Electronic Supplementary Information

Cu-Catalyzed Cyanoalkylation of Electron-deficient Alkenes with Unactivated Alkyl Bromides

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1 General information

All commercially available reagents were used without further purification unless otherwise stated. All solvents were purified and dried according to standard methods prior to use. NMR spectra were recorded on a Bruker 300 and a Bruker 400 instrument spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard unless otherwise stated. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, and br = broad signal, coupling constant (s) in Hz, integration). Data for ^{13}C NMR and ^{19}F NMR are reported in terms of chemical shift (δ, ppm). Reactions were monitored by thin layer chromatography (TLC) and column chromatography purifications were carried out using silica gel GF 254. Melting points were measured on a SCW X-4 and values are uncorrected. All new compounds were further characterized by high resolution mass spectra (ESI-HRMS).

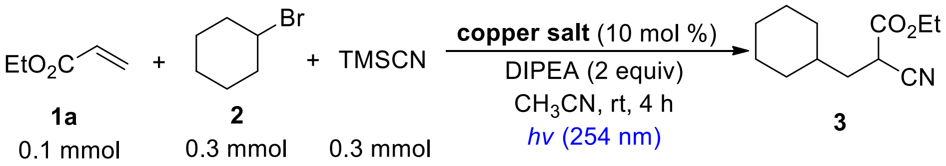
2 Synthesis of substrates 1 and 2

1a, **1b**, **1f**, **1g**, **2a**, **2l**, **2m** and **2n** were purchased from reagent companies. **1c**,[1] **1d**,[2] **1e**,[2] **1h**,[3] **2b-2c**,[4] **2d**,[5] **2e-2i**,[4] **2j**[6] and **2k**[7] were all prepared according to previous reports.

3 General procedures of cyanoalkylation of alkenes

3.1 Optimization of reaction conditions

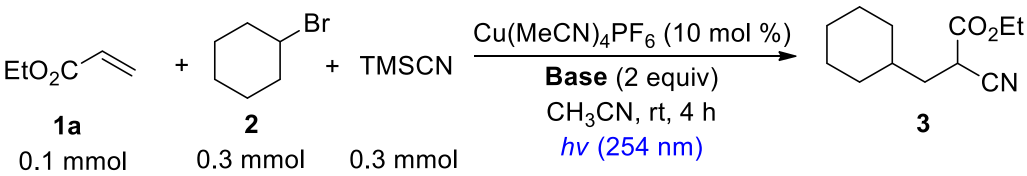
Table S1 Copper salts screening[a]



Entry	Copper salt	Yield (%)[b]
1	***$Cu(MeCN)_4PF_6$***	***32***
2[c]	$Cu(MeCN)_4PF_6$	24
3[d]	$Cu(MeCN)_4PF_6$	32
4	$Cu(MeCN)_4BF_4$	27
5	CuCl	18
6	CuBr	22
7	CuI	22
8	Cu_2O	30
9	CuSCN	20
10	CuTc	21
11	$Cu(acac)_2$	27
12	CuF_2	30
13	$CuBr_2$	30
14	$Cu(OAc)_2$	17
15	$Cu(OTf)_2$	20
16	$CuSO_4$	12

[a] 0.1 mmol scale. [b] Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] 5 mol% $Cu(MeCN)_4PF_6$ was added. [d] 15 mol% $Cu(MeCN)_4PF_6$ was added.

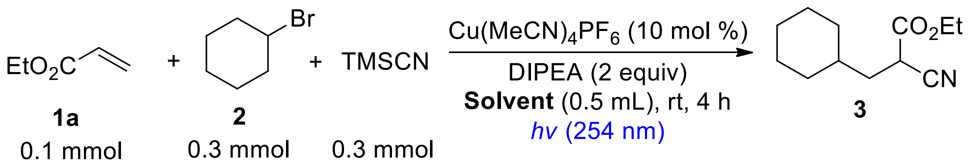
Table S2 Basisc additive screening[a]



Entry	Base	Yield (%)[b]
1	***DIPEA***	***32***
2[c]	DIPEA	28
3[d]	DIPEA	32
4	DABCO	10
5	DBU	18
6	Et_3N	24
7	DMAP	12
8	HMPA	0
9	2,6-lutidine	0
10	pyridine	0
11	TMEDA	15
12	Imidazole	0
13	Et_2NH	26
14	Bu_3N	28
15	*t*-BuOLi	16
16	*t*-BuONa	0
17	*t*-BuOK	0
18	Cs_2CO_3	0
19	K_3PO_4	0
20	$NaHCO_3$	0

[a] 0.1 mmol scale. [b] Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] 1.5 equiv of DIPEA was added. [d] 2.5 equiv of DIPEA was added.

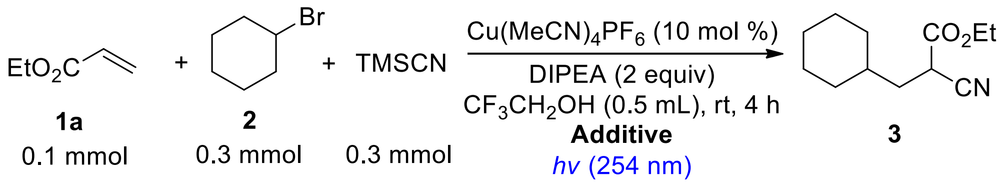
Table S3 Solvents screening[a]



Entry	Solvent	Yield (%)[b]
1	***CF_3CH_2OH***	***46***
2[c]	CF_3CH_2OH	44
3[d]	CF_3CH_2OH	38
4	CH_3OH	38
5	CH_3CH_2OH	42
6	MeCN	37
7	DMF	trace
8	DCM	6
9	DMSO	0
10	THF	0
11	DME	trace
12	Toluene	11
13	1,4-dioxane	trace
14	Acetone	16

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] 1.0 mL of CF_3CH_2OH was added. [d] 1.5 mL of CF_3CH_2OH was added.

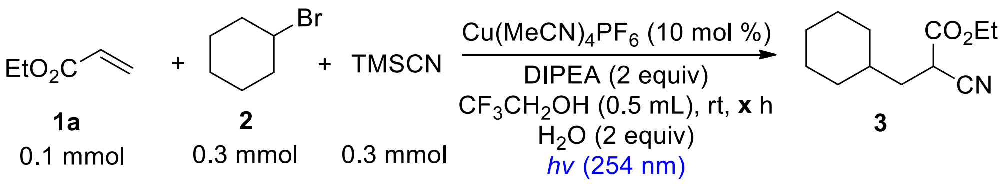
Table S4 Additives screening[a]



Entry	Additive	Yield (%)[b]
1	H_2O (1.0 equiv)	70
2	***H_2O (2.0 equiv)***	***83***

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

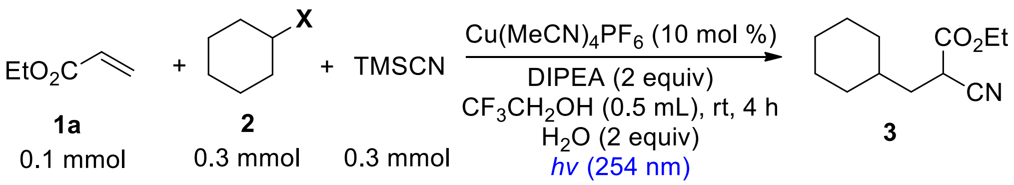
Table S5 Influences of reaction time[a]



Entry	X (h)	Yield (%)[b]
1	2	59
2	3	74
3	***4***	***83***
4	5	83
5	6	83

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

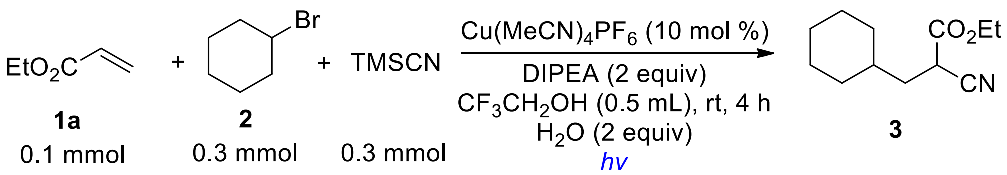
Table S6 Influences of alkyl halides[a]



Entry	X	Yield (%)[b]
1	Cl	0
2	***Br***	***83***
3	I	45

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table S7 Influences of light sources[a]



Entry	Light sources	Yield (%)[b]
1	***100 W UVC compact fluorescent light bulbs***	***83***
2	50 W UVC compact fluorescent light bulbs	57
3	80 W low-pressure mercury lamp (365 nm)	0
4	80 W UVB CFL (280-320 nm)	0
5	30 W blue LED	0
6	30 W white LED	0

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

3.2 Genreal procedure for the synthesis of 3

To an oven-dried 10 mL quartz test tube with a stirring bar was added $Cu(MeCN)_4PF_6$ (0.04 mmol, 14.9 mg). Then, air was withdrawn and backfilled with Ar (three times). CF_3CH_2OH (2.0 mL), **1** (0.4 mmol), **2** (1.2 mmol), TMSCN (1.2 mmol, 118.8 mg), DIPEA (0.8 mmol, 103.4 mg) and H_2O (0.8 mmol, 14.4 mg) were added in turn by syringe. Thereafter, the test tube was transferred to a UV photoreactor (4×25 W, see Figure S1 for details), where it was irradiated at 254 nm for 4 h. Four hours later, the reaction was quenched with water (2 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated in *vacuo* and purified by column chromatography (hexane/ethyl acetate) to afford the product **3**.

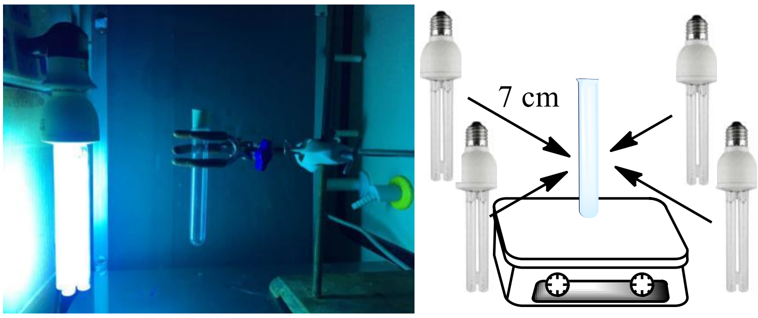
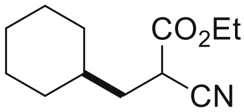


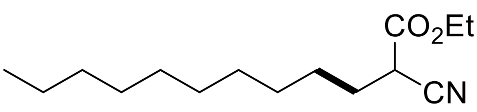
Figure S1 Placement of CFL around quartz test tube. Four 25 W UVC compact fluorescent light bulbs were placed around the quartz test tube and the distance was about 7 cm. A cardboard box lined with tin foil was placed over the lamps and stir plate. In one side of the cardboard box, part of the side was cut out, and a high-speed fan was set up into for dissipating heat.

4 Characterization of products



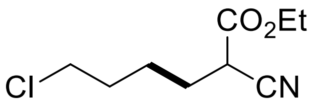
3aa

ethyl 2-cyano-3-cyclohexylpropanoate (3aa): 65.0 mg, yield: 78%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (q, *J* = 7.1 Hz, 2H), 3.56 (dd, *J* = 9.1, 6.4 Hz, 1H), 1.93 – 1.64 (m, 7H), 1.62 – 1.43 (m, 1H), 1.39 – 1.11 (m, 6H), 1.05 – 0.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.53, 116.67, 62.66, 36.95, 35.26, 35.15, 32.97, 31.90, 26.10, 25.82, 25.70, 13.91. HRMS (ESI) $C_{12}H_{19}NNaO_2$ $[M+Na]^+$ calcd: 232.1308, found: 232.1308.



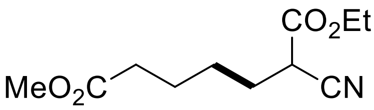
3ab

ethyl 2-cyanododecanoate (3ab): 82.0 mg, yield: 81%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, *J* = 7.1 Hz, 2H), 3.49 (t, *J* = 7.0 Hz, 1H), 1.94 (dd, *J* = 15.3, 7.5 Hz, 2H), 1.55 – 1.41 (m, 2H), 1.37 – 1.24 (m, 17H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.21, 116.58, 62.66, 37.60, 37.50, 31.80, 29.80, 29.45, 29.37, 29.21, 29.13, 28.71, 26.70, 22.61, 14.05. HRMS (ESI) $C_{15}H_{27}NNaO_2$ $[M+Na]^+$ calcd: 276.1934, found: 276.1937.



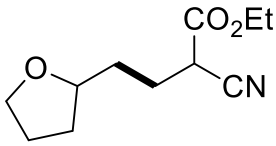
3ac

ethyl 6-chloro-2-cyanohexanoate (3ac): 62.5 mg, yield: 77%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.1 Hz, 2H), 3.55 (dt, *J* = 11.7, 6.7 Hz, 3H), 1.99 (dd, *J* = 15.5, 7.5 Hz, 2H), 1.92 – 1.79 (m, 2H), 1.77 – 1.60 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.85, 116.27, 62.87, 44.10, 37.39, 31.57, 29.02, 24.09, 13.94. HRMS (ESI) $C_9H_{14}ClNNaO_2$ $[M+Na]^+$ calcd: 226.0605, found: 226.0607.



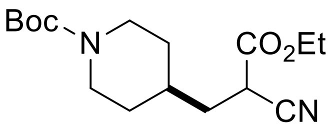
3ad

1-ethyl 7-methyl 2-cyanoheptanedioate (3ad): 67.0 mg, yield: 74%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 3.52 (t, *J* = 7.0 Hz, 1H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.97 (dd, *J* = 15.3, 7.4 Hz, 2H), 1.77 – 1.63 (m, 2H), 1.62 – 1.47 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.46, 165.94, 116.33, 62.78, 51.55, 37.35, 33.43, 29.40, 26.19, 23.98, 13.93. HRMS (ESI) $C_{11}H_{17}NNaO_4$ $[M+Na]^+$ calcd: 250.1050, found: 250.1055.



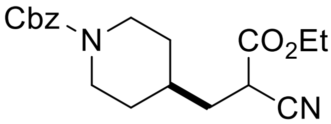
3ae

ethyl 2-cyano-4-(tetrahydrofuran-2-yl)butanoate (3ae): 61.0 mg, yield: 72%. 1:1 d.r. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.92 – 3.78 (m, 2H), 3.78 – 3.65 (m, 1.55H), 3.61 (dd, *J* = 7.8, 6.3 Hz, 0.49H), 2.24 – 1.95 (m, 3H), 1.95 – 1.82 (m, 2H), 1.77 – 1.63 (m, 2H), 1.57 – 1.41 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.18, 166.03, 116.61, 116.49, 78.50, 77.76, 67.80, 67.74, 62.68, 62.66, 37.57, 37.23, 32.53, 32.33, 31.52, 31.26, 27.30, 26.68, 25.56, 25.49, 13.94. HRMS (ESI) $C_{11}H_{17}NNaO_3$ $[M+Na]^+$ calcd: 234.1101, found: 234.1100.



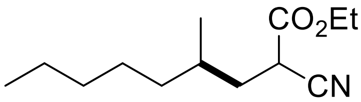
3af

***tert*-butyl 4-(2-cyano-3-ethoxy-3-oxopropyl)piperidine-1-carboxylate (3af):** 101.5 mg, yield: 82%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.1 Hz, 2H), 4.12 (d, *J* = 7.1 Hz, 2H), 3.59 (dd, *J* = 9.2, 6.1 Hz, 1H), 2.71 (br, 2H), 2.01 – 1.79 (m, 2H), 1.75 – 1.67 (m, 3H), 1.46 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.28 – 1.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.02, 154.50, 116.25, 79.31, 62.76, 43.23, 35.87, 34.97, 33.62, 31.67, 30.82, 28.26, 13.82. HRMS (ESI) $C_{16}H_{26}N_2NaO_4$ $[M+Na]^+$ calcd: 333.1784, found: 333.1785.



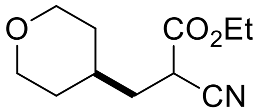
3ag

benzyl 4-(2-cyano-3-ethoxy-3-oxopropyl)piperidine-1-carboxylate (3ag): 107.0 mg, yield: 78%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (br, 5H), 5.12 (br, 2H), 4.27 (dd, *J* = 14.3, 7.1 Hz, 4H), 3.57 (dd, *J* = 9.2, 6.1 Hz, 1H), 2.79 (d, *J* = 8.3 Hz, 2H), 2.01 – 1.77 (m, 2H), 1.72 (d, *J* = 3.7 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.27 – 1.11 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.06, 155.07, 136.64, 128.44, 127.96, 127.83, 116.29, 67.03, 66.76, 62.98, 43.52, 35.86, 35.09, 33.56, 31.74, 30.73, 13.87. HRMS (ESI) $C_{19}H_{24}N_2NaO_4$ $[M+Na]^+$ calcd: 367.1628, found: 367.1624.



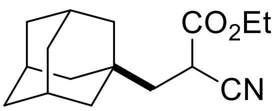
3ah

ethyl 2-cyano-4-methylnonanoate (3ah): 63.0 mg, yield: 70%. 1:1 d.r. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 3.51 – 3.41 (m, 1H), 1.96 – 1.81 (m, 1H), 1.79 – 1.55 (m, 2H), 1.30 – 1.18 (m, 11H), 0.92 – 0.78 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.57, 166.46, 116.77, 116.54, 62.72, 62.70, 36.94, 36.73, 35.90, 35.66, 35.58, 31.87, 30.75, 30.70, 26.33, 26.11, 22.55, 19.25, 18.50, 14.00, 13.94. HRMS (ESI) $C_{13}H_{23}NNaO_2$ $[M+Na]^+$ calcd: 248.1621, found: 248.1621.



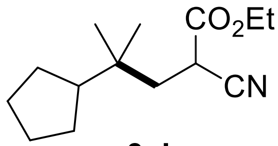
3ai

ethyl 2-cyano-3-(tetrahydro-2H-pyran-4-yl)propanoate (3ai): 63.4 mg, yield: 75%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.1 Hz, 2H), 4.02 – 3.94 (m, 2H), 3.57 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.40 (td, *J* = 11.8, 1.7 Hz, 2H), 2.01 – 1.72 (m, 3H), 1.69 – 1.61 (m, 2H), 1.46 – 1.23 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.15, 116.33, 67.51, 67.42, 62.89, 36.34, 34.88, 32.70, 32.59, 31.80, 13.93. HRMS (ESI) $C_{11}H_{17}NNaO_3$ $[M+Na]^+$ calcd: 234.1101, found: 234.1097.



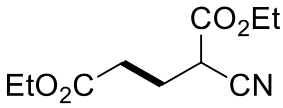
3aj

ethyl 3-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2-cyanopropanoate (3aj): 68.0 mg, yield: 65%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (q, *J* = 7.1 Hz, 2H), 3.47 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.00 (br, 3H), 1.83 – 1.49 (m, 14H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.09, 118.04, 62.84, 43.84, 41.81, 36.64, 32.55, 31.90, 28.33, 13.94. HRMS (ESI) $C_{16}H_{23}NNaO_2$ $[M+Na]^+$ calcd: 284.1621, found: 284.1615.



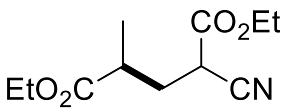
3ak

ethyl 2-cyano-4-cyclopentyl-4-methylpentanoate (3ak): 74.0 mg, yield: 78%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 3.39 (dd, *J* = 8.2, 4.9 Hz, 1H), 1.96 – 1.78 (m, 2H), 1.77 – 1.62 (m, 1H), 1.58 – 1.39 (m, 6H), 1.30 – 1.11 (m, 5H), 0.86 (d, *J* = 8.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.07, 117.91, 62.83, 49.17, 41.19, 34.98, 33.14, 33.04, 26.77, 25.62, 23.94, 13.85. HRMS (ESI) $C_{14}H_{23}NNaO_2$ $[M+Na]^+$ calcd: 260.1621, found: 260.1616.



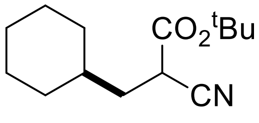
3al

diethyl 2-cyanopentanedioate (3al): 61.4 mg, yield: 72%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.1 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.76 (dd, *J* = 8.4, 6.0 Hz, 1H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.41 – 2.12 (m, 2H), 1.31 (dt, *J* = 17.3, 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.47, 165.49, 115.91, 62.84, 60.78, 36.31, 30.55, 24.68, 14.01, 13.84. HRMS (ESI) $C_{10}H_{15}NNaO_4$ $[M+Na]^+$ calcd: 236.0893, found: 236.0897.



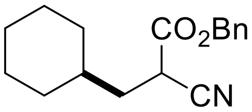
3am

diethyl 2-cyano-4-methylpentanedioate (3am): 69.0 mg, yield: 76%. 1:1 d.r. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, *J* = 7.1 Hz, 2H), 4.17 (qd, *J* = 7.1, 3.3 Hz, 2H), 3.72 (dd, *J* = 10.5, 5.3 Hz, 0.52H), 3.62 (t, *J* = 7.6 Hz, 0.46H), 2.82 – 2.59 (m, 1H), 2.41 – 2.26 (m, 1H), 2.07 (dt, *J* = 14.0, 7.0 Hz, 0.50H), 1.94 (ddd, *J* = 14.3, 10.5, 4.2 Hz, 0.54H), 1.37 – 1.22 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.61, 174.56, 165.71, 116.15, 116.04, 62.95, 62.91, 60.92, 60.89, 36.95, 36.86, 35.89, 35.32, 32.89, 17.69, 16.86, 14.09, 13.91. HRMS (ESI) $C_{11}H_{17}NNaO_4$ $[M+Na]^+$ calcd: 250.1050 found: 250.1048.



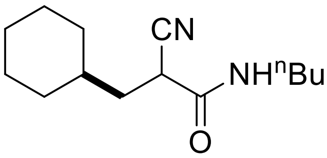
3ba

***tert*-butyl 2-cyano-3-cyclohexylpropanoate (3ba):** 77.0 mg, yield: 81%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (dd, *J* = 9.0, 6.5 Hz, 1H), 1.89 – 1.64 (m, 8H), 1.50 (s, 9H), 1.35 – 1.11 (m, 3H), 1.05 – 0.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.49, 117.05, 83.69, 36.96, 36.29, 35.21, 32.99, 31.99, 27.70, 26.13, 25.86, 25.74. HRMS (ESI) $C_{14}H_{23}NNaO_2$ $[M+Na]^+$ calcd: 260.1621, found: 260.1614.



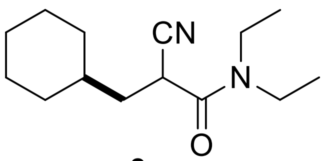
3ca

benzyl 2-cyano-3-cyclohexylpropanoate (3ca): 91.0 mg, yield: 84%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (br, 5H), 5.23 (s, 2H), 3.60 (dd, *J* = 9.0, 6.6 Hz, 1H), 1.93 – 1.66 (m, 7H), 1.56 – 1.43 (m, 1H), 1.30 – 1.08 (m, 3H), 1.01 – 0.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.44, 134.59, 128.74, 128.71, 128.41, 116.53, 68.22, 37.02, 35.35, 35.16, 32.96, 32.00, 26.13, 25.84, 25.73. HRMS (ESI) $C_{17}H_{21}NNaO_2$ $[M+Na]^+$ calcd: 294.1465, found: 294.1454.



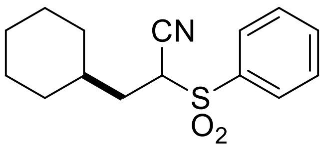
3da

***N*-butyl-2-cyano-3-cyclohexylpropanamide (3da):** 72.0 mg, yield: 76%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (br, 1H), 3.45 (dd, *J* = 9.3, 6.3 Hz, 1H), 3.29 (dd, *J* = 13.0, 6.9 Hz, 2H), 1.93 – 1.64 (m, 7H), 1.59 – 1.46 (m, 3H), 1.44 – 1.11 (m, 5H), 1.06 – 0.89 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.93, 118.57, 39.98, 37.36, 36.29, 35.41, 33.16, 31.92, 31.22, 26.12, 25.86, 25.74, 19.88, 13.60. HRMS (ESI) $C_{14}H_{24}N_2NaO$ $[M+Na]^+$ calcd: 259.1781, found: 259.1773.



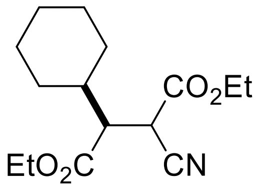
3ea

2-cyano-3-cyclohexyl-*N*,*N*-diethylpropanamide (3ea): 71.0 mg, yield: 75%. White solid. M. p. 47 –48 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (dd, *J* = 9.5, 5.9 Hz, 1H), 3.50 – 3.25 (m, 4H), 2.00 – 1.87 (m, 1H), 1.85 – 1.65 (m, 6H), 1.56 – 1.44 (m, 1H), 1.35 – 1.10 (m, 9H), 1.06 – 0.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.11, 117.82, 42.38, 41.07, 37.37, 35.22, 33.24, 32.32, 32.31, 26.16, 25.87, 25.76, 14.30, 12.62. HRMS (ESI) $C_{14}H_{24}N_2NaO$ $[M+Na]^+$ calcd: 259.1781, found: 259.1774.



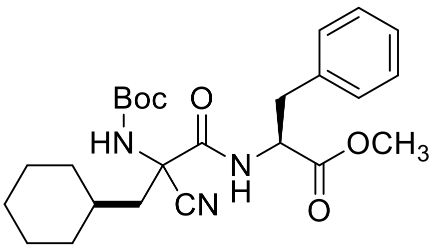
3fa

3-cyclohexyl-2-(phenylsulfonyl)propanenitrile (3fa): 80.0 mg, yield: 72%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.7 Hz, 2H), 7.78 (t, *J* = 7.4 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 2H), 4.00 (dd, *J* = 11.8, 4.2 Hz, 1H), 2.01 (ddd, *J* = 13.8, 9.9, 4.2 Hz, 1H), 1.91 – 1.63 (m, 6H), 1.59 – 1.48 (m, 1H), 1.34 – 0.83 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.56, 135.19, 129.63, 129.56, 114.17, 55.70, 35.09, 33.40, 31.61, 25.99, 25.80, 25.56. HRMS (ESI) $C_{15}H_{19}NNaO_2S$ $[M+Na]^+$ calcd: 300.1029, found: 300.1022.



