Supporting information

Direct C1 Homologation of Carboxylic Acids: Free Radical Approach Enabled by Acridine Catalysis

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General Methods

Column chromatography was carried out employing silica gel (230-400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or acidic aq. $KMnO_4$ solution. NMR spectra were recorded on Bruker Avance II 300 spectrometer. High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and time-of-flight (TOF) mass analyzer. The measurements were done in a positive ion mode (interface capillary voltage – 4500 V) or in a negative ion mode (3200 V); mass range from m/z 50 to m/z 3000. Melting points were measured with Stuart SMP30 apparatus. As a light source, Chanzon High power LED chip Purple Ultraviolet (UV 3000 mA/DC 30-34 V/100 W, operated at 60 W) was used. The distance between the reaction vessel and the LED chip was about 1 cm; the reaction set-up was used as previously described.[1]

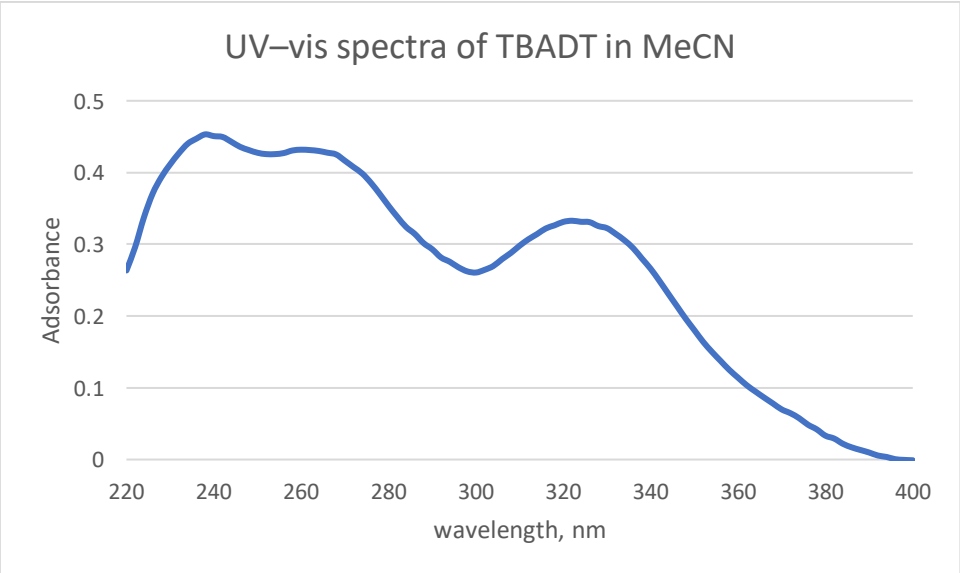
Starting materials

Acetonitrile and dichloromethane were purified by distillation over CaH_2. Ethanol was dried by refluxing over CaO, then distilled off and stored over molecular sieves MS 4Å under argon. All reagents were purchased from Sigma-Aldrich, ABCR or Acros Organics and used without further purification, except stated otherwise.

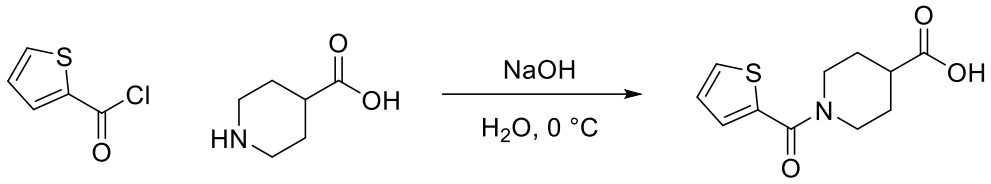
9-(2,4,6-Triisopropylphenyl)acridine (A3) was prepared according to a literature procedure.[2]

Tetrabutylammonium decatungstate (TBADT) was prepared according to a modified literature procedure.[3]

A solution of $Na_2WO_4 \cdot 2H_2O$ (1.0 g, 3.0 mmol) in water (10 mL) was heated to boiling. Hydrochloric acid (1.6 mL of 3M aq. solution) was added dropwise and the mixture was refluxed for 10 minutes. Then, the hot solution of tetrabutylammonium bromide (0.4 g, 1.25 mmol) in water (10 mL) was added dropwise with slow stirring. The mixture was additionally stirred for 20 minutes while boiling, thus generating a white solid. After cooling to room temperature, the solid was filtered, washed with water (3×4 mL) and acetone (2×4 mL), and finally dried under vacuum to yield 996 mg (90%) of TBADT.



1-(Thiophene-2-carbonyl)piperidine-4-carboxylic acid (1q).



Thiophene-2-carbonyl chloride (1 equiv, 20 mmol, 2.93 g) and a solution of NaOH (1 equiv, 20 mmol, 0.8 g) in water (10 mL) were added dropwise simultaneously from two different dropping funnels into a three-necked 100 mL flask containing a solution of piperidine-4-carboxylic acid (1 equiv, 20 mmol, 2.58 g) and NaOH (1 equiv, 20 mmol, 0.8 g) in water (20 mL) at 0 °C (ice bath). The cooling bath was removed, and mixture was stirred for 1 hour at room temperature. The mixture was cooled to 0 °C, acidified with 2M aq. HCl to pH = 4 and extracted with EtOAc (4×20 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), filtered through Na_2SO_4, concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate.

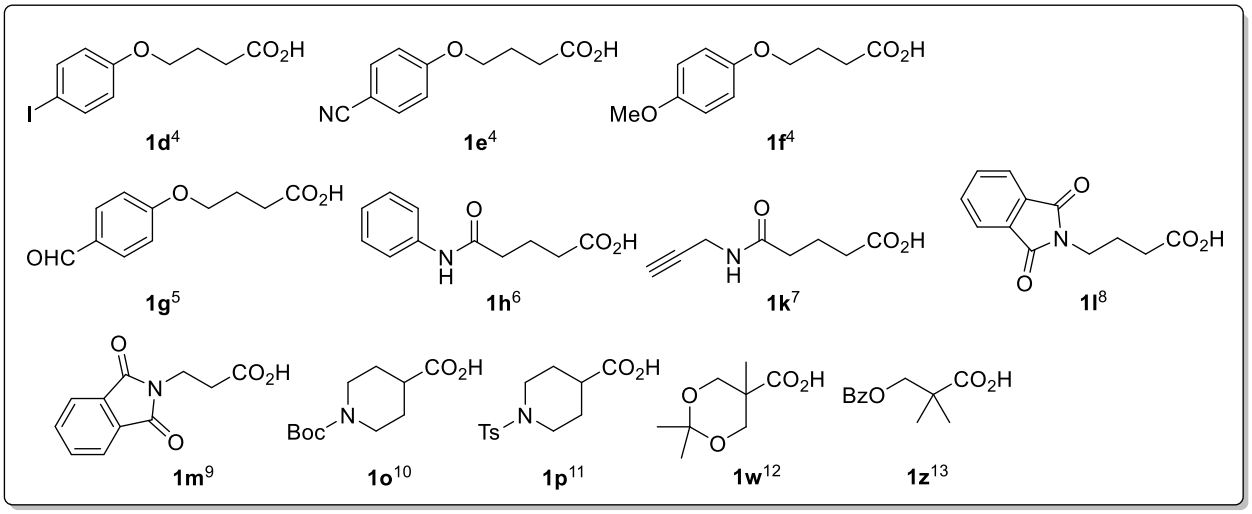
Yield 3.87 g, 81%. Colorless solid. Mp 120-122 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.97 (br s, 1H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.04 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.31 (d, *J* = 13.5 Hz, 2H), 3.18 (t, *J* = 12.3 Hz, 2H), 2.64 (tt, *J* = 10.6, 4.1 Hz, 1H), 2.07 – 1.93 (m, 2H), 1.87 – 1.68 (m, 2H).

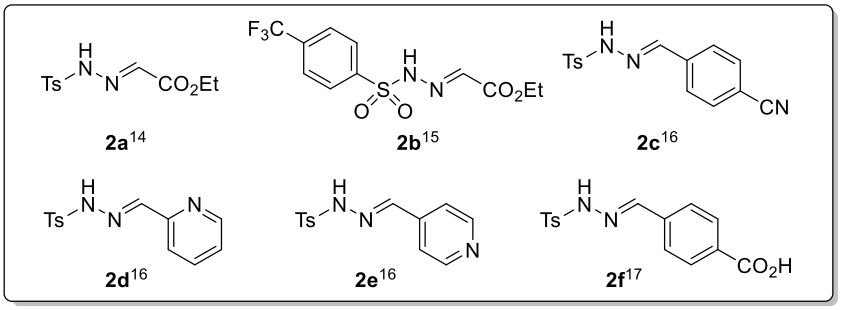
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 179.4, 164.0, 136.8, 128.9, 128.8, 126.8, 45.0 (br s), 40.7, 28.1.

HRMS (ESI): calculated for $C_{11}H_{14}NO_3S$ (M+H) 240.0689, found 240.0694.

Carboxylic acids **1d-h,k-m,o,p,w,z** were prepared according to literature procedures:



Hydrazones **2a-f** were prepared according to literature procedures:



Synthesis of esters 3 (Method A)

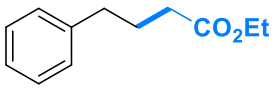
Carboxylic acid **1** (0.5 mmol, 1.0 equiv), ethyl 2-(2-tosylhydrazono)acetate **2a** (114 mg, 0.6 mmol, 1.2 equiv), TBADT (16 mg, 1.0 mol %) and 9-(2,4,6-triisopropylphenyl)acridine **A3** (19 mg, 10.0 mol %) were placed in a tube (Duran cat. no 261351155, Roth cat. no K248.1, outside diameter = 12 mm, 6 mL). The tube was evacuated and filled with argon. Dichloromethane (1.0 mL) and MeCN (1.0 mL) were added, and the solution was degassed by evaporation of about 5% of the solvent under vacuum followed by filling the tube with argon. The tube was closed with a screw cap and placed in a glass jacket for cooling (Huber minichiller 300 was used, water temperature 20 °C). Irradiation was carried out by a LED matrix (400 nm, 60 W) for 2 hours. The distance between LED chip and the reaction tube was about 1 cm. Then, the solvent was evaporated under vacuum, and the residue was dried under vacuum for additional 5 min at 65 °C (oil bath). The tube was cooled to room temperature and filled with argon. Dry ethanol (2.0 mL) and triethylamine (279 μL, 2.0 mmol, 4.0 equiv) were added. The tube was closed with a screw cap and placed in a preheated oil bath at 80 °C for 2 hours with stirring. The heating bath was removed, the tube was cooled to room temperature. For the work-up, for **3a-g,i,j,n,o,q-z**, HCl (2 mL, 1M aq. solution) was added; for, **3h,k,l,m,p**, brine (2 mL) was added. The mixture was extracted with hexanes (for **3a-c,j,n,t,u,x,y)** or MTBE (for **3d,f,o,r,s,v**) or EtOAc (for **3e,g,h,k,l,m,p,q,w,z**) (5×2 mL). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography on silica gel.

Synthesis of alkanes 5 (Method B)

Carboxylic acid **1** (0.5 mmol, 1.0 equiv), tosylhydrazone **2** (0.6 mmol, 1.2 equiv), TBADT (16 mg, 1.0 mol %) and 9-(2,4,6-triisopropylphenyl)acridine **A3** (19 mg, 10.0 mol %) were placed in a tube (Duran cat. no 261351155, Roth cat. no K248.1, outside diameter = 12 mm, 6 mL). The tube was evacuated and filled with argon. Dichloromethane (1.0 mL) and MeCN (1.0 mL) were added, and the solution was degassed by evaporation of about 5% of the solvent under vacuum followed by filling the tube with argon. The tube was closed with a screw cap and placed in a glass jacket for cooling (Huber minichiller 300 was used, water temperature 20 °C). Irradiation was carried out by a LED matrix (400 nm, 60 W) for 4 hours. The distance between LED chip and the reaction tube was about 1 cm. Then the solvent was evaporated under vacuum, and the residue was dried under vacuum for additional 5 min at 65 °C (oil bath). The tube was cooled to room temperature and filled with argon. Dry ethanol (2.0 mL) and triethylamine (279 μL, 2.0 mmol, 4.0 equiv) were further added. The tube was closed with a screw cap and placed in a preheated oil bath at 80 °C for 4 hours with stirring. Then the heating bath was removed, the tube was cooled to room temperature. For the work-up, for **5a-d,g** HCl (1M aq. solution; for **5a-d**, 2 mL; for **5g**, 4 mL) was added; for **5e,f**, brine (2 mL) was added. The mixture was extracted with MTBE (for **5a**) or hexanes (for **5b-d**) or EtOAc (**5e-g**) (5×2 mL). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography on silica gel.

Characterization of compounds

Ethyl 4-phenylbutanoate (3a).[15]



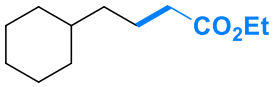
Method A. Yield 66 mg (69%).

Colorless oil. Chromatography: hexanes/EtOAc, 15/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 2H), 7.26 – 7.16 (m, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.99 (p, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.5, 141.5, 128.5, 128.4, 126.0, 60.3, 35.2, 33.7, 26.6, 14.3.

Ethyl 4-cyclohexylbutanoate (3b).[18]



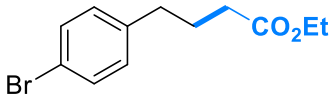
Method A. Yield 65 mg (65%).

Colorless oil. Chromatography: hexanes/EtOAc, 30/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.1 Hz, 2H), 2.24 (t, *J* = 7.5 Hz, 2H), 1.76 – 1.51 (m, 6H), 1.33 – 1.04 (m, 9H), 0.94 – 0.74 (m, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 174.0, 60.2, 37.5, 37.0, 34.8, 33.4, 26.8, 26.5, 22.5, 14.4.

Ethyl 4-(4-bromophenyl)butanoate (3c).[19]



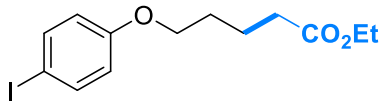
Method A. Yield 73 mg (53%).

Colorless oil. Chromatography: hexanes/EtOAc, 20/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 2.60 (t, *J* = 7.5 Hz, 1H), 2.29 (t, *J* = 7.5 Hz, 1H), 1.92 (p, *J* = 7.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 1H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.4, 140.5, 131.5, 130.3, 119.8, 60.4, 34.6, 33.6, 26.4, 14.3.

Ethyl 5-(4-iodophenoxy)pentanoate (3d).[20]



Method A. Yield 94 mg (54%).

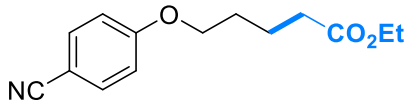
Colorless oil. Chromatography: hexanes/EtOAc, 7/1.

Final purification was performed by preparative HPLC (reversed-phase column C18, 21×250 mm, 5 μm), flow rate 8 mL·min−1; mobile phase: isocratic, acetonitrile/water, 20% water; tR = 49 min)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.9 Hz, 2H), 6.65 (d, J = 8.9 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.92 (t, J = 6.3 Hz, 2H), 2.37 (t, J = 6.6 Hz, 2H), 1.89 – 1.72 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.5, 158.9, 138.3, 117.0, 82.7, 67.6, 60.4, 34.0, 28.6, 21.7, 14.4.

Ethyl 5-(4-cyanophenoxy)pentanoate (3e).



Method A. Yield 58 mg (47%).

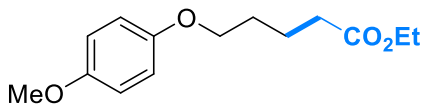
Colorless crystals. M.p. 43–45 °C. Chromatography: hexanes/EtOAc, 3/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 4.01 (t, J = 5.8 Hz, 2H), 2.37 (t, J = 6.9 Hz, 2H), 1.92 – 1.71 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.4, 162.3, 134.1, 119.4, 115.3, 103.9, 67.9, 60.5, 33.9, 28.5, 21.6, 14.3.

HRMS (ESI): calculated for $C_{14}H_{17}NO_3Na$ (M+Na) 270.1101, found 270.1107.

Ethyl 5-(4-methoxyphenoxy)pentanoate (3f).[21]



Method A. Yield 61 mg (48%).

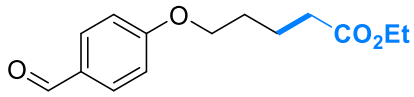
Colorless oil. Chromatography: hexanes/EtOAc, 7/1.

Final purification was performed by preparative HPLC (reversed-phase column C18, 21×250 mm, 5 μm), flow rate 8 mL·min−1; mobile phase: isocratic, acetonitrile/water, 20% water; tR = 55 min)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 4H), 4.13 (q, J = 7.1 Hz, 2H), 3.92 (t, J = 5.7 Hz, 2H), 3.76 (s, 3H), 2.37 (t, J = 6.6 Hz, 2H), 1.87 – 1.72 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.6, 153.8, 153.2, 115.5, 114.7, 68.1, 60.4, 55.8, 34.1, 28.9, 21.8, 14.3.

Ethyl 5-(4-formylphenoxy)pentanoate (3g).[22]



Method A: irradiation time 10 hours.

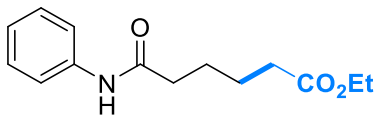
Yield 38 mg (30%).

Colorless oil. Chromatography: Gradient from hexanes/EtOAc, 5/1 to hexanes/EtOAc, 2/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 4.04 (t, J = 5.7 Hz, 2H), 2.38 (t, J = 6.8 Hz, 2H), 1.92 – 1.72 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 190.9, 173.4, 164.1, 132.1, 130.0, 114.8, 67.9, 60.5, 33.9, 28.6, 21.6, 14.3.

Ethyl 6-oxo-6-(phenylamino)hexanoate (3h).[23]



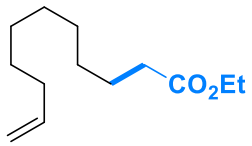
Method A. Yield 82 mg (66%).

Yellowish oil. Chromatography: Gradient from hexanes/EtOAc, 2/1 to hexanes/EtOAc, 1/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.26 (t, J = 7.7 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.41 – 2.25 (m, 4H), 1.80 – 1.57 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.8, 171.4, 138.2, 128.9, 124.1, 120.1, 60.5, 37.0, 34.0, 25.0, 24.4, 14.2.

Ethyl undec-10-enoate (3j).[24]



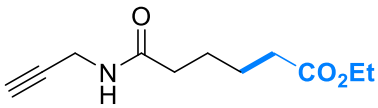
Method A. Yield 65 mg (61%).

Colorless oil. Chromatography: hexanes/EtOAc, 20/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.0, 10.1, 6.7 Hz, 1H), 4.97 (dd, J = 17.0, 2.4 Hz, 1H), 4.91 (ddt, J = 10.1, 2.4, 1.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.27 (t, J = 7.5 Hz, 2H), 2.02 (q, J = 6.7 Hz, 2H), 1.60 (p, J = 7.2 Hz, 2H), 1.41 – 1.27 (m, 10H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 174.0, 139.3, 114.3, 60.2, 34.5, 33.9, 29.4, 29.3, 29.2, 29.2, 29.0, 25.1, 14.4.

Ethyl 6-oxo-6-(prop-2-yn-1-ylamino)hexanoate (3k).



Method A. Yield 63 mg (60%).

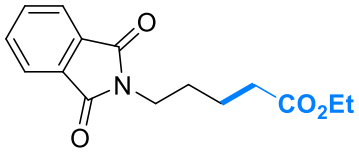
Colorless crystals. Mp 52–53 °C. Chromatography: hexanes/EtOAc, 1/1 and recrystallization from hexanes/MTBE 4/1 (yield after recrystallization is given).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.02 (dd, *J* = 5.3, 2.6 Hz, 2H), 2.29 (t, *J* = 6.4 Hz, 2H), 2.25 – 2.17 (m, 3H), 1.75 – 1.55 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.6, 172.4, 79.8, 71.5, 60.4, 35.9, 34.0, 29.2, 25.0, 24.5, 14.3.

HRMS (ESI): calculated for $C_{11}H_{18}NO_3$ (M+H) 212.1281, found 212.1283.

Ethyl 5-(1,3-dioxoisoindolin-2-yl)pentanoate (3l).[25]



Method A: reaction time with NEt_3 4 h.

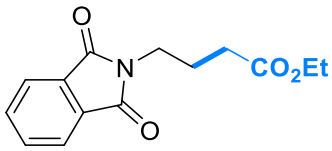
Yield 69 mg (50%).

Yellowish oil. Chromatography: hexanes/EtOAc, 4/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.67 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.66 (t, *J* = 6.6 Hz, 2H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.78 – 1.55 (m, 4H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.2, 168.4, 134.0, 132.2, 123.2, 60.4, 37.5, 33.8, 28.0, 22.2, 14.3.

Ethyl 4-(1,3-dioxoisoindolin-2-yl)butanoate (3m).[26]



Method A: reaction time with NEt_3 4 h.

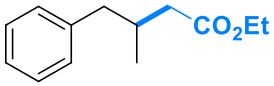
Yield 43 mg (33%).

Colorless oil. Chromatography: Gradient from hexanes/EtOAc, 3/1 to hexanes/EtOAc, 2/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.72 (t, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.00 (p, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.7, 168.4, 134.0, 132.2, 123.3, 60.6, 37.3, 31.7, 24.0, 14.3.

Ethyl 3-methyl-4-phenylbutanoate (3n).[27]



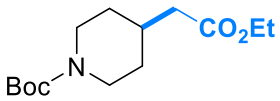
Method A. Yield 64 mg (62%).

Yellowish oil. Chromatography: hexanes/EtOAc, 20/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.2 Hz, 2H), 7.25 – 7.13 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.66 (dd, *J* = 13.3, 6.2 Hz, 1H), 2.51 (dd, *J* = 13.3, 7.1 Hz, 1H), 2.42 – 2.23 (m, 2H), 2.21 – 2.08 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.2 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.1, 140.4, 129.3, 128.3, 126.1, 60.2, 43.1, 41.3, 32.4, 19.7, 14.4.

***tert*-Butyl 4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (3o).**[15]



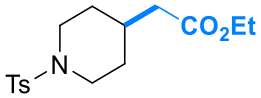
Method A. Yield 76 mg (56%).

Colorless oil. Chromatography: Gradient from hexanes/EtOAc, 10/1 to hexanes/EtOAc, 3/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (q, *J* = 7.1 Hz, 2H), 4.05 - 3.95 (m, 2H), 2.68 (t, *J* = 12.8 Hz, 2H), 2.19 (d, *J* = 7.1 Hz, 2H), 1.97 – 1.80 (m, 1H), 1.71 – 1.59 (m, 2H), 1.41 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.18 – 1.01 (m, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.5, 154.8, 79.4, 60.3, 43.8 (br s), 41.2, 33.1, 31.9, 28.5, 14.3.

Ethyl 2-(1-tosylpiperidin-4-yl)acetate (3p).[28]



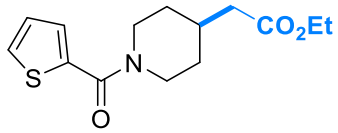
Method A. Yield 91 mg (56%).

Colorless crystals. Mp 59–61 °C. Chromatography: Gradient from hexanes/EtOAc, 3/1 to hexanes/EtOAc, 2/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.71 (d, *J* = 11.8 Hz, 2H), 2.39 (s, 3H), 2.23 (dt, *J* = 11.8, 1.9 Hz, 2H), 2.16 (d, *J* = 6.7 Hz, 2H), 1.78 – 1.56 (m, 3H), 1.41 – 1.23 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.1, 143.5, 133.0, 129.6, 127.7, 60.3, 46.2, 40.5, 32.1, 31.1, 21.5, 14.2.

Ethyl 2-(1-(thiophene-2-carbonyl)piperidin-4-yl)acetate (3q).



Method A. Yield 66 mg (47%).

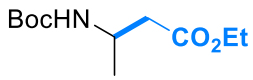
Yellowish oil. Chromatography: Gradient from hexanes/EtOAc, 3/1 to hexanes/EtOAc, 2/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 5.0 Hz, 1H), 7.23 (d, *J* = 3.7 Hz, 1H), 6.99 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.39 (d, *J* = 8.6 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.94 (t, *J* = 13.0 Hz, 2H), 2.24 (d, *J* = 7.0 Hz, 2H), 2.15 – 1.98 (m, 1H), 1.78 (d, *J* = 13.0 Hz, 2H), 1.34 – 1.13 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.2, 163.6, 137.4, 128.5, 128.3, 126.6, 60.4, 45.4, 40.9, 33.2, 32.1, 14.3.

HRMS (ESI): calculated for $C_{14}H_{20}NO_3S$ (M+H) 282.1158, found 282.1159.

Ethyl 3-((*tert*-butoxycarbonyl)amino)butanoate (3r).[15]



Method A: reaction time with NEt_3 4 h.

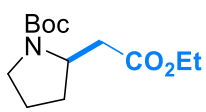
Yield 73 mg (63%).

Colorless oil. Chromatography: Gradient from hexanes/EtOAc, 5/1 to hexanes/EtOAc, 2/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (br s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.06 – 3.91 (m, 1H), 2.56 – 2.36 (m, 2H), 1.40 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 6.7 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.6, 155.2, 60.6, 43.6, 41.0, 28.5, 20.6, 14.3.

***tert*-Butyl 2-(2-ethoxy-2-oxoethyl)pyrrolidine-1-carboxylate (3s).**[15]



Method A: reaction time with NEt_3 4 h.

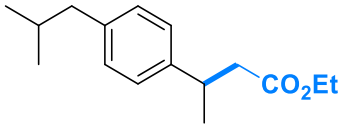
Yield 57 mg (44%).

Yellowish oil. Chromatography: hexanes/EtOAc, 3/1.

^{1}H NMR (300 MHz, $CDCl_3$, observed as a mixture of rotamers) δ 4.22 – 4.11 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.46 – 3.24 (m, 2H), 2.91 & 2.76 (d, *J* = 15.0 Hz, 1H, rotameric signals), 2.26 (dd, *J* = 15.0, 9.8 Hz, 1H), 2.02 (dq, *J* = 11.6, 7.5 Hz, 1H), 1.90 – 1.69 (m, 3H), 1.43 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, observed as a mixture of rotamers) δ 171.6, 154.3, 87.2, 60.4, 54.1, 46.6 & 46.3 (rotameric signals), 39.5 & 38.6 (rotameric signals), 31.3 & 30.6 (rotameric signals), 28.6, 23.7 & 22.9 (rotameric signals), 14.3.

Ethyl 3-(4-isobutylphenyl)butanoate (3t).



Method A. Yield 32 mg (26%).

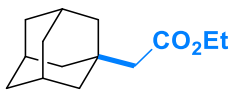
Colorless oil. Chromatography: hexanes/EtOAc, 30/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.25 (h, *J* = 7.2 Hz, 1H), 2.60 (dd, *J* = 14.9, 6.9 Hz, 1H), 2.51 (dd, *J* = 14.9, 8.3 Hz, 1H), 2.44 (d, *J* = 7.2 Hz, 2H), 1.83 (sept, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 6H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.7, 143.1, 139.8, 129.3, 126.6, 60.3, 45.2, 43.3, 36.3, 30.3, 22.5, 21.9, 14.3.

HRMS (ESI): calculated for $C_{16}H_{24}O_2Na$ (M+Na) 271.1669, found 271.1666.

Ethyl 2-(adamantan-1-yl)acetate (3u).[15]



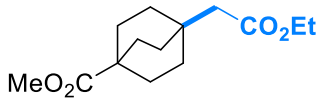
Method A. Yield 78 mg (70%).

Colorless oil. Chromatography: hexanes/EtOAc, 30/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (q, *J* = 7.1 Hz, 2H), 2.03 (s, 2H), 1.97 – 1.91 (m, 3H), 1.70 – 1.55 (m, 12H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.9, 59.9, 49.1, 42.5, 36.9, 32.8, 28.7, 14.5.

Methyl 4-(2-ethoxy-2-oxoethyl)bicyclo[2.2.2]octane-1-carboxylate (3v).



Method A. Yield 87 mg (68%).

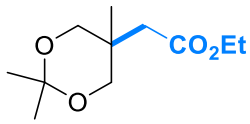
Colorless oil. Chromatography: hexanes/EtOAc, 8/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (q, *J* = 7.1 Hz, 2H), 3.58 (s, 3H), 2.05 (s, 2H), 1.80 – 1.68 (m, 6H), 1.58 – 1.44 (m, 6H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 178.2, 171.7, 60.0, 51.6, 45.7, 38.6, 30.7, 30.4, 28.4, 14.4.

HRMS (ESI): calculated for $C_{14}H_{23}O_4$ (M+H) 255.1591, found 255.1591.

Ethyl 2-(2,2,5-trimethyl-1,3-dioxan-5-yl)acetate (3w).



Method A. Yield 64 mg (59%).

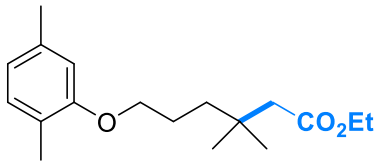
Yellowish oil. Chromatography: hexanes/EtOAc, 5/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.1 Hz, 2H), 3.70 (d, *J* = 11.8 Hz, 1H), 3.56 (d, *J* = 11.8 Hz, 1H), 2.44 (s, 2H), 1.39 (s, 3H), 1.39 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.9, 98.1, 68.9, 60.3, 39.6, 32.6, 25.7, 22.0, 19.3, 14.4.

HRMS (ESI): calculated for $C_{11}H_{20}O_4$ (M+K) 255.0993, found 255.0998.

Ethyl 6-(2,5-dimethylphenoxy)-3,3-dimethylhexanoate (3x).



Method A. Yield 88 mg (60%).

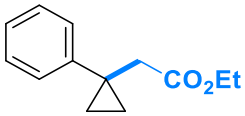
Colorless oil. Chromatography: hexanes/EtOAc, 15/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J* = 7.4 Hz, 1H), 6.73 – 6.62 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.95 (t, *J* = 6.4 Hz, 2H), 2.34 (s, 3H), 2.26 (s, 2H), 2.21 (s, 3H), 1.89 – 1.76 (m, 2H), 1.57 – 1.47 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 6H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.3, 157.1, 136.5, 130.4, 123.6, 120.7, 112.0, 68.4, 60.0, 46.1, 38.5, 33.2, 27.4, 24.5, 21.5, 15.9, 14.4.

HRMS (ESI): calculated for $C_{18}H_{29}O_2$ (M+H) 293.2111, found 293.2117.

Ethyl 2-(1-phenylcyclopropyl)acetate (3y).



Method A. Yield 45 mg (44%).

Yellowish oil. Chromatography: hexanes/EtOAc, 15/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 4H), 7.24 – 7.13 (m, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 2.61 (s, 2H), 1.17 (t, *J* = 7.2 Hz, 3H), 0.95 (dt, *J* = 11.0, 4.3 Hz, 4H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.0, 144.3, 128.6, 128.3, 126.3, 60.2, 44.9, 22.5, 14.3, 13.6.

HRMS (ESI): calculated for $C_{13}H_{16}O_2Na$ (M+Na) 227.1043, found 227.1044.

4-Ethoxy-2,2-dimethyl-4-oxobutyl benzoate (3z).

Method A. Yield 36 mg (27%).

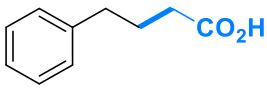
Colorless oil. Chromatography: hexanes/EtOAc, 10/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 4.16 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 6H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.7, 166.5, 133.1, 130.4, 129.7, 128.5, 72.3, 60.3, 43.6, 34.3, 24.8, 14.4.

HRMS (ESI): calculated for $C_{15}H_{21}O_4$ (M+H) 256.1434, found 256.1434.

4-Phenylbutanoic acid (4a).[29]

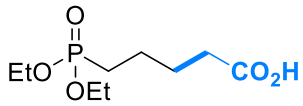


Modified Method A: after irradiation, the solvent was evaporated under vacuum, 1 mL of EtOH and NaOH (2.0 mL, 2M aq. solution) were added. The tube was closed with a screw cap and placed in a preheated oil bath at 80 °C for 2 hours with stirring. Then the heating bath was removed, the tube was cooled to room temperature. For the work-up, HCl (5 mL, 1M aq. solution) was added and the product was extracted with EtOAc (5×2 mL). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, gradient from hexanes/EtOAc, 10/1 with 1% of AcOH to hexanes/EtOAc, 5/1 with 1% of AcOH. Yielded 54 mg (65%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (br s, 1H), 7.38 – 7.27 (m, 2H), 7.27 – 7.18 (m, 3H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.01 (p, *J* = 7.5 Hz, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 180.1, 141.3, 128.6, 128.6, 126.2, 35.1, 33.5, 26.3.

5-(Diethoxyphosphoryl)pentanoic acid (4b).



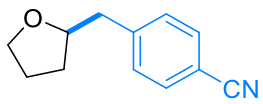
Modified Method A: the crude ethyl ester was dissolved in MeOH (0.5 mL), NaOH (1.0 mL, 2M aq, solution) was added and the mixture was stirred for 2 hours. The resulting solution was washed with MTBE (2×2 mL) and acidified to pH=2 with HCl (4M aq. solution). The product was extracted with EtOAc (5×2 mL). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, gradient from DCM/MeOH, 50/1 with 1% of AcOH to DCM/MeOH, 20/1 with 1% of AcOH. Yielded 57 mg (48%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 4.21 – 3.97 (m, 4H), 2.34 (t, *J* = 6.8 Hz, 2H), 1.85 – 1.56 (m, 6H), 1.31 (t, *J* = 7.1 Hz, 6H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 177.2, 62.0 (d, *J* = 6.6 Hz), 33.6, 25.7 (d, *J* = 17.6 Hz), 25.4 (d, *J* = 141.4 Hz), 22.0 (d, *J* = 5.0 Hz), 16.5 (d, *J* = 6.0 Hz).

HRMS (ESI): calculated for $C_9H_{20}O_5P$ (M+H) 239.1043, found. 256.1434.

4-((Tetrahydrofuran-2-yl)methyl)benzonitrile (5a).[30]



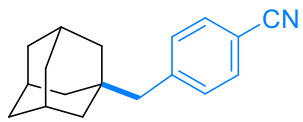
Method B. Yield 59 mg (63%).

Colorless oil. Chromatography: hexanes/EtOAc, 3/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.05 (p, *J* = 6.5 Hz, 1H), 3.86 (dt, *J* = 8.1, 6.7 Hz, 1H), 3.78 – 3.65 (m, 1H), 2.94 – 2.78 (m, 2H), 2.04 – 1.91 (m, 1H), 1.91 – 1.80 (m, 2H), 1.60 – 1.44 (m, 1H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 144.9, 132.1, 130.1, 119.1, 110.1, 7f9.2, 68.1, 42.0, 31.2, 25.7.

4-((Adamantan-1-yl)methyl)benzonitrile (5b).



Method B. Yield 65 mg (52%).

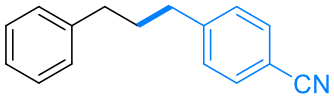
Colorless crystals. Mp 105–106 °C. Chromatography: hexanes/EtOAc, 20/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 2H), 1.97 – 1.89 (m, 3H), 1.66 (d, *J* = 12.1 Hz, 3H), 1.54 (d, *J* = 12.1 Hz, 3H), 1.45 (d, *J* = 3.0 Hz, 6H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 144.2, 131.4, 131.3, 119.3, 109.7, 51.4, 42.4, 36.9, 33.9, 28.7.

HRMS (ESI): calculated for $C_{18}H_{21}NNa$ (M+Na) 274.1566, found 274.1567.

4-(3-Phenylpropyl)benzonitrile (5c).[31]



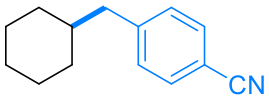
Method B. Yield 37 mg (33%).

Yellowish oil. Chromatography: hexanes/EtOAc, 15/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 2H), 7.37 – 7.26 (m, 4H), 7.26 – 7.16 (m, 3H), 2.72 (t, *J* = 7.7 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 2H), 1.98 (p, *J* = 7.7 Hz, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 148.1, 141.7, 132.3, 129.3, 128.52, 128.49, 126.1, 119.2, 109.8, 35.6, 35.4, 32.5.

4-(Cyclohexylmethyl)benzonitrile (5d).[32]



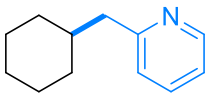
Method B. Yield 50 mg (50%).

Colorless oil. Chromatography: hexanes/EtOAc, 25/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 2.53 (d, *J* = 7.0 Hz, 2H), 1.77 – 1.43 (m, 6H), 1.29 – 1.06 (m, 3H), 1.02 – 0.84 (m, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 147.2, 132.0, 130.0, 119.3, 109.6, 44.3, 39.6, 33.1, 26.4, 26.3.

2-(Cyclohexylmethyl)pyridine (5e).[33]



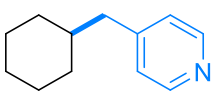
Method B. Yield 46 mg (52%).

Yellowish oil. Chromatography: hexanes/EtOAc, 5/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.8 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.10 – 7.02 (m, 2H), 2.63 (d, *J* = 7.1 Hz, 2H), 1.84 – 1.54 (m, 6H), 1.30 – 1.08 (m, 3H), 1.05 – 0.88 (m, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.4, 149.3, 136.0, 123.7, 120.9, 46.4, 38.7, 33.3, 26.6, 26.3.

4-(Cyclohexylmethyl)pyridine (5f).[34]



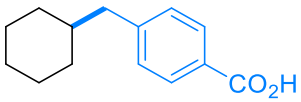
Method B. Yield 37 mg (42%).

Yellowish oil. Chromatography: Gradient from hexanes/EtOAc, 5/1 to hexanes/EtOAc, 1/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.1 Hz, 2H), 7.03 (d, *J* = 5.1 Hz, 2H), 2.44 (d, *J* = 7.0 Hz, 2H), 1.74 – 1.43 (m, 6H), 1.28 – 1.05 (m, 3H), 1.00 – 0.81 (m, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 150.3, 149.6, 124.7, 43.5, 39.1, 33.1, 26.4, 26.2.

