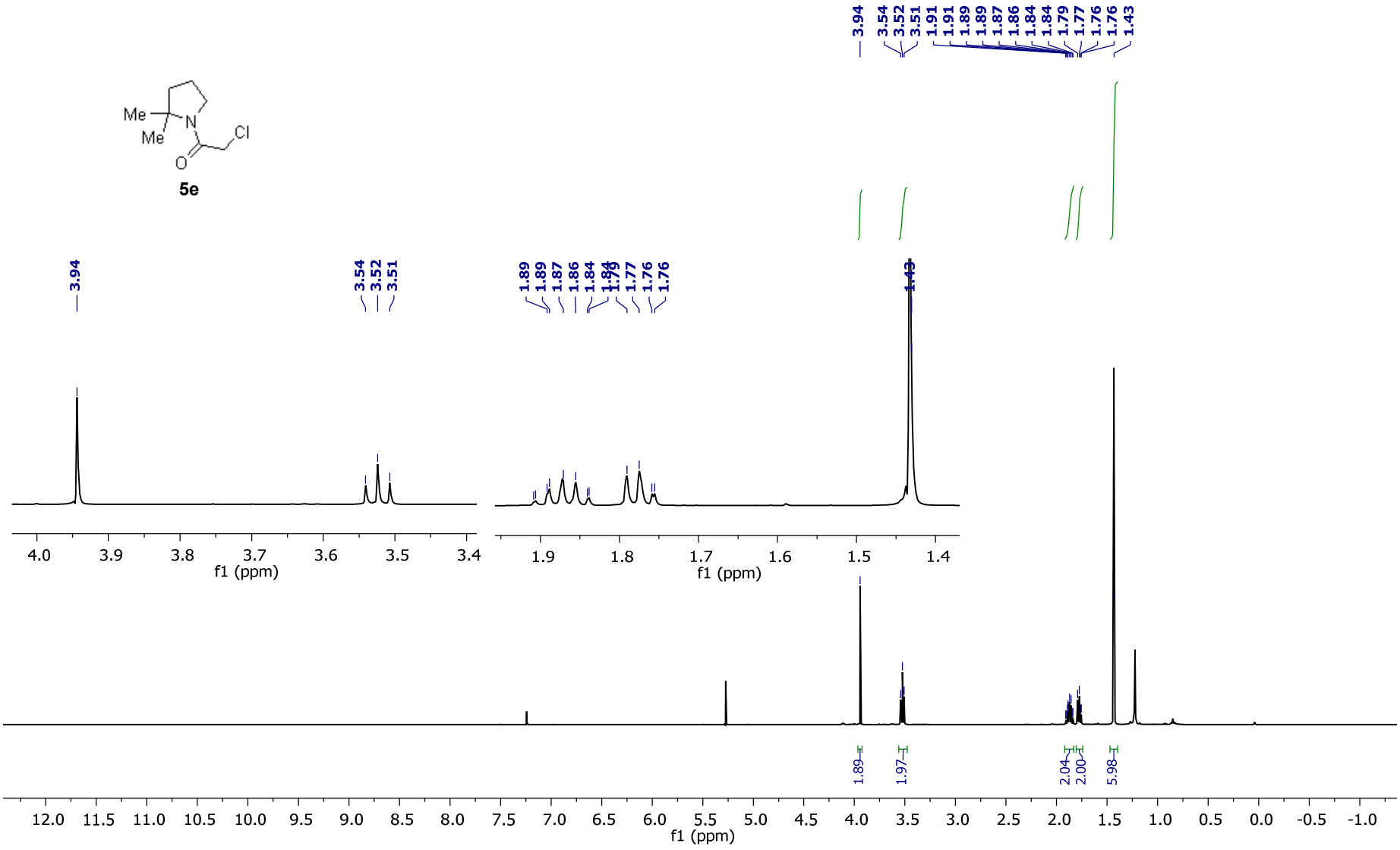

169.27
168.83
61.65
59.63
49.50
48.80
44.09
41.89
27.89
25.79
24.44
22.79
22.48
20.72
Me
Me
N
Me
O
13C-NMR (151 MHz)
5d
f1 (ppm)
f1 (ppm)

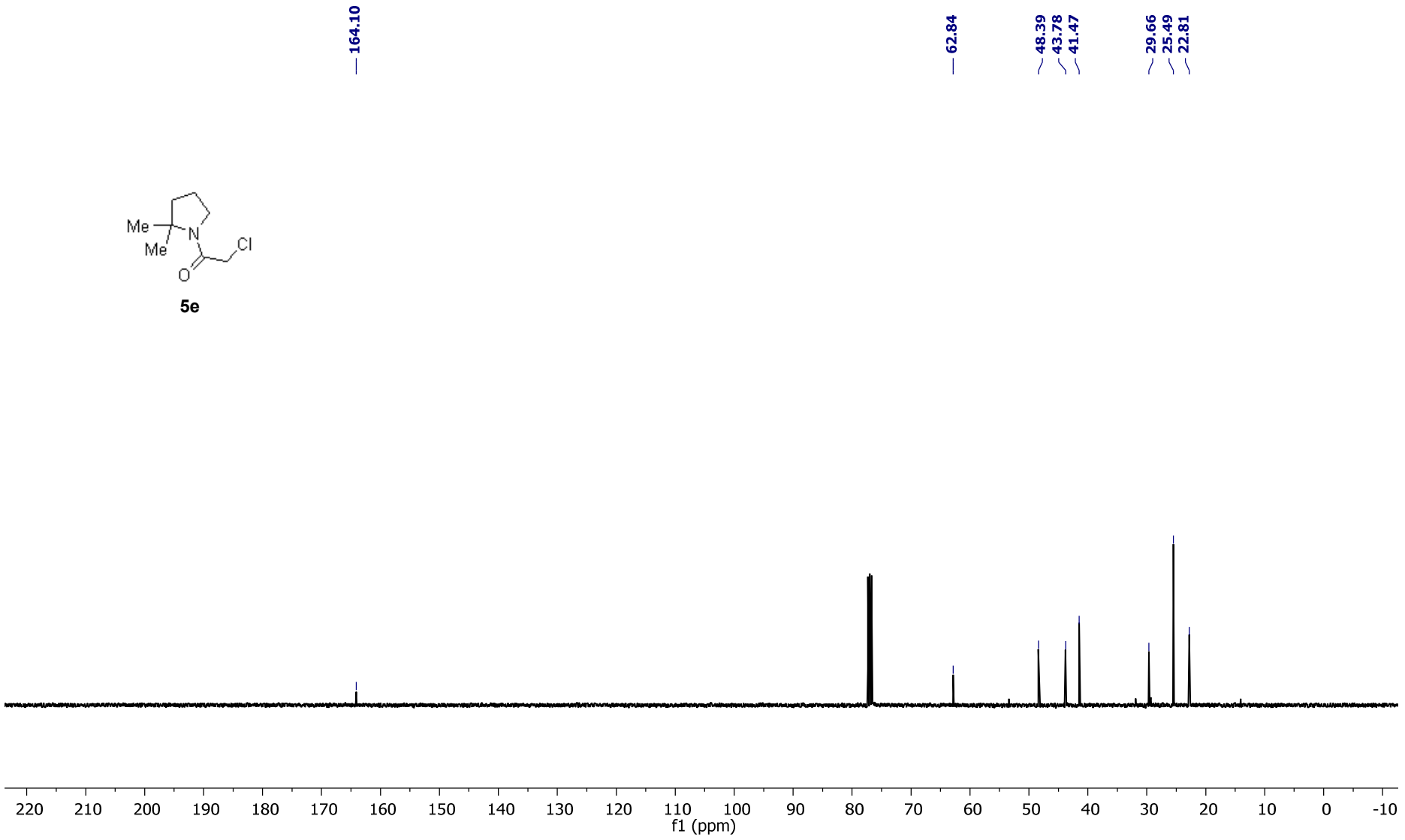

169.17
168.71
61.56
61.50
61.43
61.39
61.31
61.26
59.57
59.51
59.43
59.38
59.31
59.25
49.45
49.45
49.38
49.37
48.69
41.87
41.77
41.52
41.39
41.28
27.90
27.85
27.78
25.78
25.76
25.74
25.71
25.68
24.48
22.83
22.48
22.38
22.26
22.16
22.08
22.02
21.98
21.94
21.81
D
D
Me
Me
N
O
Me
13C-NMR (151 MHz)
D-5d
f1 (ppm)

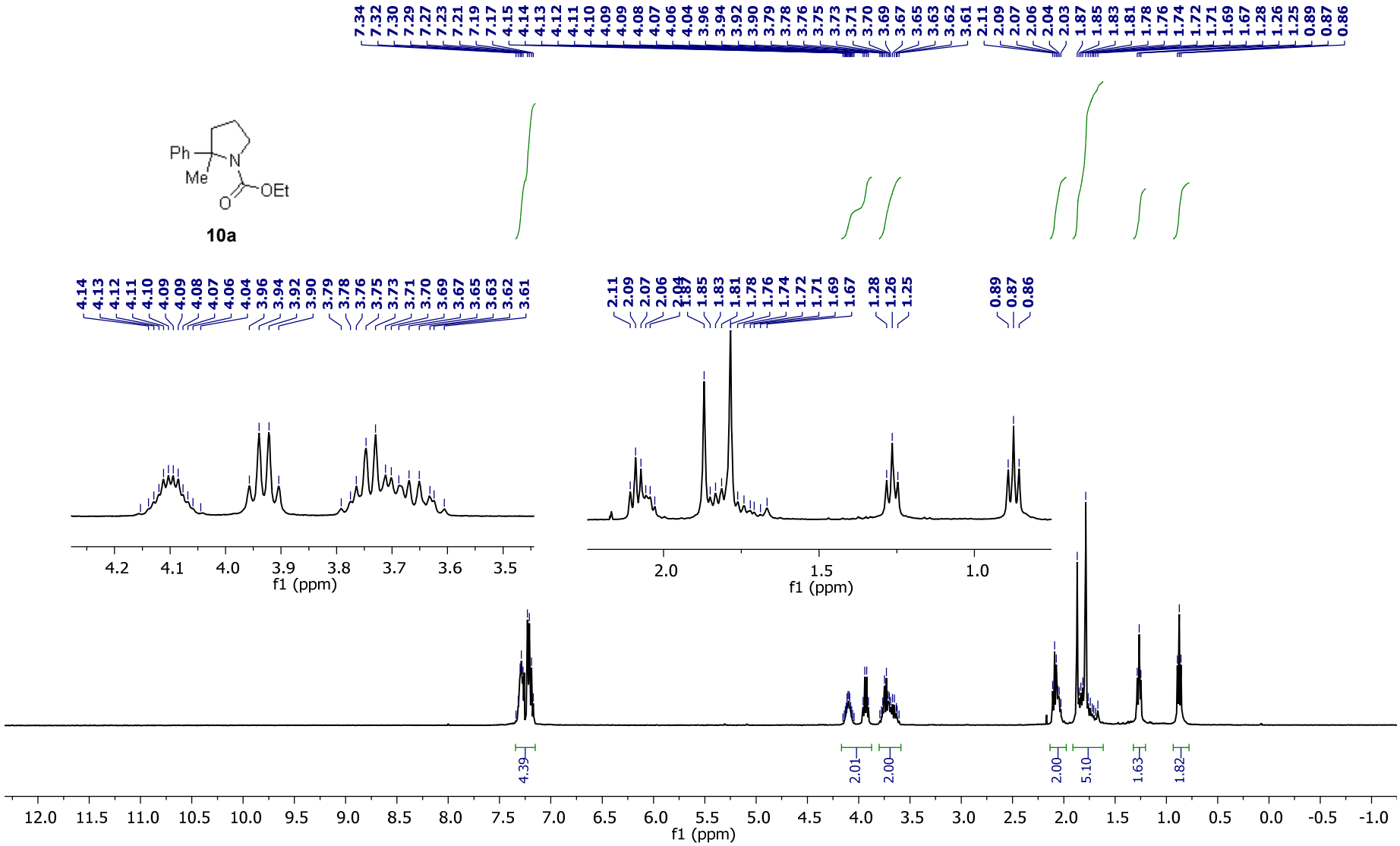

Me
Me
N
S
Me
5g
4.04
4.03
4.01
3.68
3.66
3.64
4.0 3.9 3.8 3.7 3.6
f1 (ppm)
2.04
2.03
2.01
1.95
1.95
1.93
1.92
1.90
1.89
1.88
1.88
1.87
1.86
1.85
1.85
1.85
1.84
1.83
2.10 2.05 2.00 1.95 1.90 1.85 1.80
f1 (ppm)
4.04
4.03
4.01
3.68
3.66
3.64
2.77
2.58
2.04
2.03
2.01
1.95
1.93
1.92
1.90
1.89
1.88
1.88
1.87
1.86
1.85
1.85
1.85
1.85
1.84
1.83
1.73
1.50
2.23
2.81
3.98
6.00
f1 (ppm)

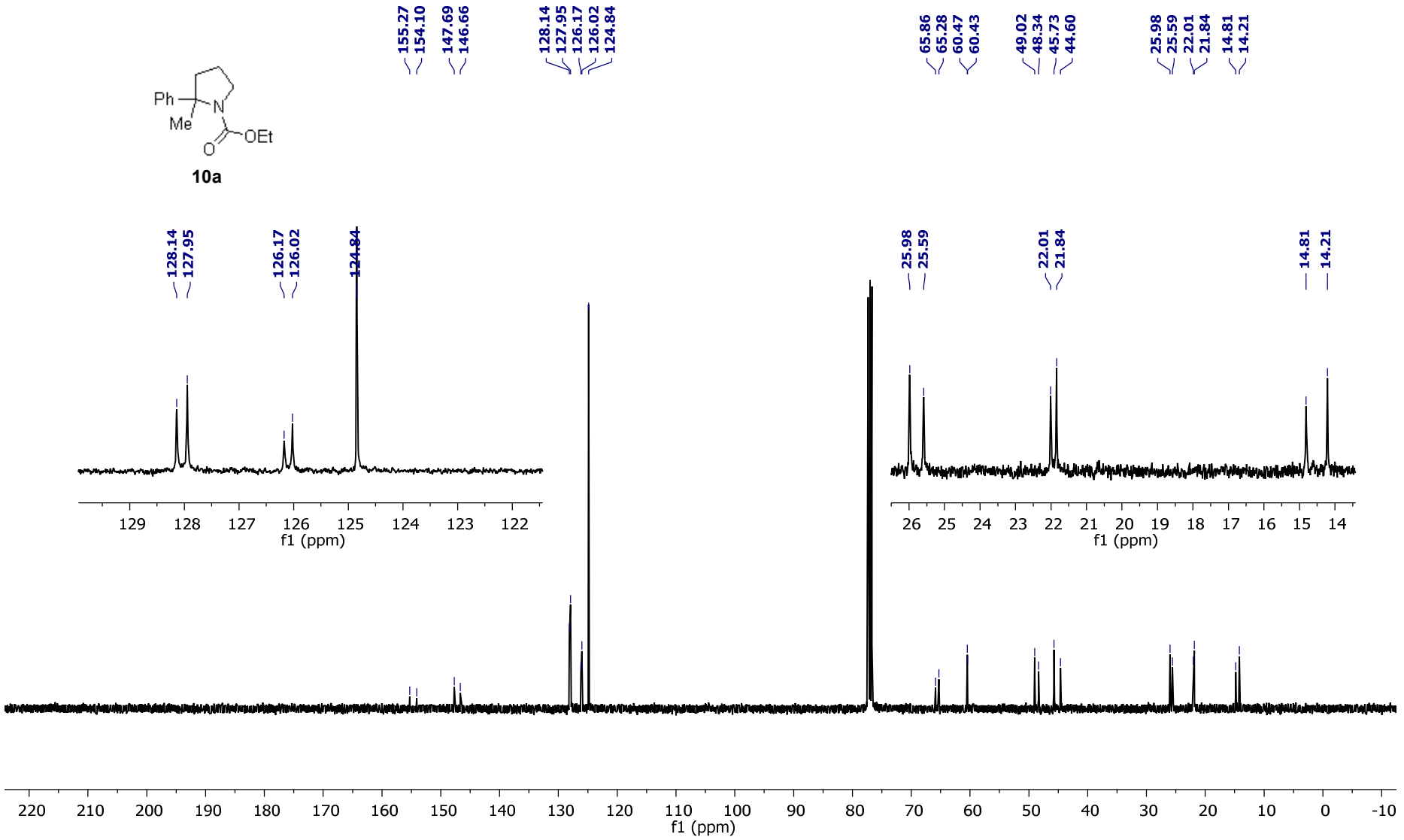

196.89
196.49
67.32
65.99
57.86
54.67
44.75
43.18
37.38
32.12
27.31
24.28
21.45
20.76
Me
Me
N
Me
S
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