3ga

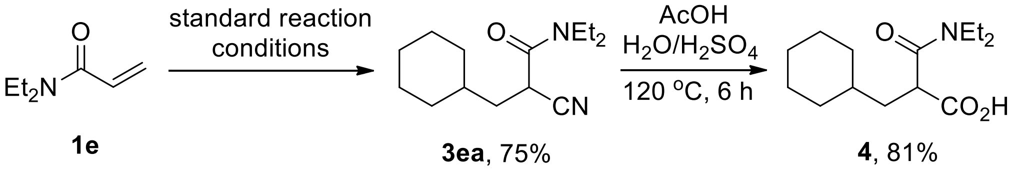
diethyl 2-cyano-3-cyclohexylsuccinate (3ga): 84.4 mg, yield: 75%. 1:1 d.r. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 – 4.12 (m, 4H), 4.04 (d, *J* = 10.3 Hz, 0.48H), 3.79 (d, *J* = 5.6 Hz, 0.51H), 2.92 (ddd, *J* = 13.6, 9.1, 4.9 Hz, 1H), 1.92 – 1.65 (m, 6H), 1.37 – 0.91 (m, 11H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.02, 170.79, 165.30, 165.16, 115.16, 115.00, 63.05, 61.19, 61.16, 50.38, 49.53, 38.46, 37.93, 37.55, 37.41, 31.60, 30.56, 30.39, 28.25, 26.38, 26.06, 25.95, 25.92, 25.80, 25.77, 14.12, 14.03, 13.86, 13.79. HRMS (ESI) $C_{15}H_{23}NNaO_4$ $[M+Na]^+$ calcd: 304.1519, found: 304.1510.



3ha

(S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-2-cyano-3-cyclohexylpropanamido)-3-phe nylpropanoate (3ha): 111.8 mg, yield: 61%. 1:1 d.r. White solid. M. p. 98 –99 °C. ^{1}H N MR (300 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 3H), 7.16 (d, *J* = 6.1 Hz, 2H), 6.97 (d, *J* = 7. 7 Hz, 0.48H), 6.80 (d, *J* = 8.0 Hz, 0.45H), 5.65 – 5.28 (m, 1H), 4.92 – 4.78 (m, 1H), 3. 73 (s, 3H), 3.18 – 3.01 (m, 2H), 1.78 – 1.59 (m, 6H), 1.45 (d, *J* = 1.3 Hz, 9H), 1.31 – 1.06 (m, 4H), 1.05 – 0.81 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.11, 153.52, 153. 44, 135.47, 135.16, 129.28, 129.08, 128.73, 127.36, 127.29, 117.57, 54.02, 53.64, 53.39, 5 2.45, 52.42, 44.05, 37.90, 37.79, 33.85, 33.77, 33.72, 33.57, 33.51, 28.08, 25.85, 25.79. H RMS (ESI) $C_{25}H_{35}N_3NaO_5$ $[M+Na]^+$ calcd: 480.2469, found: 480.2446.

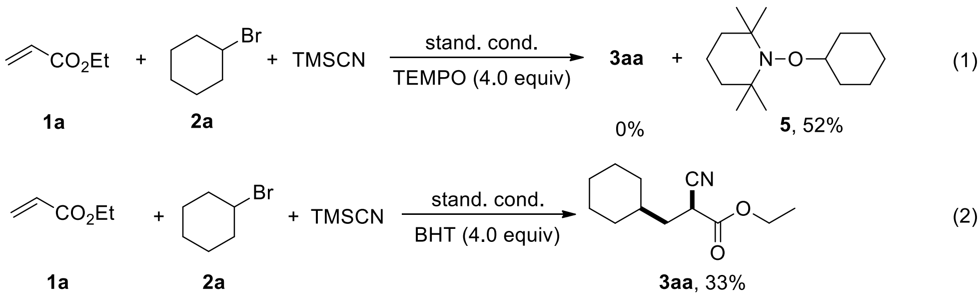
5 Synthetic application[8]



To a 10 mL round bottom flask with a stirring bar was added **3ea** (0.4 mmol, 94.5 mg), AcOH (1.0 mL), H_2O (1.0 mL), H_2SO_4 (1.0 mL), and heated to 120 °C for 1 h. Then, reaction mixture was heated to reflux for additional 6 h. The resulting mixture was cooled to room temperature and sodium hydroxide was added to adjust pH to 14. The suspension was diluted with H_2O until all the solids dissolved. The solution was washed with EA (2×20 ml) and the hydrochloric acid was added dropwise until pH = 1. The resulting mixture was extracted with EA (3×20 ml), washed with brine, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The crude material was purified by flash chromatography on silicagel to afford derivative product **4**. **2-(cyclohexylmethyl)-3-(diethylamino)-3-oxopropanoic acid (4):** 82.5 mg, yield: 81%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 – 3.48 (m, 2H), 3.42 – 3.23 (m, 3H), 1.87 (br, 2H), 1.66 (br, 5H), 1.38 – 1.09 (m, 10H), 0.98 – 0.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.51, 45.55, 42.42, 41.16, 39.98, 35.25, 33.63, 32.62, 26.35, 26.04, 25.92, 14.45, 12.71. HRMS (ESI) $C_{14}H_{25}NNaO_3$ $[M+Na]^+$ calcd: 278.1727, found: 278.1716.

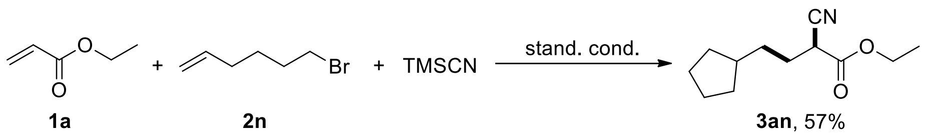
6 The mechanistic study

6.1 Radical trapping experiments



To an oven-dried 10 mL quartz test tube with a stirring bar was added $Cu(MeCN)_4PF_6$ (0.02 mmol, 7.4 mg), TEMPO (0.8 mmol, 125.0 mg) or BHT (0.8 mmol, 176.3 mg). Then, air was withdrawn and backfilled with Ar (three times). CF_3CH_2OH (1.0 mL), **1a** (0.2 mmol, 20.0 mg), **2a** (0.6 mmol, 97.2 mg), TMSCN (0.6 mmol, 59.4 mg), DIPEA (0.4 mmol, 51.7 mg) and H_2O (0.4 mmol, 7.2 mg) were added in turn by syringe. Thereafter, the test tube was transferred to a UV photoreactor (4×25 W, see Figure S1 for details), where it was irradiated at 254 nm for 4 h. Four hours later, the reaction was quenched with water (2 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated in *vacuo* and purified by column chromatography (hexane/ethyl acetate) to afford the product **5**. **5**: 25.0 mg, yield: 52%. The NMR data are consistent with a previous report.[9]

6.2 Radical clock experiment

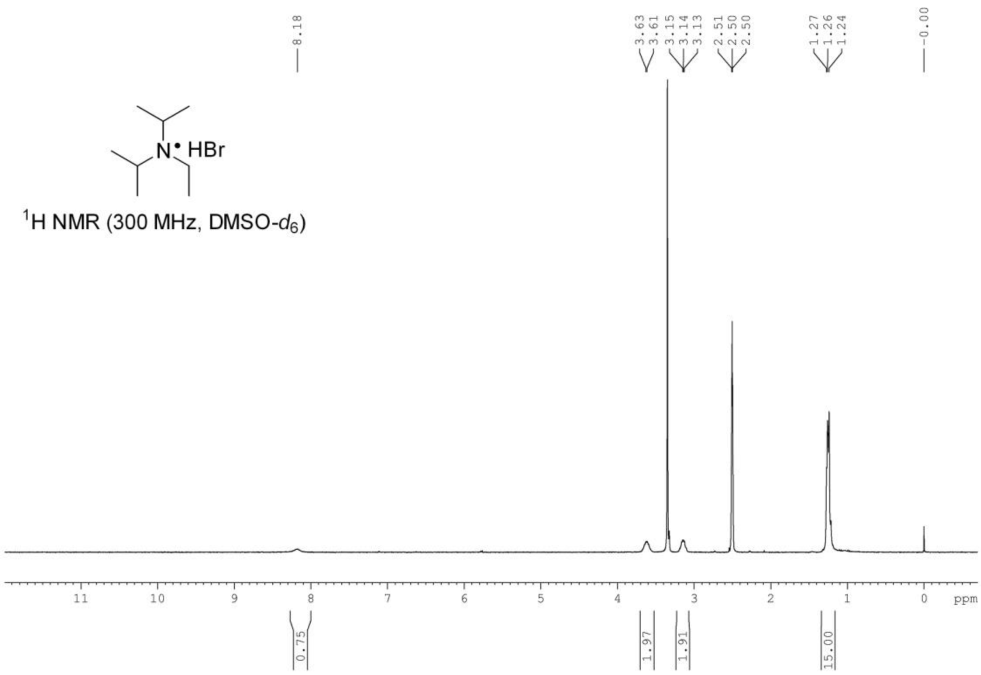


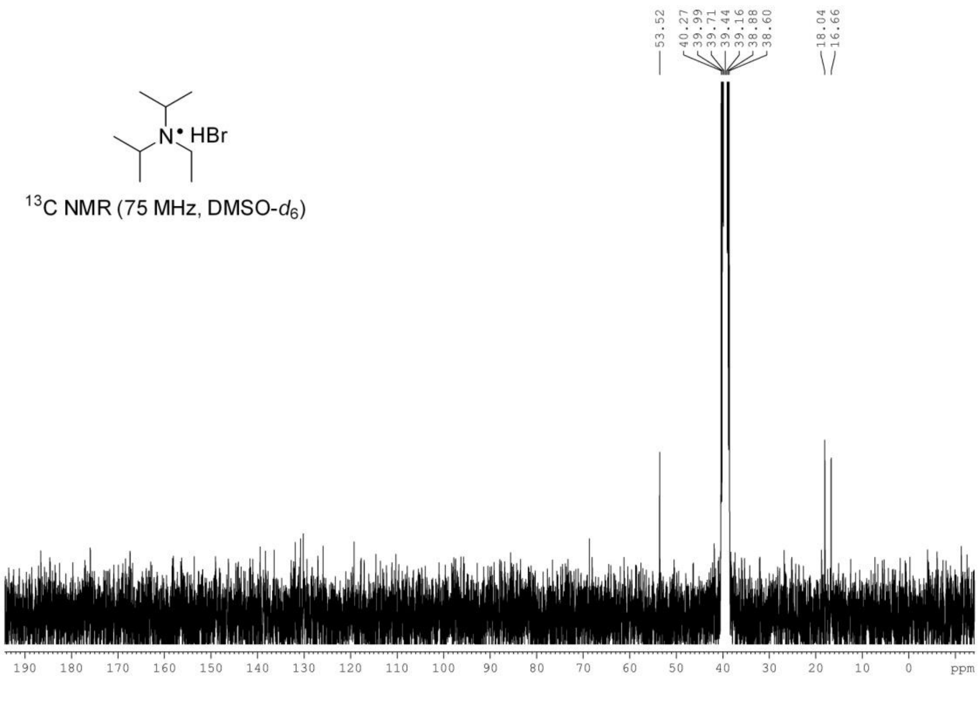
(3)

To an oven-dried 10 mL quartz test tube with a stirring bar was added Cu(MeCN)$_4$PF$_6$ (0.04 mmol, 14.9 mg). Then, air was withdrawn and backfilled with Ar (three times). CF_3CH_2OH (2.0 mL), **1a** (0.4 mmol, 40.0 mg), **2** (1.2 mmol, 194.4 mg), TMSCN (1.2 mmol, 118.8 mg), DIPEA (0.8 mmol, 103.4 mg) and H_2O (0.8 mmol, 14.4 mg) were added in turn by syringe. Thereafter, the test tube was transferred to a UV photoreactor (4×25 W, see Figure S1 for details), where it was irradiated at 254 nm for 4 h. Four hours later, the reaction was quenched with water (2 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated in *vacuo* and purified by column chromatography (hexane/ethyl acetate) to afford the product **3an**. **ethyl 2-cyano-4-cyclopentylbutanoate (3an):** 47.4 mg, yield: 57%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, J = 7.1 Hz, 2H), 3.48 (t, J = 6.9 Hz, 1H), 2.02 – 1.90 (m, 2H), 1.85 – 1.68 (m, 3H), 1.67 – 1.45 (m, 6H), 1.33 (t, J = 7.1 Hz, 3H), 1.15 – 1.07 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.23, 116.62, 62.69, 39.35, 37.78, 33.06, 32.50, 32.34, 29.13, 25.06, 13.99. HRMS (ESI) $C_{12}H_{19}NNaO_2$ $[M+Na]^+$ calcd: 232.1308, found: 232.1305.

6.3 Analysis of by-product

When the reaction mixture was taken out from UV photoreactor, we found that white precipitate was separated out. The residue was filtered, washed by EtOAc and vacuum drying. According to the analysis of NMR spectra, the white precipitate is (i-Pr)$_2$EtN•HBr. ^{1}H NMR (300 MHz, DMSO) δ 8.18 (br, 1H), 3.70 – 3.52 (m, 2H), 3.21 – 3.06 (m, 2H), 1.31 – 1.16 (m, 15H). ^{13}C NMR (75 MHz, DMSO) δ 53.52, 18.04, 16.66.





6.4 Calculation of Apparent Quantum Efficiency (A. Q. E)

In theory, one photon can motivate one C-Br bond to produce an alkyl radical. The energy of one photon (E_{photon}) with wavelength of λ_{inc} (nm) is calculated using the following equation：

$$E_{photon} = \frac{hc}{\lambda_{inc}} = \frac{6.63 \times 10^{-34}\ \mathrm{J \cdot s} \times 3 \times 10^{8}\ \mathrm{m \cdot s^{-1}}}{254 \times 10^{-9}\ \mathrm{m}} = 7.8 \times 10^{-19}\ \mathrm{J}$$

where h (J·s) is Planck's constant, c (m·s^{-1}) is the speed of light and λ_{inc} (m) is the wavelength of the incident light. And the total energy of the incident monochromatic light (E_{total}) is calculated using the following equation:

$$E_{total} = PSt = 0.11\ \mathrm{W \cdot cm^{-2}} \times 1.05\ \mathrm{cm^2} \times 4 \times 3600\ \mathrm{s} = 1.66 \times 10^3\ \mathrm{J}$$

where P ($\mathrm{W \cdot cm^{-2}}$) is the power density of the incident light, S ($\mathrm{cm^2}$) is the irradiation area and t (s) is the photoreaction time. The total number of incident photons can be obtained through the following equation:

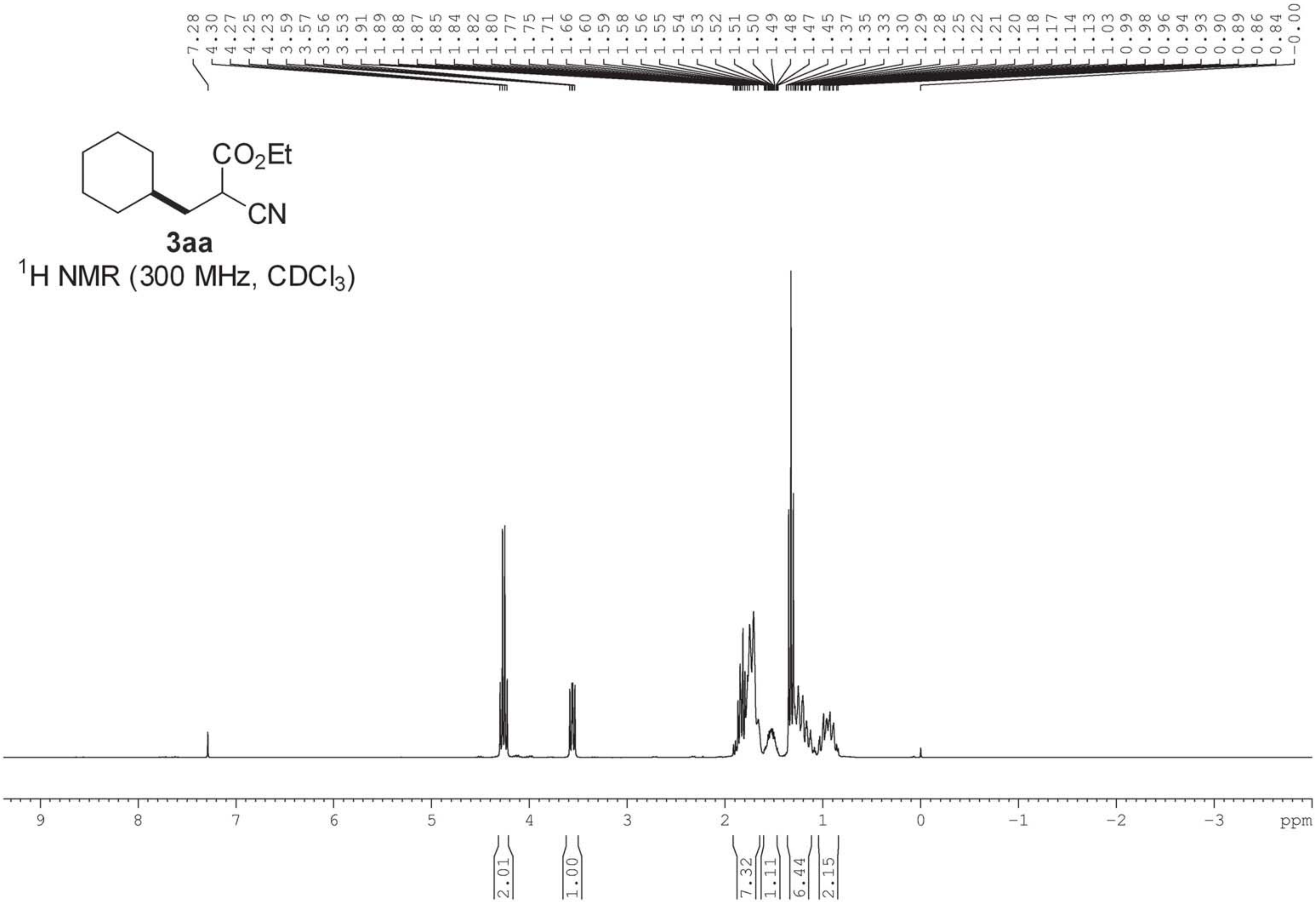
$$Number\ of\ incident\ photons = \frac{E_{total}}{E_{photon}} = \frac{1.66 \times 10^3\ \mathrm{J}}{7.8 \times 10^{-19}\ \mathrm{J}} = 2.13 \times 10^{21} = 3.5\ \mathrm{mmol}$$

As a result, the apparent quantum yield (A.Q.Y.) is defined as follows:

$$\mathrm{A.Q.Y.}\ (\%) = \frac{Number\ of\ product\ \mathbf{3a}}{Number\ of\ incident\ photons} = \frac{0.083\ \mathrm{mmol}}{3.5\ \mathrm{mmol}} = 2.37\%$$

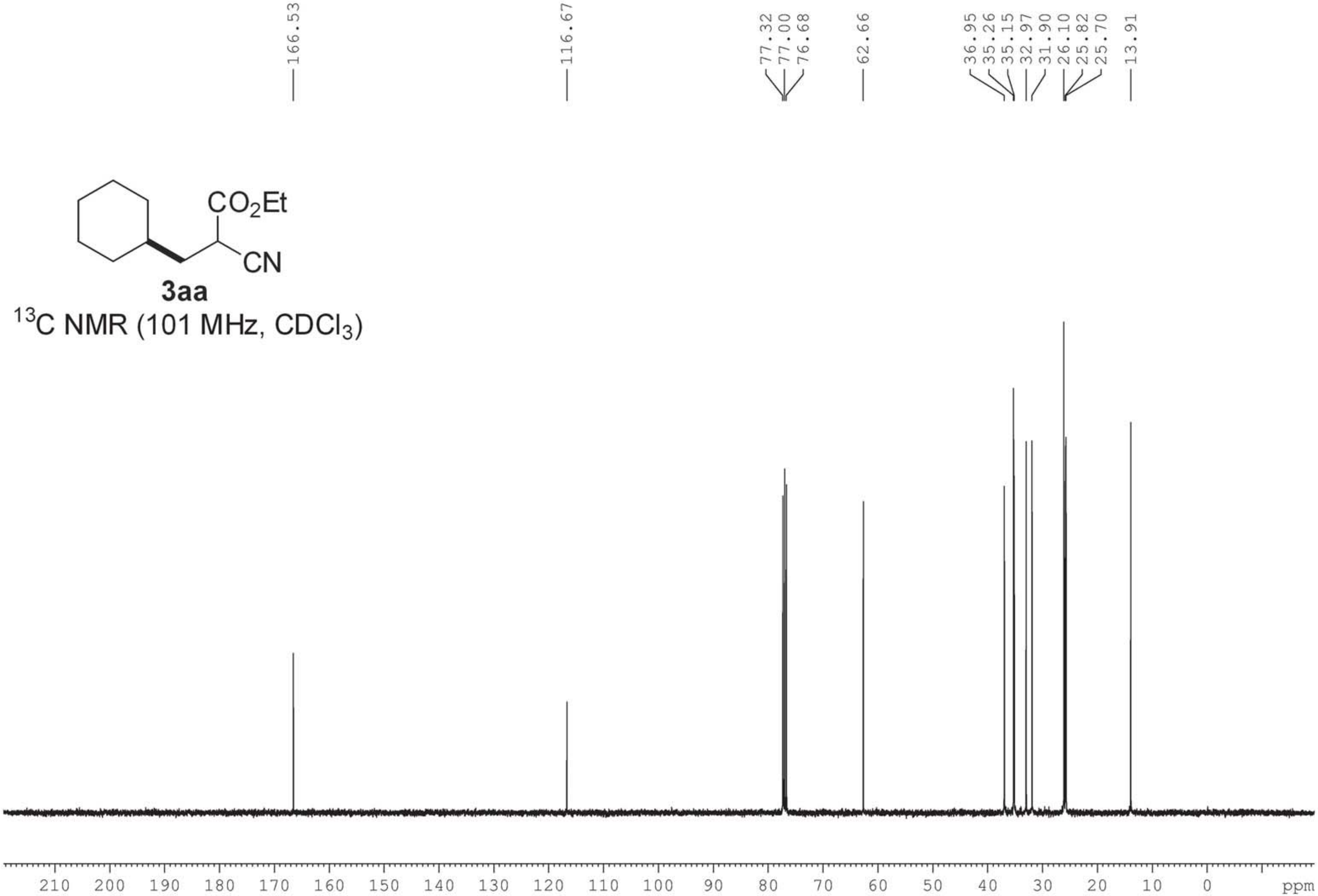
7 References

1. M. Pittelkow and J. B. Christensen, *Org. Lett.*, 2005, **7**, 12958.
2. M. Fu, L. Chen, Y. Jiang, Z.-X. Jiang and Z. Yang, *Org. Lett.*, 2016, **18**, 3481.
3. F. Bartoccini, S. Bartolucci, S. Lucarini and G. Piersanti, *Eur. J. Org. Chem.*, 2015, **2015**, 3352.
4. H.-Q. Do, S. Bachman, A. C. Bissember, J. C. Peters and G. C. Fu, *J. Am. Chem. Soc.*, 2014, **136**, 2162.
5. A. Nortcliffe, I. N. Fleming, N. P. Botting and D. O'Hagan, *Tetrahedron*, 2014, **70**, 8343.
6. A. S. Dudnik and G. C. Fu, *J. Am. Chem. Soc.*, 2012, **134**, 10693.
7. B. Yang and Z. Lu, *J. Org. Chem.*, 2016, **81**, 7288.
8. Q. Guo, M. Wang, Y. Wang, Z. Xu and R. Wang, *Chem. Commun.*, 2017, **53**, 12317.
9. C. Wang, Y. Lei, M. Guo, Q. Shang, H. Liu, Z. Xu and R. Wang, *Org. Lett.*, 2017, **19**, 6412.