4-(Cyclohexylmethyl)benzoic acid (5g).[35]



Method B: 2,4,6-collidine (1.2 equiv) was added.

Yield 47 mg (43%).

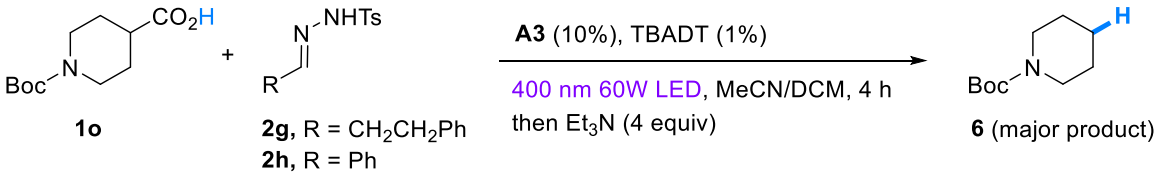
Colorless crystals. M.p. 175–178 °C. Chromatography: hexanes/EtOAc, 5/1 with 1% of AcOH.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 2.58 (d, *J* = 7.0 Hz, 2H), 1.77 – 1.50 (m, 6H), 1.32 – 1.12 (m, 3H), 1.08 – 0.88 (m, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.4, 148.2, 130.2, 129.4, 126.9, 44.3, 39.8, 33.2, 26.6, 26.4.

Scope limitations

For tosylhydrazones **2** without acceptor groups in the aldehyde part, the radical addition step is ineffective. Presumably, in these cases intermediate alkyl radical can react with H-[W] species faster than undergo addition at the C=N bond. Thus, instead of alkylation products, the product of acid decarboxylation is formed.

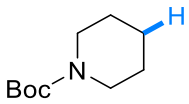


1o

2g, R = CH_2CH_2Ph
2h, R = Ph

6 (major product)

***tert*-Butyl piperidine-1-carboxylate (6).**[36]



Reaction of **1o** with **2g** (Method B). Yield 44 mg (47%).

Reaction of **1o** with **2h** (Method B). Yield 57 mg (62%).

Colorless oil. Chromatography: hexanes/EtOAc, 15/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (t, *J* = 5.2 Hz, 4H), 1.59 – 1.43 (m, 6H), 1.43 (s, 9H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.0, 79.2, 44.7 (br s), 28.6, 25.8, 24.6.