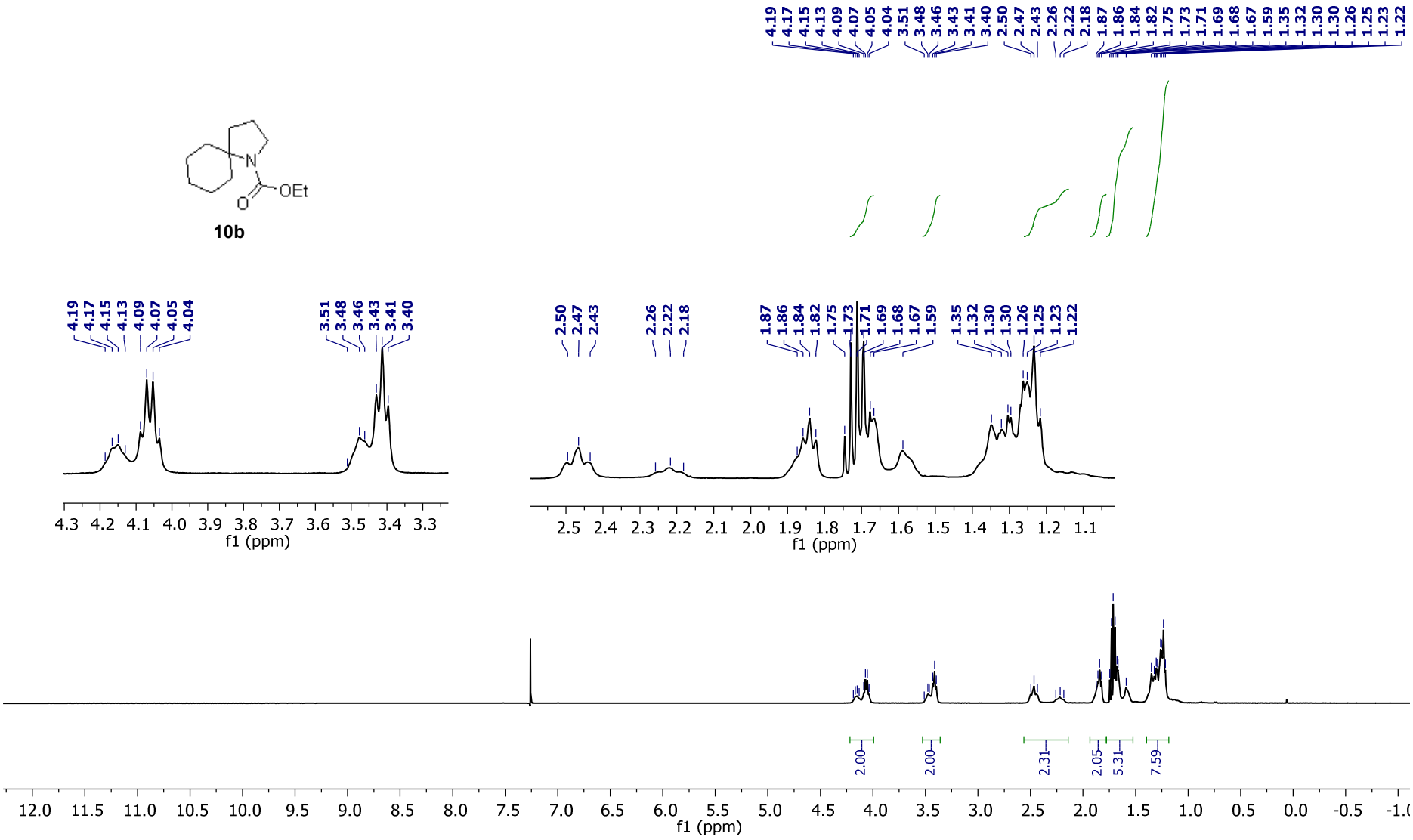
5g

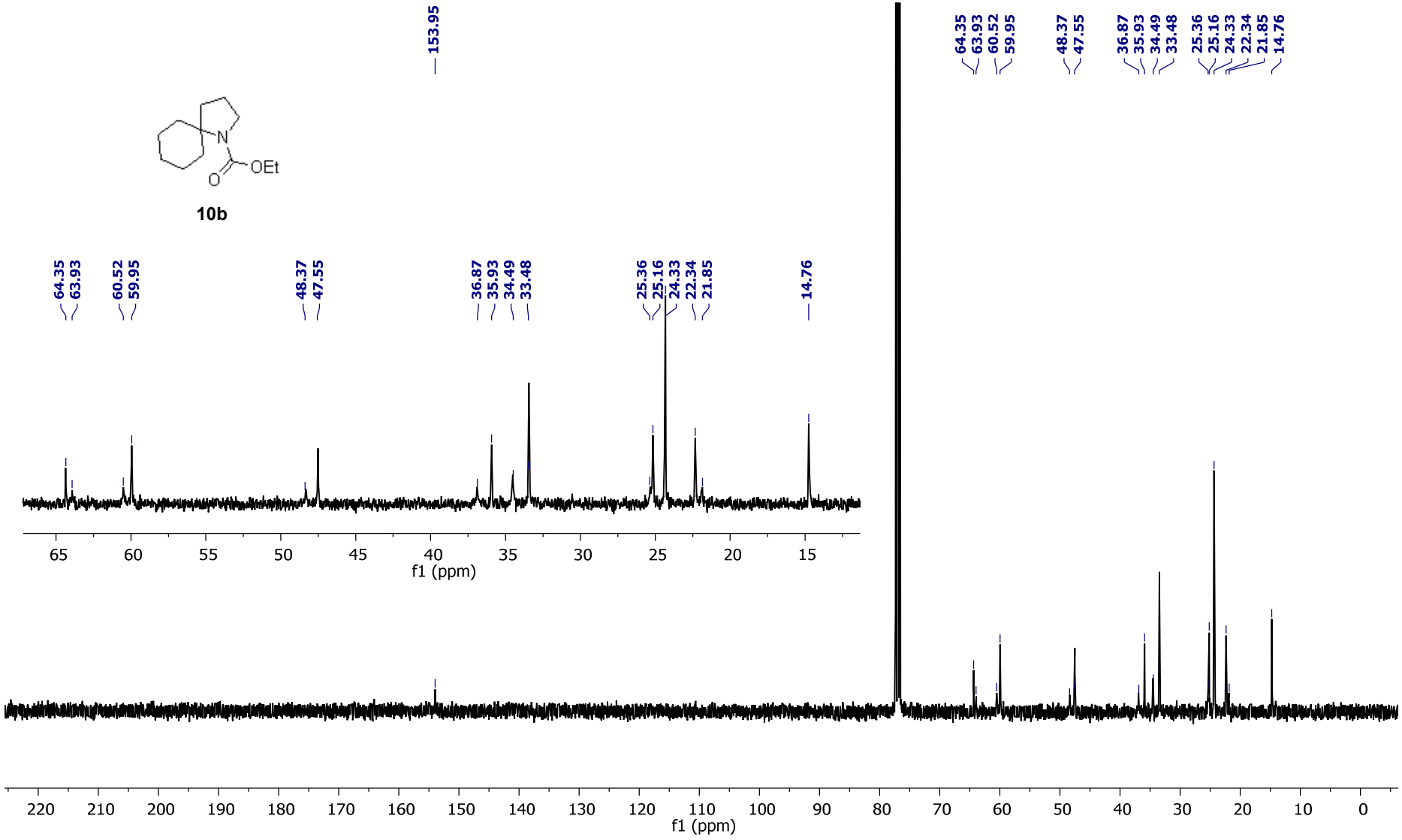

Me
Me
N
O
Cl
5e
3.94
3.54
3.52
3.51
1.91
1.91
1.89
1.89
1.87
1.86
1.84
1.84
1.79
1.77
1.76
1.76
1.43
1.89
1.89
1.87
1.86
1.84
1.77
1.76
1.76
4.0
3.9
3.8
3.7
3.6
3.5
3.4
f1 (ppm)
1.9
1.8
1.7
1.6
1.5
1.4
f1 (ppm)
1.89
1.97
2.04
2.00
5.98
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

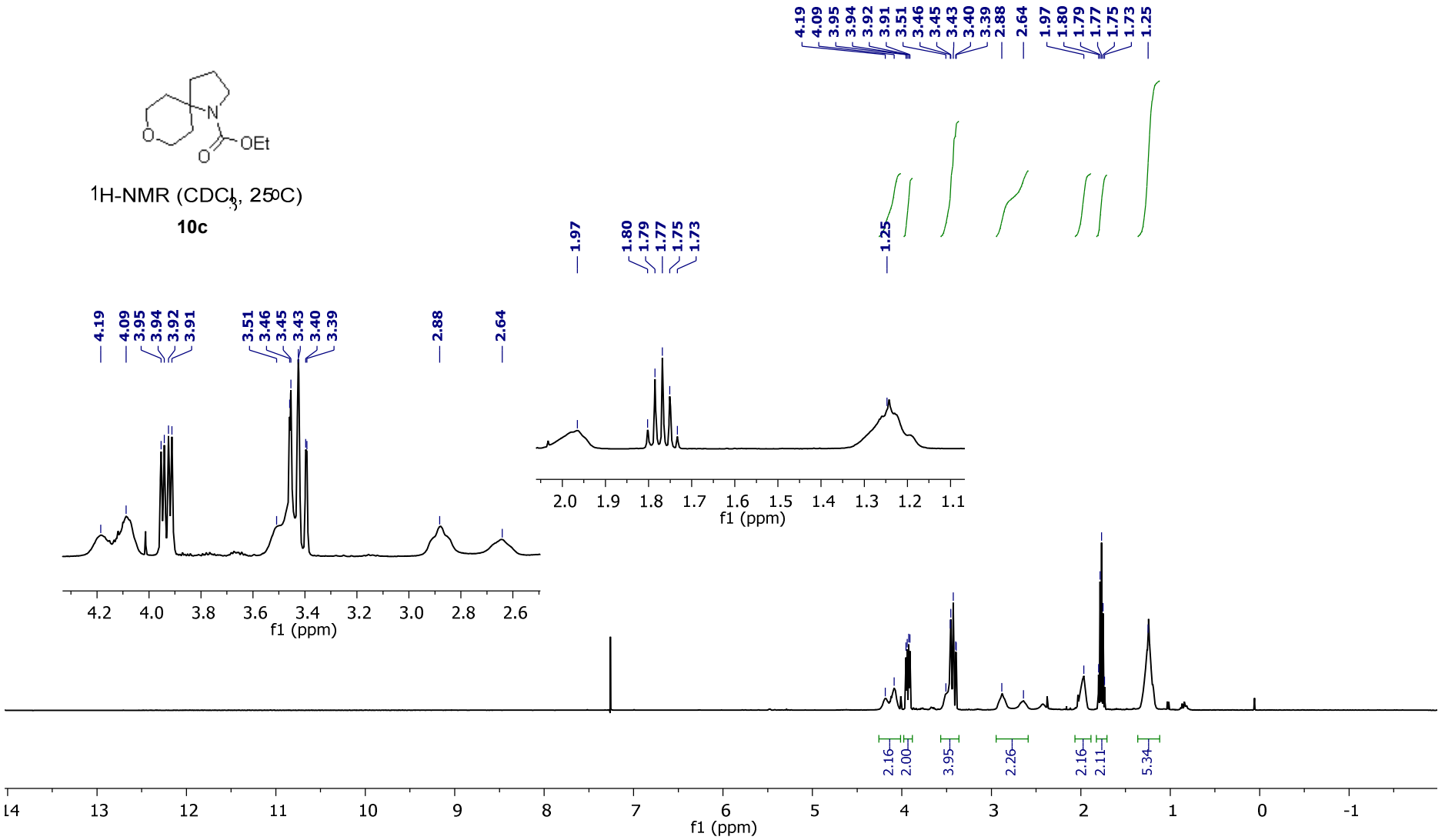

164.10
62.84
48.39
43.78
41.47
29.66
25.49
22.81
Me
Me
N
O
Cl
5e
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.34 7.32 7.30 7.29 7.27 7.23 7.21 7.19 7.17 4.15 4.14 4.13 4.12 4.11 4.10 4.09 4.09 4.08 4.07 4.06 4.04 3.96 3.94 3.92 3.90 3.79 3.78 3.76 3.75 3.73 3.71 3.70 3.69 3.67 3.65 3.63 3.62 3.61 2.11 2.09 2.07 2.06 2.04 2.03 1.87 1.85 1.83 1.81 1.78 1.76 1.74 1.72 1.71 1.69 1.67 1.28 1.26 1.25 0.89 0.87 0.86
Ph
Me
N
OEt
O
10a
4.14 4.13 4.12 4.11 4.10 4.09 4.09 4.08 4.07 4.06 4.04 3.96 3.94 3.92 3.90 3.79 3.78 3.76 3.75 3.73 3.71 3.70 3.69 3.67 3.65 3.63 3.62 3.61
4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5
f1 (ppm)
2.11 2.09 2.07 2.06 2.04 1.87 1.85 1.83 1.81 1.78 1.76 1.74 1.72 1.71 1.69 1.67 1.28 1.26 1.25 0.89 0.87 0.86
2.0 1.5 1.0
f1 (ppm)
4.39 2.01 2.00 2.00 5.10 1.63 1.82
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


155.27
154.10
147.69
146.66
128.14
127.95
126.17
126.02
124.84
65.86
65.28
60.47
60.43
49.02
48.34
45.73
44.60
25.98
25.59
22.01
21.84
14.81
14.21
Ph
Me
N
O
OEt
10a
f1 (ppm)
f1 (ppm)
f1 (ppm)


4.19 4.17 4.15 4.13 4.09 4.07 4.05 4.04 3.51 3.48 3.46 3.43 3.41 3.40 2.50 2.47 2.43 2.26 2.22 2.18 1.87 1.86 1.84 1.82 1.75 1.73 1.71 1.69 1.68 1.67 1.59 1.35 1.32 1.30 1.30 1.26 1.25 1.23 1.22
N
O
OEt
10b
f1 (ppm)
2.00 2.00 2.31 2.05 5.31 7.59
f1 (ppm)


153.95
64.35
63.93
60.52
59.95
48.37
47.55
36.87
35.93
34.49
33.48
25.36
25.16
24.33
22.34
21.85
14.76
N
O
OEt
10b
f1 (ppm)
f1 (ppm)


