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N-Heterocyclic Olefins as Efficient Phase-Transfer Catalysts for Base-Promoted Alkylation Reactions

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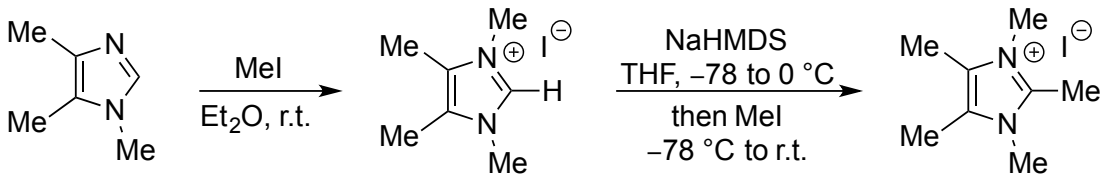
General methods

Reactions, unless otherwise stated, were conducted under a positive pressure of dry nitrogen in oven-dried glassware. Toluene, hexane, CH_2Cl_2, tetrahydrofuran (THF), and diethyl ether were dried with an SPS apparatus. Commercially available reagents were used as purchased unless otherwise noted. Analytical thin layer chromatography was performed using silica gel plates precoated with silica gel 60 F_{254} (0.2 mm). Flash chromatography employed 230-400 mesh silica gel. Solvents used for chromatography are quoted as volume/volume ratios.

NMR spectroscopy was performed at 298 K using either a Bruker Avance III 300 (300.13 MHz, ^{1}H; 75.5 MHz, ^{13}C; BBFO probe), a Avance I 300 (300.13 MHz, ^{1}H; 75.5 MHz, ^{13}C; BBFO probe), a Avance III 400 (400.13 MHz, ^{1}H; 100.6 MHz, ^{13}C; BBFO probe or Prodigy cryoprobe), a Varian Mercury 300 (300.13 MHz, ^{1}H), a Varian Inova 400 (400.13 MHz, ^{1}H; 100.6 MHz, ^{13}C), or a Varian Inova 600 (600.13 MHz, ^{1}H; 150.0 MHz, ^{13}C). Data is expressed in parts per million (ppm) downfield shift from tetramethylsilane with residual solvent as an internal reference (δ 7.26 ppm for chloroform, 5.27 ppm for dichloromethane, 1.94 ppm for acetonitrile, and 2.09 ppm for the toluene methyl group) and is reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J in Hz) and integration (number of protons). ^{13}C NMR spectra were recorded at 298 K with complete proton decoupling. Data is expressed in parts per million (ppm) downfield shift relative to the internal reference (δ 77.2 ppm for the central peak of deuterated chloroform).

Infrared spectra were obtained on a ThermoNicolet Avatar 370 FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). HRMS were performed at the Bioanalytical Mass Spectrometry Facility within the Mark Wainwright Analytical Centre at the University of New South Wales on an Orbitrap LTQ XL (Thermo Fisher Scientific, San Jose, CA, USA) ion trap mass spectrometer. Melting points were determined on a LLG MPM-H2 instrument.

Catalyst synthesis



A

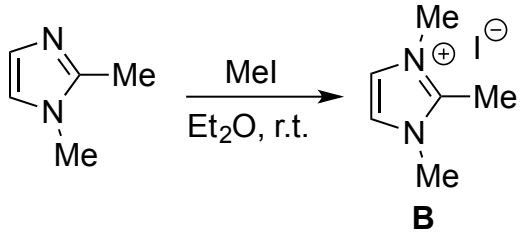
The tetramethyl imidazolium intermediate was synthesized according to a modified literature procedure of Fürstner.[1] 6.6 mL (15.0 g, 106.0 mmol, 1.5 equiv.) methyl iodide was slowly added to a solution of 7.8 g (70.8 mmol, 1.0 equiv.) 1,4,5-trimethyl imidazole in 90 mL dry ether and the reaction mixture was stirred overnight at ambient temperature. The resulting white suspension was filtered, the filter cake washed with dry ether (3x, 50 mL), and subsequently dried in vacuum to yield 17.66 g (70.0 mmol, 99%) 1,3,4,5-tetramethyl imidazolium iodide as colorless powder.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 3.86 (d, J = 0.5 Hz, 6H), 2.24 (s, 6H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 135.6, 127.2, 34.4, 8.8 ppm.

A suspension of 2.52 g (10.0 mmol, 1.0 equiv.) 1,3,4,5-tetramethyl imidazolium iodide in 50 mL dry THF under nitrogen atmosphere at −78 °C was slowly treated with 10.2 mL (10.2 mmol, 1.0 equiv.) NaHMDS solution (1 M in THF), stirred for 10 min at −78 °C and then slowly warmed to 0 °C. Subsequently, the reaction mixture was cooled to −78 °C and 1.0 mL (16.1 mmol, 1.6 equiv.) methyl iodide was added dropwise. The reaction mixture was slowly warmed to ambient temperature and continued overnight. After the addition of 50 mL dry ether, the resulting suspension was filtered and the filter cake washed with dry ether (50 mL). Dissolving the filter cake in dry dichloromethane, a second filtration, and removal of the volatiles under reduced pressure gave the crude product, which was recrystallized from hot chloroform to yield 2.52 g (9.47 mmol, 95%) **A** as off-white needles.[2]

[1] A. Fürstner, M. Alcarazo, R. Goddard, C. W. Lehmann, *Angew. Chemie Int. Ed.* **2008**, *47*, 3210–3214.
[2] T. Peppel, C. Roth, K. Fumino, D. Paschek, M. Köckerling, R. Ludwig, *Angew. Chemie Int. Ed.* **2011**, *50*, 6661–6665.

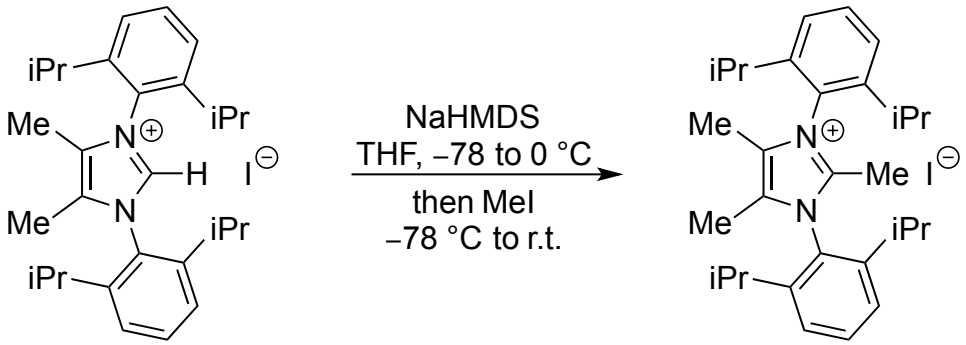
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 6H), 2.82 (s, 3H), 2.24 (s, 6H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 142.9, 125.9, 33.3, 12.7, 9.3 ppm.



B

Catalyst **B** was synthesized according to a literature procedure of Fürstner.[1] A solution of 20.4 g (212 mmol, 1.0 equiv.) 1,2-dimethyl imidazole in 170 mL dry ether was treated with 20.0 mL (45.6 g, 321 mmol, 1.5 equiv.) methyl iodide and stirred for 3 days at ambient temperature. The resulting white suspension was filtered, the filter cake washed with dry ether (1x, 100 mL), and the solid residue dried in vacuum to give 49.0 g (206 mmol, 97%) of the title compound as colorless solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.46 (s, 2H), 3.83 (s, 6H), 2.63 (s, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)**[3] δ 122.6, 36.6, 11.9 ppm.



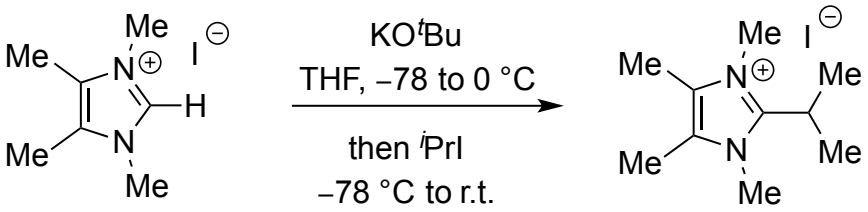
C

Under argon 25 mL dry THF were added to 2.05 g (4.52 mmol, 1.0 equiv.) 1,3-bis(2,6-di*i*-propylphenyl)-4,5-dimethyl-1*H*-imidazol-3-ium chloride and the resulting suspension treated dropwise with 4.6 mL (4.6 mmol, 1.0 equiv.) NaHMDS solution (1 M in THF) at −78 °C. After slowly warming to 0 °C over 2 hours and cooling to −78 °C 0.42 mL (0.96 g, 6.75 mmol, 1.5 equiv.) methyl iodide were slowly added and the reaction mixture gradually warmed to room temperature overnight. 30 mL dry ether

[3] The C2 carbon signal could not be observed.

were added, the mixture filtered, and the filter cake washed with dry ether (3x, 20mL). Subsequently the filter cake was dissolved in dry dichloromethane, filtered again, and the filtrate concentrated under reduced pressure to yield 2.39 g (4.28 mmol, 95%) 2-methyl imidazolium iodide **C**.

^{1}H NMR (300 MHz, CD_3CN) δ 7.66 - 7.74 (m, 2H), 7.50 - 7.57 (m, 4H), 2.34 (spt, J = 6.8 Hz, 4H), 2.02 - 2.09 (m, 9H), 1.25 (d, J = 6.8 Hz, 12H), 1.16 (d, J = 6.9 Hz, 12H) ppm; **^{13}C NMR (75 MHz, CD_3CN)** δ 145.3, 143.3, 132.8, 128.8, 127.0, 125.8, 29.1, 24.2, 24.2, 12.2, 10.4 ppm; IR (ATR) 3150, 3068, 2960, 2939, 1630, 1602, 1536, 1468 cm^{-1}; ESI-MS *m/z*: 431.3 ([M−I]$^+$, 100%); Anal. Calcd. for $C_{30}H_{43}N_2^+$: *m/z* = 431.3421; found 431.3422.

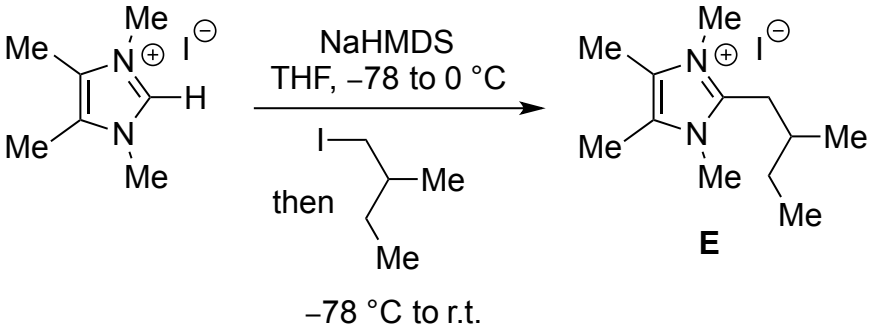


D

To a suspension of 1.24 g (4.92 mmol, 1.0 equiv.) 1,3,4,5-tetramethyl imidazolium iodide in 25 mL dry THF under argon 0.56 g (4.99 mmol, 1.0 equiv.) potassium *t*-butoxide were added and the reaction mixture stirred for 20 min. 0.74 mL (1.26 g, 7.41 mmol, 1.5 equiv.) 2-iodopropane were added dropwise and the reaction mixture slowly warmed to room temperature. A second portion of 0.56 g (4.99 mmol, 1.0 equiv.) potassium *t*-butoxide followed by 0.74 ml (1.26 g, 7.41 mmol, 1.5 equiv.) 2-iodo propane were added and the reaction continued overnight at ambient temperature. The off-white suspension was concentrated under reduced pressure and the residue purified by flash chromatography (CH_2Cl_2/MeOH) to obtain 0.40 g (1.36 mmol, 28%) 2-isopropyl imidazolium salt **D**.[4]

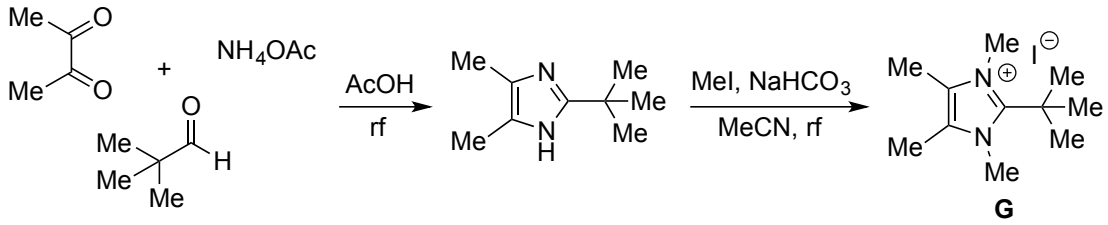
^{1}H NMR (400 MHz, CD_3CN) δ 3.65 (s, 6H), 3.59 (spt, J = 7.3 Hz, 1H), 2.18 (s, 6H), 1.39 (d, J = 7.3 Hz, 6H) ppm; **^{13}C NMR (100 MHz, CD_3CN)** δ 148.8, 126.9, 33.4, 25.8, 18.8, 9.0 ppm.

[4] A. R. Chianese, B. M. Zeglis, R. H. Crabtree, *Chem. Commun.* **2004**, 2176–2177.



A suspension of 504 mg (2.00 mmol, 1.0 equiv.) 1,3,4,5-tetramethyl imidazolium iodide in 10 mL THF under argon was cooled to −78 °C and treated dropwise with 2.0 mL (2.00 mmol, 1.0 equiv.) of NaHMDS solution (1 M in THF). After stirring for 2 h at −78 °C a solution of 597 mg (3.01 mmol, 1.5 equiv.) 1-iodo-2-methylbutane in 4 mL THF was slowly added and the reaction continued for 2.5 d at ambient temperature. The product is precipitated by adding 50 mL Et_2O, filtered off, washed with 50 mL Et_2O. The resulting solid is suspended in 50 mL CH_2Cl_2, subsequently, filtered and washed with 50 mL CH_2Cl_2. The filtrate is concentrated and the crude product purified by flash chromatography (CH_2Cl_2/MeOH) to obtain NHO precursor **E** as yellowish crystalline solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.73 (s, 6H), 3.11 (dd, J_1 = 15.9 Hz, J_2 = 6.4 Hz, 1H), 2.93 (dd, J_1 = 15.9, J_2 = 8.9 Hz, 1H), 2.26 (s, 6H), 1.74 - 1.83 (m, 1H), 1.25 - 1.49 (m, 2H), 0.87 - 1.00 (m, 6H) ppm; **^{13}C NMR (150 MHz, $CDCl_3$)** δ 145.3, 126.2, 34.7, 33.6, 32.2, 29.5, 19.2, 11.6, 9.5 ppm; **m.p.** 127-129 °C; **IR (ATR)** 3015, 2965, 2917, 2875, 2669, 2105, 2047, 1958, 1648, 1532, 1442, 1376, 1353, 1236, 1124, 1092, 1039, 962, 903, 827, 780, 709 cm^{-1}; **ESI-MS** m/z: 195.2 ([M−I]$^+$, 100%); Anal. Calcd. for $C_{12}H_{23}N_2^+$: *m/z* = 195.1856; found 195.1846.



Catalyst **G** was synthesized according to a modified literature procedure from Crabtree.[4] A solution of 6.3 g (81.7 mmol, 4.0 equiv.) ammonium acetate and 2.2 g (25.5 mmol, 1.2 equiv.) trimethyl acetaldehyde in 8 mL acetic acid was heated to 90

°C and treated with 1.8 mL (1.77 g, 20.6 mmol, 1.0 equiv.) 2,3-butanedione. The reaction mixture was refluxed for 2 h, cooled to room temperature, and extracted with hexane (3x, 10 mL). The acid layer was neutralized with saturated Na_2CO_3-solution and extracted with ether (2x, 100 mL). The combined ether layers were dried with Na_2SO_4, the solvent removed under reduced pressure, and the crude product recrystallized from ether to obtain 0.63 g (4.14 mmol, 20%) 2-*tert*-butyl-4,5-dimethyl-1*H*-imidazole as pale red solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (br. s, 1H), 2.11 (s, 6H), 1.34 (s, 9H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)**[5] δ 153.5, 32.7, 29.9, 10.9 ppm; IR (ATR) 3300, 2960, 2934, 1632, 1612, 1530, 1460 cm^{-1}; **ESI-MS** *m/z*: 153.1 ($[M+H]^+$, 100%); Anal. Calcd. for $C_9H_{17}N_2^+$: *m/z* = 153.1386; found 153.1387.

0.86 g (10.2 mmol, 4.1 equiv.) $NaHCO_3$ and 0.4 mL (0.91 g, 6.43 mmol, 2.6 equiv.) methyl iodide were added to a solution of 0.38 g (2.50 mmol, 1.0 equiv.) 2-*tert*-butyl-4,5-dimethyl-1*H*-imidazole in 80 mL dry acetonitrile. The reaction mixture was heated to reflux for 16 h and after completion cooled to room temperature. After the removal of the volatiles under reduced pressure, the residue was taken in dichloromethane, filtered through a short plug of Celite®, and layered with ether. The crystals were collected and dried in vauum to yield 0.73 g (2.06 mmol, 82%) imidazolium iodide **G** as colorless needles.

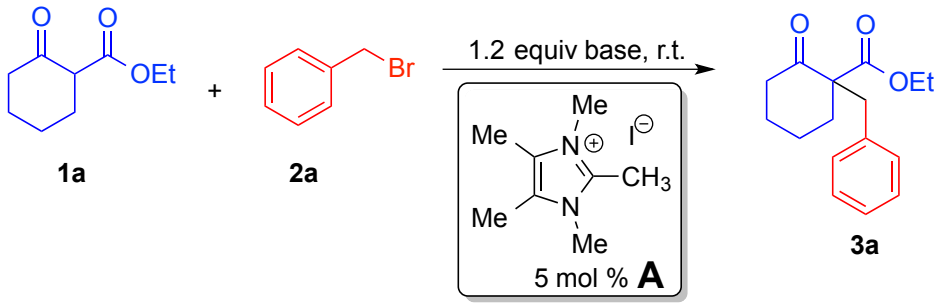
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 6H), 2.25 (s, 6H), 1.66 (s, 9H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 149.3, 127.4, 36.7, 35.6, 30.6, 10.4 ppm; IR (ATR) 3150, 3072, 2952, 2941, 1620, 1523, 1457 cm^{-1}; **ESI-MS** *m/z*: 181.2 ($[M-I]^+$, 100%); Anal. Calcd. for $C_{11}H_{21}N_2^+$: *m/z* = 181.1699; found 181.1698.

Free NHO catalyst F was prepared according to literature procedure.[6]

[5] The C2 carbon signal could not be observed.
[6] Naumann, S.; Thomas, A. W.; Dove, A. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 9550–9554.

Optimization of the reaction conditions

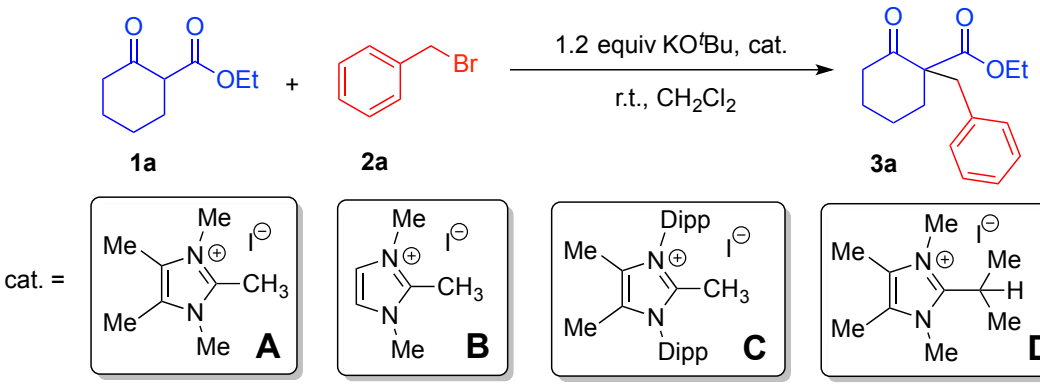
Table 1. Optimization of the NHO-catalyzed phase-transfer alkylation reaction.[a]



Entry	Solvent	Base	Time [min]	Yield [%][b]
1	toluene	KO^{t}Bu	30	94
2	hexane	KO^{t}Bu	60	93
3	Et_2O	KO^{t}Bu	60	93
4	THF	KO^{t}Bu	10	92
5	CH_2Cl_2	KO^{t}Bu	5	94
6	CH_2Cl_2	K_2CO_3	>1 d[c]	16
7	CH_2Cl_2	K_3PO_4	>1 d[c]	28
8	CH_2Cl_2	KOH	180	89
9	CH_2Cl_2	KH	5	80
10	CH_2Cl_2	KHMDS	>1 d[c]	66

[a] The reactions were carried out with 1.0 mmol of **1a**, 1.2 mmol of base, and 1.25 mmol of benzyl bromide (**2a**) in the presence 0.05 mmol NHO precursor **A** in 4 mL of solvent at ambient temperature. [b] Yield of the isolated products. [c] The reaction was not completed after one day.

Table 2. Screening of different catalysts and loadings for the NHO-catalyzed phase-transfer alkylation reaction.[a]



Entry	Catalyst	Cat. [mol %]	Time [min]	Yield [%][b]
1	**A**	5	5	94
2	**B**	5	10	95
3	**C**	5	5	93
4	**D**	5	15	94
5	**A**	2	10	95
6	**A**	1	20	94
7	**A**	0.5	40	93

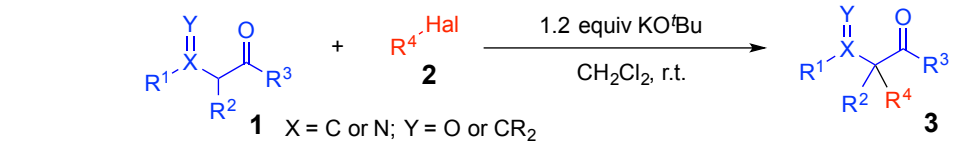
[a] The reactions were carried out with 1.0 mmol of **1a**, 1.2 mmol of KO^{t}Bu, and 1.25 mmol of benzyl bromide (**2a**) in 4 mL of CH_2Cl_2. [b] Yield of the isolated products. DIPP = 2,6-di(^{i}Pr)C_6H_3

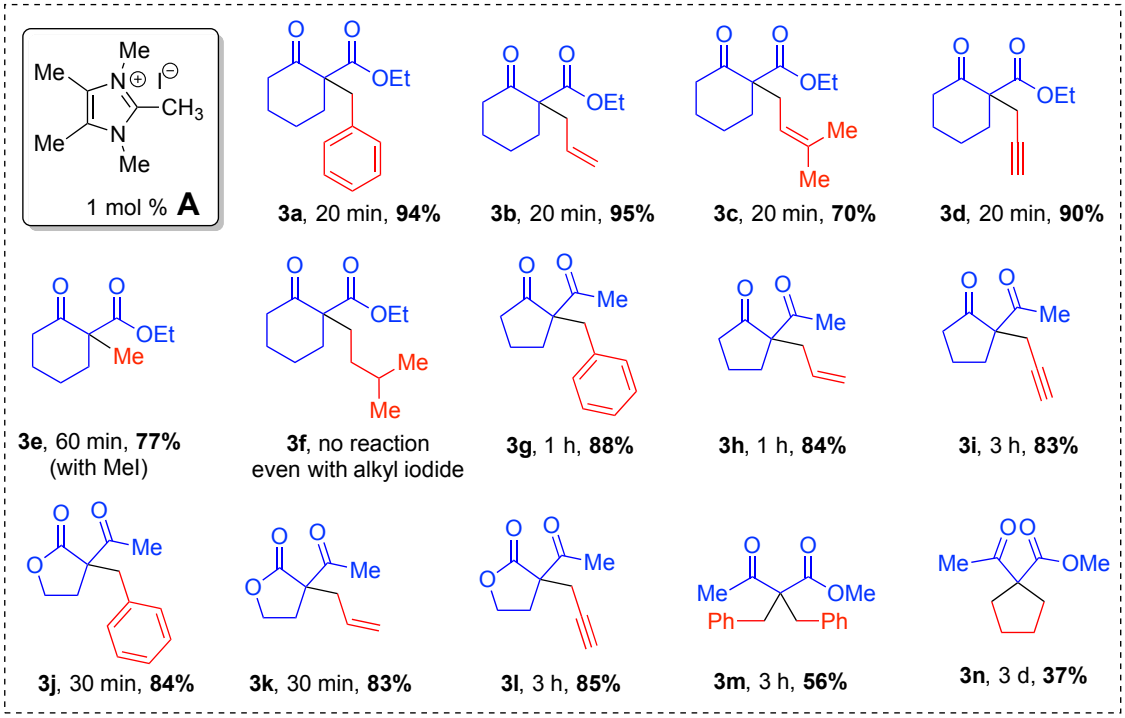
General procedure for the substrate scope of alkylation reactions with NHOs as phase-transfer catalysts

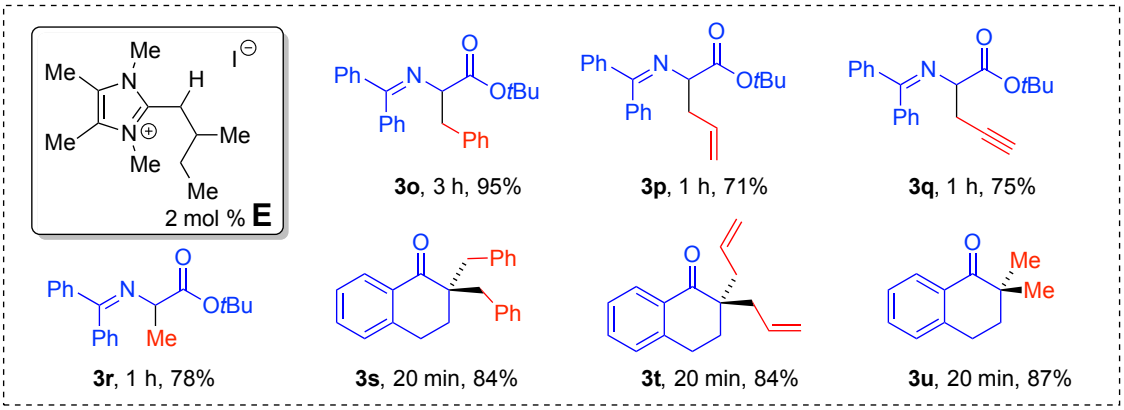
To a mixture of 1.2 mmol (1.2 equiv.) potassium *t*-butoxide, 10 μmol (1 mol %) NHO azolium salt catalyst, and 1.0 mmol (1.0 equiv.) β-ketoester **1** in 4 mL of CH_2Cl_2 (*c* = 0.25 M), 1.2 mmol (1.2 equiv.) alkyl halide **2** was added. The resulting suspension was stirred until TLC showed the complete conversion of the starting material. Subsequently the reaction mixture was concentrated under a flow of nitrogen and the resulting crude product purified by flash chromatography (*n*-hexane/ethyl acetate).