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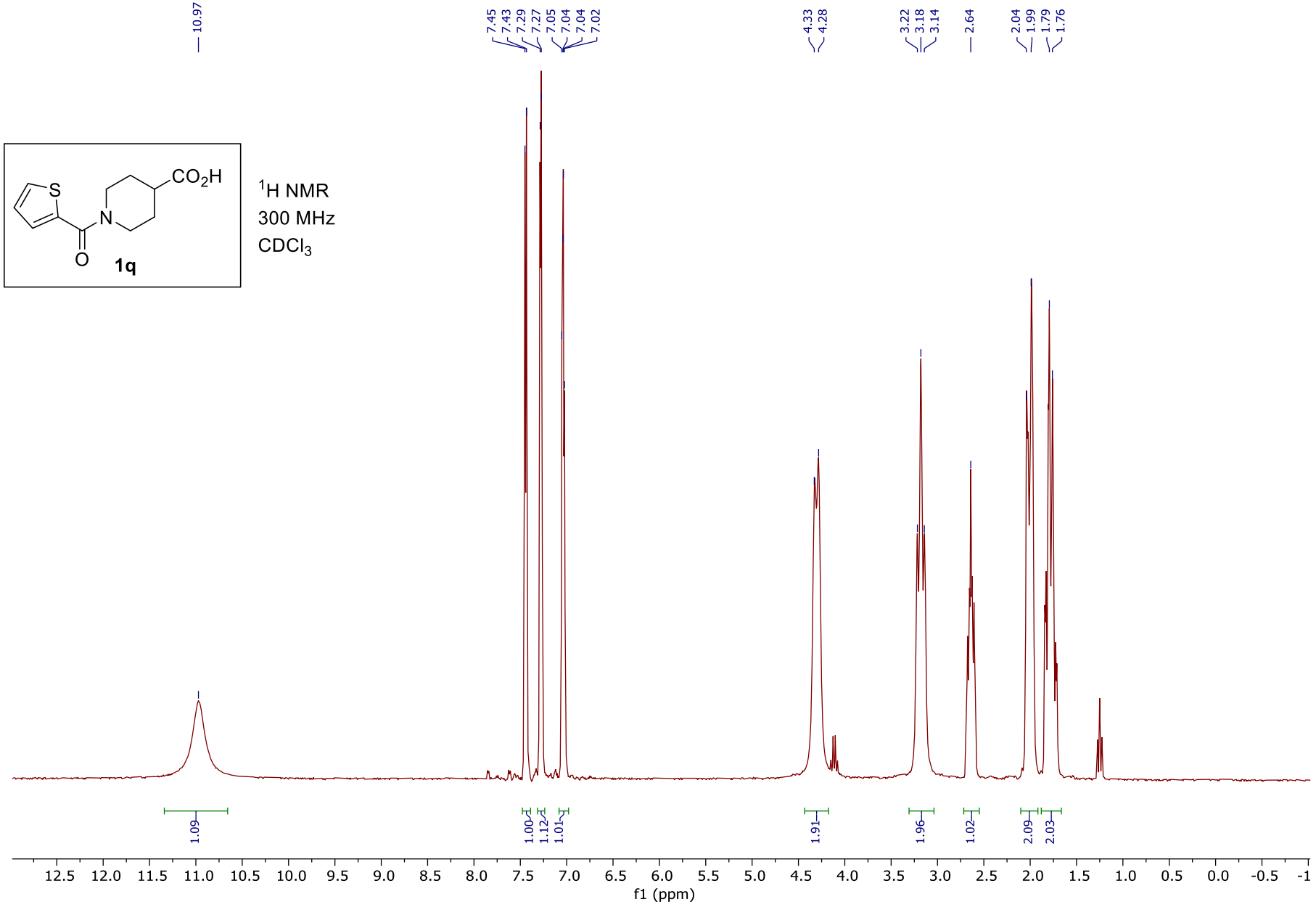
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7.04
7.04
7.02
4.33
4.28
3.22
3.18
3.14
2.64
2.04
1.99
1.79
1.76
CO2H
S
N
O
1q
1H NMR
300 MHz
CDCl3
1.09
1.00
1.12
1.01
1.91
1.96
1.02
2.09
2.03
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
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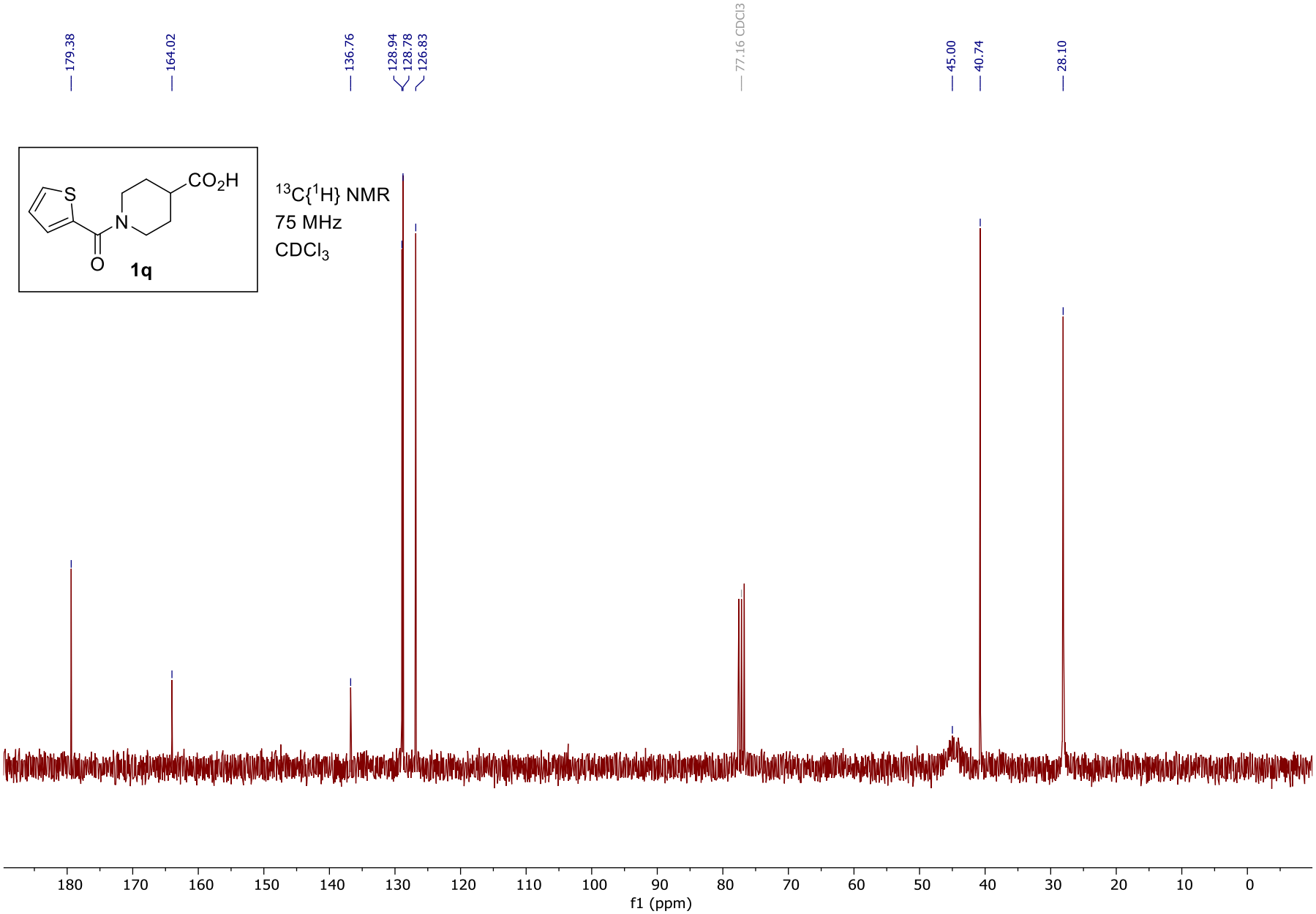
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N
O
1q
13C{1H} NMR
75 MHz
CDCl3
180
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100
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50
40
30
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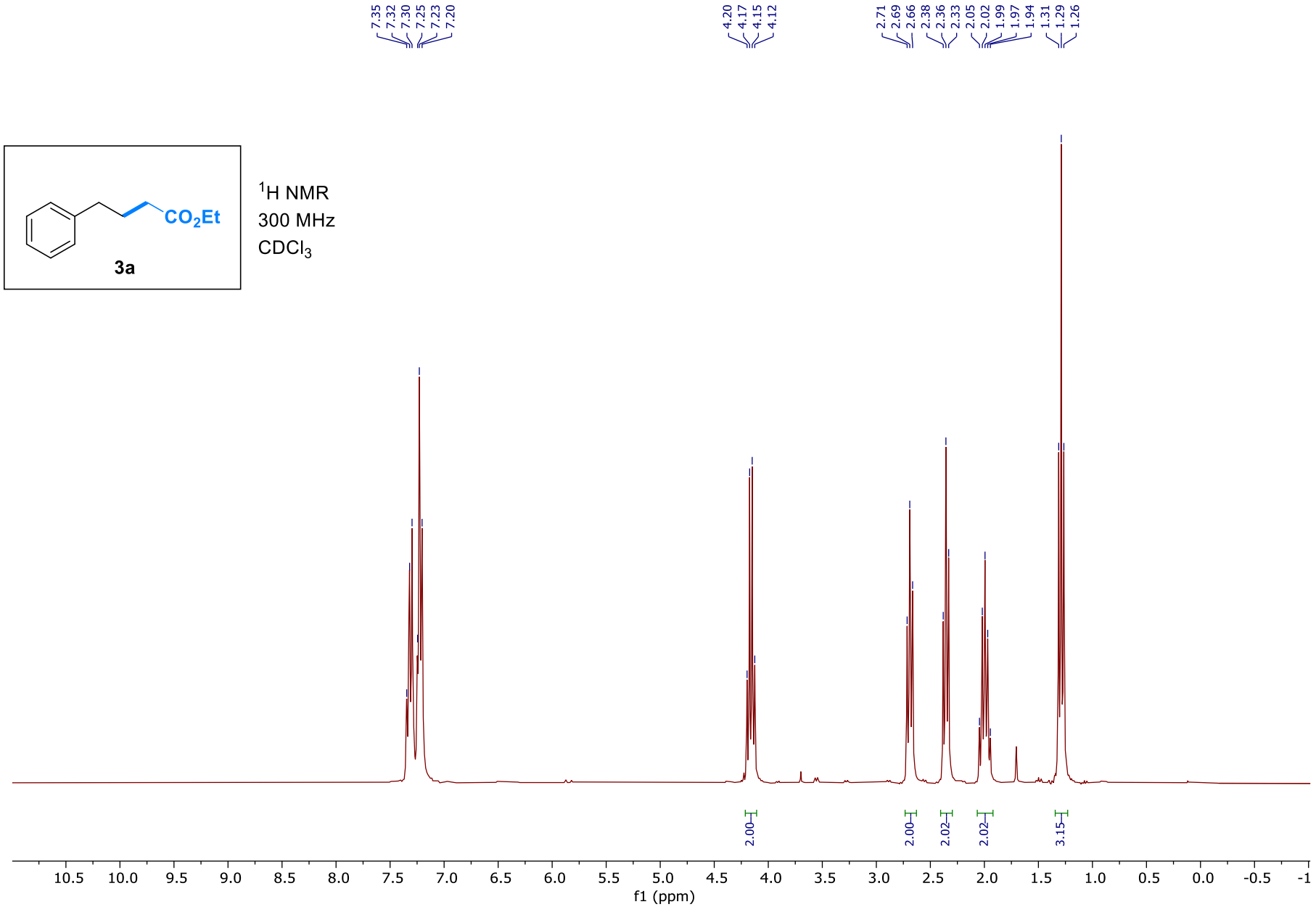
f1 (ppm)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2.38
2.36
2.33
2.05
2.02
1.99
1.97
1.94
1.31
1.29
1.26
CO2Et
3a
1H NMR
300 MHz
CDCl3
2.00
2.00
2.02
2.02
3.15
10.5
10.0
9.5
9.0
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6.5
6.0
5.5
5.0
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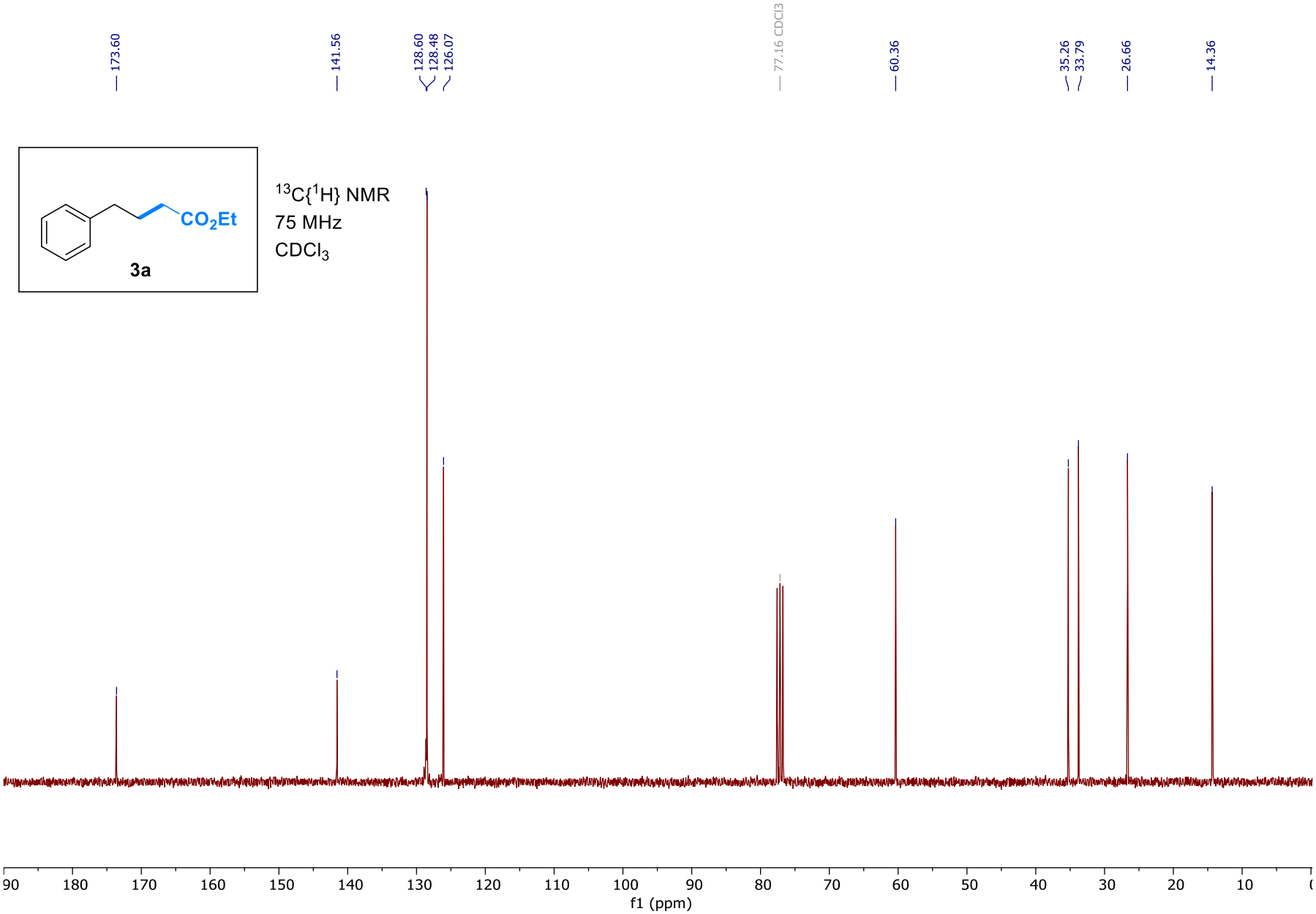
-1
f1 (ppm)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20
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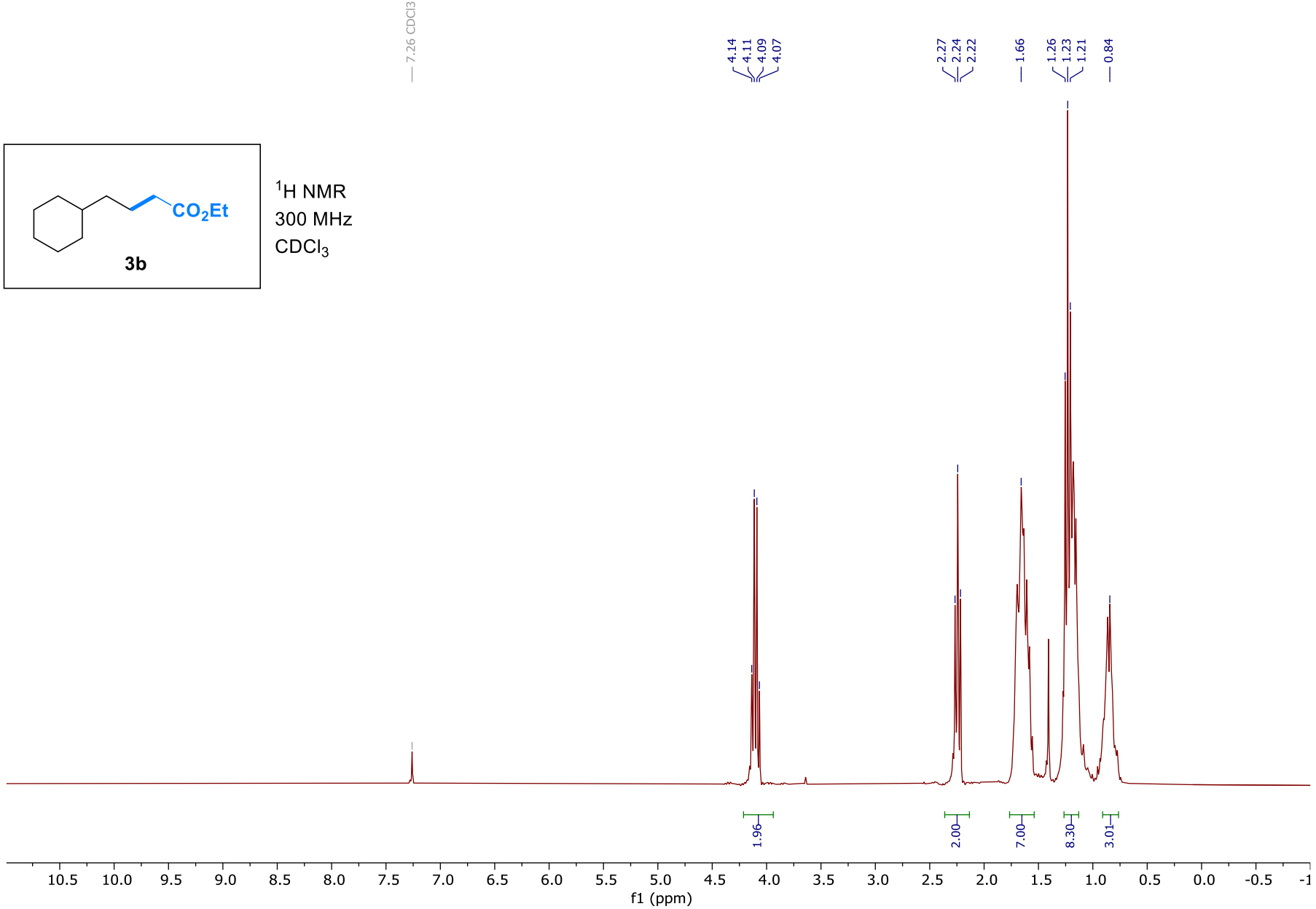
f1 (ppm)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3b
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3.01
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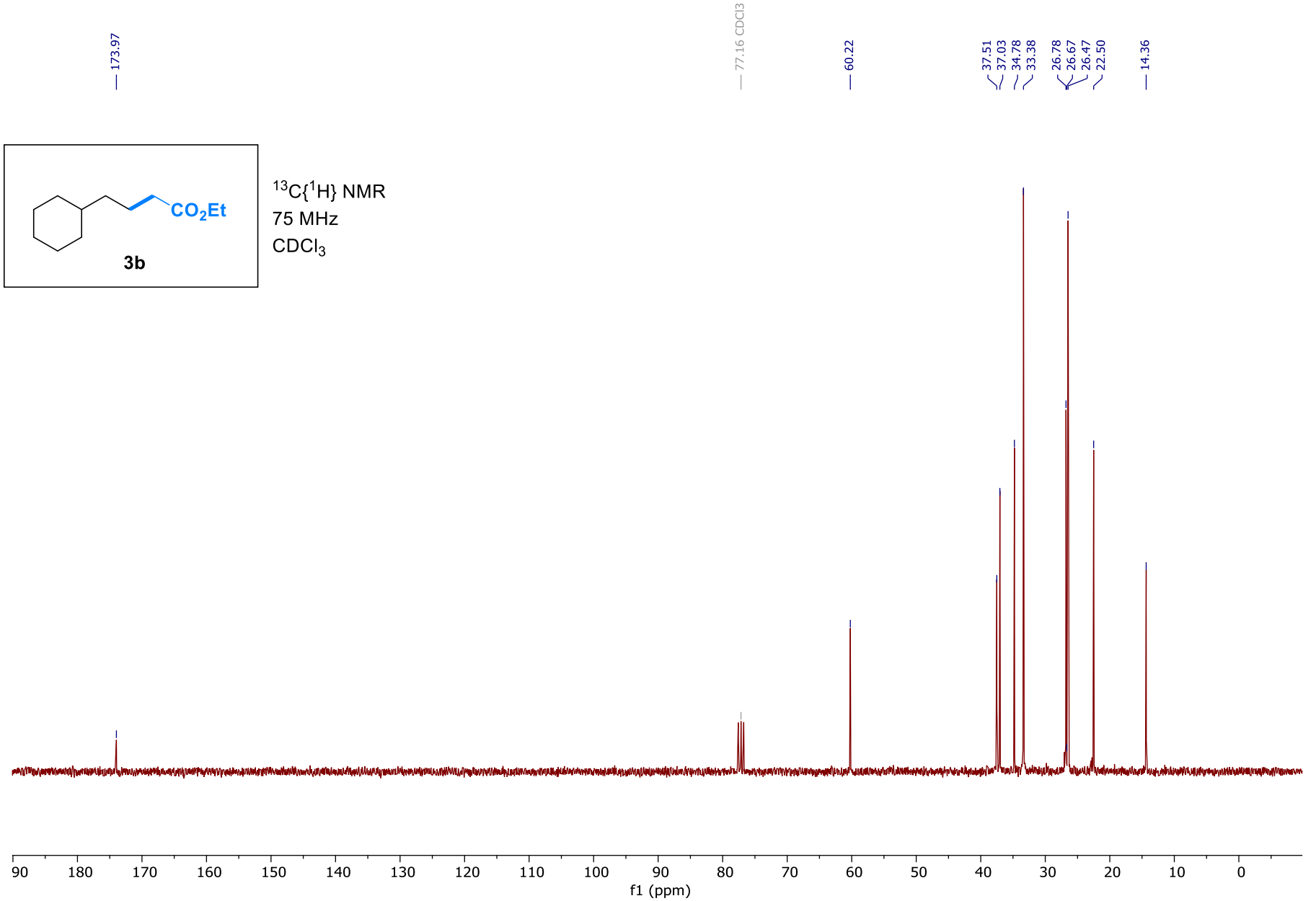
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CO2Et
3b
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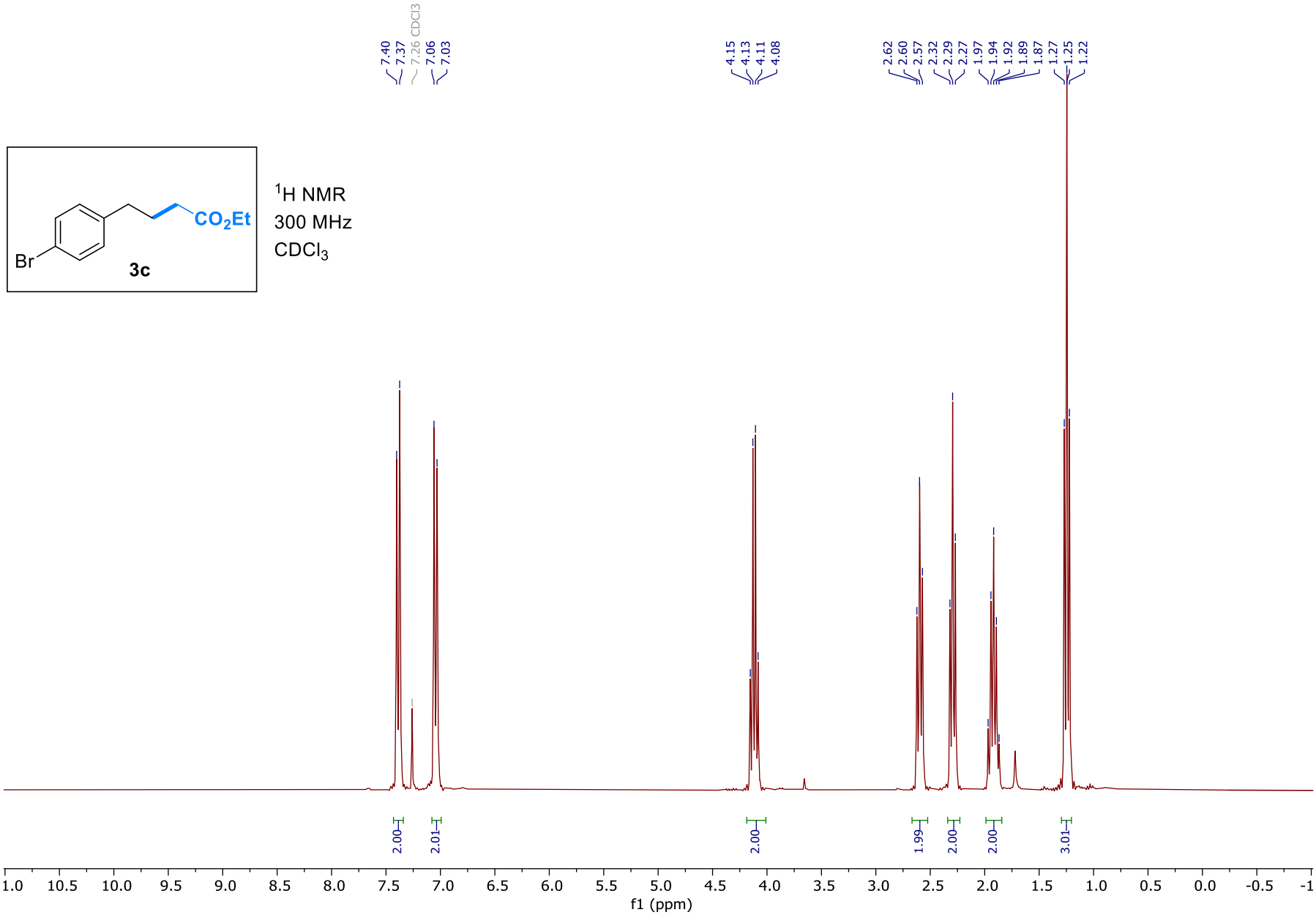
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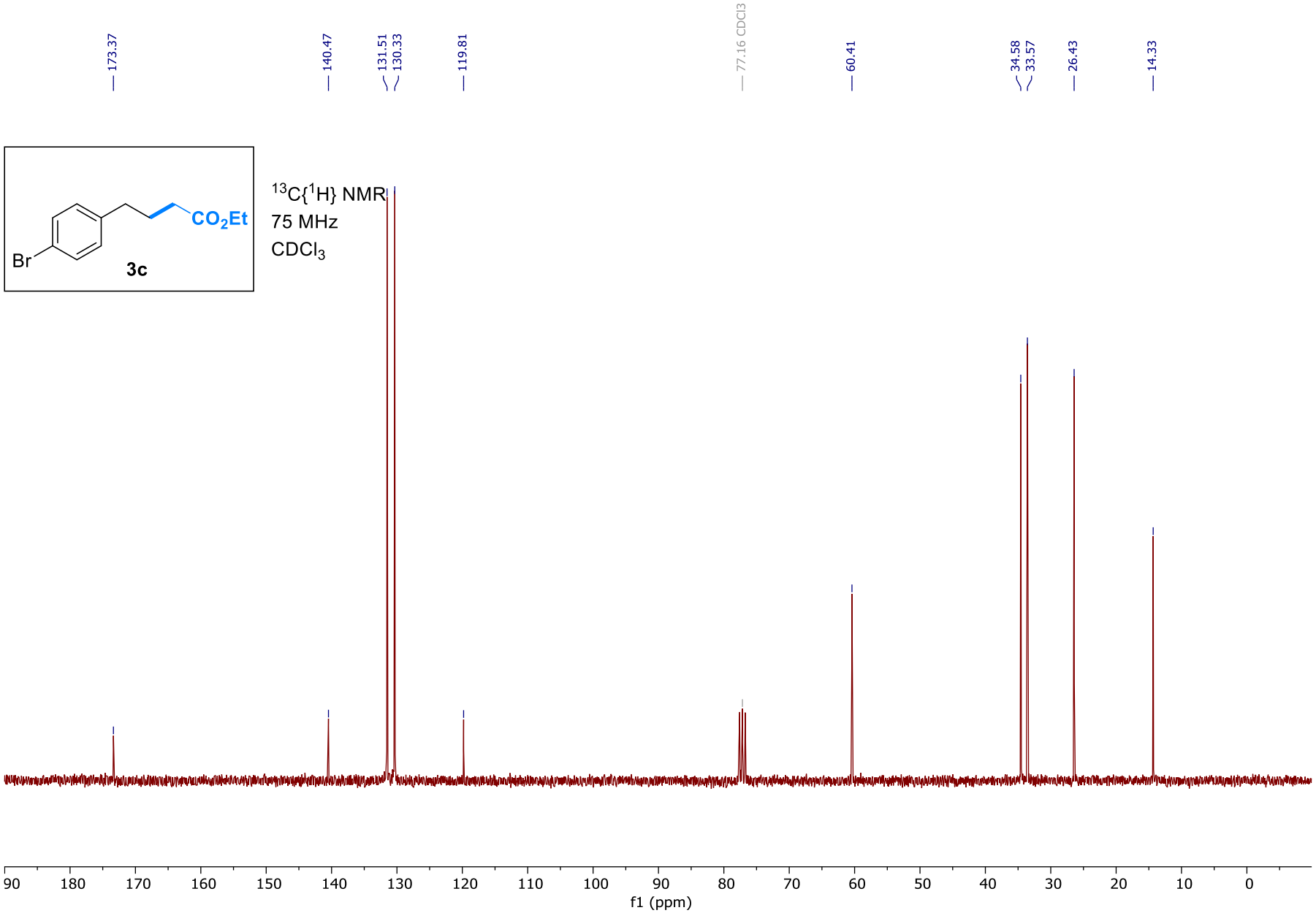
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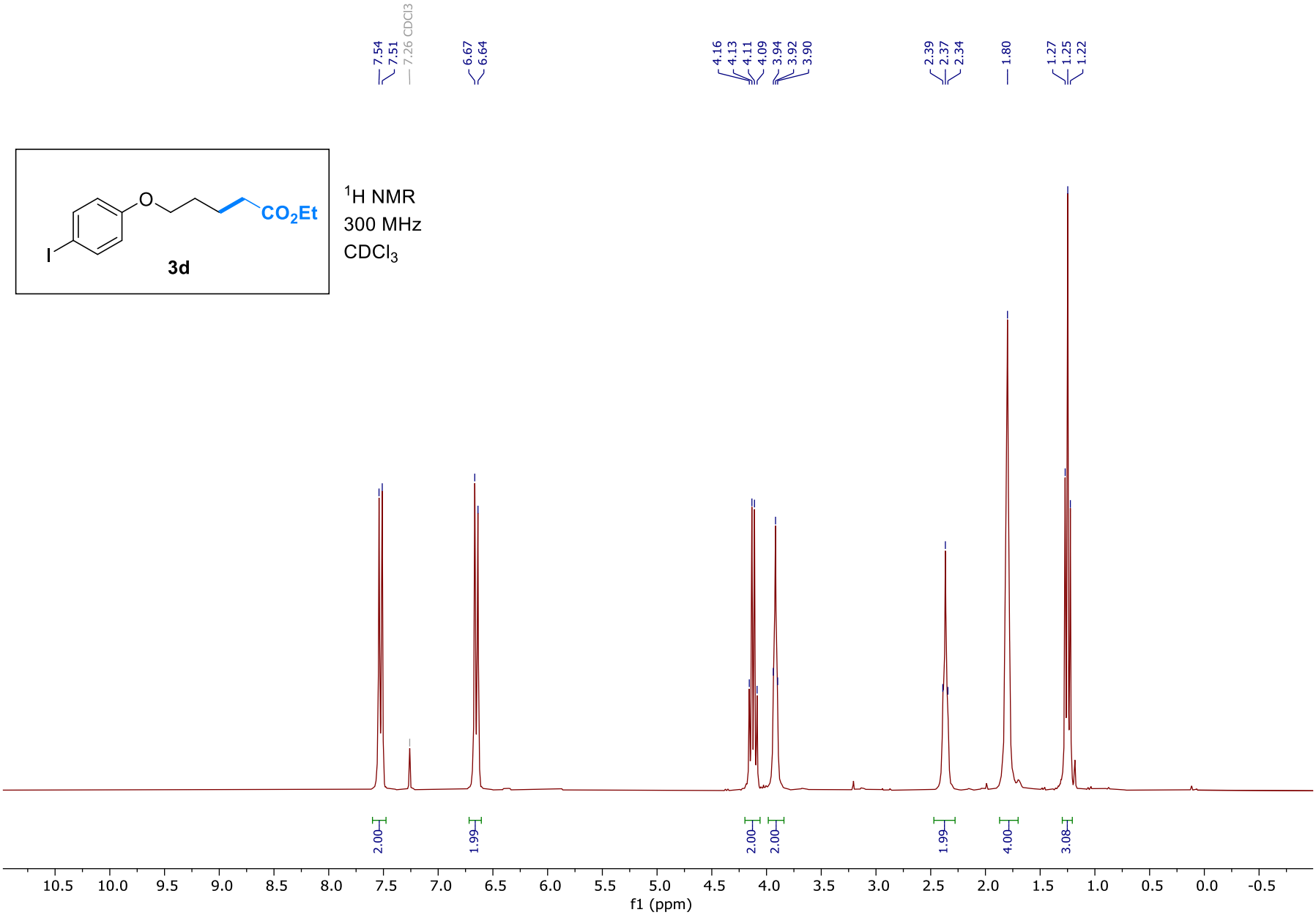
f1 (ppm)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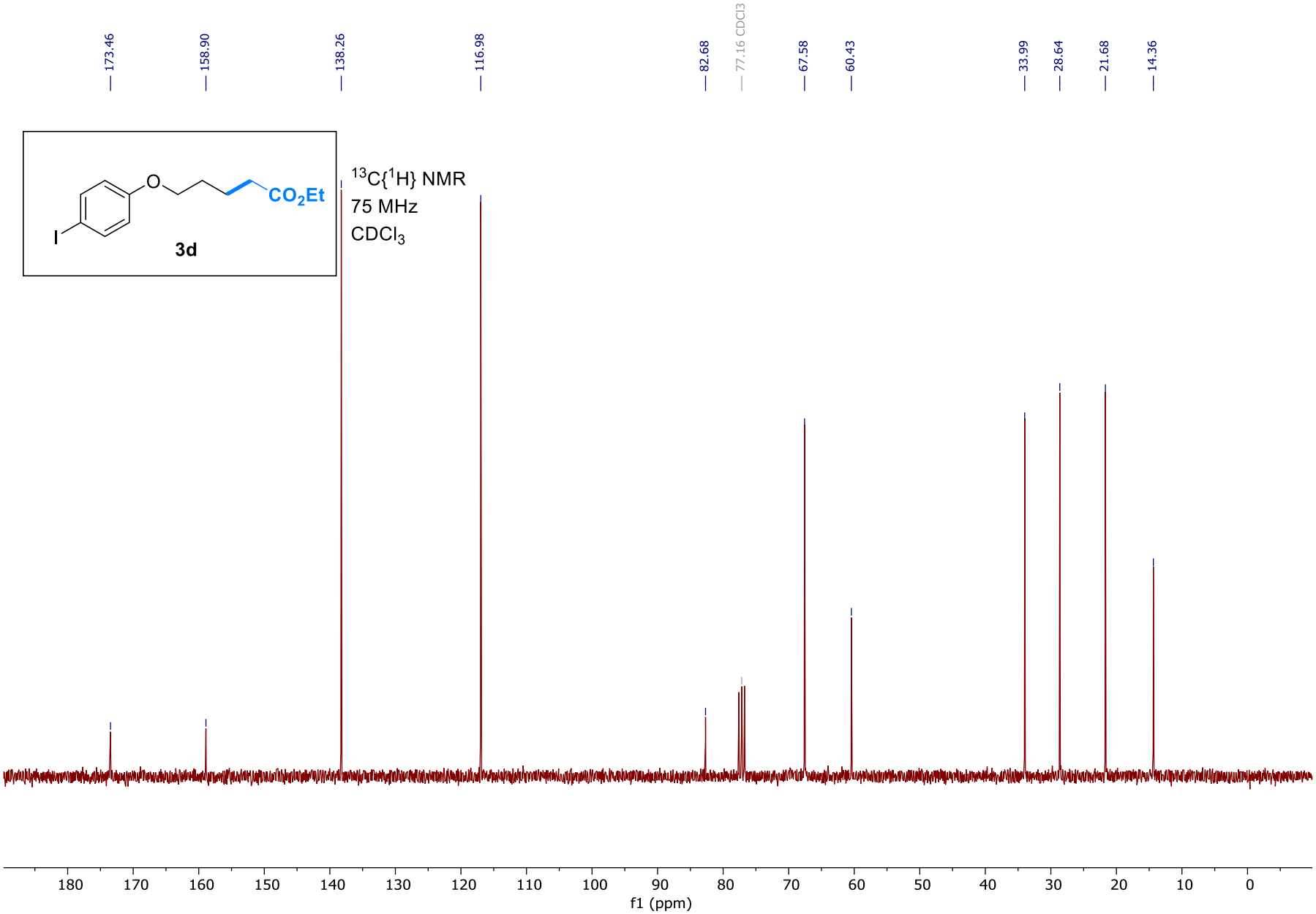
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CO2Et
I
3d
13C{1H} NMR
75 MHz
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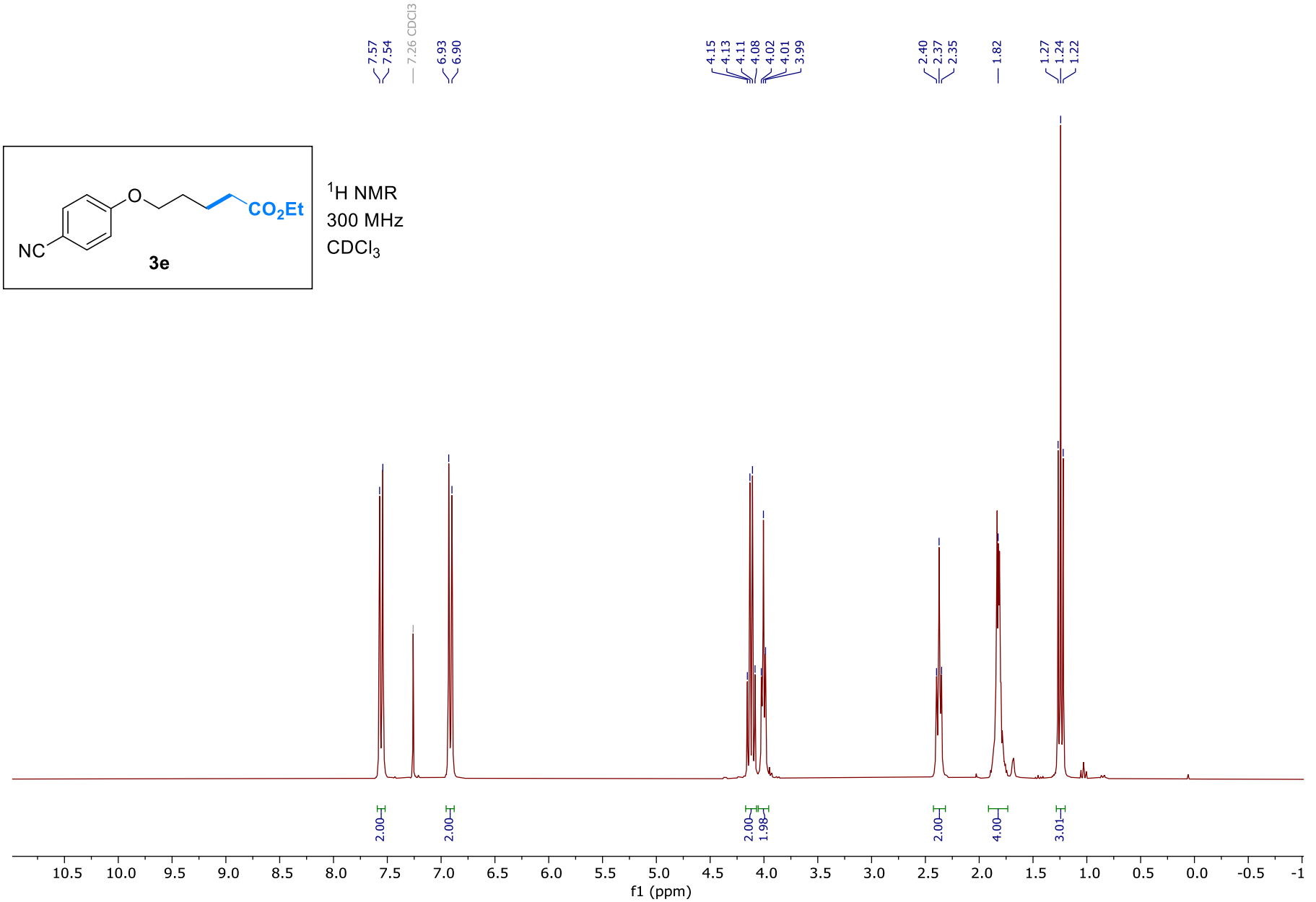
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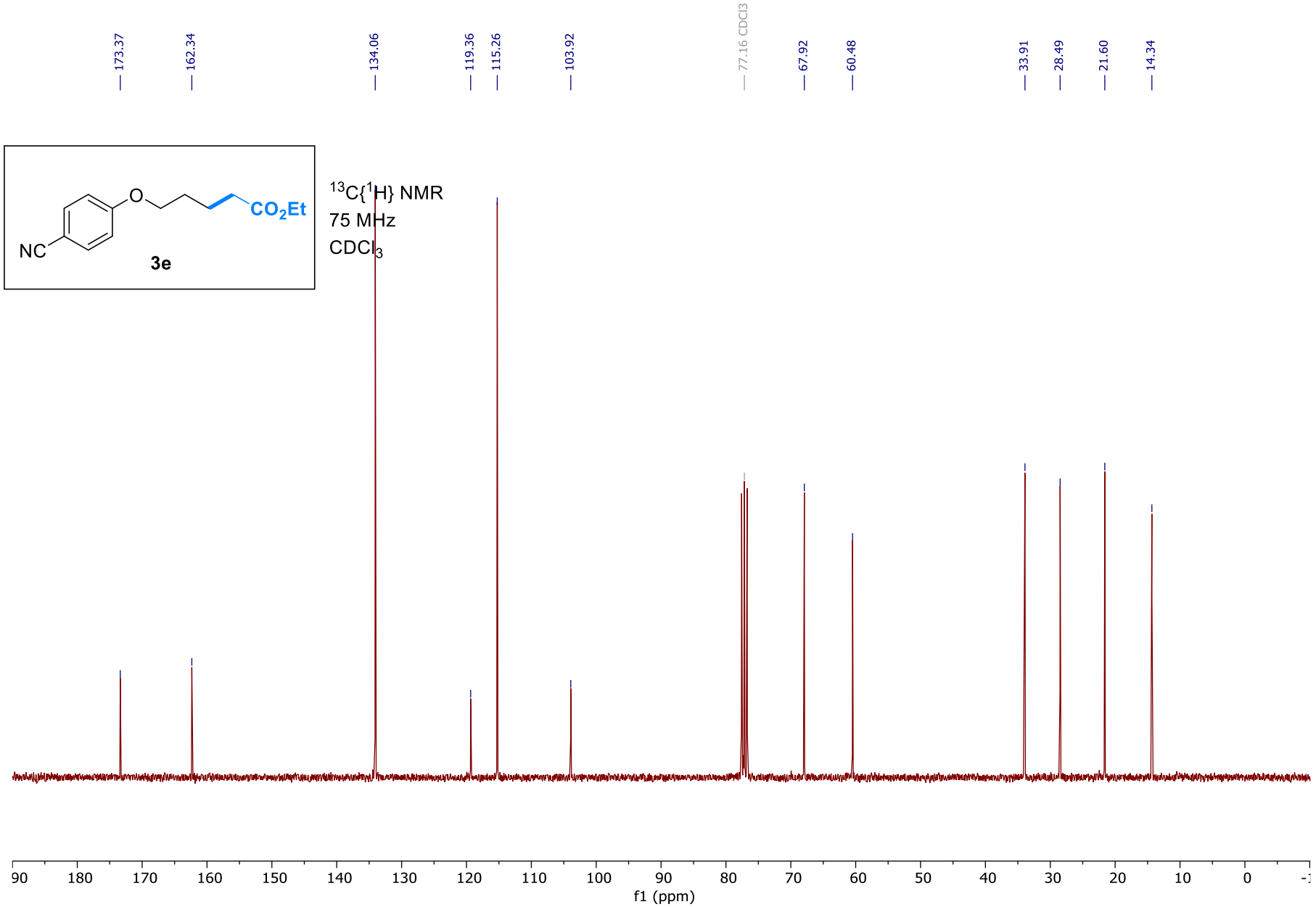
2.40
2.37
2.35
1.82
1.27
1.24
1.22
O
CO2Et
NC
3e
1H NMR
300 MHz
CDCl3
2.00
2.00
2.00
1.98
2.00
4.00
3.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)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14.34
NC
O
CO2Et
3e
13C{1H} NMR
75 MHz
CDCl3
90
180
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50
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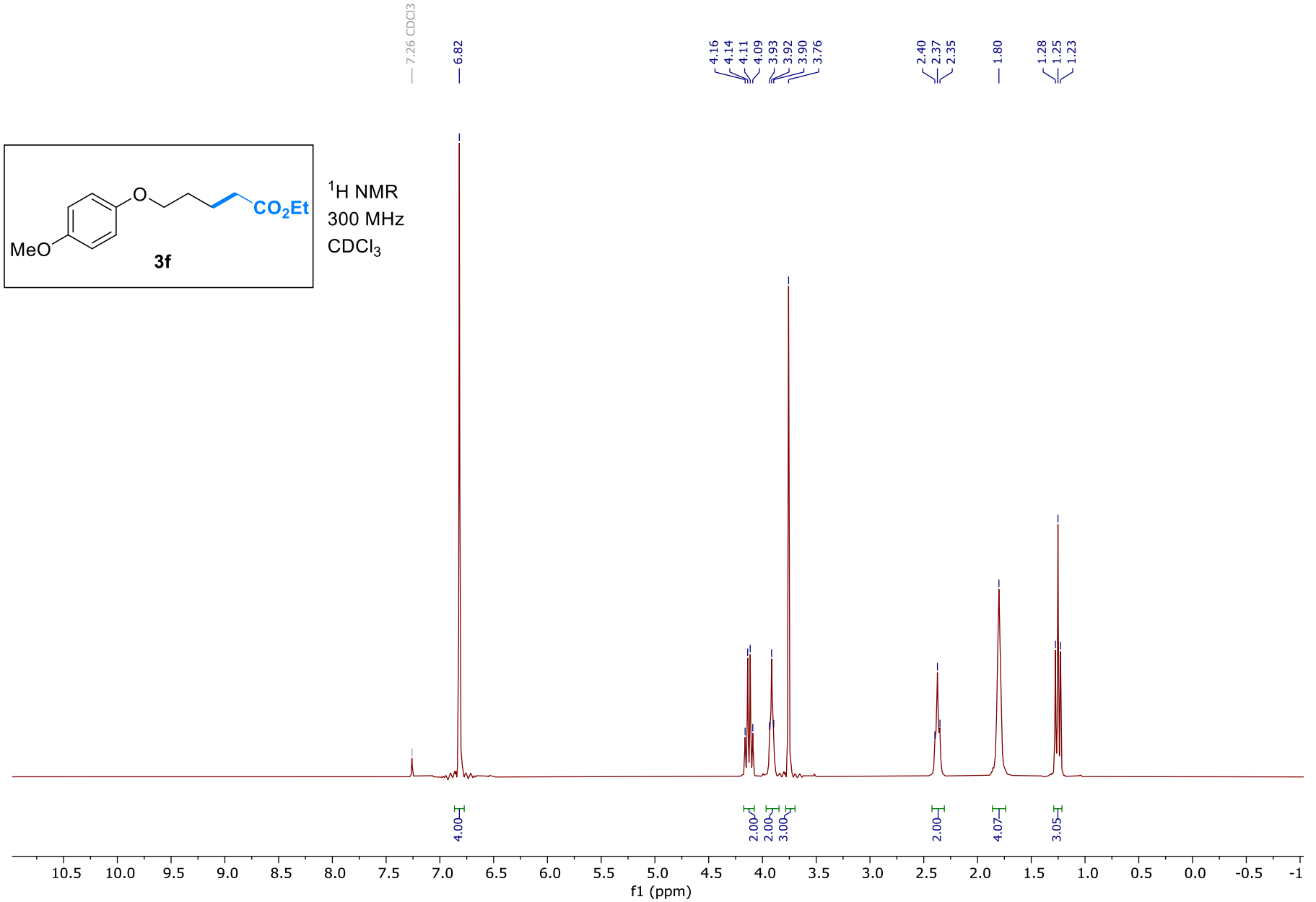
f1 (ppm)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2.35
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1.28
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3f
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2.00
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3.00
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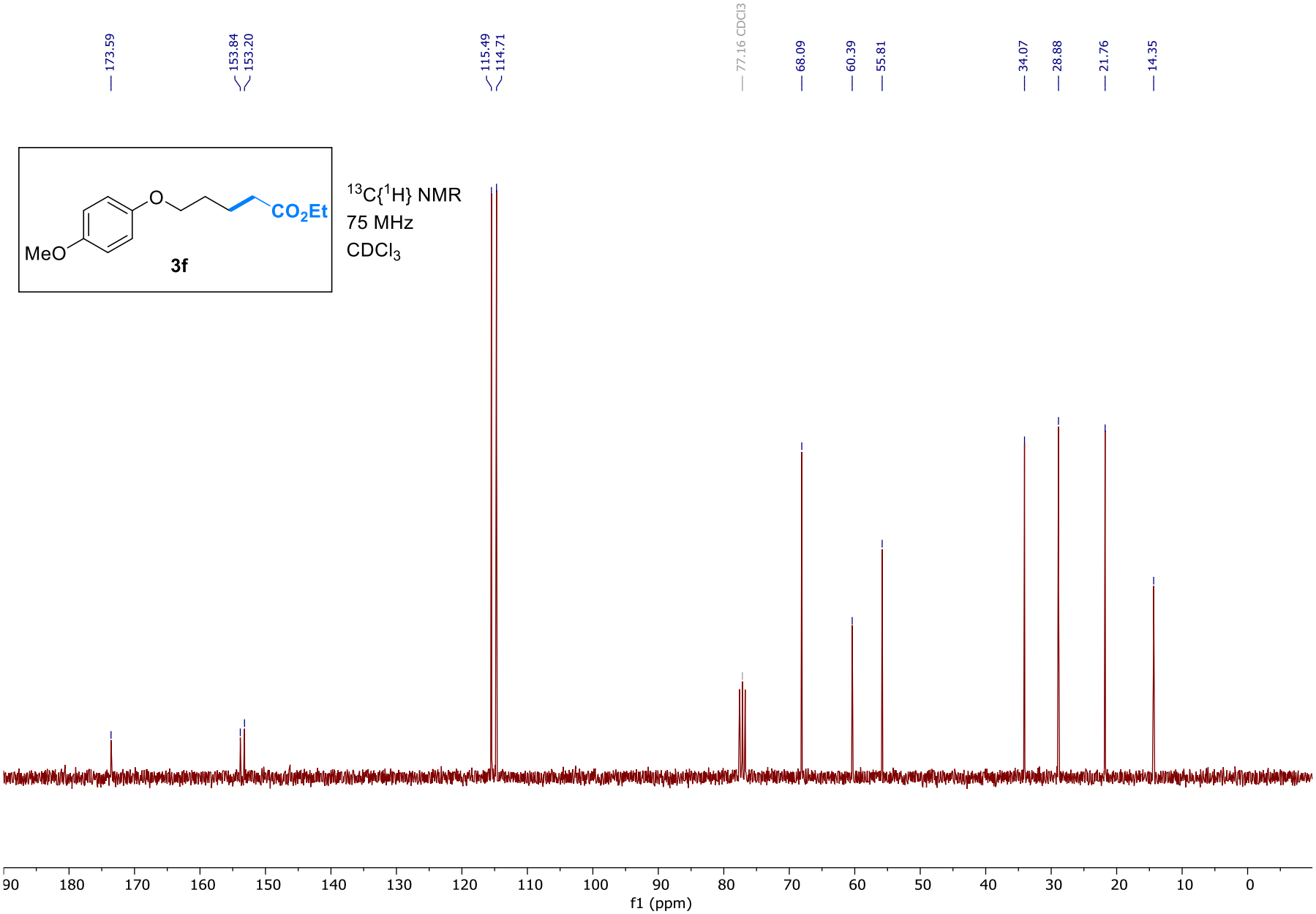
4.07
3.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)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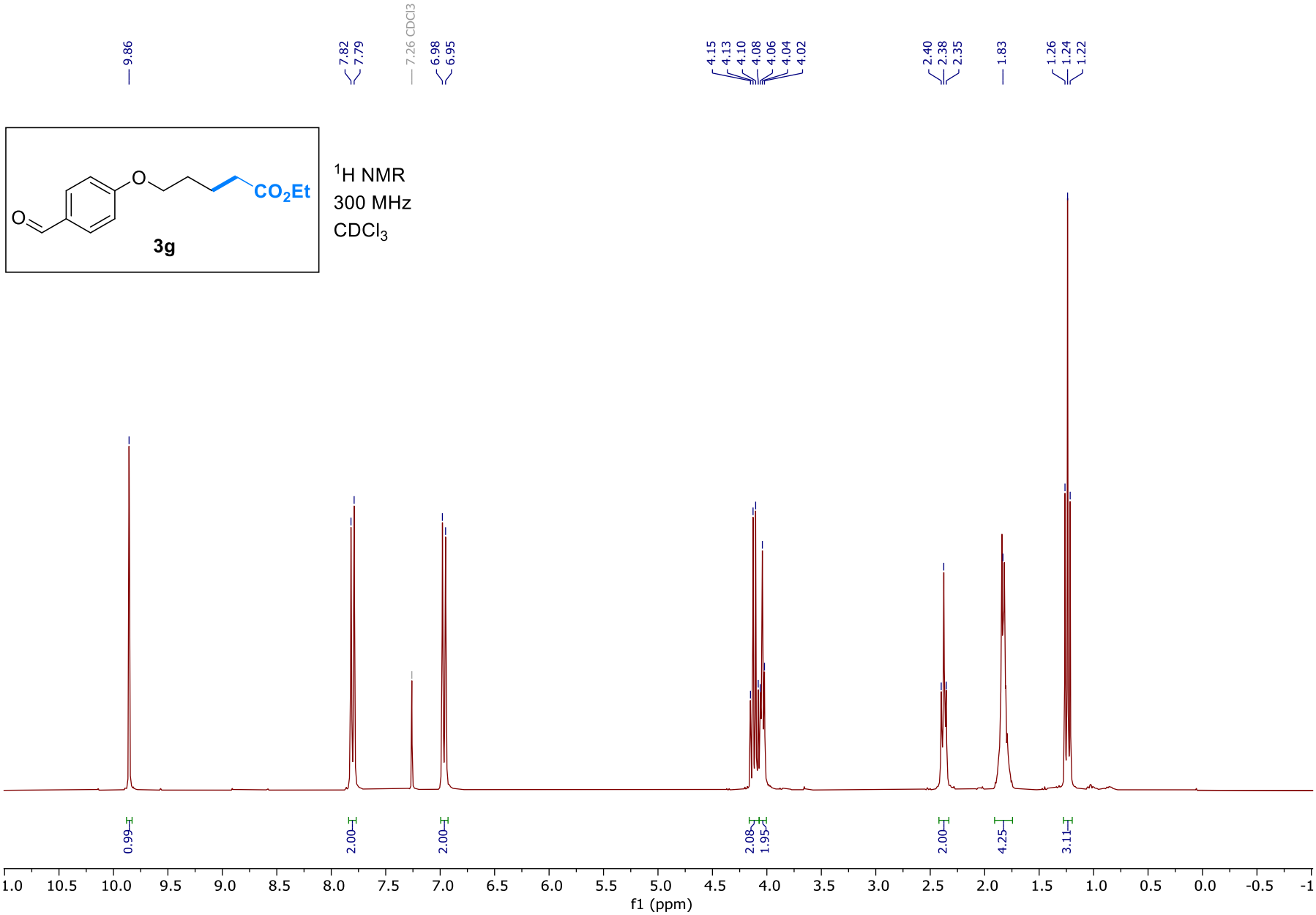
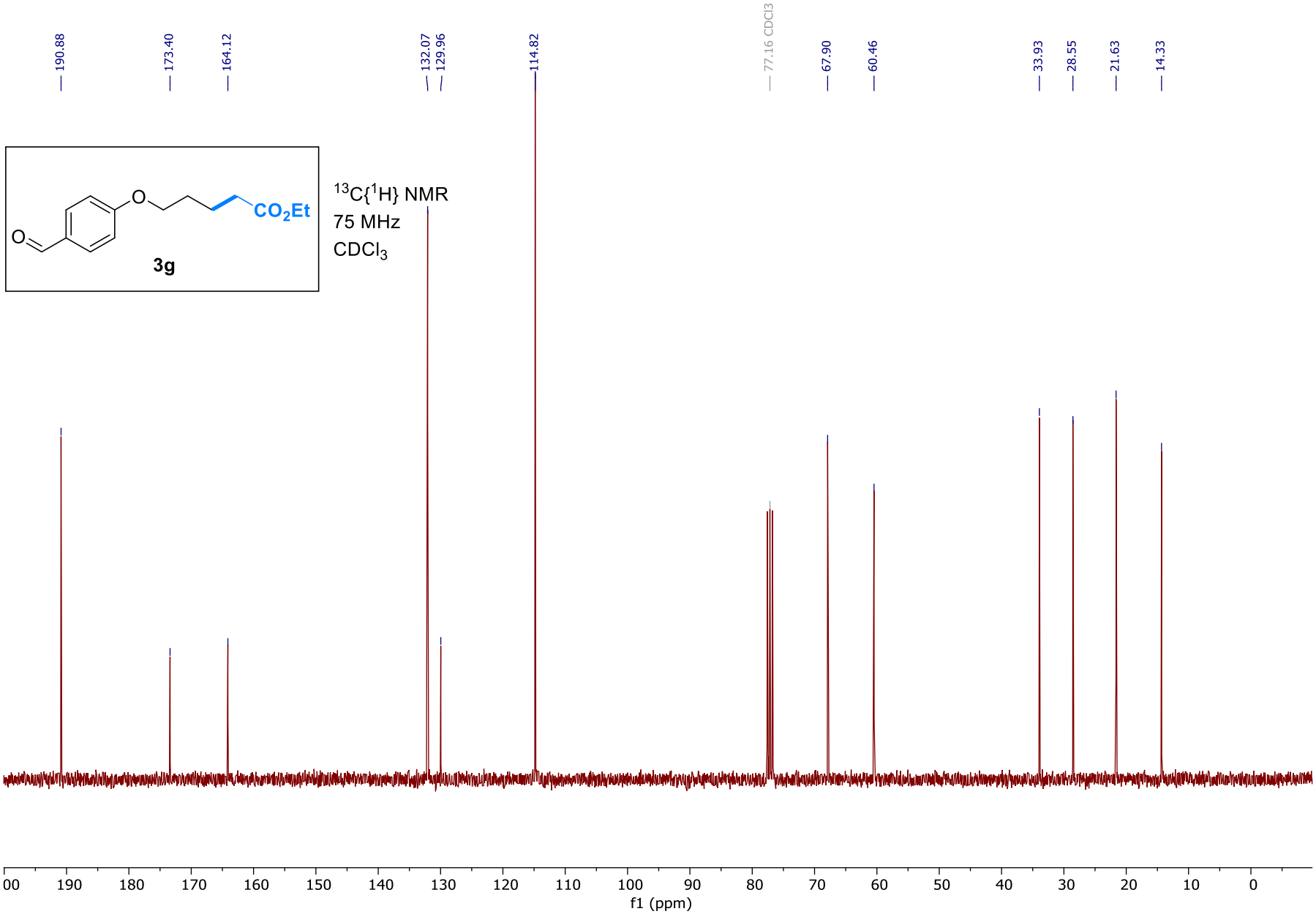
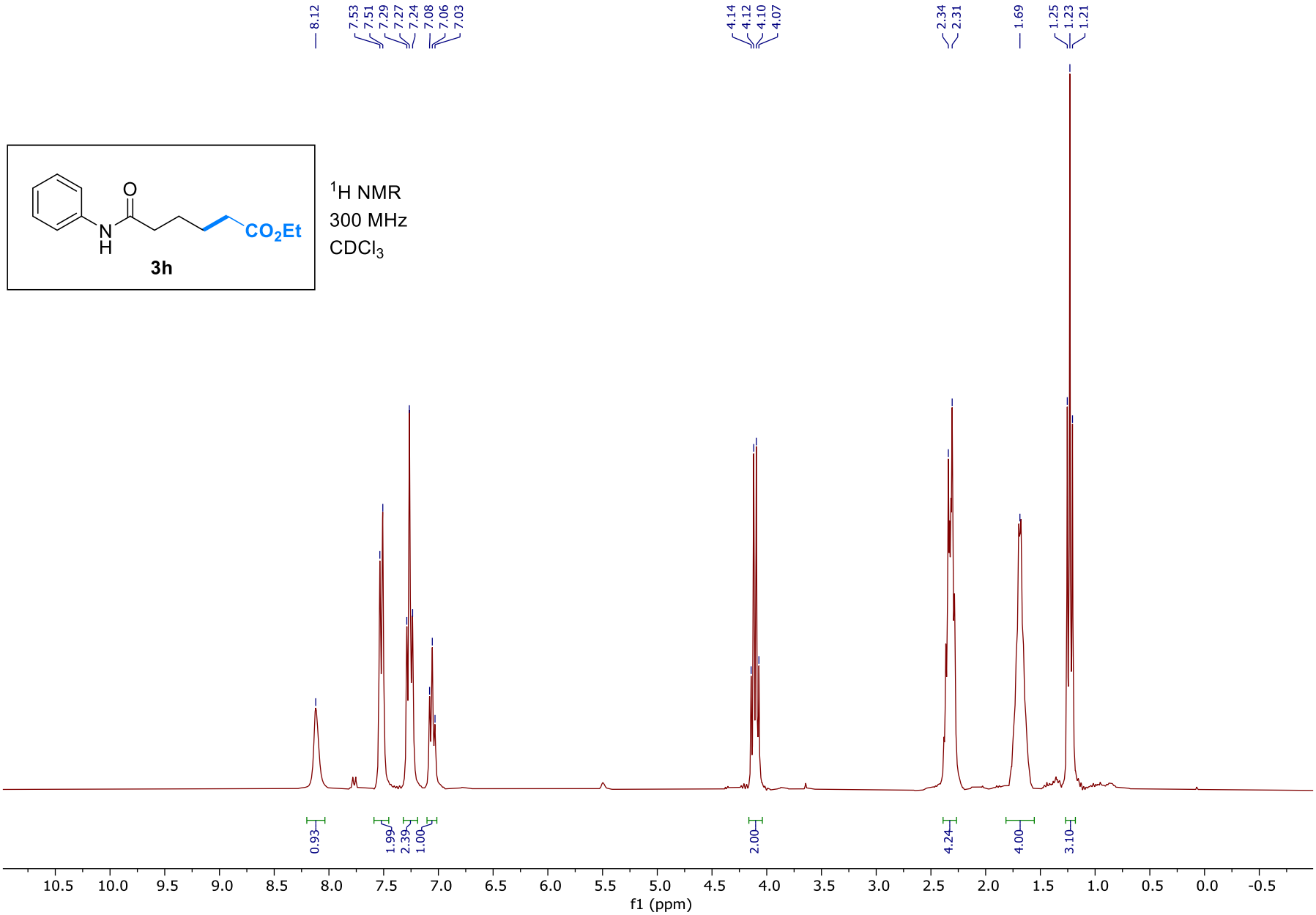
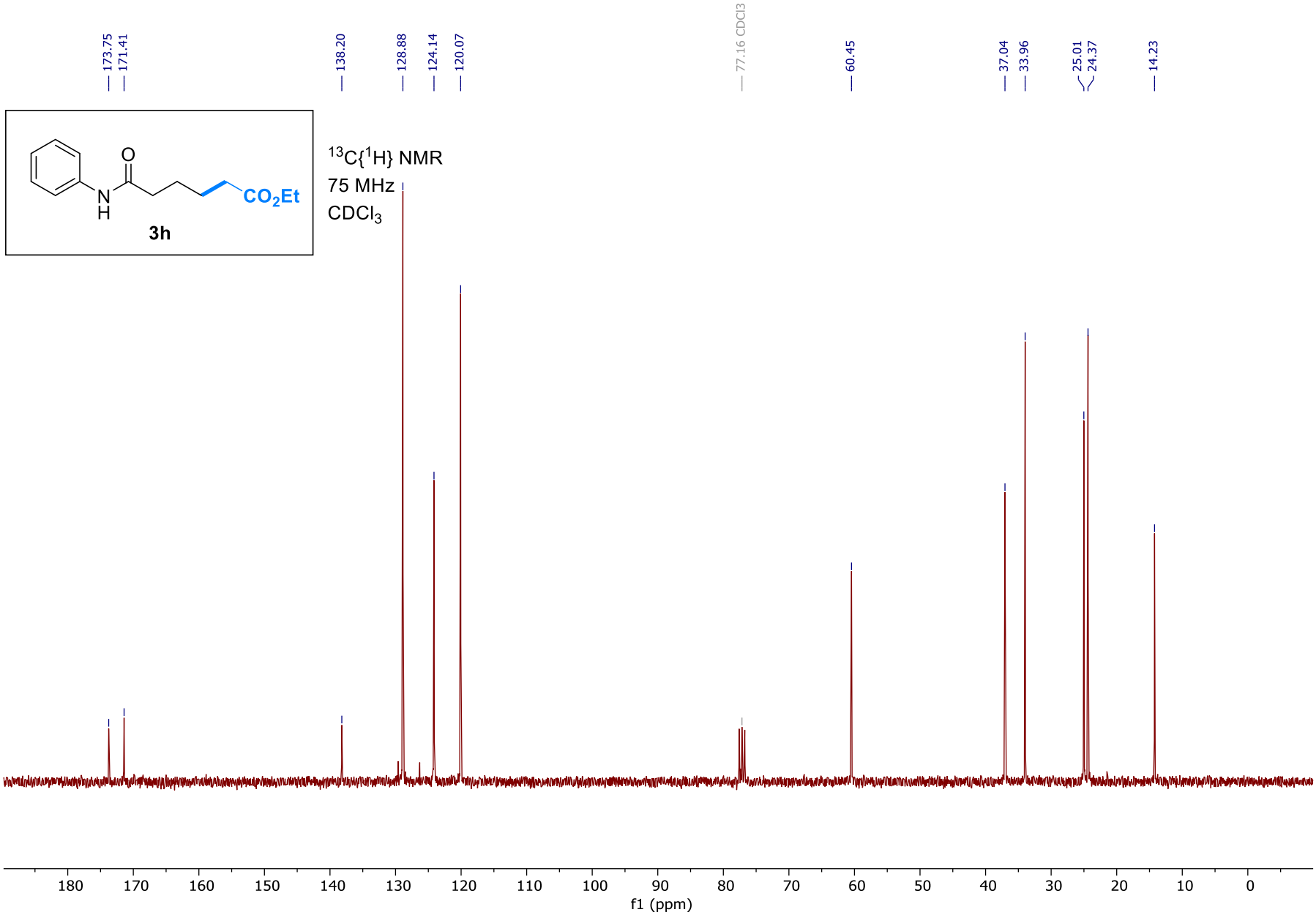
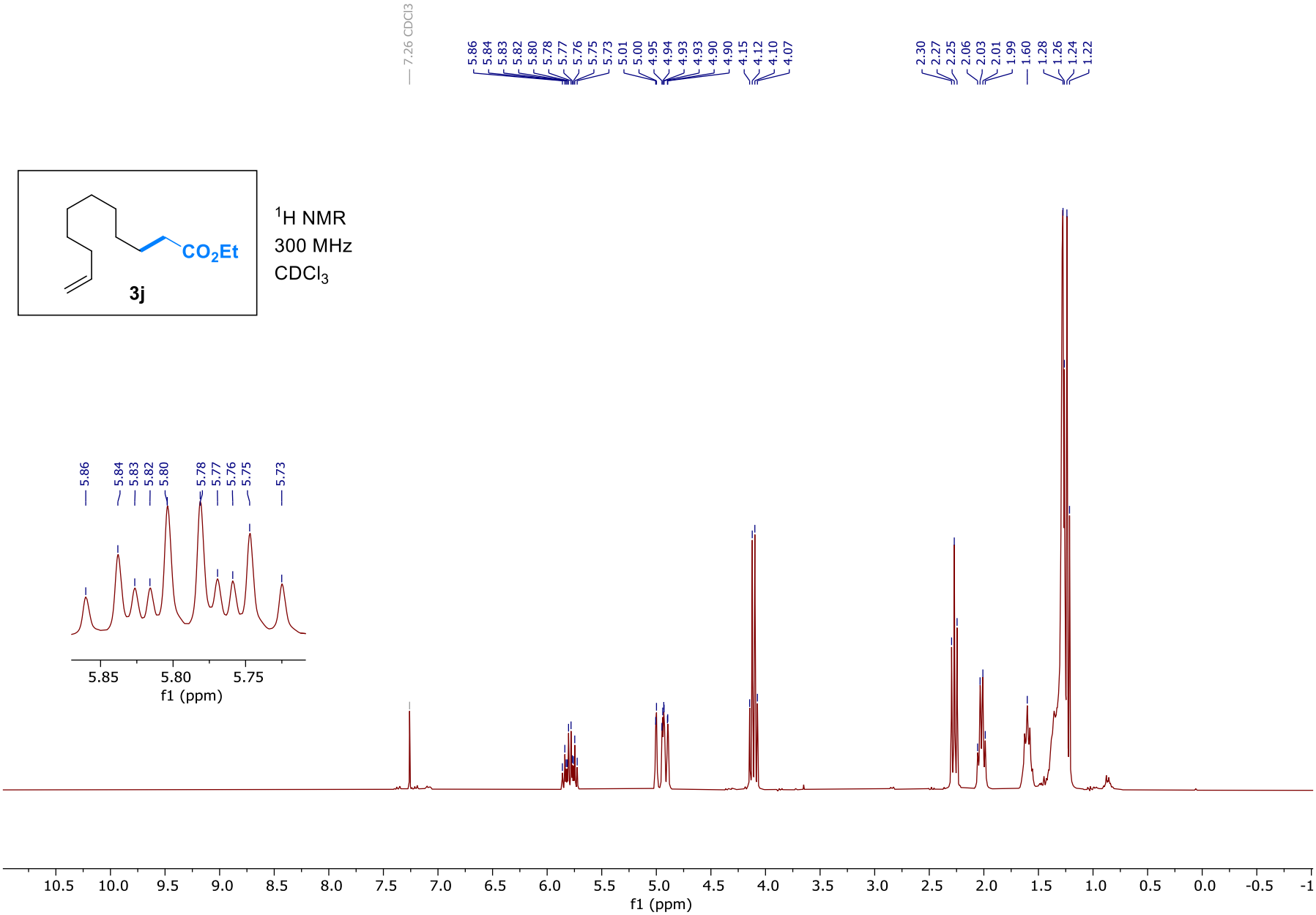
21.76
14.35
MeO
O
CO2Et
3f
13C{1H} NMR
75 MHz
CDCl3
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