1H-NMR (CDCl3, 25oC)
10c
OEt
4.19
4.09
3.95
3.94
3.92
3.91
3.51
3.46
3.45
3.43
3.40
3.39
2.88
2.64
1.97
1.80
1.79
1.77
1.75
1.73
1.25
2.16
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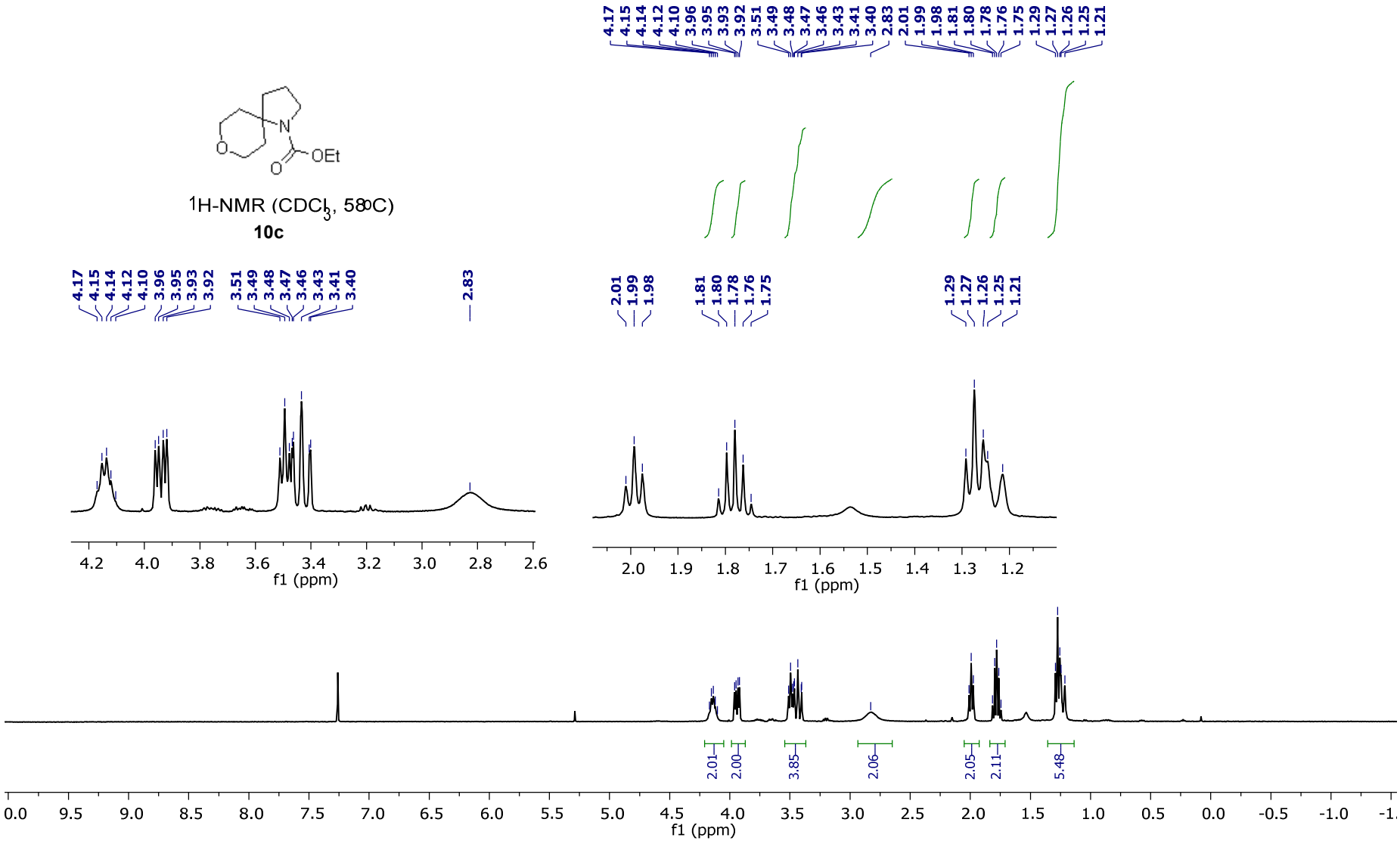
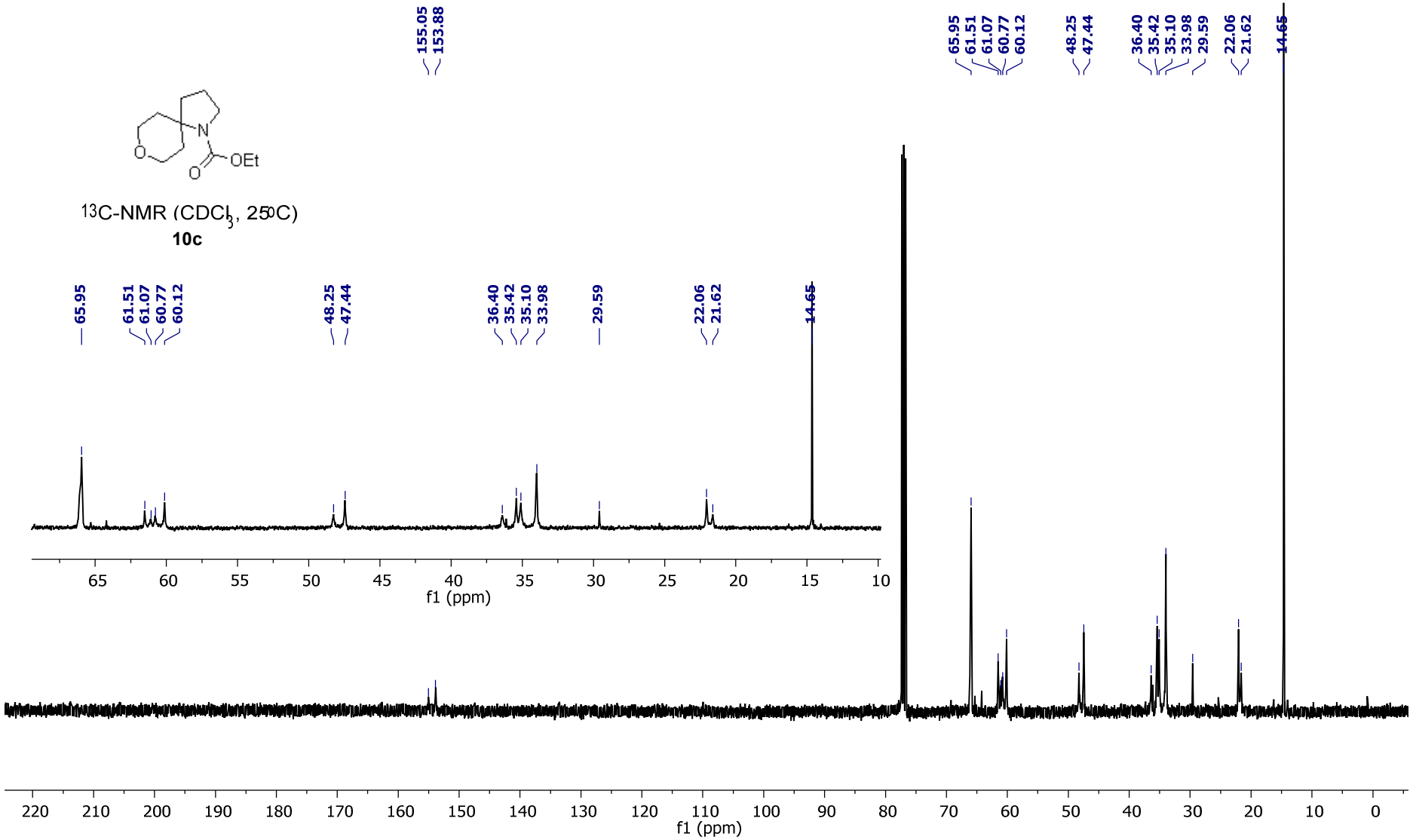
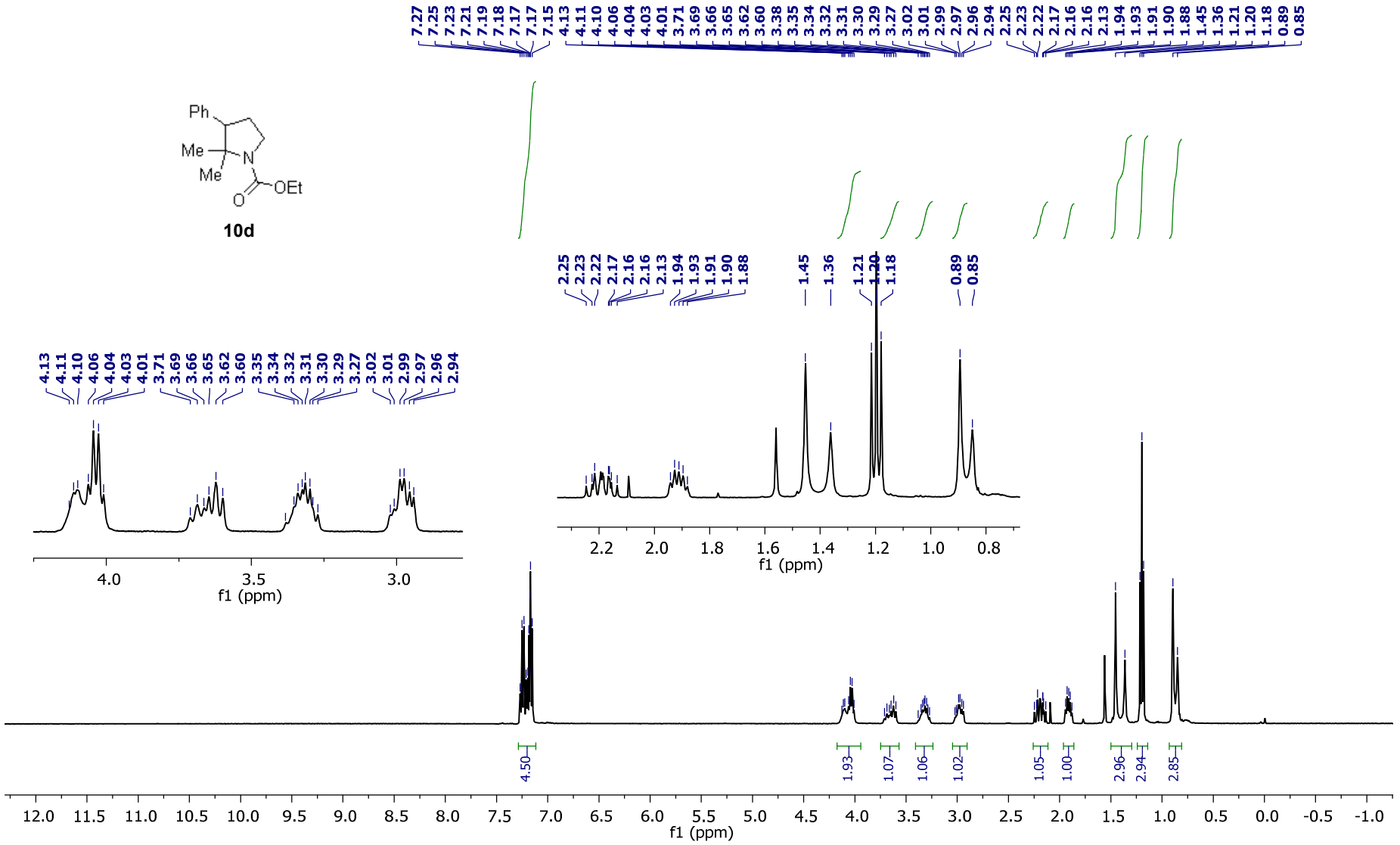
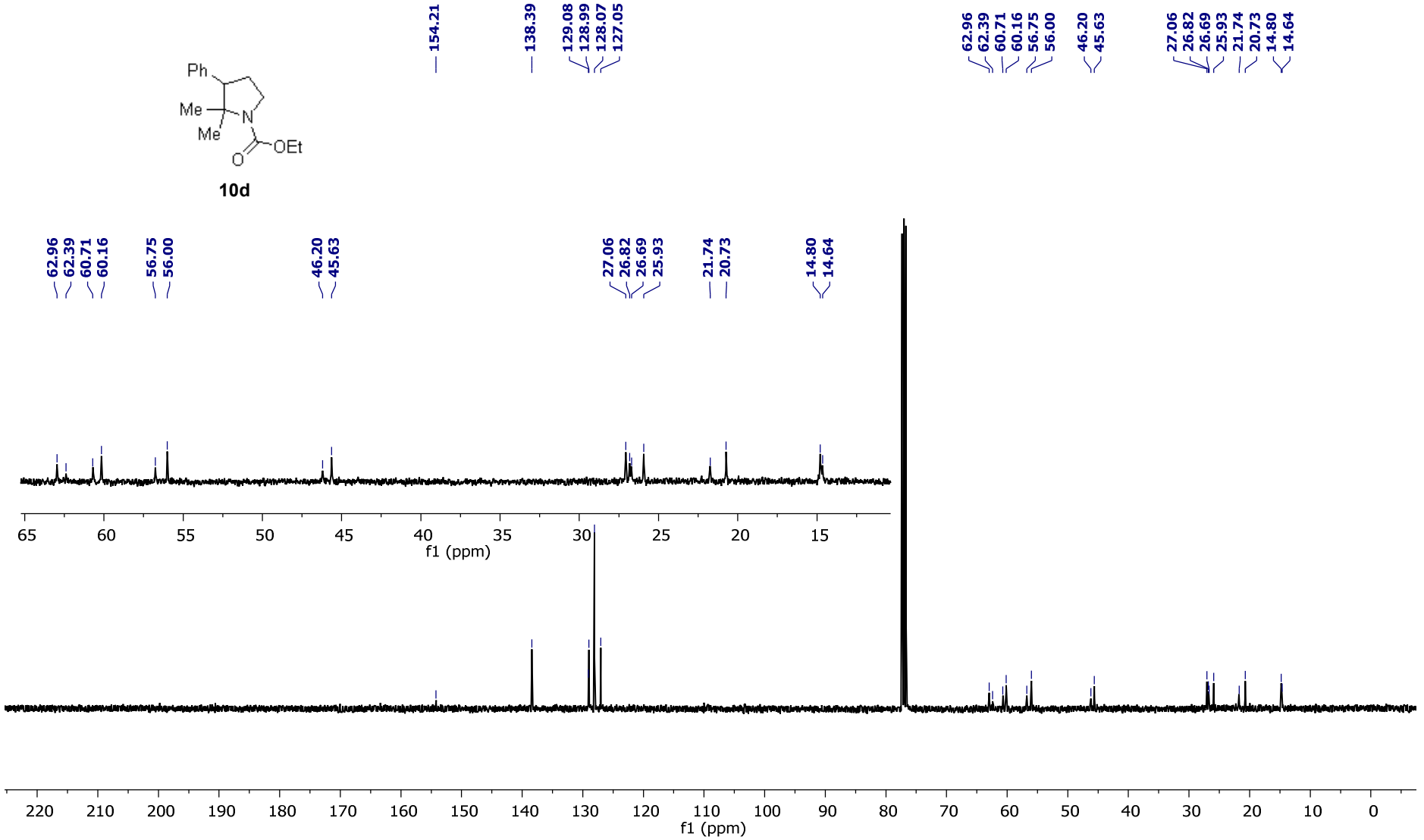
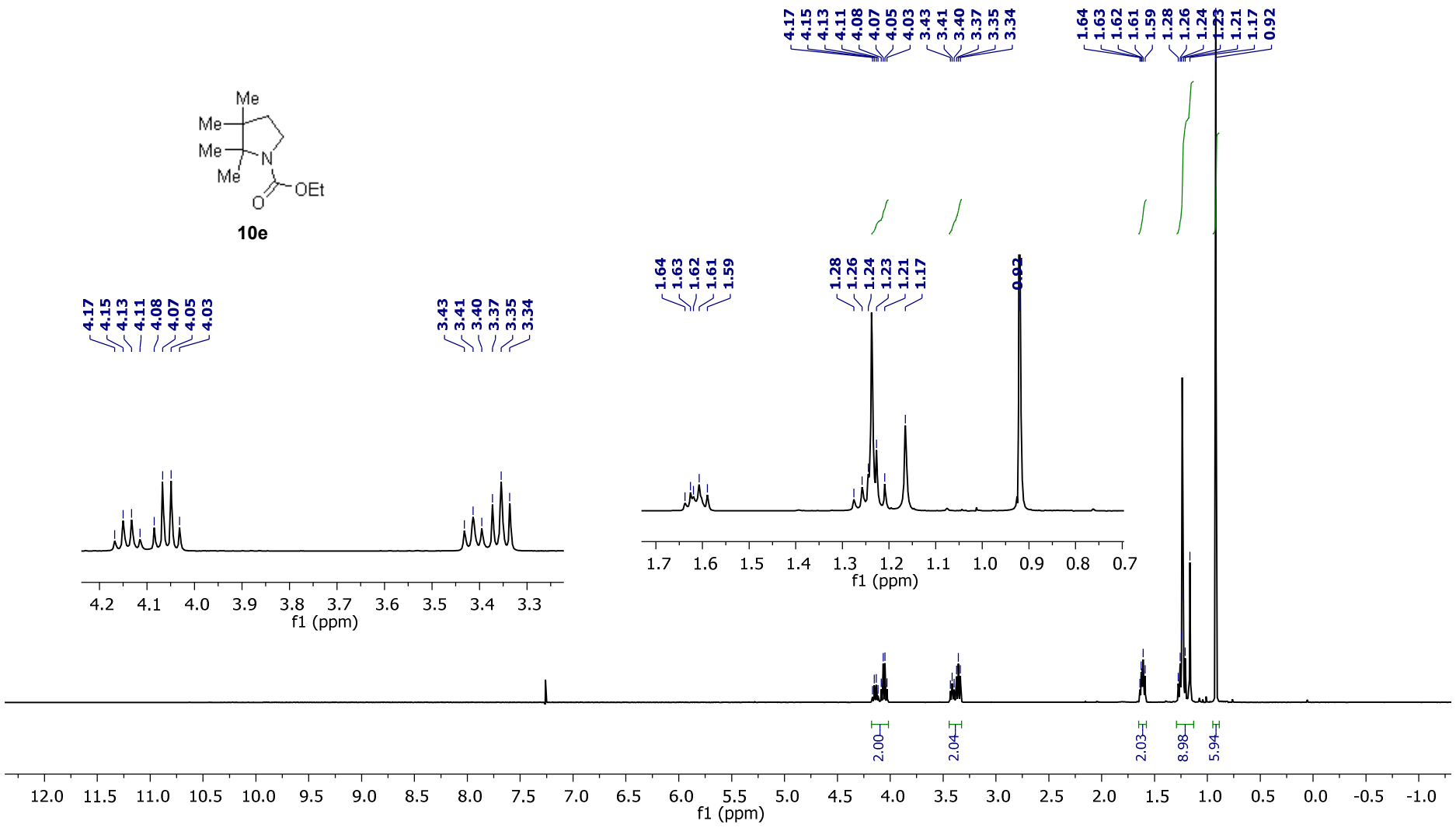
3.95
2.26
2.16
2.11
5.34
f1 (ppm)