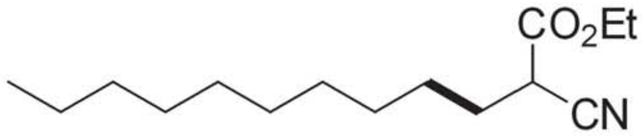


3aa

^1H NMR (300 MHz, $CDCl_3$)

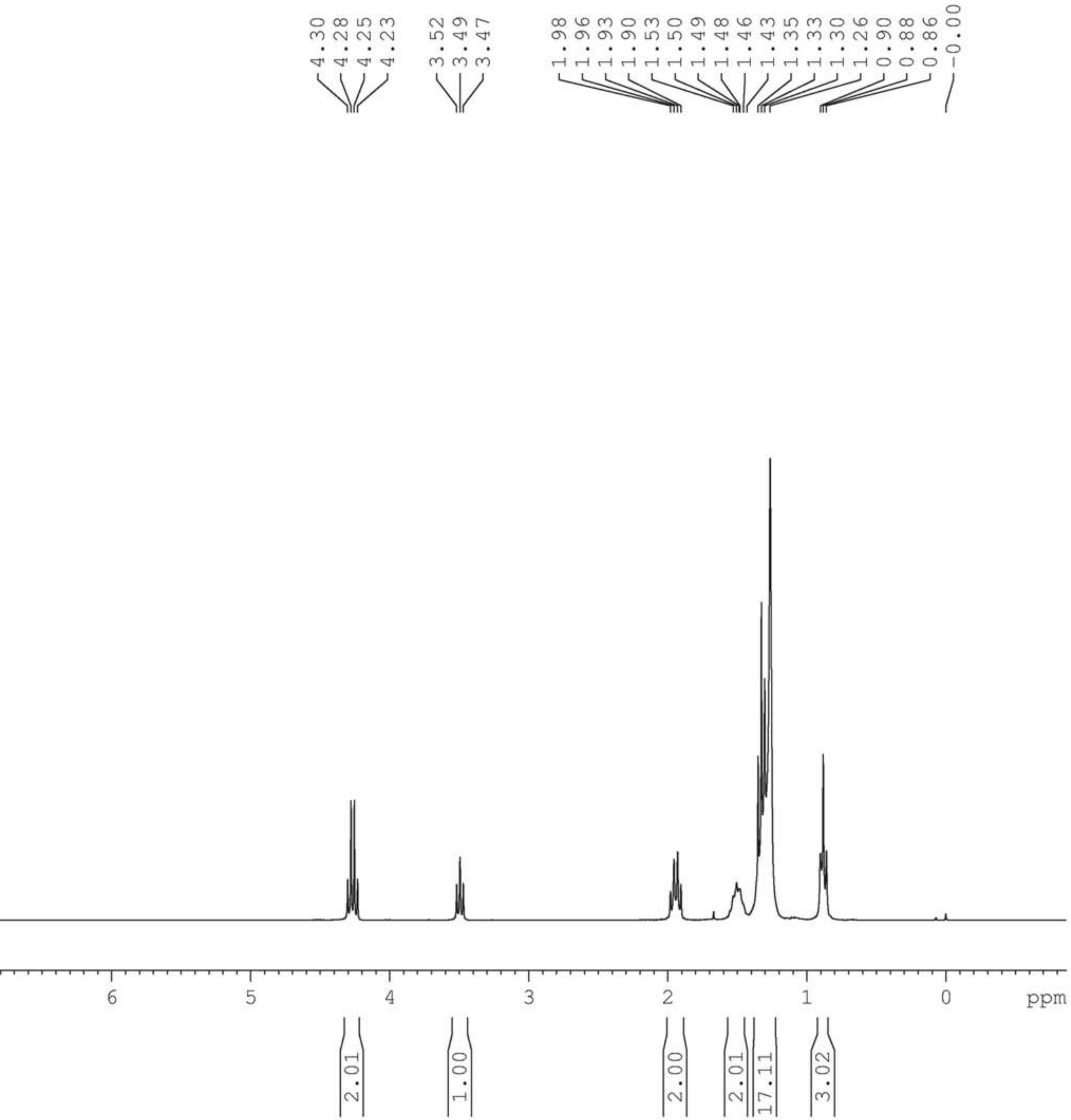


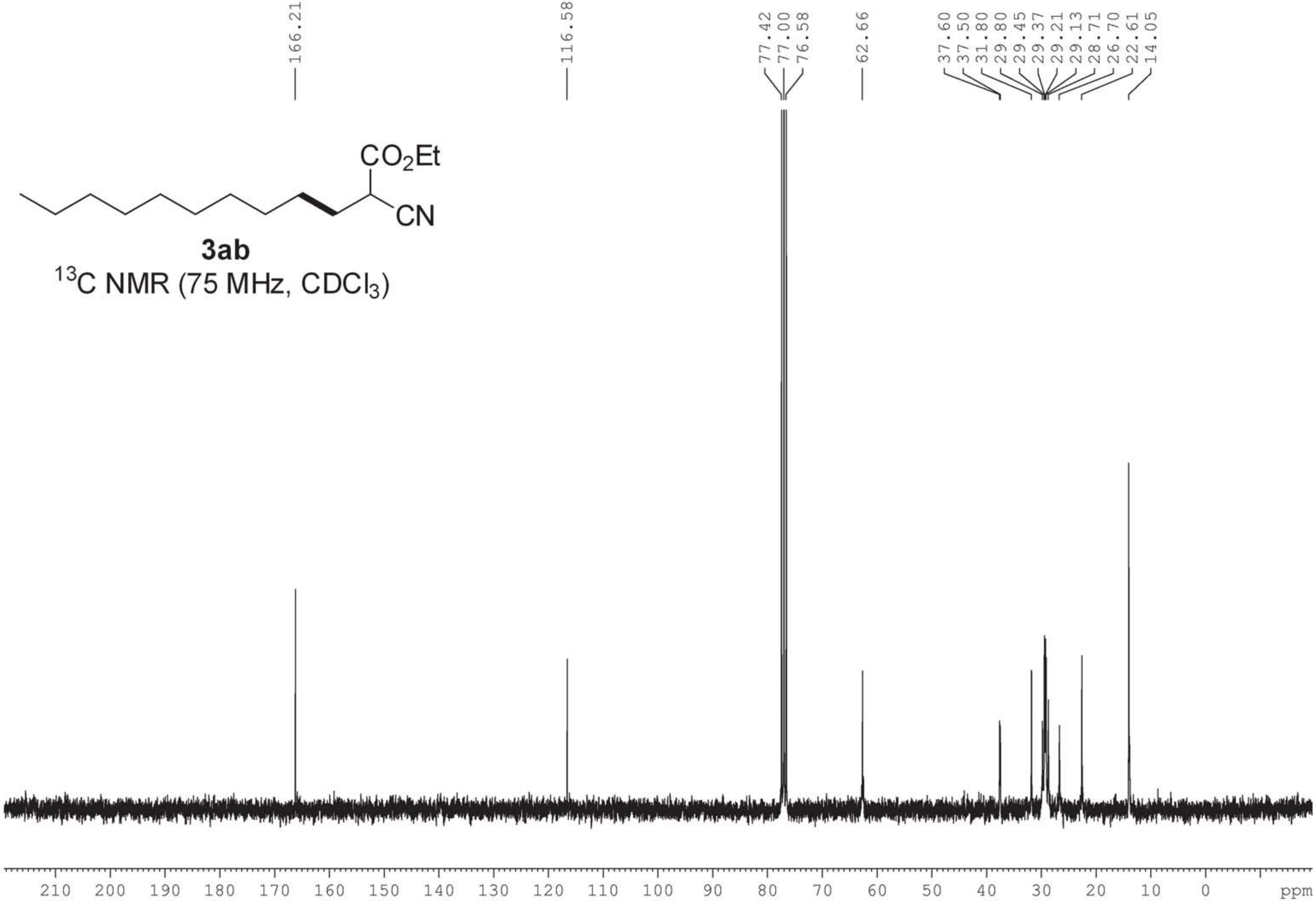
CO2Et
CN
3aa
13C NMR (101 MHz, CDCl3)
166.53
116.67
77.32
77.00
76.68
62.66
36.95
35.26
35.15
32.97
31.90
26.10
25.82
25.70
13.91
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



3ab

^{1}H NMR (300 MHz, $CDCl_3$)

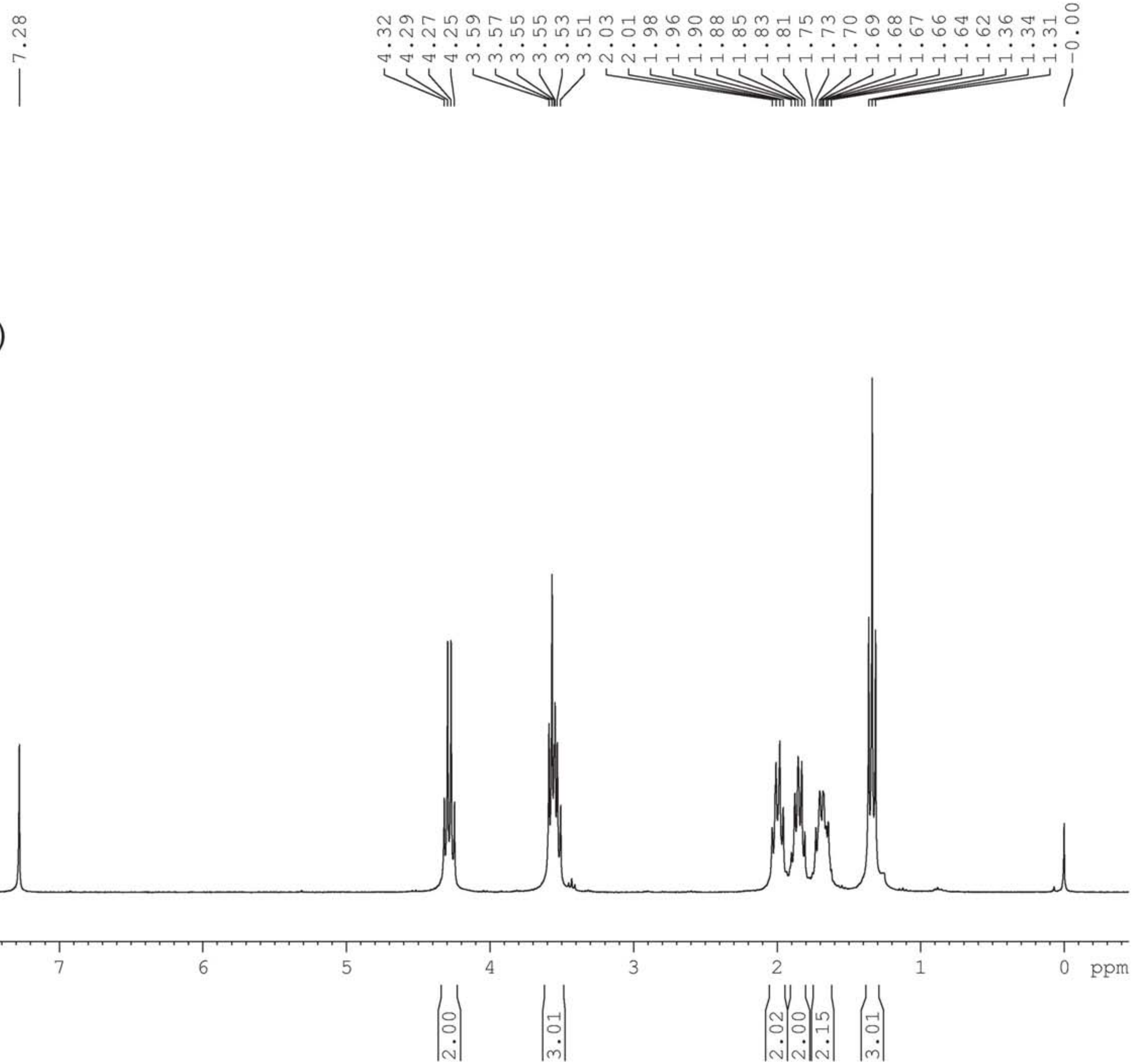




166.21
116.58
77.42
77.00
76.58
62.66
37.60
37.50
31.80
29.80
29.45
29.37
29.21
29.13
28.71
26.70
22.61
14.05
CO_2Et
CN
3ab
^{13}C NMR (75 MHz, $CDCl_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

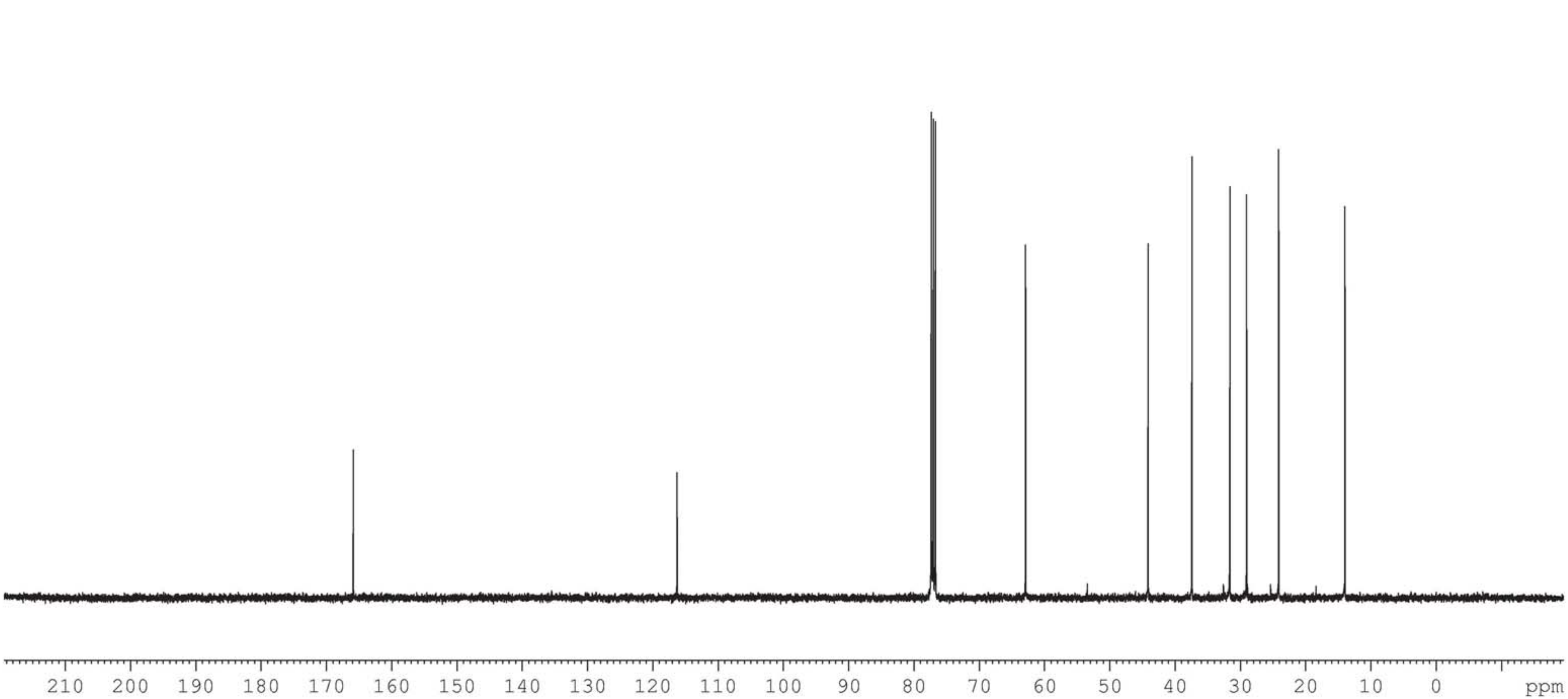
3ac

^1H NMR (300 MHz, $CDCl_3$)



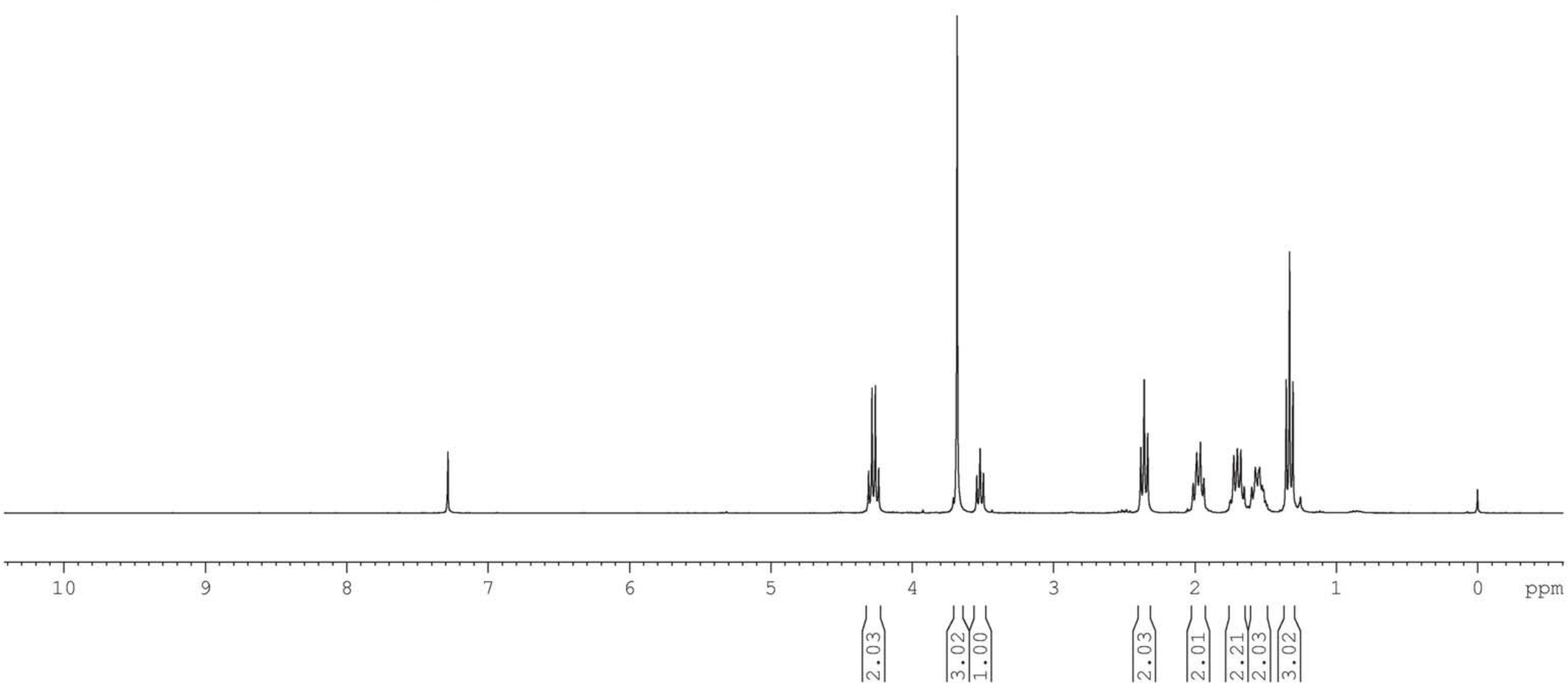
3ac

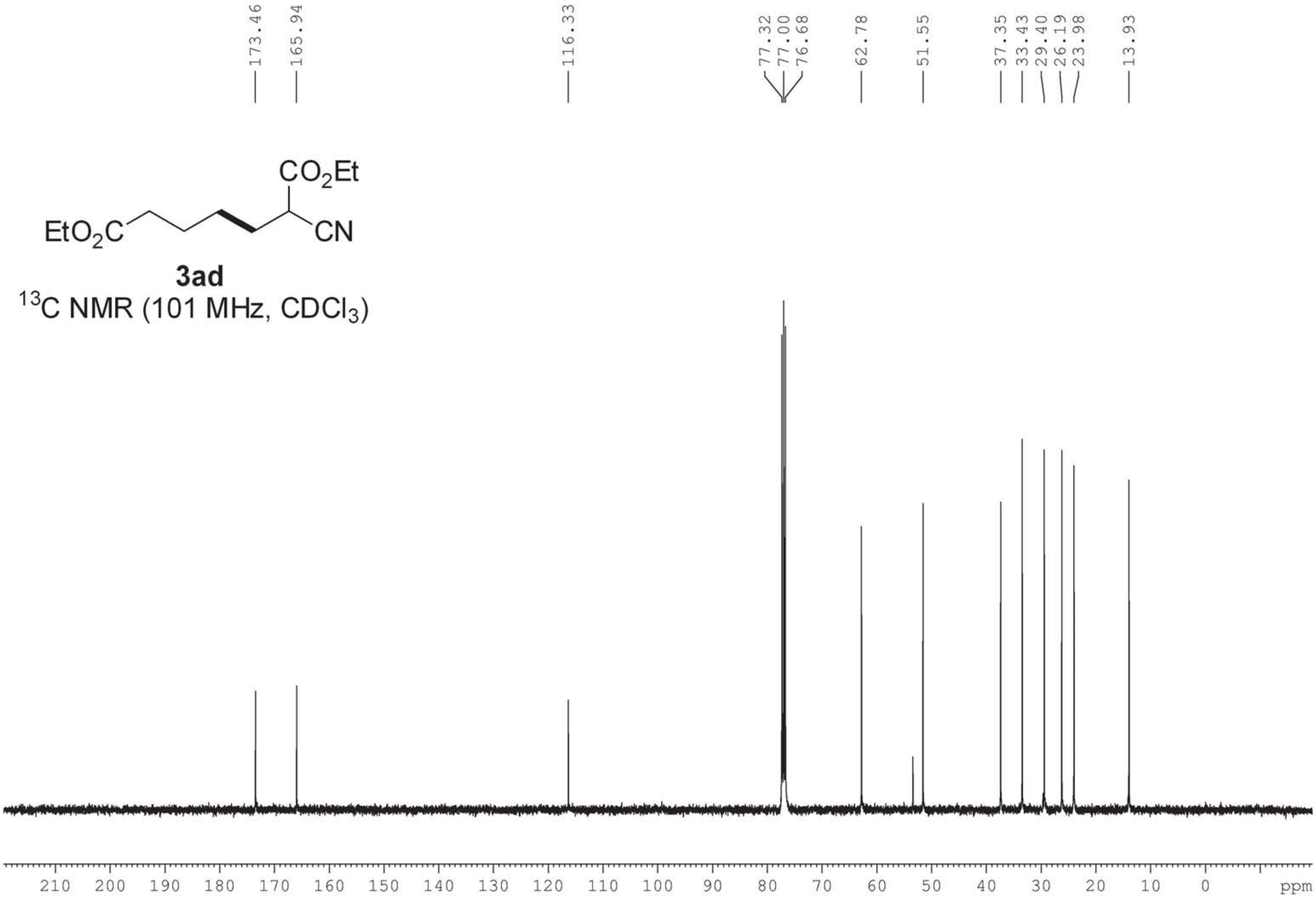
^{13}C NMR (101 MHz, $CDCl_3$)



3ad

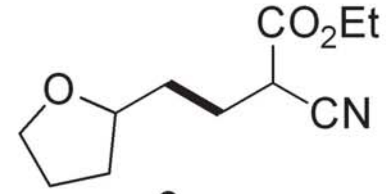
^{1}H NMR (300 MHz, $CDCl_3$)





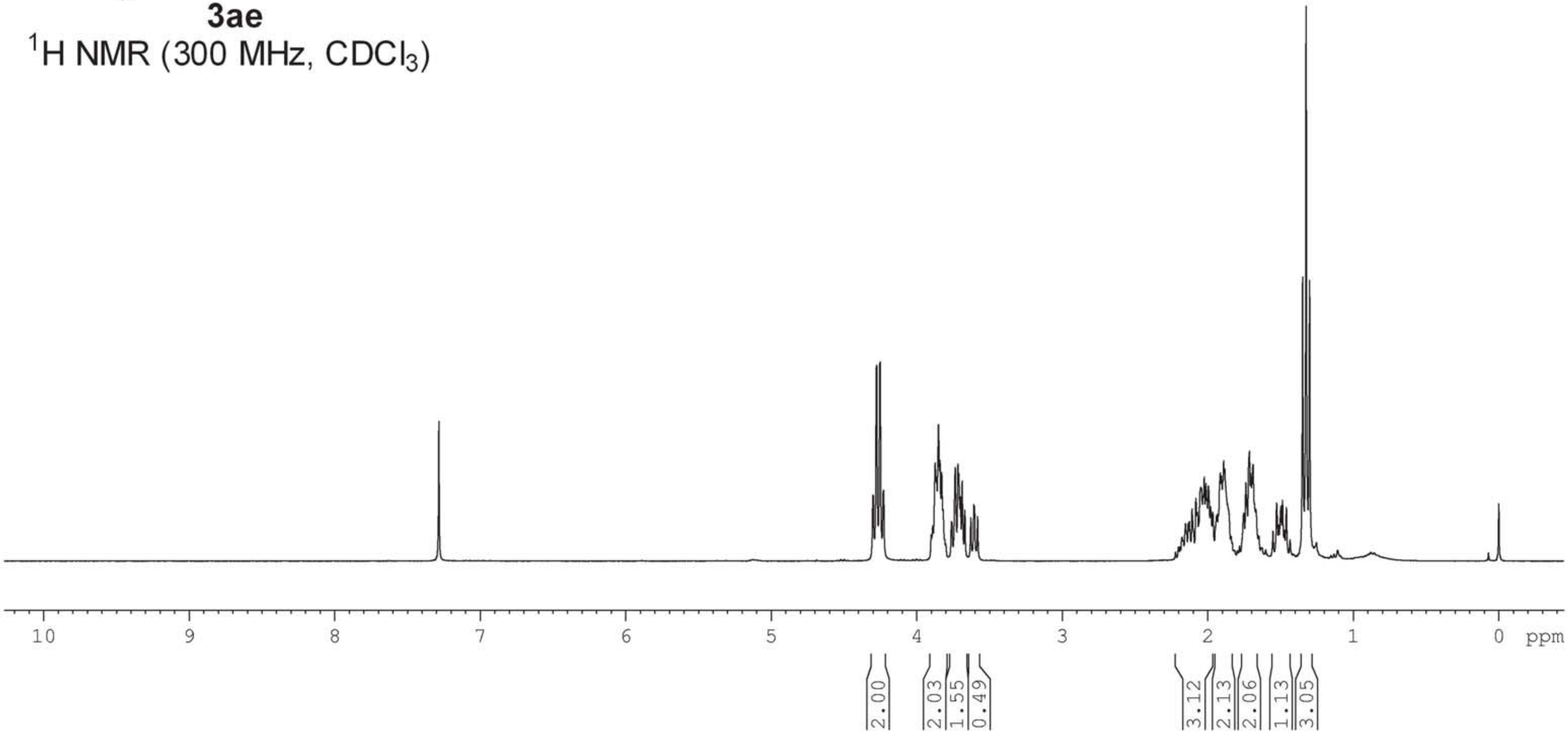
3ad

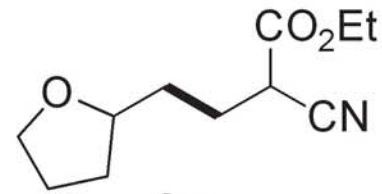
^{13}C NMR (101 MHz, $CDCl_3$)



3ae

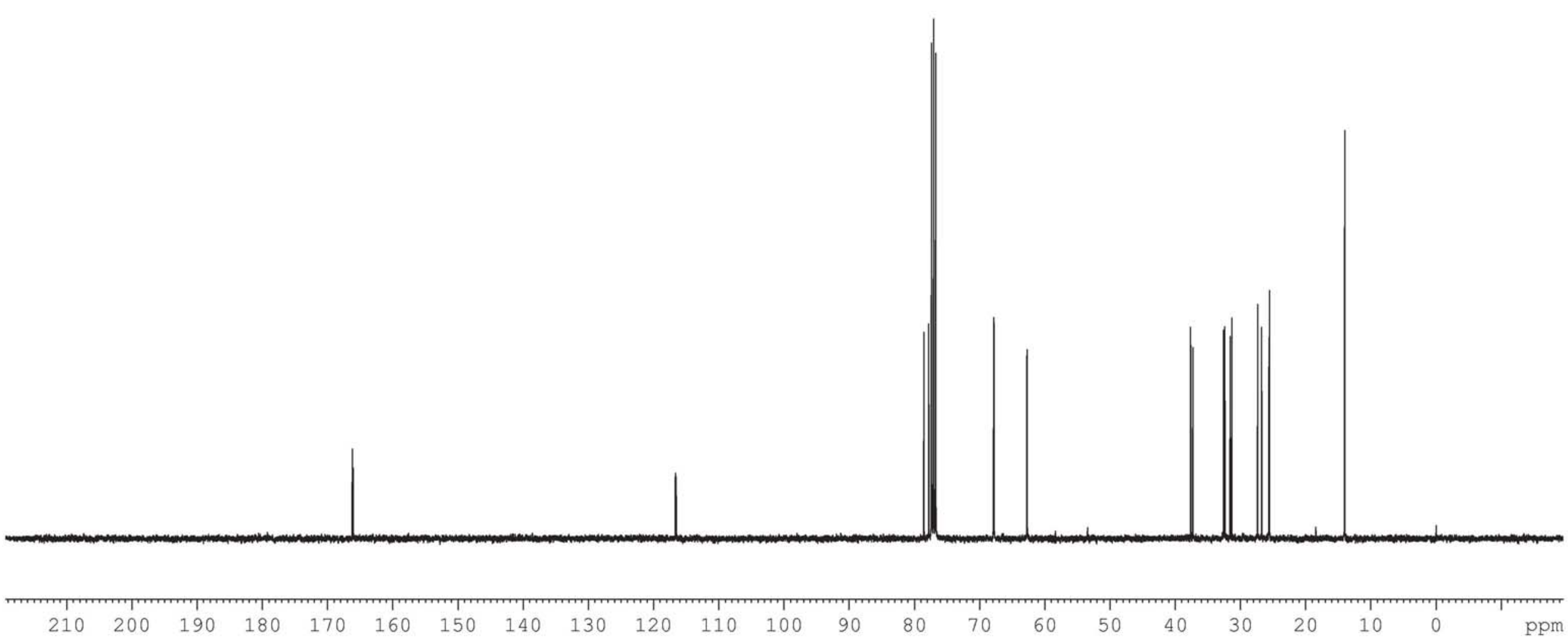
^{1}H NMR (300 MHz, $CDCl_3$)