Substrate scope studies

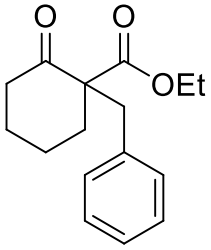
Scheme 2. Substrate scope of the NHO-catalyzed alkylation reaction





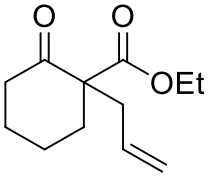


Ethyl 1-benzyl-2-oxocyclohexanecarboxylate[7] **(3a):** Prepared according to the general procedure from ethyl 2-oxocyclohexanonecarboxylate and benzyl bromide to yield the title compound as colorless oil (245 mg, 0.94 mmol, 94% yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.30 (m, 3H), 7.06-7.15 (m, 2H), 3.99-4.19 (m, 2H), 3.31 (d, J = 13.7 Hz, 1H), 2.87 (d, J = 13.7 Hz, 1H), 2.33-2.54 (m, 3H), 1.94-2.08 (m, 1H), 1.58-1.78 (m, 3H), 1.38-1.52 (m, 1H), 1.17 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 207.5, 171.2, 136.8, 130.5, 128.1, 126.8, 62.3, 61.4, 41.4, 40.6, 36.1, 27.8, 22.7, 14.1 ppm.

Ethyl 1-allyl-2-oxocyclohexanecarboxylate[8] **(3b):** Prepared according to the general procedure from ethyl 2-oxocyclohexanonecarboxylate and allyl bromide to yield the title compound as colorless oil (200 mg, 0.95 mmol, 95% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 - 5.80 (m, 1H), 4.96 - 5.06 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 2.59 (dd, J_1 = 13.9 Hz, J_2 = 7.0 Hz, 1H), 2.38 - 2.51 (m, 3H), 2.32 (dd, J_1 = 13.9 Hz, J_2 = 7.8 Hz, 1H), 1.93 - 2.05 (m, 1H), 1.54 - 1.80 (m, 3H), 1.38 - 1.50 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 207.6, 171.6, 133.5, 118.4, 61.3, 61.0, 41.2, 39.4, 35.9, 27.6, 22.6, 14.3 ppm.

Ethyl 1-(3-methylbut-2-enyl)-2-oxocyclohexanecarboxylate[8] **(3c):** Prepared according to the general procedure from ethyl 2-oxocyclohexanonecarboxylate and dimethylallyl bromide (prenyl bromide) to yield the title compound as colorless oil (167 mg, 0.70 mmol, 70% yield).

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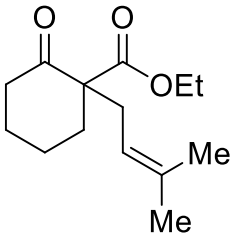
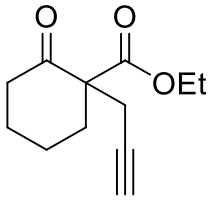
[7] Guerrab, Z.; Daou, B.; Fkih-Tetouani, S.; Ahmar, M.; Cazes, B. *Tetrahedron* **2007**, *63*, 3367–3379.
[8] McCarthy Cole, B.; Han, L.; Snider, B. B. *J. Org. Chem.* **1996**, *61*, 7832–7847.



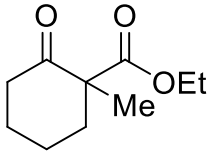
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 - 5.08 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.39 - 2.59 (m, 4H), 2.31 (dd, J_1 = 14.5 Hz, J_2 = 7.8 Hz, 1H), 1.94 - 2.04 (m, 1H), 1.59 - 1.77 (m, 6H), 1.58 (s, 3H), 1.38 - 1.47 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 208.0, 171.9, 134.8, 118.8, 61.3, 61.2, 41.3, 35.7, 33.4, 27.7, 26.1, 22.7, 17.9, 14.2 ppm.

Ethyl 2-oxo-1-(prop-2-ynyl)cyclohexanecarboxylate[9] (3d): Prepared according to the general procedure from ethyl 2-oxocyclohexanonecarboxylate and propargyl bromide to yield the title compound as colorless oil (189 mg, 0.91 mmol, 90% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (q, J = 7.1 Hz, 2H), 2.75 (dd, J_1 = 17.0 Hz, J_2 = 2.7 Hz, 1H), 2.67 (dq, J_1 = 13.7 Hz, J_2 = 3.2 Hz, 1H), 2.56 (dd, J_1 = 17.0 Hz, J_2 = 2.7 Hz, 1H), 2.39 - 2.50 (m, 2H), 1.99 - 2.09 (m, 2H), 1.76 - 1.84 (m, 2H), 1.58 - 1.71 (m, 2H), 1.26 (t, J_1 = 7.1 Hz, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.1, 170.5, 79.7, 71.4, 61.8, 60.1, 41.0, 35.5, 27.5, 24.9, 22.5, 14.2 ppm.

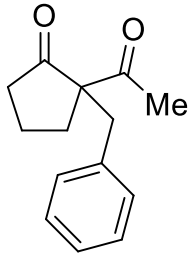
Ethyl 1-methyl-2-oxocyclohexanecarboxylate[10] (3e): Prepared according to the general procedure from ethyl 2-oxocyclohexanonecarboxylate and methyl iodide to yield the title compound as colorless oil (141 mg, 0.77 mmol, 77% yield).



[9] Shanmugam, P.; Srinivasan, R.; Rajagopalan, K. *Tetrahedron* **1997**, *53*, 11685–11692.
[10] Shneider, O. S.; Pisarevsky, E.; Fristrup, P.; Szpilman, A. M. *Org. Lett.* **2015**, *17*, 282–285.

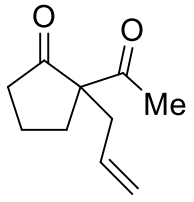
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 - 4.26 (m, 2H), 2.40 - 2.56 (m, 3H), 1.95 - 2.07 (m, 1H), 1.56 - 1.79 (m, 3H), 1.39 - 1.51 (m, 1H), 1.21 - 1.31 (m, 6H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 208.5, 173.2, 61.4, 57.3, 40.8, 38.4, 27.7, 22.8, 21.4, 14.2 ppm.

2-Acetyl-2-benzylcyclopentanone (3g): Prepared according to the general procedure from 2-acetylcyclopentanone and benzyl bromide to yield the title compound as colorless oil (171 mg, 0.79 mmol, 79% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 - 7.30 (m, 3H), 7.05 - 7.11 (m, 2H), 3.26 (d, J = 13.9 Hz, 1H), 3.07 (d, J = 13.9 Hz, 1H), 2.53 - 2.62 (m, 1H), 2.23 - 2.35 (m, 4H), 1.97 - 2.11 (m, 1H), 1.68 - 1.83 (m, 2H), 1.53 - 1.66 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 216.2, 204.0, 136.6, 129.8, 128.7, 127.1, 69.9, 40.3, 39.0, 30.2, 26.5, 19.5 ppm; IR (ATR) 3280, 2924, 1715, 1700, 1655, 1445 cm^{-1}; **ESI-MS** m/z: 234.1 ($[M+NH_4]^+$, 100%), 217.1 ($[M+H]^+$, 32%); Anal. Calcd. for $C_{14}H_{17}O_2^+$: *m/z* = 217.1223; found 217.1224.

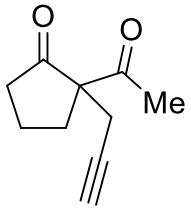
2-Acetyl-2-allylcyclopentanone[11] (3h): Prepared according to the general procedure from 2-acetylcyclopentanone and allyl bromide to yield the title compound as colorless oil (78 mg, 0.47 mmol, 47 % yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 - 5.67 (m, 1H), 5.01 - 5.18 (m, 2H), 2.56 - 2.77 (m, 2H), 2.14 - 2.50 (m, 6H), 1.69 - 1.97 (m, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 215.6, 204.0, 132.6, 119.2, 68.6, 39.3, 38.7, 30.4, 26.3, 19.5 ppm.

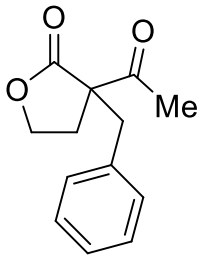
[11] Kimura, M.; Mukai, R.; Tanigawa, N.; Tanaka, S.; Tamaru, Y. *Tetrahedron* **2003**, *59*, 7767–7777.

2-Acetyl-2-(prop-2-ynyl)cyclopentanone (3i): Prepared according to the general procedure from 2-acetylcyclopentanone and propargyl bromide to yield the title compound as colorless oil (136 mg, 0.83 mmol, 83% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 - 2.85 (m, 1H), 2.64 - 2.75 (m, 1H), 2.50 - 2.60 (m, 1 H), 2.24 - 2.44 (m, 2H), 2.18 - 2.24 (m, 3H), 1.87 - 2.05 (m, 4H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 214.4, 202.8, 79.4, 71.4, 67.2, 38.6, 31.0, 26.3, 24.5, 19.5 ppm; IR (ATR) 3230, 2932, 2109, 1712, 1637, 1465 cm^{-1}; **ESI-MS** m/z: 187.1 ($[M+Na]^+$, 100%), 165.1 ($[M+H]^+$, 41%); Anal. Calcd. for $C_{10}H_{13}O_2^+$: *m/z* = 165.0910; found 165.0911.

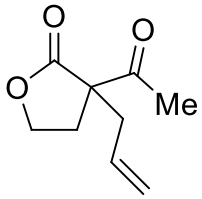
3-Acetyl-3-benzyldihydrofuran-2(3*H*)-one[12] (3j): Prepared according to the general procedure from 3-acetyldihydrofuran-2(3*H*)-one and benzyl bromide to yield the title compound as colorless oil (189 mg, 0.87 mmol, 85% yield).



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 - 7.38 (m, 3H), 7.13 - 7.20 (m, 2H), 4.06 (q, J = 8.4 Hz, 1H), 3.79 (td, J_1 = 8.8 Hz, J_2 = 4.2 Hz, 1H), 3.43 (d, J =14.0 Hz, 1H), 3.11 (d, J = 14.0 Hz, 1H), 2.80 (ddd, J_1 = 12.9 Hz, J_2 = 7.8 Hz, J_3 = 4.2 Hz, 1H), 2.42 (s, 3H), 2.11 (dt, J_1 = 13.1 Hz, J_2 = 8.4 Hz, 1 H) ppm; **^{13}C NMR (150 MHz, $CDCl_3$)** δ 202.3, 175.7, 135.2, 129.7, 129.0, 127.7, 66.4, 62.6, 40.0, 28.4, 26.1 ppm.

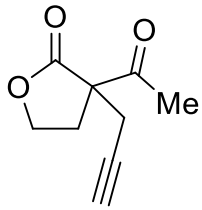
3-Acetyl-3-allyldihydrofuran-2(3*H*)-one[12] (3k): Prepared according to the general procedure from 3-acetyldihydrofuran-2(3*H*)-one and allyl bromide to yield the title compound as colorless oil (143 mg, 0.85 mmol, 84% yield).

[12] Teixeira, L. H. P.; de Souza, M. C. B. V; Ramos, M. da C. K. V; de Aquino Neto, F. R.; Barreiro, E. J.; Fraga, C. A. M. *Synth. Commun.* **2002**, *32*, 505–526.



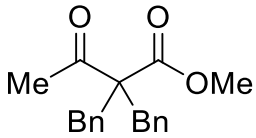
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.55 - 5.66 (m, 1H), 5.16 - 5.23 (m, 2H), 4.29 (dt, J_1 = 8.9 Hz, J_2 = 3.5 Hz, 1H), 4.19 (td, J_1 = 8.9 Hz, J_2 = 7.4 Hz, 1H), 2.88 (ddd, J_1 = 13.4 Hz, J_2 = 7.4 Hz, J_3 = 3.5 Hz, 1H), 2.78 (dd, J_1 = 14.4 Hz, J_2 = 7.5 Hz, 1H), 2.64 (dd, J_1 = 14.4 Hz, J_2 = 7.5 Hz, 1H), 2.35 (s, 3H), 2.11 (dt, J_1 = 13.4 Hz, J_2 = 8.9 Hz, 1H) ppm; **^{13}C NMR (150 MHz, $CDCl_3$)** δ 202.2, 175.3, 131.4, 120.4, 66.5, 61.2, 39.2, 28.9, 25.9 ppm.

3-Acetyl-3-(prop-2-ynyl)dihydrofuran-2(3*H*)-one[12] (3l): Prepared according to the general procedure from 3-acetyldihydrofuran-2(3*H*)-one and propargyl bromide to yield the title compound as colorless oil (141 mg, 0.85 mmol, 85% yield).



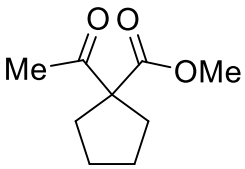
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 - 4.42 (m, 1H), 4.23 - 4.32 (m, 1H), 2.90 - 3.00 (m, 2H), 2.69 - 2.78 (m, 1H), 2.27 - 2.38 (m, 4H), 2.08 (t, J = 2.7 Hz, 1 H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 200.9, 174.2, 78.1, 72.4, 66.8, 60.4, 29.7, 25.8, 24.9 ppm.

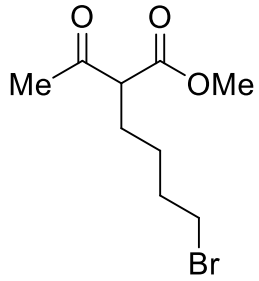
Methyl 2,2-dibenzyl-3-oxobutanoate (3m): Prepared according to the general procedure from methyl 3-oxobutanoate and benzyl bromide (2.4 equiv.) to yield the title compound as colorless oil (169 mg, 0.57 mmol, 56% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 - 7.31 (m, 6H), 7.08 - 7.14 (m, 4H), 3.67 (s, 3H), 3.21 (s, 4H), 1.94 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 205.8, 172.3, 136.4, 130.2, 128.5, 127.1, 66.3, 52.2, 40.0, 29.3 ppm; IR (ATR) 3262, 2937, 1710, 1656, 1455 cm^{-1}; **ESI-MS** m/z: 319.1 ($[M+Na]^+$, 100%), 297.1 ($[M+H]^+$, 70%); Anal. Calcd. for $C_{19}H_{21}O_3^+$: *m/z* = 297.1485; found 297.1486.

Methyl 1-acetylcyclopentanecarboxylate[13] (3n): Prepared according to the general procedure from methyl 3-oxobutanoate and 1,4-dibromo butane with 2.4 equiv. potassium *t*-butoxide and 5 mol % NHO azolium salt **A** to yield the title compound as colorless oil (67 mg, 0.39 mmol, 37% yield, contains the mono alkylation intermediate as inseparable impurity[14]).

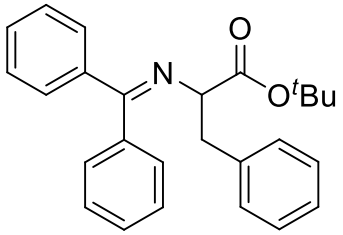




impurity

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 - 3.76 (m, 4H), 3.40 - 3.50[a] (m, 1H), 2.27[a] (s, 1H), 2.06 - 2.17 (m, 7H), 1.91 - 2.02[a] (m, 1H), 1.54 - 1.77 (m, 4H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.1, 174.2, 66.9, 62.1[a], 52.7, 52.5[a], 50.0[a], 33.8[a], 33.2, 31.3[a], 29.3[a], 27.4[a], 26.6, 25.8 ppm.

***tert*-Butyl 2-(diphenylmethyleneamino)-3-phenylpropanoate [15] (3o):** Prepared according to the general procedure with 2 mol % NHO-catalyst **E** from *tert*-butyl 2-(diphenylmethyleneamino)acetate and benzyl bromide to yield the title compound as yellow oil (92 mg, 0.24 mmol, 95% yield).

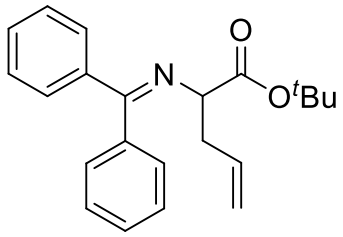


^{1}H NMR (600 MHz, acetone-d_6) δ 7.54 - 7.61 (m, 2H), 7.32 - 7.45 (m, 6H), 7.14 - 7.24 (m, 3H), 7.04 - 7.10 (m, 2H), 6.69 (br. s., 2H), 4.09 (dd, J_1 = 8.9 Hz, J_2 = 4.5 Hz, 1H), 3.21 (dd, J_1 = 13.4 Hz, J_2 = 4.5 Hz, 1H), 3.07 (dd, J_1 = 13.4 Hz, J_2 = 8.9 Hz, 1H), 1.41 (s, 9H) ppm; **^{13}C NMR (151 MHz, acetone-d_6)** δ 175.2, 174.8, 144.7,

[13] Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1996**, *61*, 73–81.
[14] NMR signals of the impurity are marked with a superscript a.
[15] Belding, L.; Stoyanov, P.; Dudding, T. *J. Org. Chem.* **2016**, 81, 553–558.

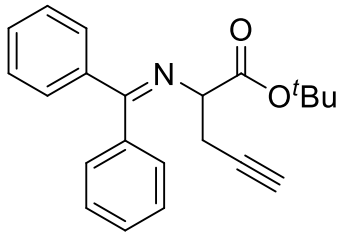
143.7, 141.5, 135.4, 135.0, 133.6, 133.5, 133.3, 133.2, 132.8, 131.3, 85.5, 73.2, 44.4, 32.4 ppm.

***tert*-Butyl 2-(diphenylmethyleneamino)pent-4-enoate[15] (3p):** Prepared according to the general procedure with 2 mol % NHO-catalyst **E** from *tert*-butyl 2-(diphenylmethyleneamino)acetate and allyl bromide to yield the title compound as yellow oil (121 mg, 0.36 mmol, 71% yield).



^{1}H NMR (600 MHz, acetone-d_6) δ 7.60 - 7.65 (m, 2H), 7.46 - 7.58 (m, 3H), 7.34 - 7.46 (m, 3H), 7.19 - 7.25 (m, 2H), 5.69 - 5.79 (m, 1H), 4.94 - 5.10 (m, 2H), 3.97 (dd, J_1 = 7.4 Hz, J_2 = 5.4 Hz, 1H), 2.61 - 2.69 (m, 1H), 2.49 - 2.59 (m, 1H), 1.42 (s, 9H) ppm; **^{13}C NMR (151 MHz, acetone-d_6)** δ 171.1, 170.5, 140.7, 137.6, 136.0, 131.3, 129.6, 129.5, 129.5, 129.0, 128.9, 117.6, 81.3, 66.9, 38.9, 28.4 ppm.

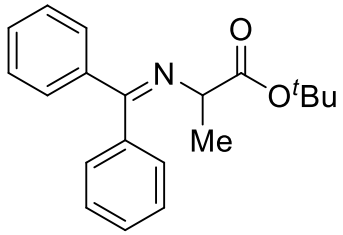
***tert*-Butyl 2-(diphenylmethyleneamino)pent-4-ynoate[16] (3q):** Prepared according to the general procedure with 2 mol % NHO-catalyst **E** from *tert*-butyl 2-(diphenylmethyleneamino)acetate and propargyl bromide to yield the title compound as yellow oil (126 mg, 0.38 mmol, 75% yield).



^{1}H NMR (600 MHz, acetone-d_6) δ 7.61 - 7.67 (m, 2H), 7.48 - 7.58 (m, 3H), 7.42 - 7.47 (m, 1H), 7.35 - 7.41 (m, 2H), 7.29 - 7.34 (m, 2H), 4.13 (dd, J_1 = 8.2 Hz, J_2 = 5.2 Hz, 1H), 2.75 - 2.82 (m, 1H), 2.63 - 2.71 (m, 1H), 2.38 (t, J = 2.7 Hz, 1H), 1.44 (s, 9H) ppm; **^{13}C NMR (151 MHz, acetone-d_6)** δ 171.7, 170.0, 140.6, 137.2, 131.4, 129.7, 129.7, 129.5, 129.2, 129.0, 82.0, 81.9, 71.9, 66.0, 28.3, 23.8 ppm.

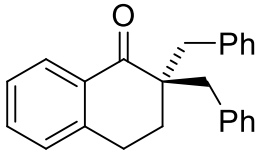
[16] Nun, P.; Pérez, V.; Calmès, M.; Martinez, J.; Lamaty, F. *Chem. - A Eur. J.* **2012**, *18*, 3773–3779.

***tert*-butyl 2-(diphenylmethyleneamino)propanoate[17] (3r):** Prepared according to the general procedure with 2 mol % NHO-catalyst **E** from *tert*-butyl 2-(diphenylmethyleneamino)acetate and methyl iodide to yield the title compound as yellow oil (120 mg, 0.39 mmol, 78% yield).



^{1}H NMR (600 MHz, acetone-d_6) δ 7.59 - 7.66 (m, 2H), 7.47 - 7.58 (m, 3H), 7.42 (d, J = 7.4 Hz, 1H), 7.34 - 7.39 (m, 2H), 7.20 - 7.29 (m, 2H), 3.99 (q, J = 6.6 Hz, 1H), 1.42 (s, 9H), 1.32 (d, J = 6.6 Hz, 3H) ppm; **^{13}C NMR (151 MHz, acetone-d_6)** δ 172.1, 169.6, 140.7, 137.5, 131.2, 129.6, 129.6, 129.4, 129.0, 128.7, 80.9, 62.2, 28.3, 19.3 ppm.

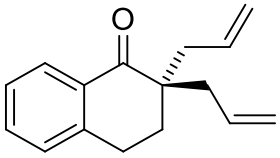
2,2-dibenzyl-3,4-dihydronaphthalen-1(2*H*)-one[18] (3s): Prepared according to the general procedure with 2 mol% NHO-catalyst **E**, KO^{t}Bu (2.4 equiv.) from α-tetralone and benzyl bromide (2.4 equiv.) to yield the title compound as yellow oil (140 mg, 0.43 mmol, 84% yield).



^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H), 7.40 (dt, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.08 - 7.24 (m, 11H), 3.30 (d, J = 13.4 Hz, 2H), 3.01 (t, J = 6.4 Hz, 2H), 2.64 (d, J = 13.4 Hz, 2H), 1.91 (t, J = 6.4 Hz, 2H) ppm; **^{13}C NMR (151 MHz, $CDCl_3$)** δ 200.7, 143.1, 137.4, 133.3, 132.5, 131.0, 128.7, 128.2, 128.1, 126.8, 126.5, 50.9, 41.6, 29.3, 25.5 ppm.

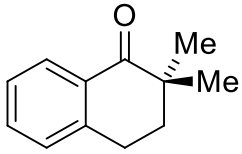
[17] Bouhlel, A.; Zhou, D.; Li, A.; Yuan, L.; Rich, K. M.; McConathy, J. *J. Med. Chem.* **2015**, *58*, 3817–3829.
[18] Díez-Barra, E.; Merino, S.; Sánchez-Verdú, P.; Torres, J. *Tetrahedron* **1997**, *53*, 11437–11448.