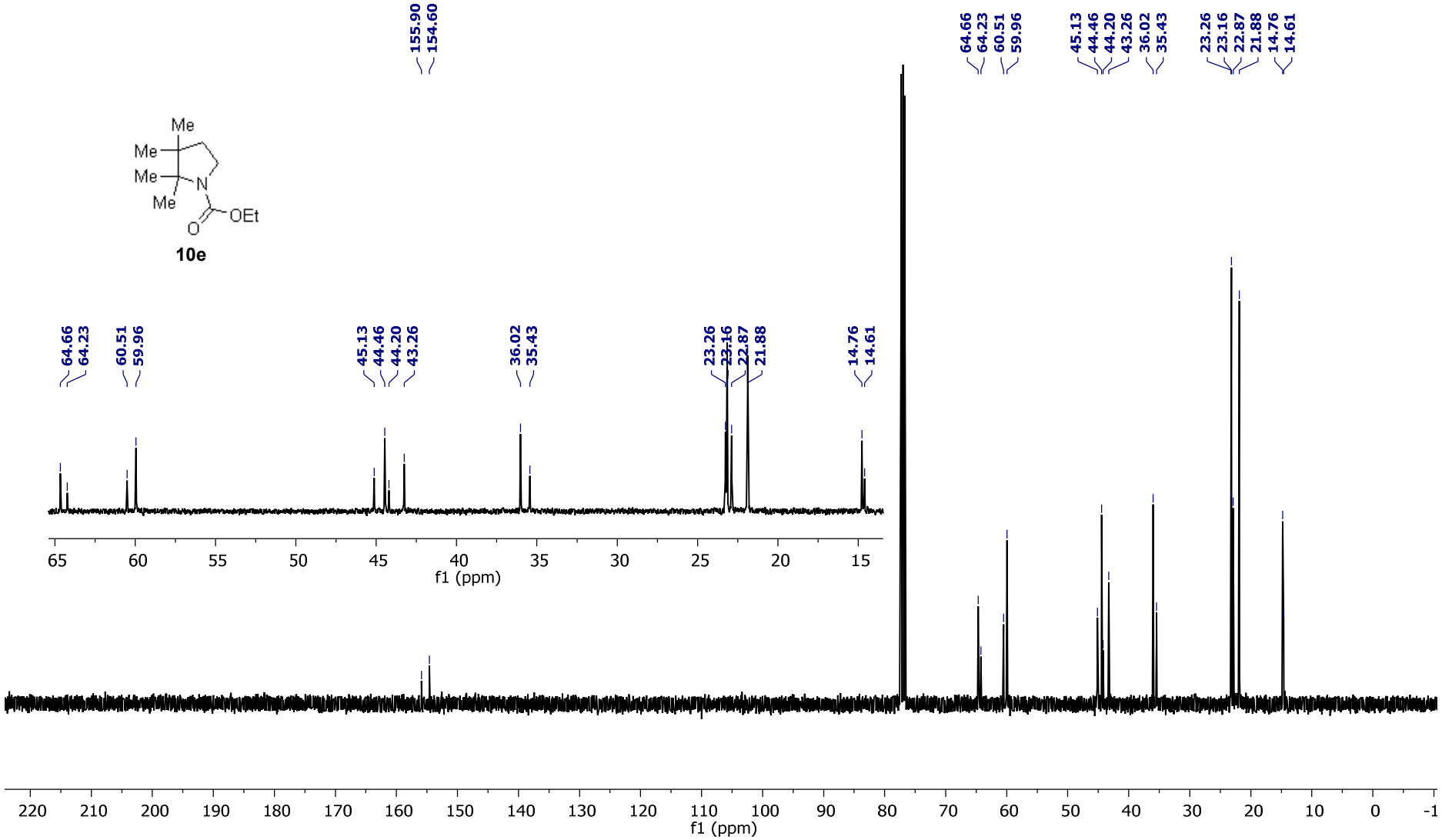

4.17 4.15 4.14 4.12 4.10 3.96 3.95 3.93 3.92 3.51 3.49 3.48 3.47 3.46 3.43 3.41 3.40 2.83 2.01 1.99 1.98 1.81 1.80 1.78 1.76 1.75 1.29 1.27 1.26 1.25 1.21
O
N
O
OEt
1H-NMR (CDCl3, 58ºC)
10c
f1 (ppm)
2.01 2.00 3.85 2.06 2.05 2.11 5.48

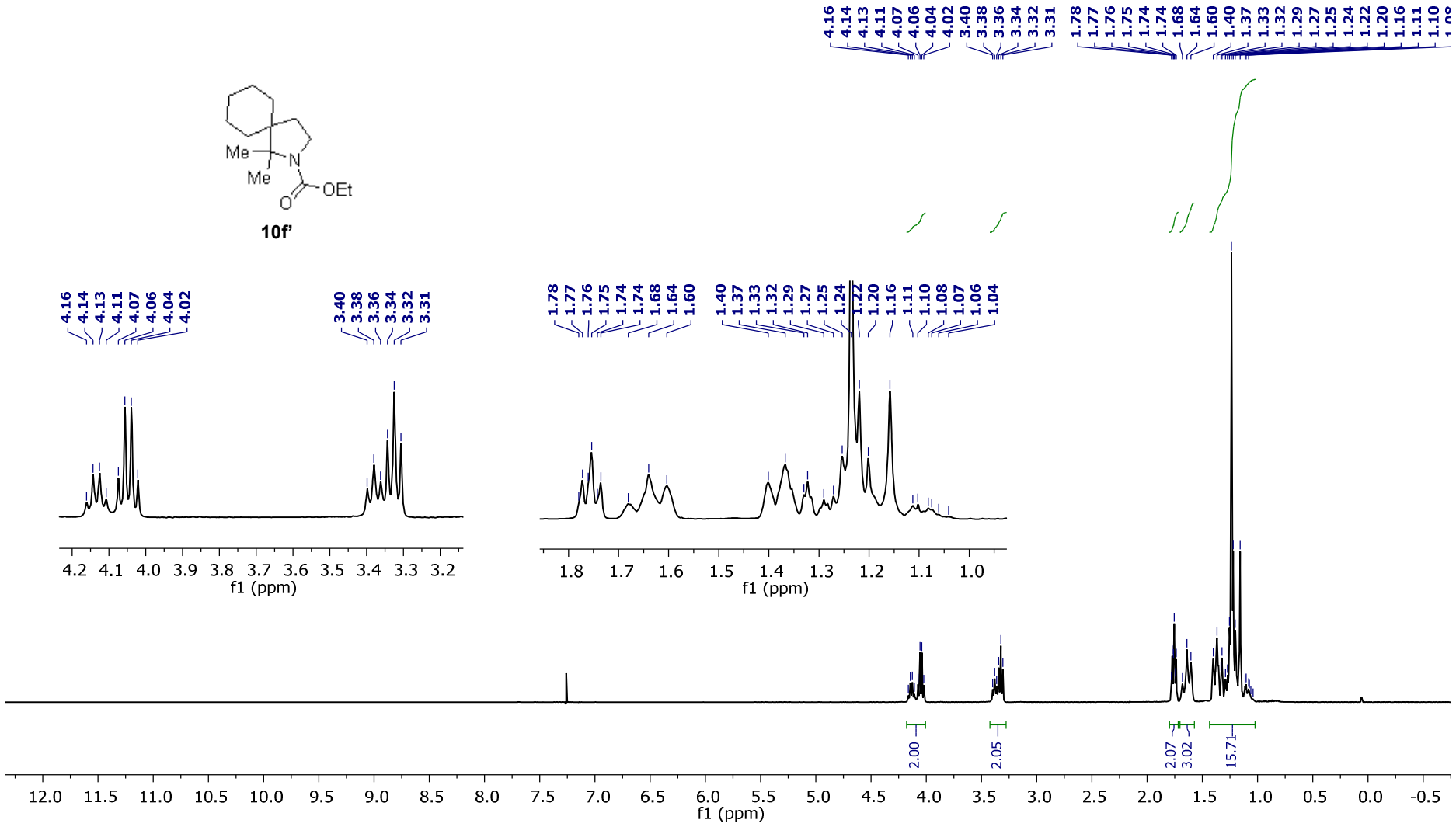

155.05
153.88
65.95
61.51
61.07
60.77
60.12
48.25
47.44
36.40
35.42
35.10
33.98
29.59
22.06
21.62
14.65
O
N
O
OEt
13C-NMR (CDCl3, 25oC)
10c
f1 (ppm)
f1 (ppm)

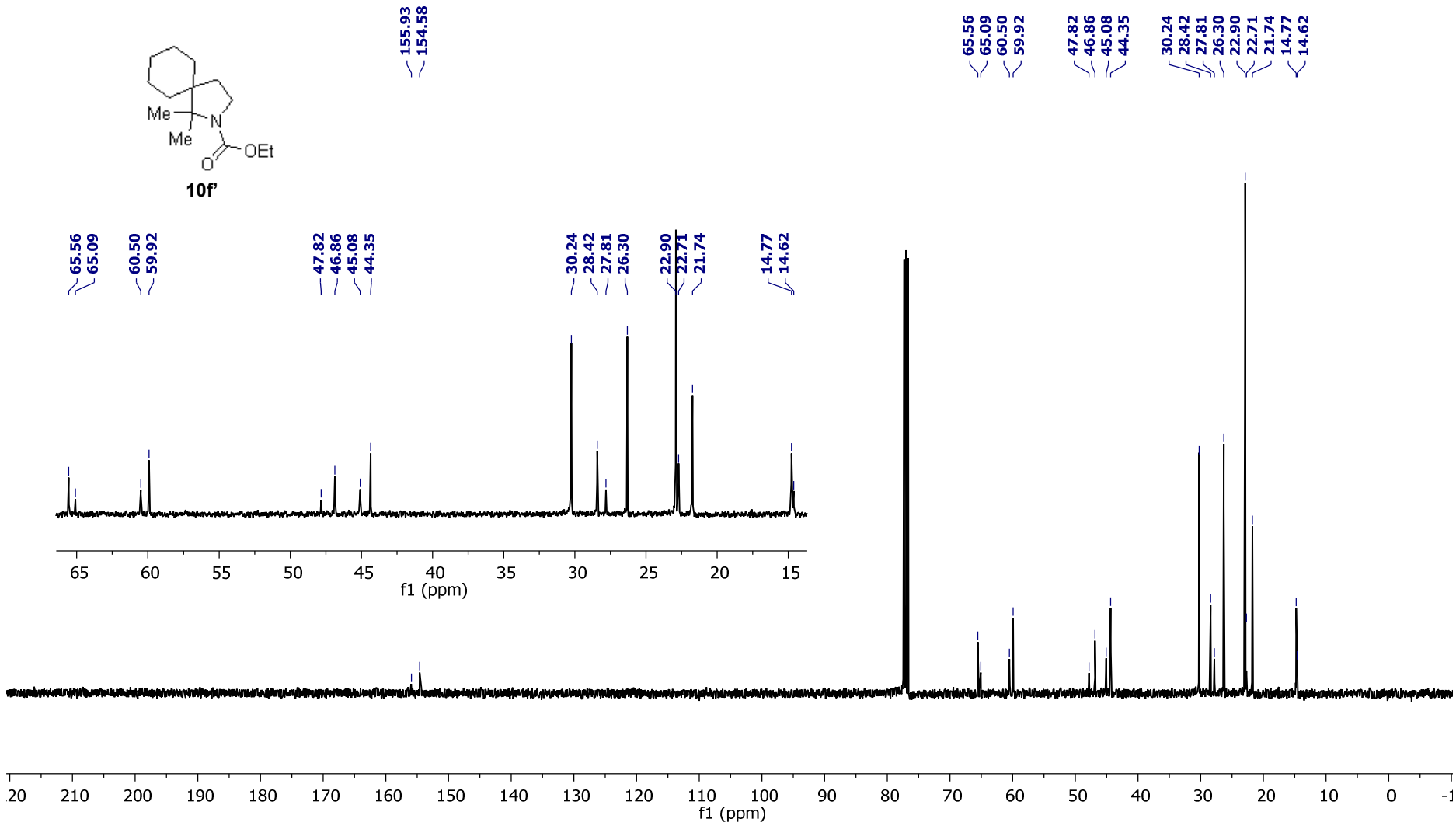

Ph
Me
Me
N
O
OEt
10d
7.27 7.25 7.23 7.21 7.19 7.18 7.17 7.17 7.15 4.13 4.11 4.10 4.06 4.04 4.03 4.01 3.71 3.69 3.66 3.65 3.62 3.60 3.38 3.35 3.34 3.32 3.31 3.30 3.29 3.27 3.02 3.01 2.99 2.97 2.96 2.94 2.25 2.23 2.22 2.17 2.16 2.16 2.13 1.94 1.93 1.91 1.90 1.88 1.45 1.36 1.21 1.20 1.18 0.89 0.85
f1 (ppm)
4.50 1.93 1.07 1.06 1.02 1.05 1.00 2.96 2.94 2.85

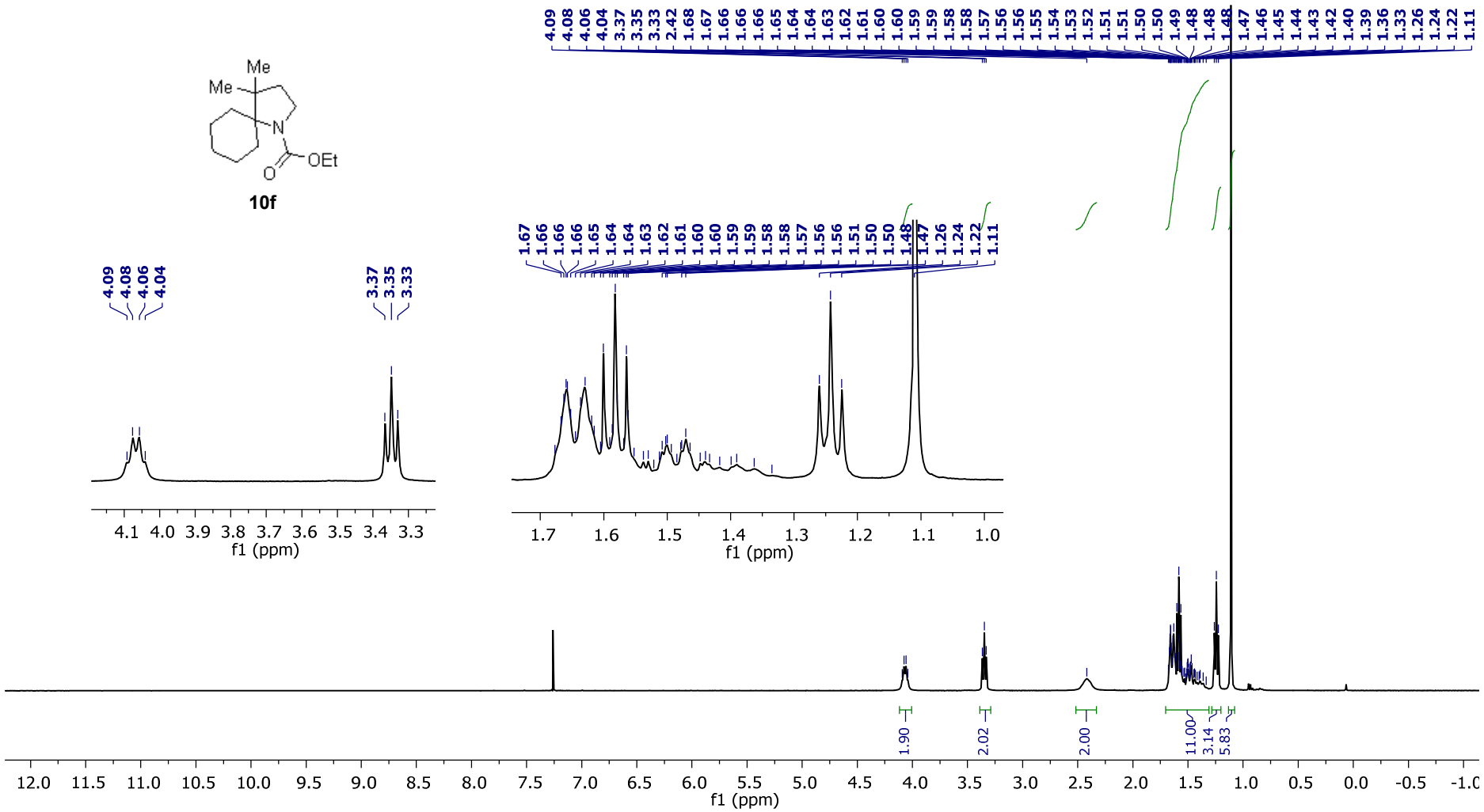

154.21
138.39
129.08
128.99
128.07
127.05
62.96
62.39
60.71
60.16
56.75
56.00
46.20
45.63
27.06
26.82
26.69
25.93
21.74
20.73
14.80
14.64
Ph
Me
Me
N
O
OEt
10d
f1 (ppm)
f1 (ppm)