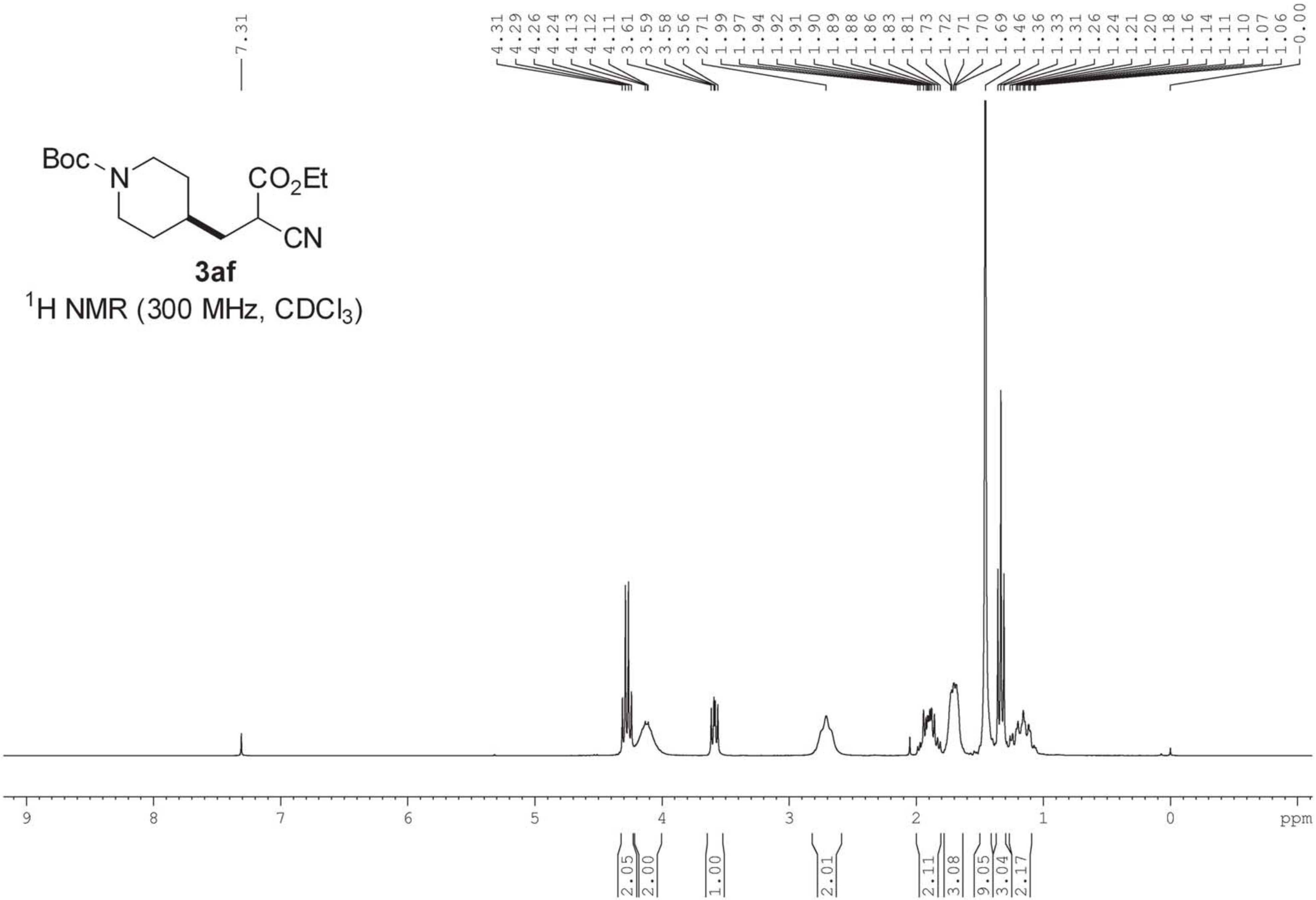


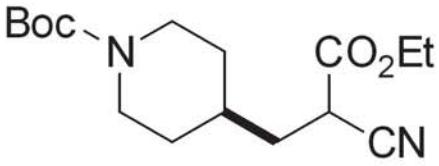


3ae

^{13}C NMR (101 MHz, $CDCl_3$)

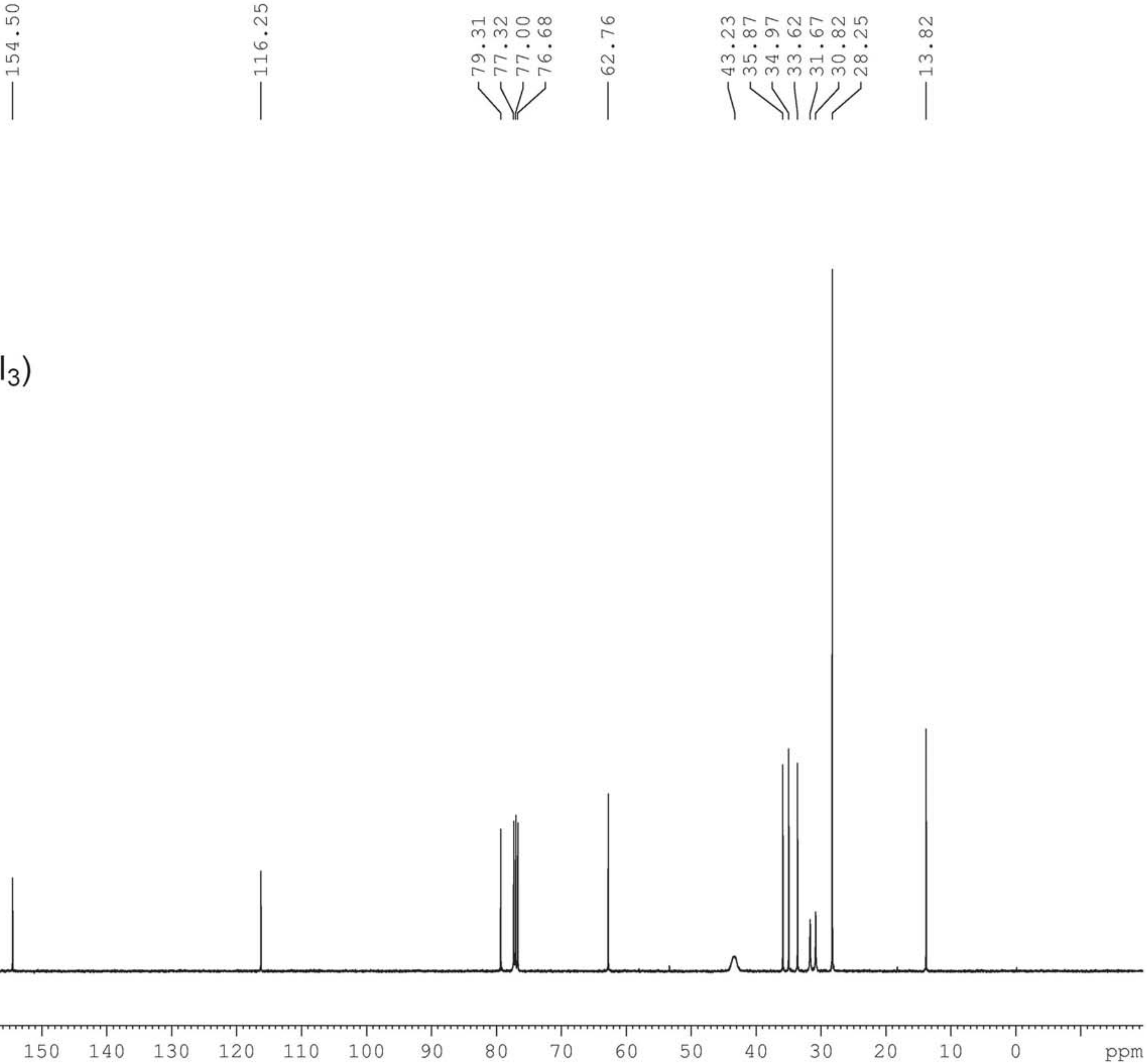


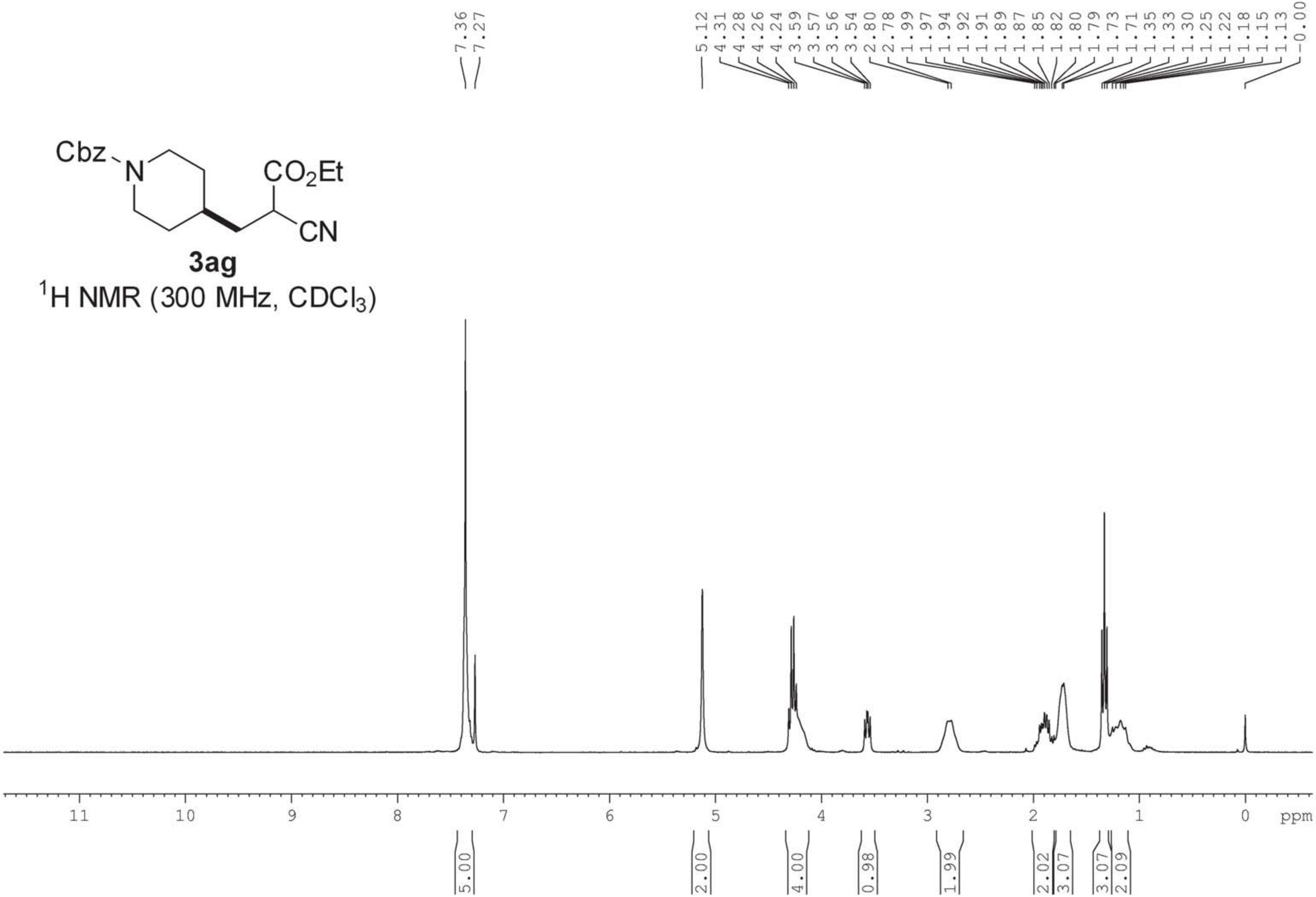

Boc
N
CO2Et
CN
3af
1H NMR (300 MHz, CDCl3)
7.31
4.31 4.29 4.26 4.24 4.13 4.12 4.11 3.61 3.59 3.58 3.56 2.71 1.99 1.97 1.94 1.92 1.91 1.90 1.89 1.88 1.86 1.83 1.81 1.73 1.72 1.71 1.70 1.69 1.46 1.36 1.33 1.31 1.26 1.24 1.21 1.20 1.18 1.16 1.14 1.11 1.10 1.07 1.06 -0.00
9 8 7 6 5 4 3 2 1 0 ppm
2.05 2.00 1.00 2.01 2.11 3.08 9.05 3.04 2.17

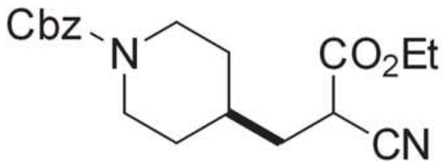


3af

^{13}C NMR (101 MHz, $CDCl_3$)

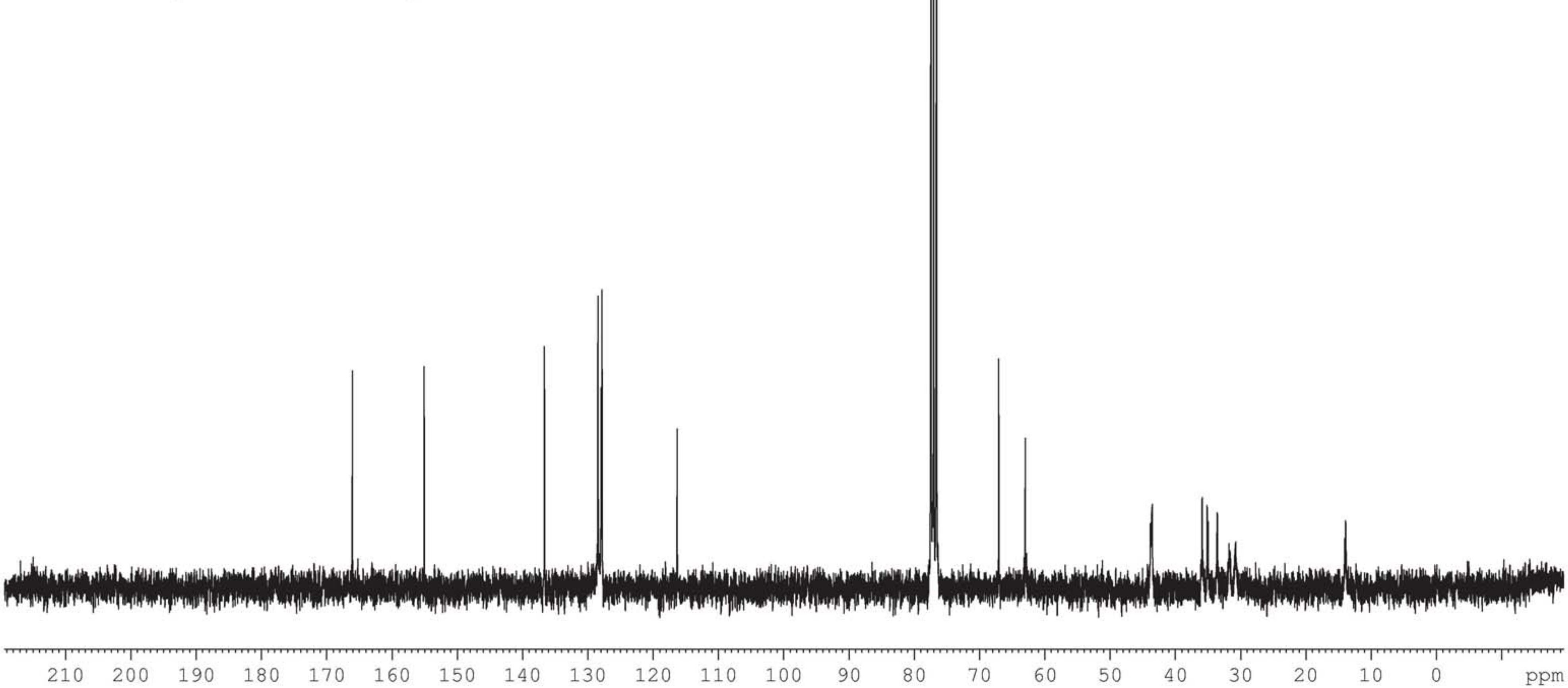


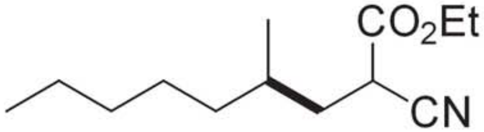

Cbz
N
CO2Et
CN
3ag
1H NMR (300 MHz, CDCl3)
7.36
7.27
5.12
4.31
4.28
4.26
4.24
3.59
3.57
3.56
3.54
2.80
2.78
1.99
1.97
1.94
1.92
1.91
1.89
1.87
1.85
1.82
1.80
1.79
1.73
1.71
1.35
1.33
1.30
1.25
1.22
1.18
1.15
1.13
-0.00
11
10
9
8
7
6
5
4
3
2
1
0
ppm
5.00
2.00
4.00
0.98
1.99
2.02
3.07
3.07
2.09



3ag

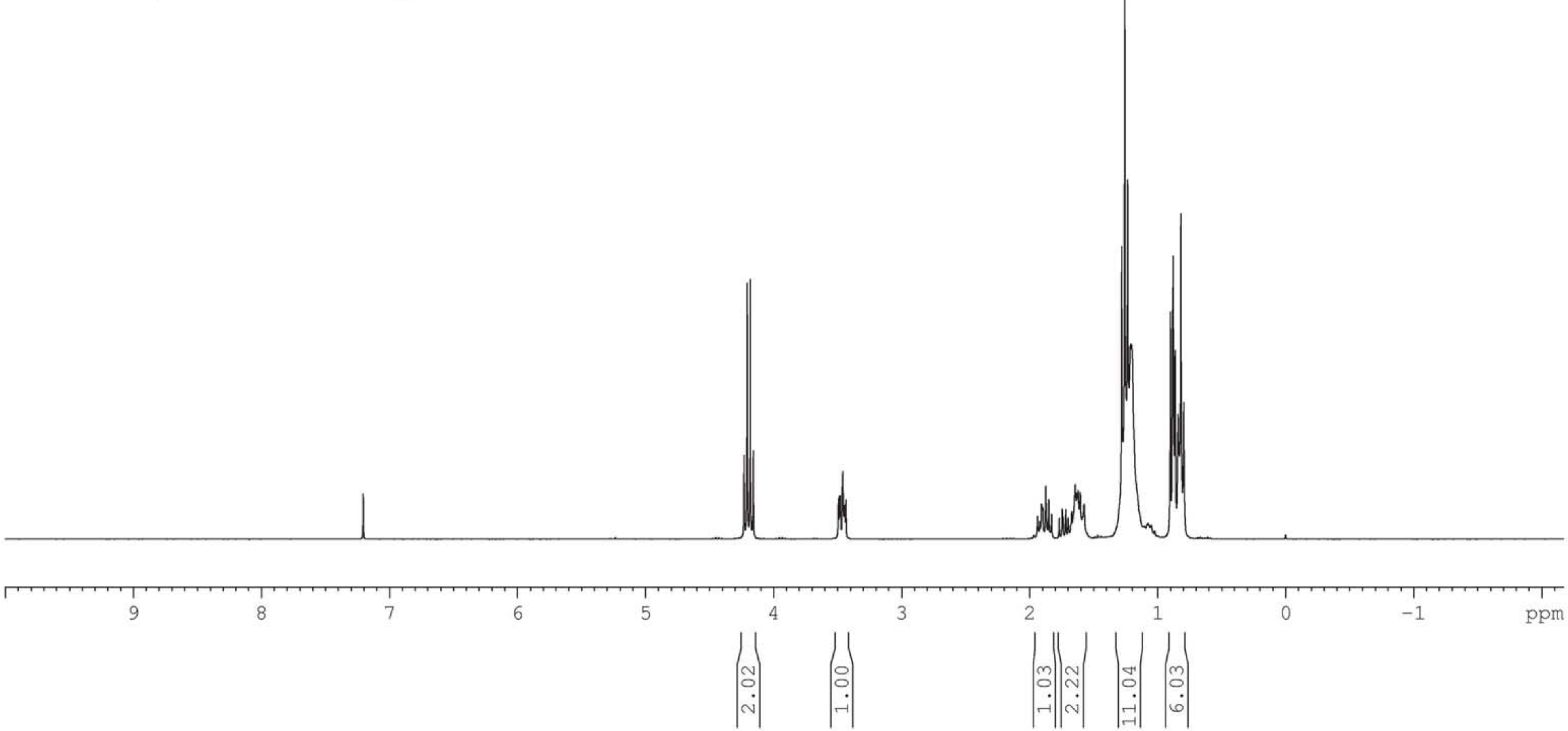
^{13}C NMR (75 MHz, $CDCl_3$)

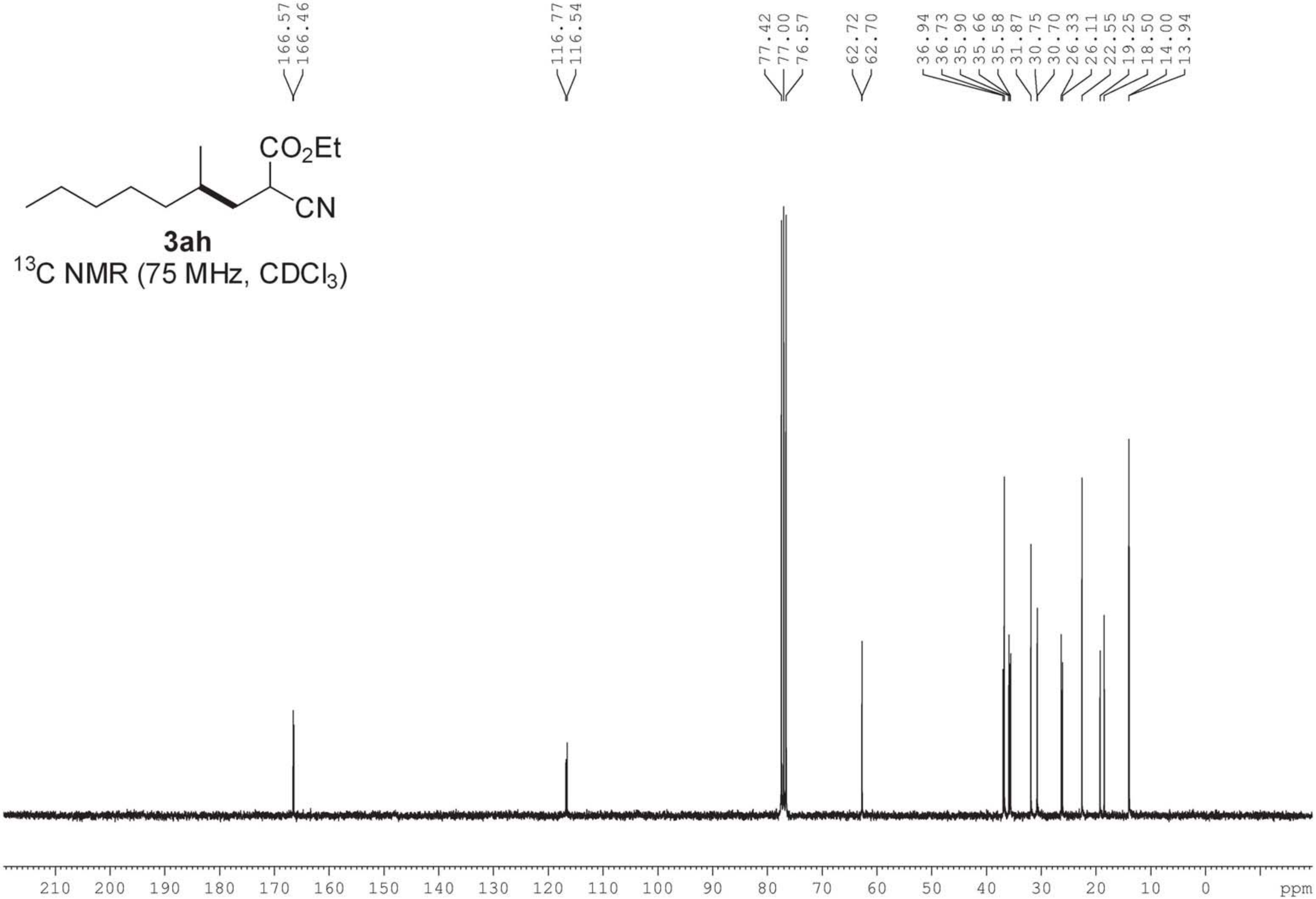




3ah

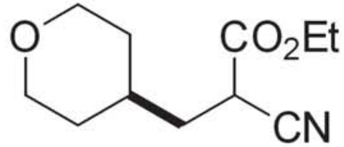
^{1}H NMR (300 MHz, $CDCl_3$)