2,2-diallyl-3,4-dihydronaphthalen-1(2*H*)-one[18] (3t): Prepared according to the general procedure with 2 mol% NHO-catalyst, KO^{t}Bu (2.4 equiv.) from α-tetralone and allyl bromide (2.4 equiv.) to yield the title compound as yellow oil (101 mg, 0.45 mmol, 84% yield).



^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1H), 7.45 (dt, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 5.71 - 5.83 (m, 2H), 5.01 - 5.11 (m, 4H), 2.98 (t, J = 6.4 Hz, 2H), 2.50 (dd, J_1 = 14.1 Hz, J_2 = 7.2 Hz, 2H), 2.28 (dd, J_1 = 14.1 Hz, J_2 = 7.7 Hz, 2H), 2.03 (t, J = 6.4 Hz, 2H) ppm; **^{13}C NMR (151 MHz, $CDCl_3$)** δ 200.9, 143.3, 134.0, 133.2, 132.0, 128.8, 128.1, 126.8, 118.4, 47.9, 39.3, 30.7, 25.2 ppm.

2,2-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one[19] (3u): Prepared according to the general procedure with 2 mol% NHO-catalyst, KO^{t}Bu (2.4 equiv.) from α-tetralone and methyl iodide (2.4 equiv.) to yield the title compound as yellow oil (80 mg, 0.46 mmol, 87% yield).

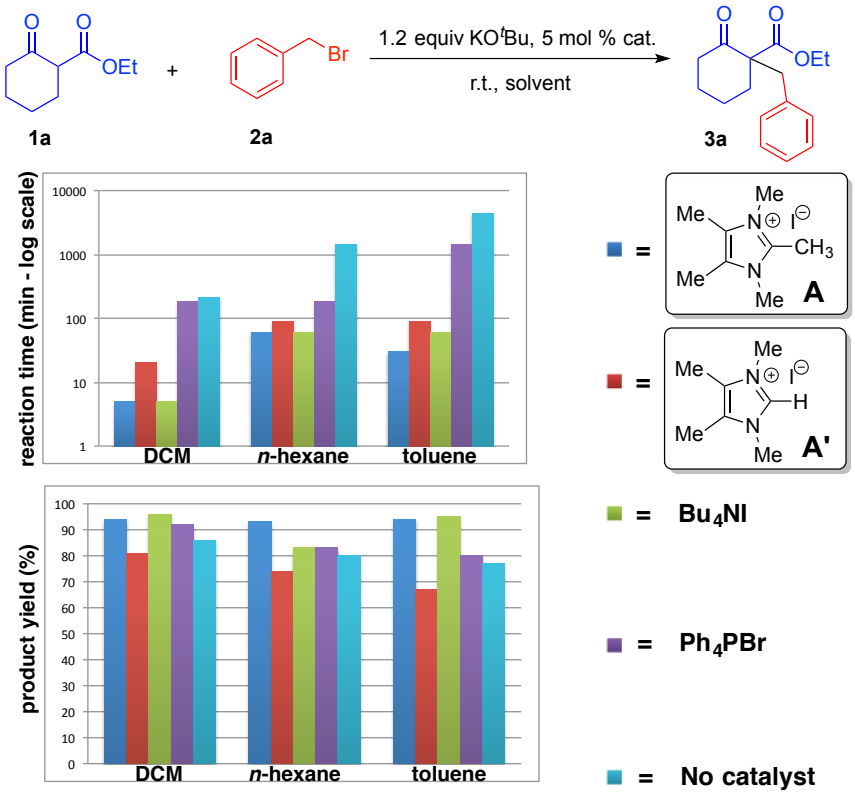


^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H), 7.45 (dt, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 7.7 Hz, 1H), 2.98 (t, J = 6.4 Hz, 2H), 1.98 (t, J = 6.4 Hz, 2H), 1.22 (s, 6H) ppm; **^{13}C NMR (151 MHz, $CDCl_3$)** δ 203.0, 143.5, 133.1, 131.5, 128.8, 128.1, 126.7, 41.7, 36.7, 25.8, 24.5 ppm.

[19] Gao, B.; Xie, Y.; Shen, Z.; Yang, L.; Huang, H. *Org. Lett.* **2015**, *17*, 4968–4971.

Comparison with other phase-transfer catalytic systems

Figure 1. Comparative studies with other phase-transfer catalysts



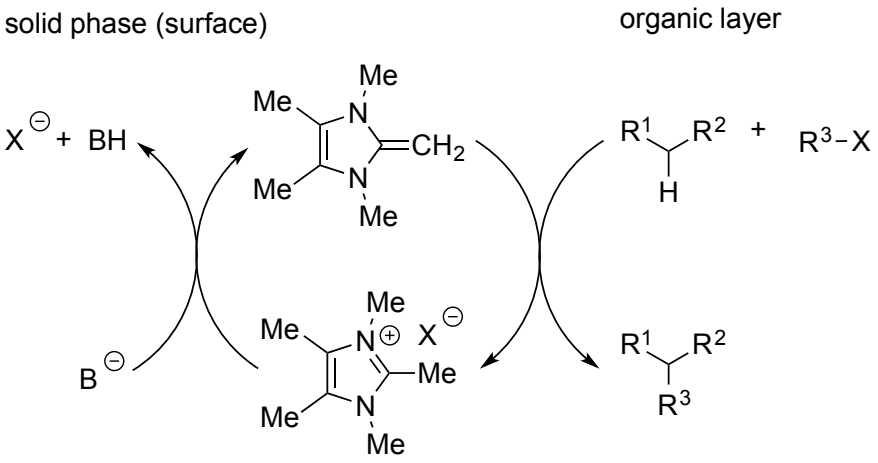
Yield *vs* Catalyst		yield [%]	
Catalyst	DCM	*n*-hexane	toluene
NHO precursor **A**	94	93	94
NHC precursor **A'**	81	74	67
tetrabutylammonium iodide	96	83	95
tetraphenylphosphonium bromide	92	83	80
without catalyst	86	80	77

Reaction time(*) *vs* Catalyst		reaction time [min]	
Catalyst	DCM	*n*-hexane	toluene
NHO precursor **A**	5	60	30
NHC precursor **A'**	20	90	90
tetrabutylammonium iodide	5	60	60
tetraphenylphosphonium bromide	180	180	1440
without catalyst	210	1440	4320

(*) Reaction time at 100% conversion monitored by TLC

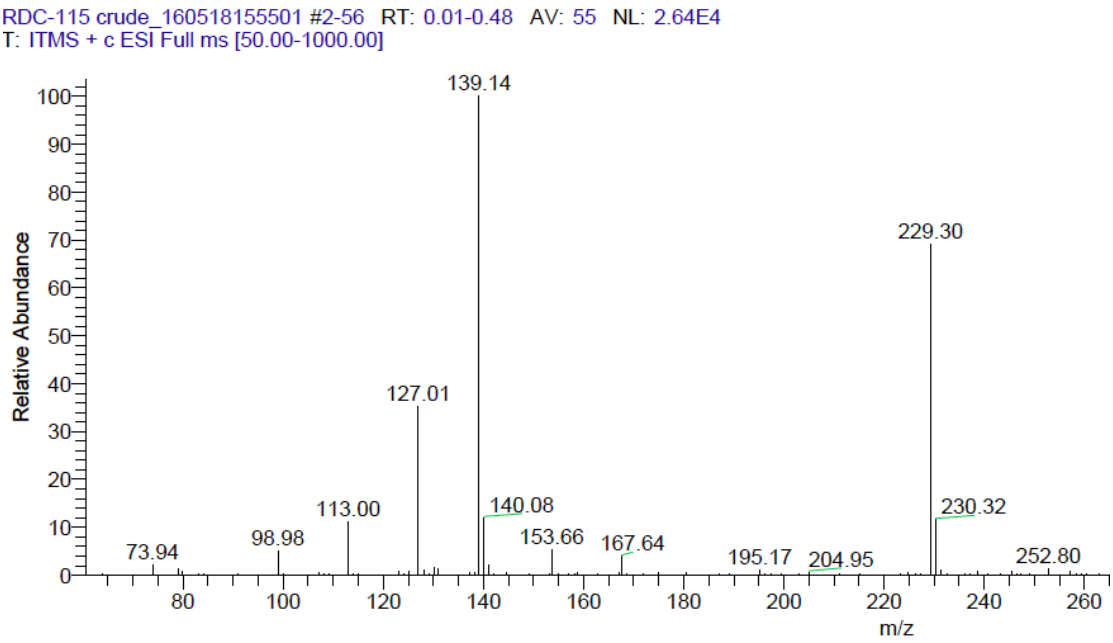
Mechanistic studies

Proposed Mechanism:



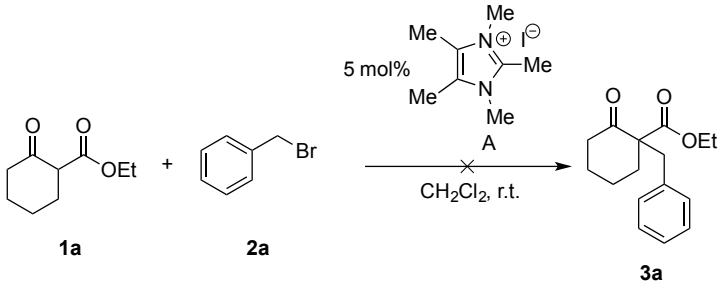
We carried out the suggested experiment of catalyst **A** in the presence of 1.0 equivalent of potassium *tert*-butoxide and 1.0 equivalent of benzyl bromide in DCM under the reported optimized PTC conditions for *180 minutes*. After the reaction work-up we found that the product mixture contained the catalyst **A** ([M+] = 139.1) and its benzylated derivative ([M+] = 229.3) in ~1.5:1 ratio (see MS spectrum below). These results suggest that NHO catalyst **F** was formed throughout the reaction process and, moreover, underline the fact that NHOs are strong nucleophiles.

The nucleophilic reaction of NHO **F** to benzylbromide, however, is significantly slower than that of the deprotonated β-ketoester substrate. Hence, we believe that the benzylated NHO should not have formed in significant amount during our standard PTC reactions (normally completed in *less than 30 minutes*), ruling out the possibility for it to act as the competitive catalyst beside NHO precursor **A**.



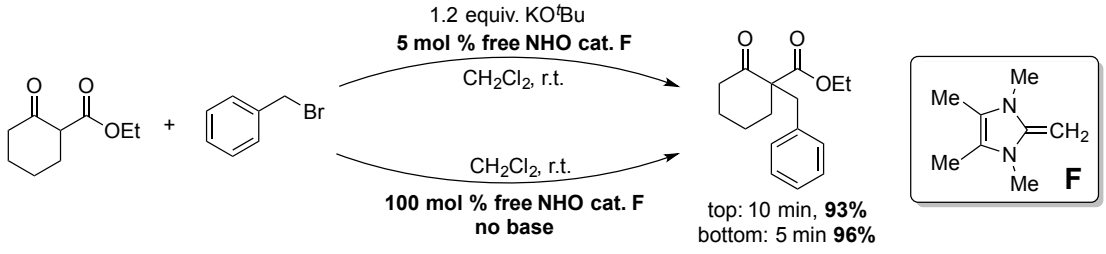
Control experiments

1 Reaction without base

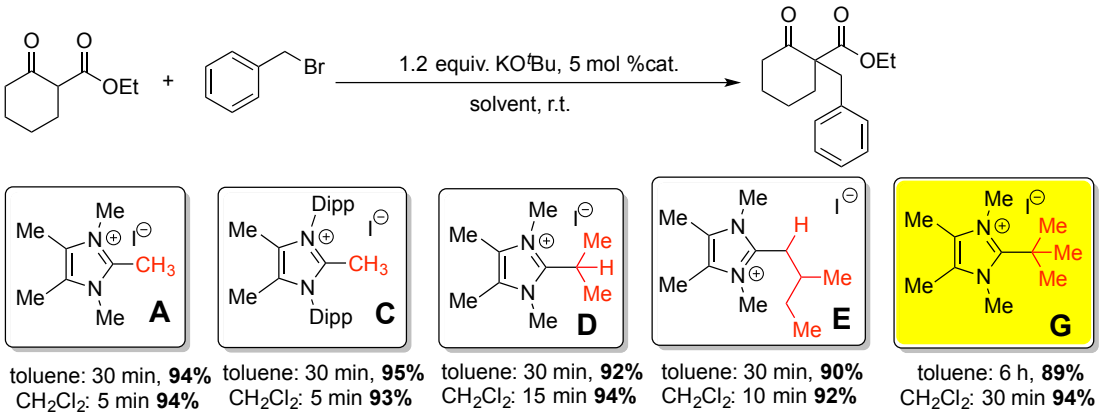


1a **2a** **3a**

2 Experiment with the free NHO



3 Blocked reactive site at the catalyst



toluene: 30 min, **94%**
CH_2Cl_2: 5 min **94%**

toluene: 30 min, **95%**
CH_2Cl_2: 5 min **93%**

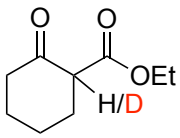
toluene: 30 min, **92%**
CH_2Cl_2: 15 min **94%**

toluene: 30 min, **90%**
CH_2Cl_2: 10 min **92%**

toluene: 6 h, **89%**
CH_2Cl_2: 30 min **94%**

4 Deuterium-labelling experiments

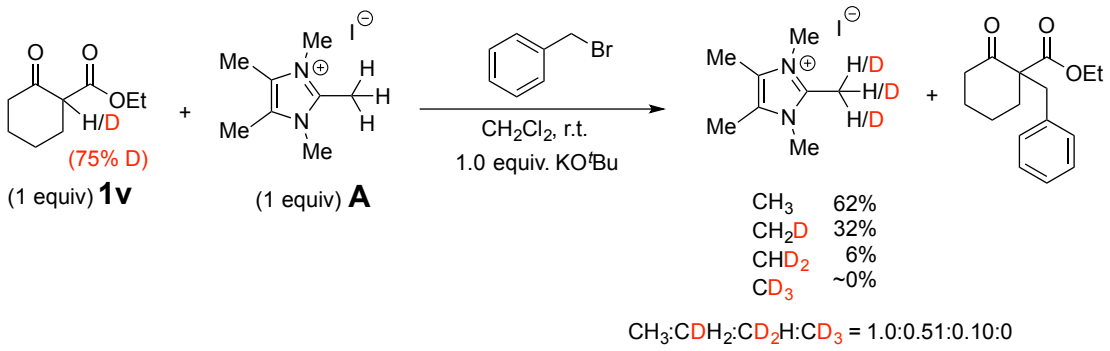
a) Deuterium transfer from substrate to catalyst



75%D

Under argon 0. 71 g (17.7 mmol, 2.4 equiv.) NaH (60 wt% in mineral oil) was washed with hexane (5x, 5 mL) and dried in vacuum. After the addition of 10 mL dry Et_2O, the suspension was cooled to 0 °C and 1.2 mL (1.28 g, 7.52 mmol, 1.0 equiv.) ethyl 2-oxocyclohexanecarboxylate were added dropwise. The reaction was continued for 20 min at 0 °C and the ice bath removed. Subsequently, 5 mL D_2O and 5 mL D_3CCOOD were added, the layers separated, the solvent removed under reduced pressure, and product dried in vacuum to obtain 1.07 g (6.25 mmol,) of the deuterated β-ketoester (**1v**); the deuterium incorporation at the marked position was determined to be 75% as determined using ^{1}H NMR spectroscopy.

^{1}H NMR (300 MHz, C_6D_6) 12.91 (br. s.,0.15H), 3.83 - 4.11 (m, 2H), 3.05 (dd, J_1 = 10.3, J_2 = 5.6 Hz, 0.1H), 2.02 - 2.29 (m, 4H), 1.96 (t, J = 11.4 Hz, 0.5H), 1.79 (ddd, J_1 = 14.2, J_2 = 9.8, J_3 = 5.4 Hz, 0.4H), 1.58 - 1.73 (m, 0.4H), 1.19 - 1.42 (m, 5H), 0.86 - 1.09 (m, 3H) pm.



With **1v** being 75% deuterated, the probability distribution for the occurrence for the deuteration on catalyst **A** (through the *in situ* formation of the free NHO **A'**) is calculated as below. It should be noted that this assumes protonation and deuteration are equally distributed across four sites (the methyl group on **A** and one other; either **1v** or the *t*-butanol) – that is, complete equilibration and no equilibrium isotope effects.

Original component: H/D (**1v**, 1 equiv, 75% D) CH_3 (**A**, 1 equiv)

H:D = (0.25 + 3):0.75 = 3.25:0.75 = 13:3

Theoretical probability distribution for:

$CH_3 = (13/16)^3 = 0.536$

$CDH_2 = 3*(3/16)*(13/16)^2 = 0.371$

$CD_2H = 3*(13/16)*(3/16)^2 = 0.086$

$CD_3 = (3/16)^3 = 0.007$

Normalized theoretical distribution for

$CH_3 = 1.0$

$CDH_2 = 0.69$

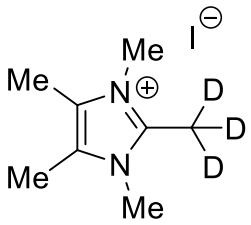
$CD_2H = 0.16$

$CD_3 = 0.01$

The CH_3:CDH_2:CD_2H:CD_3 experimental ratio of 1.0:0.51:0.10:0 was similar to the theoretical ratio of 1.0:0.69:0.16:0.01, indicating that there was a significant deuterium transfer during the reaction. The values being reduced relative to the theoretical distribution may indicate the participation of the 'normal' PTC pathway or

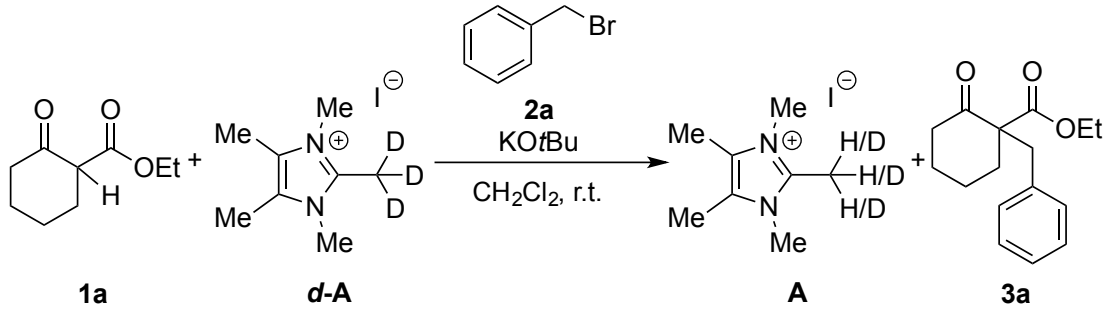
some incorporation of deuterium at other sites (such as the other alpha position on the product **3a**) though none was observed or some preferential / incomplete deuterium exchange. However, the small differences relative to the theoretical probability distribution suggest such contributions are minor.

b) H-transfer from substrate to deuterated catalyst



A suspension of 279 mg (1.11 mmol, 1.0 equiv.) 1,3,4,5-tetramethyl imidazolium iodide in 5 mL dry THF under argon atmosphere at −78 °C was slowly treated with 0.55 mL (1.10 mmol, 1.0 equiv.) NaHMDS-solution (2 M in THF), stirred for 10 min at −78 °C and then slowly warmed to −10 °C. Subsequently, the reaction mixture was cooled to −78 °C and 0.5 mL (1.14 g, 7.87 mmol, 7.1 equiv.) d^3-methyl iodide (99.5% D) was added dropwise. The reaction mixture was slowly warmed to ambient temperature and continued overnight. After the addition of 5 mL dry ether, the resulting suspension was filtered and the filter cake washed with dry ether (5 mL). Dissolving the filter cake in dry dichloromethane, a second filtration, and removal of the volatiles under reduced pressure gave the crude product, which was recrystallized from hot chloroform to yield 202 mg (0.75 mmol, 68% yield, 87% deuterium incorporation at the C2-methyl group, determined using ^{1}H NMR spectroscopy) *d*-**A** as off-white needles.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 6H), 2.80 (m, 0.4H), 2.24 (s, 6H) ppm.



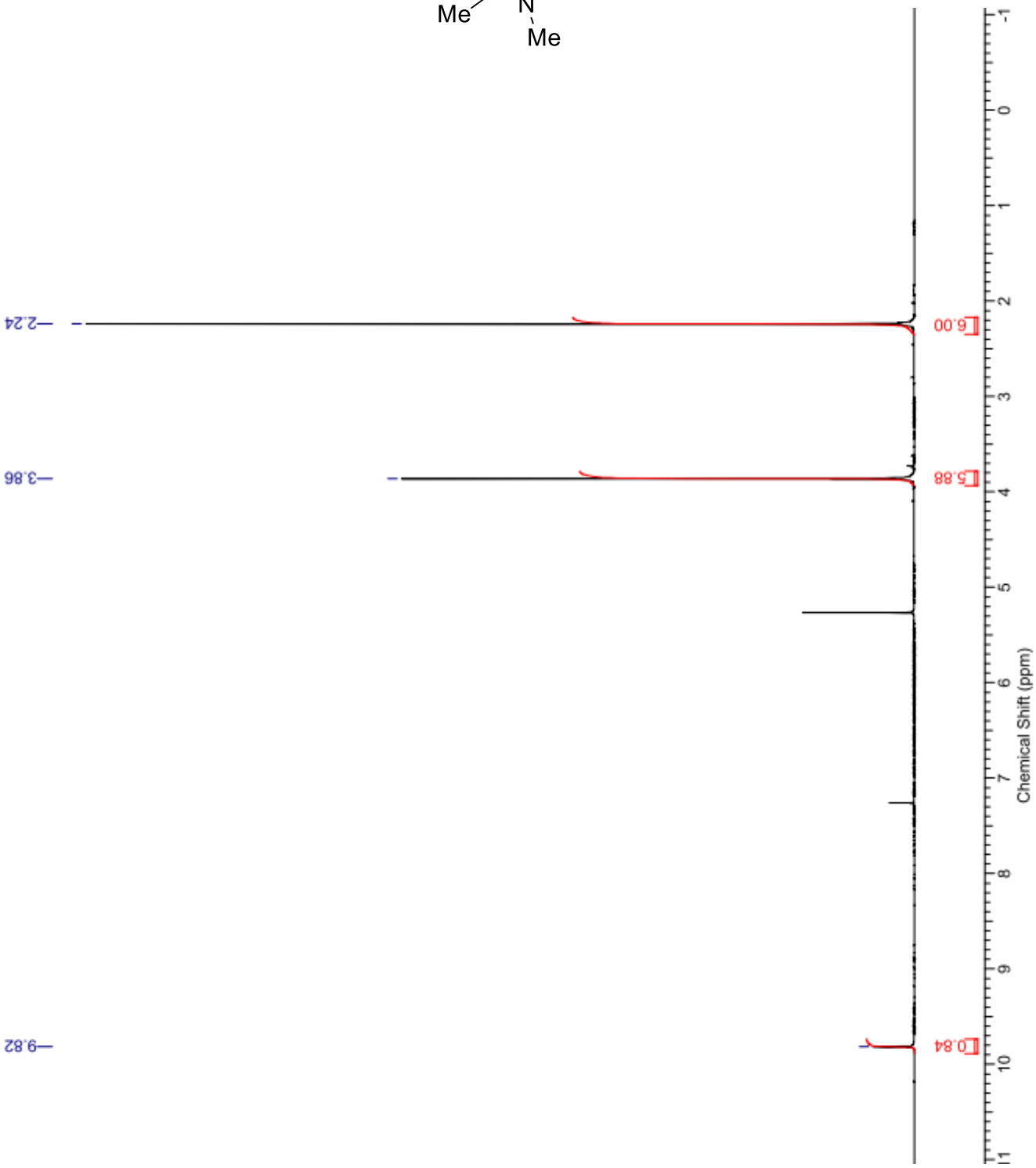
1a	+	*d*-A	+	KO^tBu	⟶	A	+	3a
1	:	1	:	1				
	CH_3	7%				CH_3	12%	
	CH_2D	9%				CH_2D	16%	
	CHD_2	5%				CHD_2	12%	
	CD_3	79%				CD_3	60%	

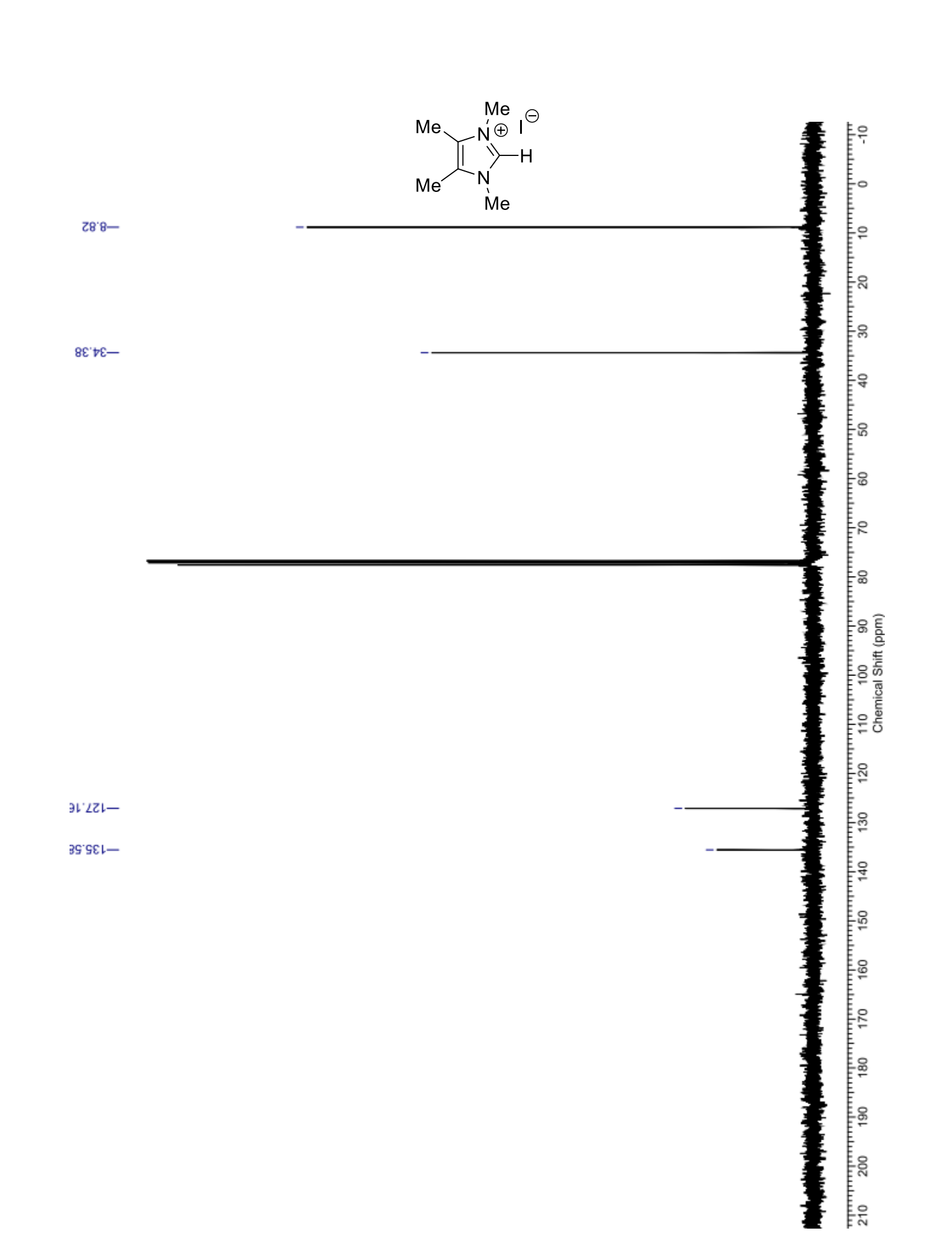
87% D at the C2-methyl group equates to an original ratio of D to H to be considered as 2.61:1.39. So, as above:

Theoretical probability distribution of $CD_3 = (2.61/4)^3 = 0.28$
Experimental value = 0.60

This definitely suggests that deuterium exchange was incomplete in this case. The origin of the difference is not clear.