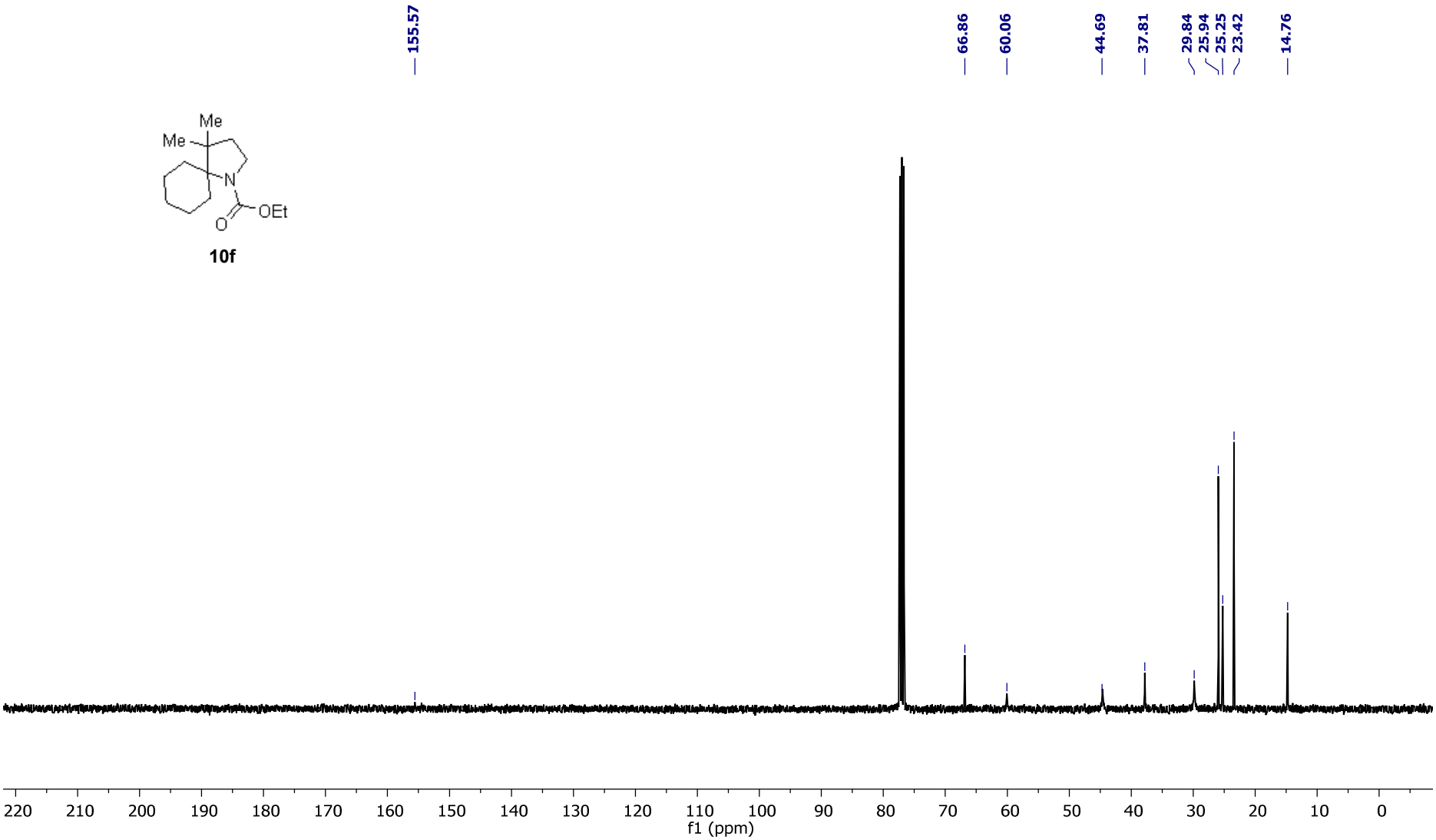

Me
Me
Me
Me
N
O
OEt
10e
4.17
4.15
4.13
4.11
4.08
4.07
4.05
4.03
3.43
3.41
3.40
3.37
3.35
3.34
1.64
1.63
1.62
1.61
1.59
1.28
1.26
1.24
1.23
1.21
1.17
0.92
f1 (ppm)
2.00
2.04
2.03
8.98
5.94

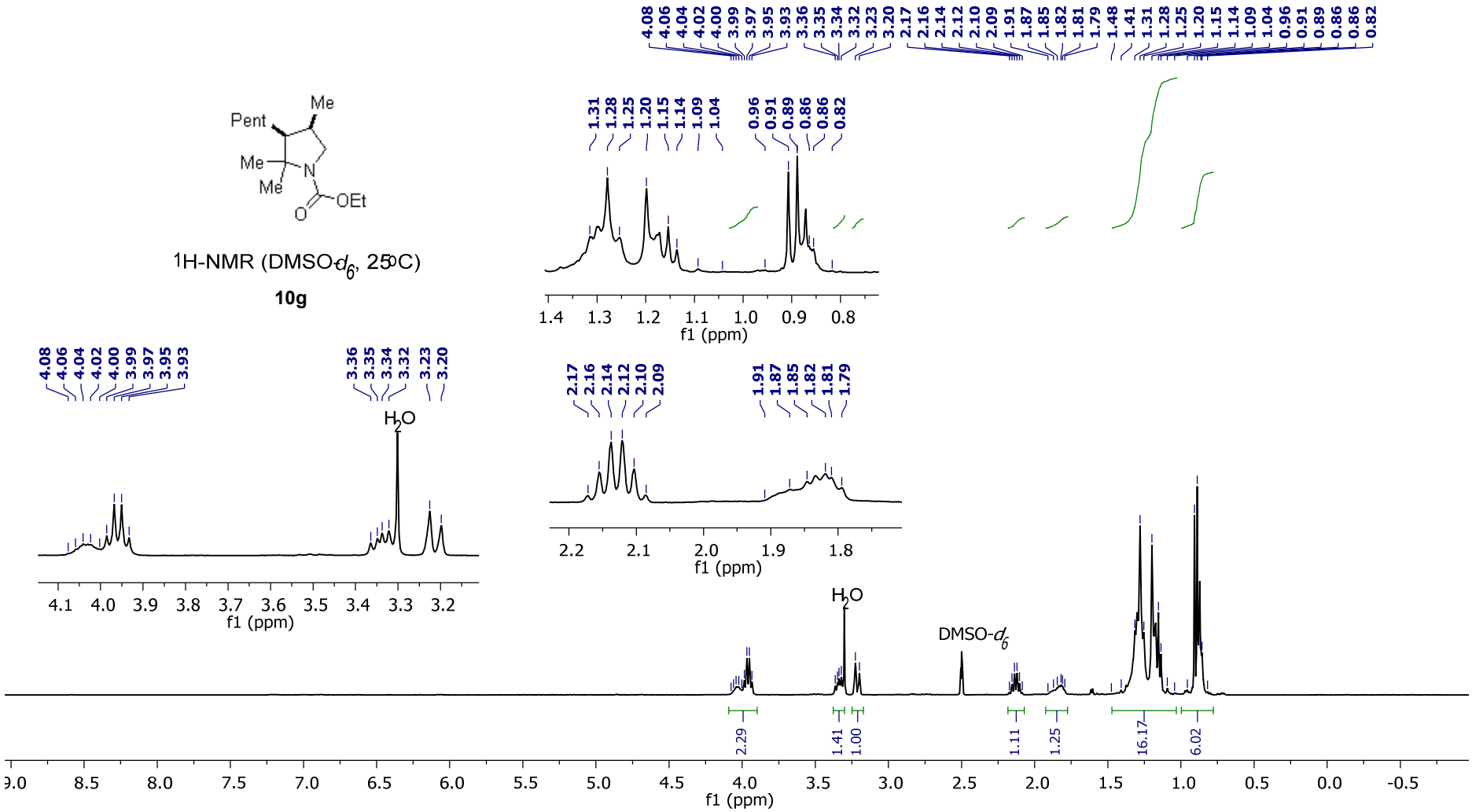

155.90
154.60
64.66
64.23
60.51
59.96
45.13
44.46
44.20
43.26
36.02
35.43
23.26
23.16
22.87
21.88
14.76
14.61
Me
Me
Me
Me
N
O
OEt
10e
f1 (ppm)
f1 (ppm)

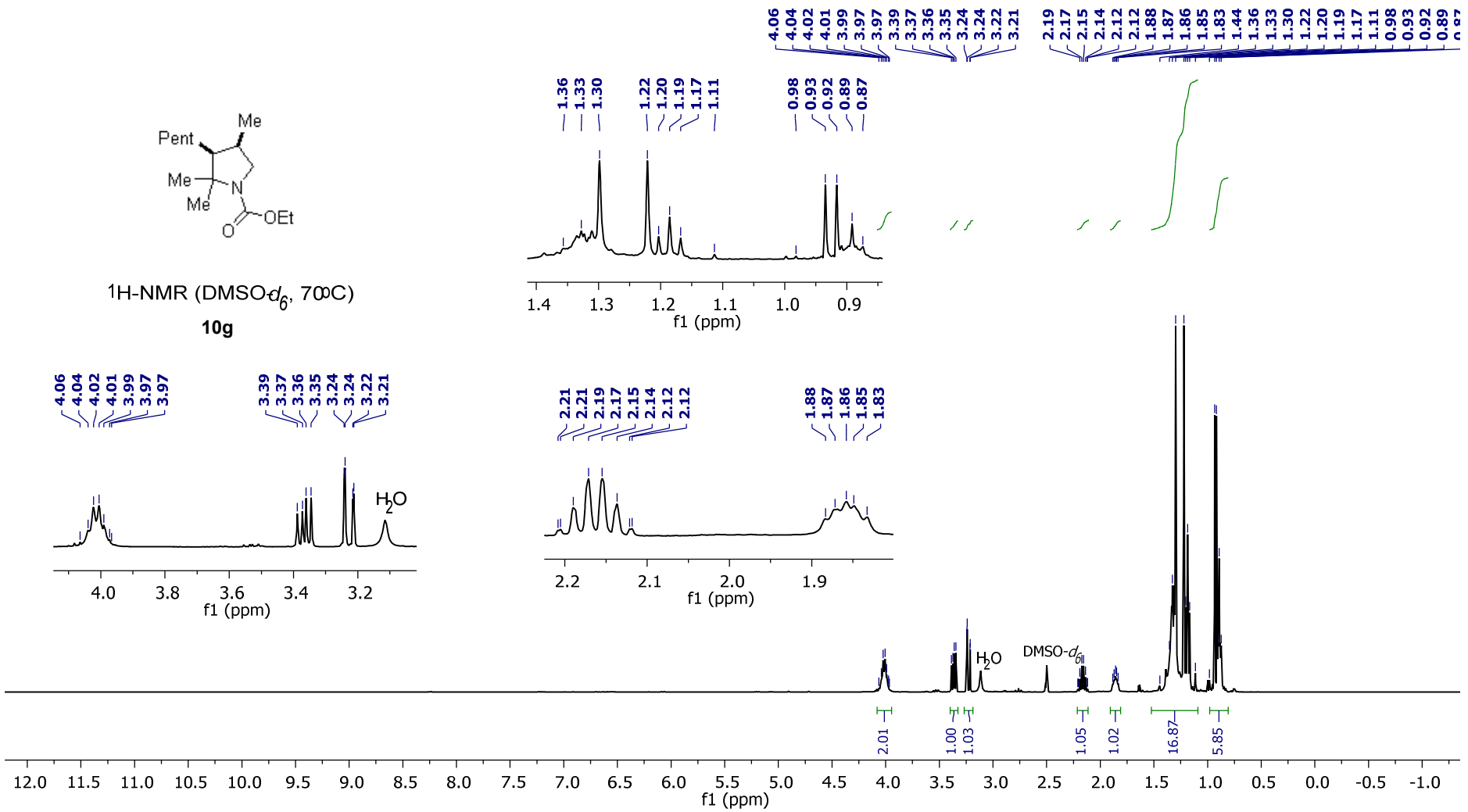

Me
Me
N
O
OEt
10f'
4.16 4.14 4.13 4.11 4.07 4.06 4.04 4.02
3.40 3.38 3.36 3.34 3.32 3.31
1.78 1.77 1.76 1.75 1.74 1.74 1.68 1.64 1.60
1.40 1.37 1.33 1.32 1.29 1.27 1.25 1.24 1.22 1.20 1.16 1.11 1.10 1.08 1.07 1.06 1.04
4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2
f1 (ppm)
1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0
f1 (ppm)
2.00
2.05
2.07
3.02
15.71
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

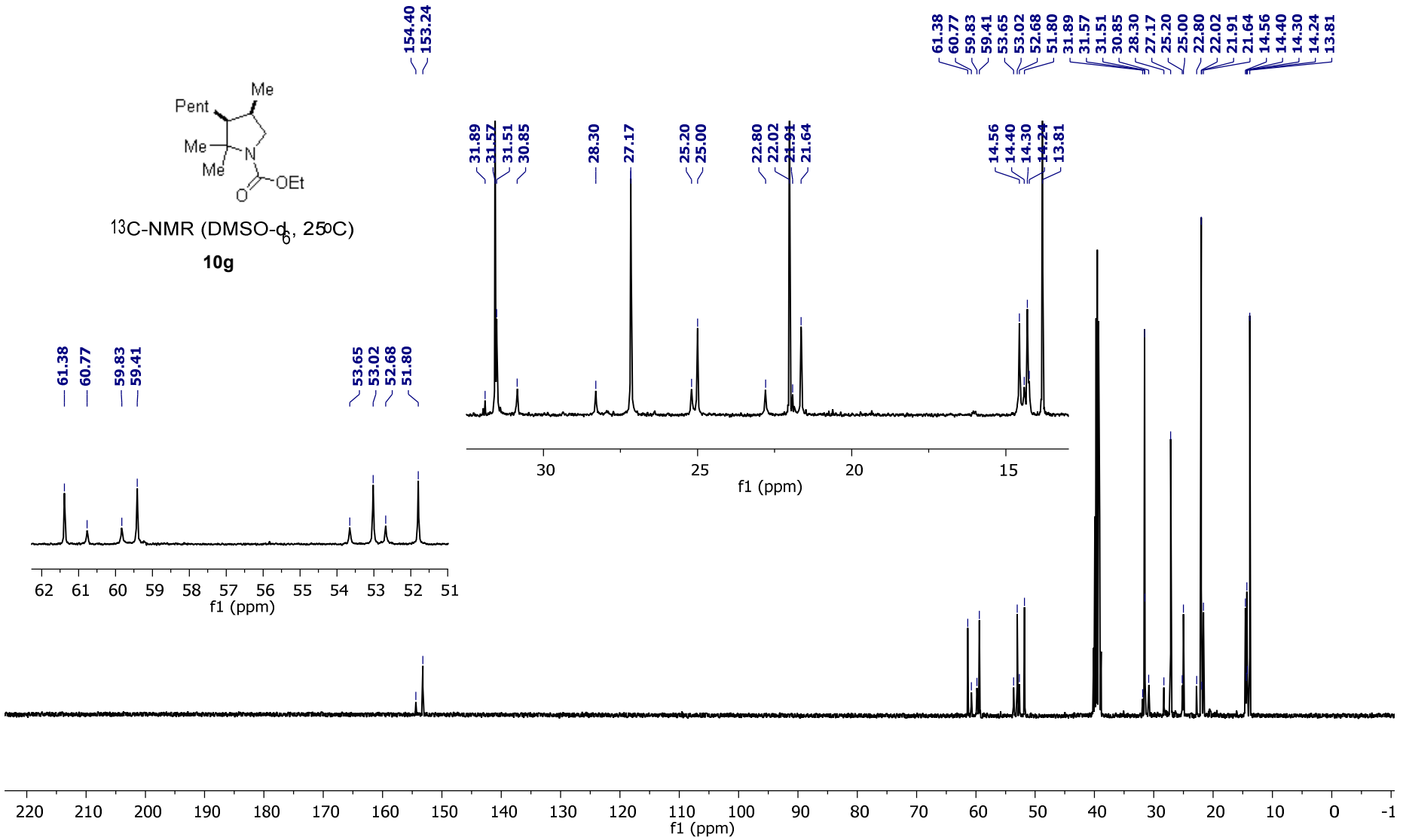

155.93
154.58
65.56
65.09
60.50
59.92
47.82
46.86
45.08
44.35
30.24
28.42
27.81
26.30
22.90
22.71
21.74
14.77
14.62
Me
Me
N
OEt
O
10f'
f1 (ppm)