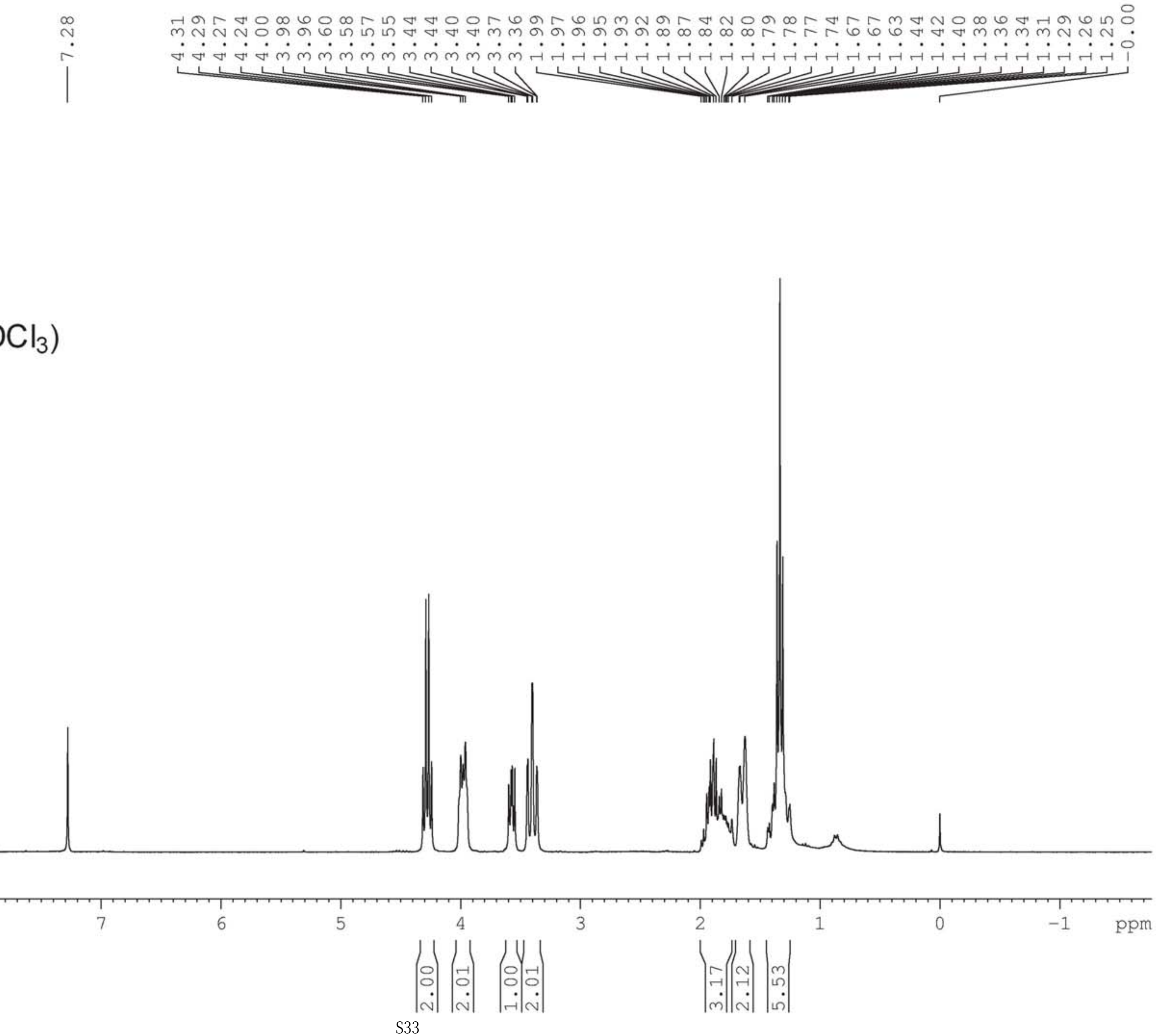
3ah

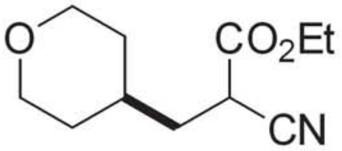
^{13}C NMR (75 MHz, $CDCl_3$)



3ai

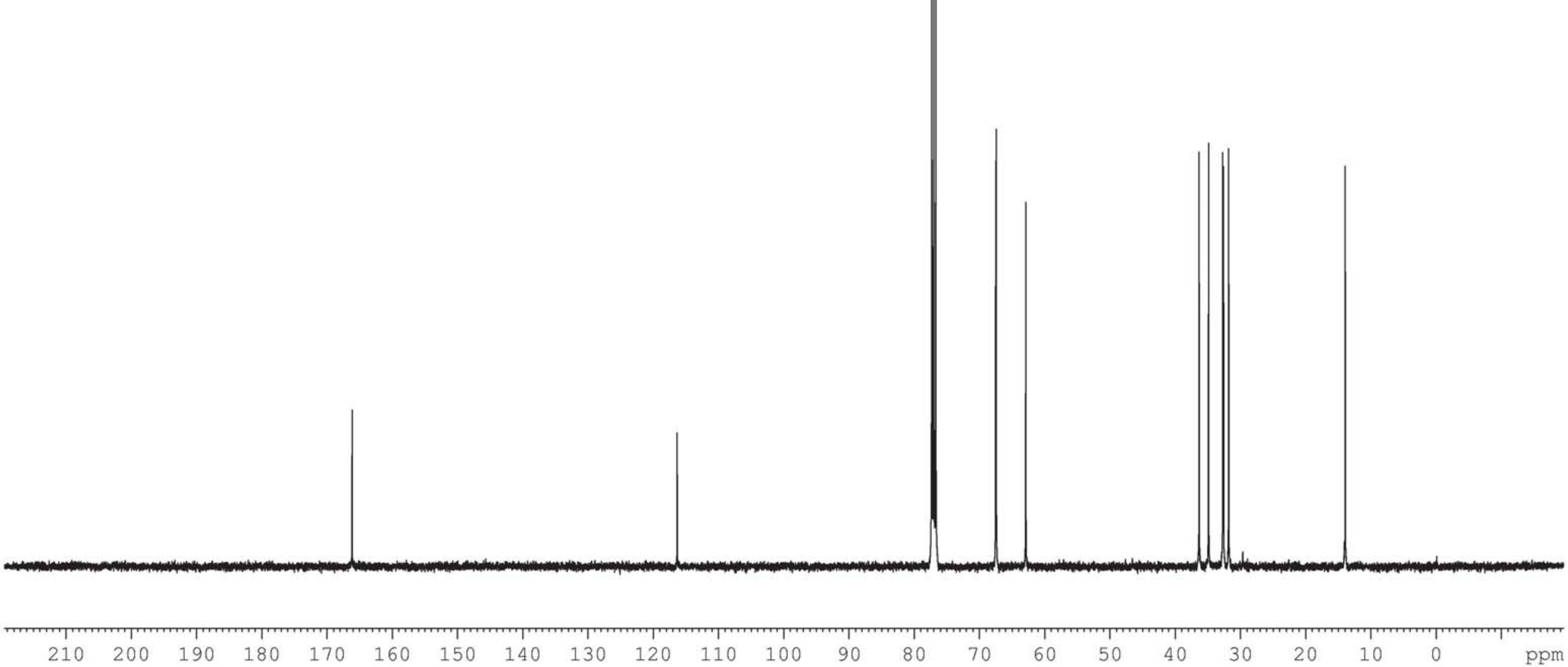
^{1}H NMR (300 MHz, $CDCl_3$)

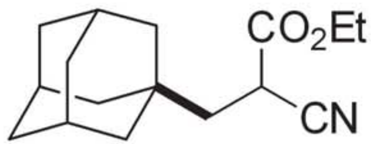




3ai

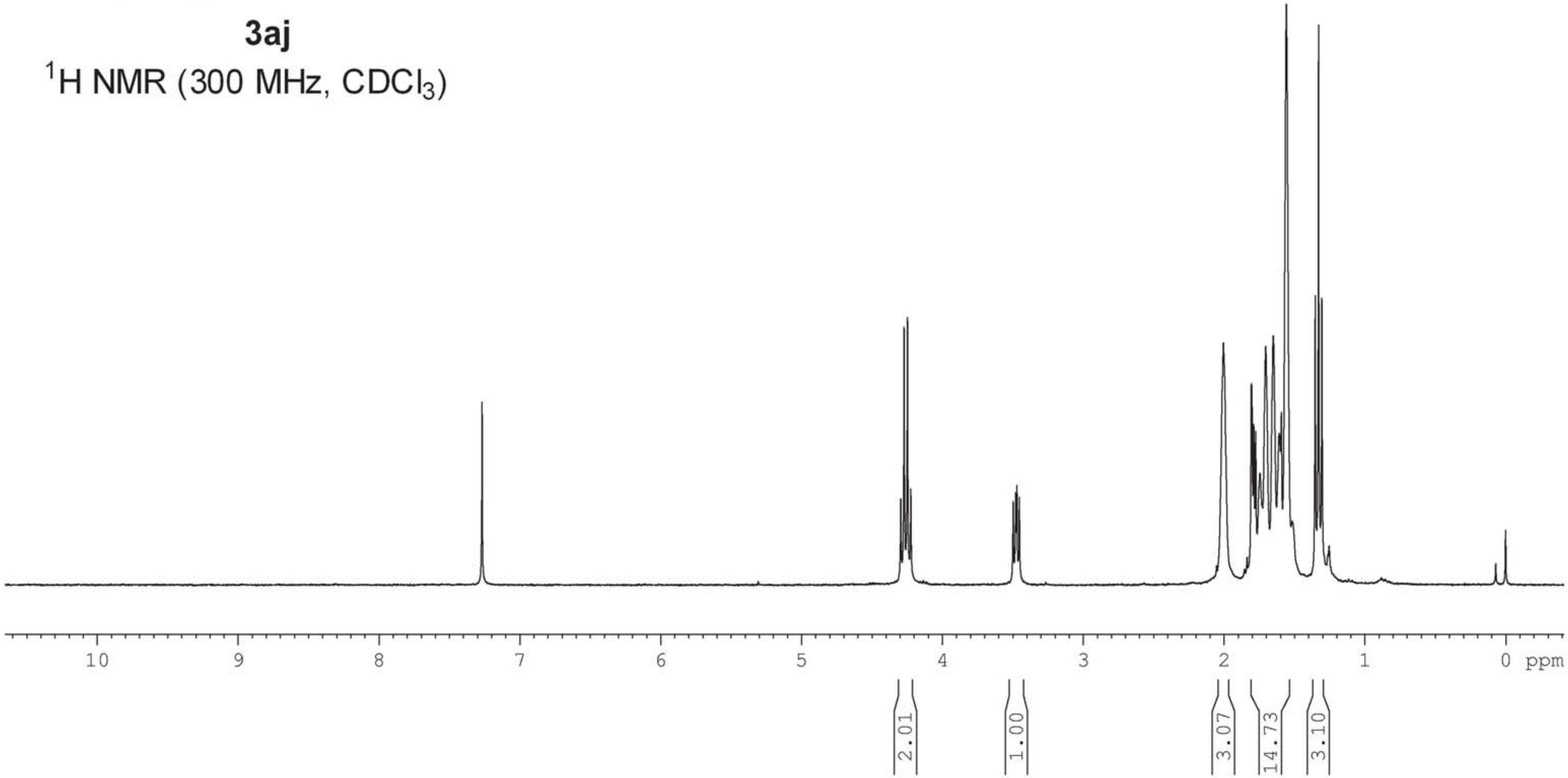
^{13}C NMR (101 MHz, $CDCl_3$)

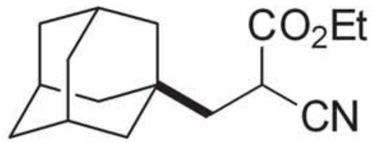




3aj

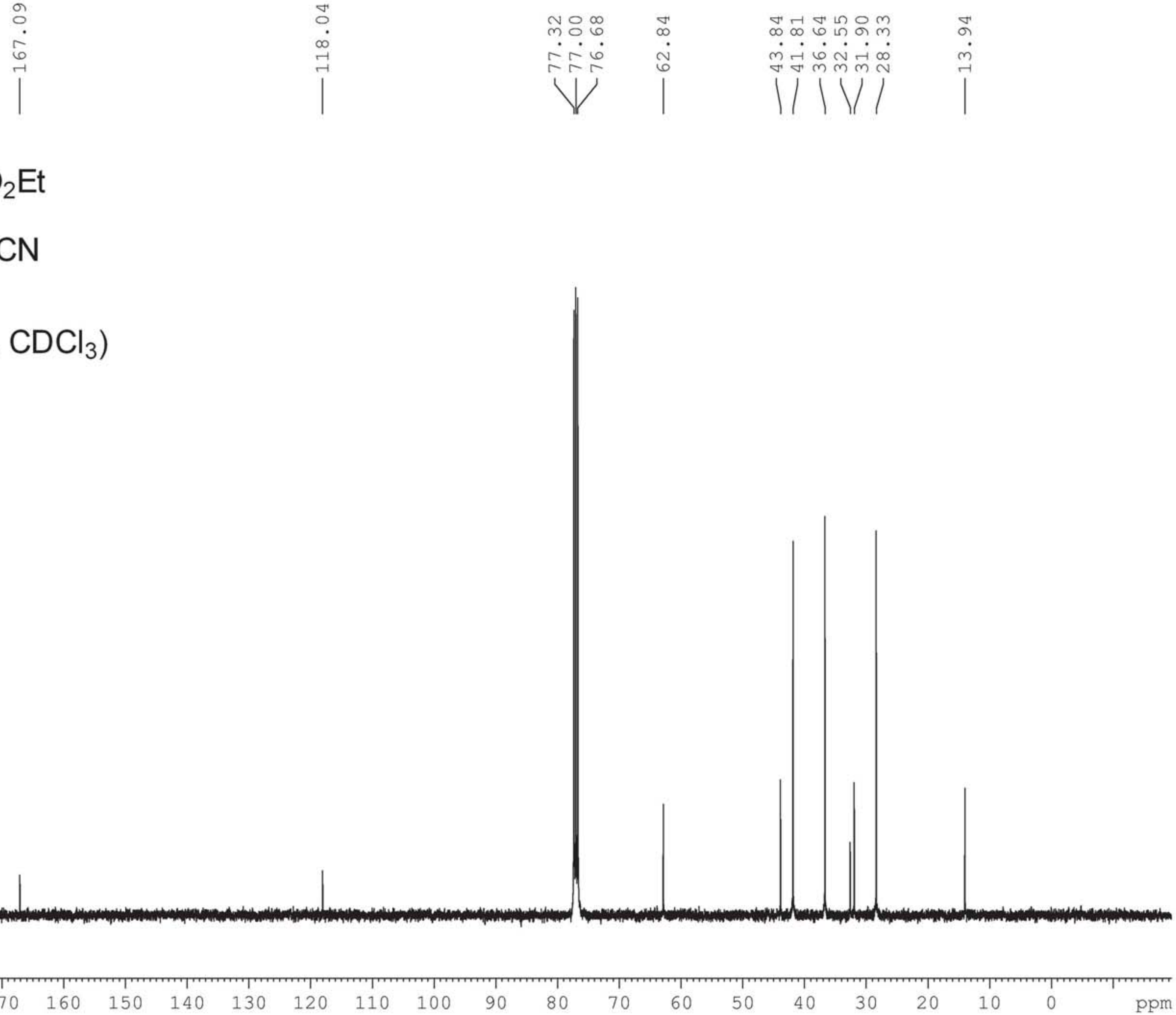
^{1}H NMR (300 MHz, $CDCl_3$)

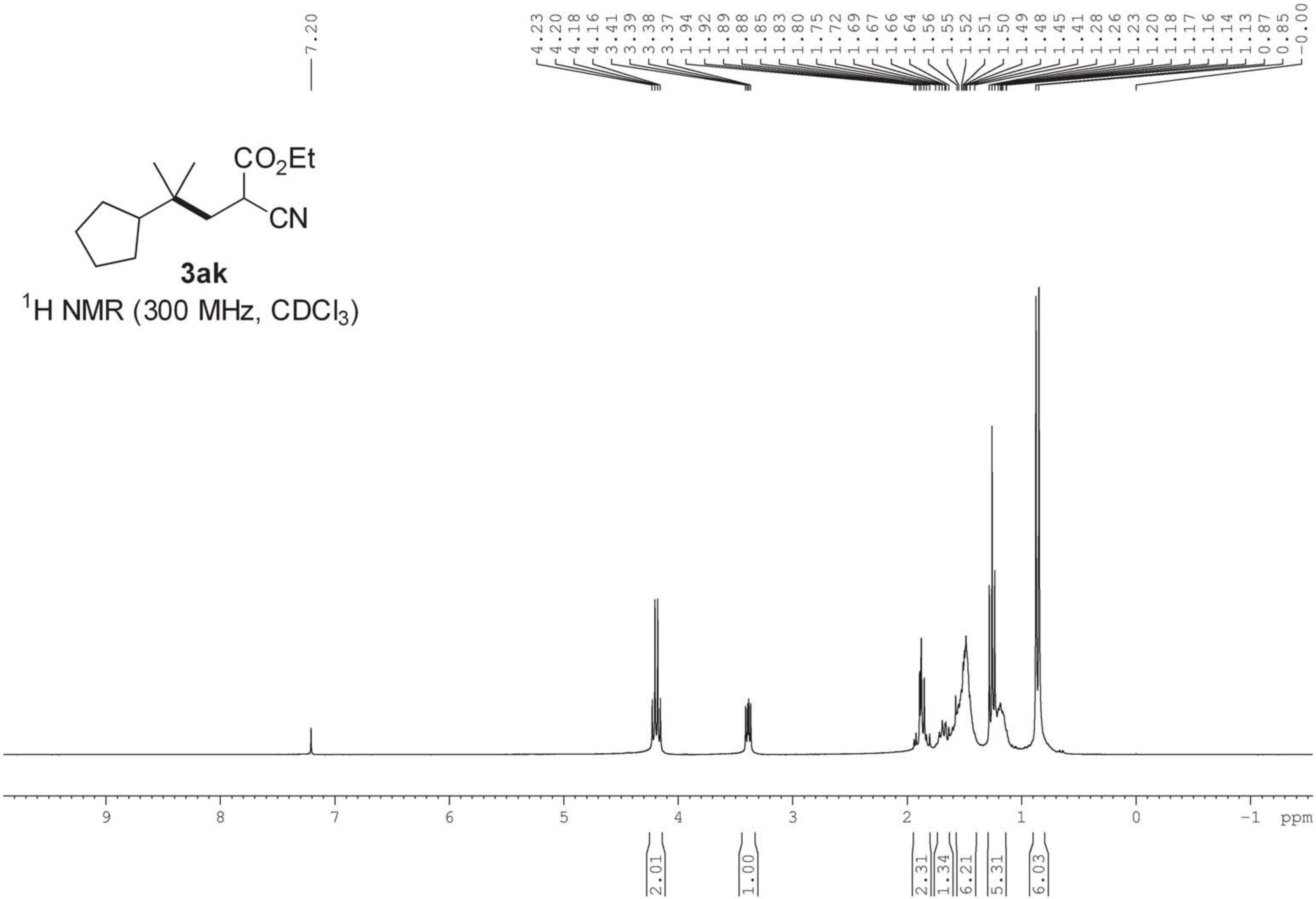


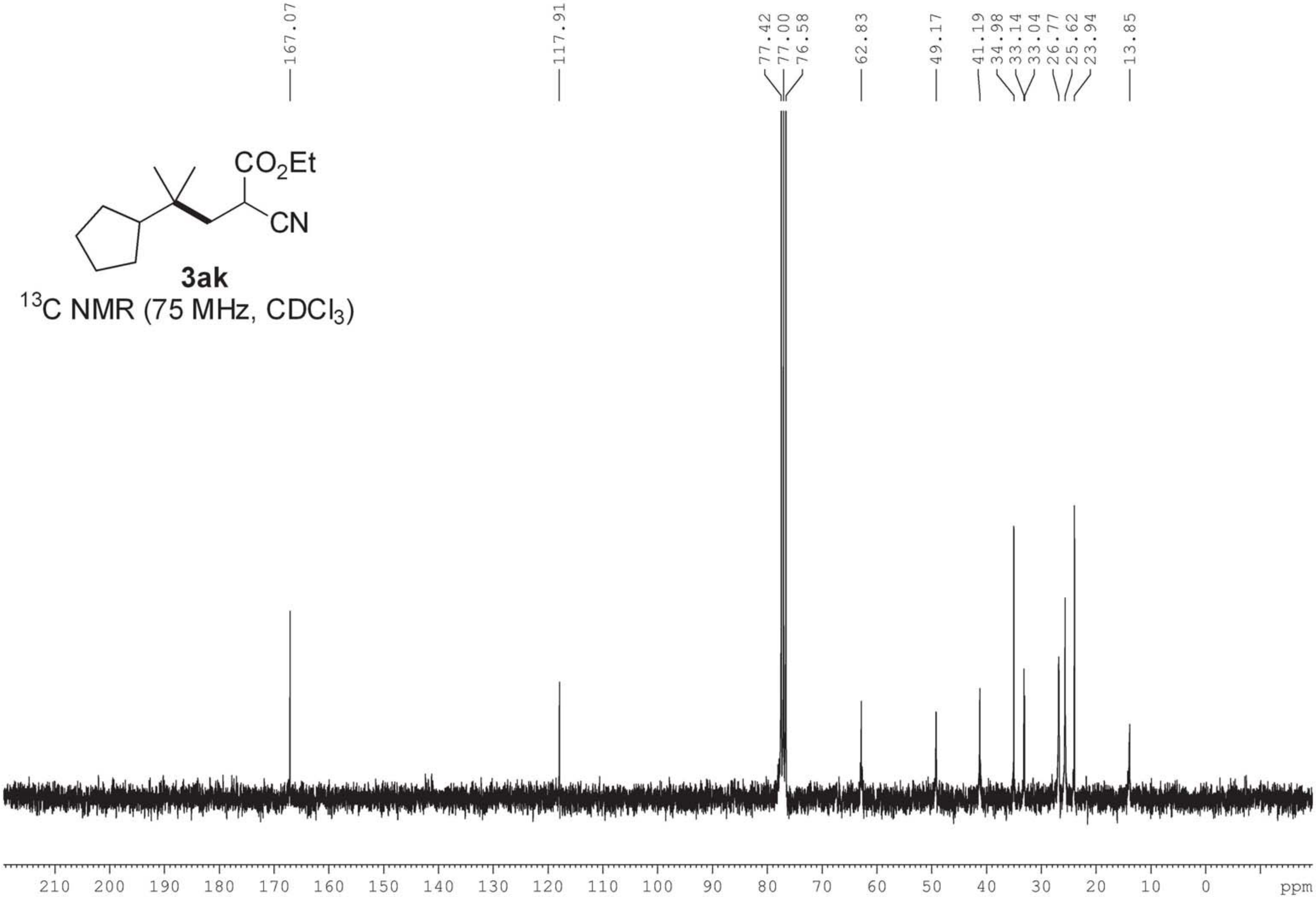


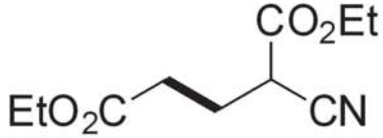
3aj

^{13}C NMR (101 MHz, $CDCl_3$)



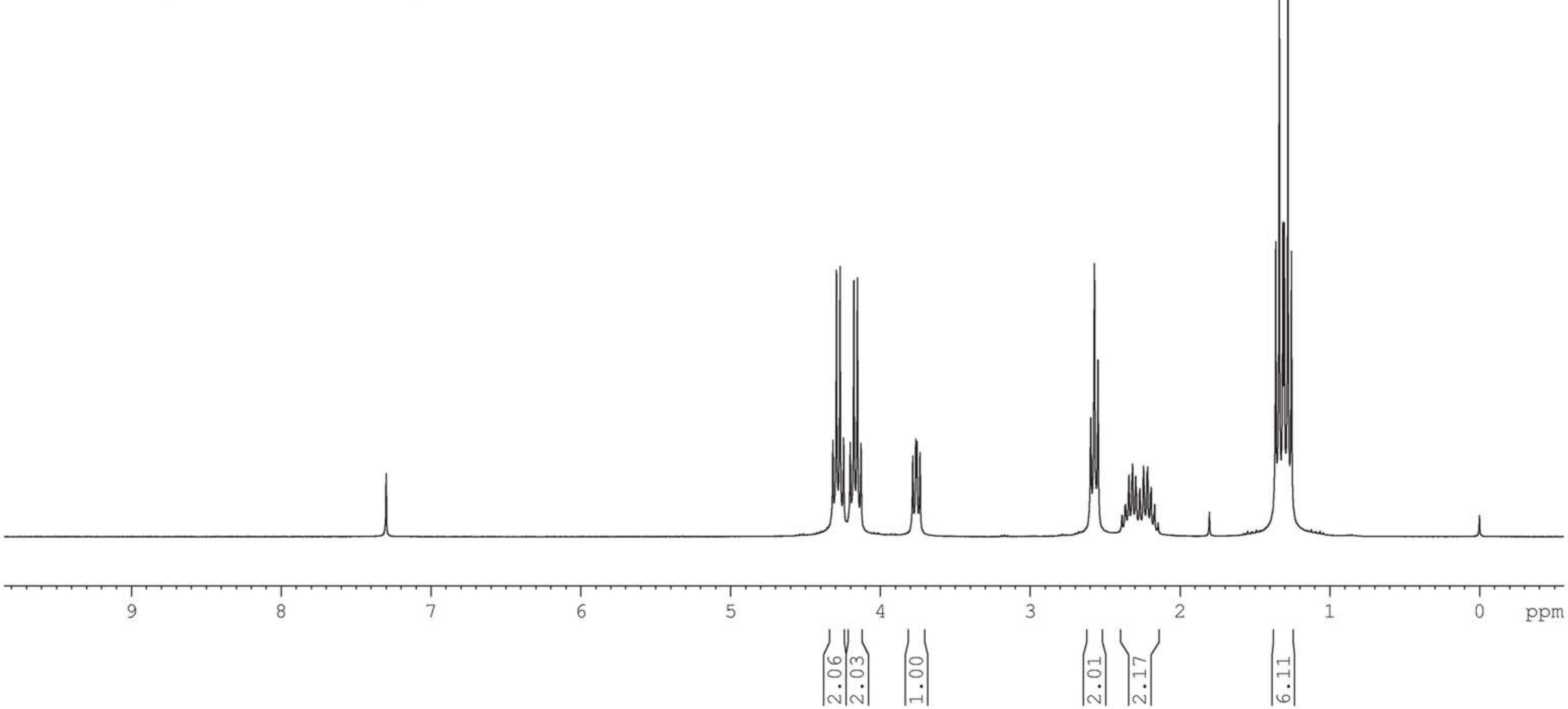

CO2Et
CN
3ak
1H NMR (300 MHz, CDCl3)
7.20
4.23 4.20 4.18 4.16 3.41 3.39 3.38 3.37 1.94 1.92 1.89 1.88 1.85 1.83 1.80 1.75 1.72 1.69 1.67 1.66 1.64 1.56 1.55 1.52 1.51 1.50 1.49 1.48 1.45 1.41 1.28 1.26 1.23 1.20 1.18 1.17 1.16 1.14 1.13 0.87 0.85 -0.00
9 8 7 6 5 4 3 2 1 0 -1 ppm
2.01 1.00 2.31 1.34 6.21 5.31 6.03