Spectra

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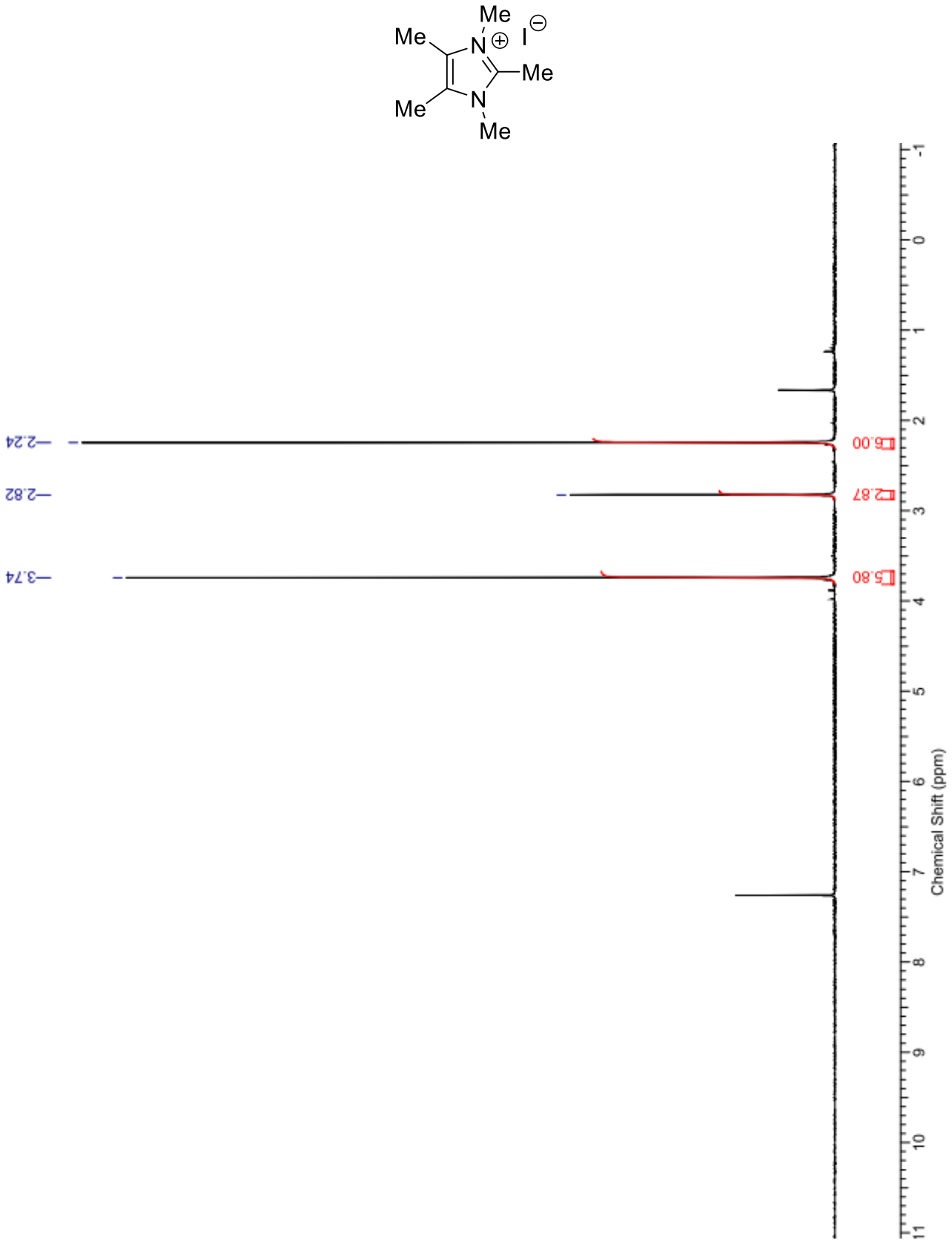
Me
N
I
H
N
Me
Me
8.82
34.38
127.16
135.56
Chemical Shift (ppm)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N
I
Me
Me
N
Me
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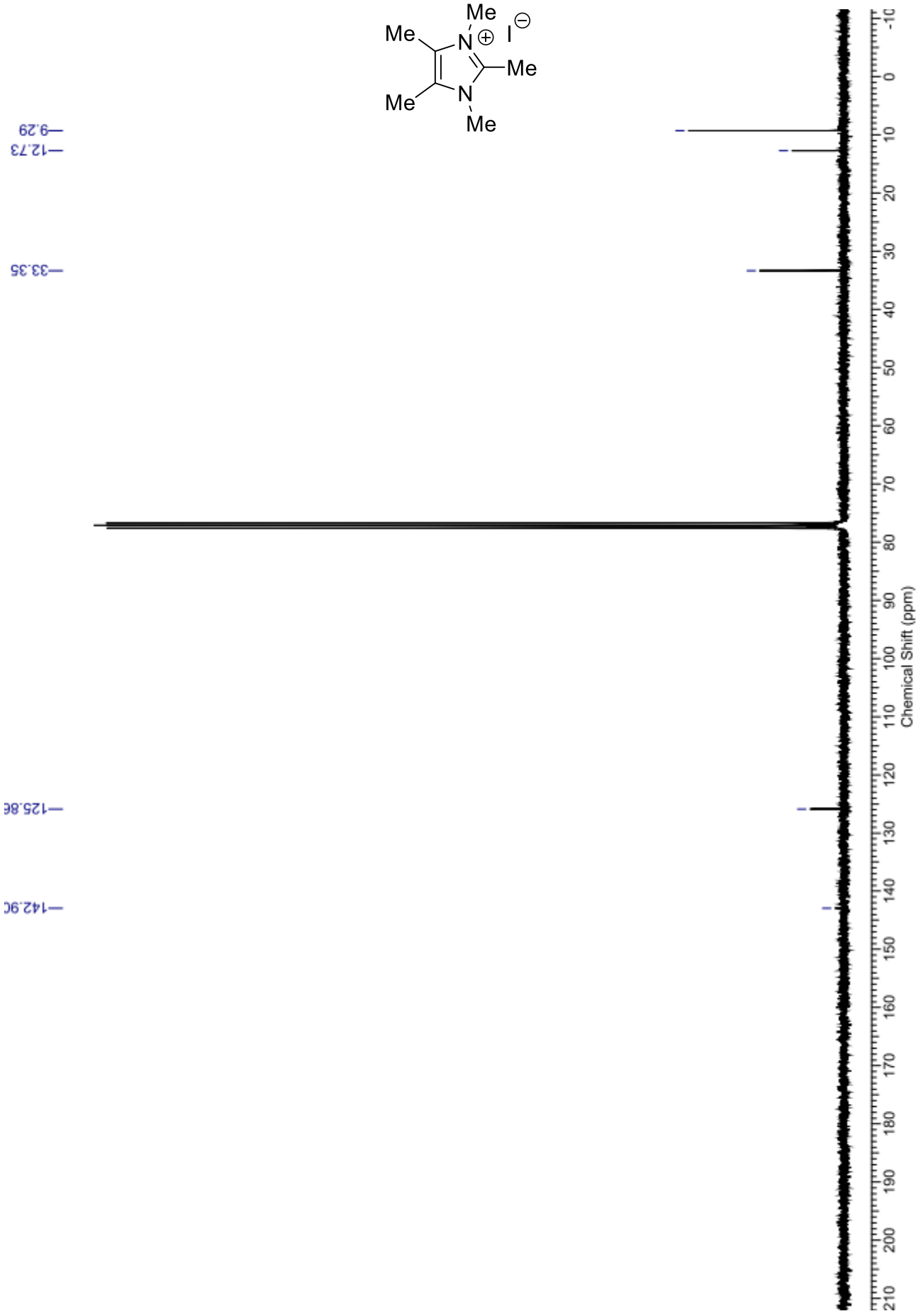
2.87
5.80
Chemical Shift (ppm)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Me
Me
N
Me
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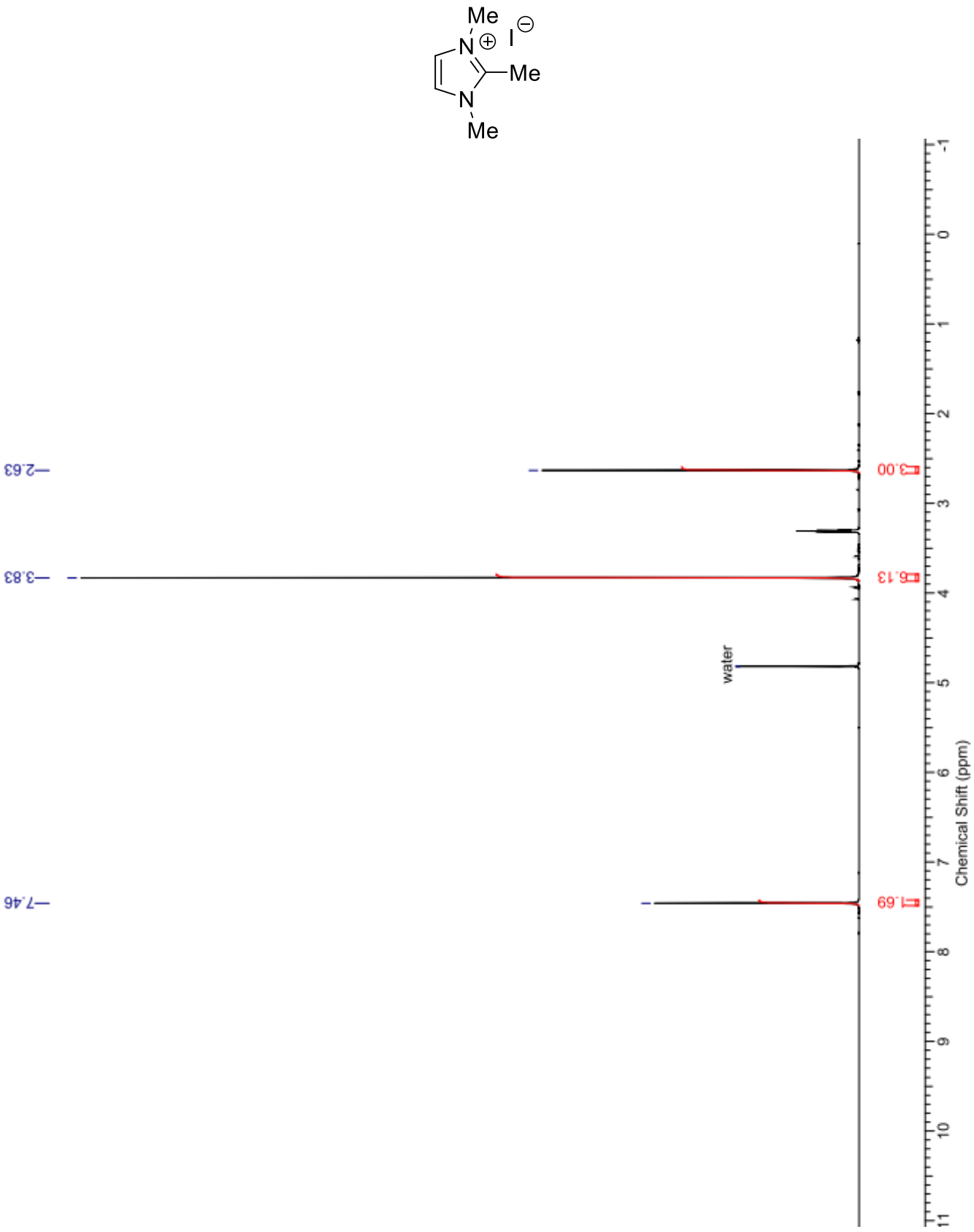
12.73
33.35
125.86
142.90
Chemical Shift (ppm)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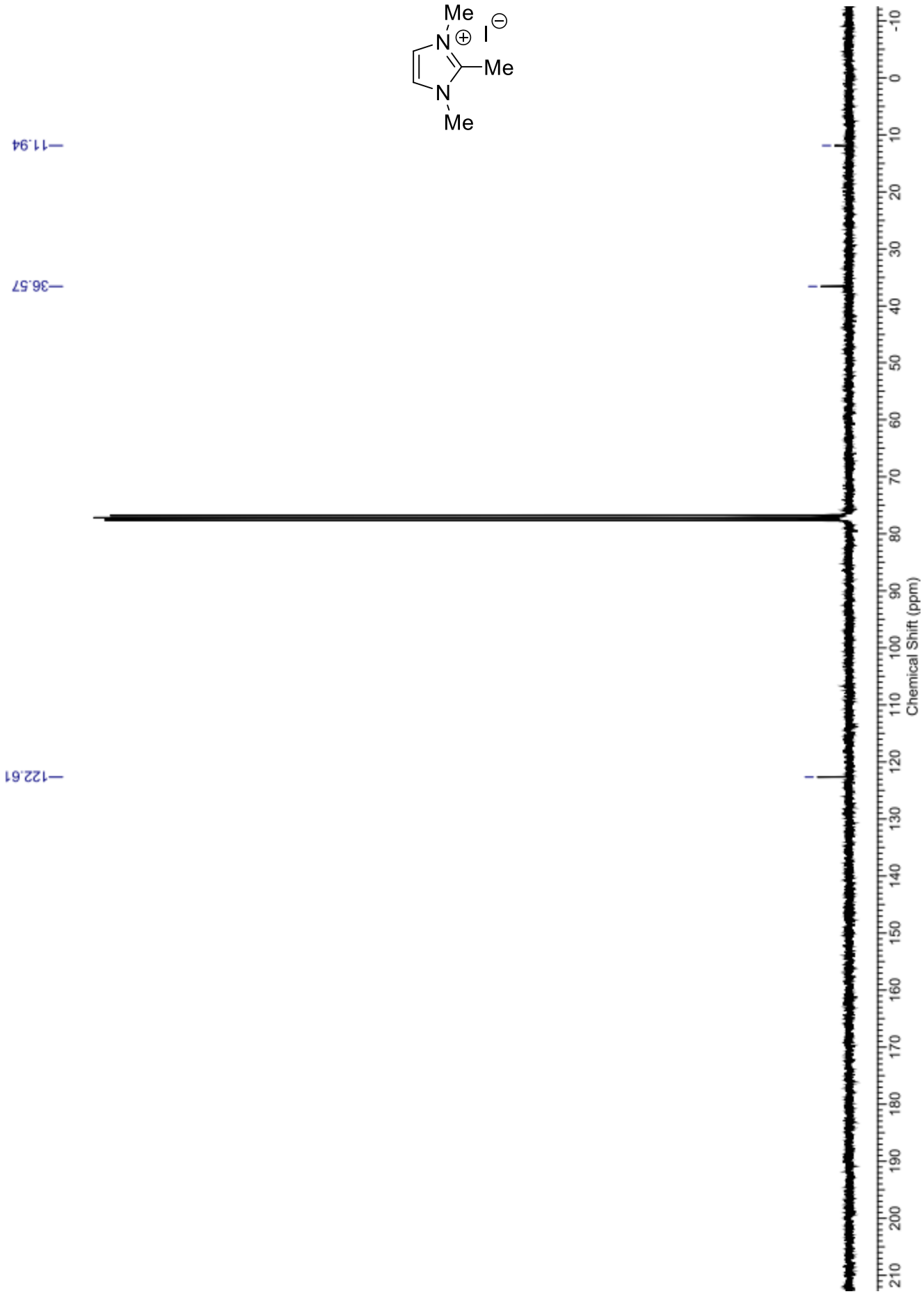
Me
N
Me
7.46
3.83
2.63
water
1.69
6.13
3.00
Chemical Shift (ppm)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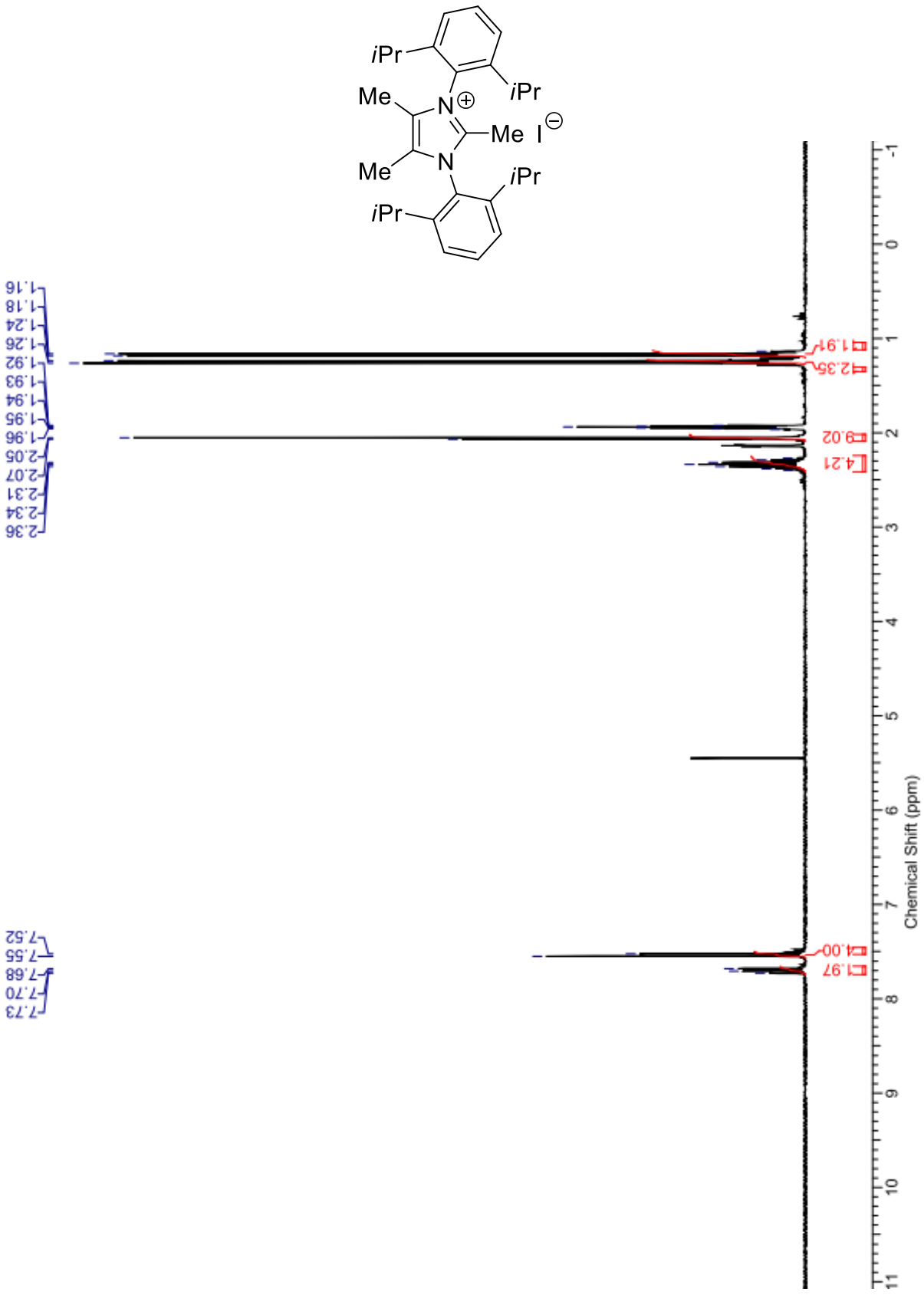
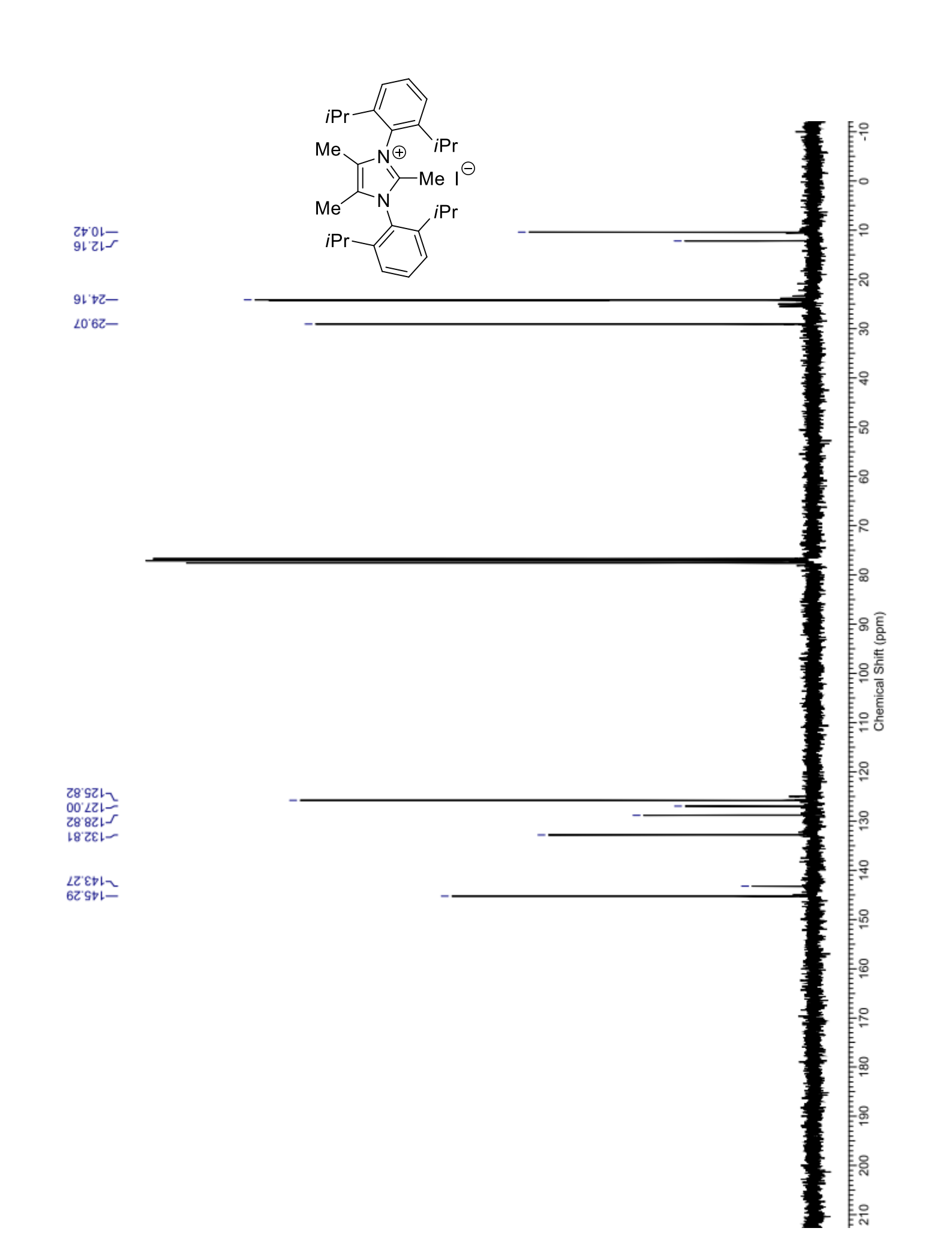
I
Me
N
Me
11.94
36.57
122.61
Chemical Shift (ppm)