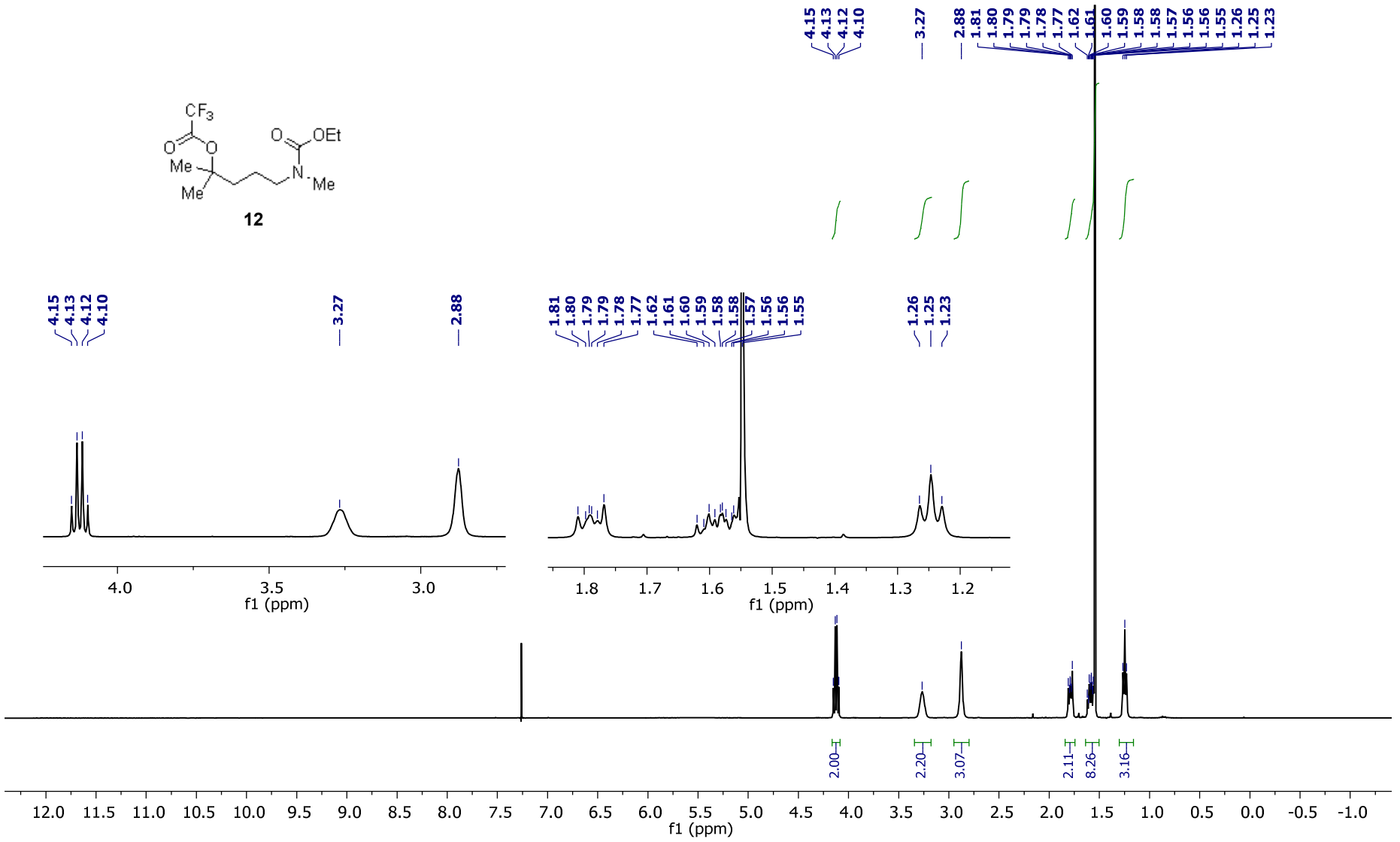

Me
Me
N
O
OEt
10f
4.09 4.08 4.06 4.04 3.37 3.35 3.33 2.42 1.68 1.67 1.66 1.66 1.66 1.65 1.64 1.64 1.63 1.62 1.61 1.60 1.60 1.59 1.59 1.58 1.58 1.57 1.56 1.56 1.55 1.54 1.53 1.52 1.51 1.51 1.50 1.50 1.49 1.48 1.48 1.47 1.46 1.45 1.44 1.43 1.42 1.40 1.39 1.36 1.33 1.26 1.24 1.22 1.11
4.09 4.08 4.06 4.04
3.37 3.35 3.33
4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3
f1 (ppm)
1.67 1.66 1.66 1.66 1.65 1.64 1.64 1.63 1.62 1.61 1.60 1.60 1.59 1.59 1.58 1.58 1.57 1.56 1.56 1.51 1.50 1.50 1.48 1.47 1.26 1.24 1.22 1.11
1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0
f1 (ppm)
1.90
2.02
2.00
11.00
3.14
5.83
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

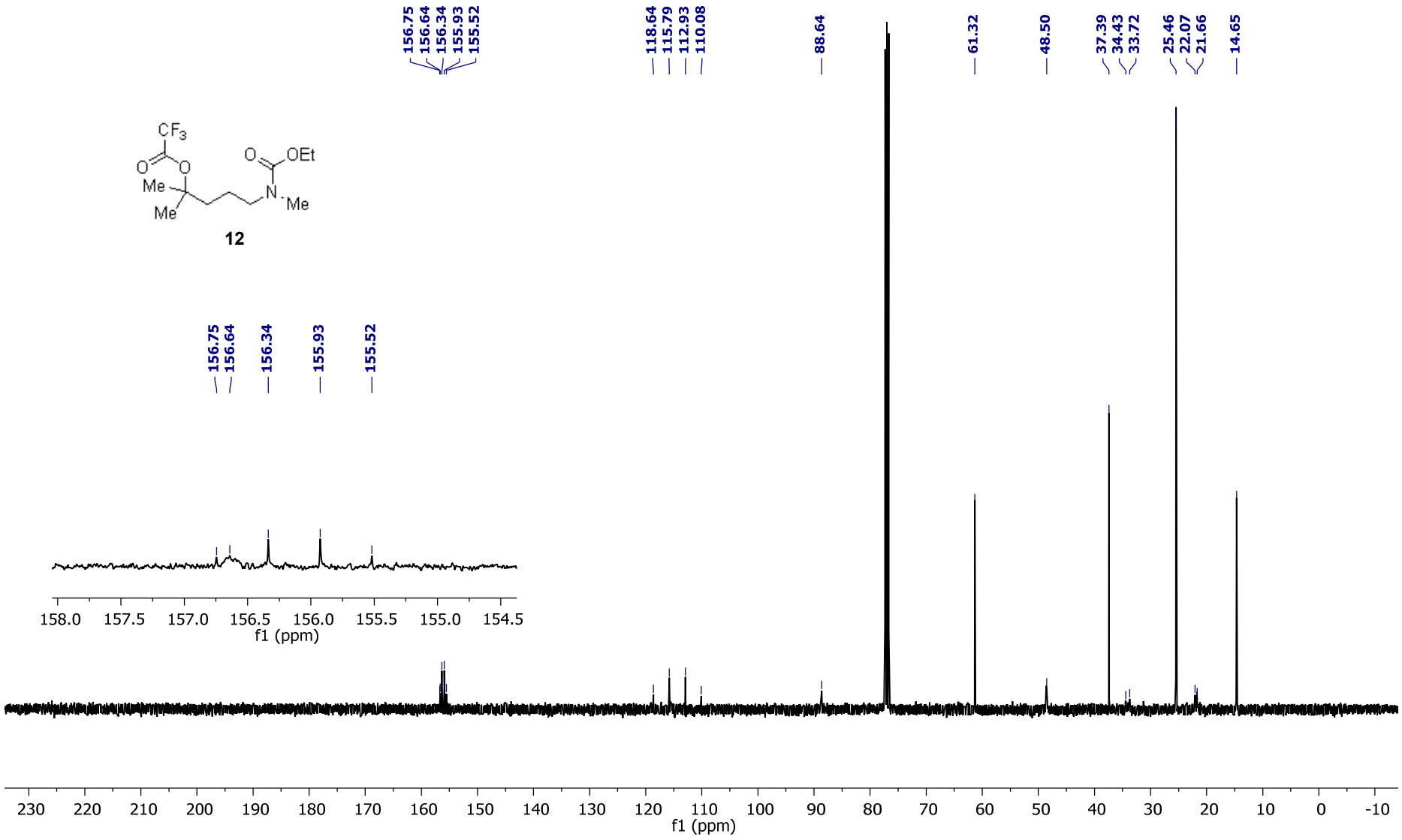

155.57
66.86
60.06
44.69
37.81
29.84
25.94
25.25
23.42
14.76
Me
Me
N
O
OEt
10f
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

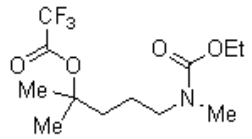

Me
Pent
Me
Me
N
O
OEt
1H-NMR (DMSO-d6, 25°C)
10g
H2O
DMSO-d6
f1 (ppm)


Pent
Me
Me
Me
N
O
OEt
1H-NMR (DMSO-d6, 70ºC)
10g
H2O
DMSO-d6
f1 (ppm)


154.40
153.24
61.38
60.77
59.83
59.41
53.65
53.02
52.68
51.80
31.89
31.57
31.51
30.85
28.30
27.17
25.20
25.00
22.80
22.02
21.91
21.64
14.56
14.40
14.30
14.24
13.81
Me
Pent
Me
Me
N
O
OEt
13C-NMR (DMSO-d6, 25oC)
10g
f1 (ppm)
f1 (ppm)
f1 (ppm)

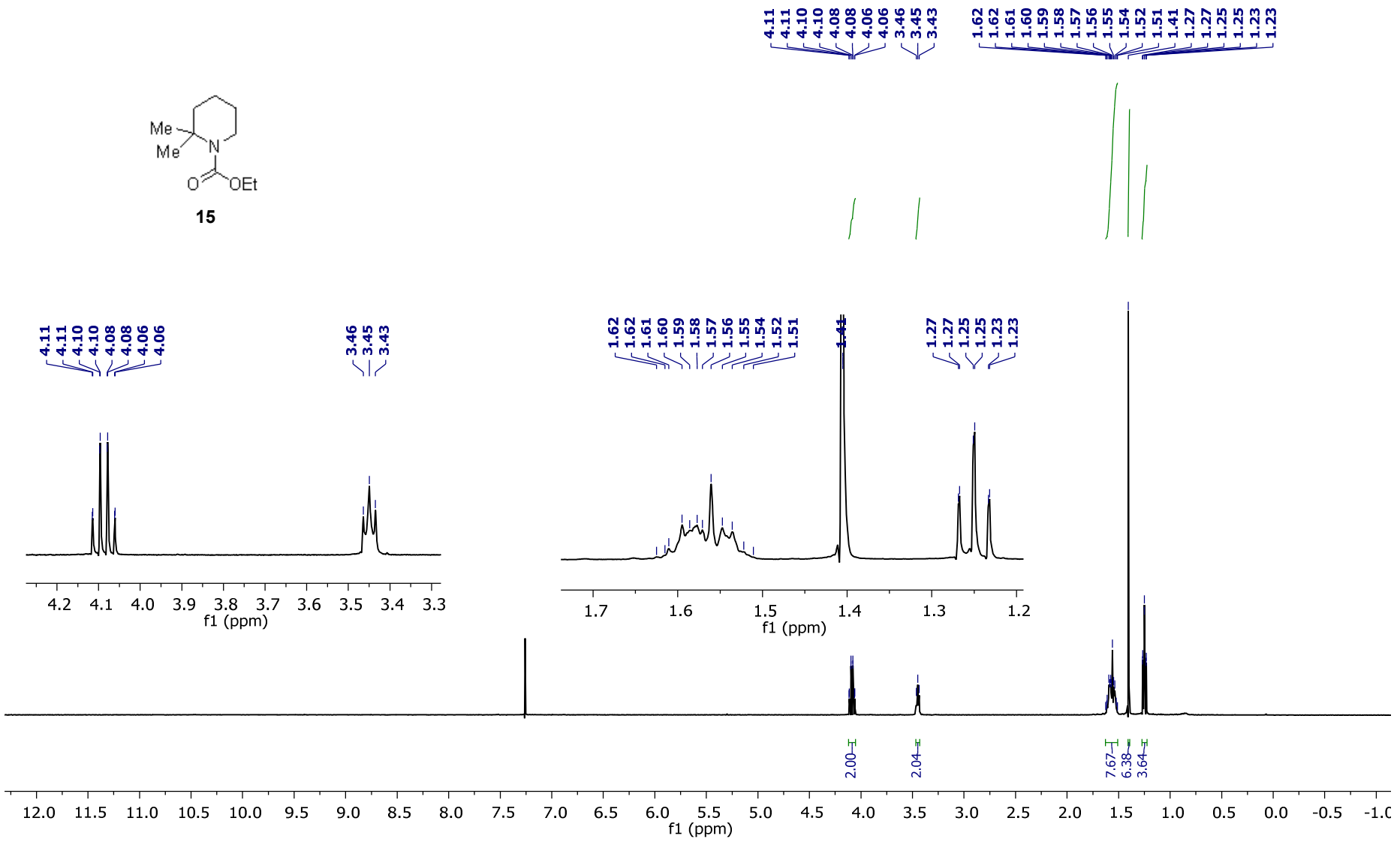

CF3
O
O
O
OEt
Me
Me
N
Me
12
4.15
4.13
4.12
4.10
3.27
2.88
1.81
1.80
1.79
1.79
1.78
1.77
1.62
1.61
1.60
1.59
1.58
1.58
1.57
1.56
1.56
1.55
1.26
1.25
1.23
4.0
3.5
3.0
f1 (ppm)
1.8
1.7
1.6
1.5
1.4
1.3
1.2
f1 (ppm)
2.00
2.20
3.07
2.11
8.26
3.16
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

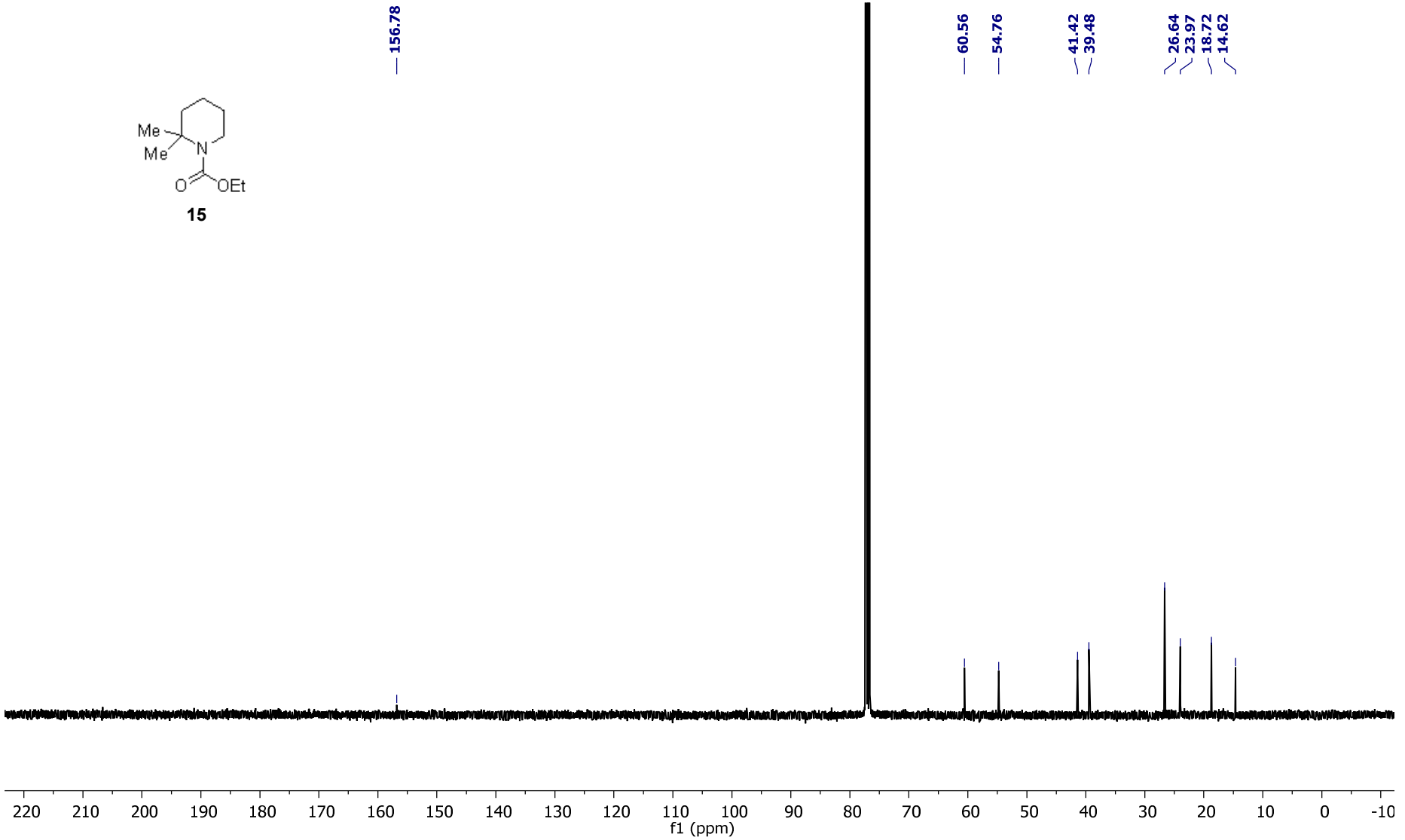

156.75
156.64
156.34
155.93
155.52
118.64
115.79
112.93
110.08
88.64
61.32
48.50
37.39
34.43
33.72
25.46
22.07
21.66
14.65
CF3
O
O
O
OEt
Me
Me
N
Me
12
158.0
157.5
157.0
156.5
156.0
155.5
155.0
154.5
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