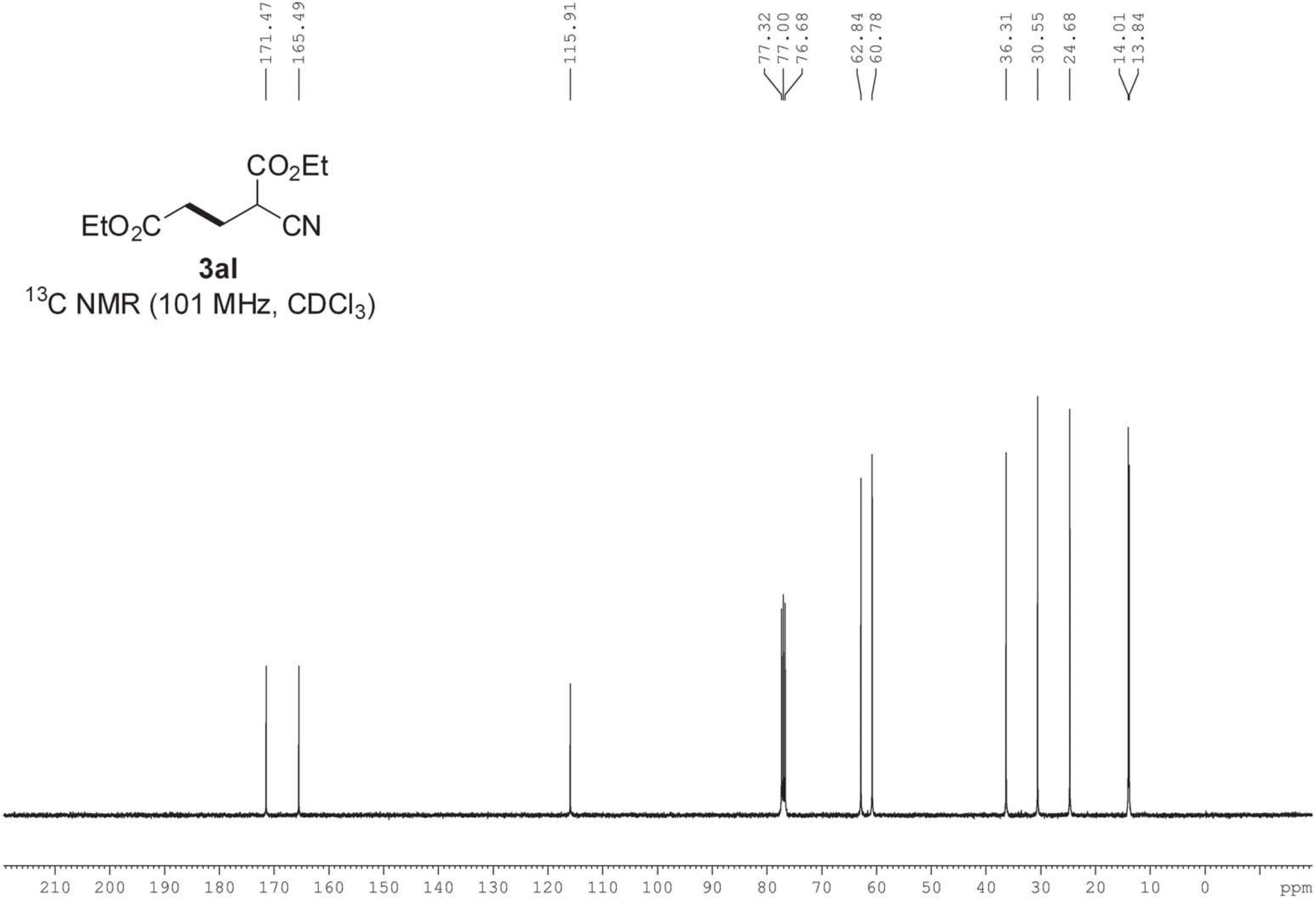

167.07
117.91
77.42
77.00
76.58
62.83
49.17
41.19
34.98
33.14
33.04
26.77
25.62
23.94
13.85
CO2Et
CN
3ak
13C NMR (75 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



3al

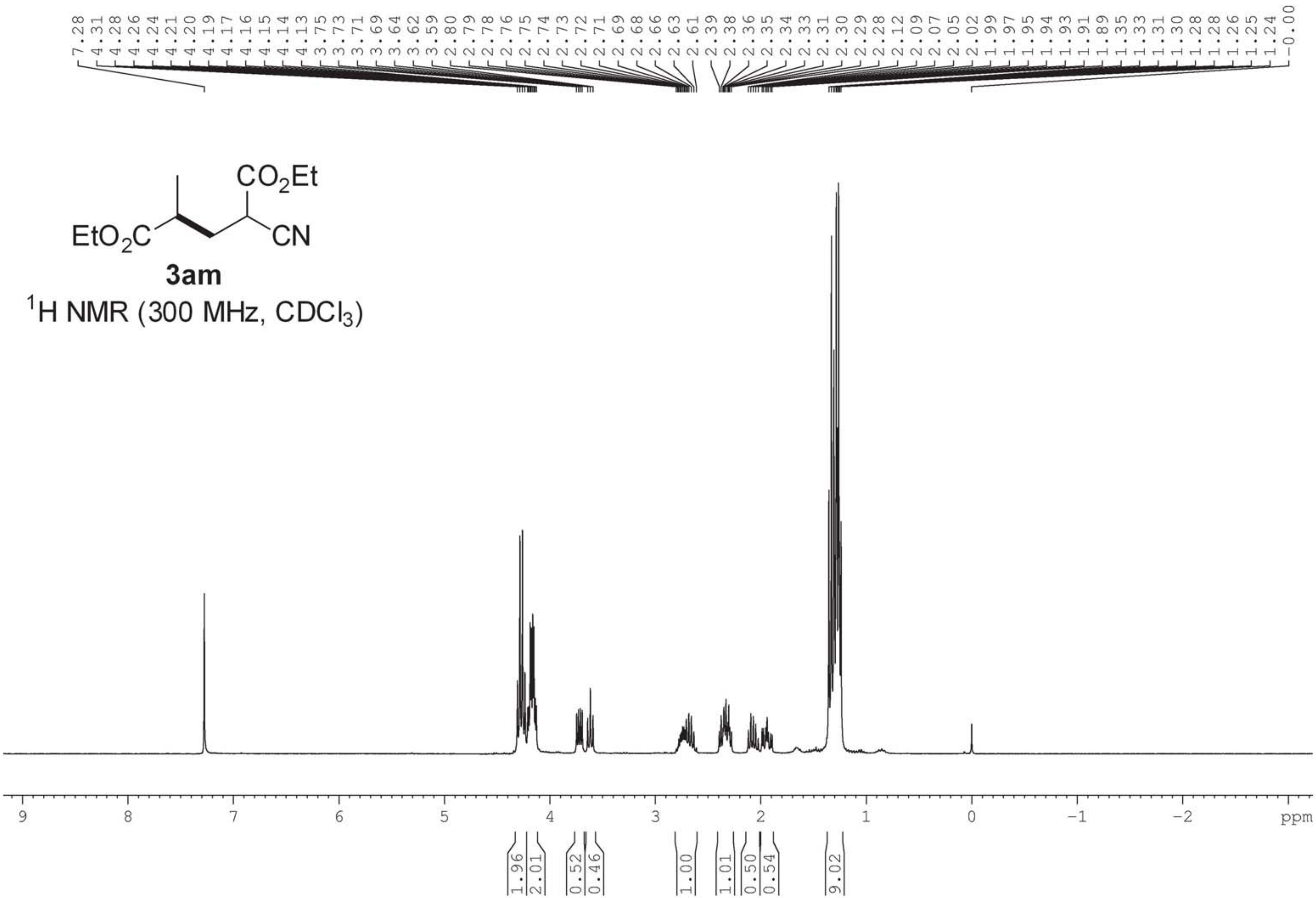
^{1}H NMR (300 MHz, $CDCl_3$)

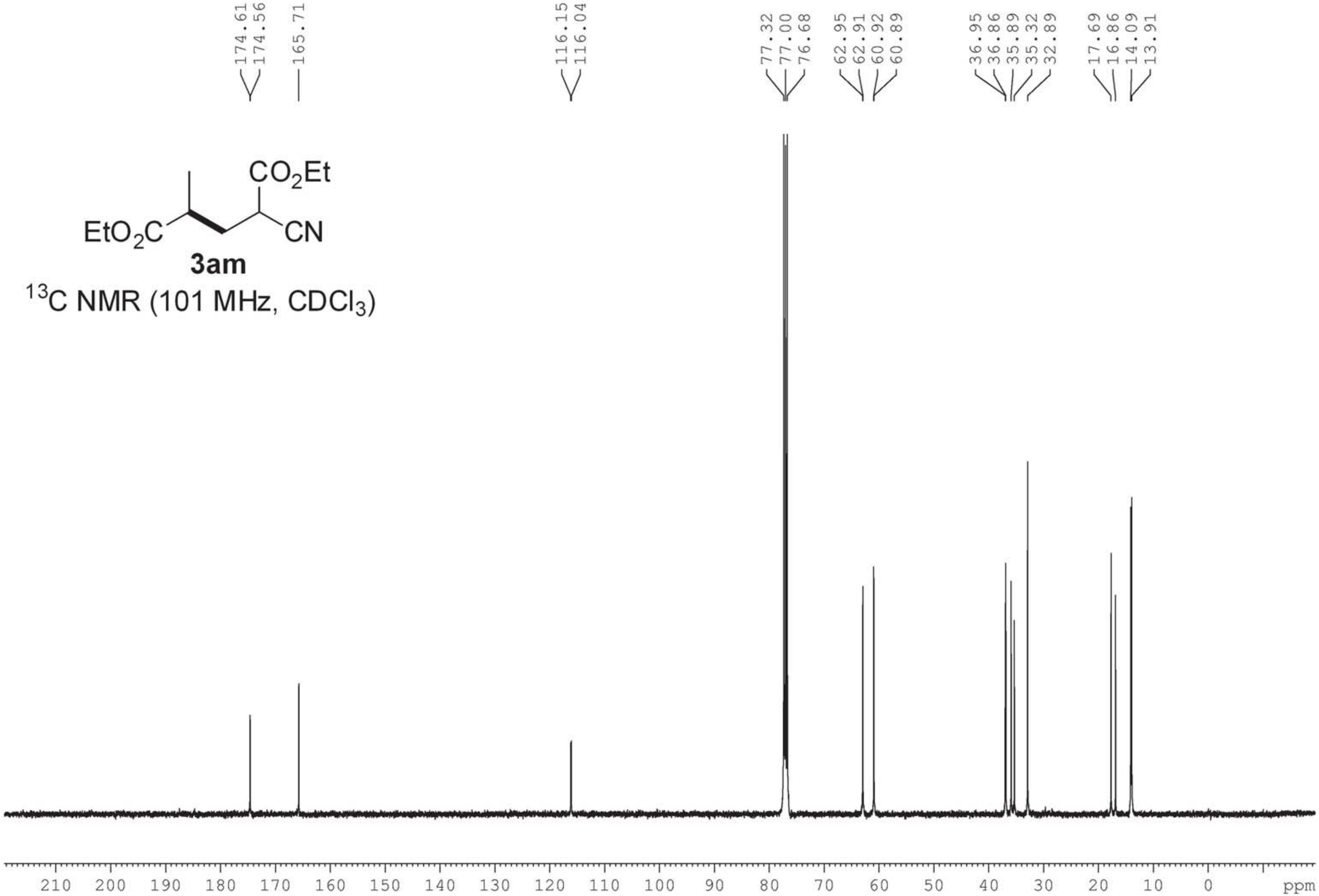




3al

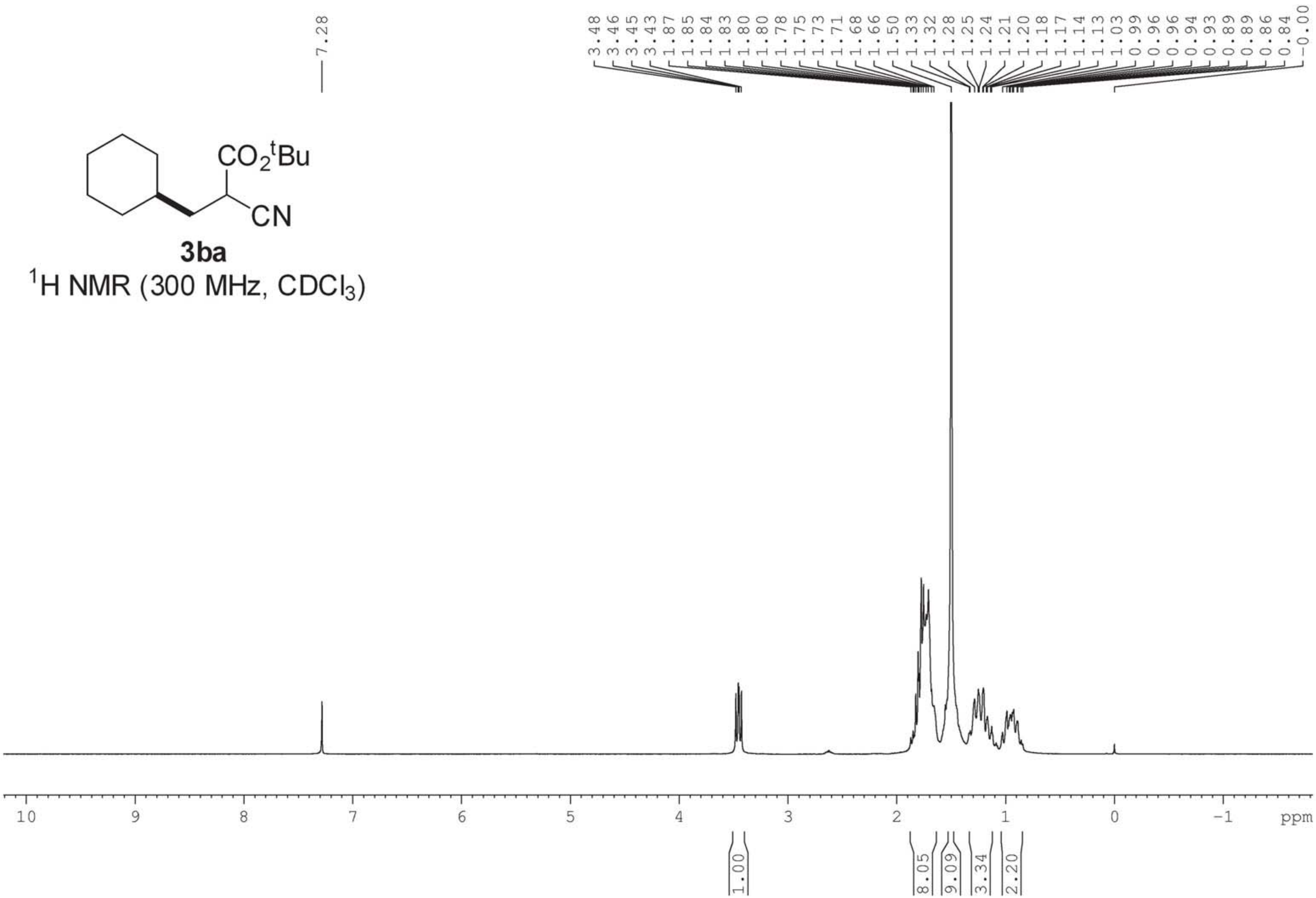
^{13}C NMR (101 MHz, $CDCl_3$)

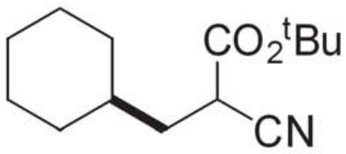

CO2Et
EtO2C
CN
3am
1H NMR (300 MHz, CDCl3)
7.28 4.31 4.28 4.26 4.24 4.21 4.20 4.19 4.17 4.16 4.15 4.14 4.13 3.75 3.73 3.71 3.69 3.64 3.62 3.59 2.80 2.79 2.78 2.76 2.75 2.74 2.73 2.72 2.71 2.69 2.68 2.66 2.63 2.61 2.39 2.38 2.36 2.35 2.34 2.33 2.31 2.30 2.29 2.28 2.12 2.09 2.07 2.05 2.02 1.99 1.97 1.95 1.94 1.93 1.91 1.89 1.35 1.33 1.31 1.30 1.28 1.28 1.26 1.25 1.24 -0.00
9 8 7 6 5 4 3 2 1 0 −1 −2 ppm
1.96 2.01 0.52 0.46 1.00 1.01 0.50 0.54 9.02


174.61
174.56
165.71
116.15
116.04
77.32
77.00
76.68
62.95
62.91
60.92
60.89
36.95
36.86
35.89
35.32
32.89
17.69
16.86
14.09
13.91
CO2Et
EtO2C
CN
3am
13C NMR (101 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

3ba

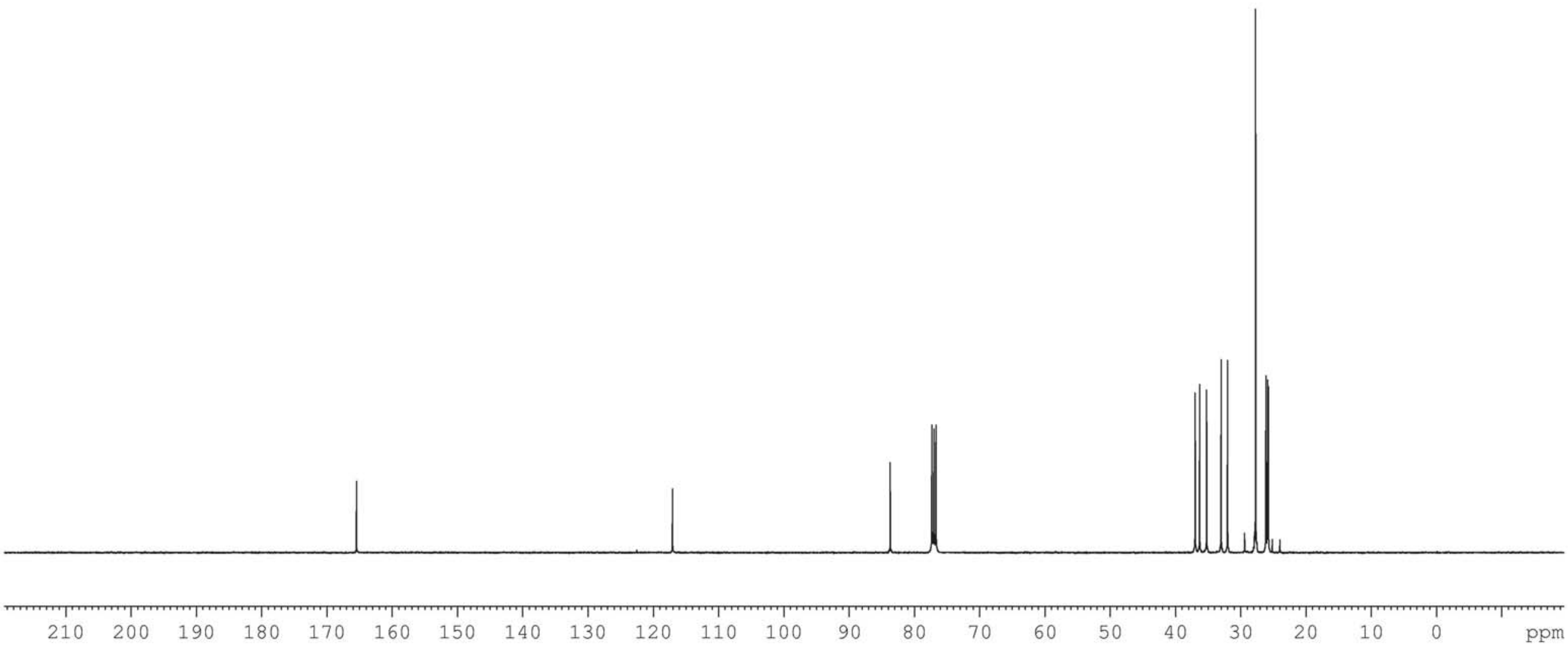
^{1}H NMR (300 MHz, $CDCl_3$)

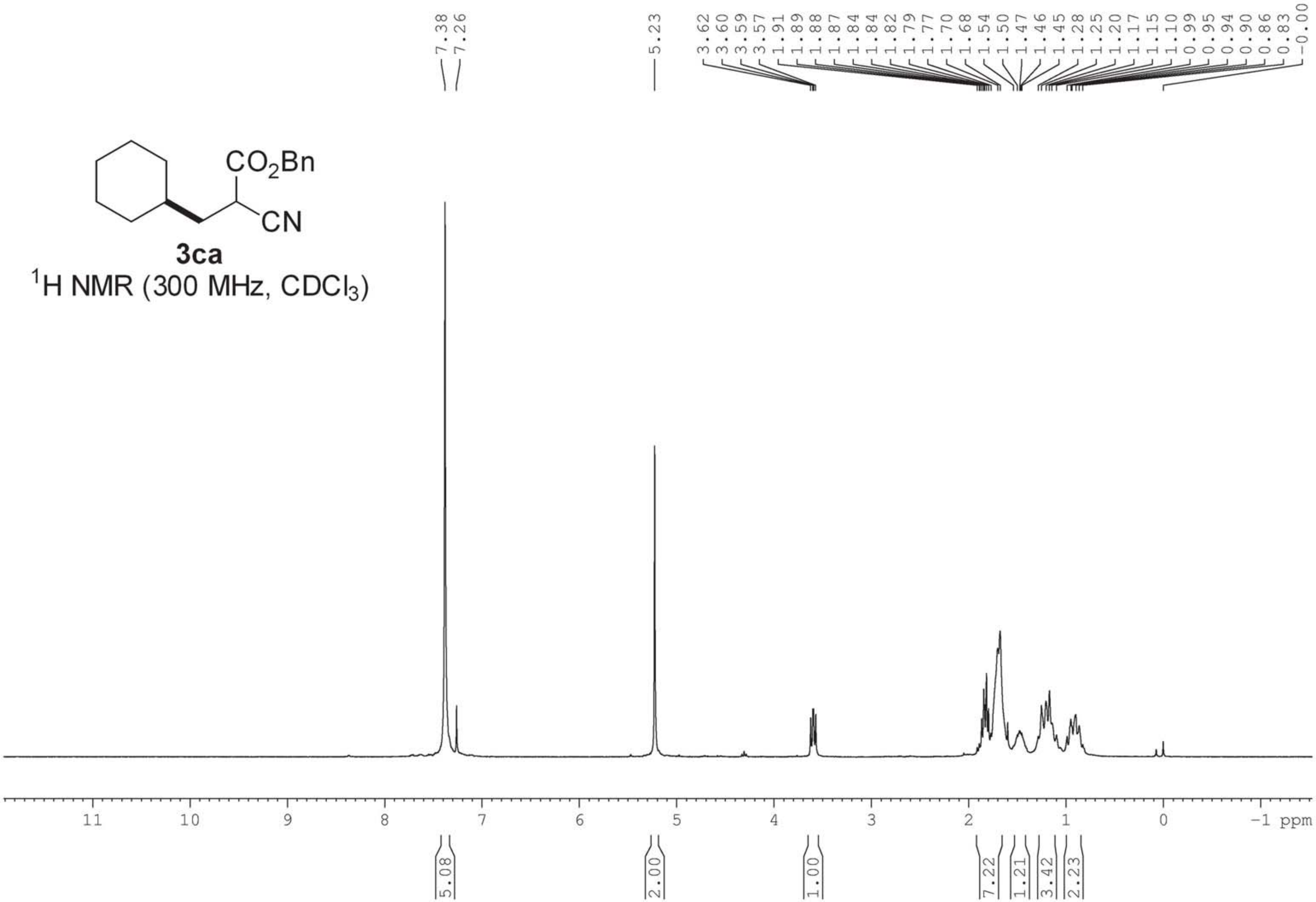


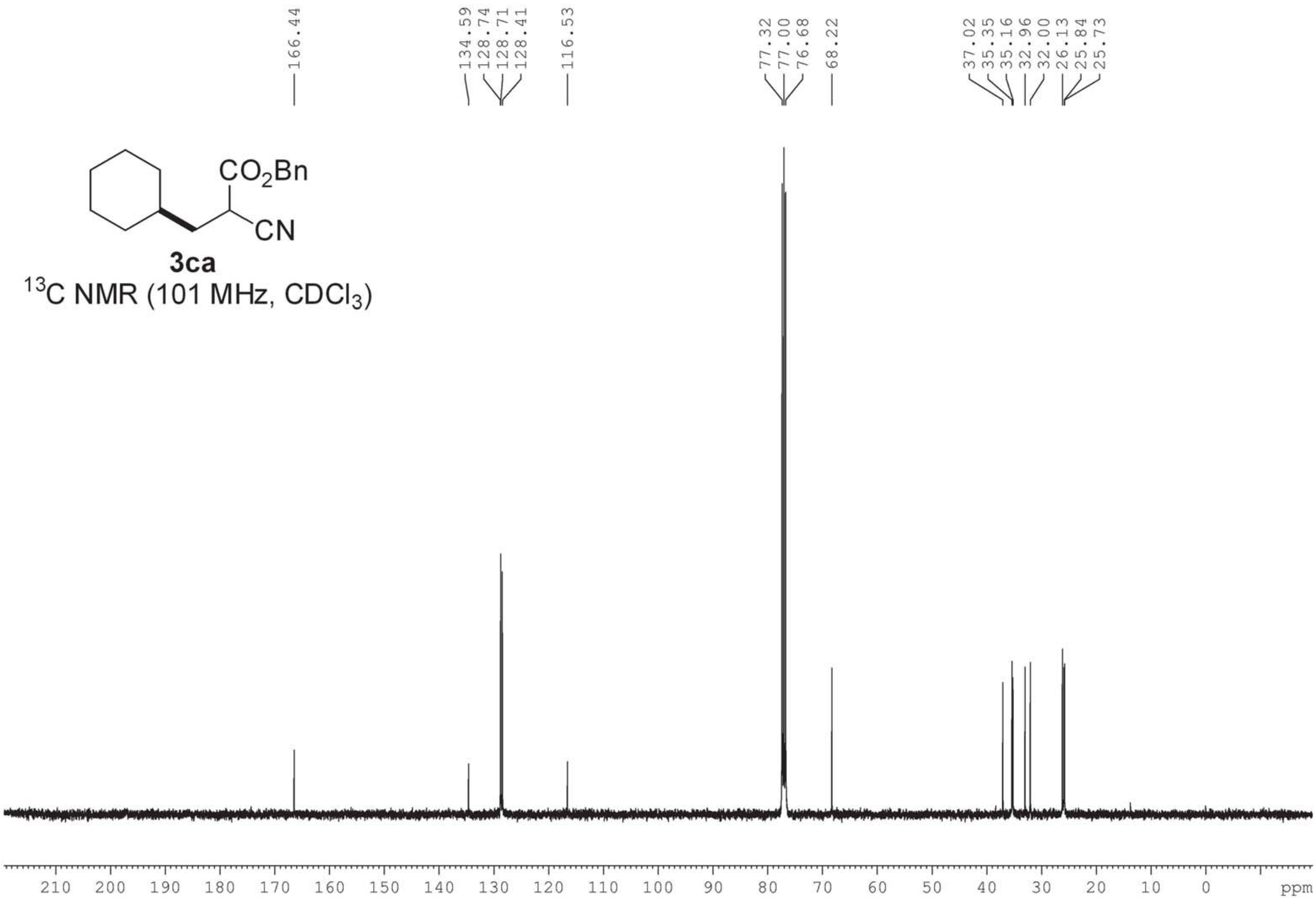


3ba

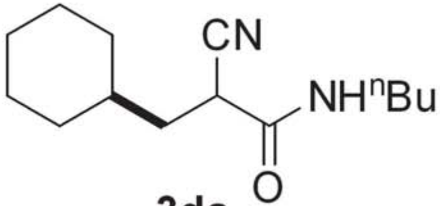
^{13}C NMR (101 MHz, $CDCl_3$)