iPr
iPr
Me
N
Me
I
Me
N
iPr
iPr
1.16
1.18
1.24
1.26
1.92
1.93
1.94
1.95
1.96
2.05
2.07
2.31
2.34
2.36
7.52
7.55
7.68
7.70
7.73
1.91
2.35
9.02
4.21
4.00
1.97
Chemical Shift (ppm)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Me
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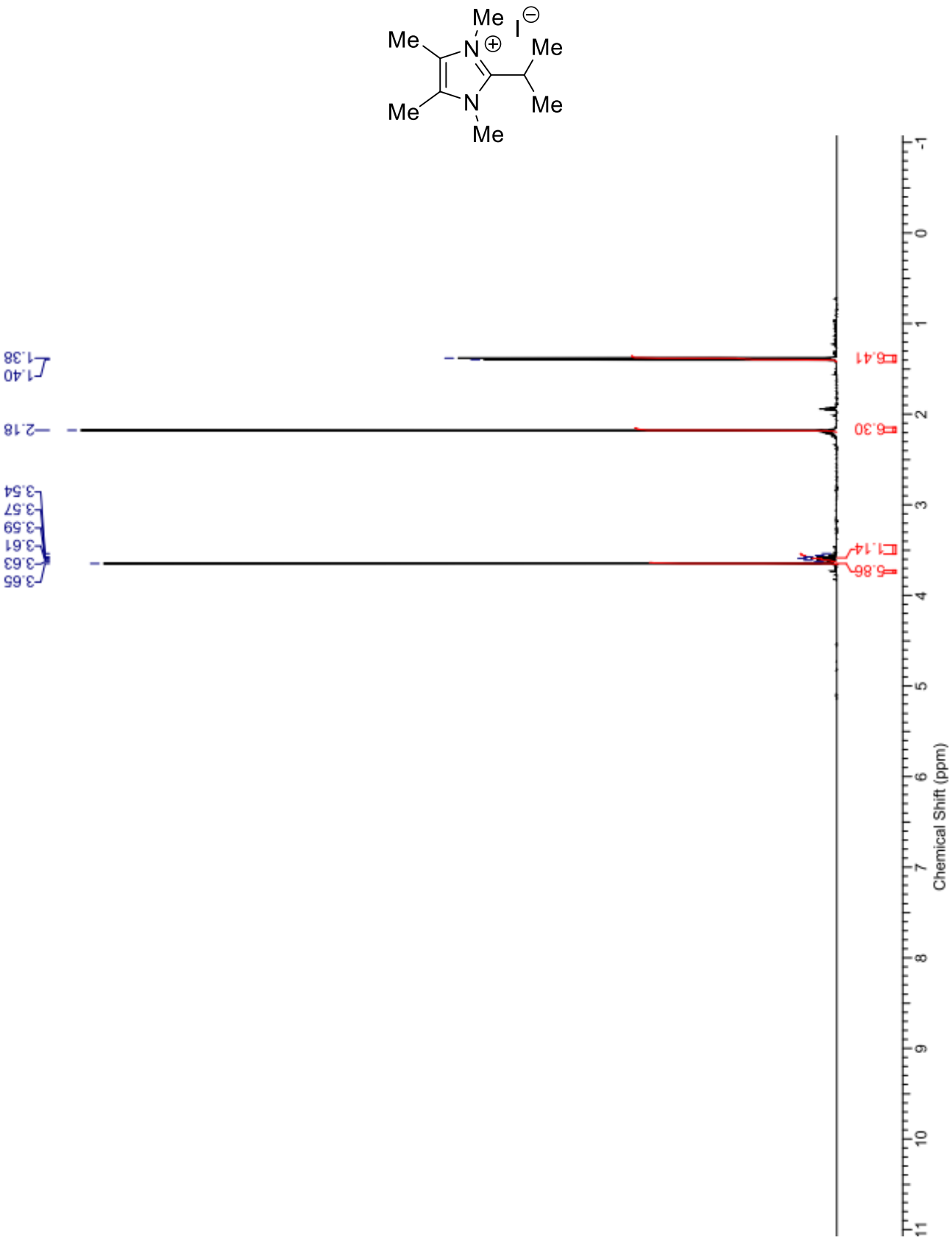
Me
I
Me
N
iPr
iPr
10.42
12.16
24.16
29.07
125.82
127.00
128.82
132.81
143.27
145.29
Chemical Shift (ppm)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I
Me
N
Me
Me
N
Me
Me
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2.18
3.54
3.57
3.59
3.61
3.63
3.65
5.41
5.30
1.14
5.86
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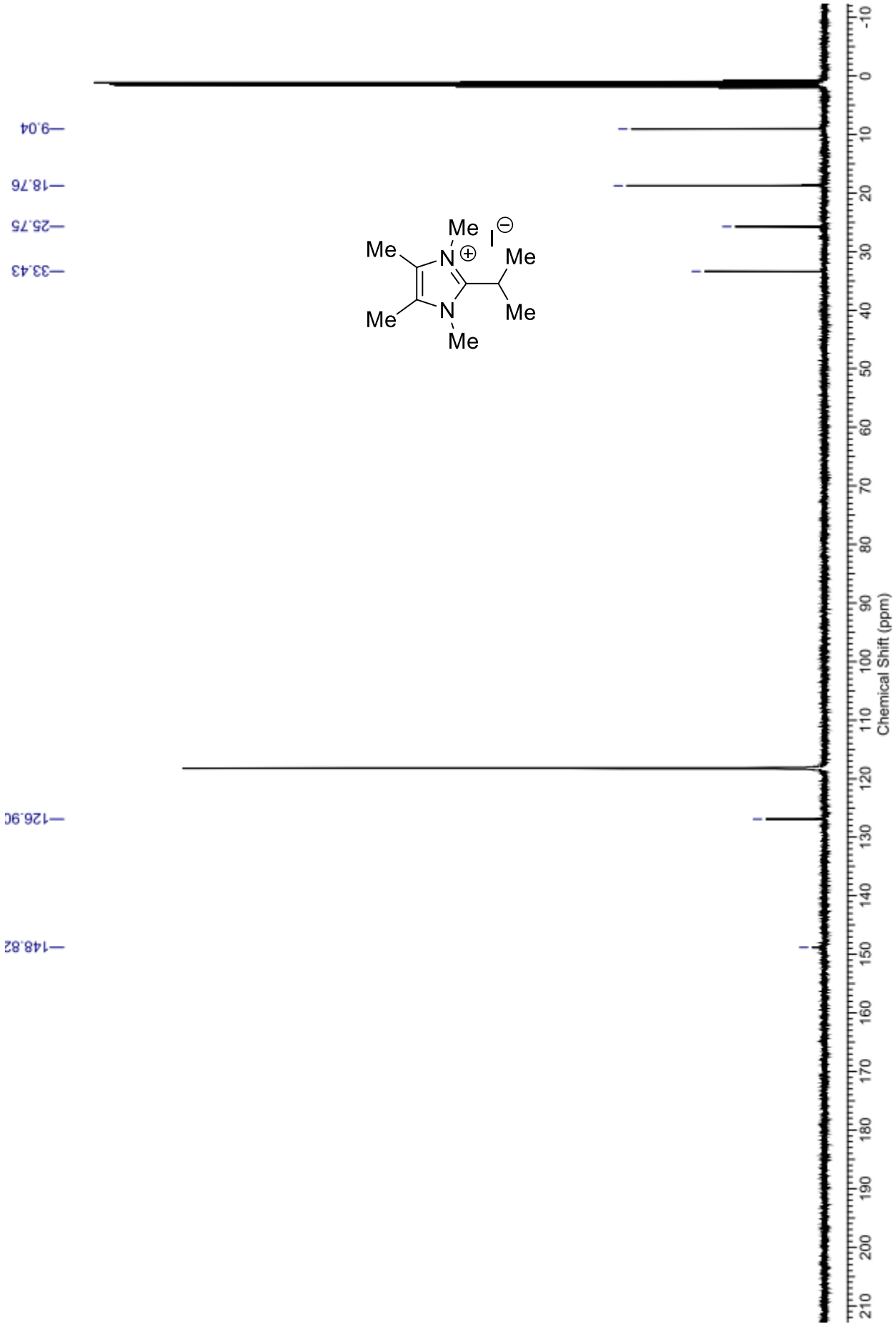
0
1
2
3
4
5
6
7
8
9
10
11
Chemical Shift (ppm)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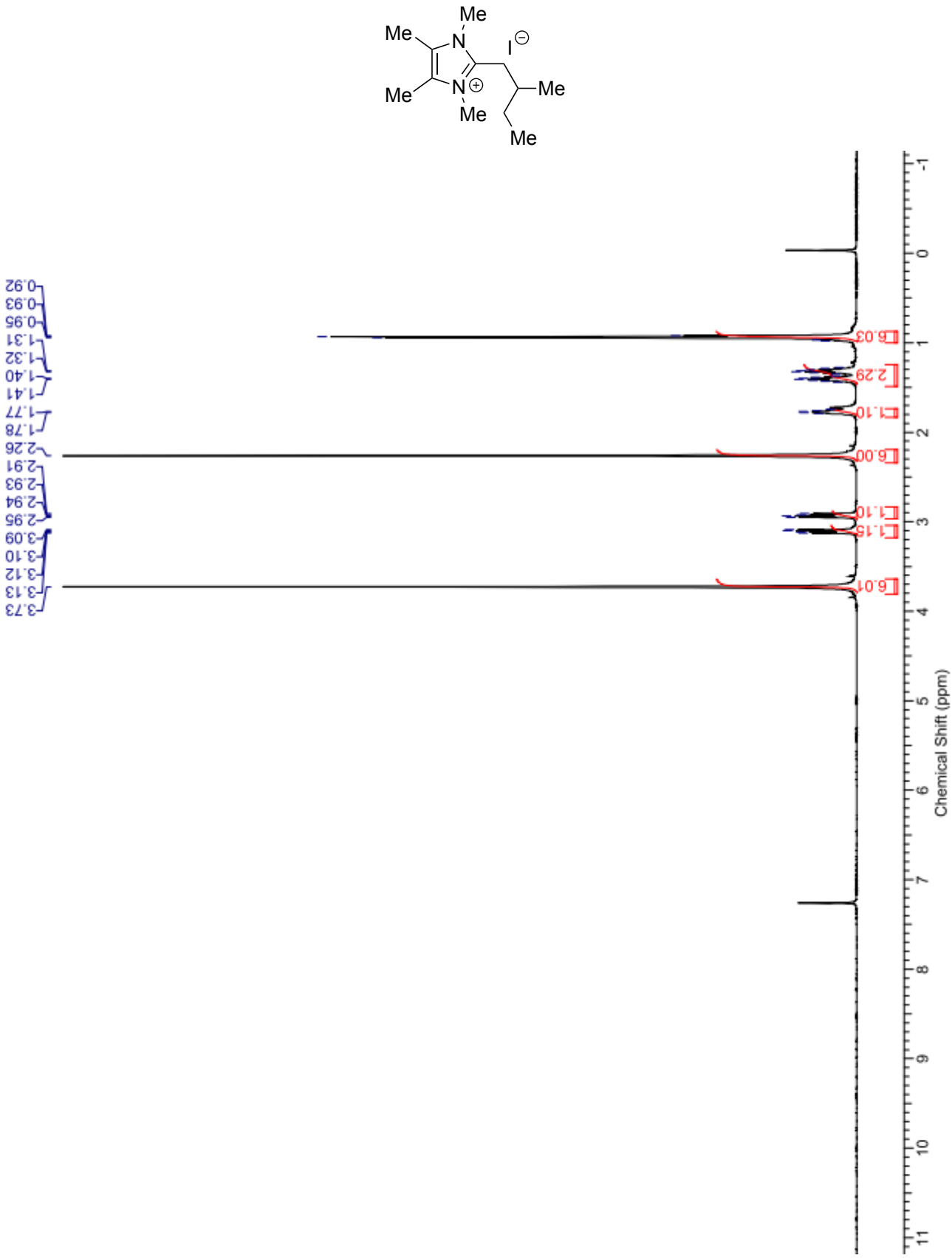
Me
Me
Me
Me
Me
I
Chemical Shift (ppm)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Me
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Me
N
Me
Me
Me
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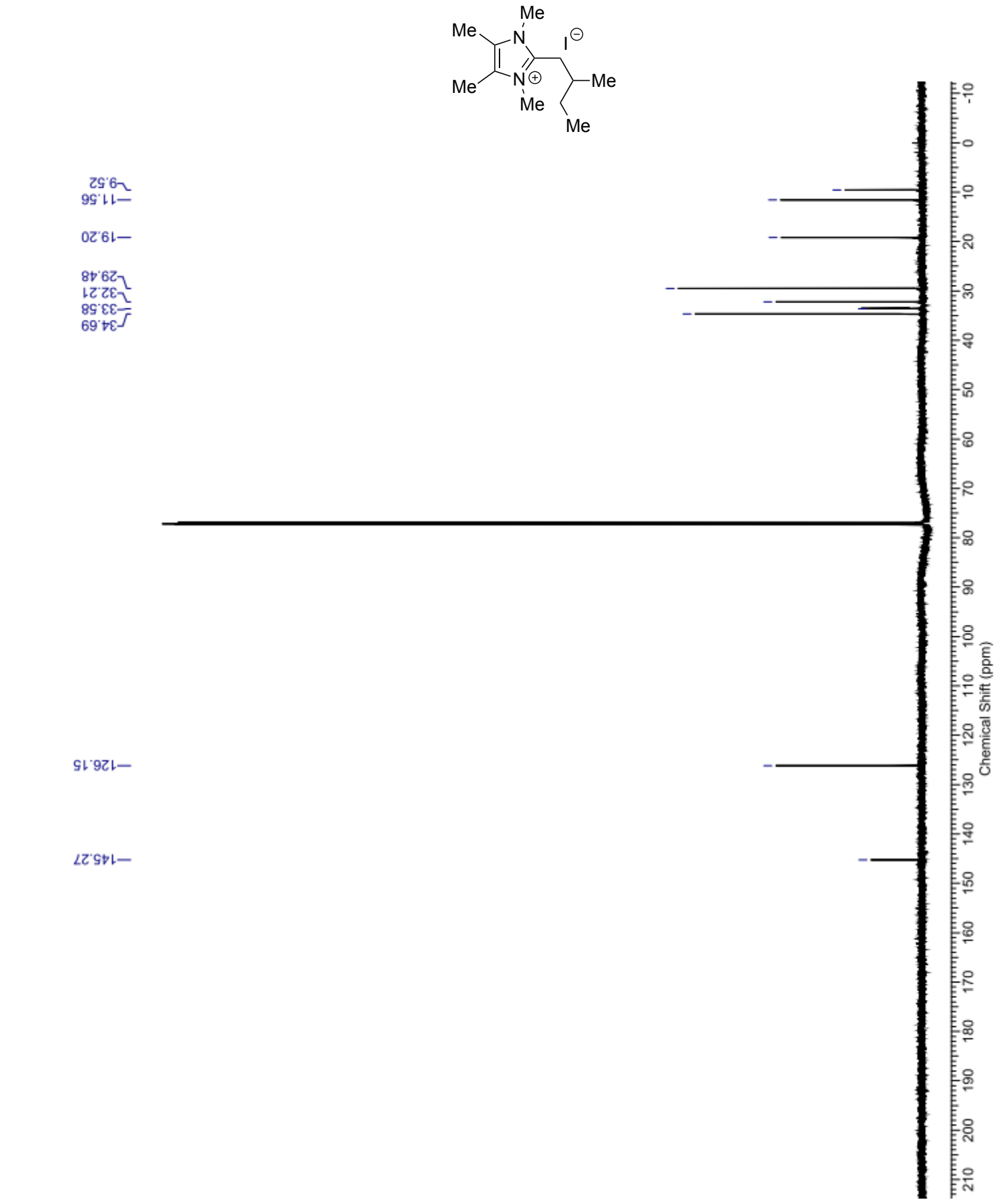
0.95
1.31
1.32
1.40
1.41
1.77
1.78
2.26
2.91
2.93
2.94
2.95
3.09
3.10
3.12
3.13
3.73
6.03
2.29
1.10
6.00
1.10
1.15
6.01
-1
0
1
2
3
4
5
6
7
8
9
10
11
Chemical Shift (ppm)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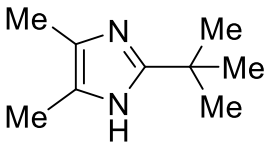
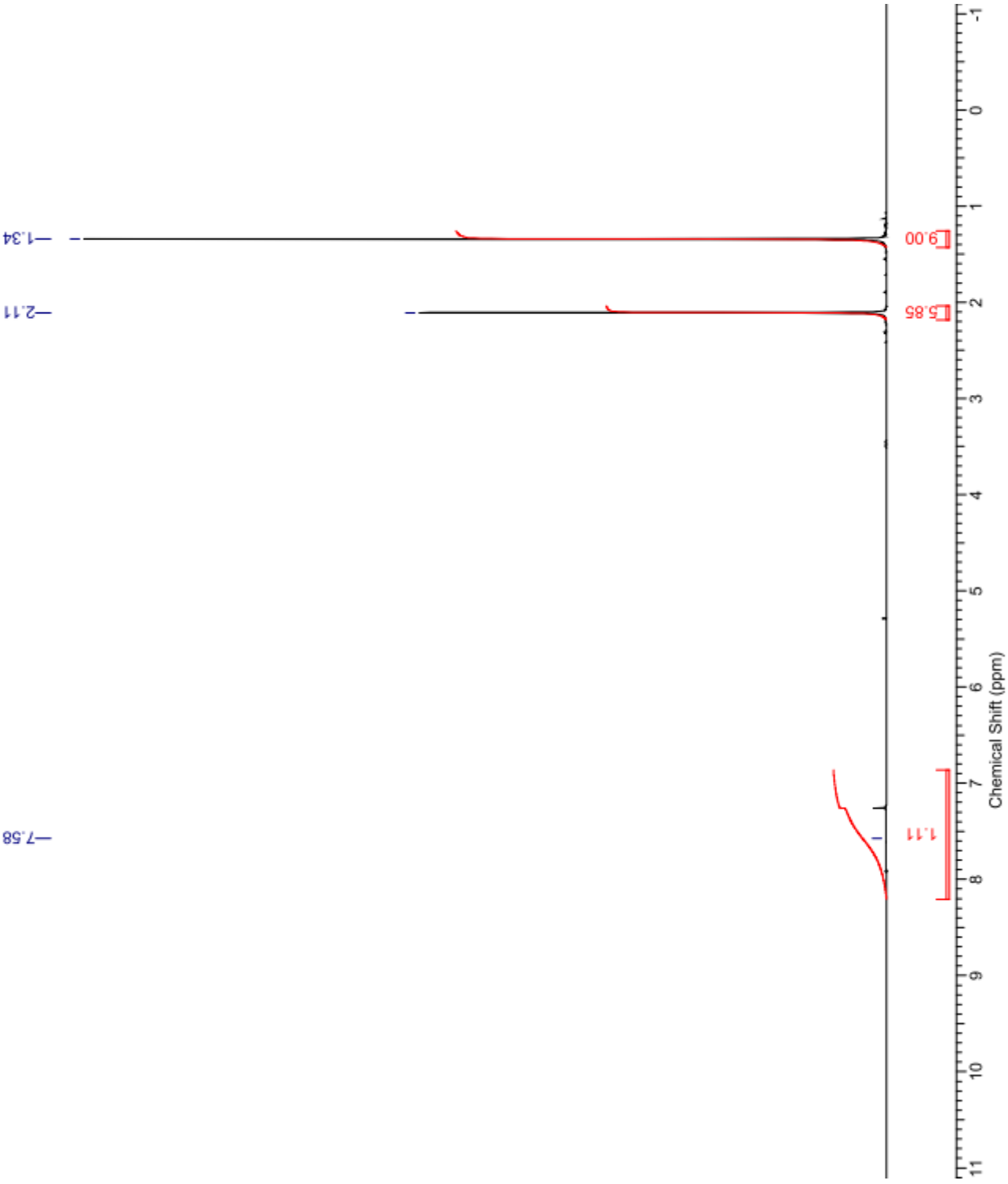
126.15
145.27
Chemical Shift (ppm)


Me
N
Me
Me
Me
N
H
Me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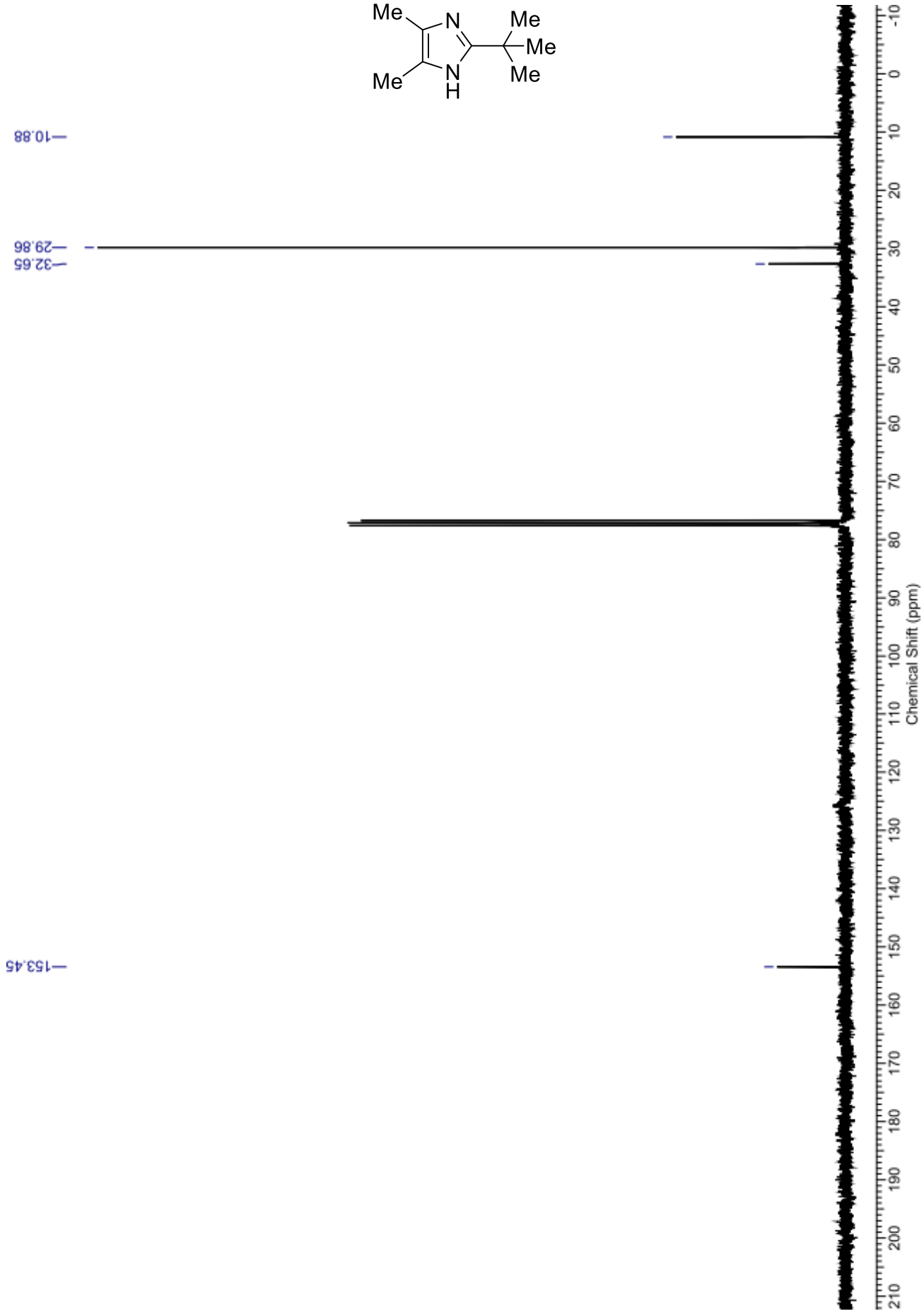
9.00
5.85
1.11
Chemical Shift (ppm)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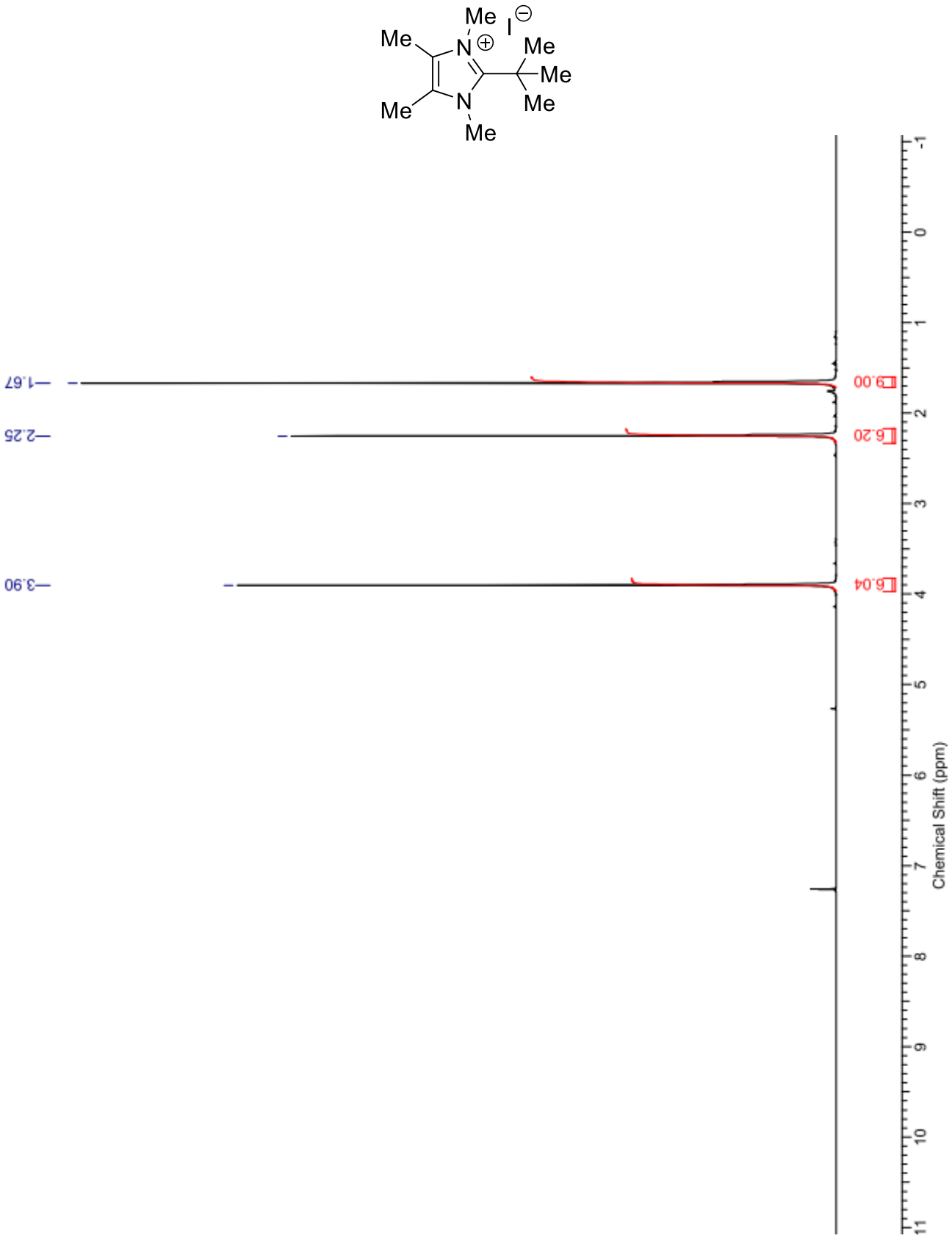
N
Me
Me
Me
N
H
10.88
29.86
32.65
153.45
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Chemical Shift (ppm)