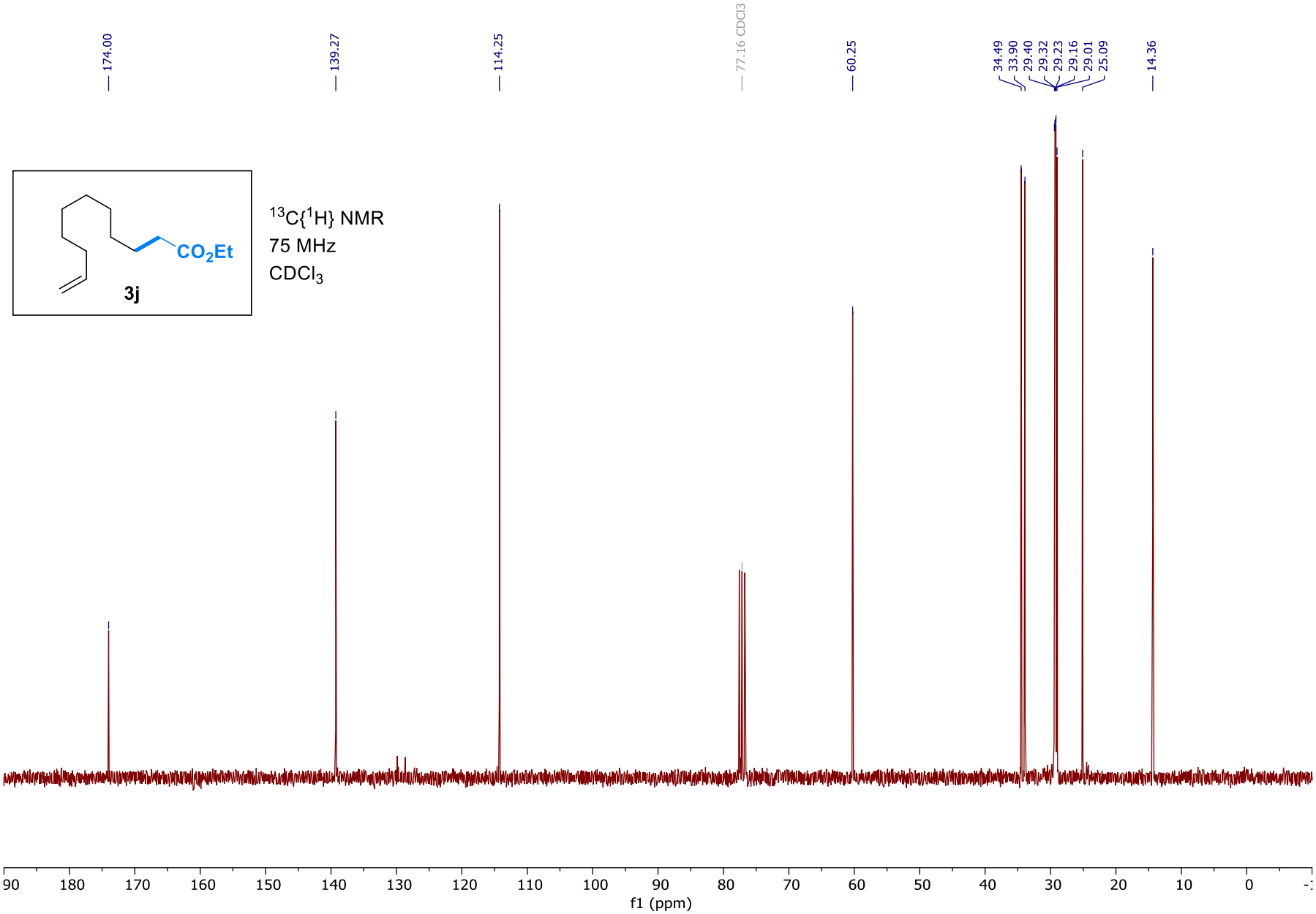

9.86
7.82
7.79
7.26 CDCl3
6.98
6.95
4.15
4.13
4.10
4.08
4.06
4.04
4.02
2.40
2.38
2.35
1.83
1.26
1.24
1.22
O
O
CO2Et
3g
1H NMR
300 MHz
CDCl3
0.99
2.00
2.00
2.08
1.95
2.00
4.25
3.11
f1 (ppm)

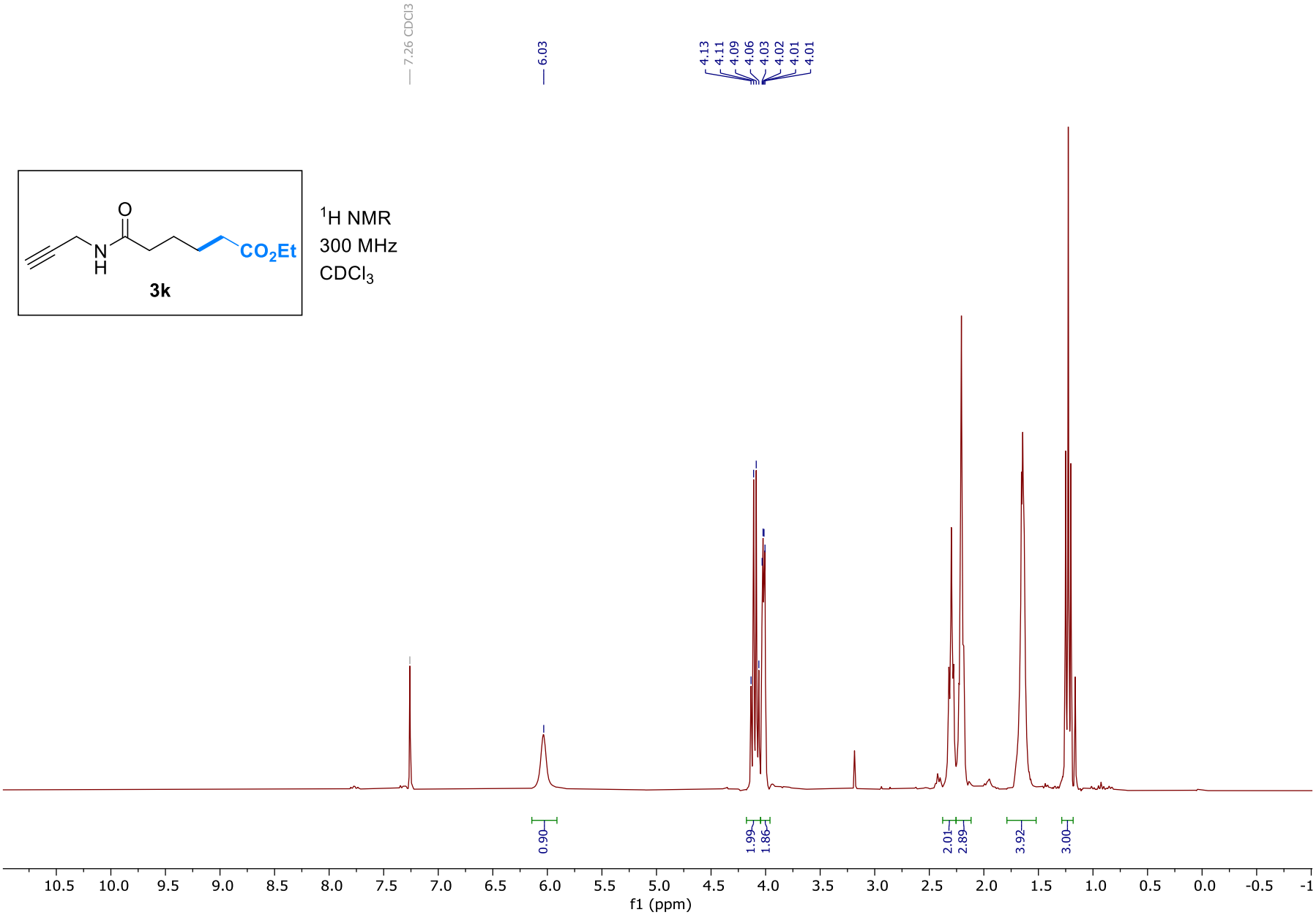

190.88
173.40
164.12
132.07
129.96
114.82
77.16 CDCl3
67.90
60.46
33.93
28.55
21.63
14.33
O
O
CO2Et
3g
13C{1H} NMR
75 MHz
CDCl3
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

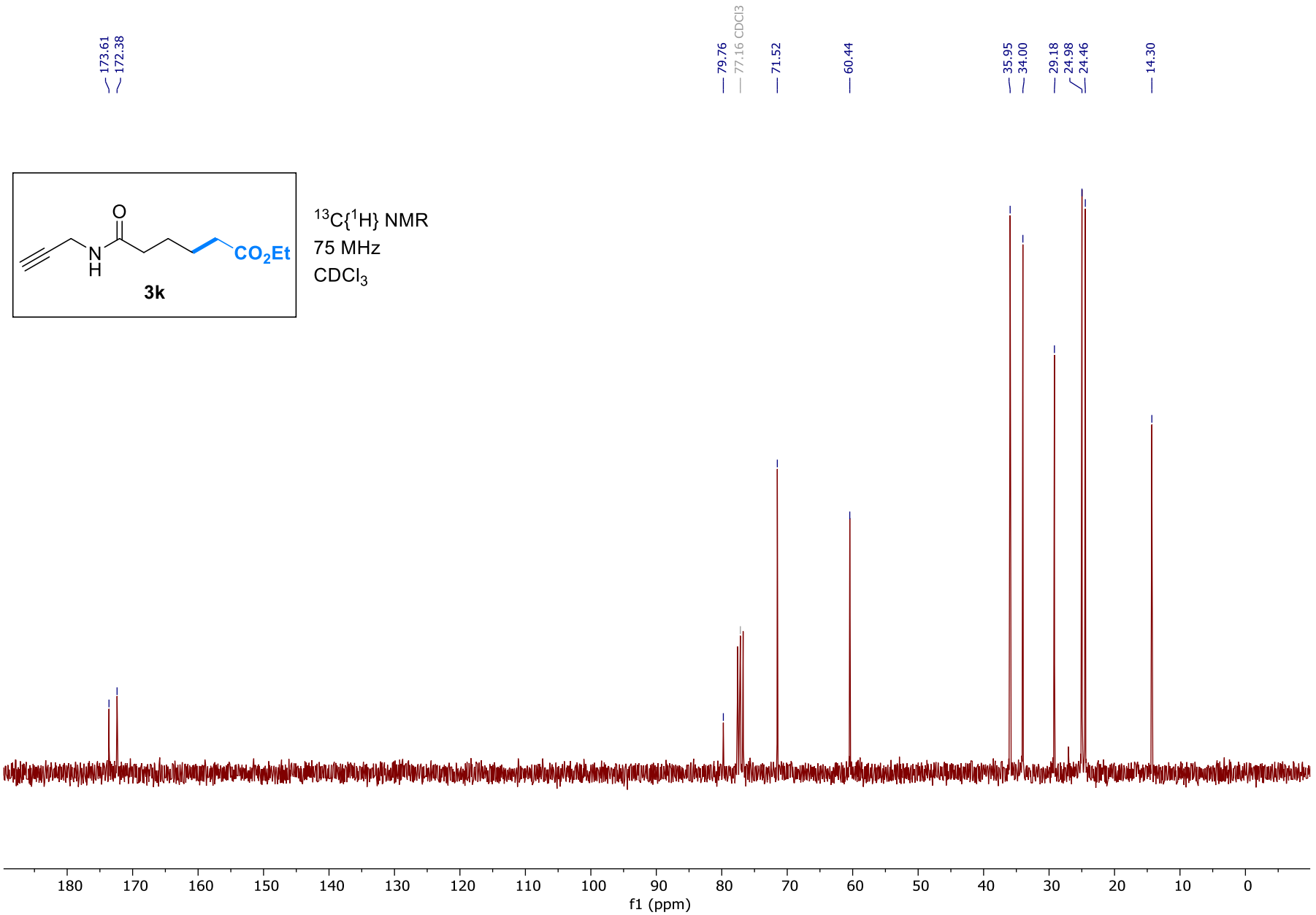

8.12
7.53
7.51
7.29
7.27
7.24
7.08
7.06
7.03
4.14
4.12
4.10
4.07
2.34
2.31
1.69
1.25
1.23
1.21
O
N
H
CO2Et
3h
1H NMR
300 MHz
CDCl3
0.93
1.99
2.39
1.00
2.00
4.24
4.00
3.10
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

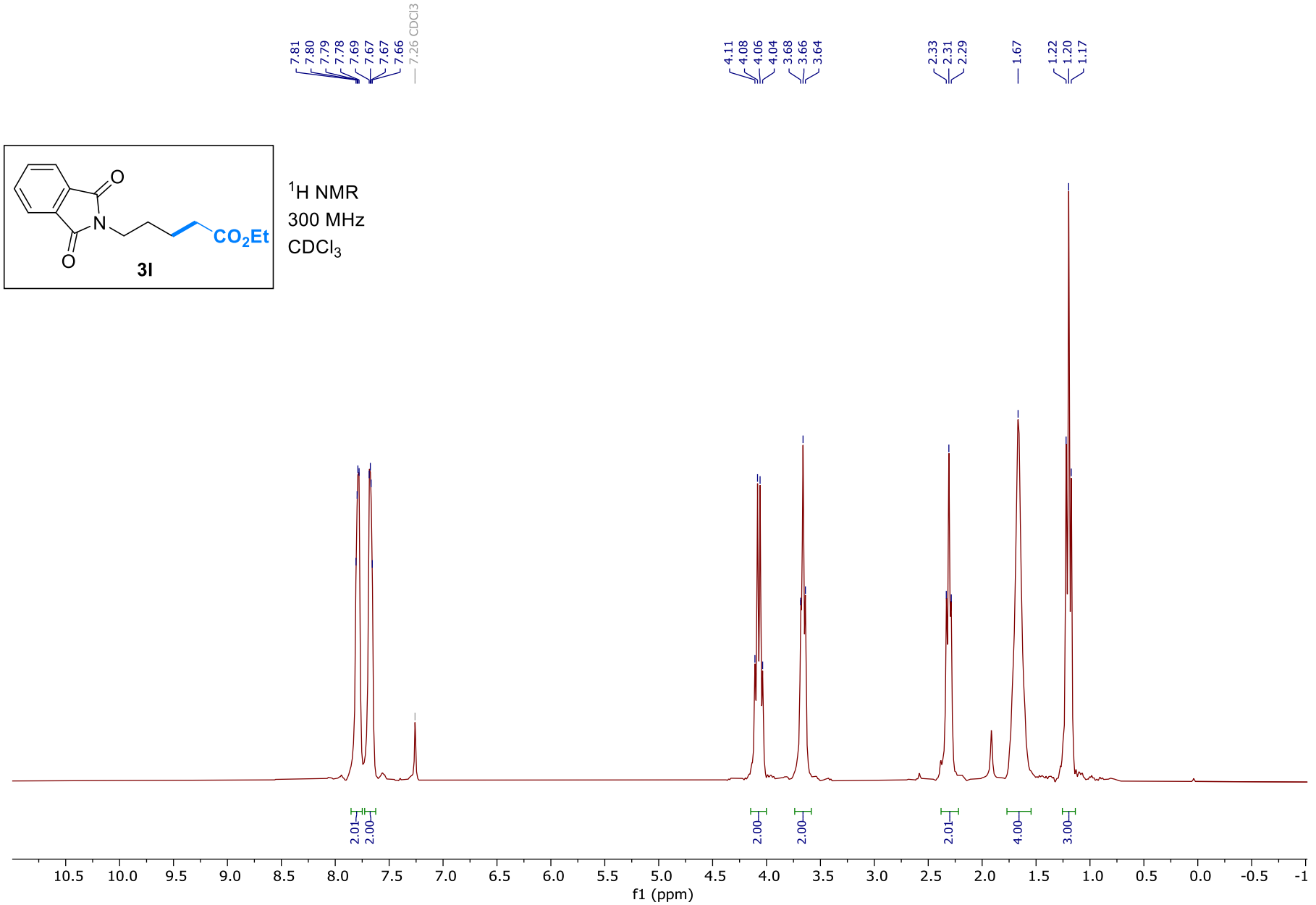

173.75
171.41
138.20
128.88
124.14
120.07
77.16 CDCl3
60.45
37.04
33.96
25.01
24.37
14.23
O
N
H
CO2Et
3h
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

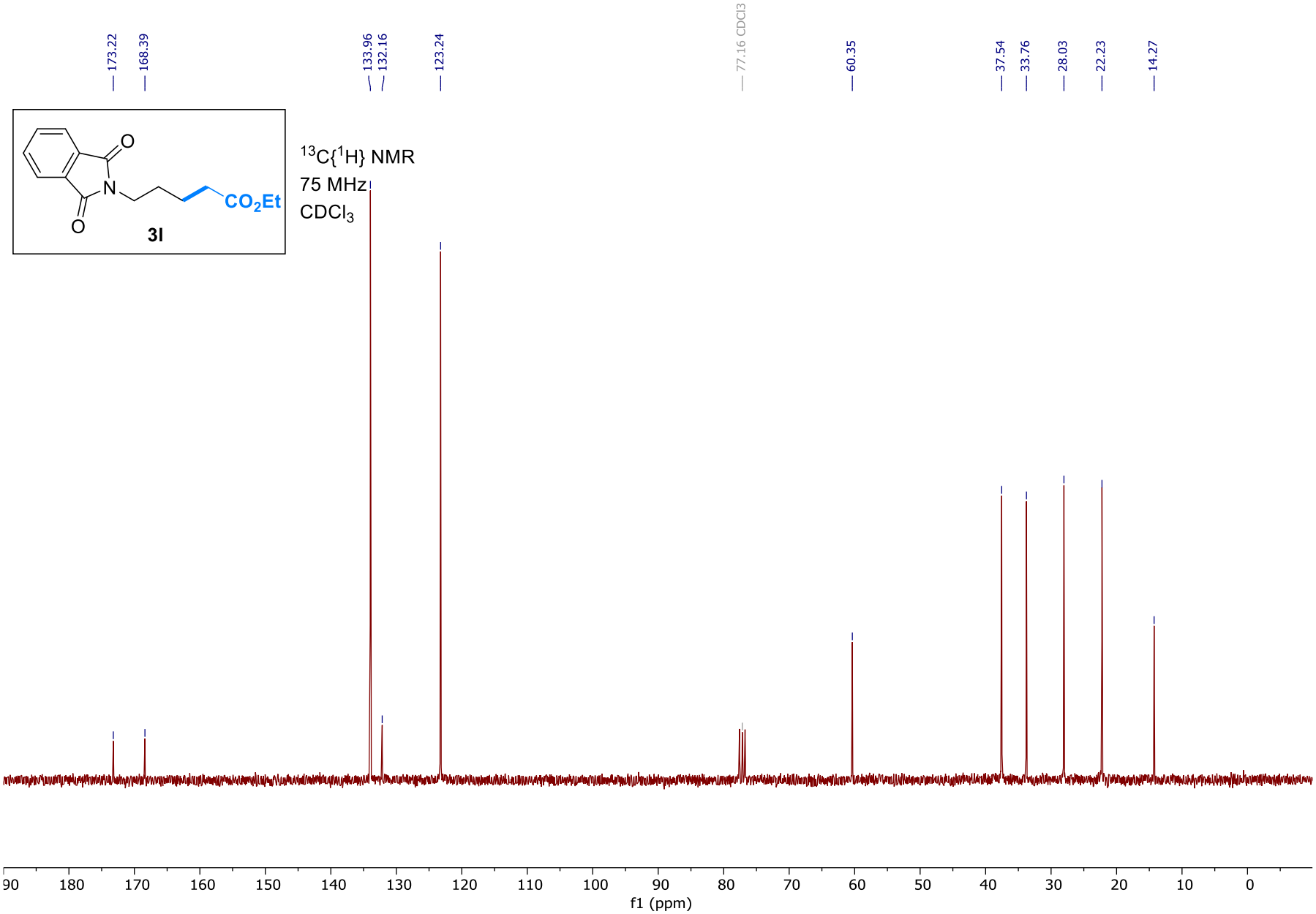

7.26 CDCl3
5.86
5.84
5.83
5.82
5.80
5.78
5.77
5.76
5.75
5.73
5.01
5.00
4.95
4.94
4.93
4.93
4.90
4.90
4.15
4.12
4.10
4.07
2.30
2.27
2.25
2.06
2.03
2.01
1.99
1.60
1.28
1.26
1.24
1.22
CO2Et
3j
1H NMR
300 MHz
CDCl3
5.85
5.80
5.75
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

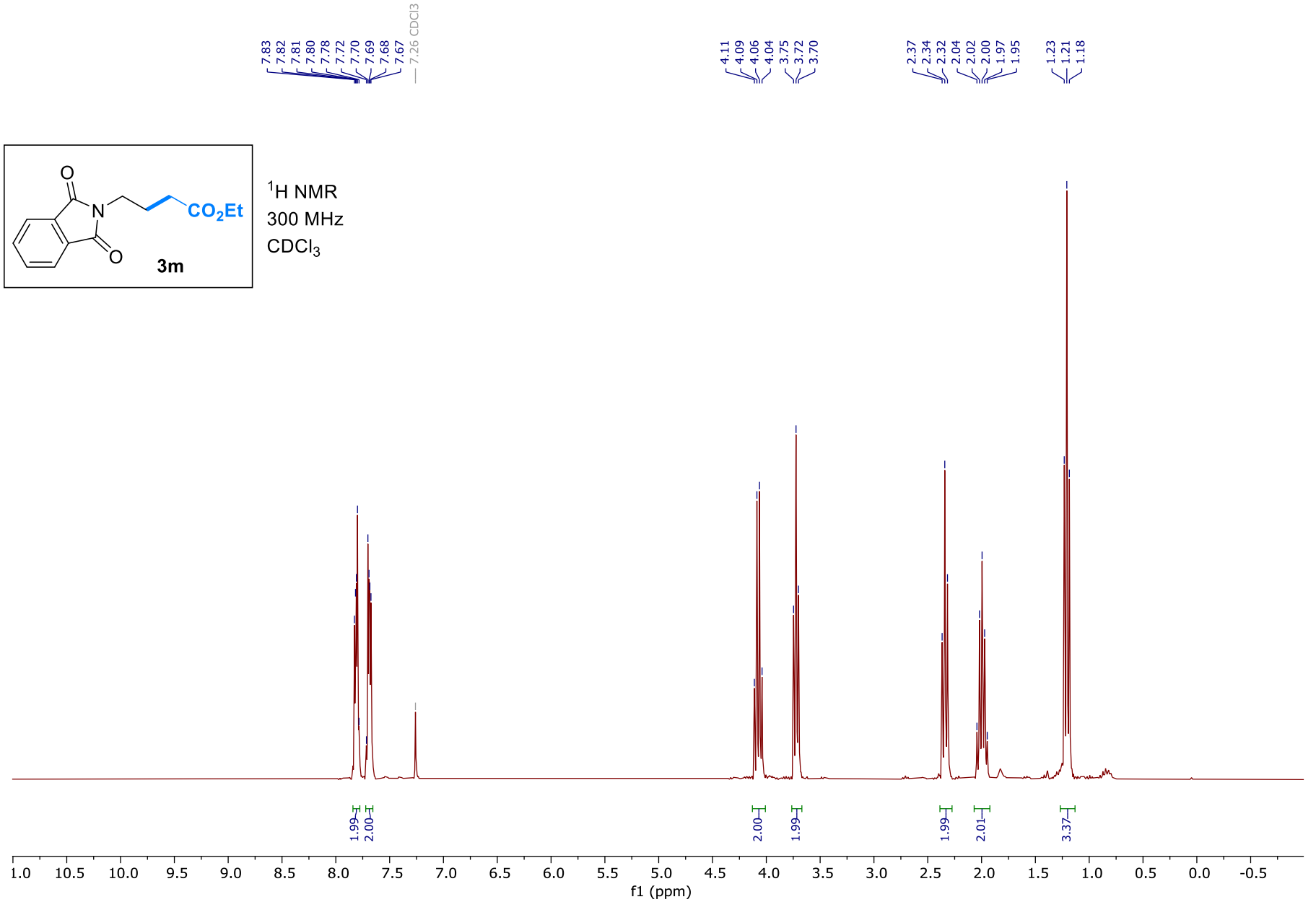

174.00
139.27
114.25
77.16 CDCl3
60.25
34.49
33.90
29.40
29.32
29.23
29.16
29.01
25.09
14.36
CO2Et
3j
13C{1H} NMR
75 MHz
CDCl3
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

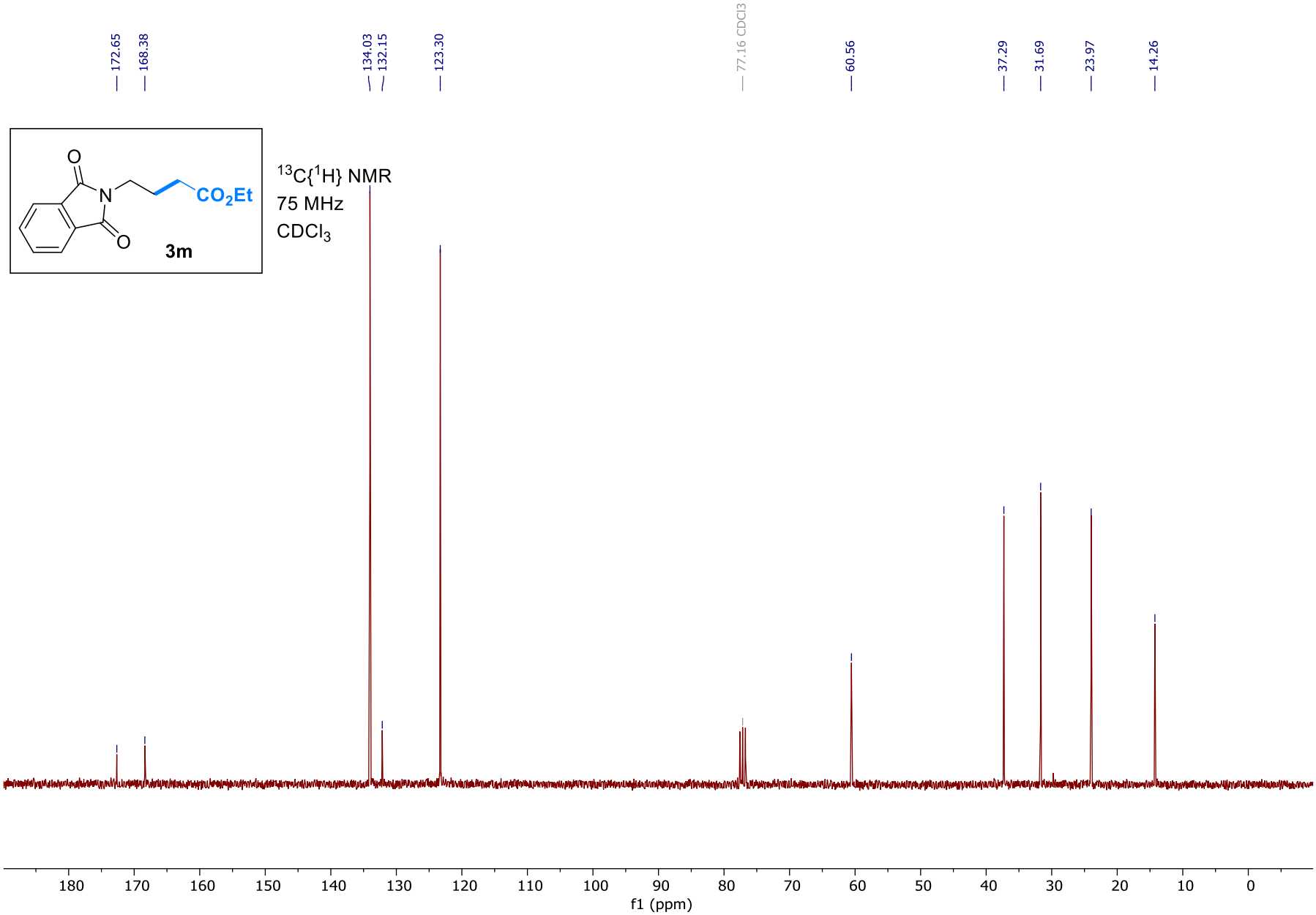

7.26 CDCl3
6.03
4.13
4.11
4.09
4.06
4.03
4.02
4.01
4.01
O
N
H
CO2Et
3k
1H NMR
300 MHz
CDCl3
0.90
1.99
1.86
2.01
2.89
3.92
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

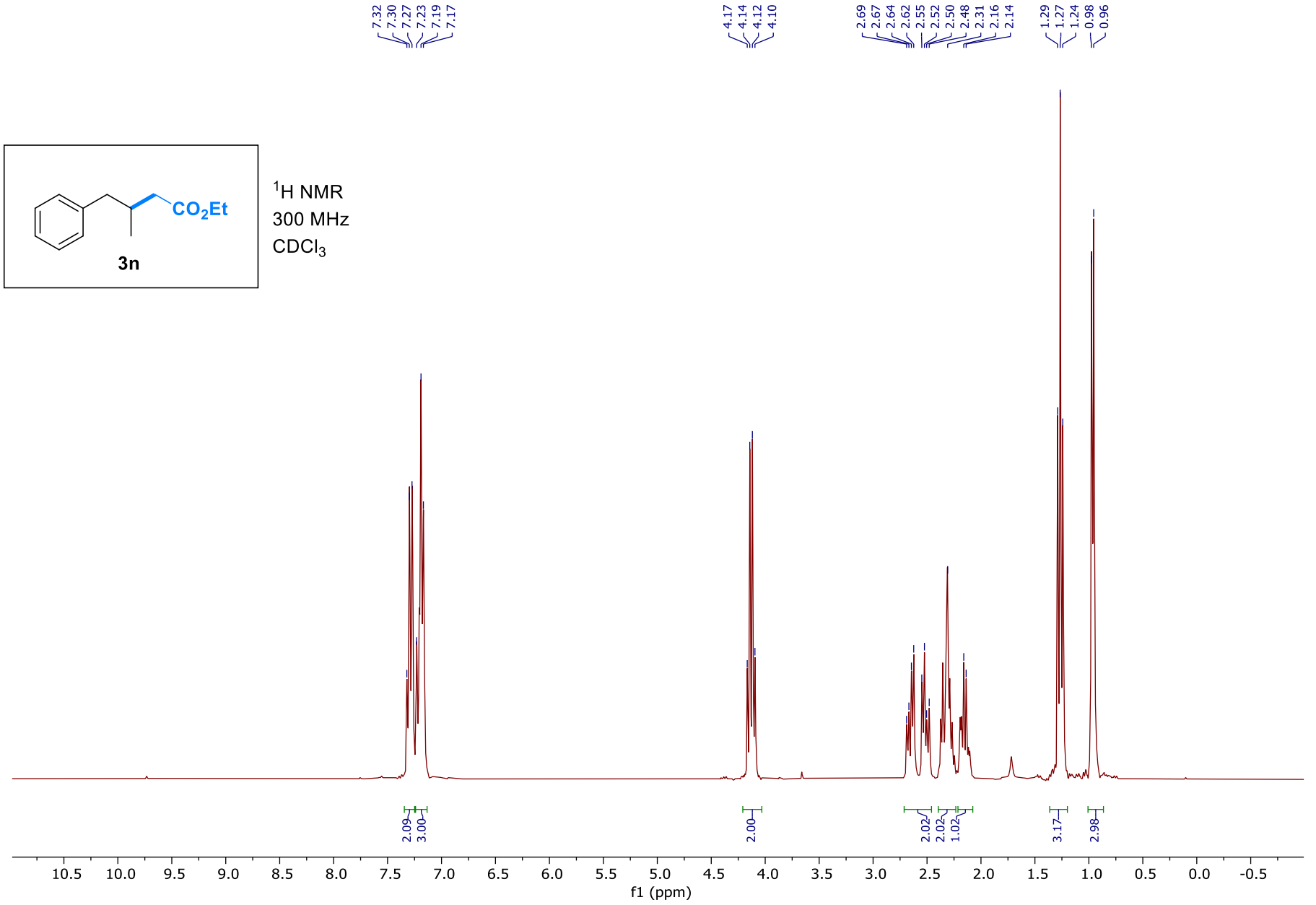

173.61
172.38
79.76
77.16 CDCl3
71.52
60.44
35.95
34.00
29.18
24.98
24.46
14.30
O
N
H
CO2Et
3k
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

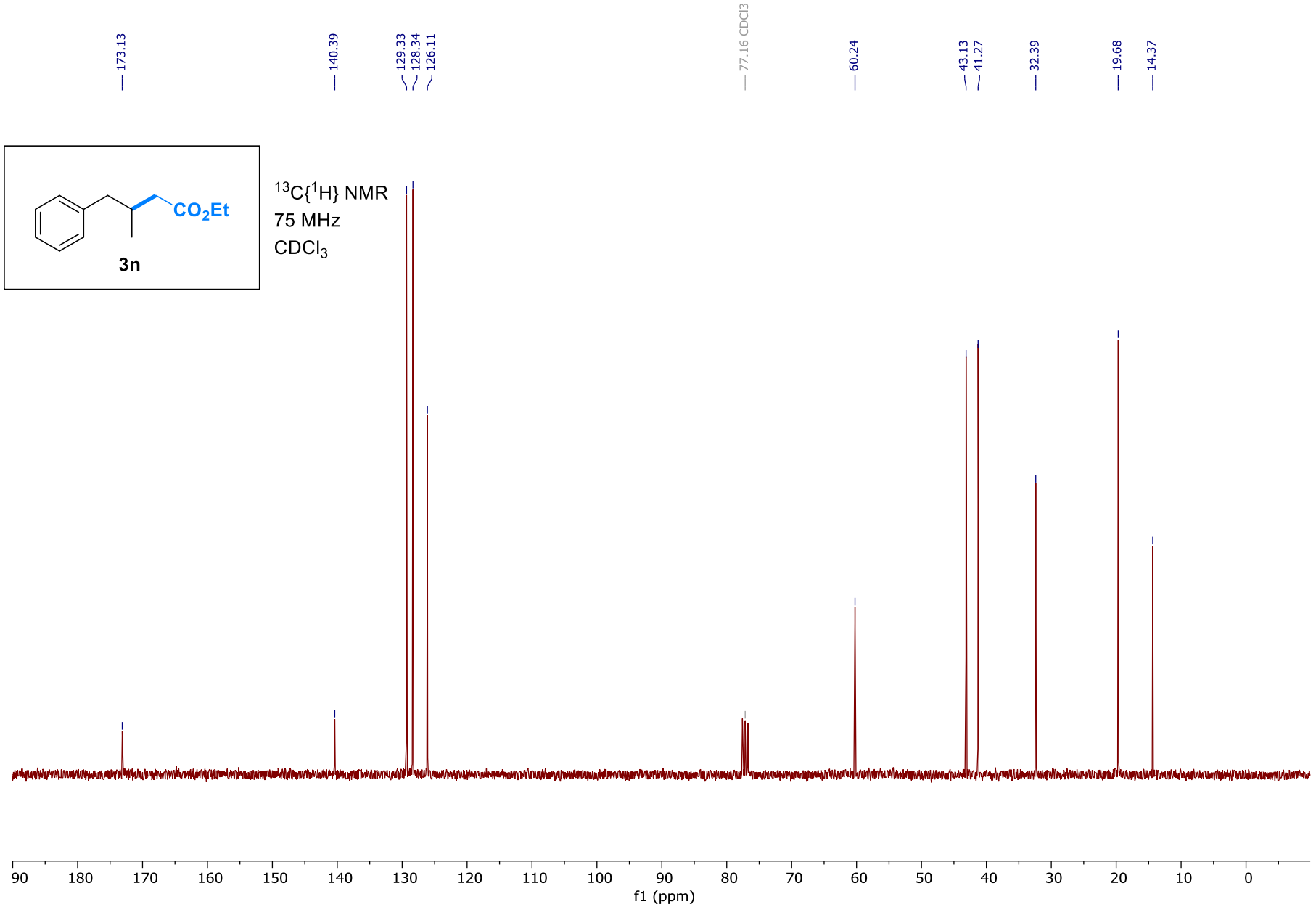

7.81
7.80
7.79
7.78
7.69
7.67
7.67
7.66
7.26 CDCl3
4.11
4.08
4.06
4.04
3.68
3.66
3.64
2.33
2.31
2.29
1.67
1.22
1.20
1.17
O
N
O
CO2Et
3l
1H NMR
300 MHz
CDCl3
2.01
2.00
2.00
2.00
2.01
4.00
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

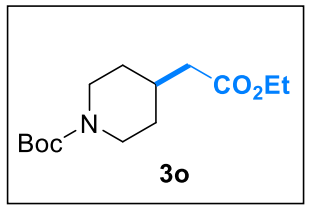

173.22
168.39
133.96
132.16
123.24
77.16 CDCl3
60.35
37.54
33.76
28.03
22.23
14.27
O
N
O
CO2Et
3l
13C{1H} NMR
75 MHz
CDCl3
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.83
7.82
7.81
7.80
7.78
7.72
7.70
7.69
7.68
7.67
7.26 CDCl3
4.11
4.09
4.06
4.04
3.75
3.72
3.70
2.37
2.34
2.32
2.04
2.02
2.00
1.97
1.95
1.23
1.21
1.18
O
N
O
CO2Et
3m
1H NMR
300 MHz
CDCl3
1.99
2.00
2.00
1.99
1.99
2.01
3.37
1.0
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)


172.65
168.38
134.03
132.15
123.30
77.16 CDCl3
60.56
37.29
31.69
23.97
14.26
O
N
O
CO2Et
3m
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