CO2Bn
CN
3ca
1H NMR (300 MHz, CDCl3)
7.38
7.26
5.23
3.62
3.60
3.59
3.57
1.91
1.89
1.88
1.87
1.84
1.84
1.82
1.79
1.77
1.70
1.68
1.54
1.50
1.47
1.46
1.45
1.28
1.25
1.20
1.17
1.15
1.10
0.99
0.95
0.94
0.90
0.86
0.83
-0.00
11
10
9
8
7
6
5
4
3
2
1
0
-1 ppm
5.08
2.00
1.00
7.22
1.21
3.42
2.23

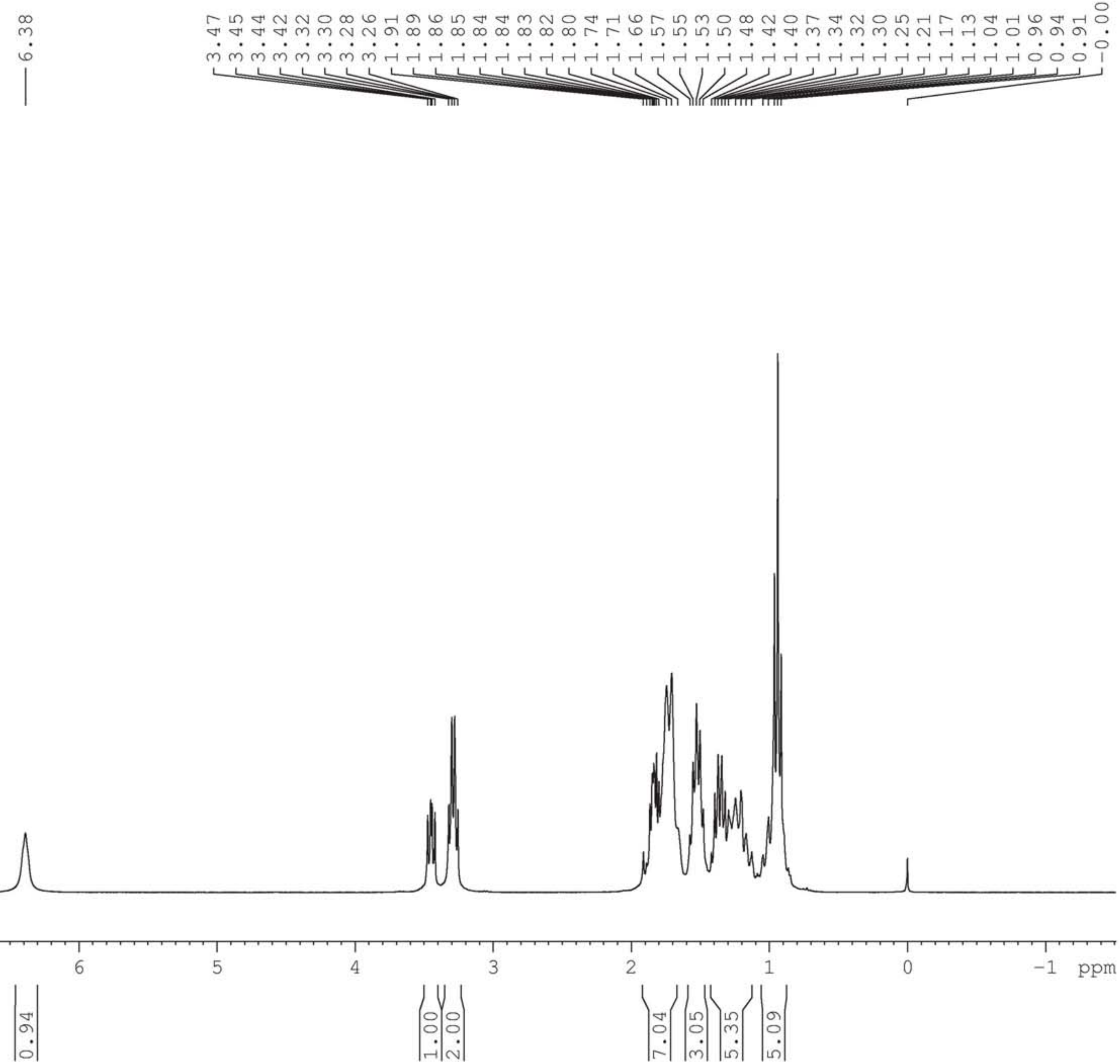


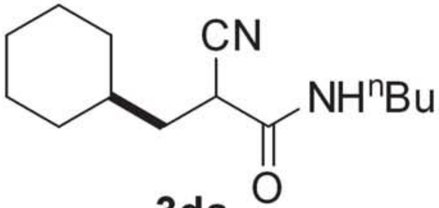
166.44
134.59
128.74
128.71
128.41
116.53
77.32
77.00
76.68
68.22
37.02
35.35
35.16
32.96
32.00
26.13
25.84
25.73
CO2Bn
CN
3ca
13C NMR (101 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



3da

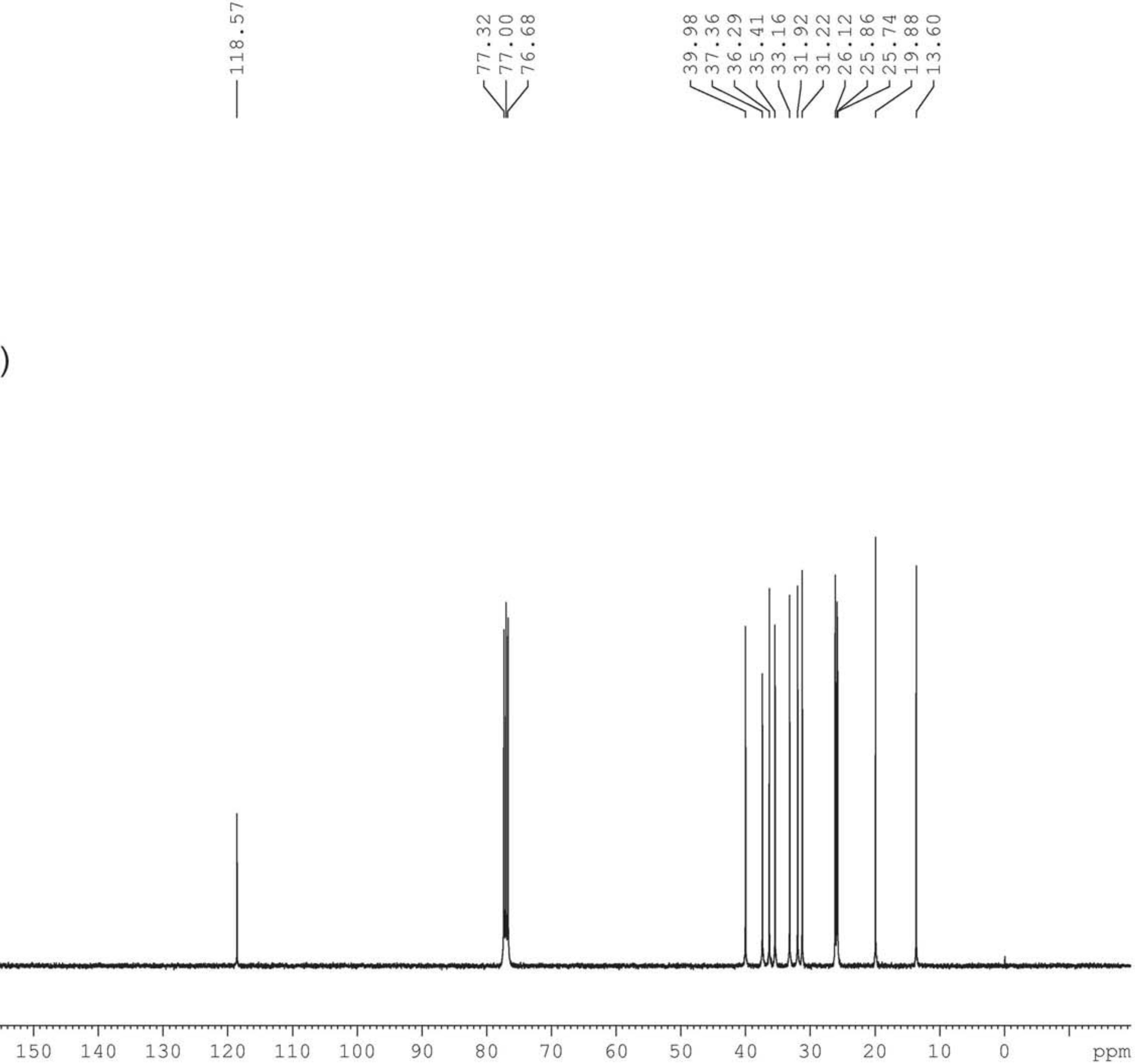
^{1}H NMR (300 MHz, $CDCl_3$)

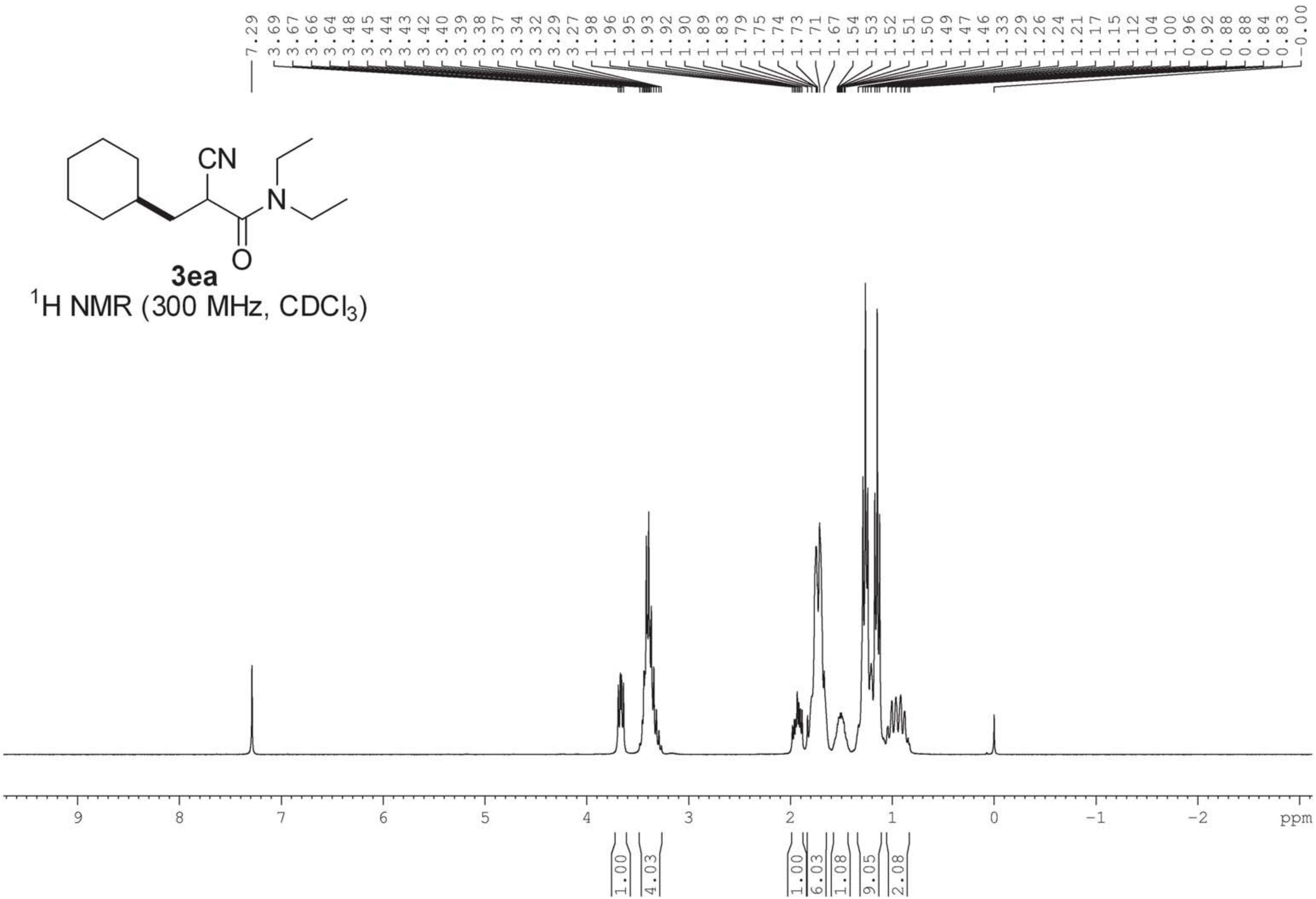


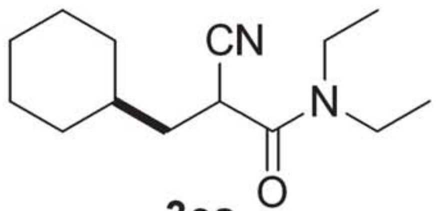


3da

^{13}C NMR (101 MHz, $CDCl_3$)

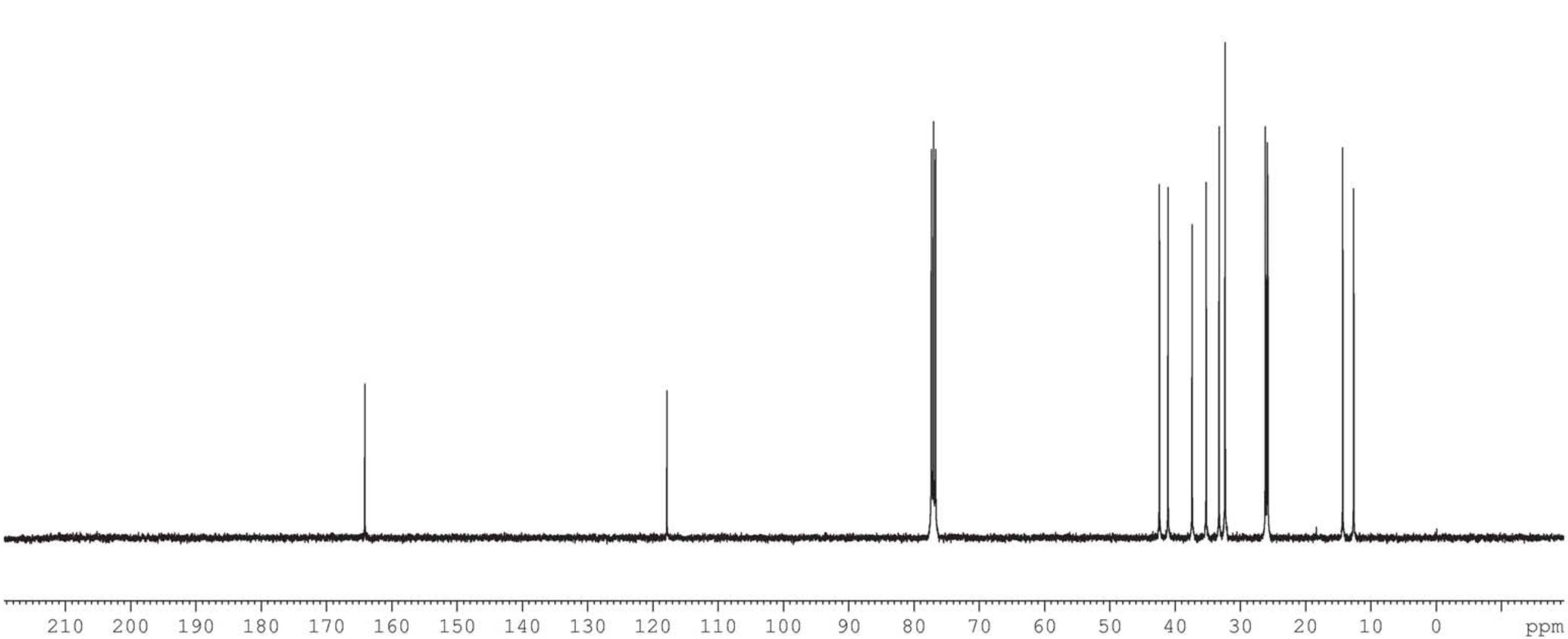


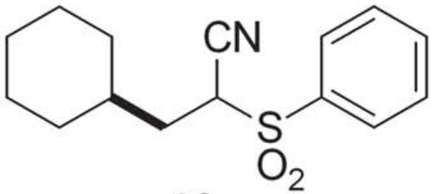

CN
N
O
3ea
1H NMR (300 MHz, CDCl3)
7.29 3.69 3.67 3.66 3.64 3.48 3.45 3.44 3.43 3.42 3.40 3.39 3.38 3.37 3.34 3.32 3.29 3.27 1.98 1.96 1.95 1.93 1.92 1.90 1.89 1.83 1.79 1.75 1.74 1.73 1.71 1.67 1.54 1.53 1.52 1.51 1.50 1.49 1.47 1.46 1.33 1.29 1.26 1.24 1.21 1.17 1.15 1.12 1.04 1.00 0.96 0.92 0.88 0.88 0.84 0.83 -0.00
9 8 7 6 5 4 3 2 1 0 −1 −2 ppm
1.00 4.03 1.00 6.03 1.08 9.05 2.08



3ea

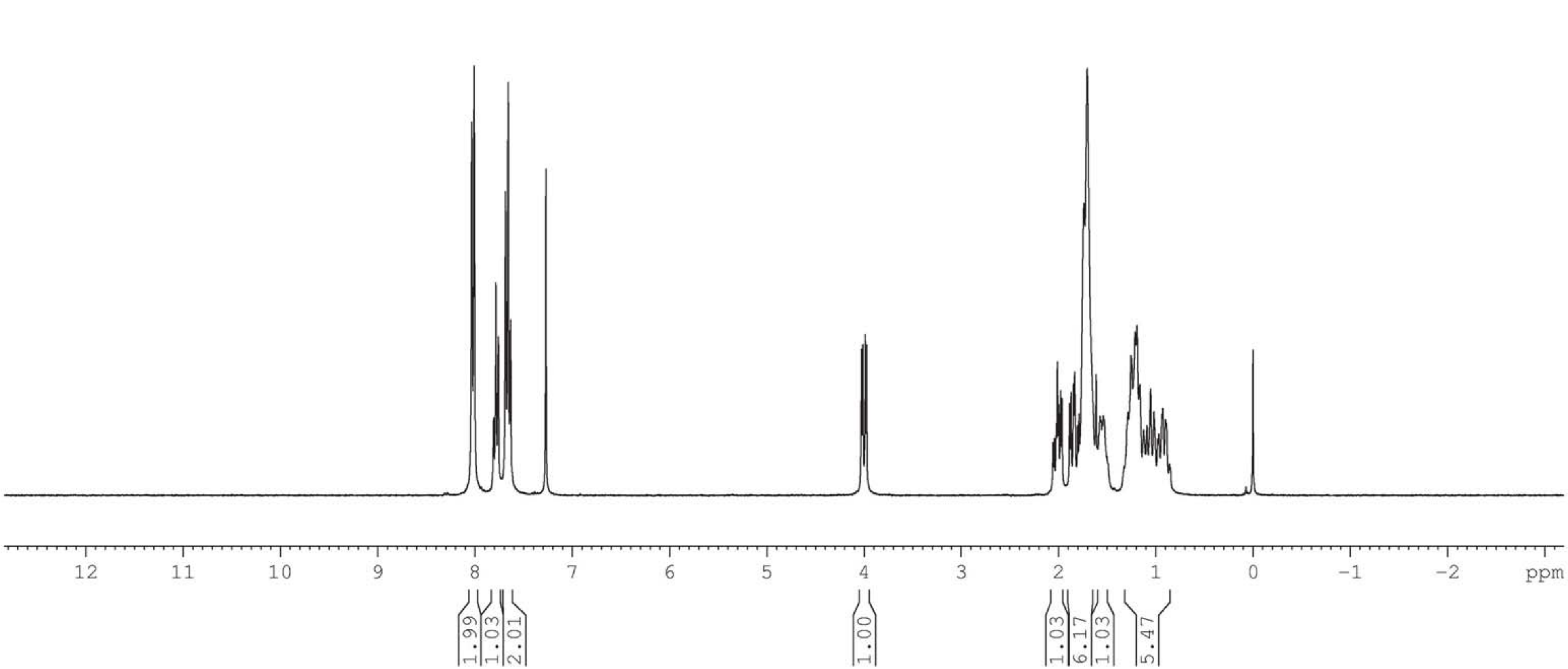
^{13}C NMR (101 MHz, $CDCl_3$)

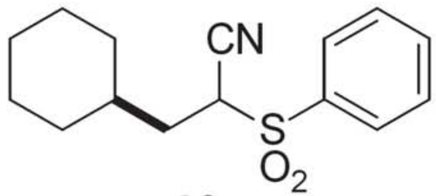




3fa

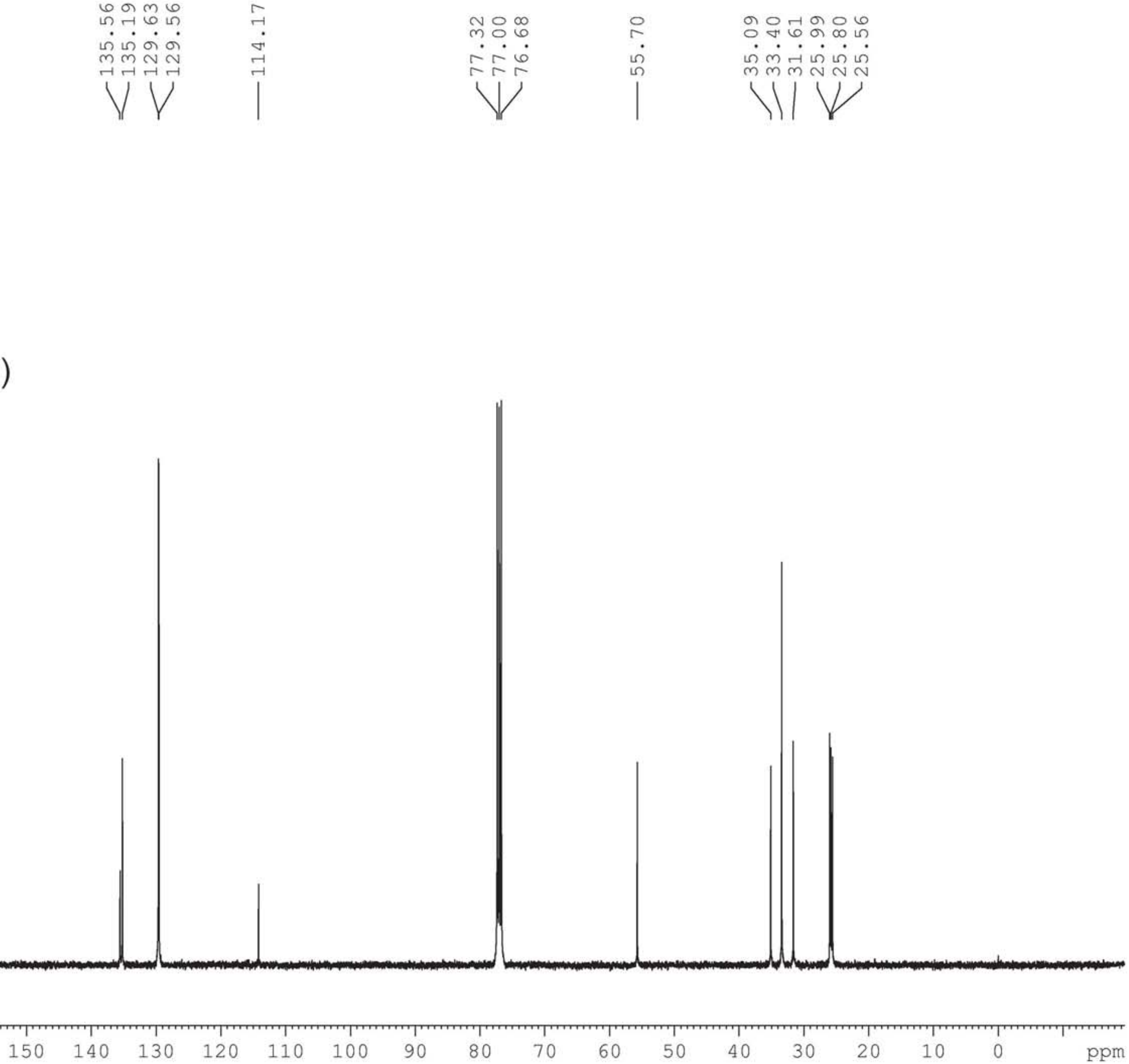
^{1}H NMR (300 MHz, $CDCl_3$)

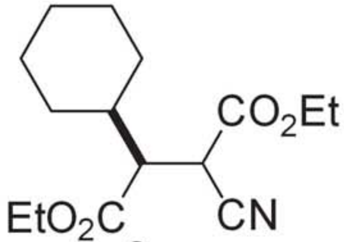




3fa

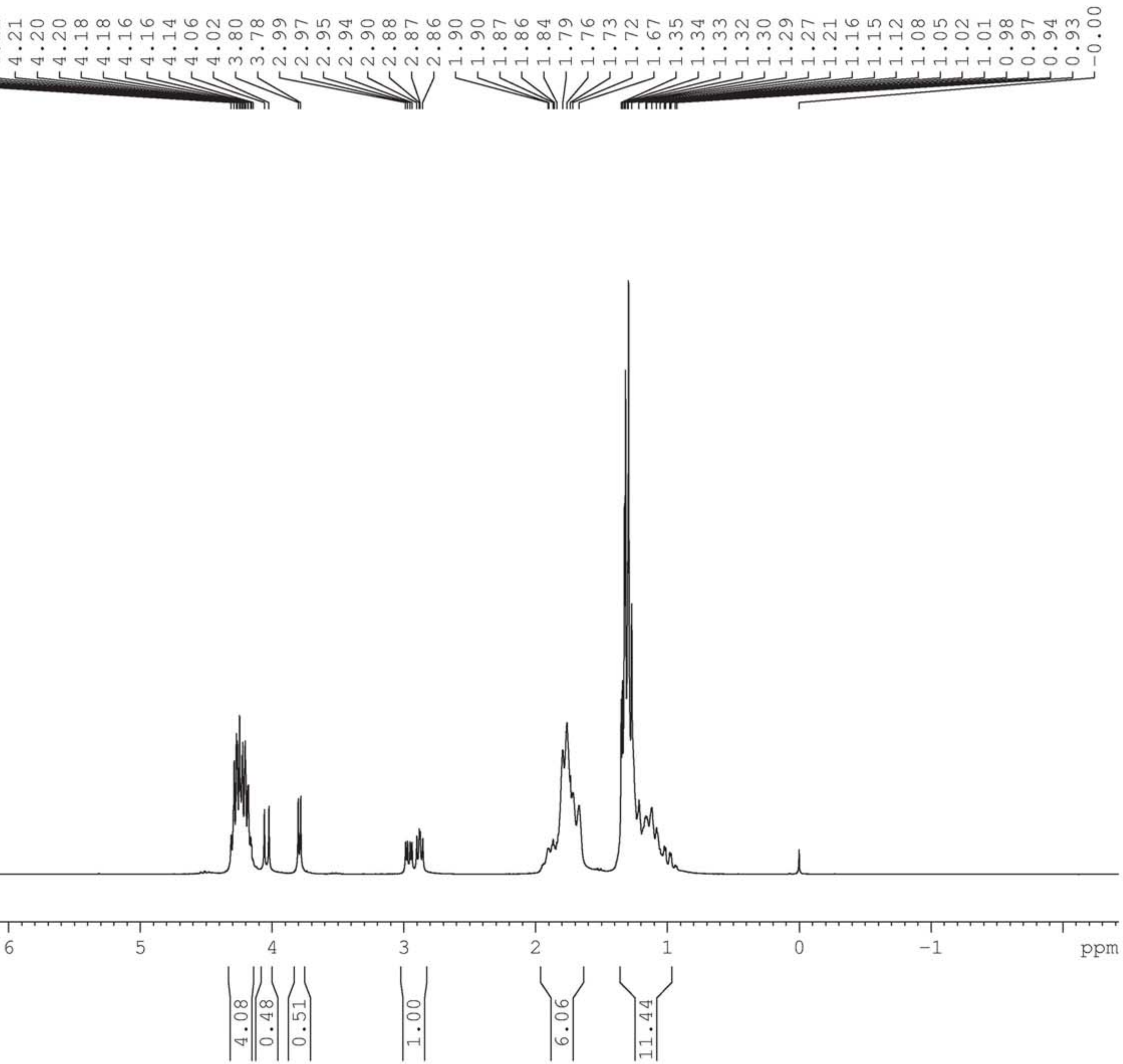
^{13}C NMR (101 MHz, $CDCl_3$)