Me
I
Me
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Me
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Me
N
Me
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1.67
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3.90
9.00
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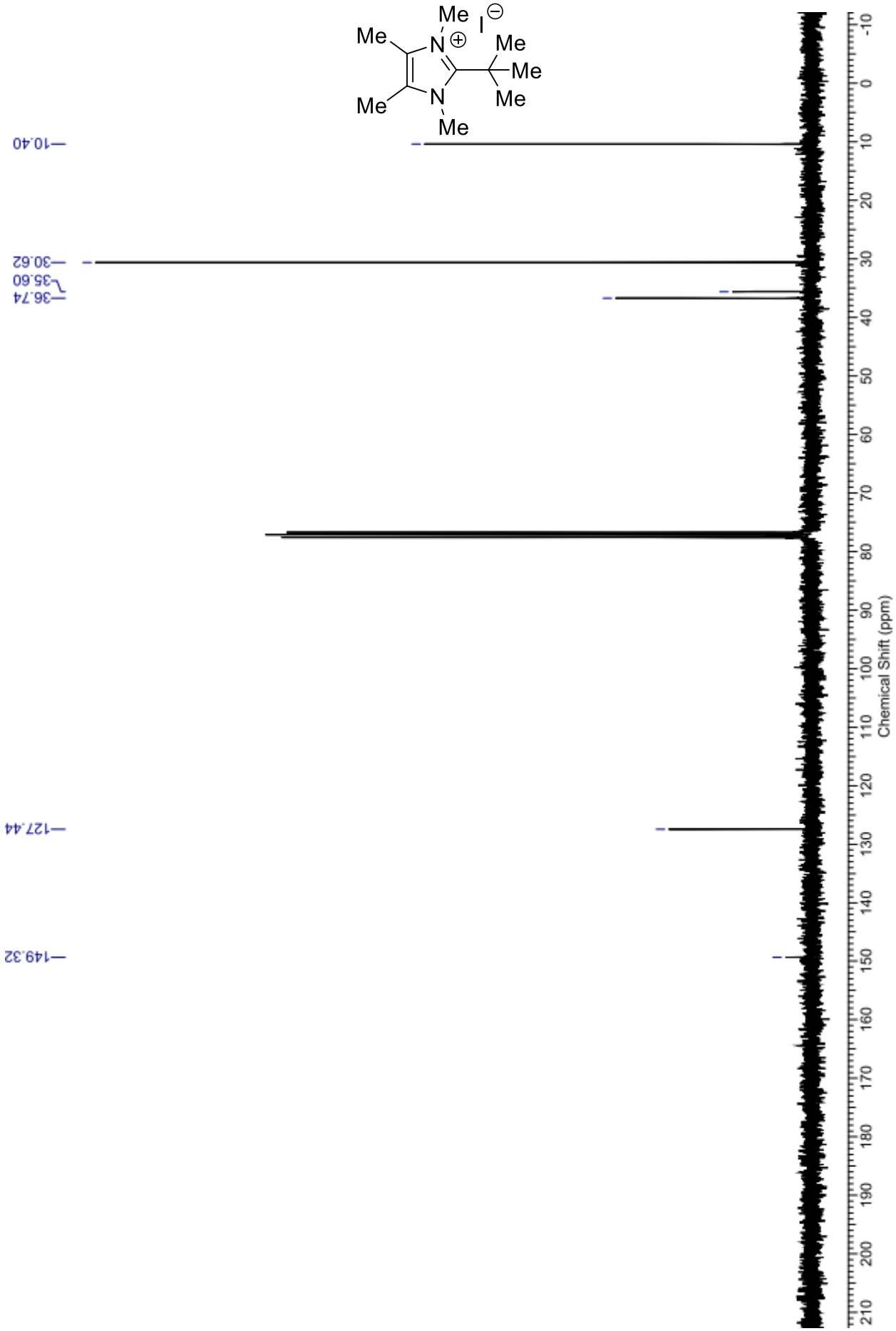
6.04
Chemical Shift (ppm)


Me
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N
Me
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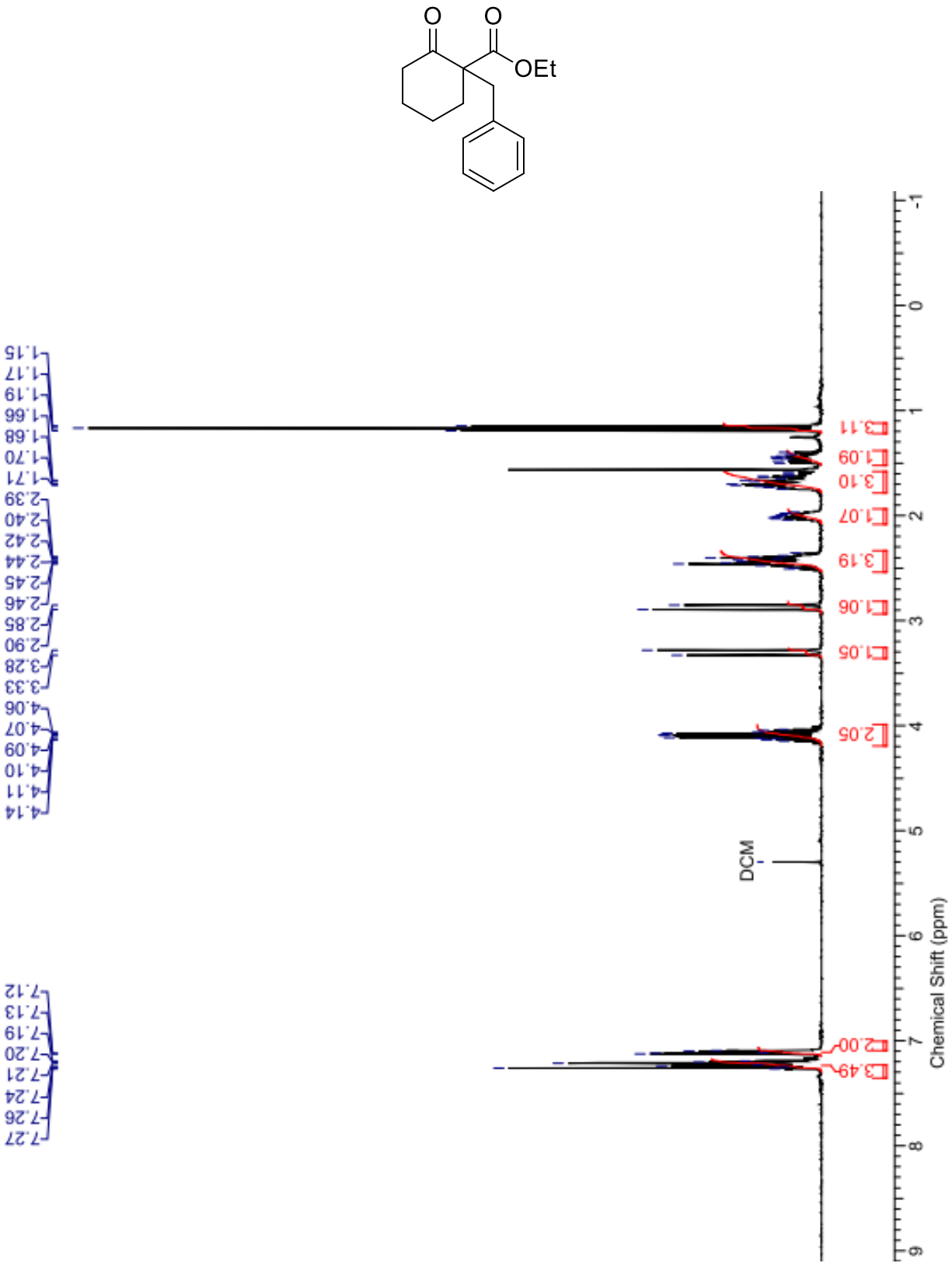
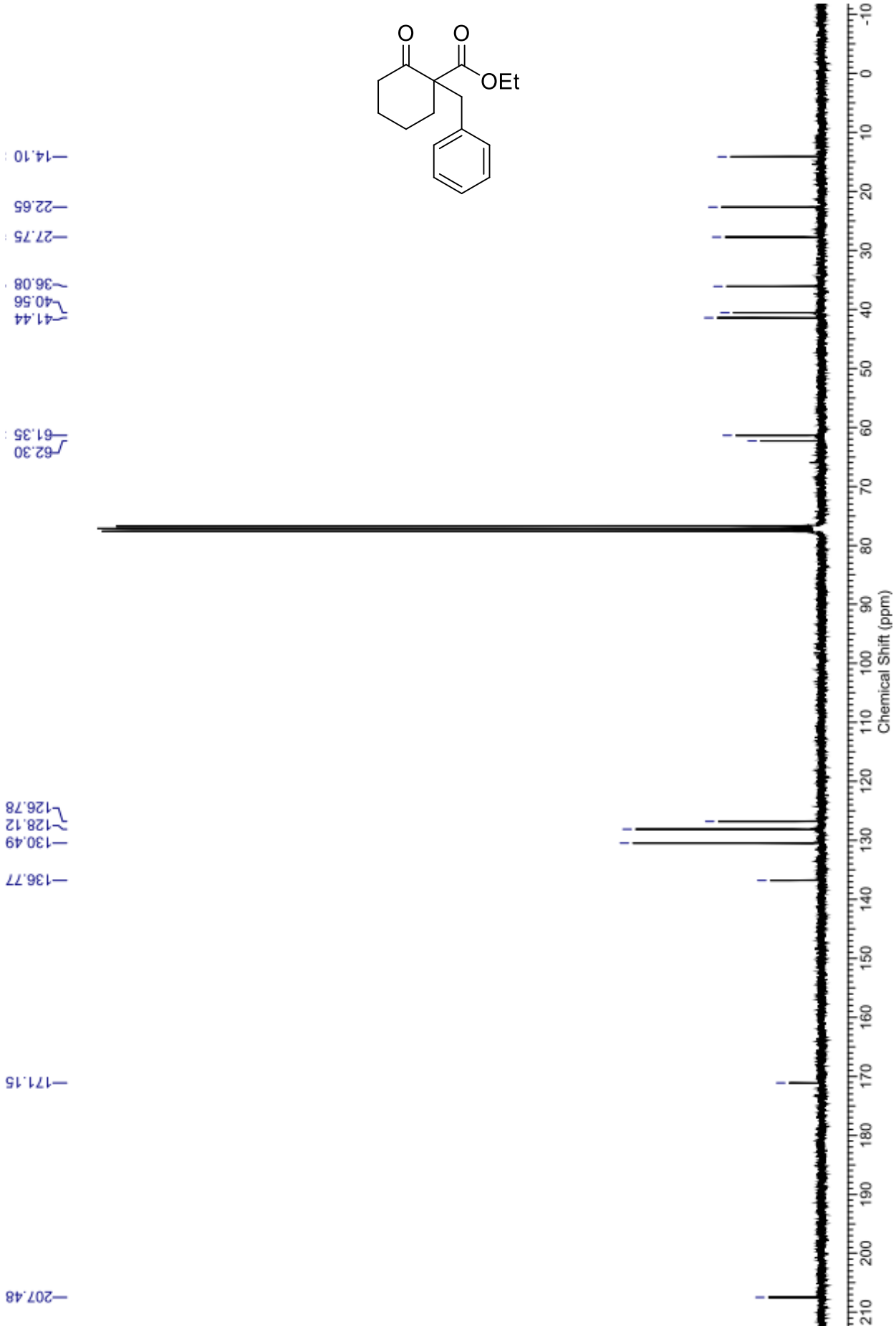
35.60
36.74
127.44
149.32
Chemical Shift (ppm)