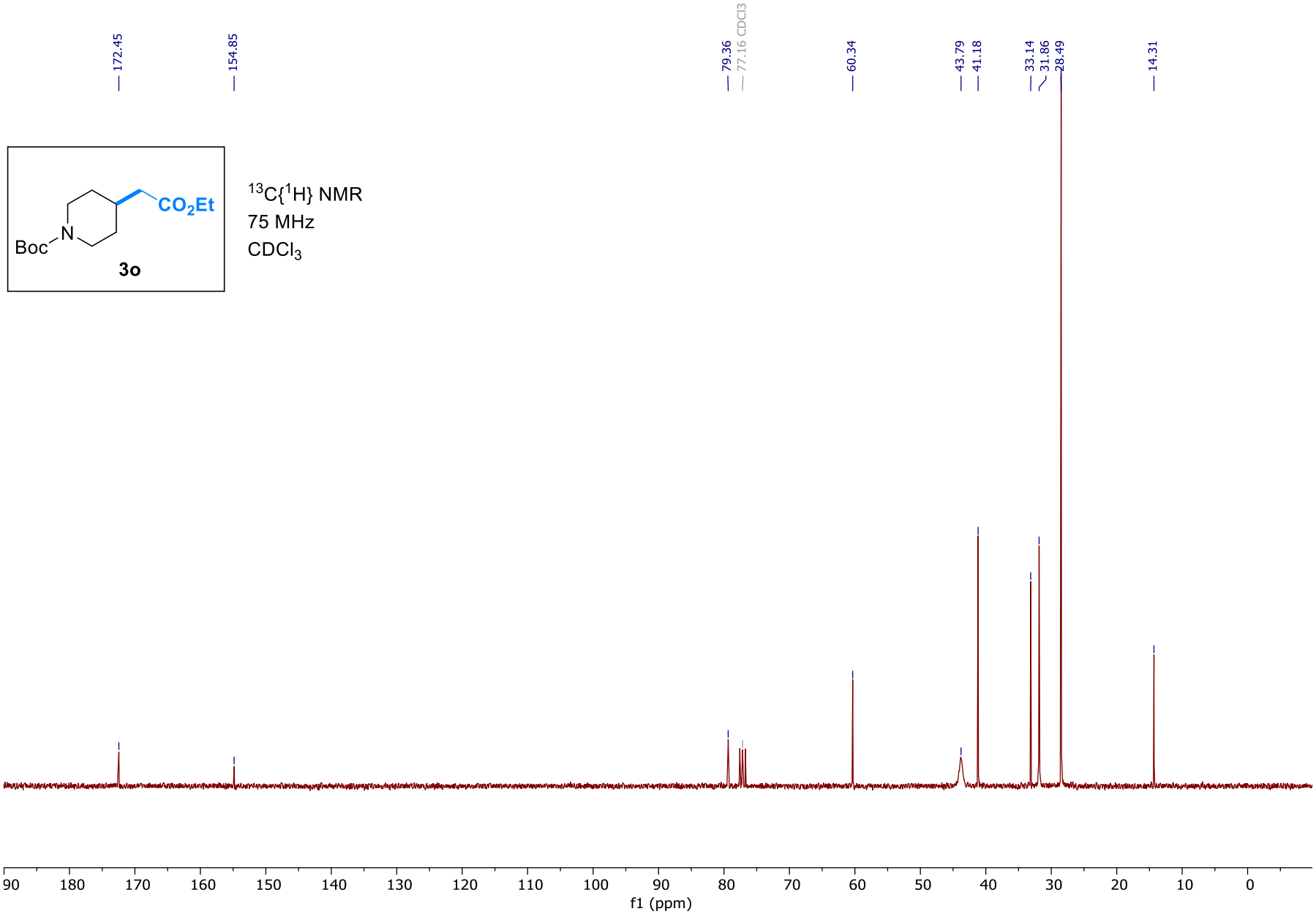

7.32
7.30
7.27
7.23
7.19
7.17
4.17
4.14
4.12
4.10
2.69
2.67
2.64
2.62
2.55
2.52
2.50
2.48
2.31
2.16
2.14
1.29
1.27
1.24
0.98
0.96
CO2Et
3n
1H NMR
300 MHz
CDCl3
2.09
3.00
2.00
2.02
2.02
1.02
3.17
2.98
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

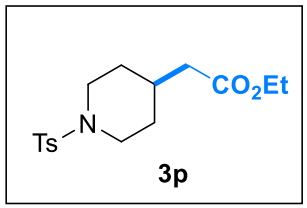

173.13
140.39
129.33
128.34
126.11
77.16 CDCl3
60.24
43.13
41.27
32.39
19.68
14.37
CO2Et
3n
13C{1H} NMR
75 MHz
CDCl3
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



3o

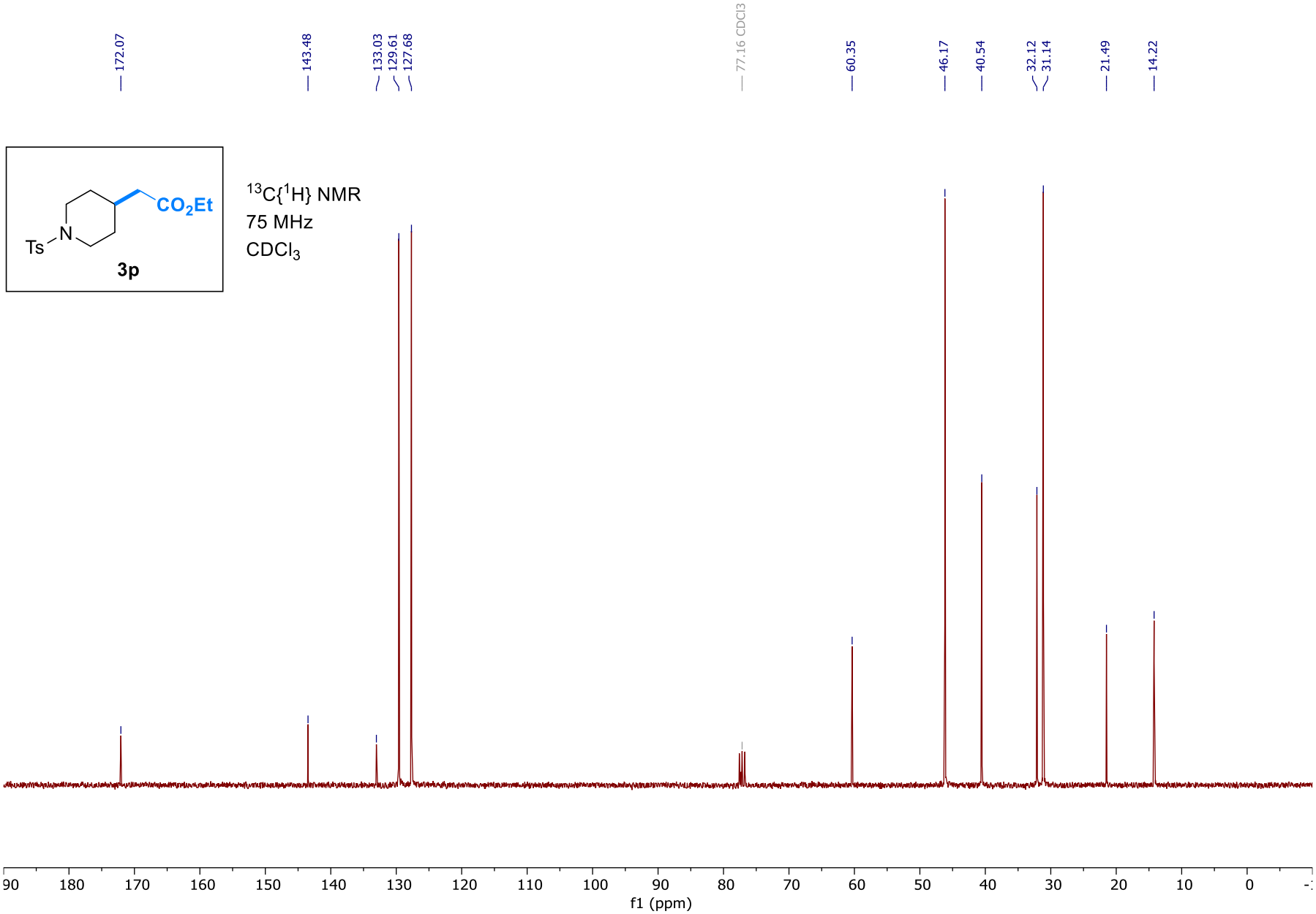
^{1}H NMR
300 MHz
$CDCl_3$

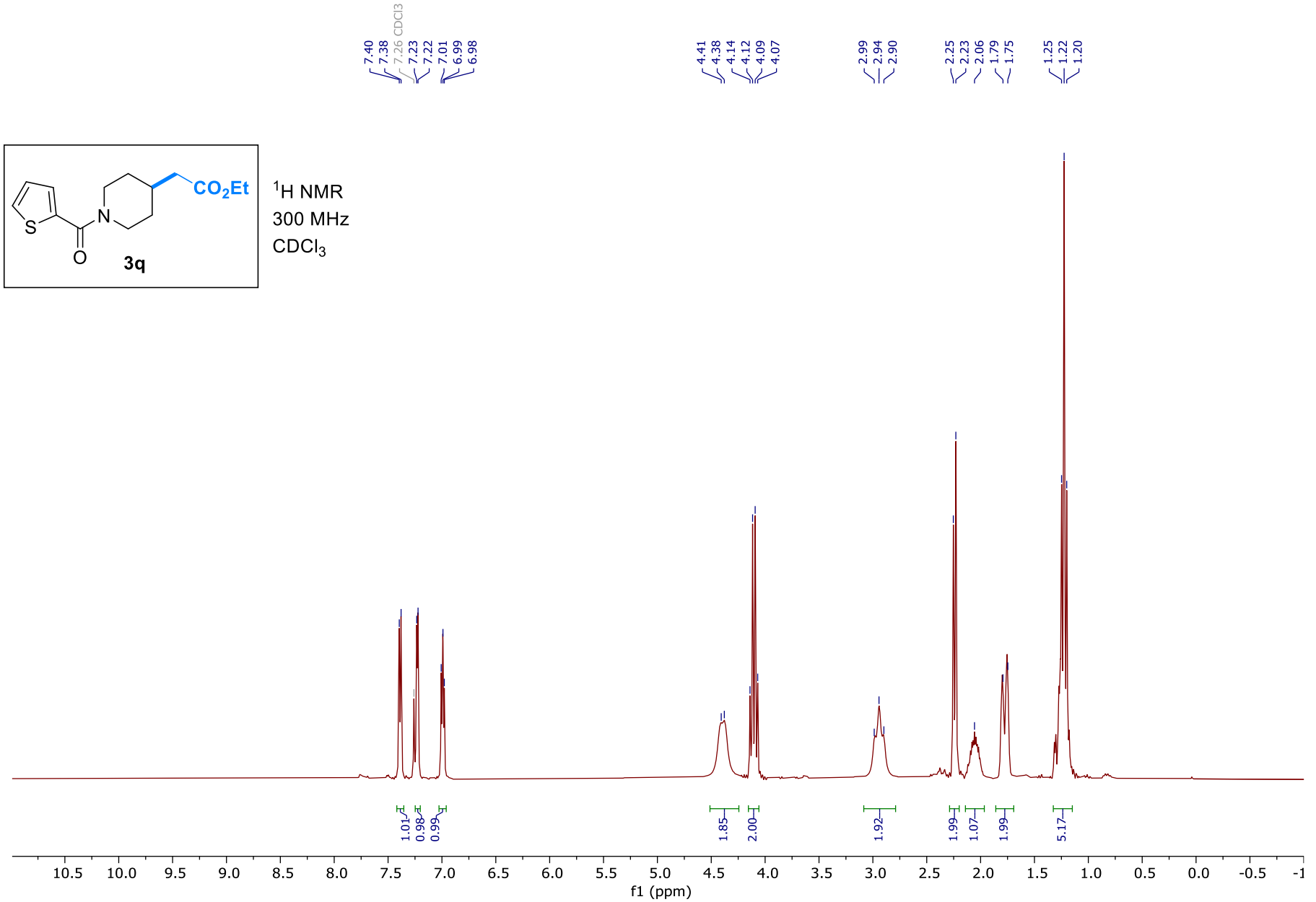

172.45
154.85
79.36
77.16 CDCl3
60.34
43.79
41.18
33.14
31.86
28.49
14.31
CO2Et
Boc
N
3o
13C{1H} NMR
75 MHz
CDCl3
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

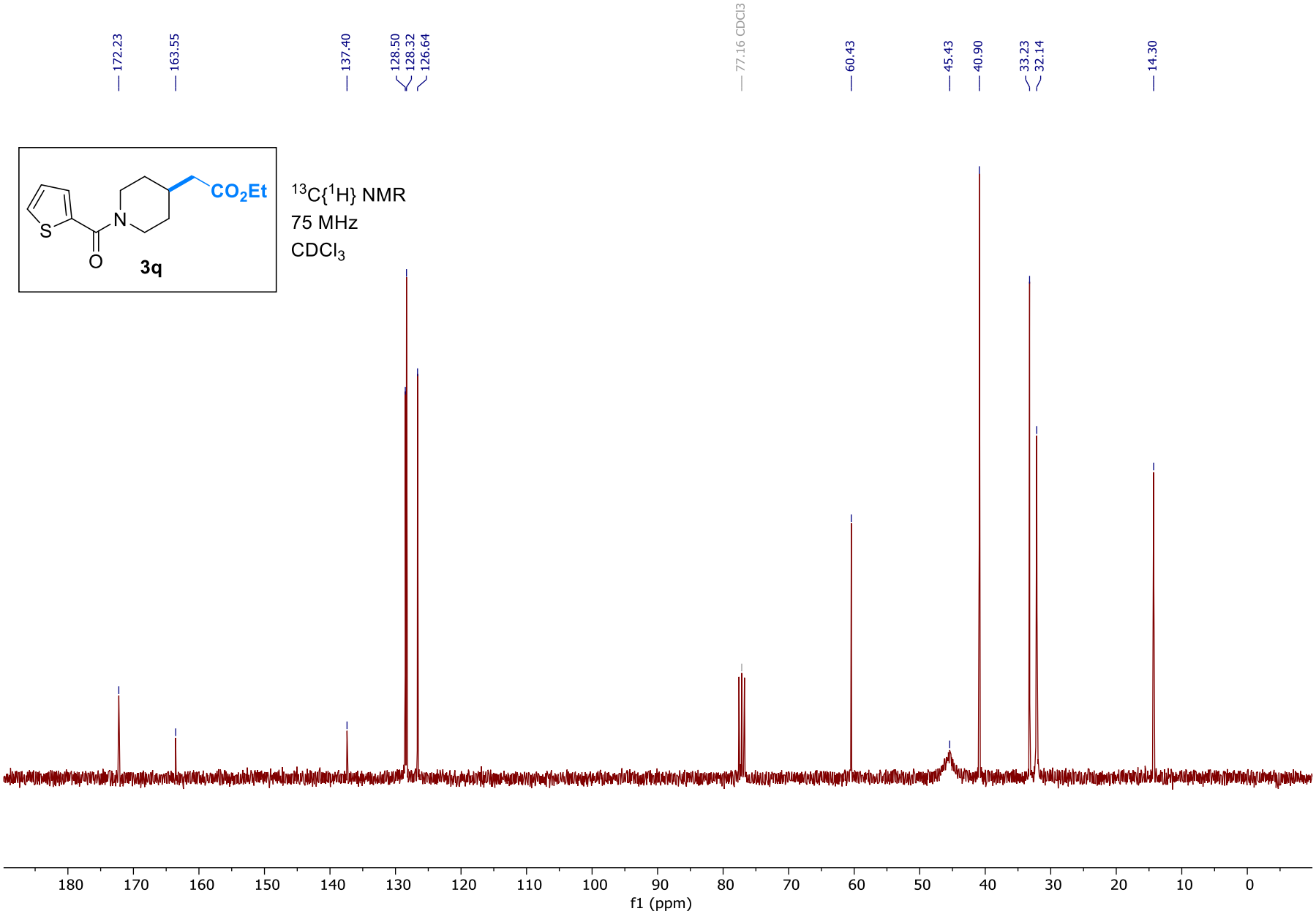


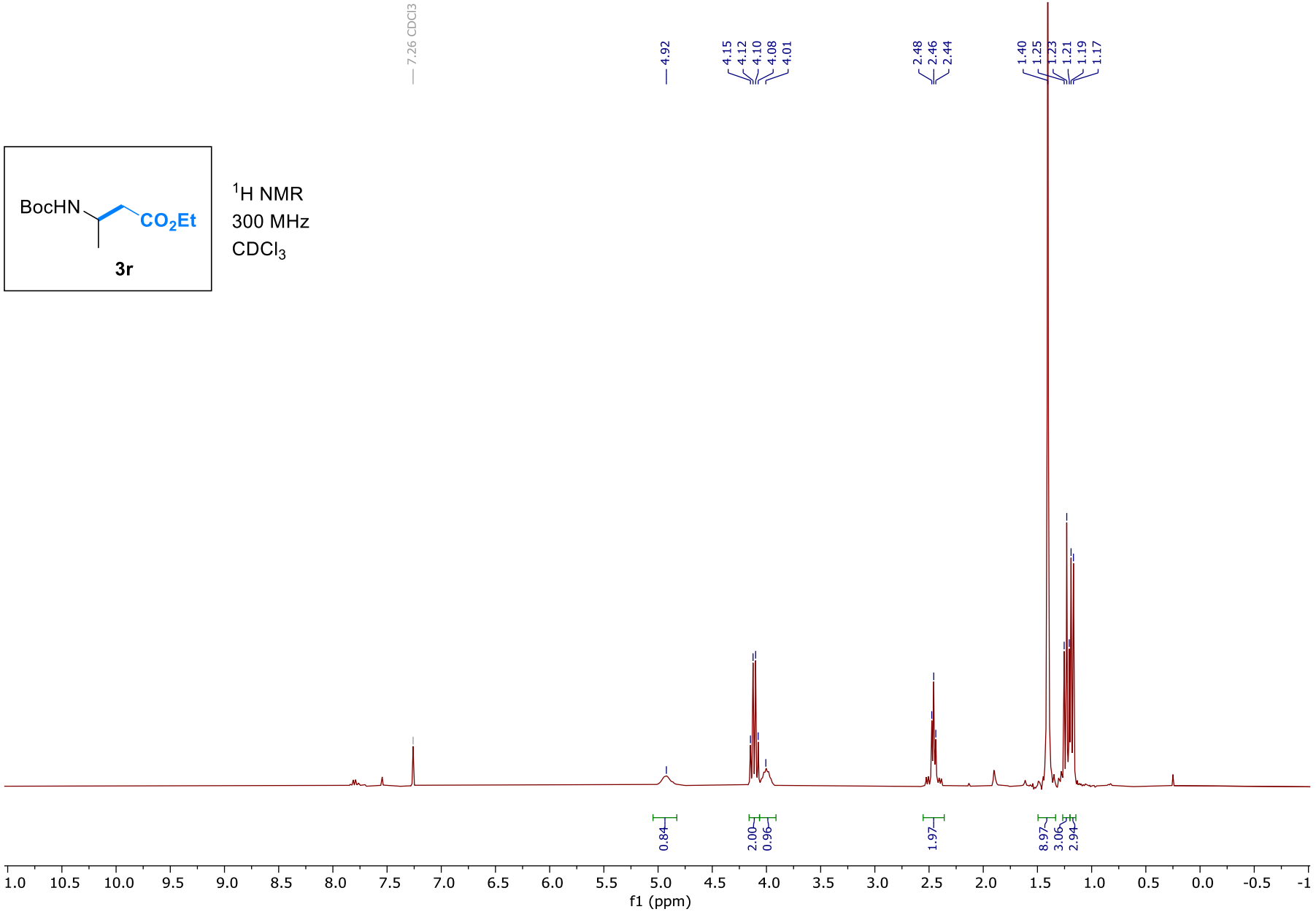
3p

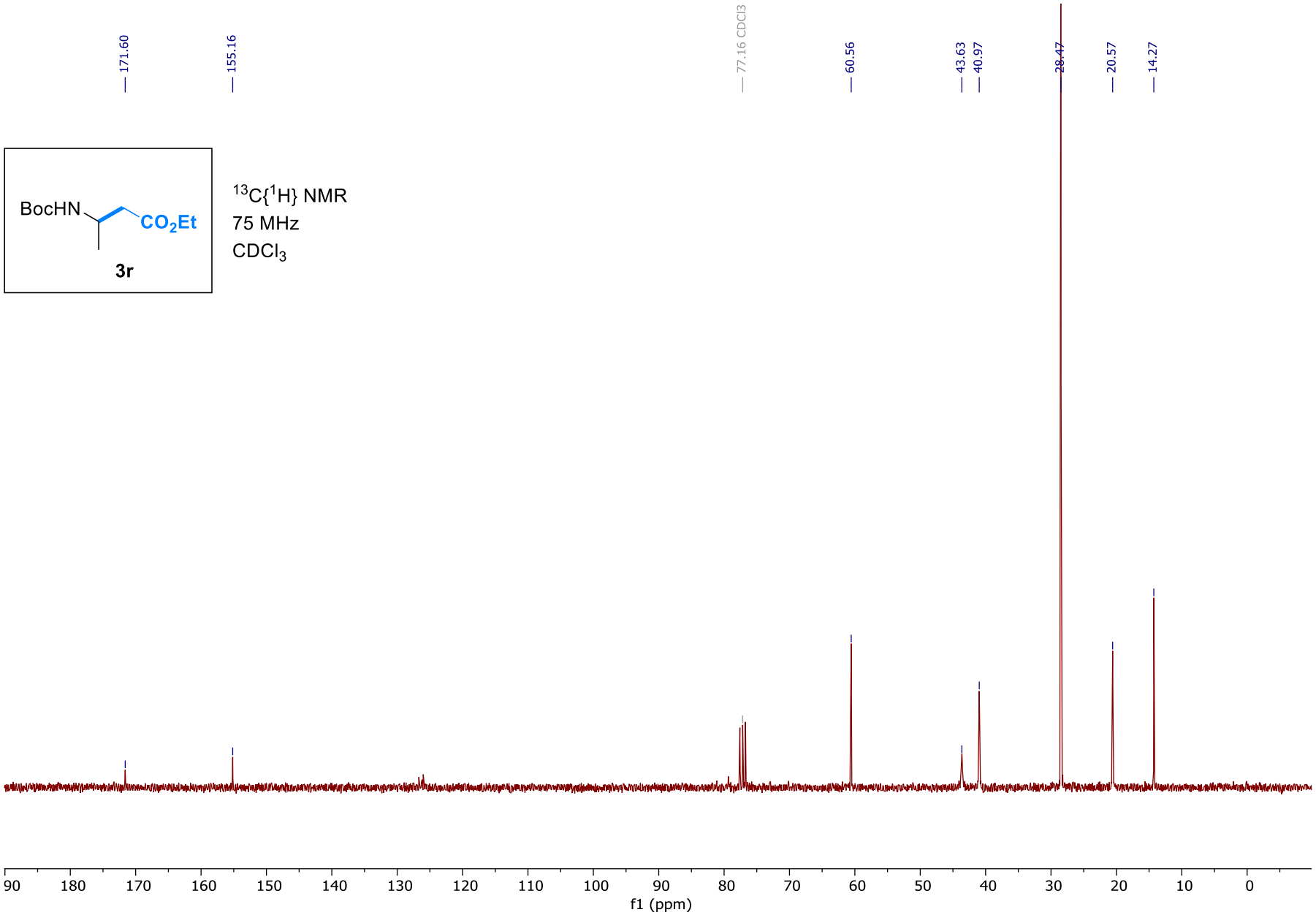
^{1}H NMR
300 MHz
$CDCl_3$

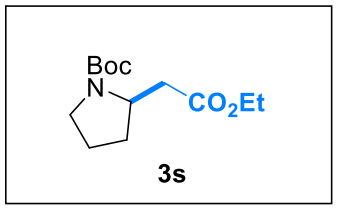

172.07
143.48
133.03
129.61
127.68
77.16 CDCl3
60.35
46.17
40.54
32.12
31.14
21.49
14.22
CO2Et
N
Ts
3p
13C{1H} NMR
75 MHz
CDCl3
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.40
7.38
7.26 CDCl3
7.23
7.22
7.01
6.99
6.98
4.41
4.38
4.14
4.12
4.09
4.07
2.99
2.94
2.90
2.25
2.23
2.06
1.79
1.75
1.25
1.22
1.20
CO2Et
N
S
O
3q
1H NMR
300 MHz
CDCl3
1.01
0.98
0.99
1.85
2.00
1.92
1.99
1.07
1.99
5.17
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
f1 (ppm)


172.23
163.55
137.40
128.50
128.32
126.64
77.16 CDCl3
60.43
45.43
40.90
33.23
32.14
14.30
CO2Et
N
S
O
3q
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

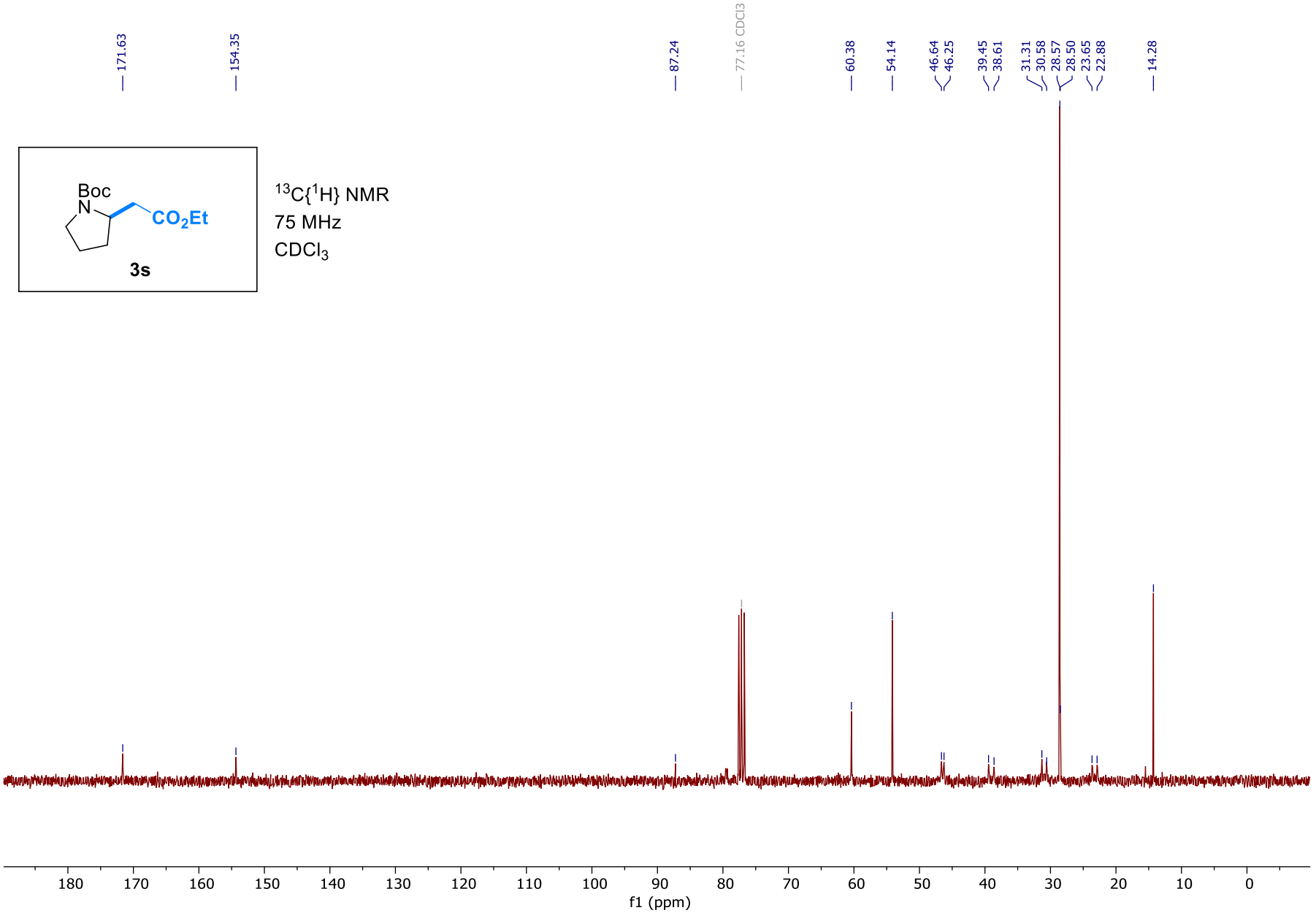

BocHN
CO2Et
3r
1H NMR
300 MHz
CDCl3
7.26 CDCl3
4.92
4.15
4.12
4.10
4.08
4.01
2.48
2.46
2.44
1.40
1.25
1.23
1.21
1.19
1.17
0.84
2.00
0.96
1.97
8.97
3.06
2.94
f1 (ppm)

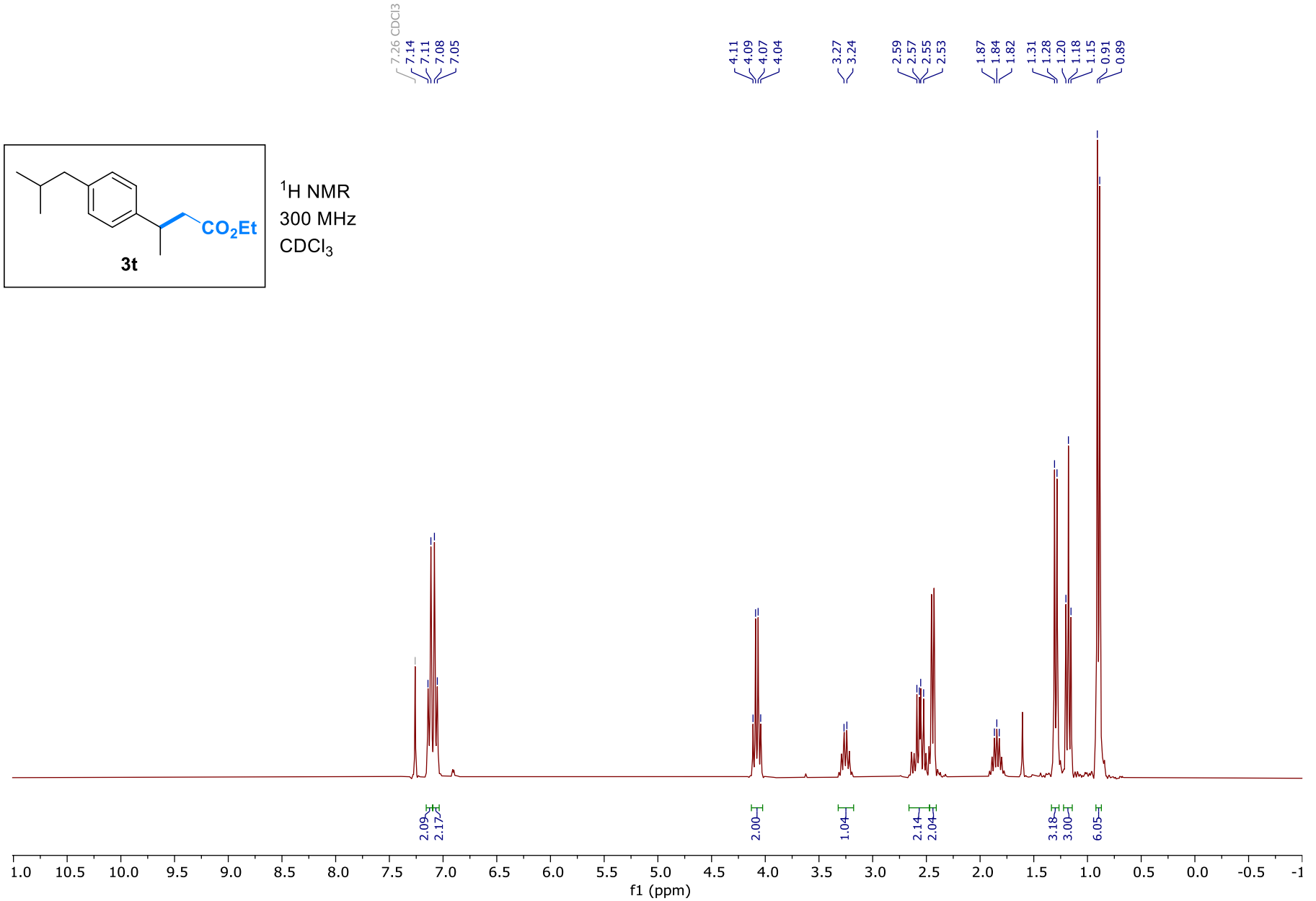

171.60
155.16
77.16 CDCl3
60.56
43.63
40.97
28.47
20.57
14.27
BocHN
CO2Et
3r
13C{1H} NMR
75 MHz
CDCl3
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

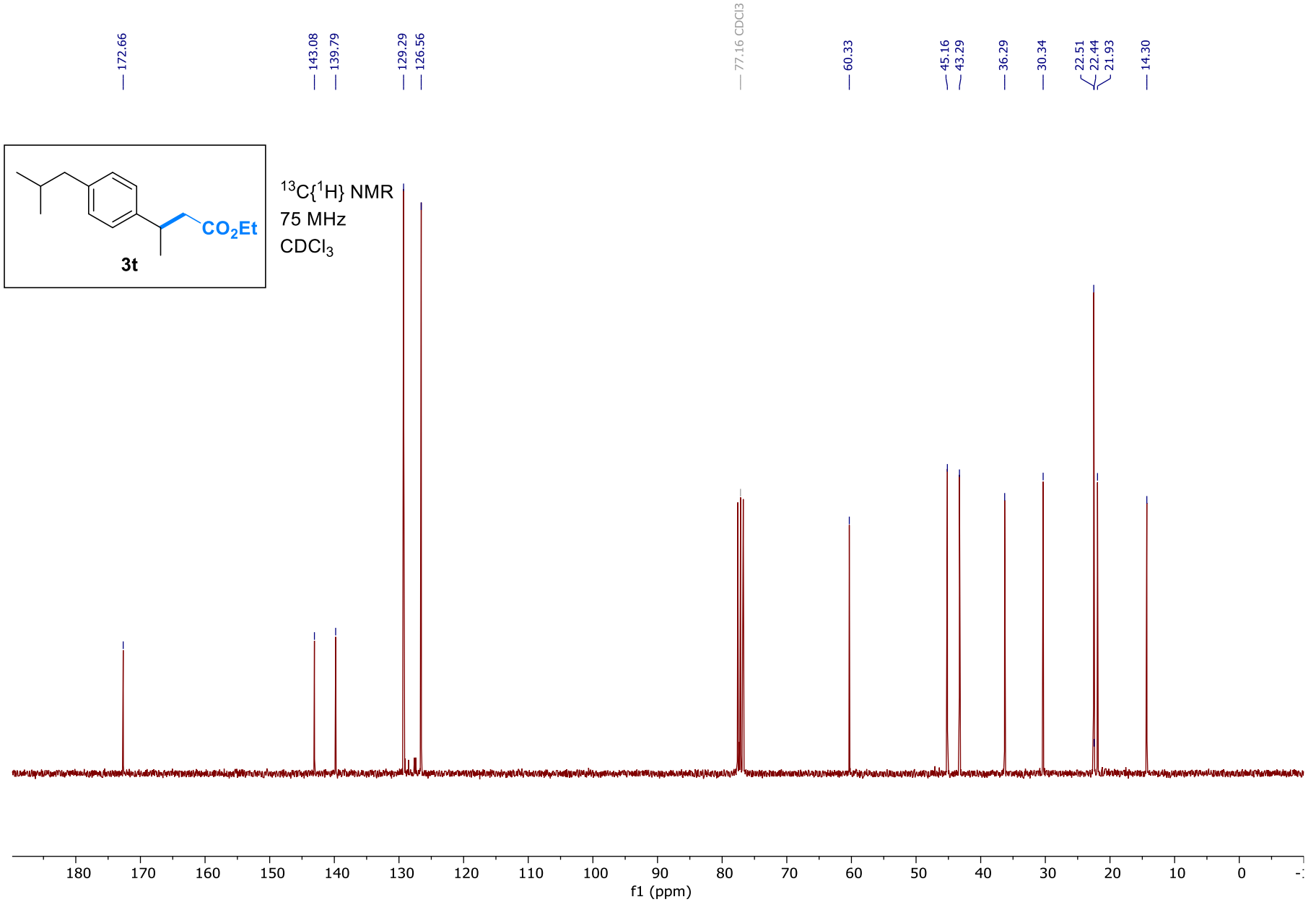


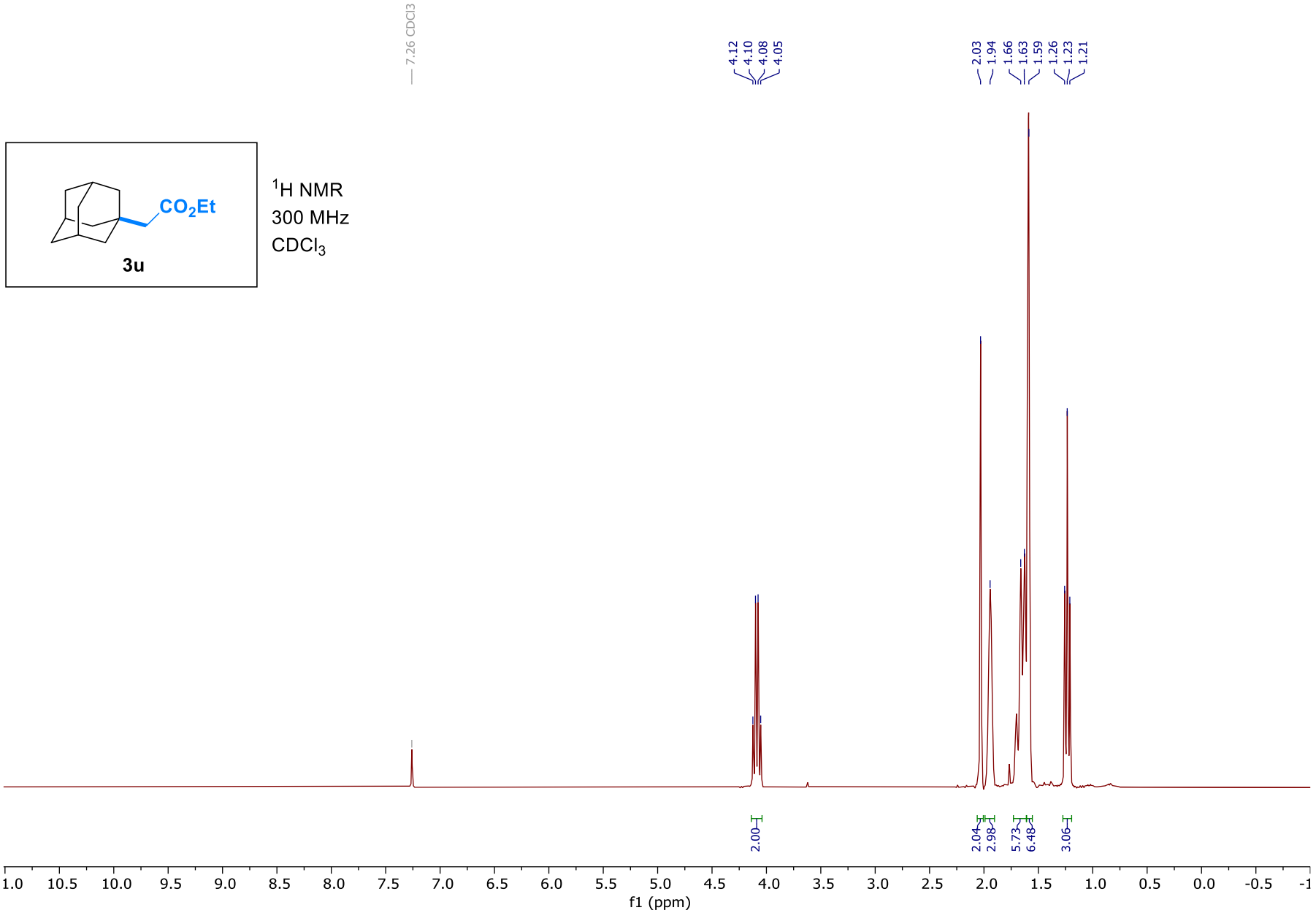
3s

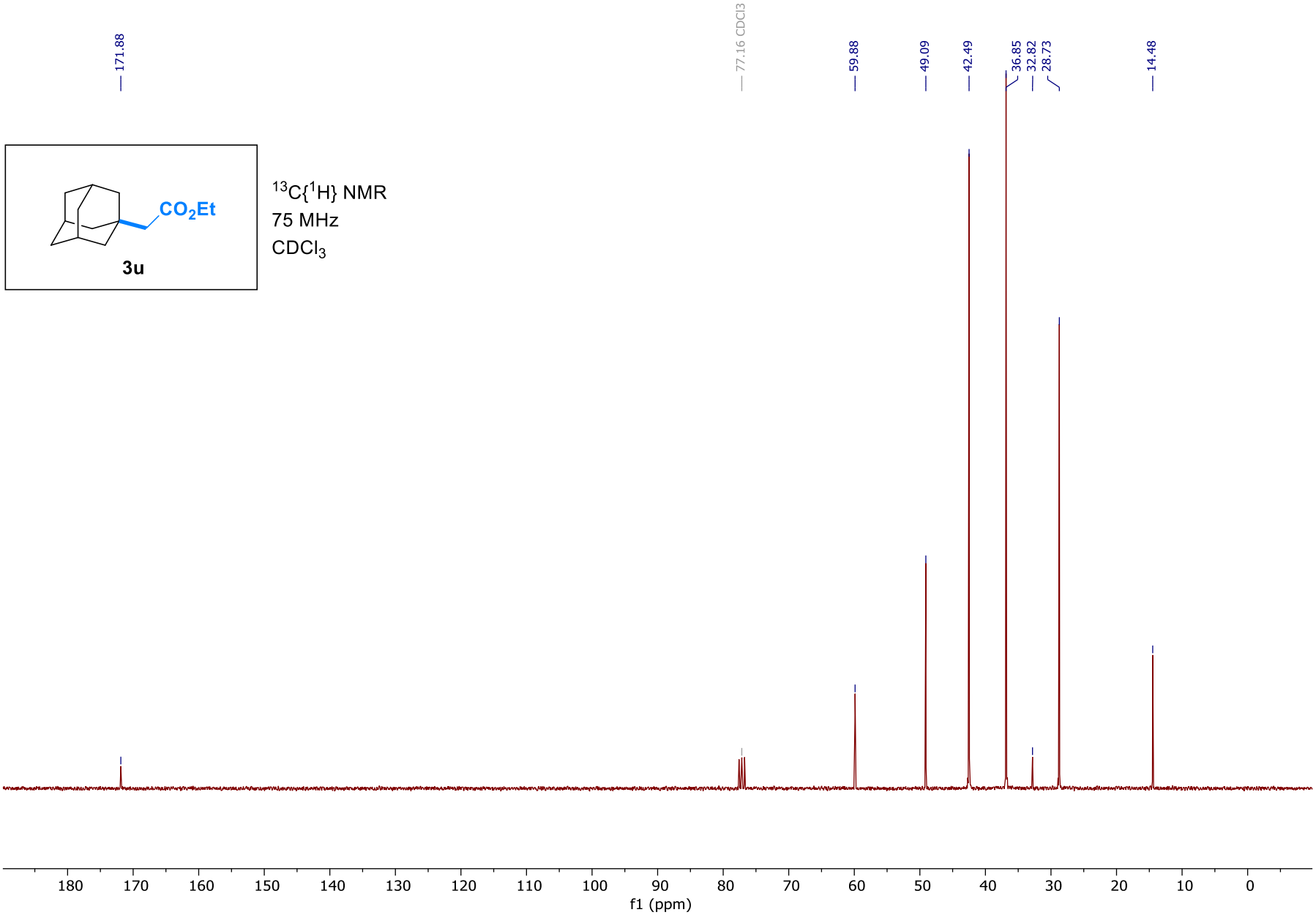
^{1}H NMR
300 MHz
$CDCl_3$

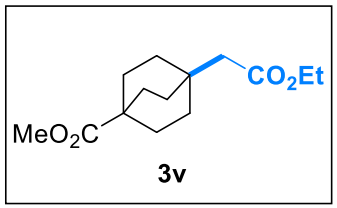

171.63
154.35
87.24
77.16 CDCl3
60.38
54.14
46.64
46.25
39.45
38.61
31.31
30.58
28.57
28.50
23.65
22.88
14.28
Boc
N
CO2Et
3s
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.26 CDCl3
7.14
7.11
7.08
7.05
4.11
4.09
4.07
4.04
3.27
3.24
2.59
2.57
2.55
2.53
1.87
1.84
1.82
1.31
1.28
1.20
1.18
1.15
0.91
0.89
CO2Et
3t
1H NMR
300 MHz
CDCl3
2.09
2.17
2.00
1.04
2.14
2.04
3.18
3.00
6.05
f1 (ppm)