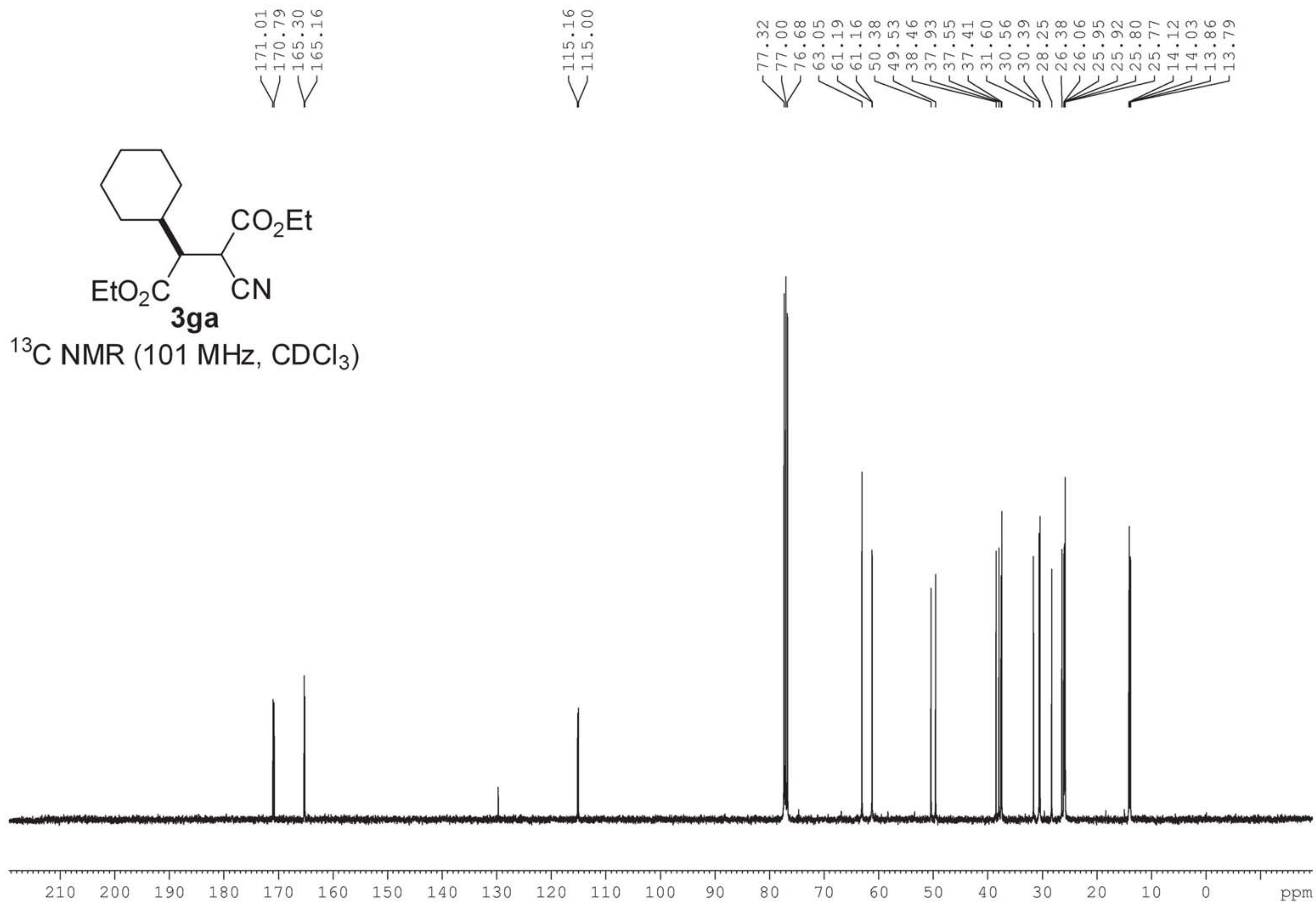


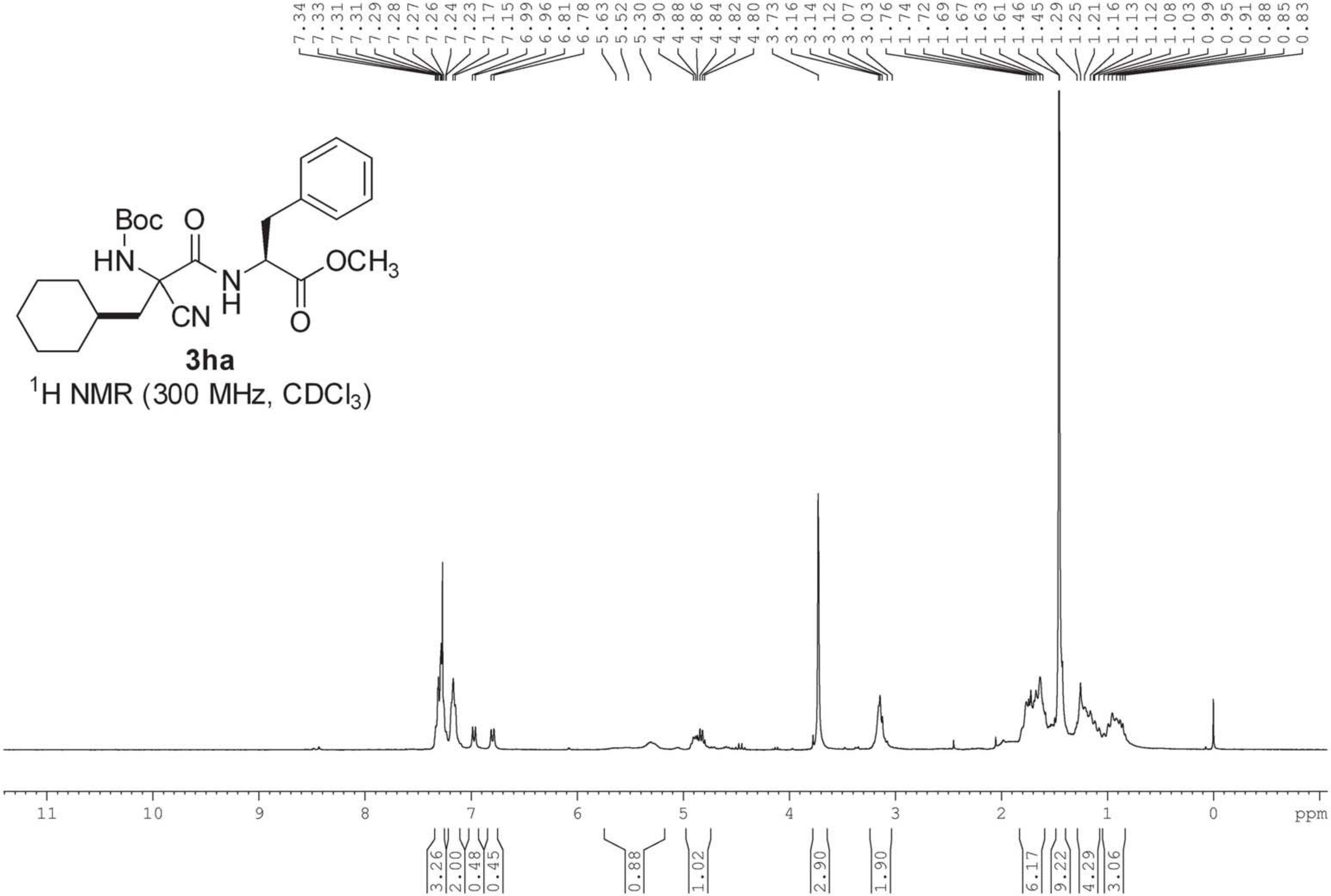


3ga

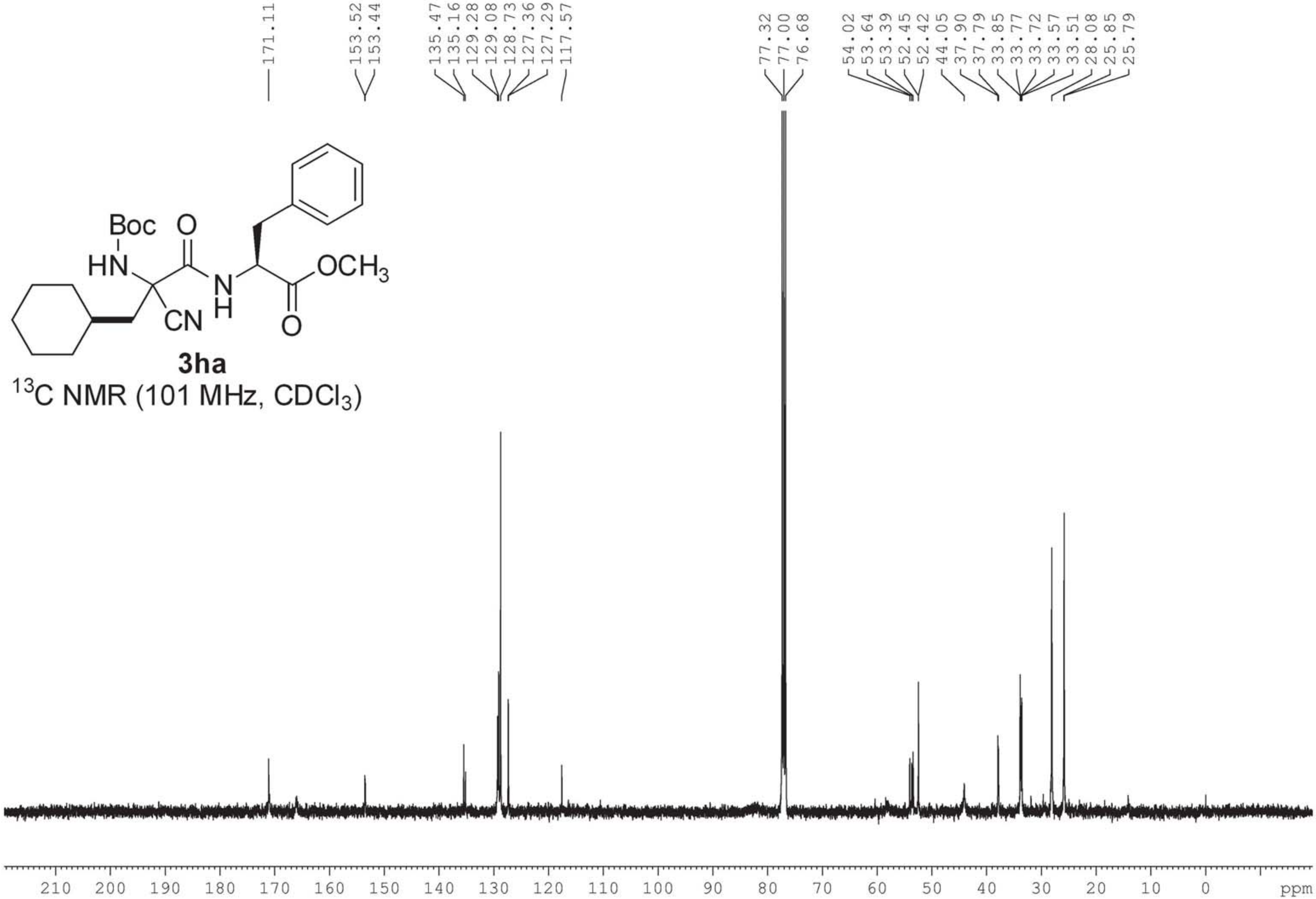
^1H NMR (300 MHz, $CDCl_3$)

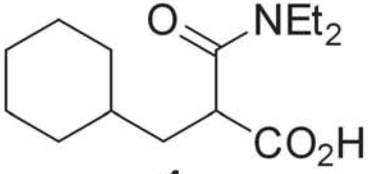



171.01
170.79
165.30
165.16
115.16
115.00
77.32
77.00
76.68
63.05
61.19
61.16
50.38
49.53
38.46
37.93
37.55
37.41
31.60
30.56
30.39
28.25
26.38
26.06
25.95
25.92
25.80
25.77
14.12
14.03
13.86
13.79
CO_2Et
EtO_2C
CN
3ga
^{13}C NMR (101 MHz, $CDCl_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



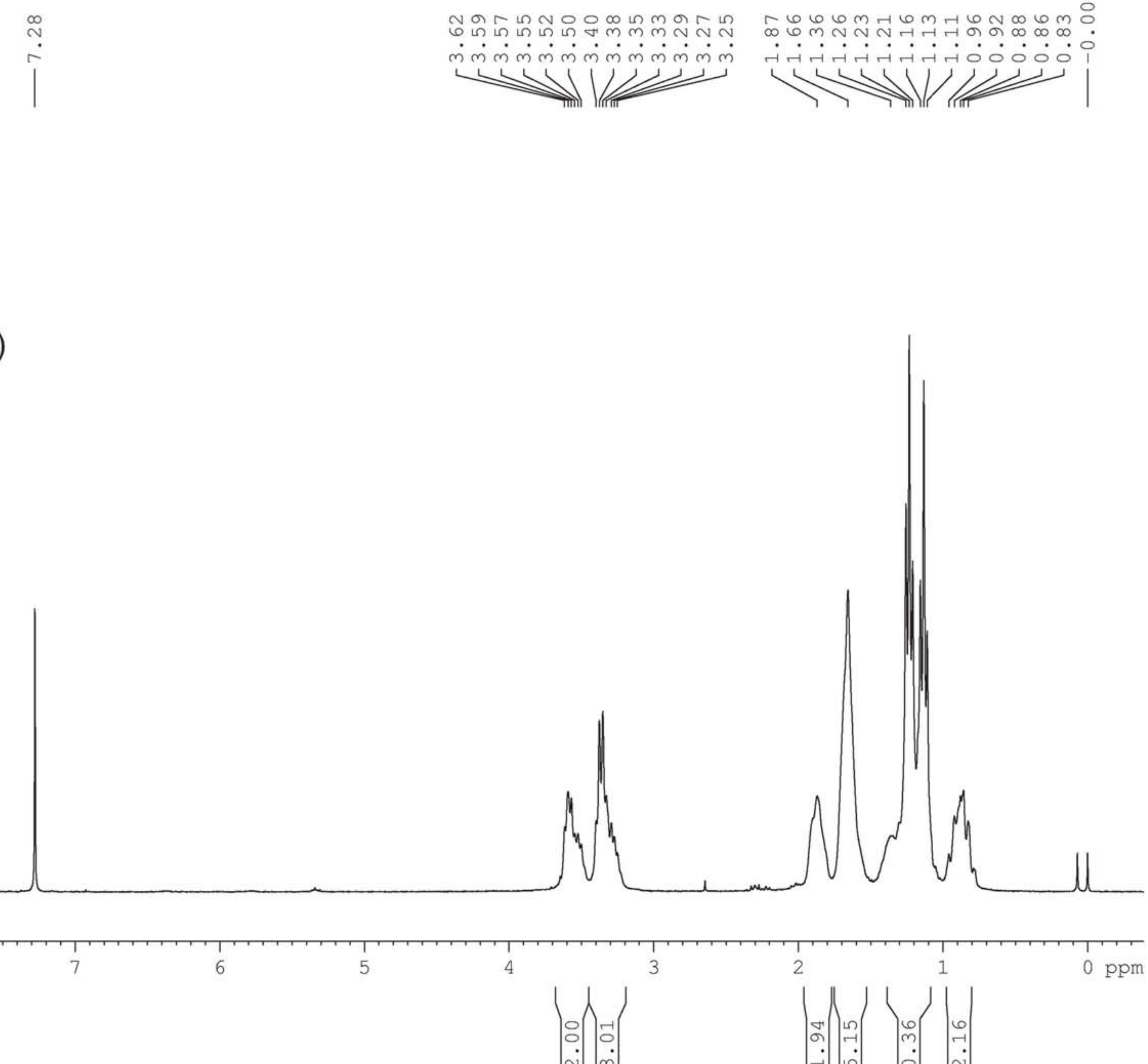
Boc
HN
O
N
H
OCH3
CN
O
3ha
1H NMR (300 MHz, CDCl3)
7.34 7.33 7.31 7.31 7.29 7.28 7.27 7.26 7.24 7.23 7.17 7.15 6.99 6.96 6.81 6.78 5.63 5.52 5.30 4.90 4.88 4.86 4.84 4.82 4.80 3.73 3.16 3.14 3.12 3.07 3.03 1.76 1.74 1.72 1.69 1.67 1.63 1.61 1.46 1.45 1.29 1.25 1.21 1.16 1.13 1.12 1.08 1.03 0.99 0.95 0.91 0.88 0.85 0.83
11 10 9 8 7 6 5 4 3 2 1 0 ppm
3.26 2.00 0.48 0.45 0.88 1.02 2.90 1.90 6.17 9.22 4.29 3.06

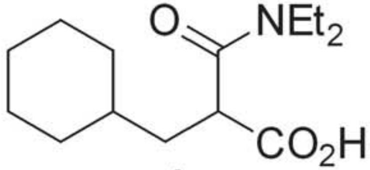

171.11
153.52
153.44
135.47
135.16
129.28
129.08
128.73
127.36
127.29
117.57
77.32
77.00
76.68
54.02
53.64
53.39
52.45
52.42
44.05
37.90
37.79
33.85
33.77
33.72
33.57
33.51
28.08
25.85
25.79
Boc
O
HN
N
H
OCH3
CN
O
3ha
13C NMR (101 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



4

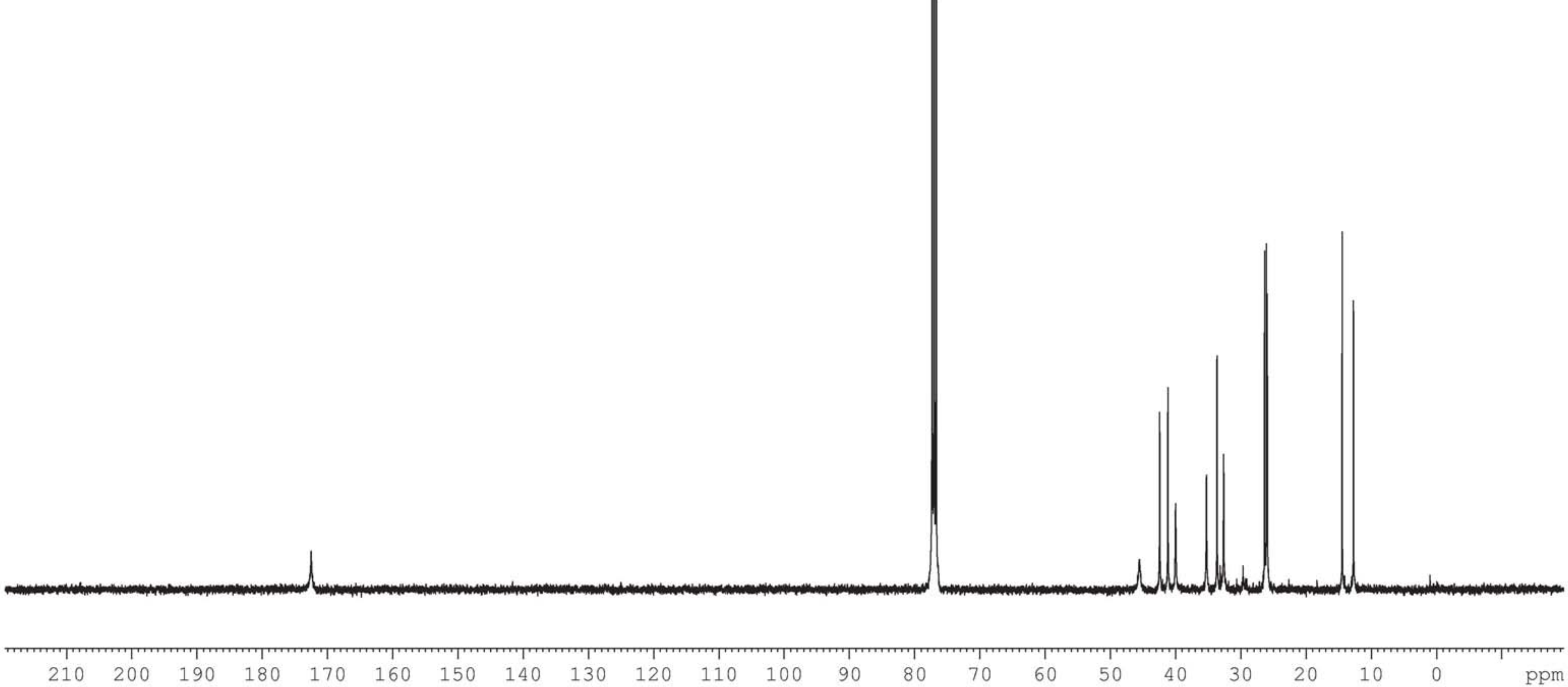
^{1}H NMR (300 MHz, $CDCl_3$)

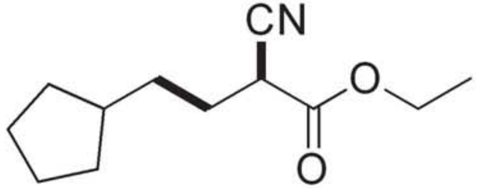




4

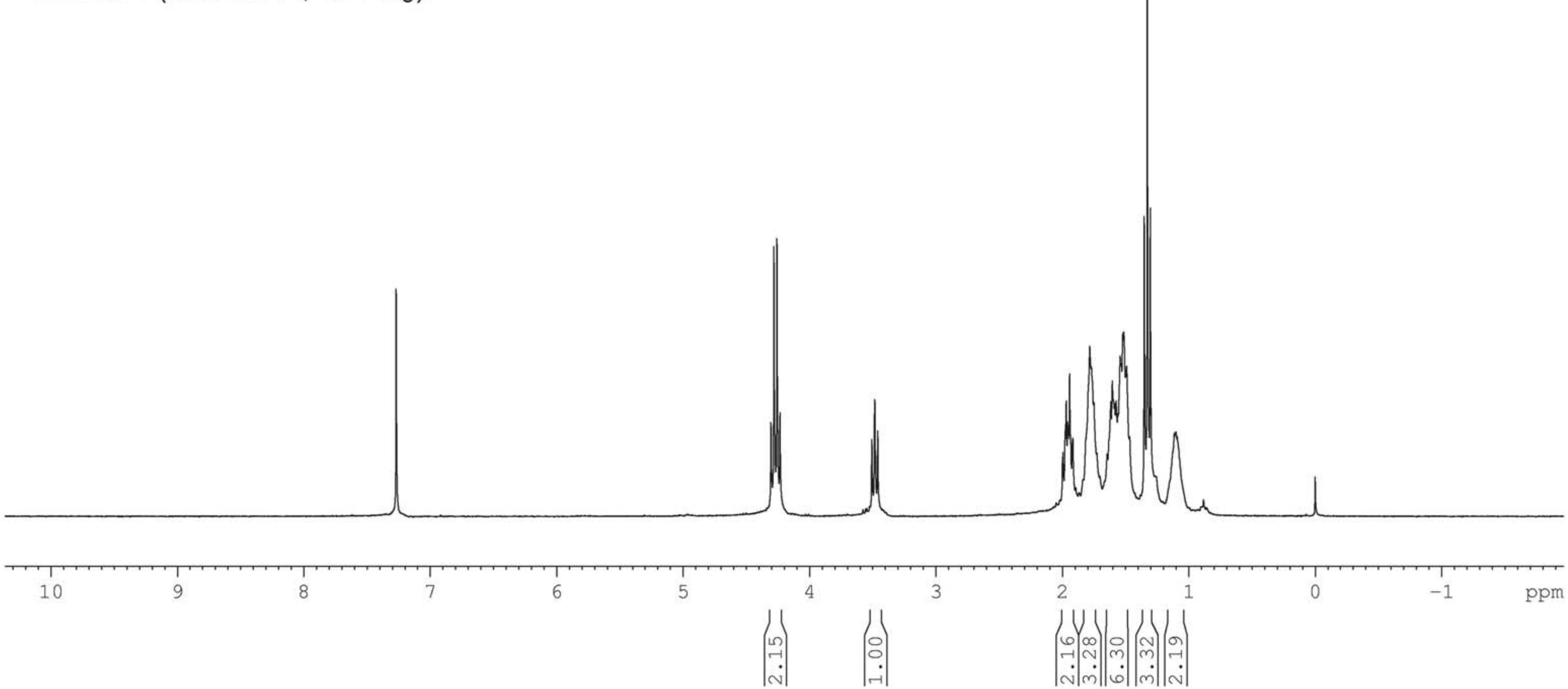
^{13}C NMR (101 MHz, $CDCl_3$)

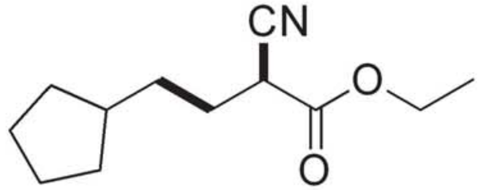




3an

^{1}H NMR (300 MHz, $CDCl_3$)





3an

^{13}C NMR (101 MHz, $CDCl_3$)