O
O
OEt
DCM
Chemical Shift (ppm)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O
OEt
14.10
22.65
27.75
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40.56
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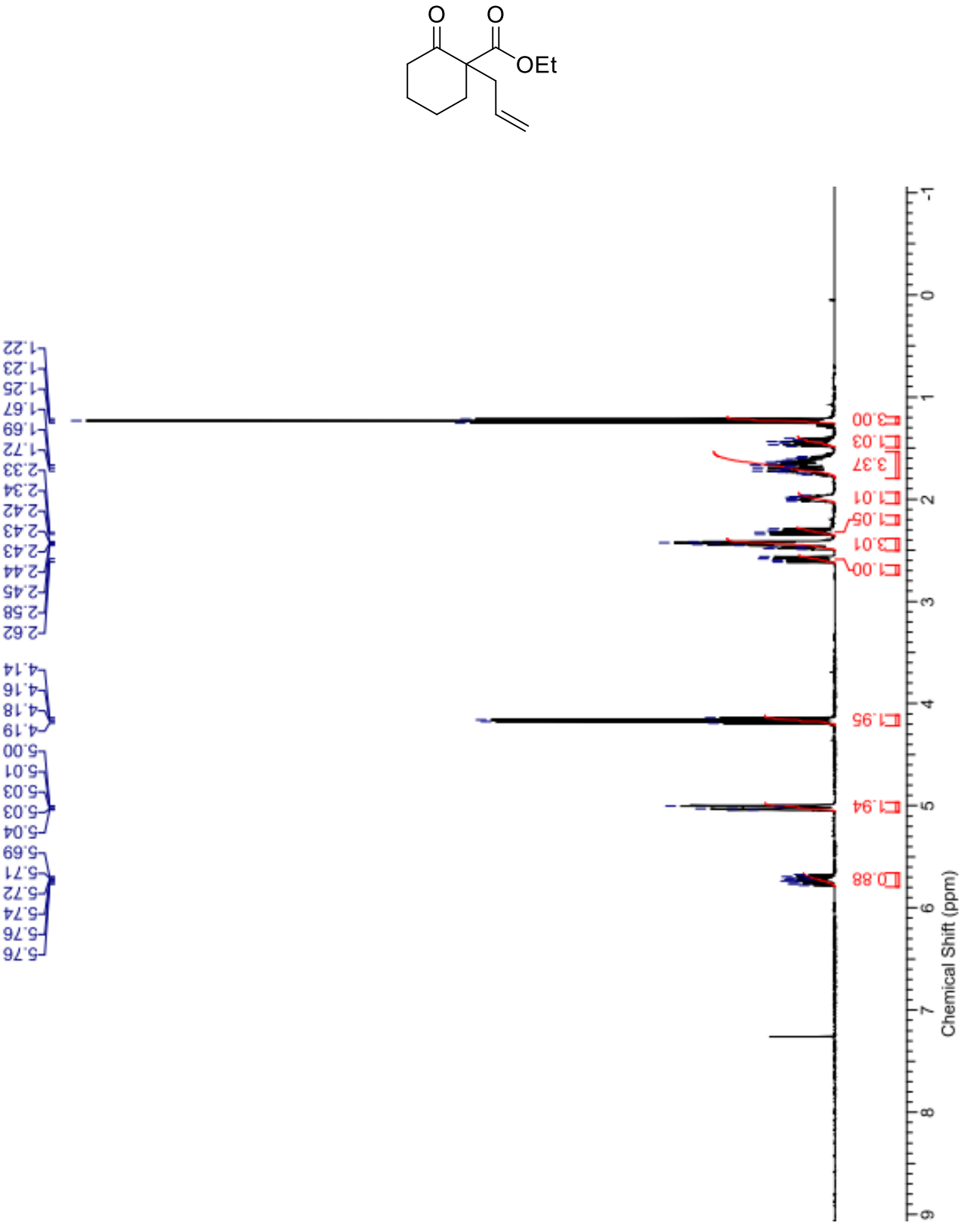
128.12
130.49
136.77
171.15
207.48
Chemical Shift (ppm)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O
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1.23
1.25
1.67
1.69
1.72
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2.34
2.42
2.43
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2.44
2.45
2.58
2.62
4.14
4.16
4.18
4.19
5.00
5.01
5.03
5.03
5.04
5.69
5.71
5.72
5.74
5.76
5.76
3.00
1.03
3.37
1.01
1.05
3.01
1.00
1.95
1.94
0.88
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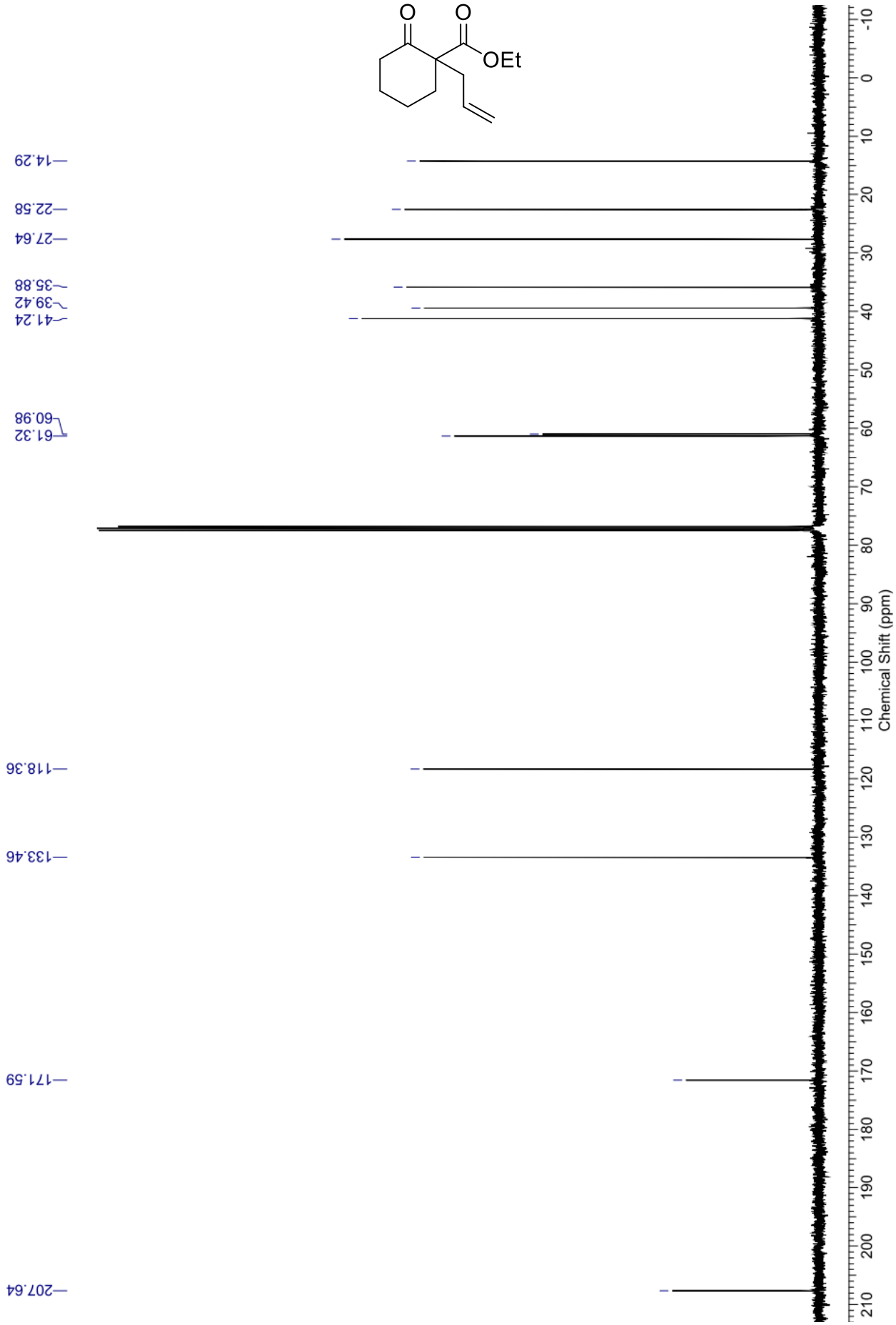
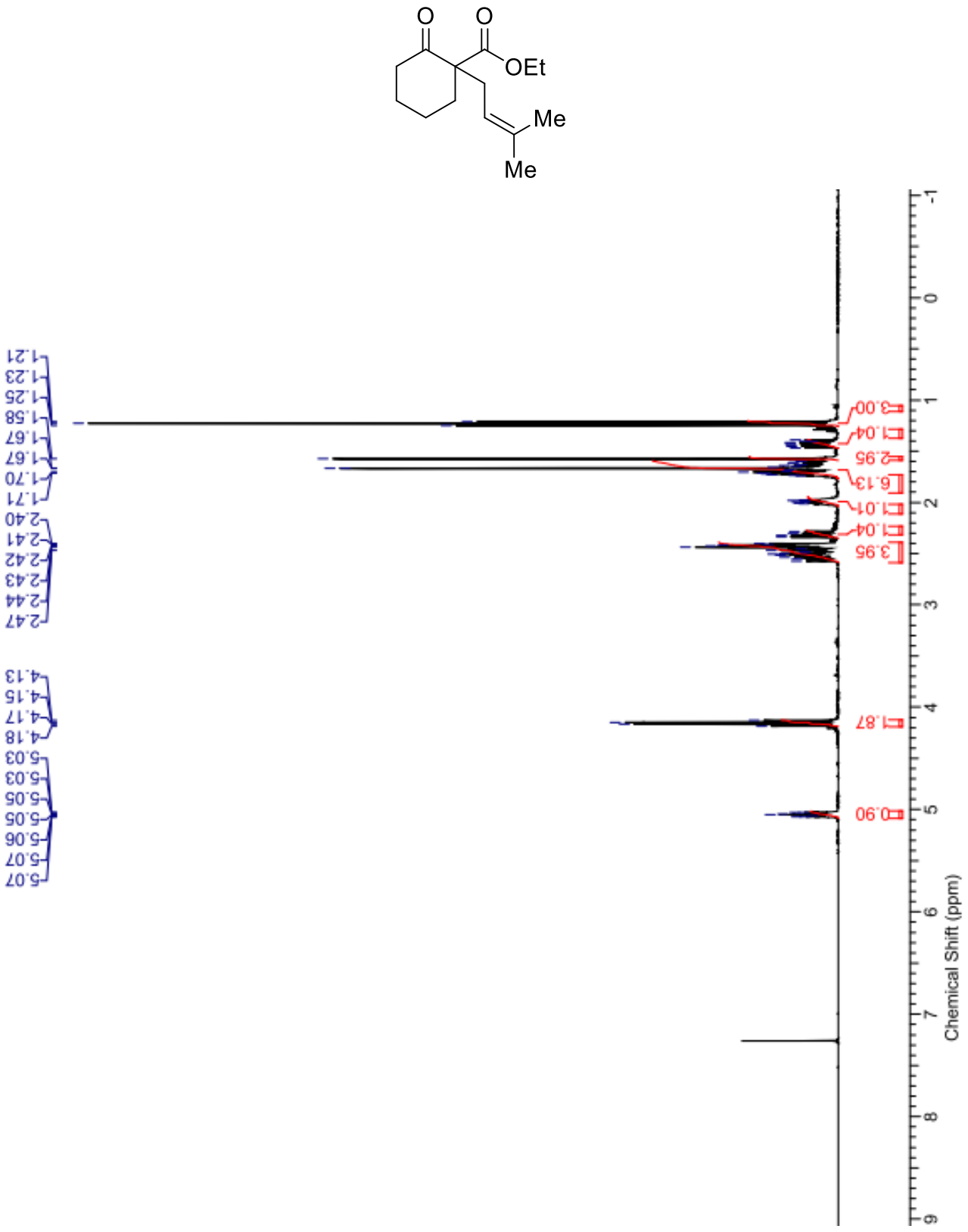
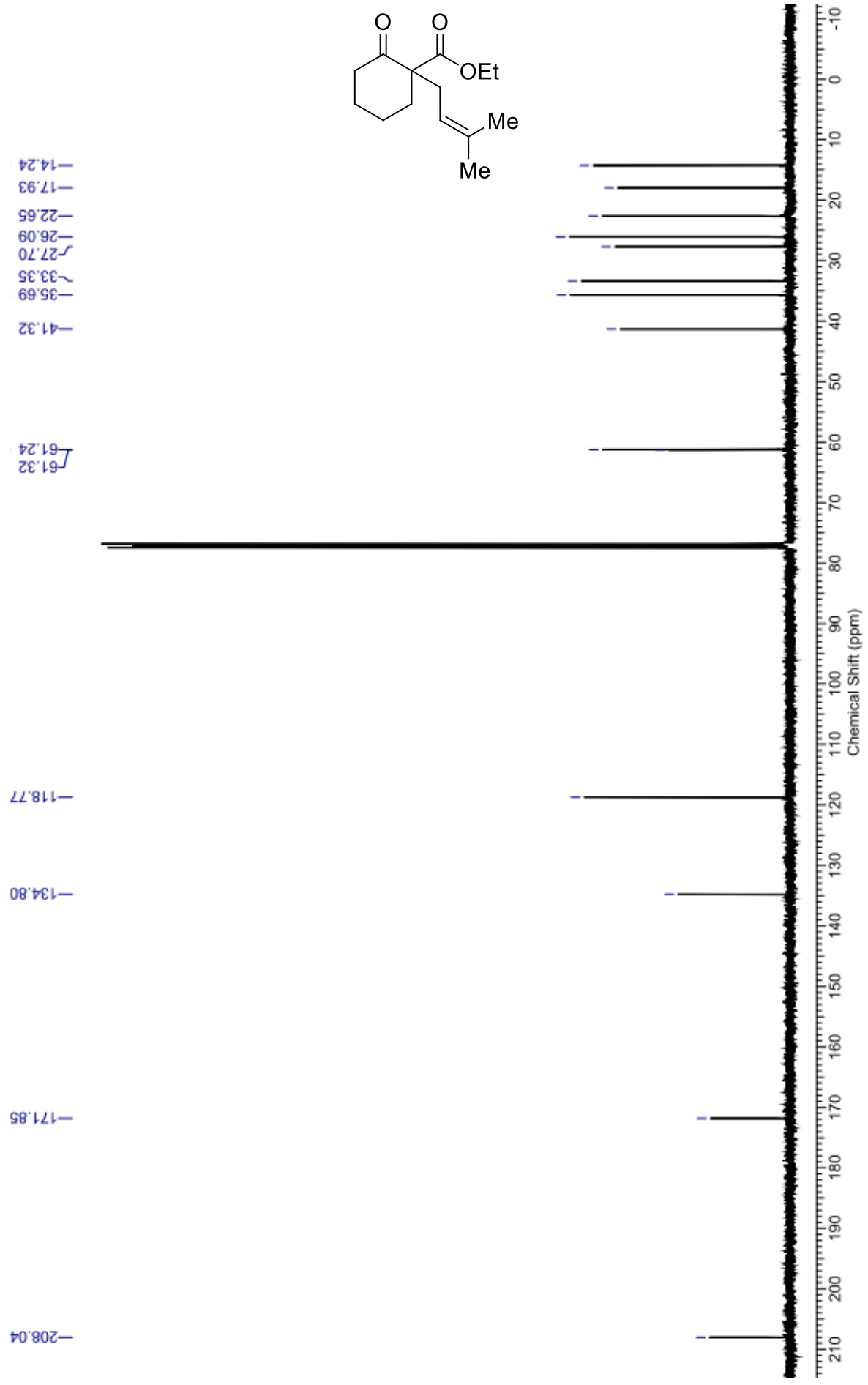
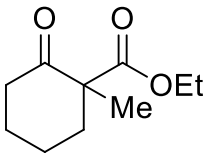
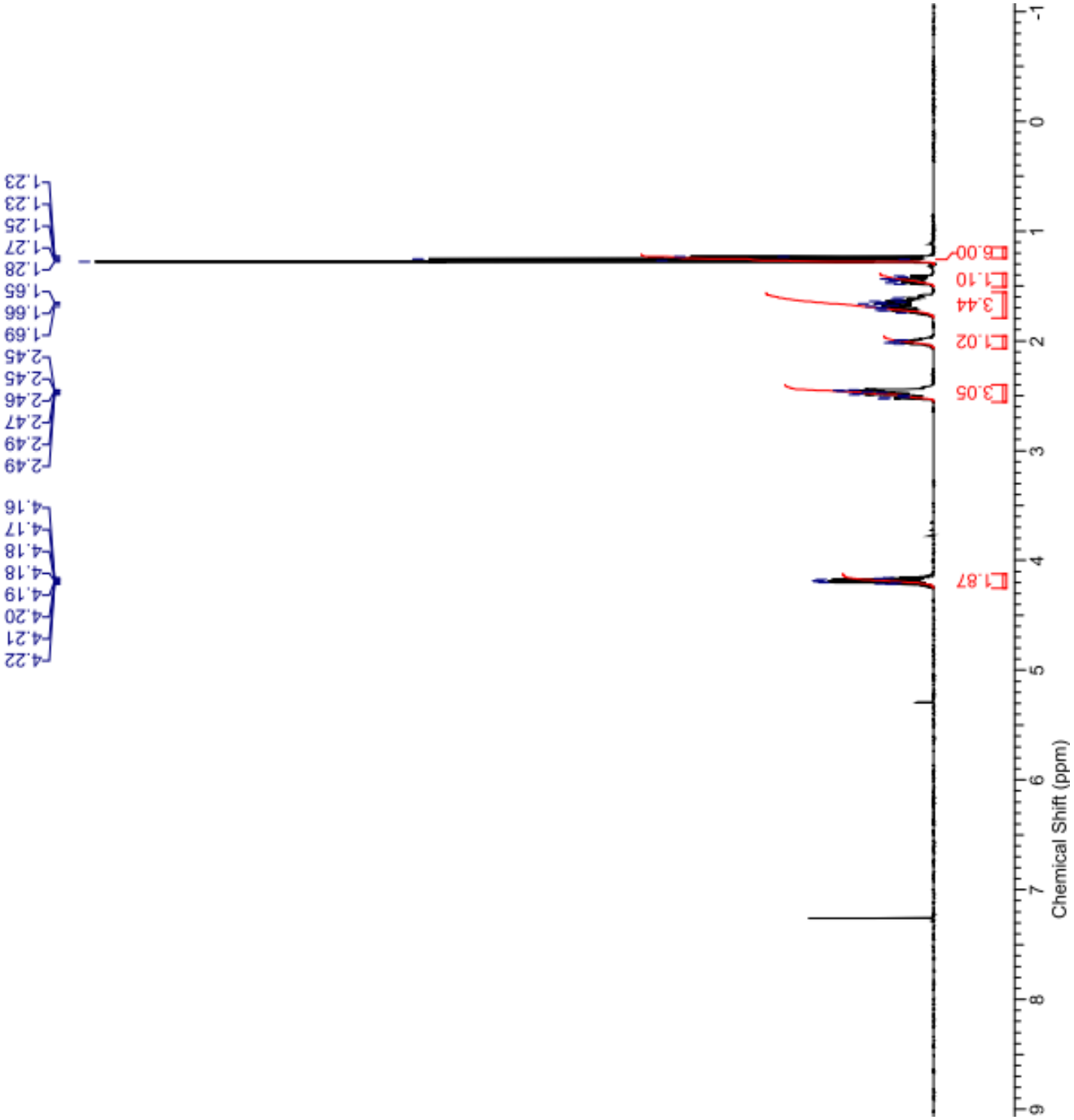
0
1
2
3
4
5
6
7
8
9
Chemical Shift (ppm)

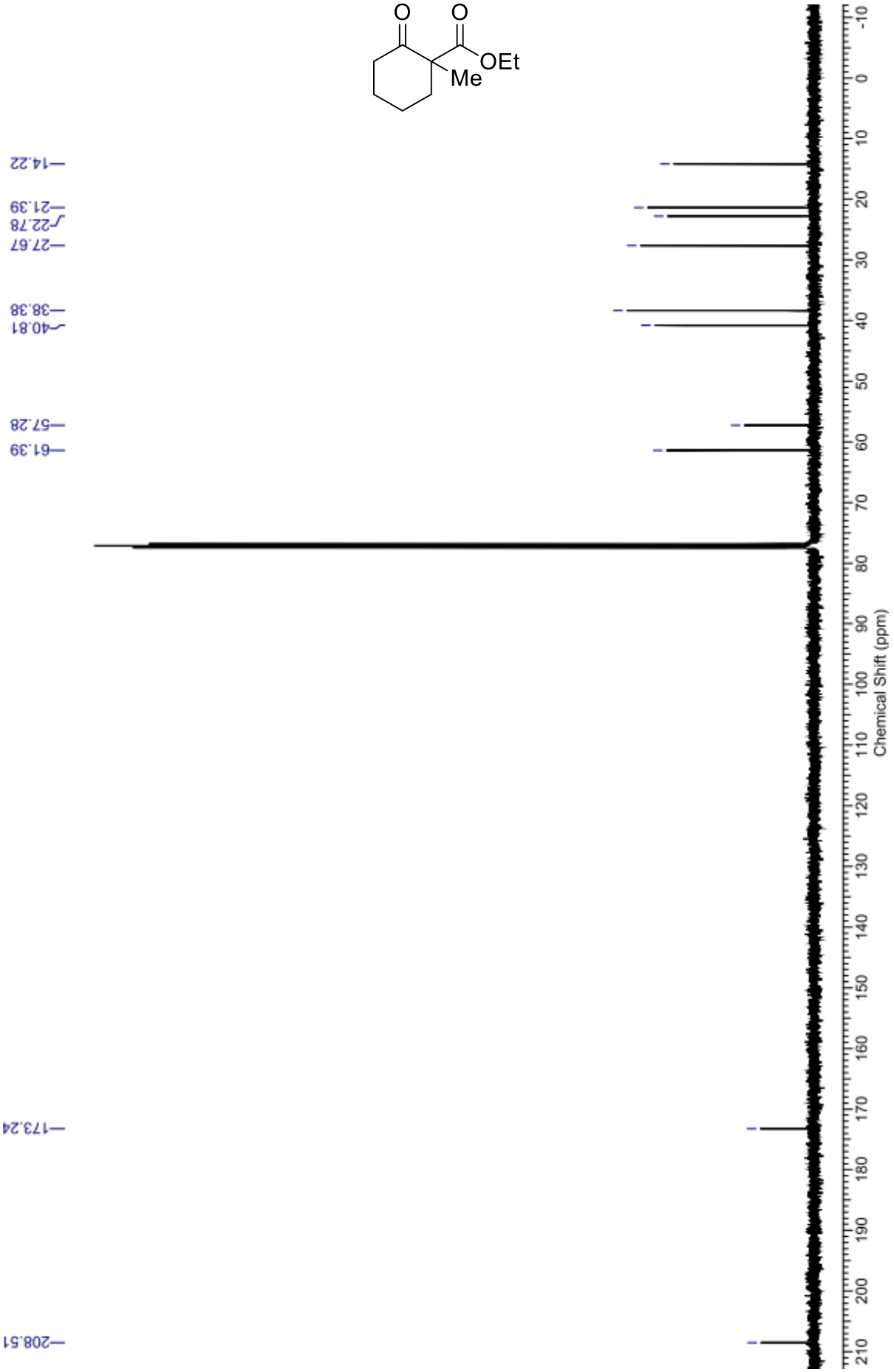

O
O
OEt
14.29
22.58
27.64
35.88
39.42
41.24
60.98
61.32
118.36
133.46
171.59
207.64
Chemical Shift (ppm)

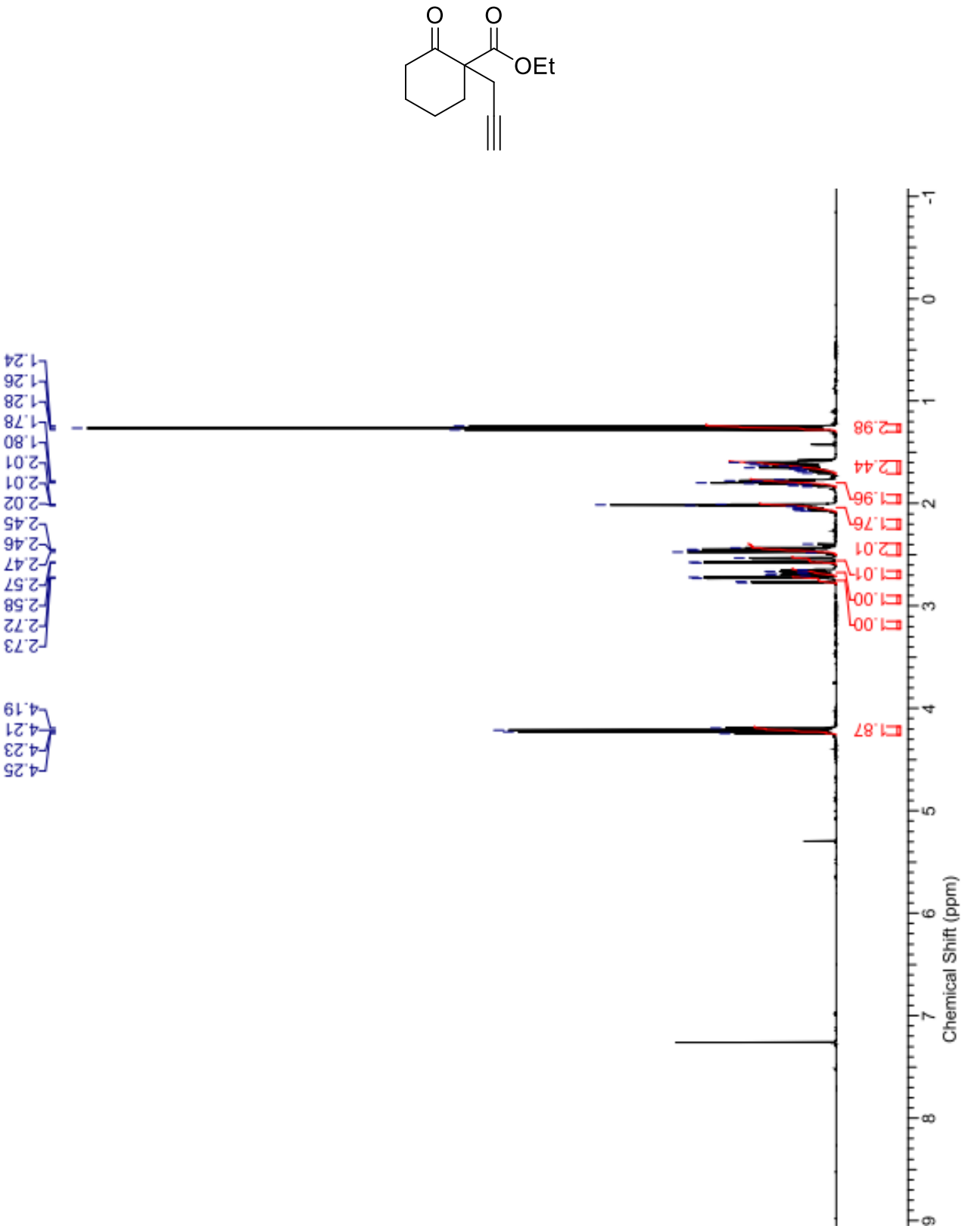

O
O
OEt
Me
Me
1.21
1.23
1.25
1.58
1.67
1.67
1.70
1.71
2.40
2.41
2.42
2.43
2.44
2.47
4.13
4.15
4.17
4.18
5.03
5.03
5.05
5.05
5.06
5.07
5.07
3.00
1.04
2.95
6.13
1.01
1.04
3.95
1.87
0.90
Chemical Shift (ppm)

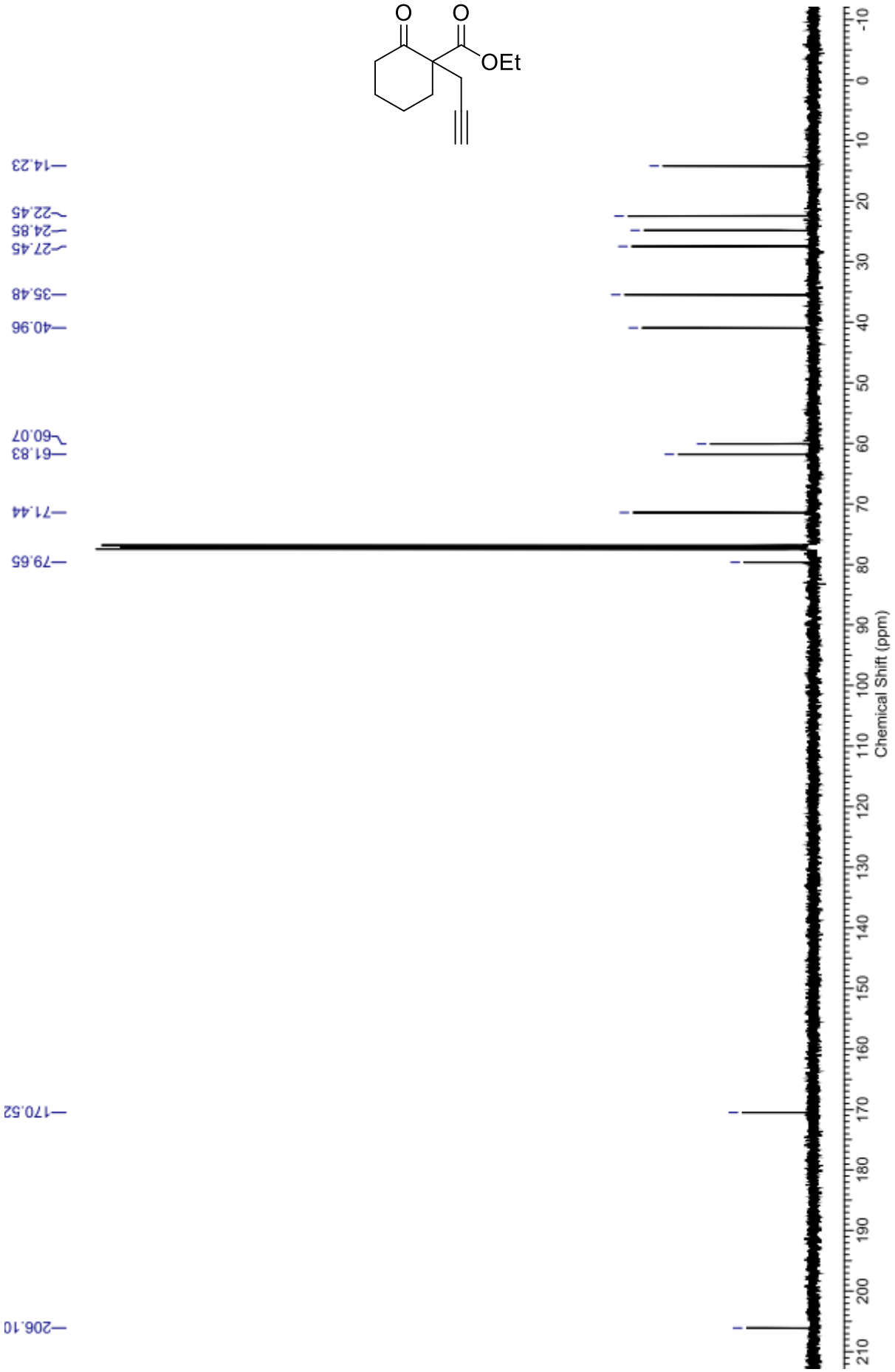

O
O
OEt
Me
Me
14.24
17.93
22.65
26.09
27.70
33.35
35.69
41.32
61.24
61.32
118.77
134.80
171.85
208.04
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Chemical Shift (ppm)