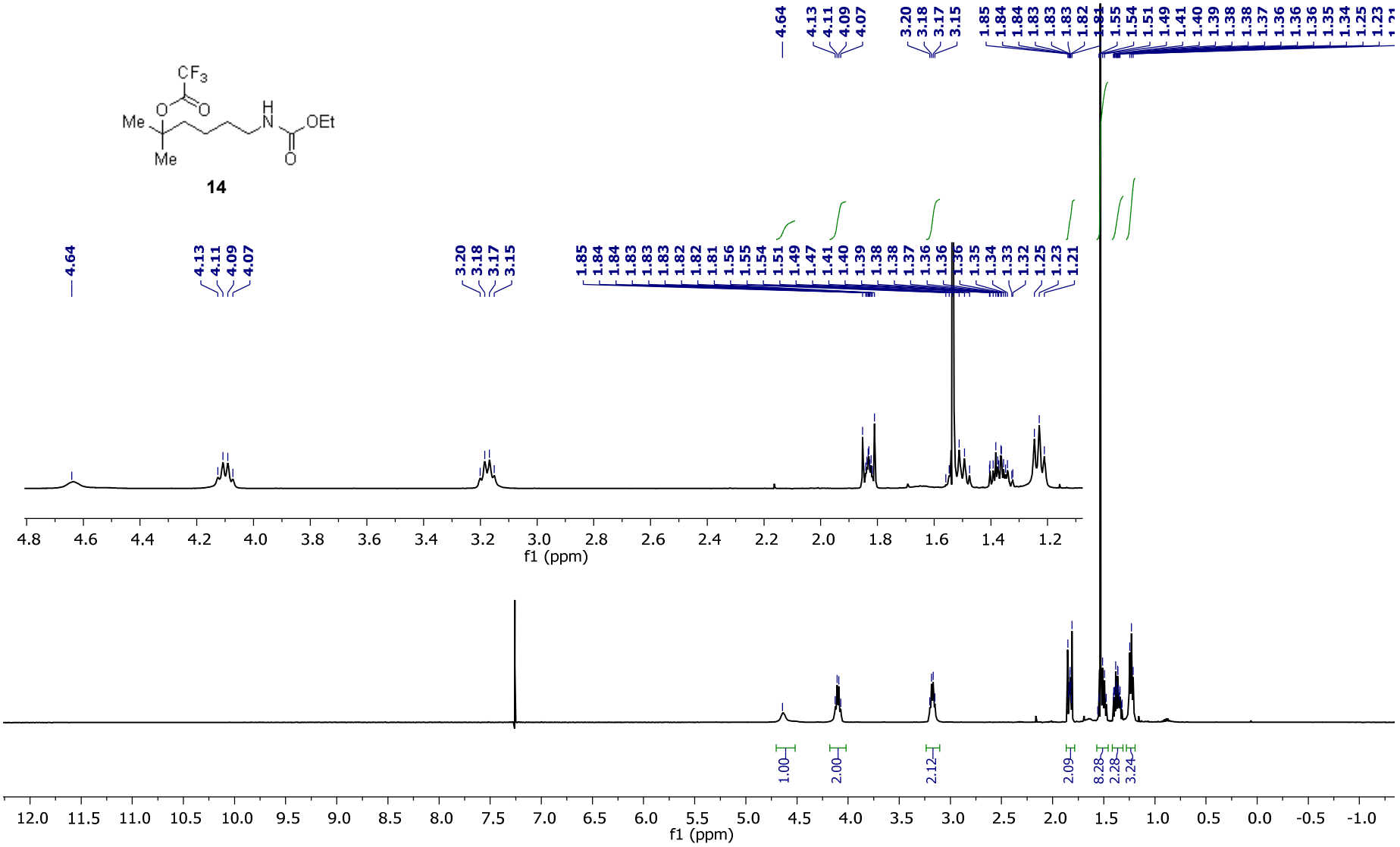

CF3
O
O
O
OEt
Me
Me
N
Me

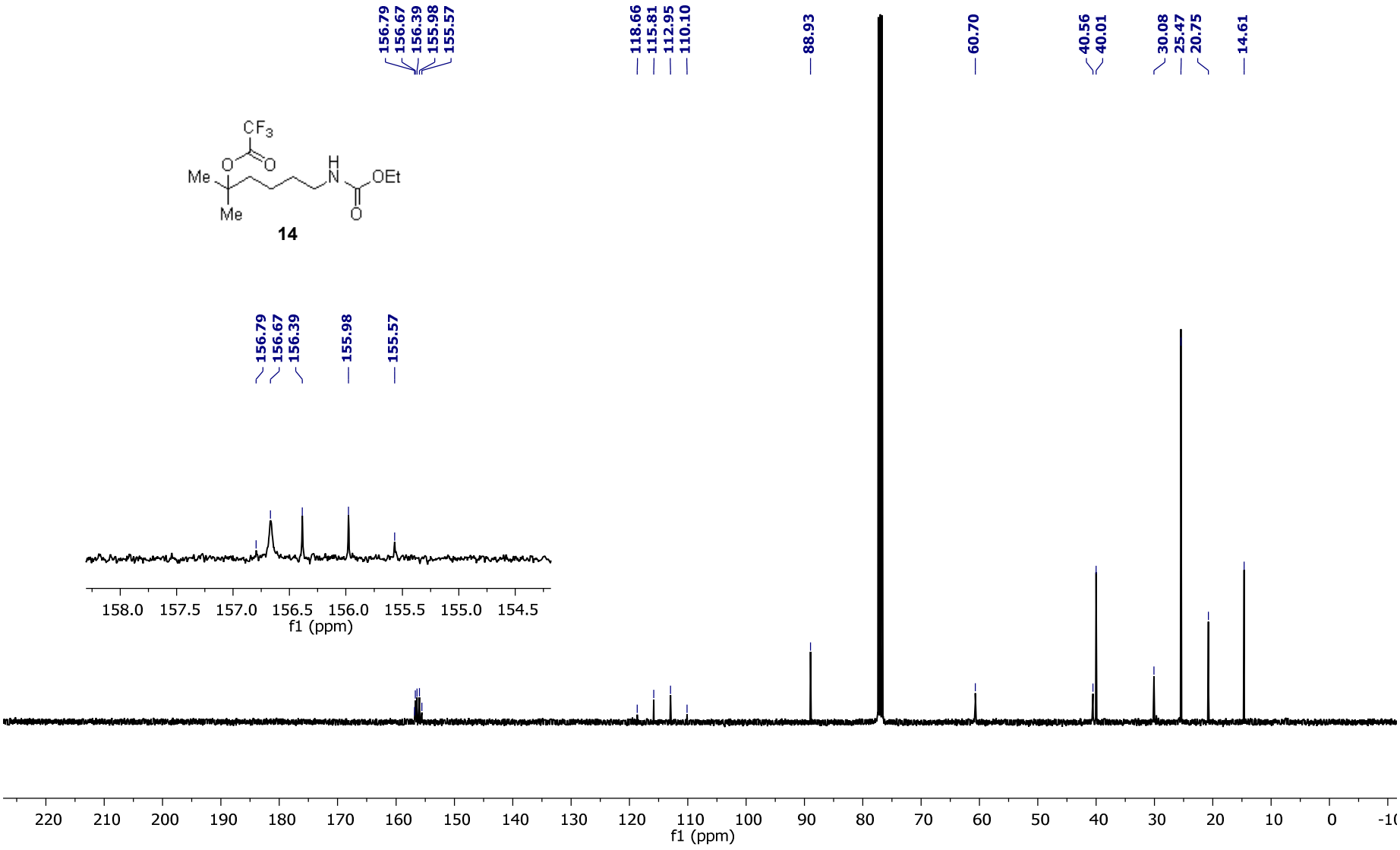
12

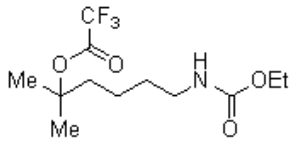
-75.84
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


Me
Me
N
O
OEt
15
4.11
4.11
4.10
4.10
4.08
4.06
4.06
3.46
3.45
3.43
1.62
1.62
1.61
1.60
1.59
1.58
1.57
1.56
1.55
1.54
1.52
1.51
1.41
1.27
1.27
1.25
1.25
1.23
1.23
f1 (ppm)
2.00
2.04
7.67
6.38
3.64


156.78
60.56
54.76
41.42
39.48
26.64
23.97
18.72
14.62
Me
Me
N
O
OEt
15
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

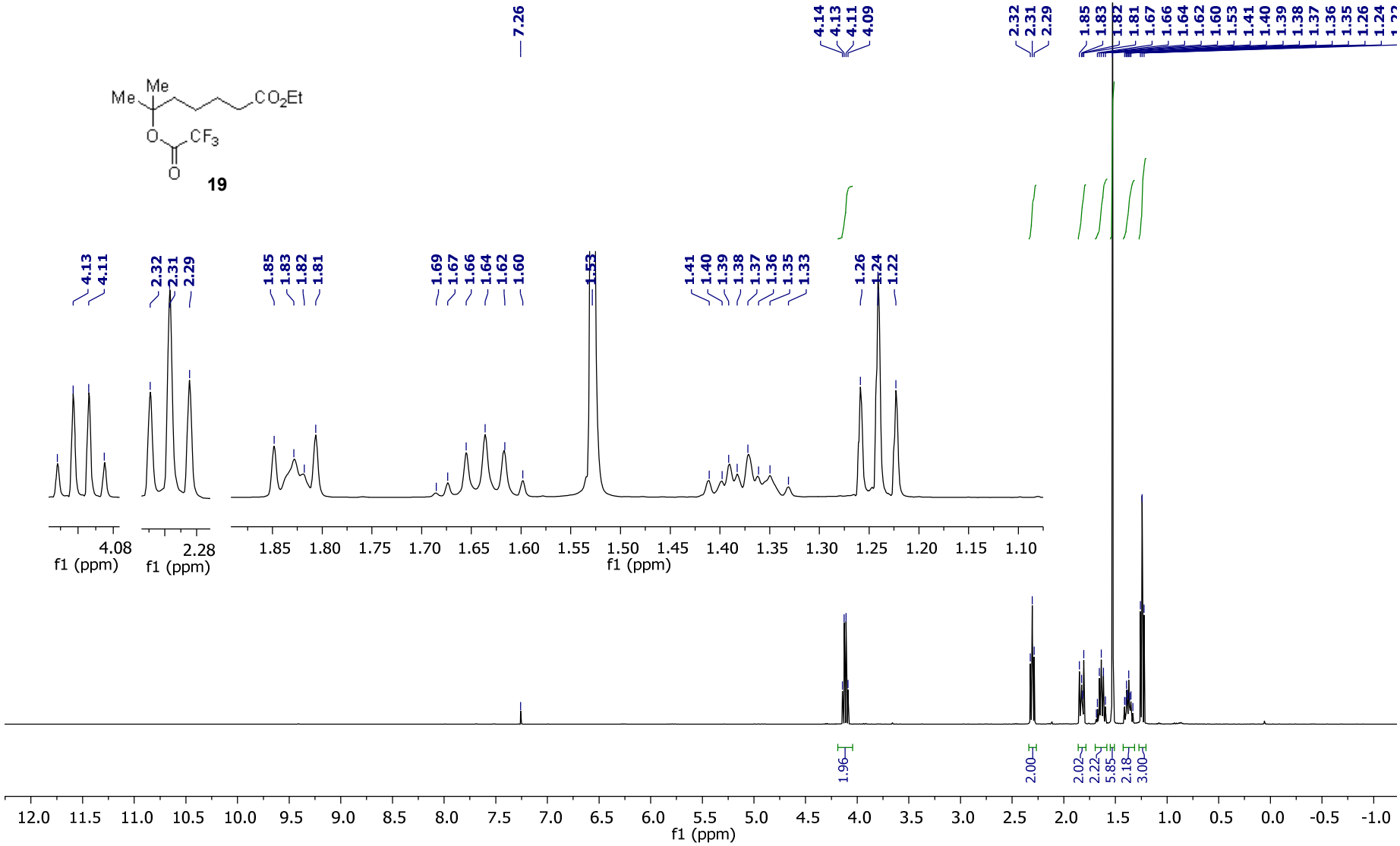

CF3
O
O
Me
Me
H
N
OEt
O
14
4.64
4.13
4.11
4.09
4.07
3.20
3.18
3.17
3.15
1.85
1.84
1.84
1.83
1.83
1.83
1.82
1.82
1.81
1.56
1.55
1.54
1.51
1.49
1.47
1.41
1.40
1.39
1.38
1.38
1.37
1.36
1.36
1.35
1.34
1.33
1.32
1.25
1.23
1.21
f1 (ppm)
1.00
2.00
2.12
2.09
8.28
2.28
3.24
f1 (ppm)

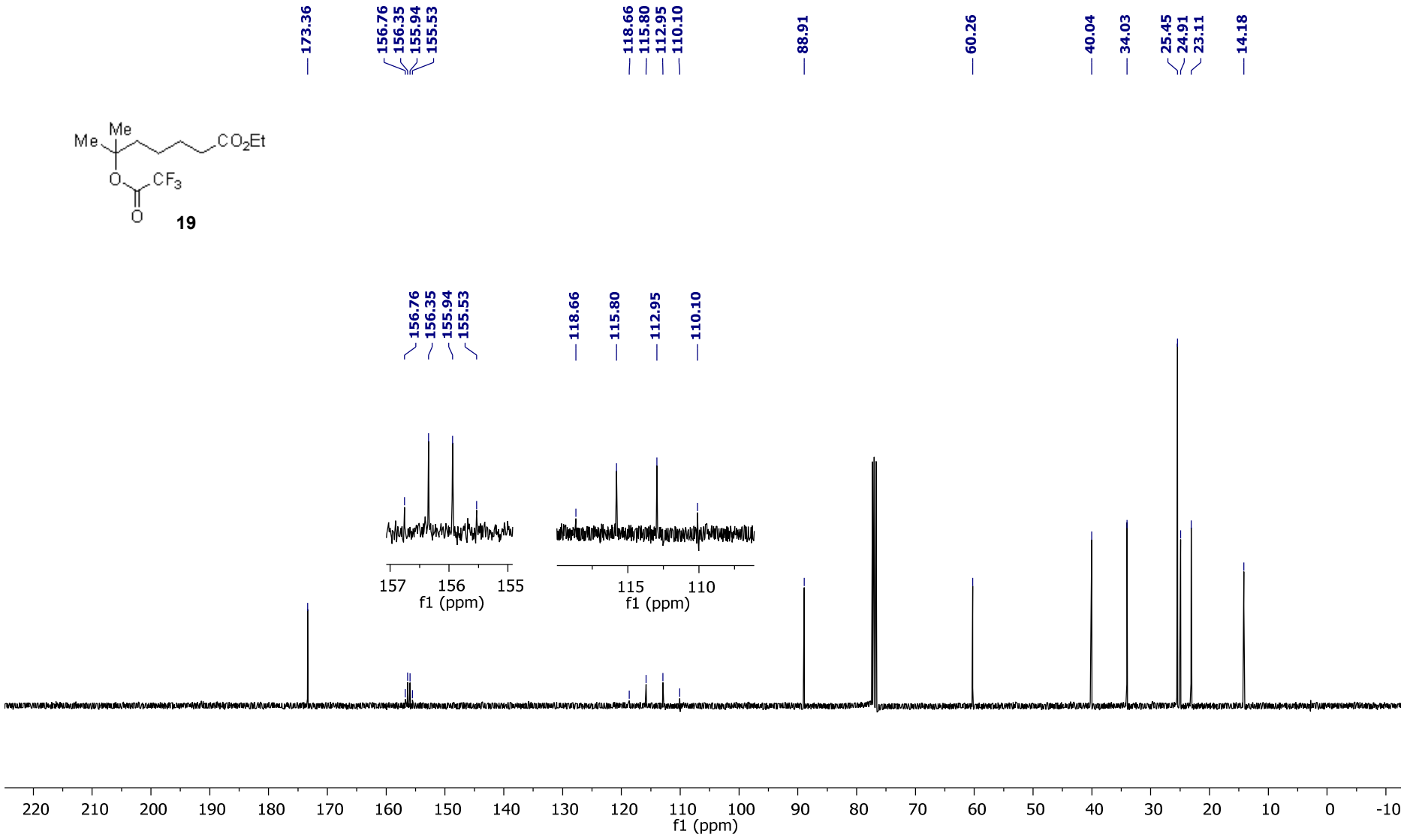

156.79
156.67
156.39
155.98
155.57
118.66
115.81
112.95
110.10
88.93
60.70
40.56
40.01
30.08
25.47
20.75
14.61
CF3
O
O
Me
H
N
OEt
O
Me
14
158.0 157.5 157.0 156.5 156.0 155.5 155.0 154.5
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