172.66
143.08
139.79
129.29
126.56
77.16 CDCl3
60.33
45.16
43.29
36.29
30.34
22.51
22.44
21.93
14.30
CO2Et
3t
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

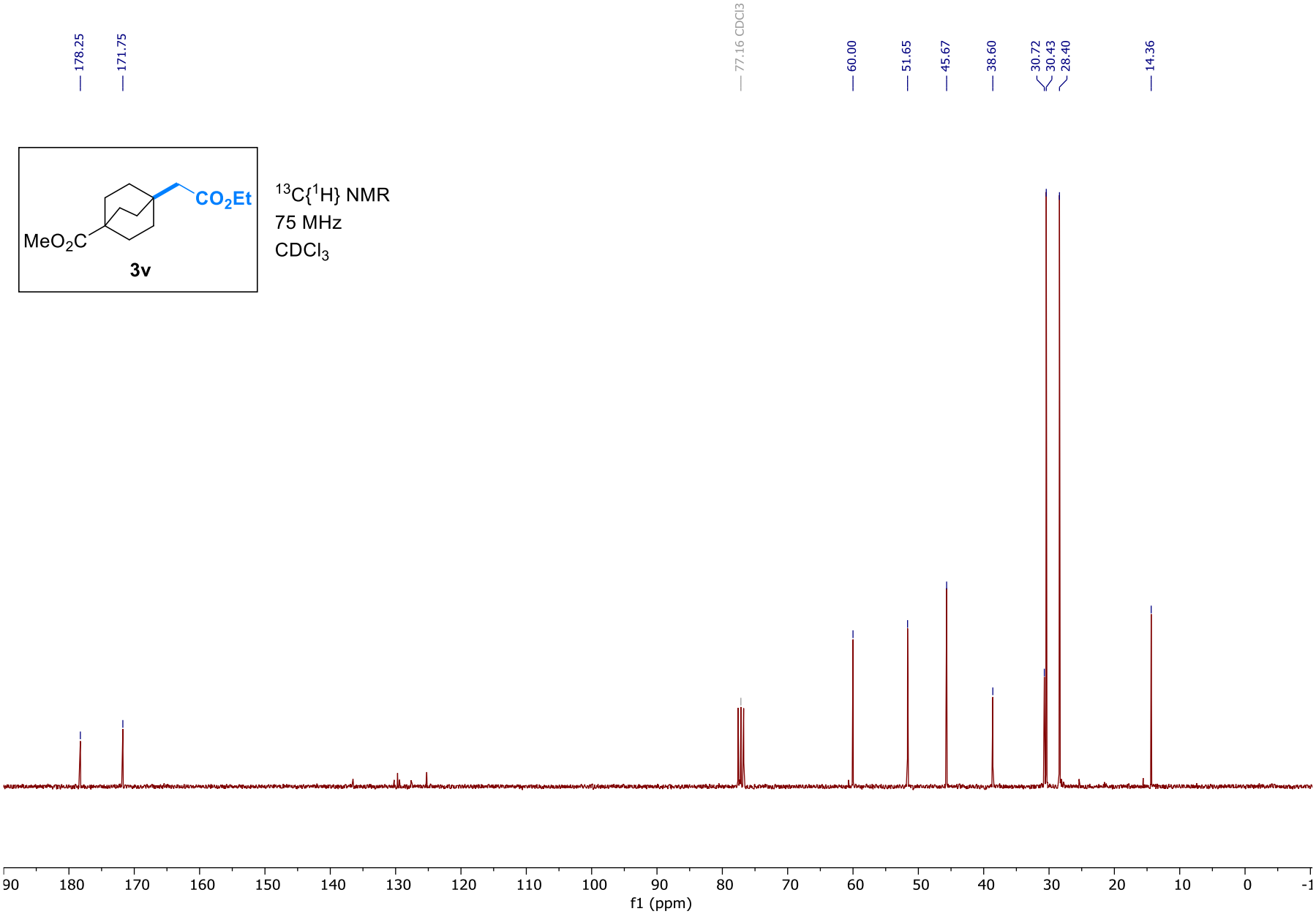

CO2Et
3u
1H NMR
300 MHz
CDCl3
7.26 CDCl3
4.12
4.10
4.08
4.05
2.03
1.94
1.66
1.63
1.59
1.26
1.23
1.21
2.00
2.04
2.98
5.73
6.48
3.06
f1 (ppm)

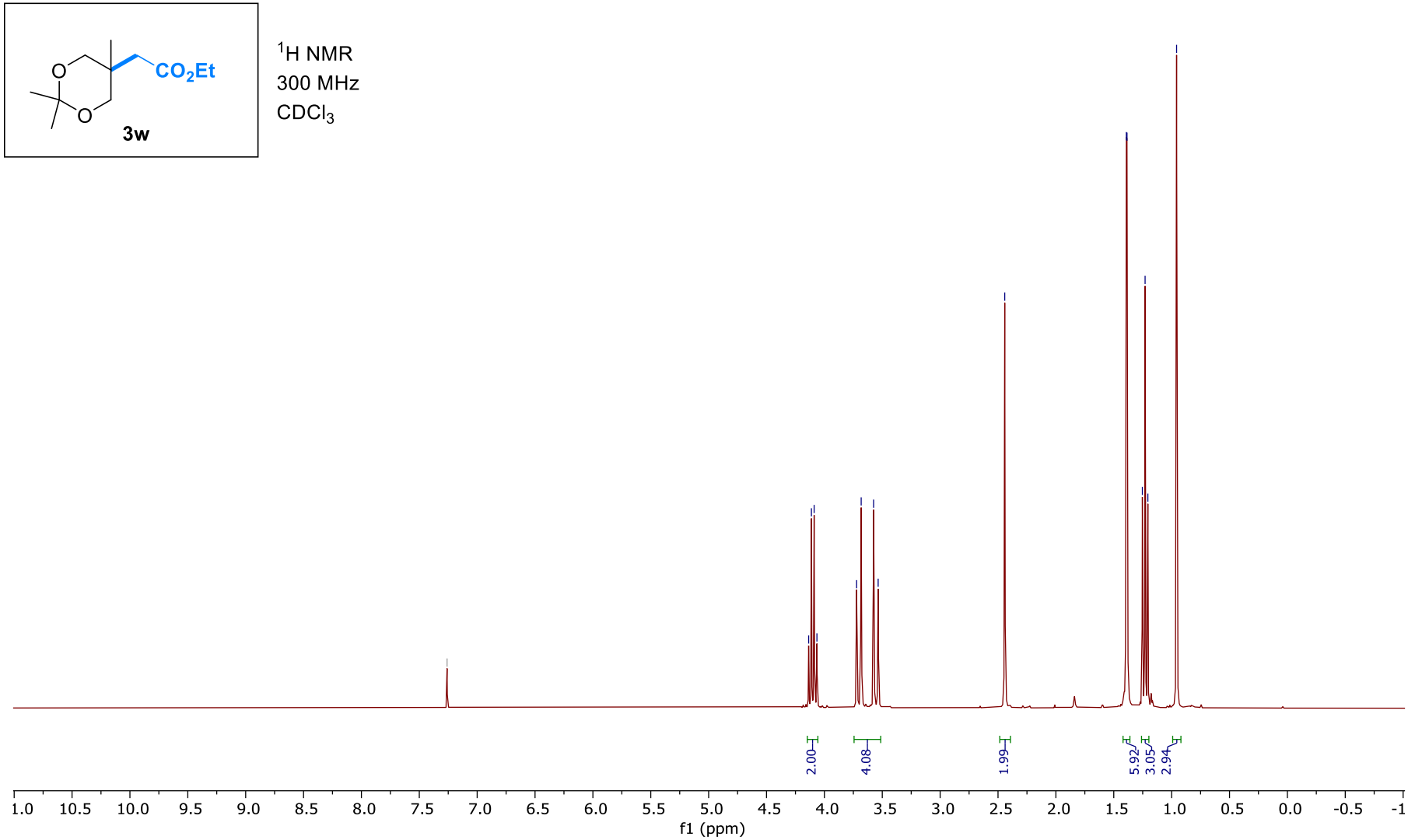

171.88
77.16 CDCl3
59.88
49.09
42.49
36.85
32.82
28.73
14.48
CO2Et
3u
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

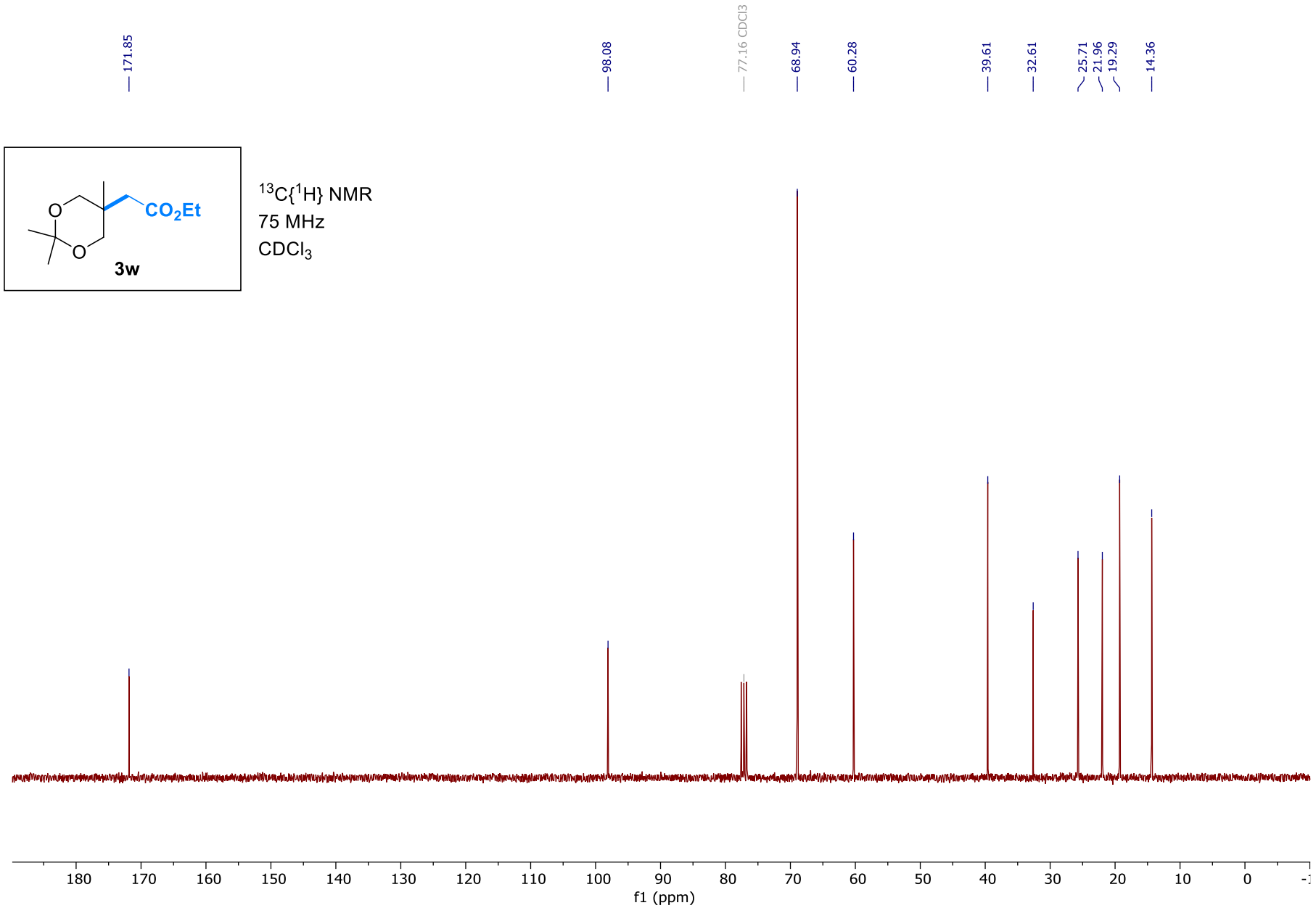


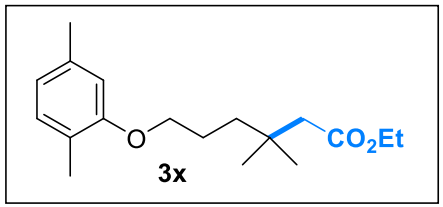
3v

^{1}H NMR
300 MHz
$CDCl_3$


178.25
171.75
77.16 CDCl3
60.00
51.65
45.67
38.60
30.72
30.43
28.40
14.36
CO2Et
MeO2C
3v
13C{1H} NMR
75 MHz
CDCl3
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

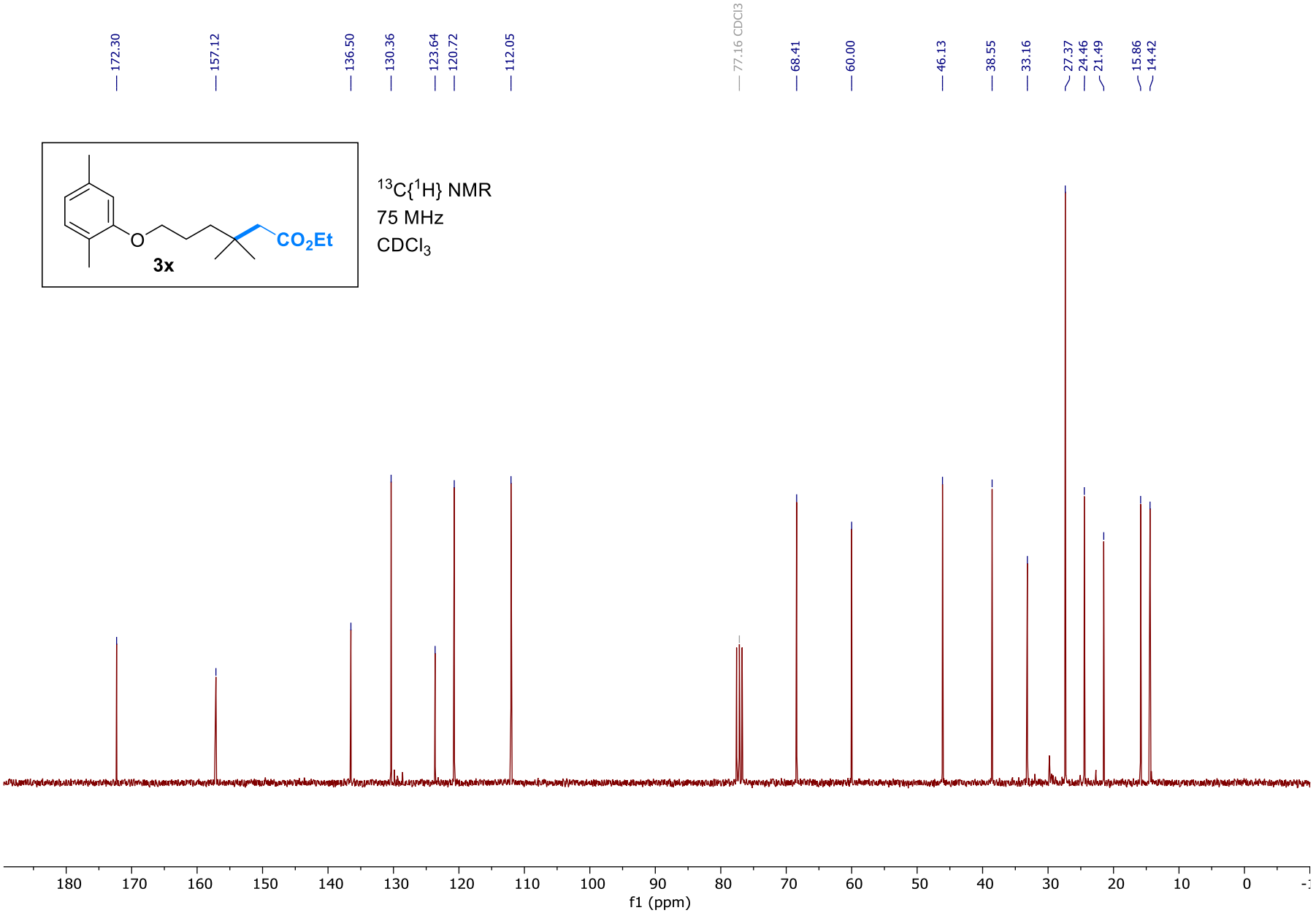

7.26 CDCl3
4.14
4.11
4.09
4.06
3.72
3.68
3.57
3.54
2.44
1.39
1.39
1.25
1.23
1.21
0.96
CO2Et
O
O
3w
1H NMR
300 MHz
CDCl3
2.00
4.08
1.99
5.92
3.05
2.94
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

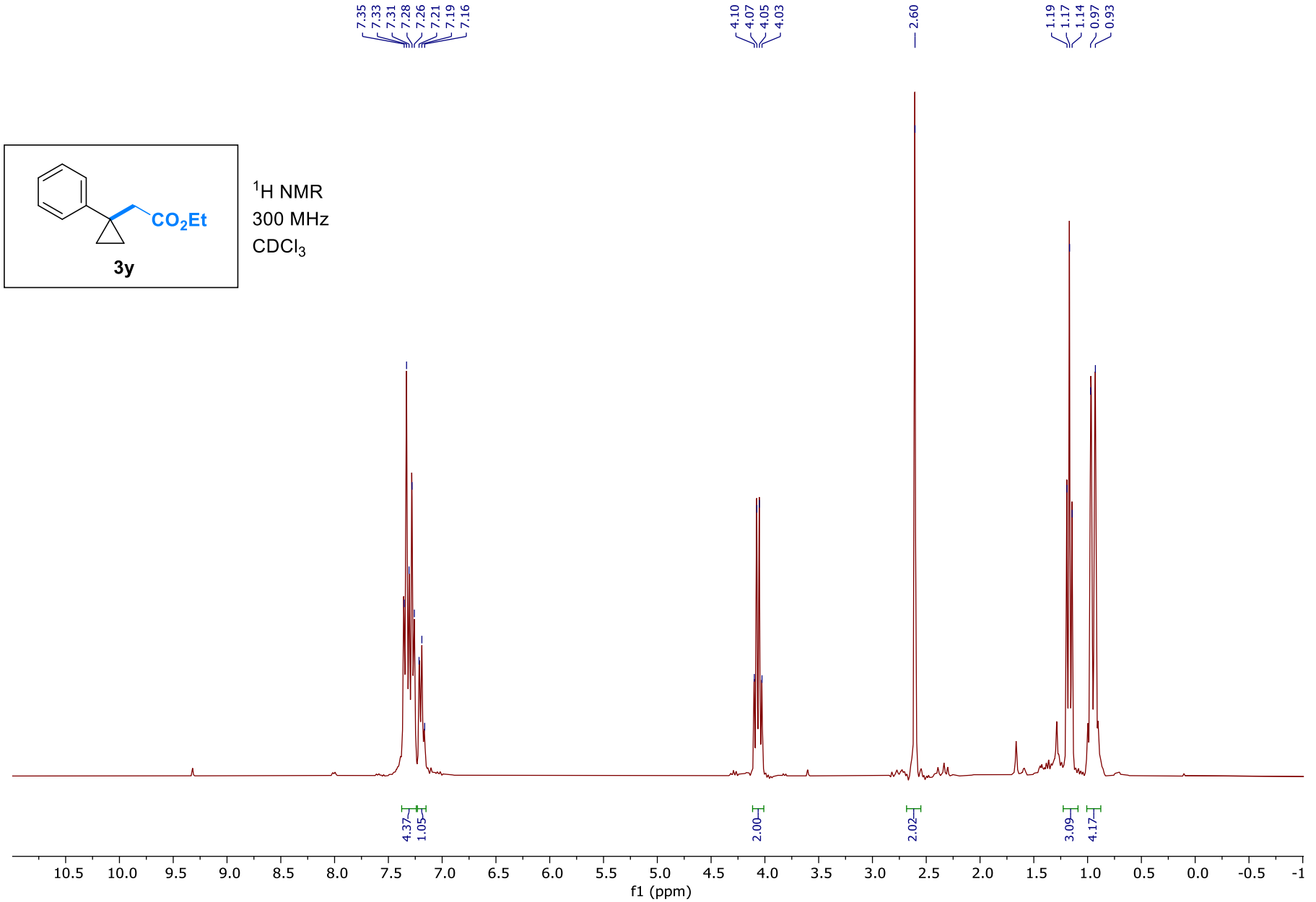

171.85
98.08
77.16 CDCl3
68.94
60.28
39.61
32.61
25.71
21.96
19.29
14.36
CO2Et
O
O
3w
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

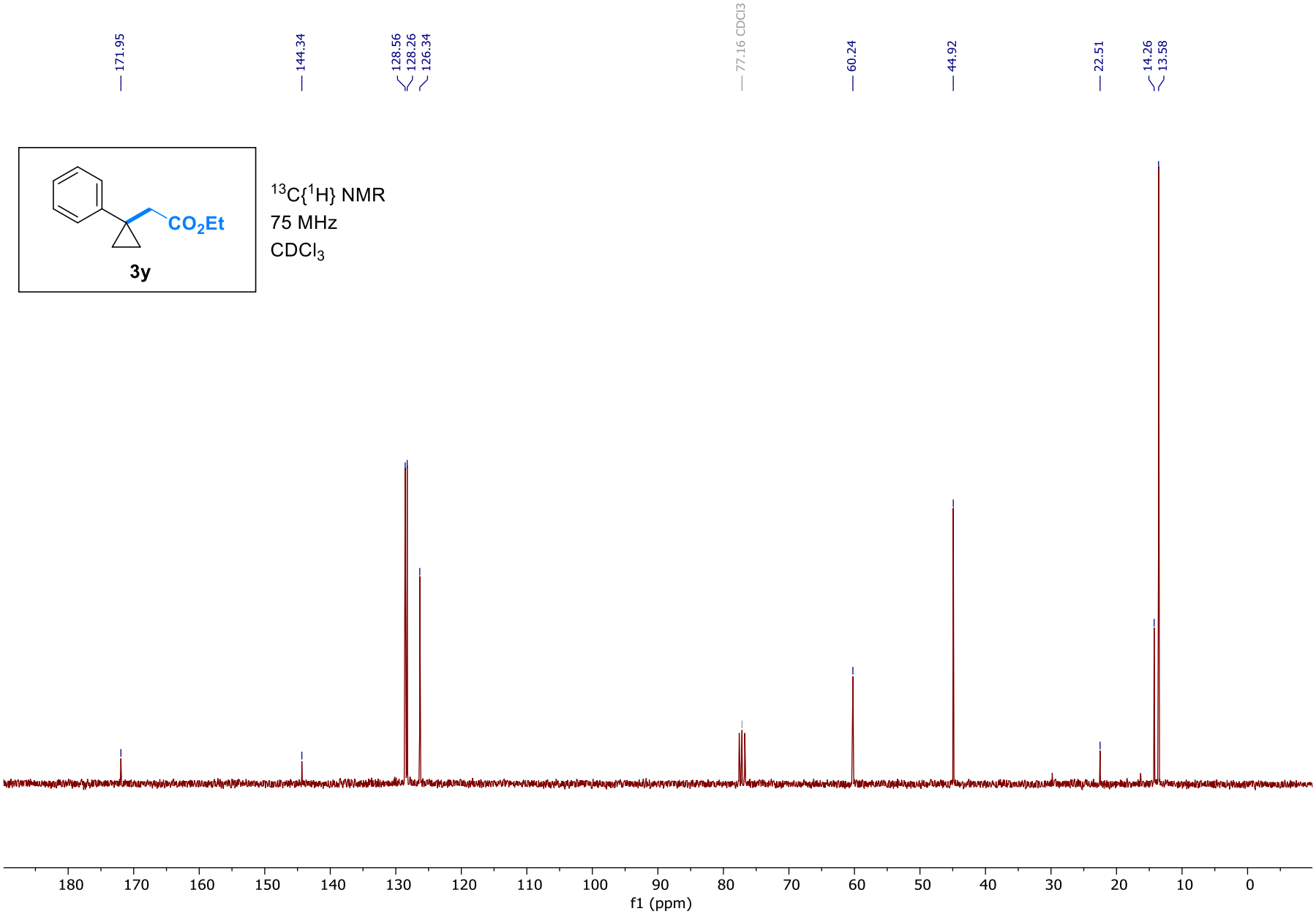


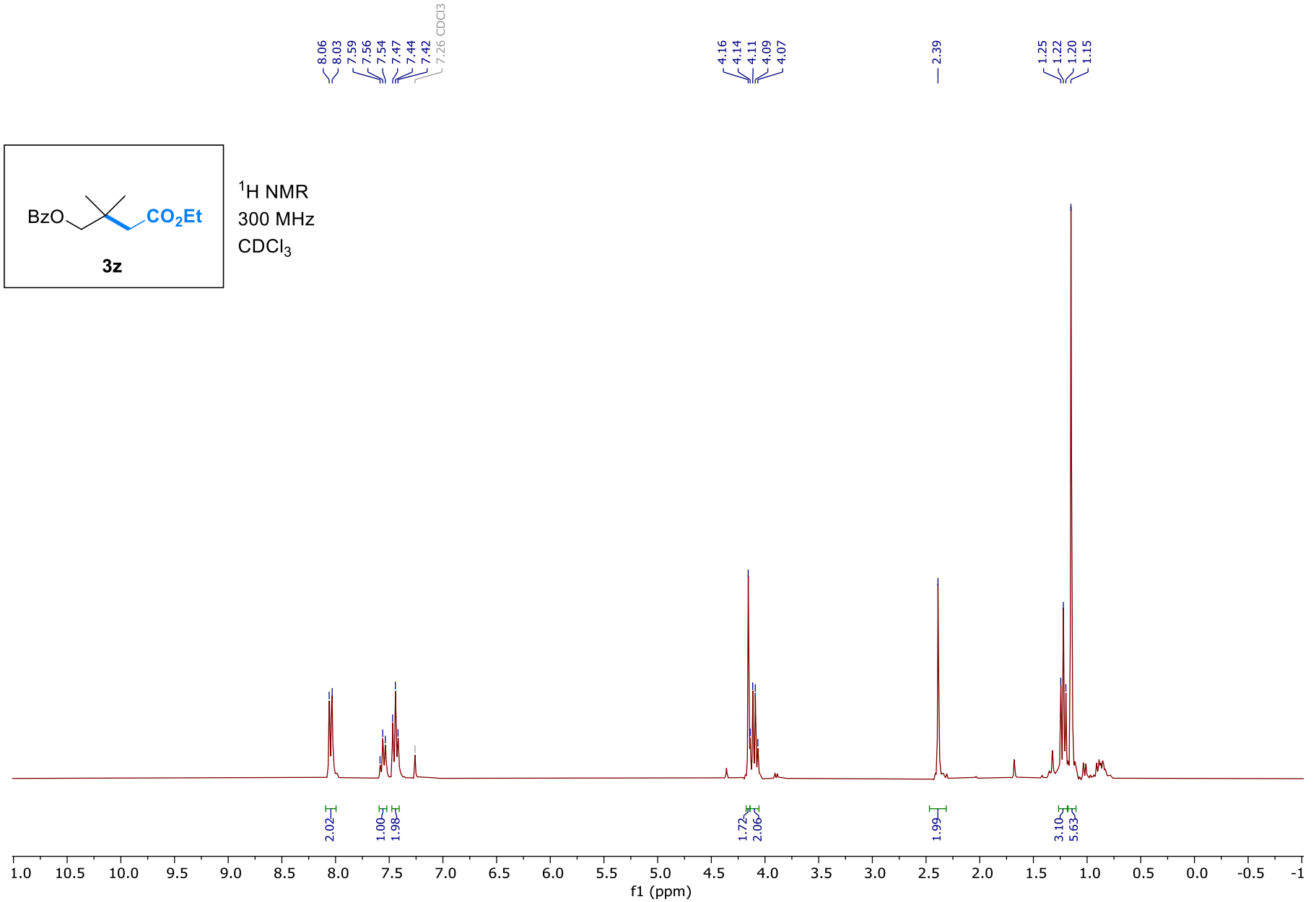
3x

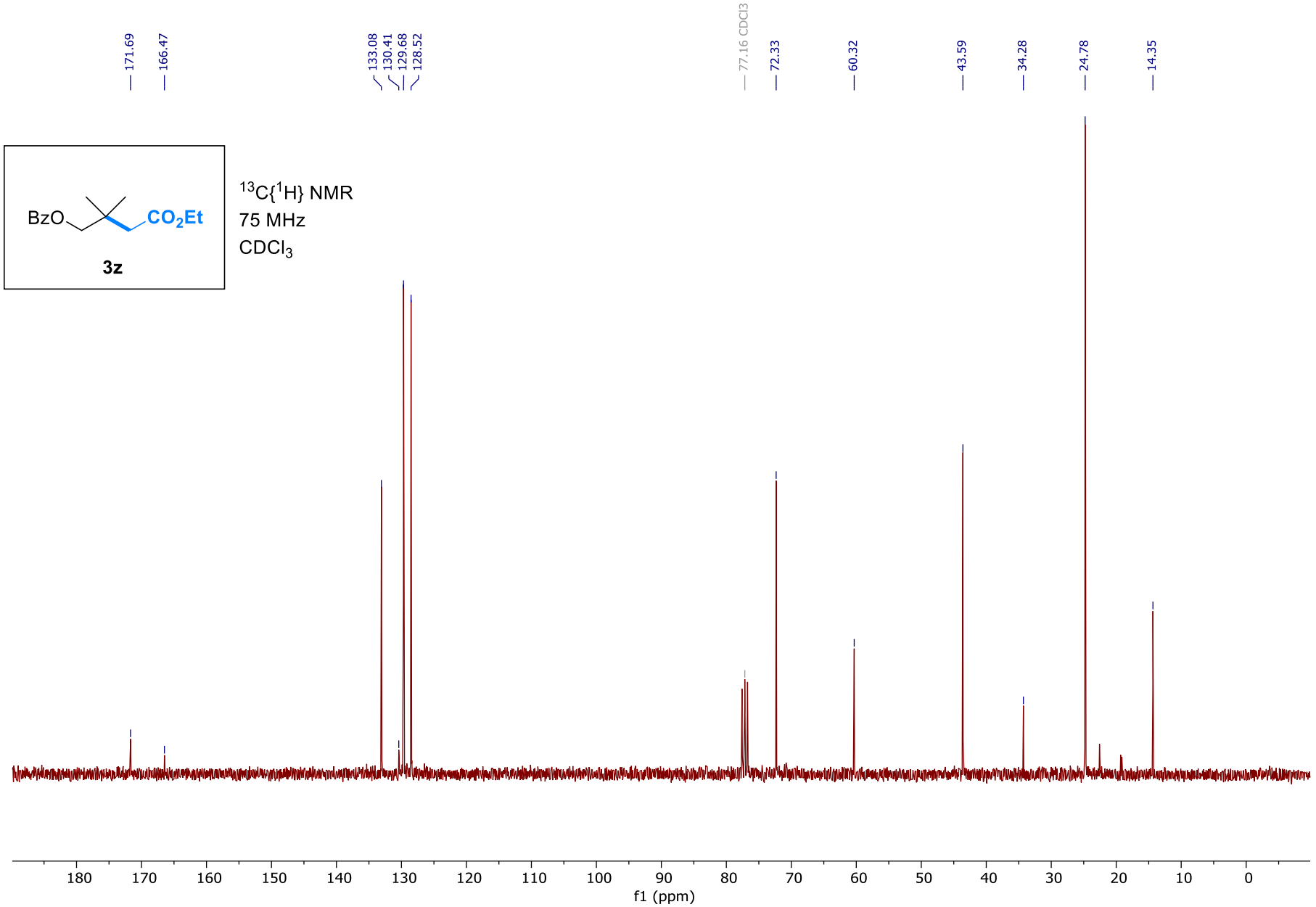
^{1}H NMR
300 MHz
$CDCl_3$

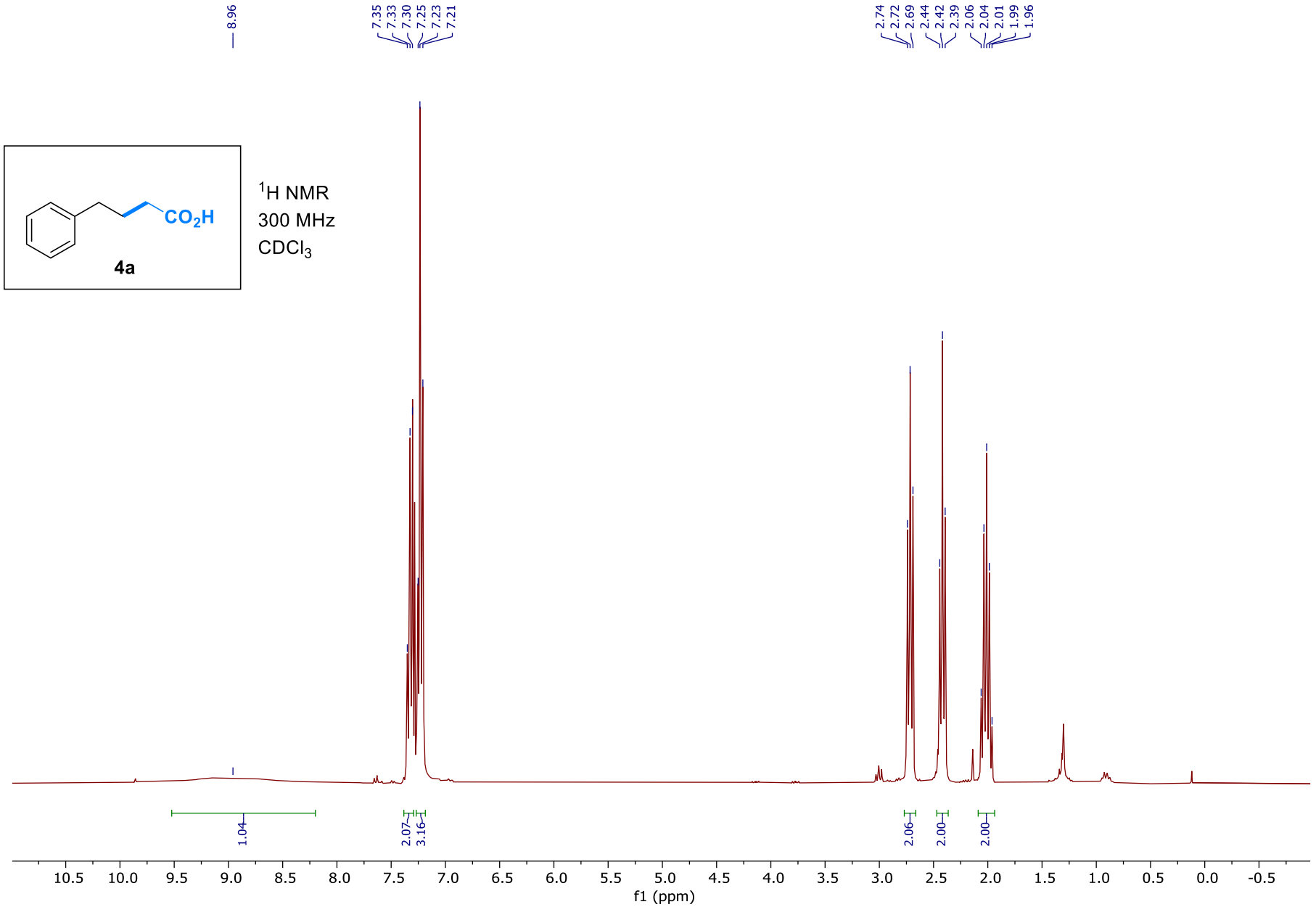

172.30
157.12
136.50
130.36
123.64
120.72
112.05
77.16 CDCl3
68.41
60.00
46.13
38.55
33.16
27.37
24.46
21.49
15.86
14.42
O
CO2Et
3x
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

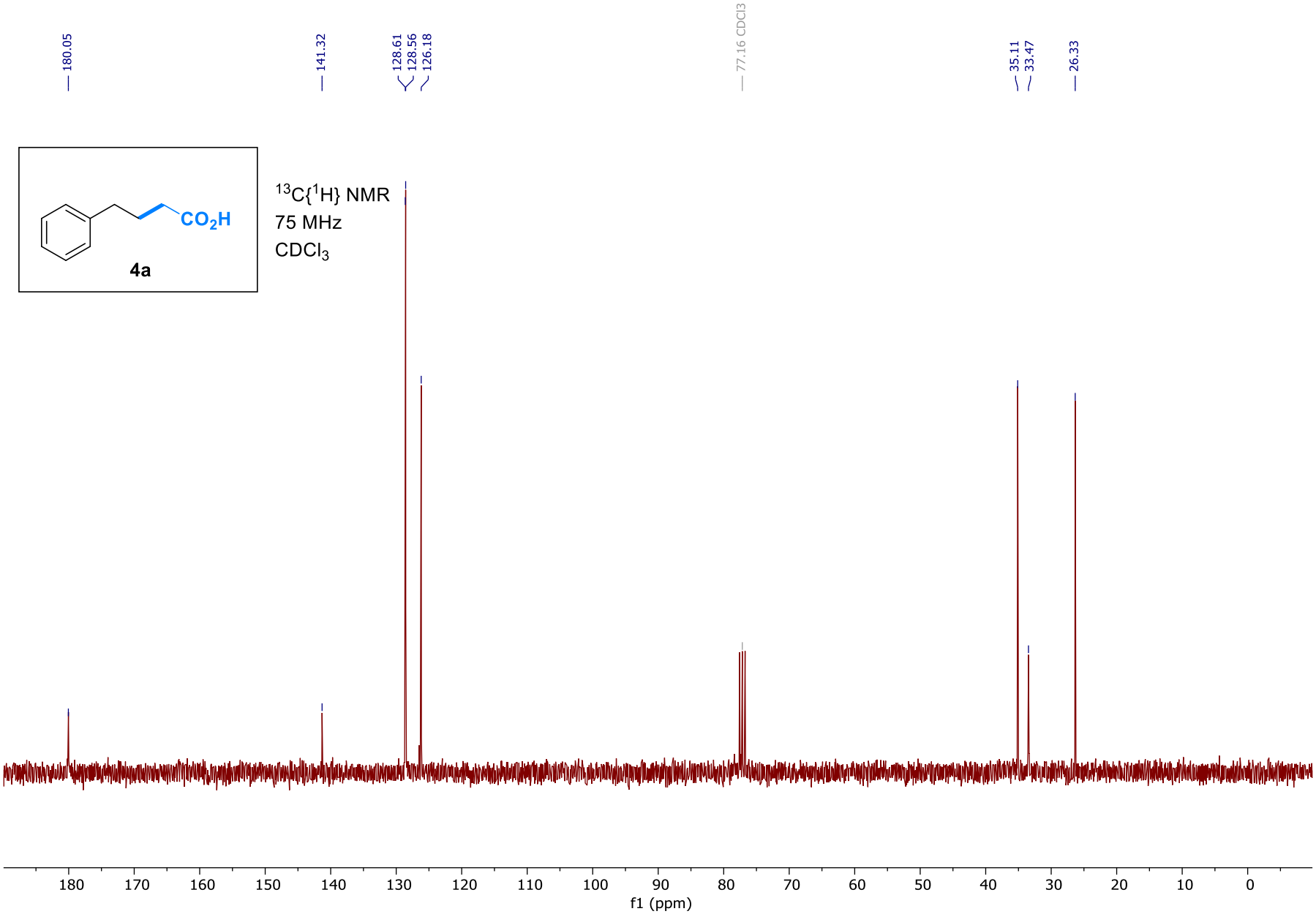

7.35
7.33
7.31
7.28
7.26
7.21
7.19
7.16
4.10
4.07
4.05
4.03
2.60
1.19
1.17
1.14
0.97
0.93
CO2Et
3y
1H NMR
300 MHz
CDCl3
4.37
1.05
2.00
2.02
3.09
4.17
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

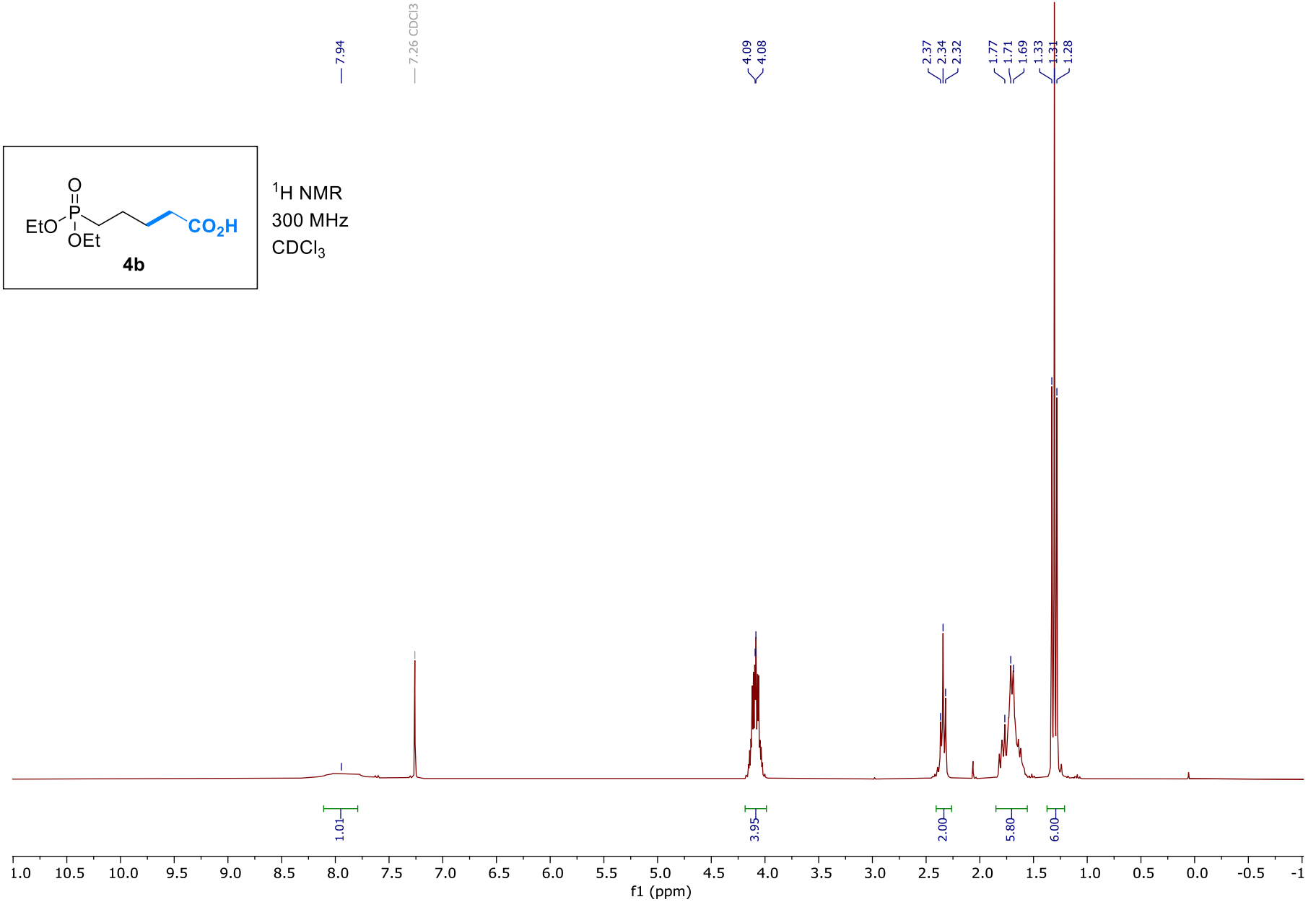

171.95
144.34
128.56
128.26
126.34
77.16 CDCl3
60.24
44.92
22.51
14.26
13.58
CO2Et
3y
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

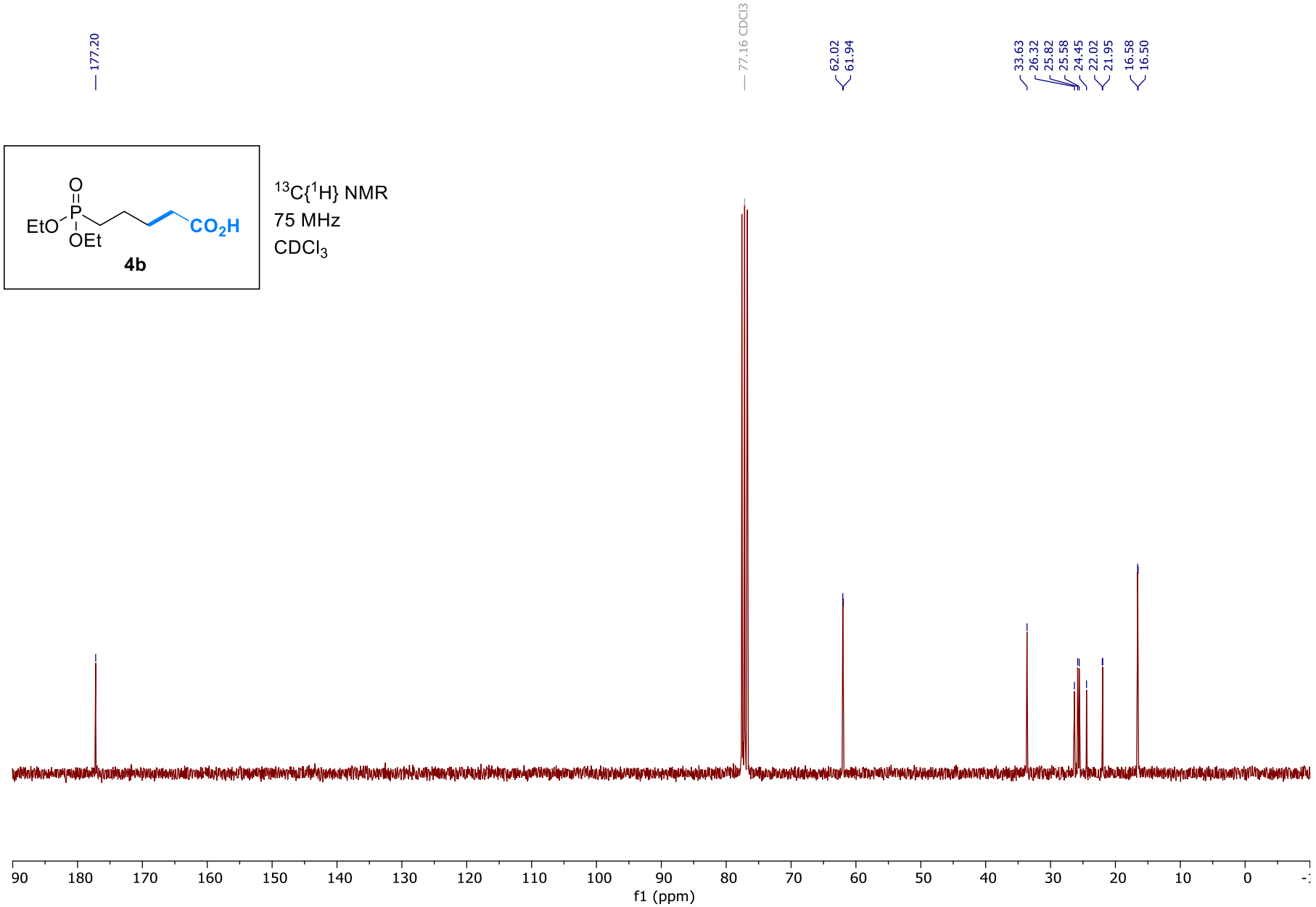

8.06
8.03
7.59
7.56
7.54
7.47
7.44
7.42
7.26 CDCl3
4.16
4.14
4.11
4.09
4.07
2.39
1.25
1.22
1.20
1.15
BzO
CO2Et
3z
1H NMR
300 MHz
CDCl3
2.02
1.00
1.98
1.72
2.06
1.99
3.10
5.63
f1 (ppm)

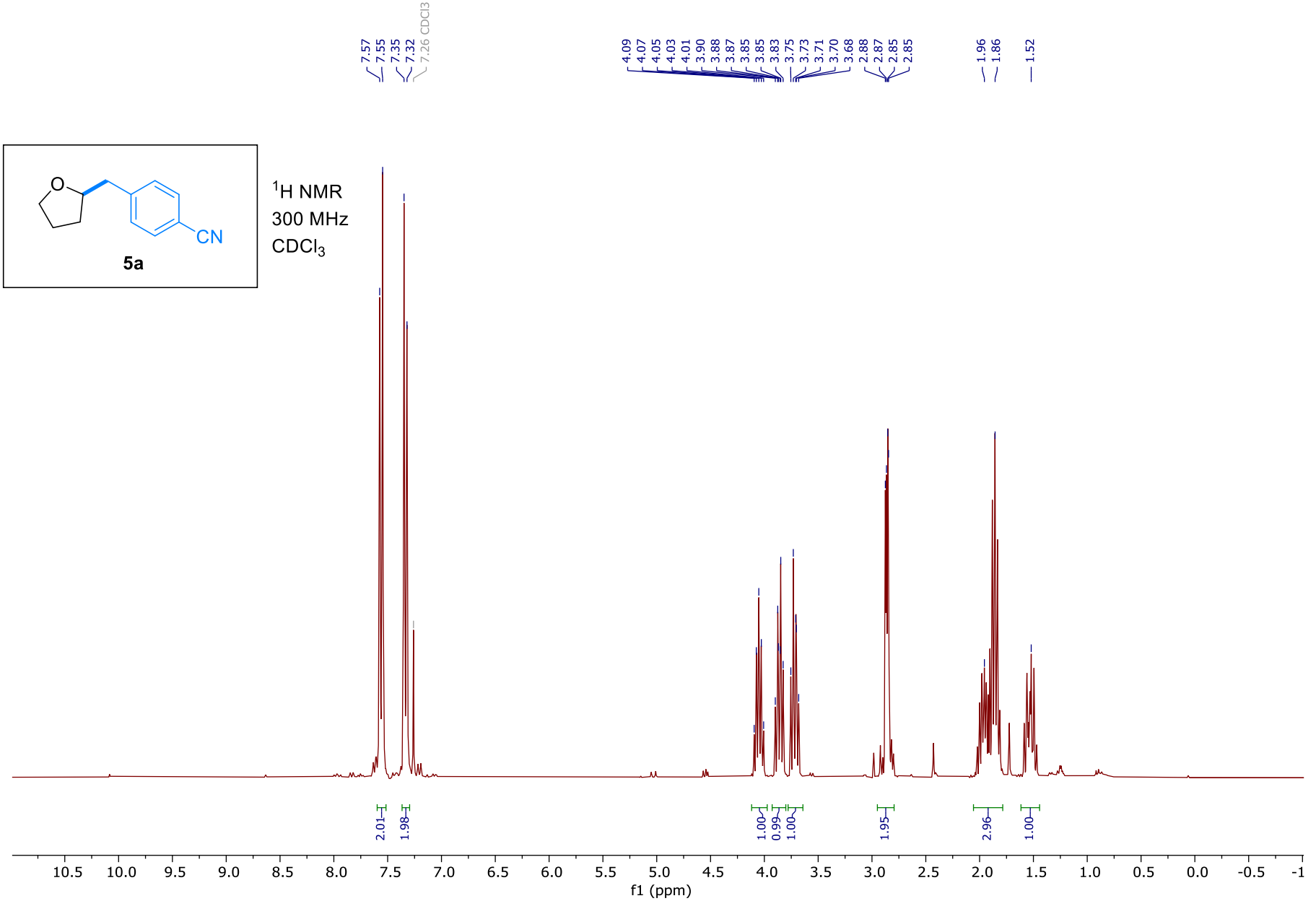

171.69
166.47
133.08
130.41
129.68
128.52
77.16 CDCl3
72.33
60.32
43.59
34.28
24.78
14.35
BzO
CO2Et
3z
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

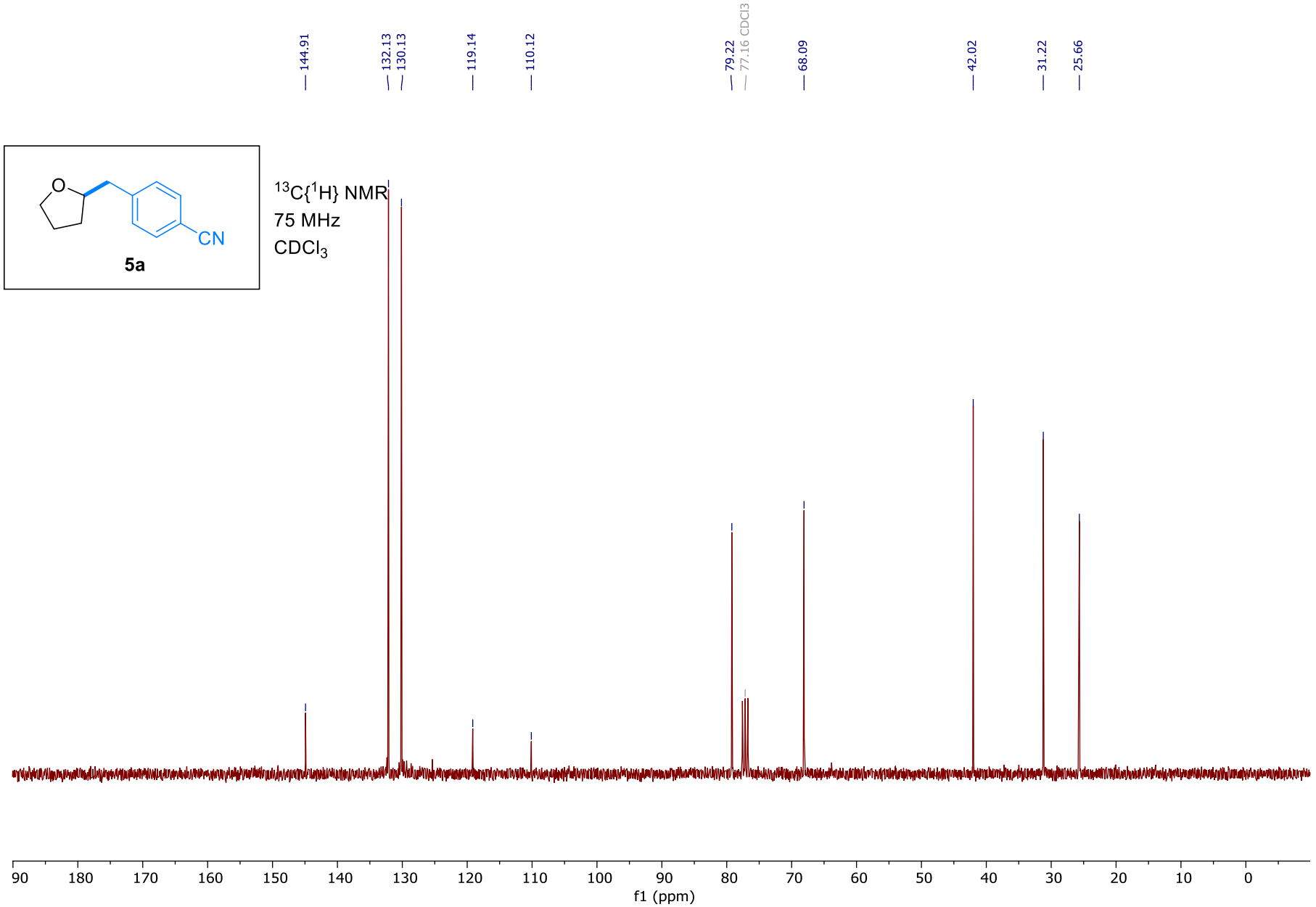

8.96
7.35
7.33
7.30
7.25
7.23
7.21
2.74
2.72
2.69
2.44
2.42
2.39
2.06
2.04
2.01
1.99
1.96
CO2H
4a
1H NMR
300 MHz
CDCl3
1.04
2.07
3.16
2.06
2.00
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

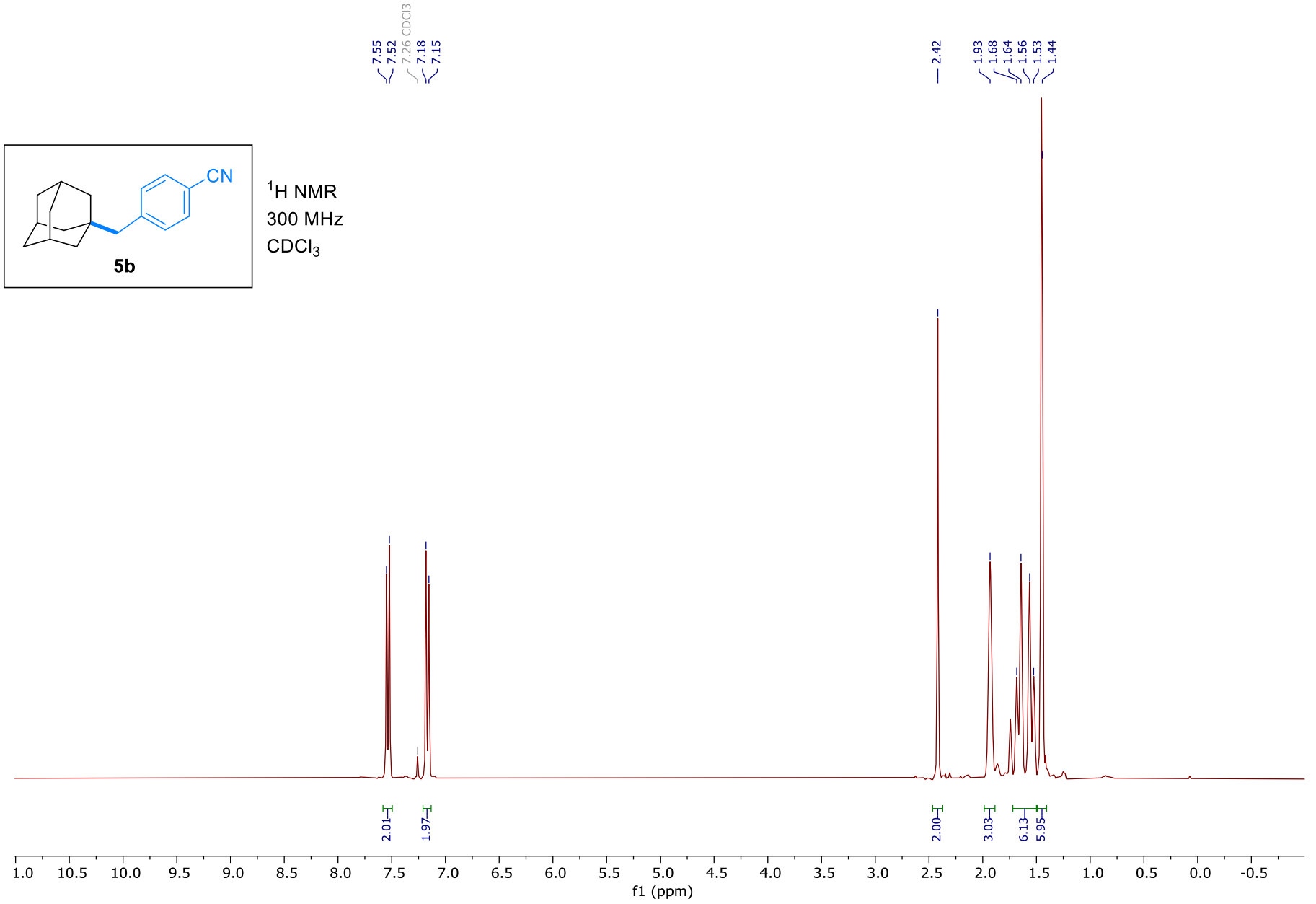

180.05
141.32
128.61
128.56
126.18
77.16 CDCl3
35.11
33.47
26.33
CO2H
4a
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

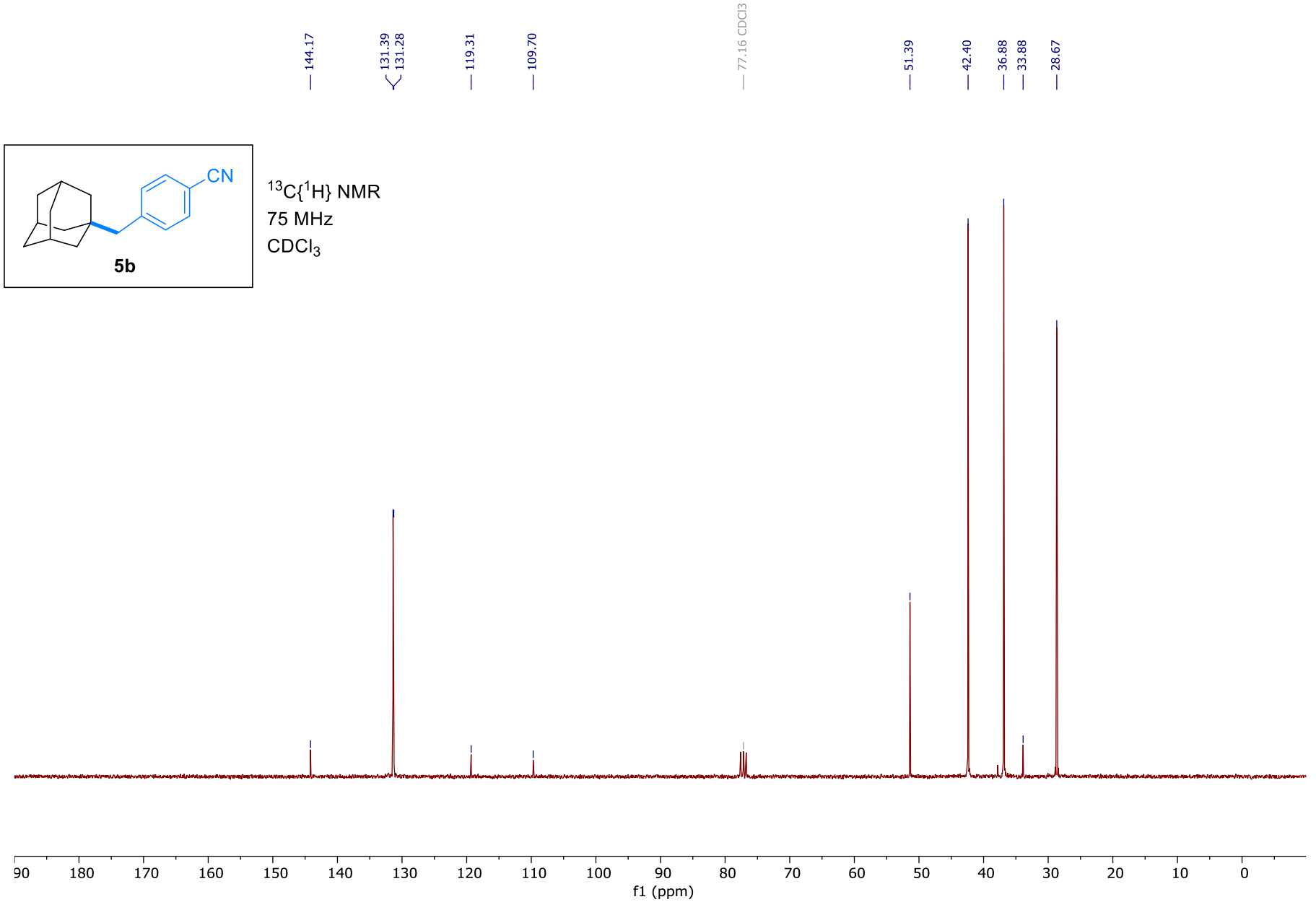

7.94
7.26 CDCl3
4.09
4.08
2.37
2.34
2.32
1.77
1.71
1.69
1.33
1.31
1.28
EtO
OEt
CO2H
4b
1H NMR
300 MHz
CDCl3
1.01
3.95
2.00
5.80
6.00
f1 (ppm)

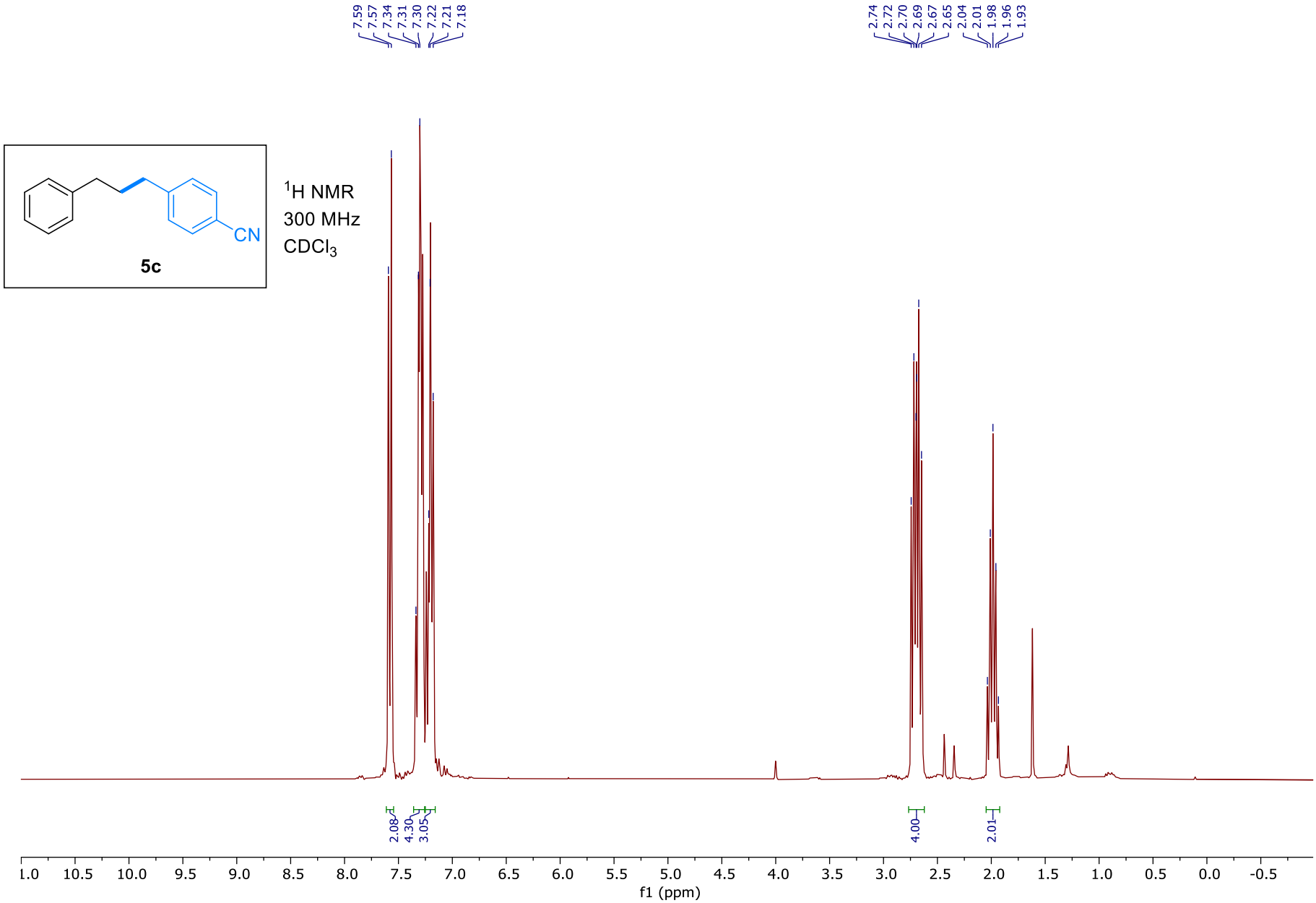

177.20
77.16 CDCl3
62.02
61.94
33.63
26.32
25.82
25.58
24.45
22.02
21.95
16.58
16.50
EtO
P
O
OEt
CO2H
4b
13C{1H} NMR
75 MHz
CDCl3
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

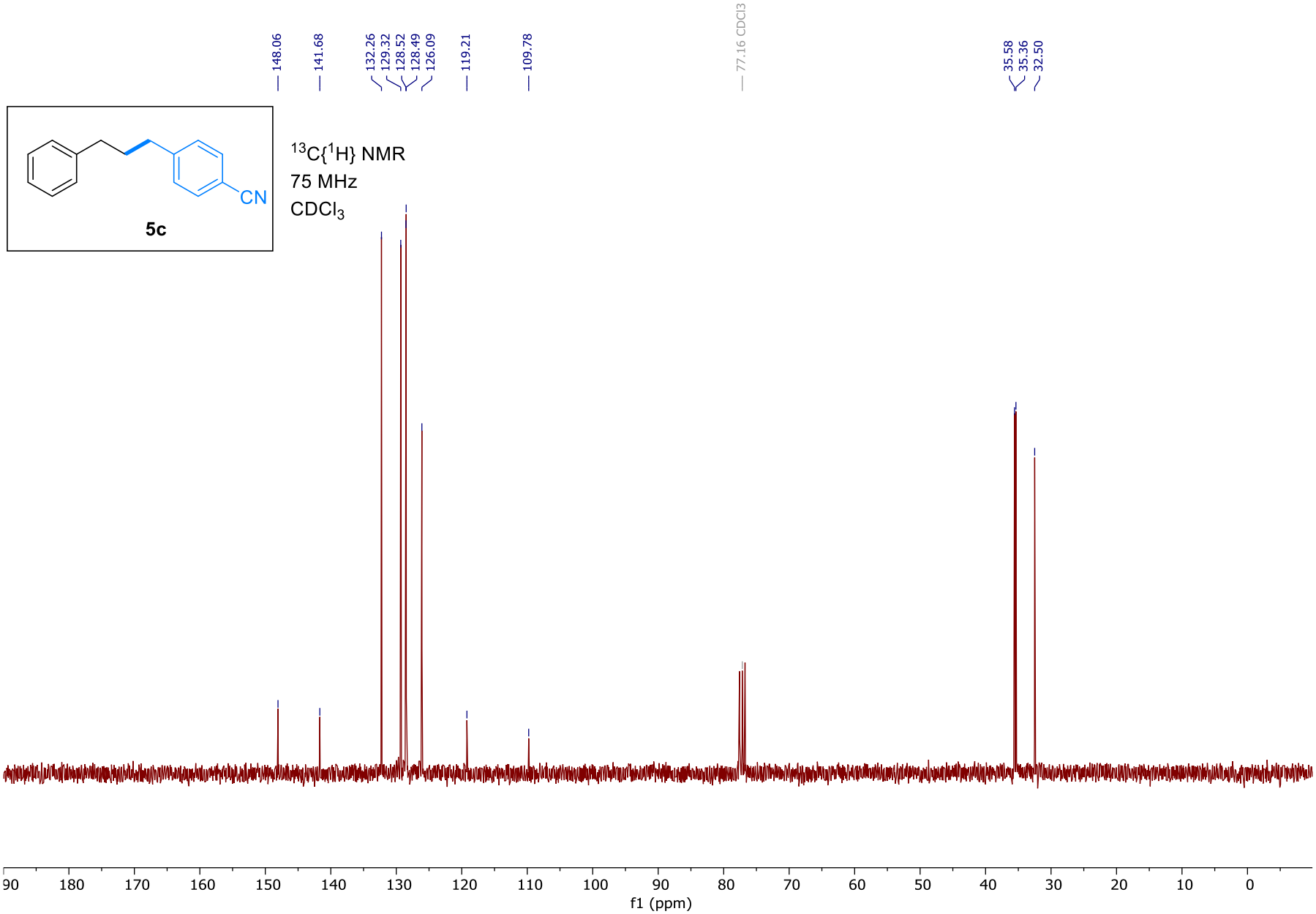

7.57
7.55
7.35
7.32
7.26 CDCl3
4.09
4.07
4.05
4.03
4.01
3.90
3.88
3.87
3.85
3.85
3.83
3.75
3.73
3.71
3.70
3.68
2.88
2.87
2.85
2.85
1.96
1.86
1.52
O
CN
5a
1H NMR
300 MHz
CDCl3
2.01
1.98
1.00
0.99
1.00
1.95
2.96
1.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