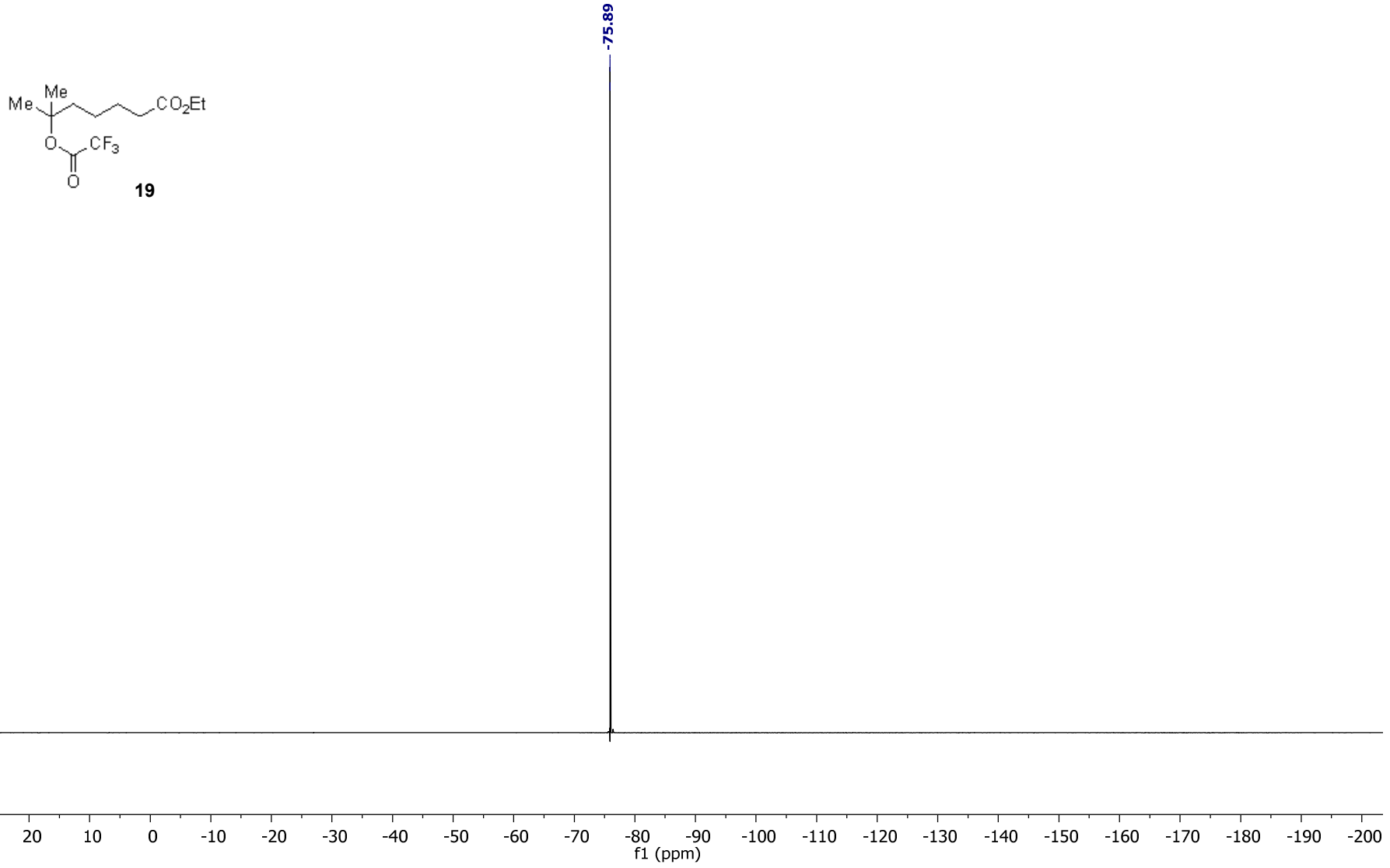

CF3
O
O
H
N
OEt
Me
Me
O

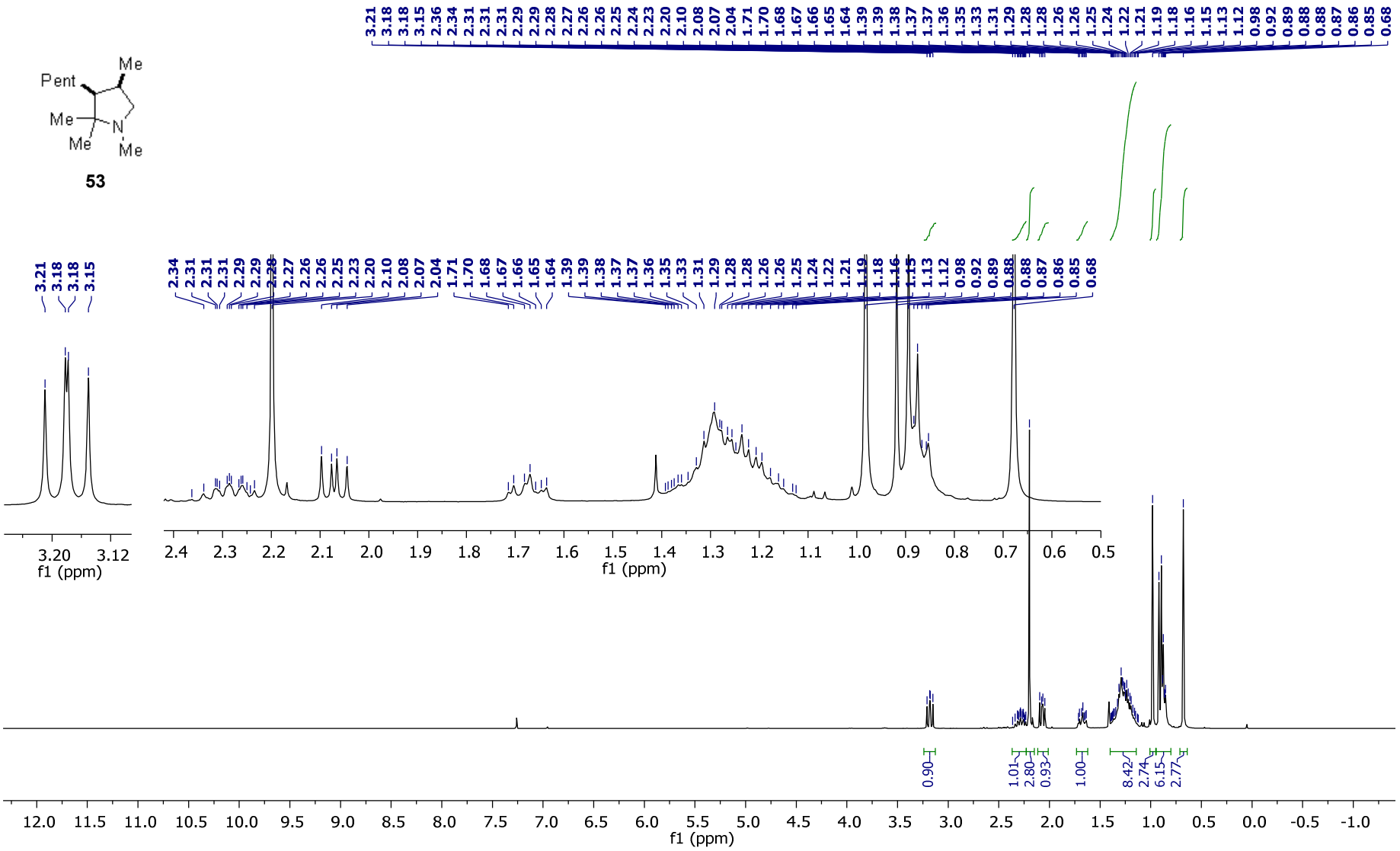
14

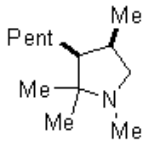
-75.83
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


Me
Me
CO2Et
O
CF3
O
19
7.26
4.14
4.13
4.11
4.09
2.32
2.31
2.29
1.85
1.83
1.82
1.81
1.67
1.66
1.64
1.62
1.60
1.53
1.41
1.40
1.39
1.38
1.37
1.36
1.35
1.33
1.26
1.24
1.22
4.08
2.28
f1 (ppm)
1.96
2.00
2.02
2.22
5.85
2.18
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

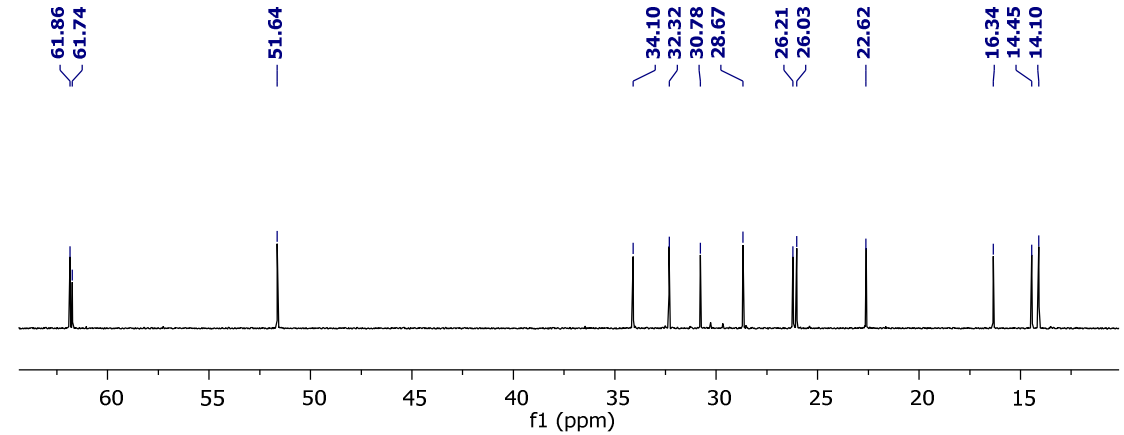

173.36
156.76
156.35
155.94
155.53
118.66
115.80
112.95
110.10
88.91
60.26
40.04
34.03
25.45
24.91
23.11
14.18
Me
Me
CO2Et
O
CF3
O
19
157
156
155
f1 (ppm)
115
110
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

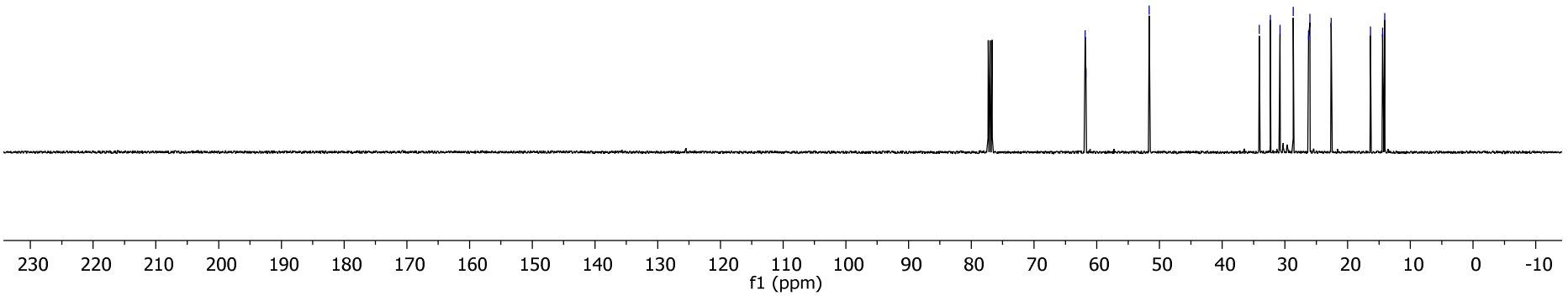

-75.89
Me
Me
CO2Et
O
CF3
O
19
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

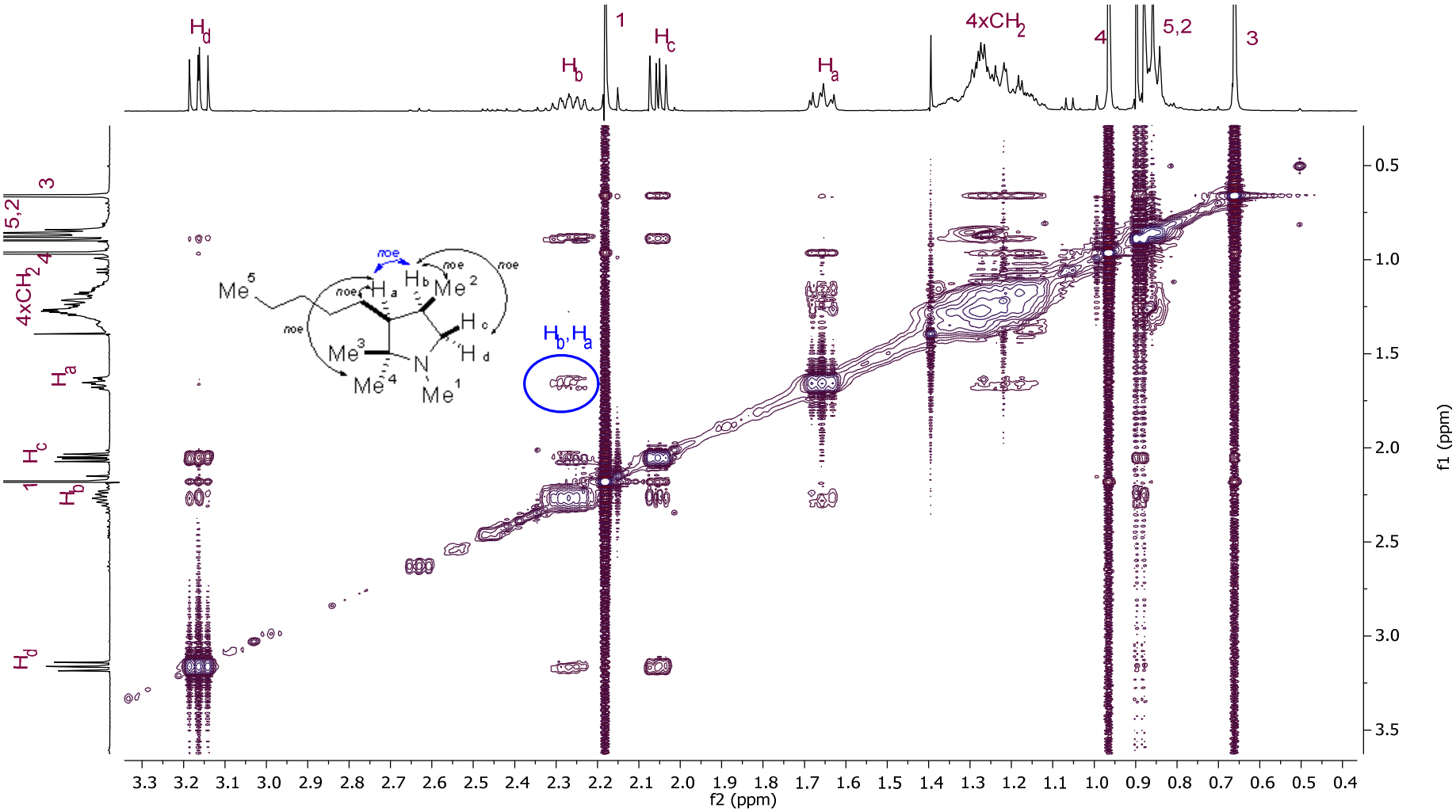

Pent
Me
Me
Me
N
Me
53
f1 (ppm)
f1 (ppm)
f1 (ppm)


Pent
Me
Me
Me
N
Me

53


61.86
61.74
51.64
34.10
32.32
30.78
28.67
26.21
26.03
22.62
16.34
14.45
14.10
60
55
50
45
40
35
30
25
20
15
f1 (ppm)


61.86
61.74
51.64
34.10
32.32
30.78
28.67
26.21
26.03
22.62
16.34
14.45
14.10
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Hd
Hb
1
Hc
Ha
4xCH2
4
5,2
3
Hb,Ha
noe
Me5
Ha
Hb
Me2
Hc
Hd
Me3
N
Me4
Me1
f2 (ppm)
f1 (ppm)