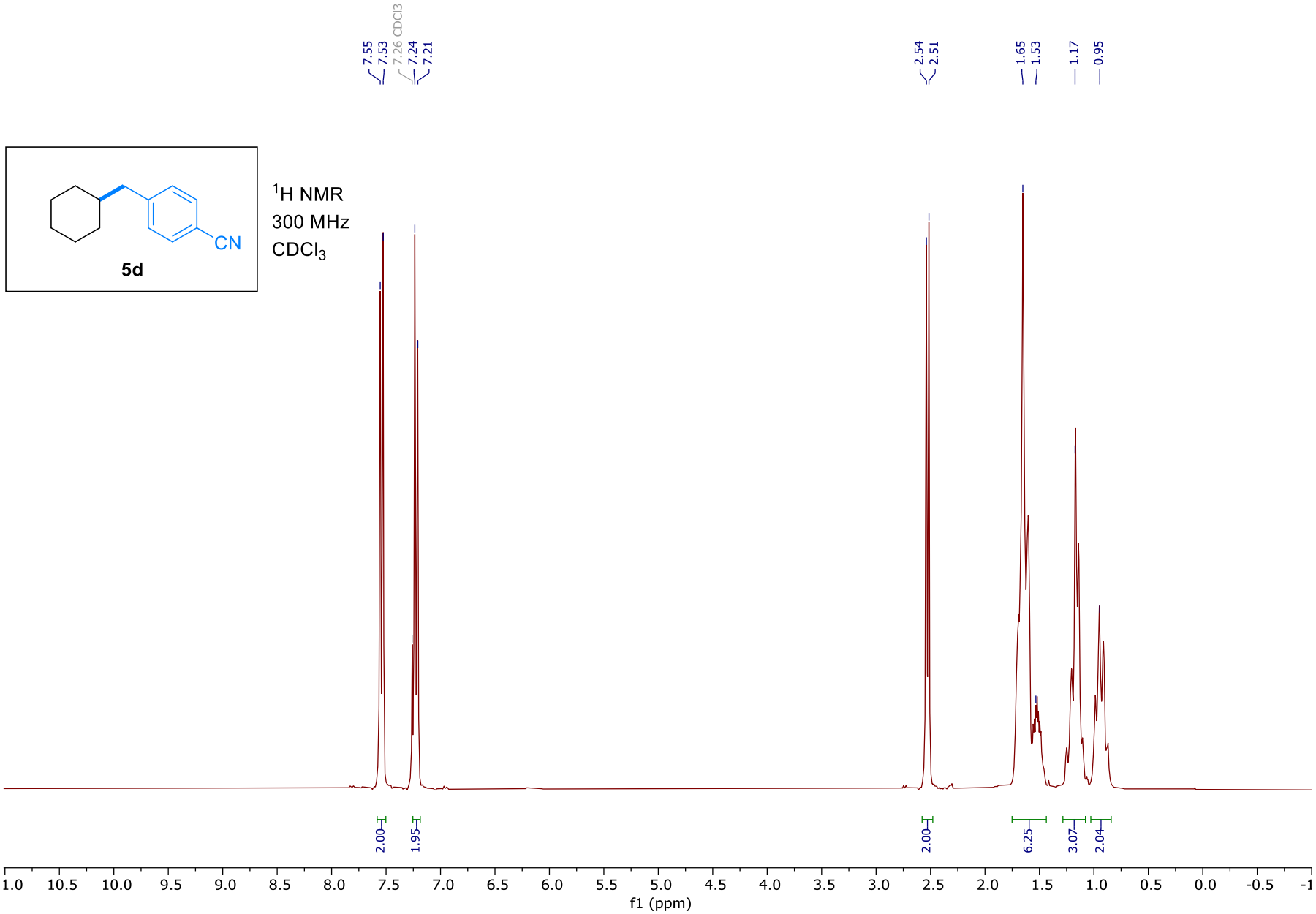

144.91
132.13
130.13
119.14
110.12
79.22
77.16 CDCl3
68.09
42.02
31.22
25.66
O
CN
5a
13C{1H} NMR
75 MHz
CDCl3
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

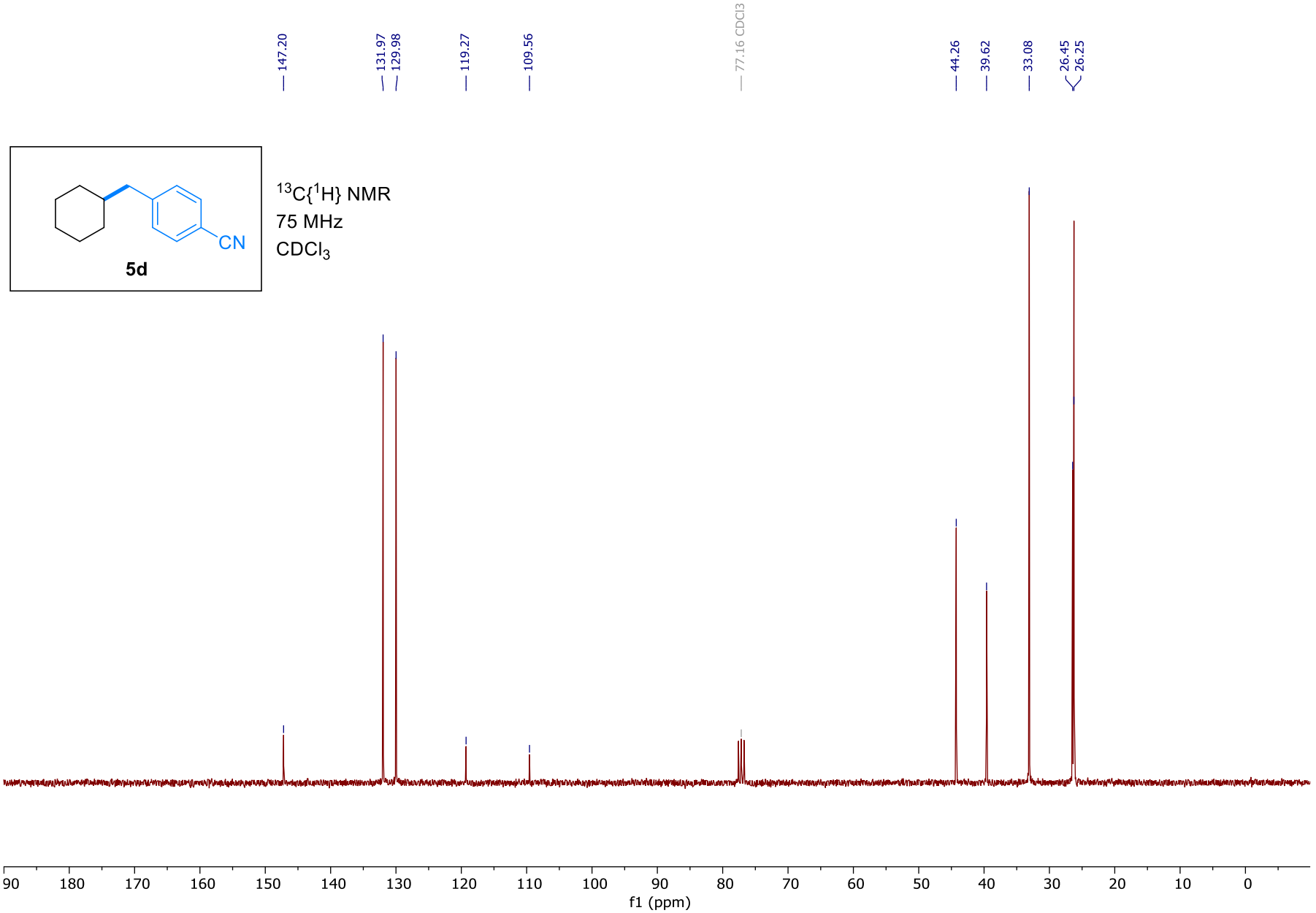

CN
5b
^{1}H NMR
300 MHz
$CDCl_3$
7.55
7.52
7.26 CDCl3
7.18
7.15
2.42
1.93
1.68
1.64
1.56
1.53
1.44
2.01
1.97
2.00
3.03
6.13
5.95
f1 (ppm)

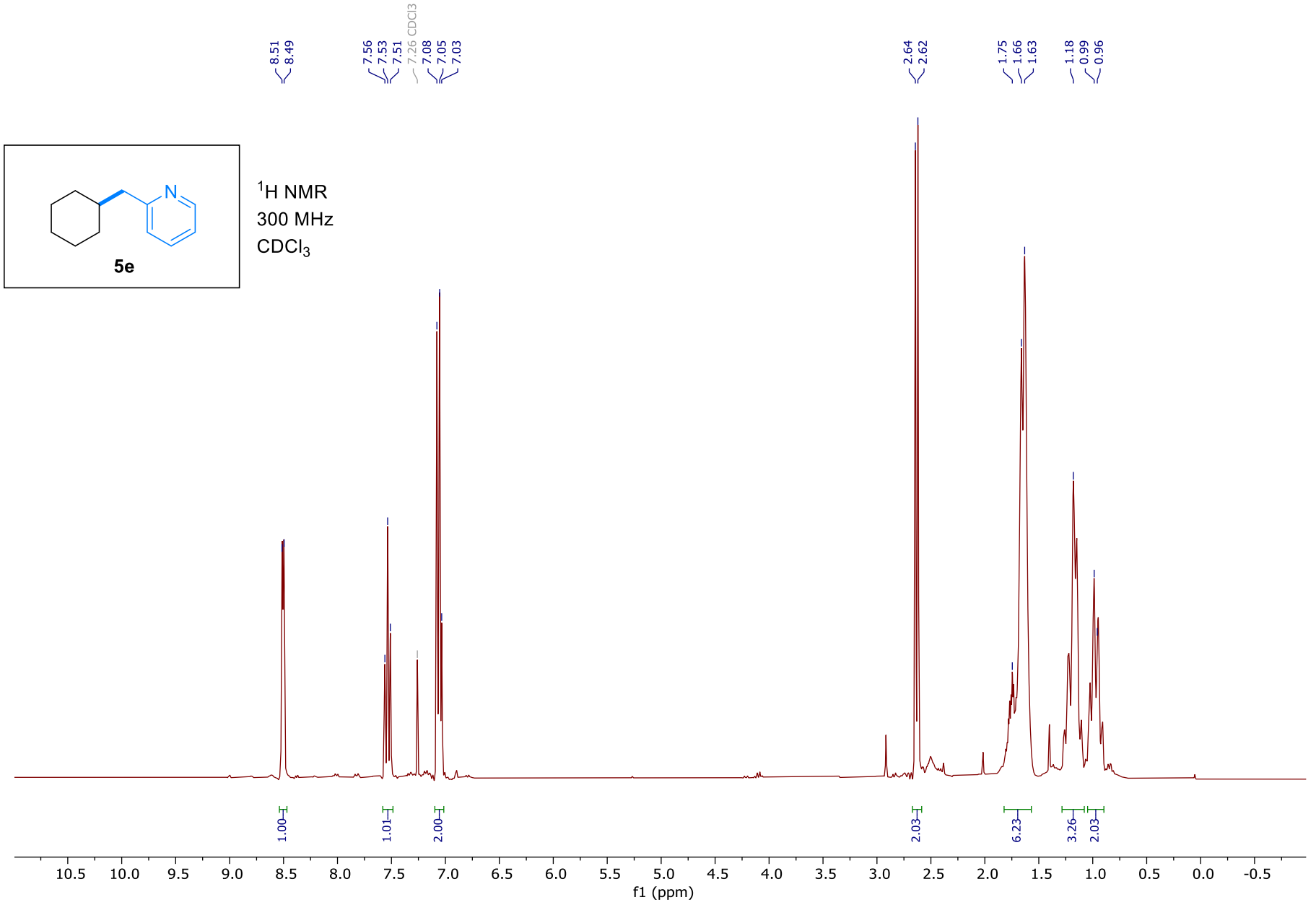

144.17
131.39
131.28
119.31
109.70
77.16 CDCl3
51.39
42.40
36.88
33.88
28.67
CN
5b
$^{13}C\{^{1}H\}$ NMR
75 MHz
$CDCl_3$
f1 (ppm)

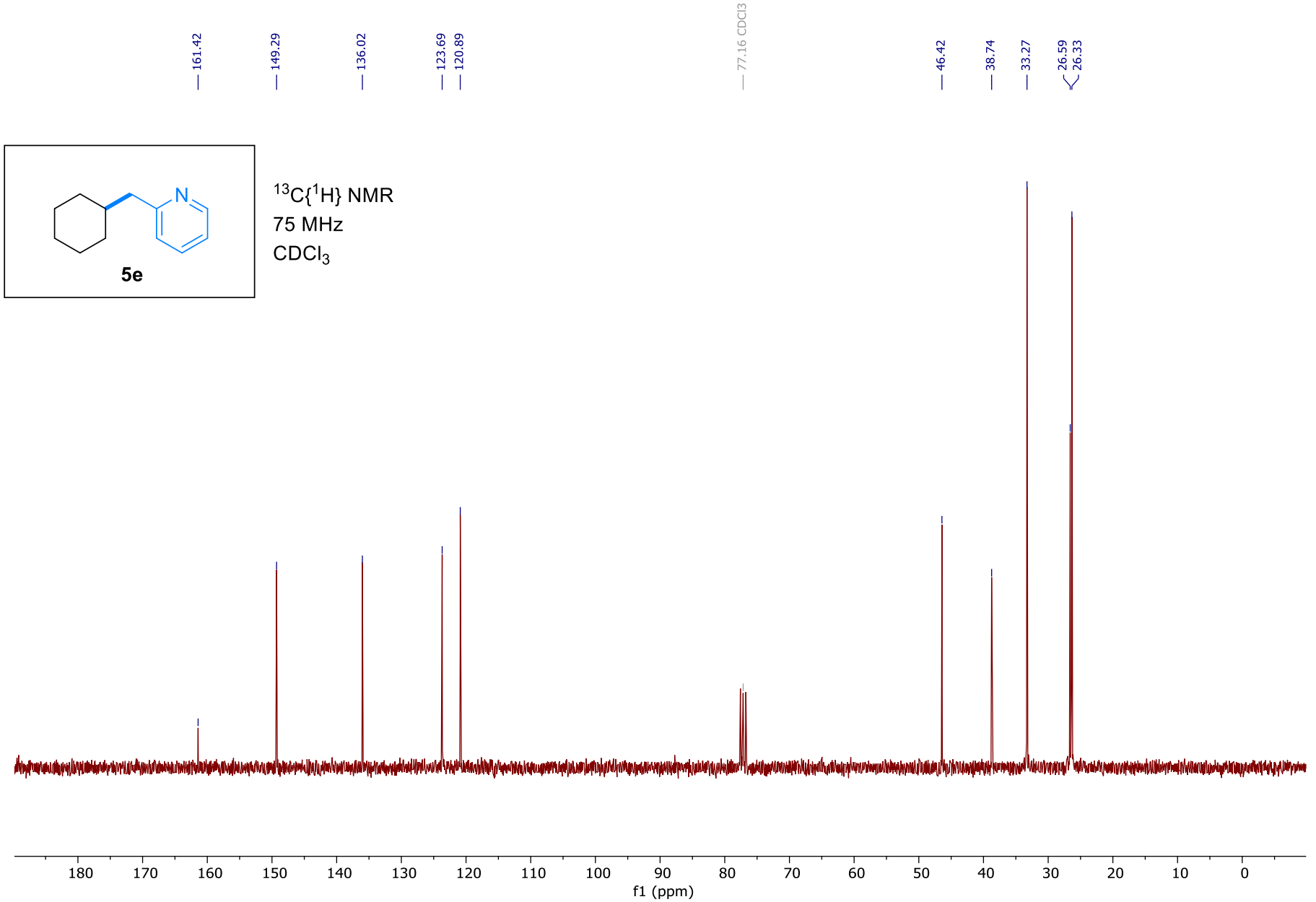

7.59
7.57
7.34
7.31
7.30
7.22
7.21
7.18
2.74
2.72
2.70
2.69
2.67
2.65
2.04
2.01
1.98
1.96
1.93
CN
5c
1H NMR
300 MHz
CDCl3
2.08
4.30
3.05
4.00
2.01
f1 (ppm)

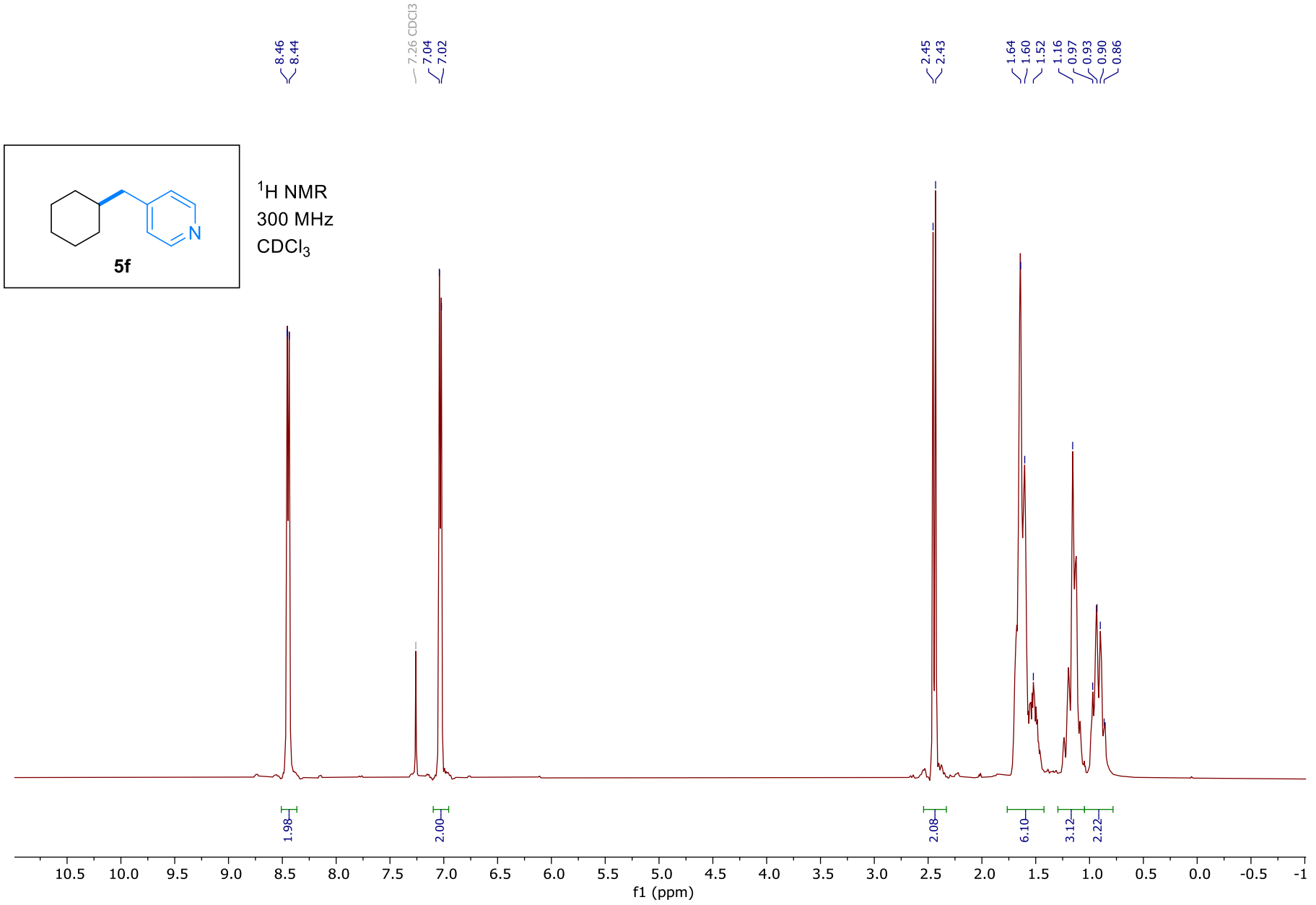

148.06
141.68
132.26
129.32
128.52
128.49
126.09
119.21
109.78
77.16 CDCl3
35.58
35.36
32.50
CN
5c
$^{13}C\{^{1}H\}$ NMR
75 MHz
$CDCl_3$
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

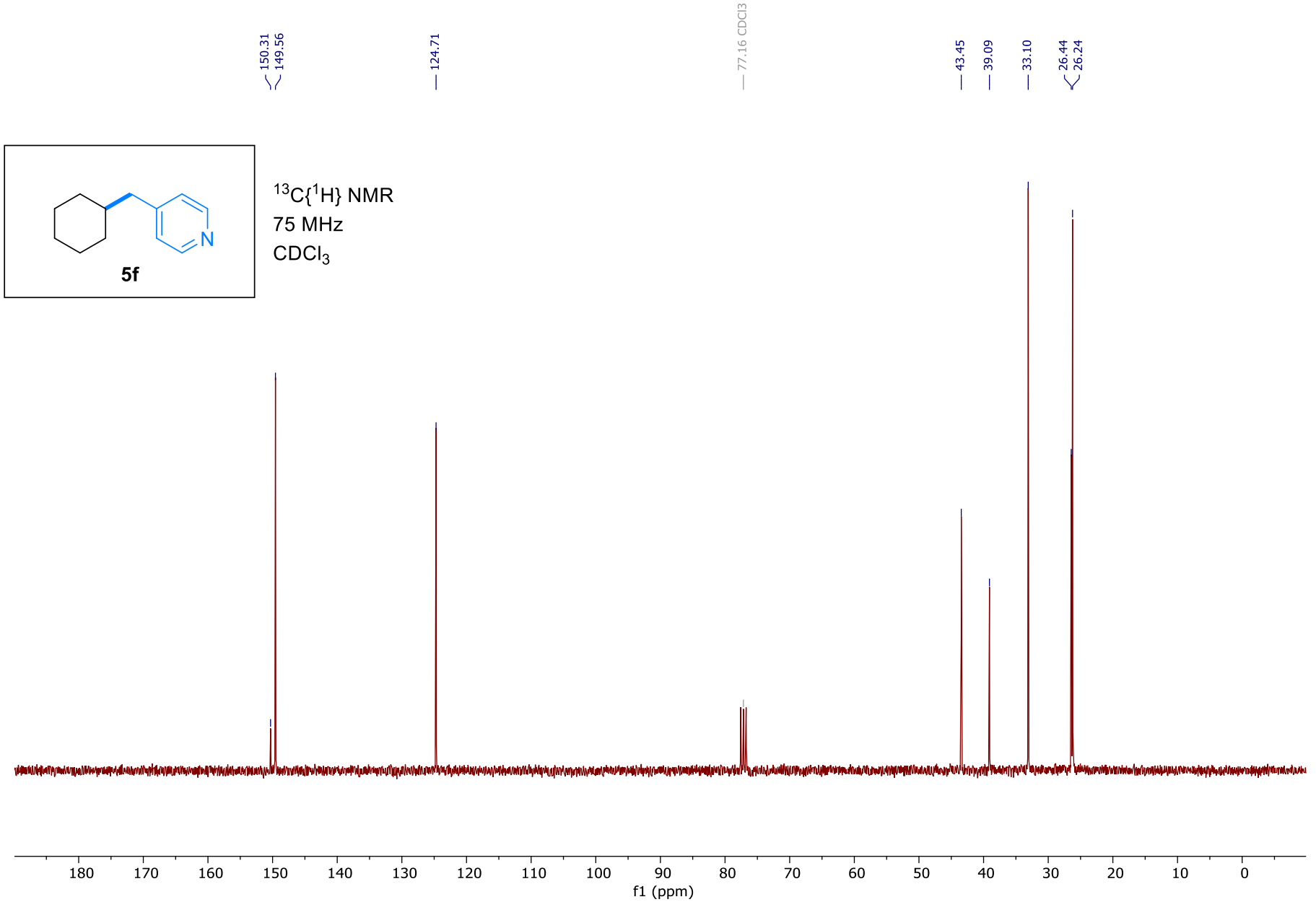

7.55
7.53
7.26 CDCl3
7.24
7.21
2.54
2.51
1.65
1.53
1.17
0.95
CN
5d
^{1}H NMR
300 MHz
$CDCl_3$
2.00
1.95
2.00
6.25
3.07
2.04
f1 (ppm)

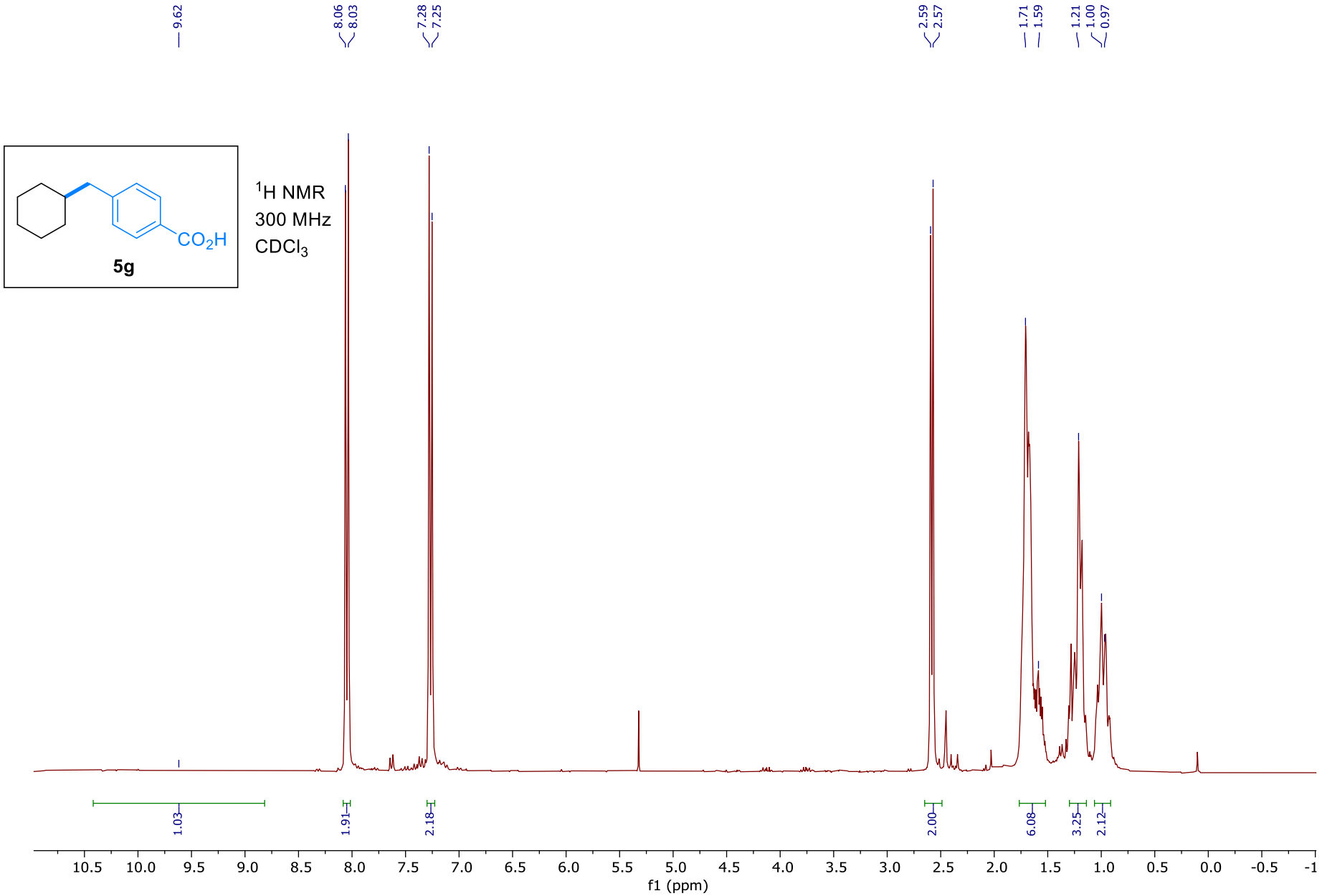

147.20
131.97
129.98
119.27
109.56
77.16 CDCl3
44.26
39.62
33.08
26.45
26.25
CN
5d
$^{13}C\{^{1}H\}$ NMR
75 MHz
$CDCl_3$
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

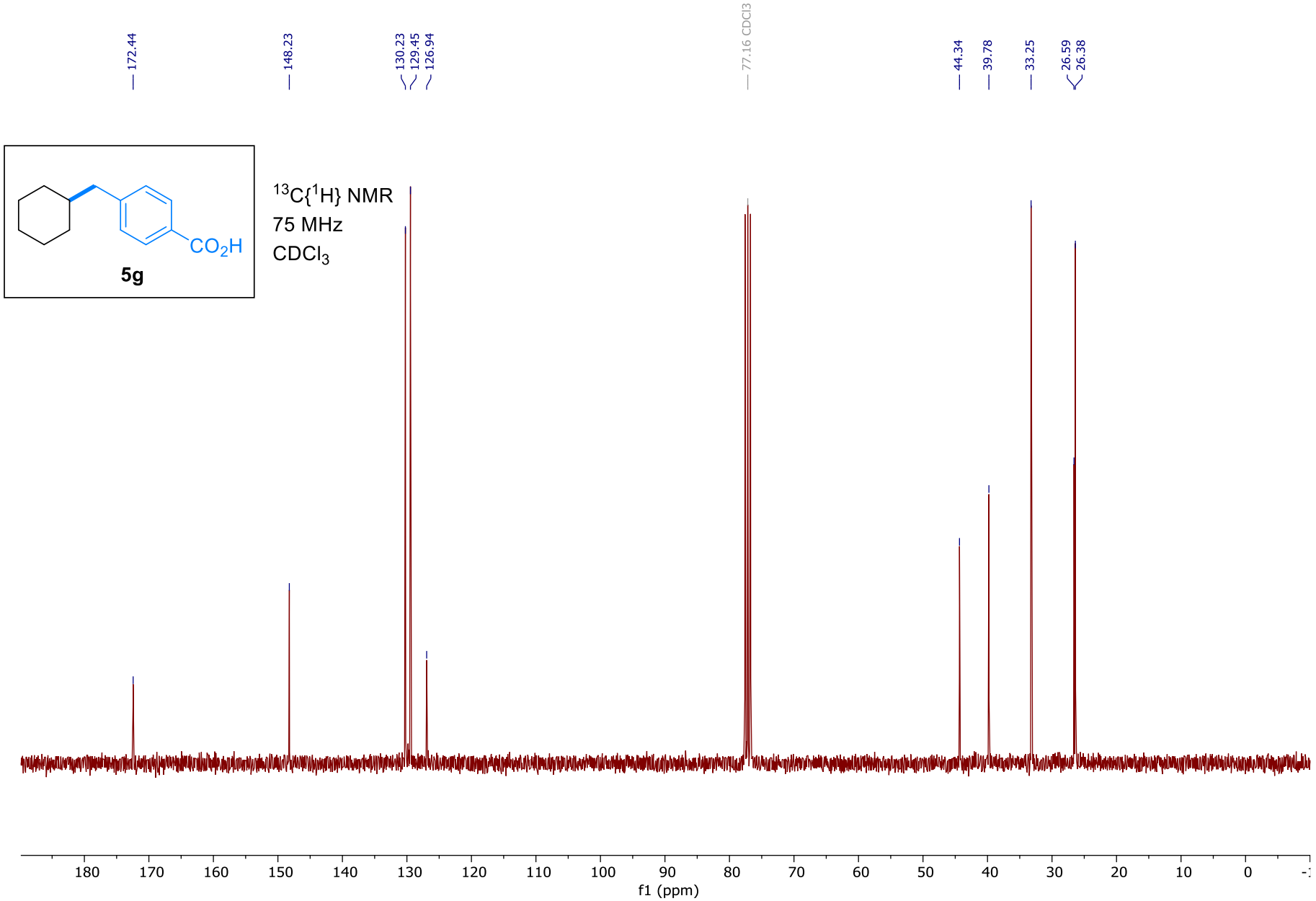

8.51
8.49
7.56
7.53
7.51
7.26 CDCl3
7.08
7.05
7.03
2.64
2.62
1.75
1.66
1.63
1.18
0.99
0.96
N
5e
1H NMR
300 MHz
CDCl3
1.00
1.01
2.00
2.03
6.23
3.26
2.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

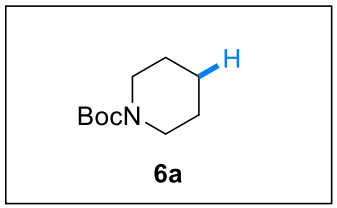

161.42
149.29
136.02
123.69
120.89
77.16 CDCl3
46.42
38.74
33.27
26.59
26.33
N
5e
$^{13}C\{^{1}H\}$ NMR
75 MHz
$CDCl_3$
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.46
8.44
7.26 CDCl3
7.04
7.02
2.45
2.43
1.64
1.60
1.52
1.16
0.97
0.93
0.90
0.86
N
5f
1H NMR
300 MHz
CDCl3
1.98
2.00
2.08
6.10
3.12
2.22
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
f1 (ppm)


150.31
149.56
124.71
77.16 CDCl3
43.45
39.09
33.10
26.44
26.24
N
5f
$^{13}C\{^{1}H\}$ NMR
75 MHz
$CDCl_3$
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

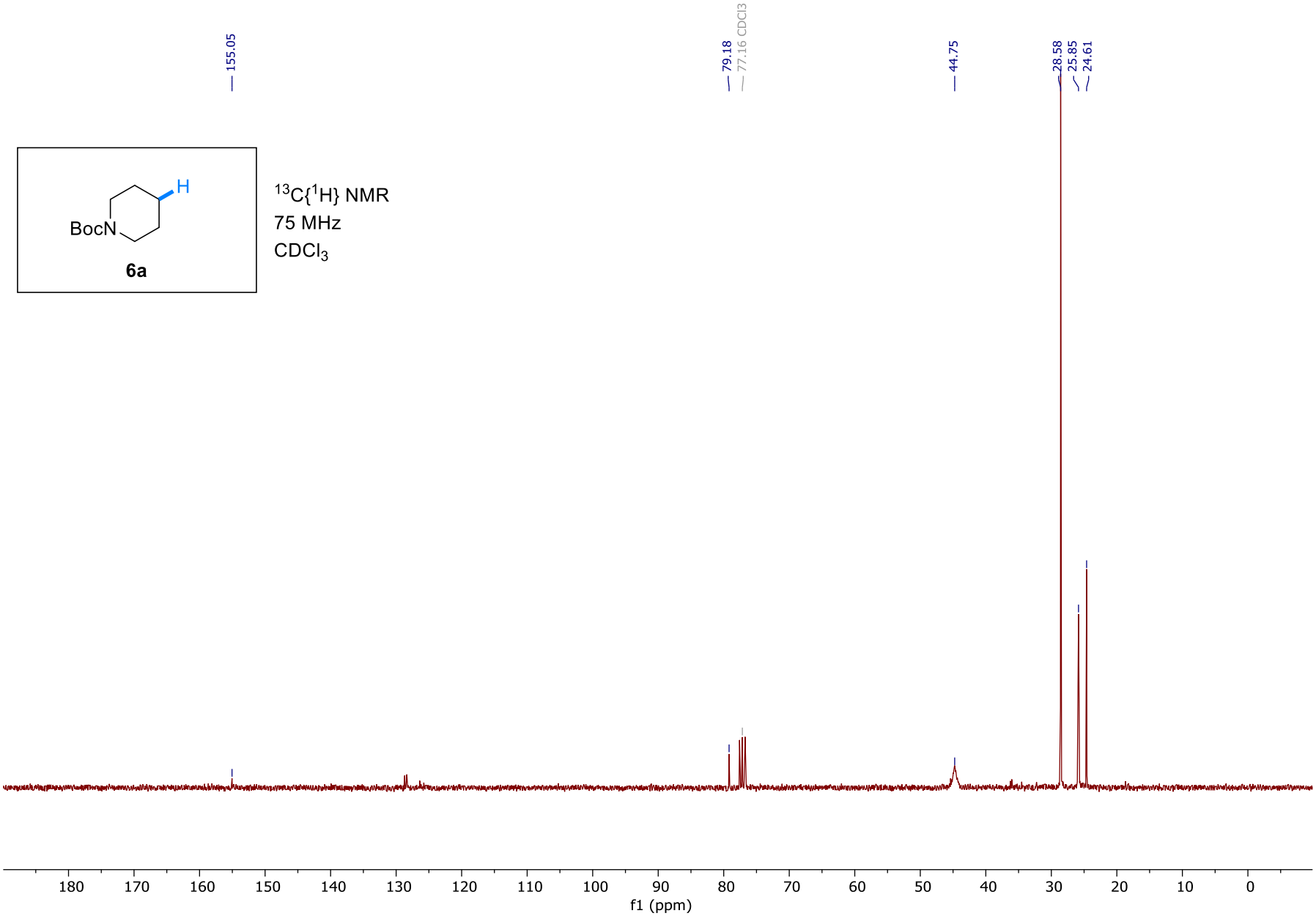

9.62
8.06
8.03
7.28
7.25
2.59
2.57
1.71
1.59
1.21
1.00
0.97
CO2H
5g
1H NMR
300 MHz
CDCl3
1.03
1.91
2.18
2.00
6.08
3.25
2.12
f1 (ppm)


172.44
148.23
130.23
129.45
126.94
77.16 CDCl3
44.34
39.78
33.25
26.59
26.38
CO2H
5g
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



6a

^{1}H NMR
300 MHz
$CDCl_3$


155.05
79.18
77.16 CDCl3
44.75
28.58
25.85
24.61
BocN
H
6a
13C{1H} NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)