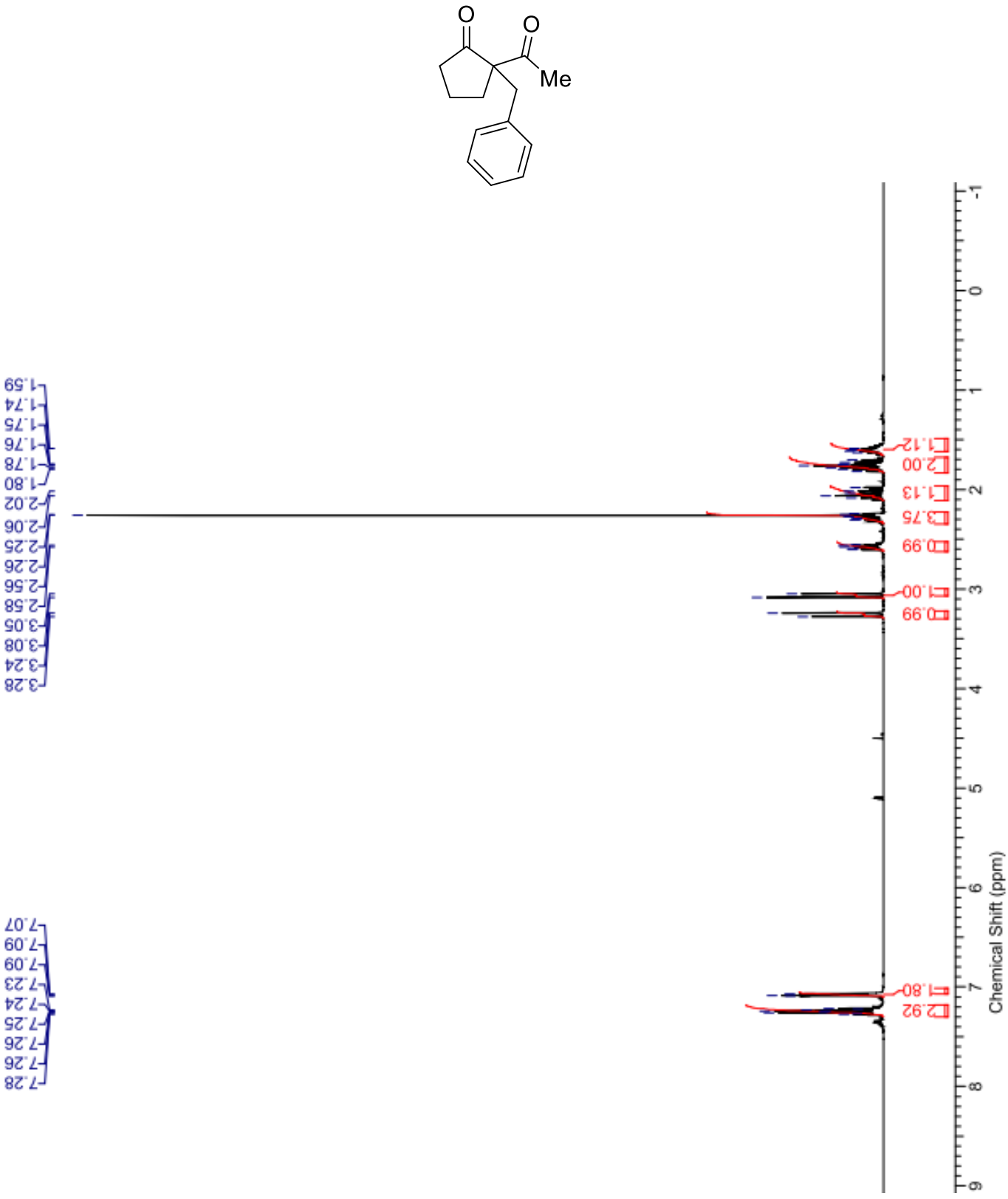

O
O
OEt
Me

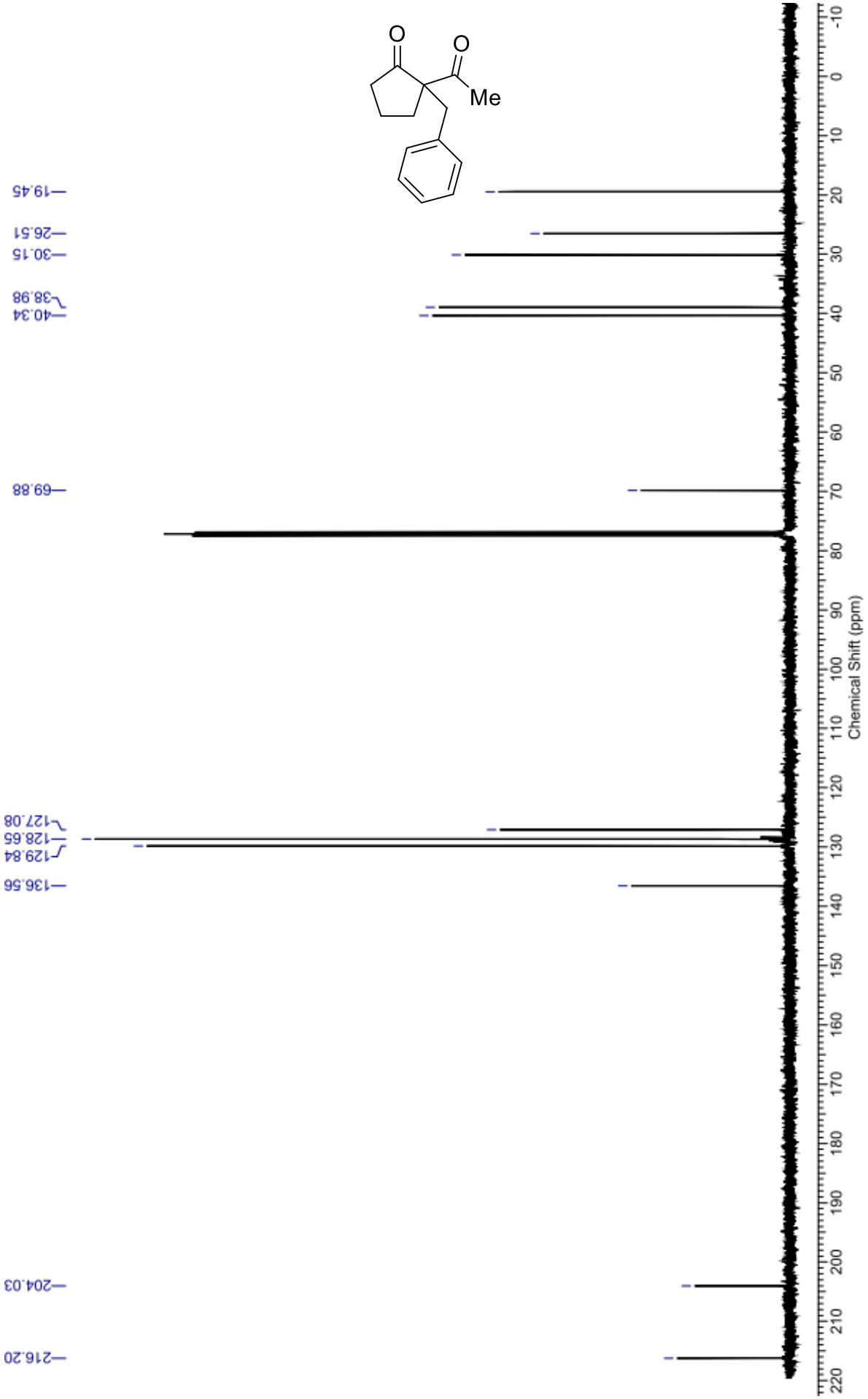

1.23
1.23
1.25
1.27
1.28
1.65
1.66
1.69
2.45
2.45
2.46
2.47
2.49
2.49
4.16
4.17
4.18
4.18
4.19
4.20
4.21
4.22
5.00
1.10
3.44
1.02
3.05
1.87
Chemical Shift (ppm)

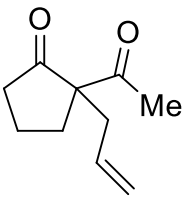

O
O
OEt
Me
14.22
21.39
22.78
27.67
38.38
40.81
57.28
61.39
173.24
208.51
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Chemical Shift (ppm)

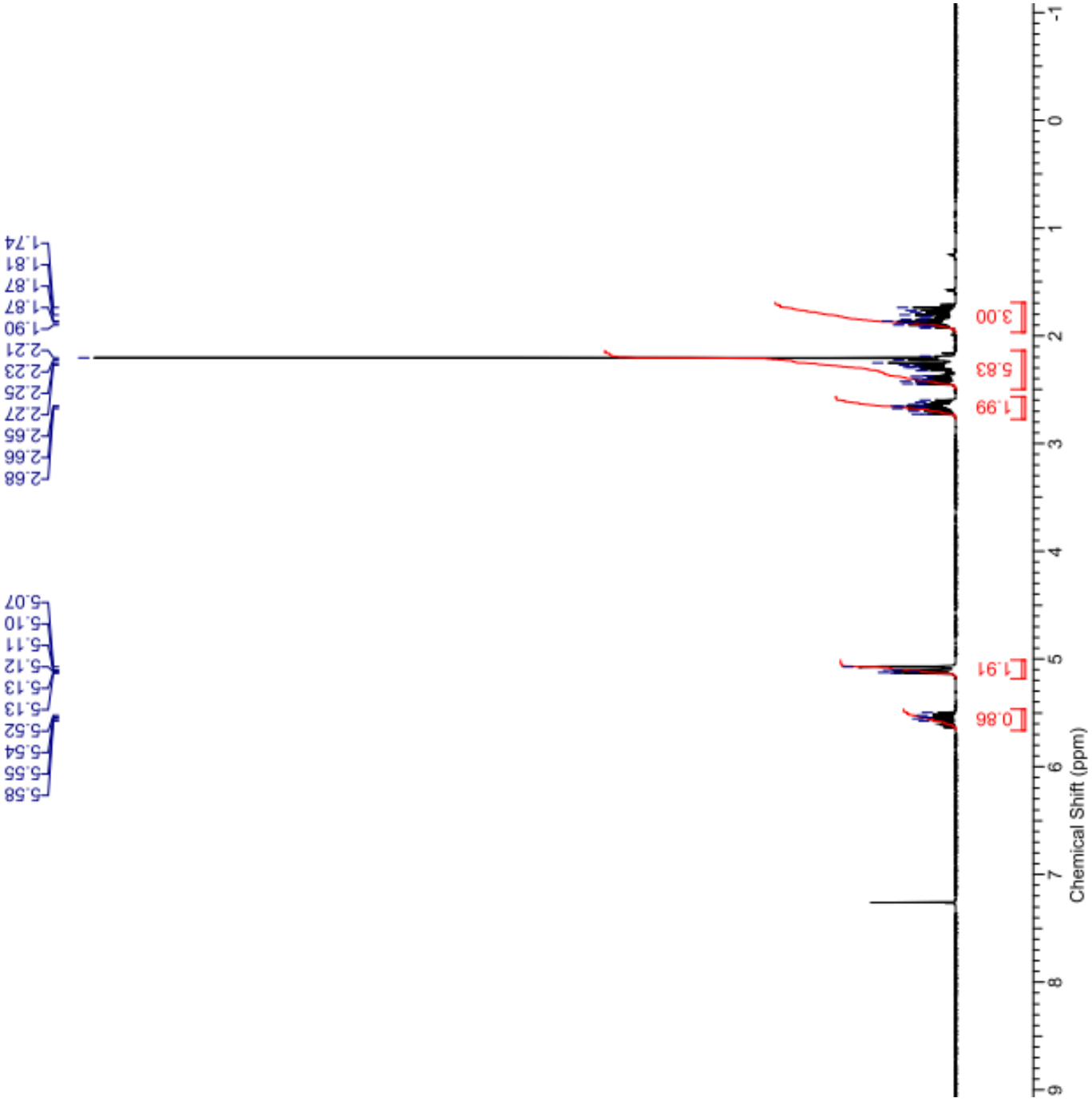

O
O
OEt
1.24
1.26
1.28
1.78
1.80
2.01
2.01
2.02
2.45
2.46
2.47
2.57
2.58
2.72
2.73
4.19
4.21
4.23
4.25
2.98
2.44
1.96
1.76
2.01
1.01
1.00
1.00
1.87
Chemical Shift (ppm)

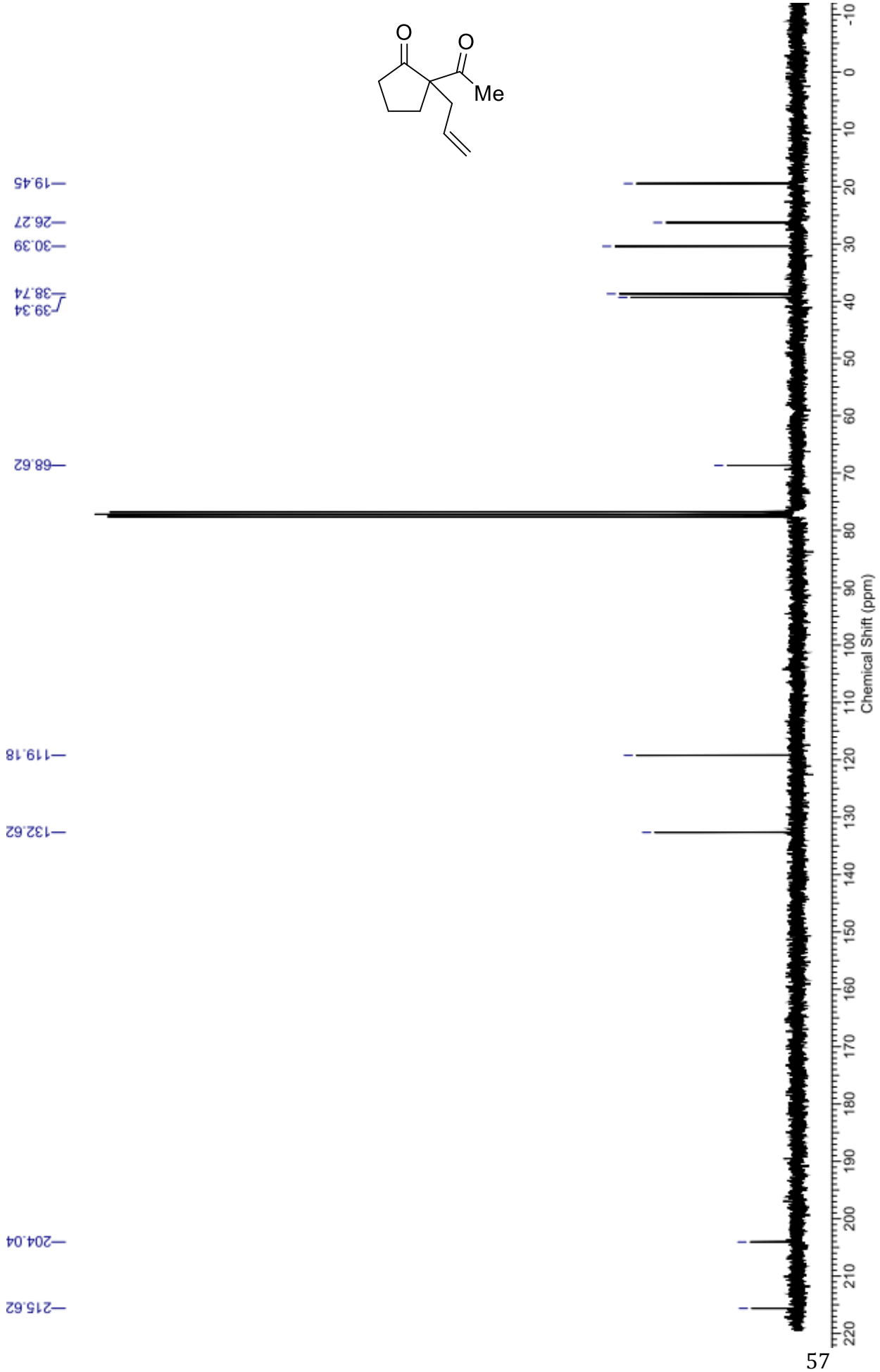

O
O
OEt
14.23
22.45
24.85
27.45
35.48
40.96
60.07
61.83
71.44
79.65
170.52
206.10
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Chemical Shift (ppm)

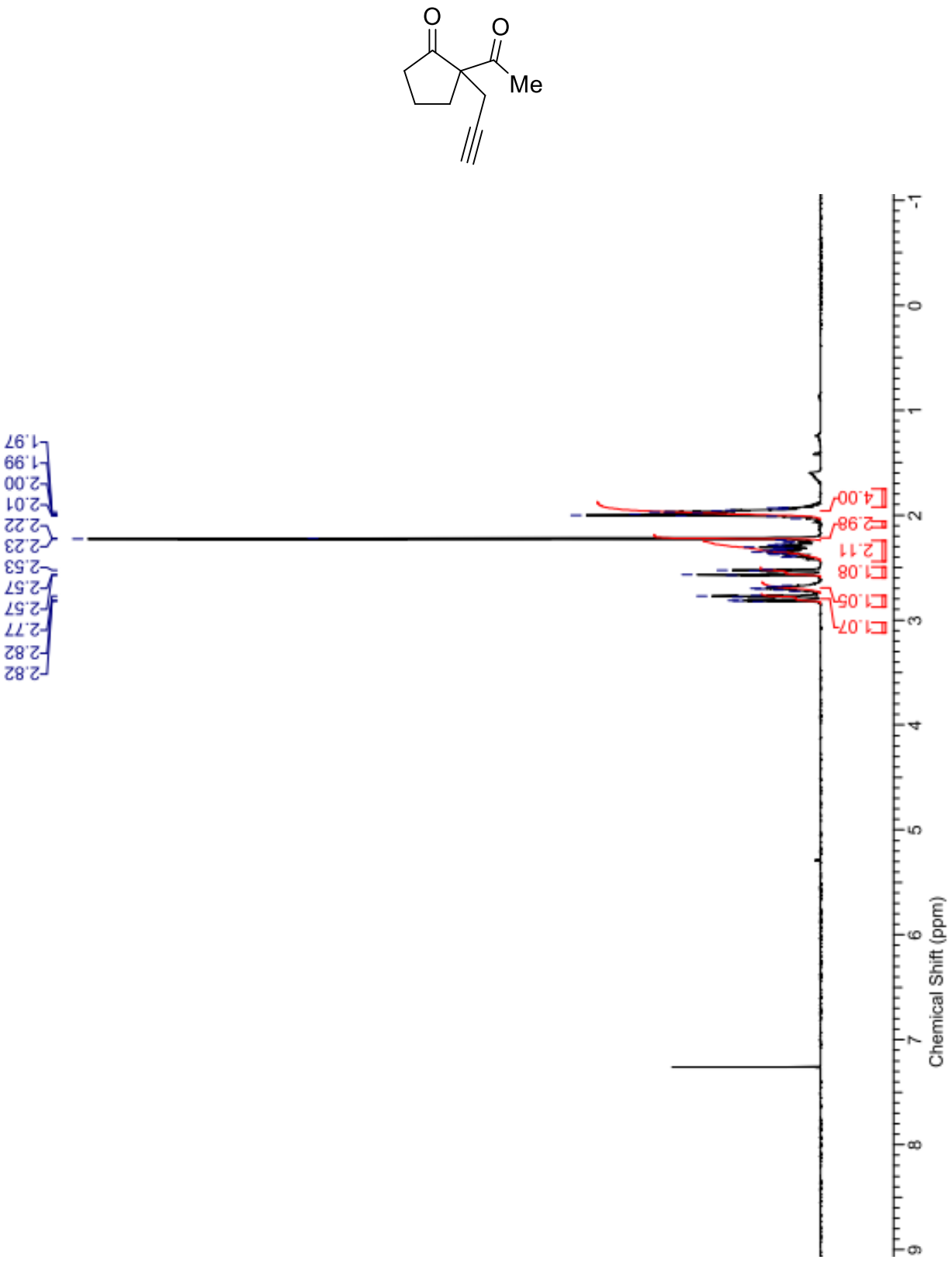

O
O
Me
1.59
1.74
1.75
1.76
1.78
1.80
2.02
2.06
2.25
2.26
2.56
2.58
3.05
3.08
3.24
3.28
7.07
7.09
7.09
7.23
7.24
7.25
7.26
7.26
7.28
1.12
2.00
1.13
3.75
0.99
1.00
0.99
1.80
2.92
Chemical Shift (ppm)

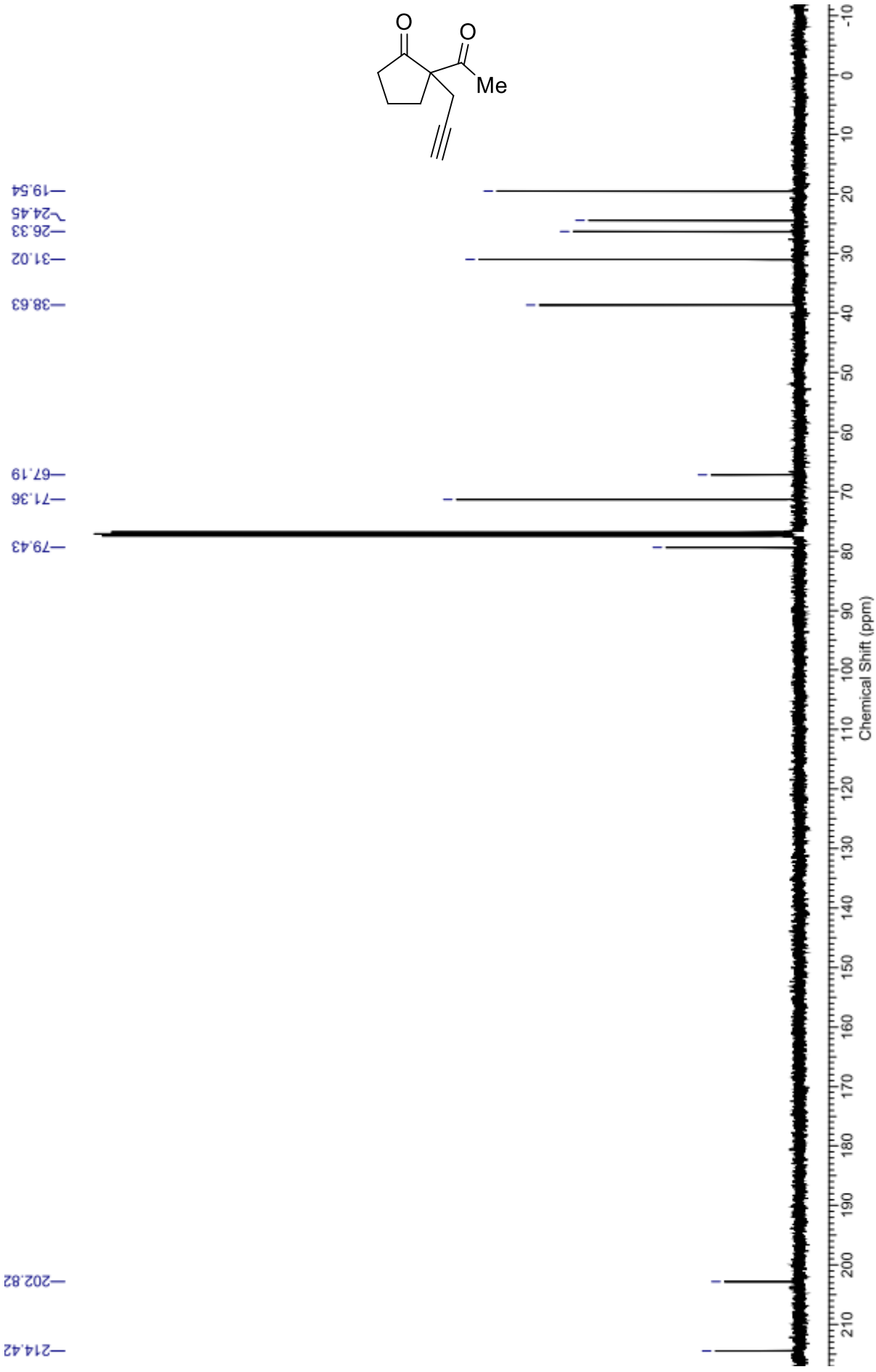

O
O
Me
19.45
26.51
30.15
38.98
40.34
69.88
127.08
128.65
129.84
136.56
204.03
216.20
Chemical Shift (ppm)

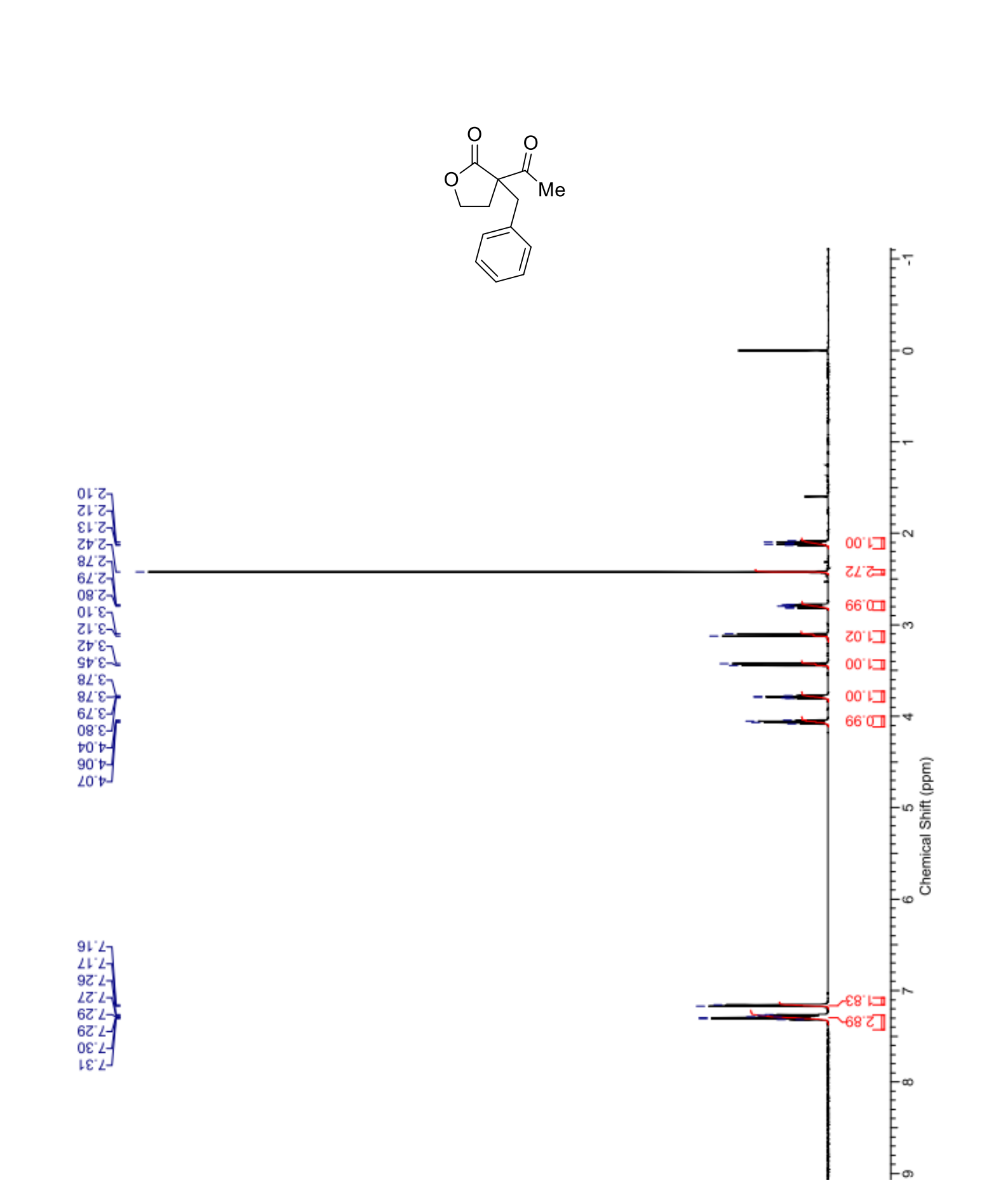

O
O
Me

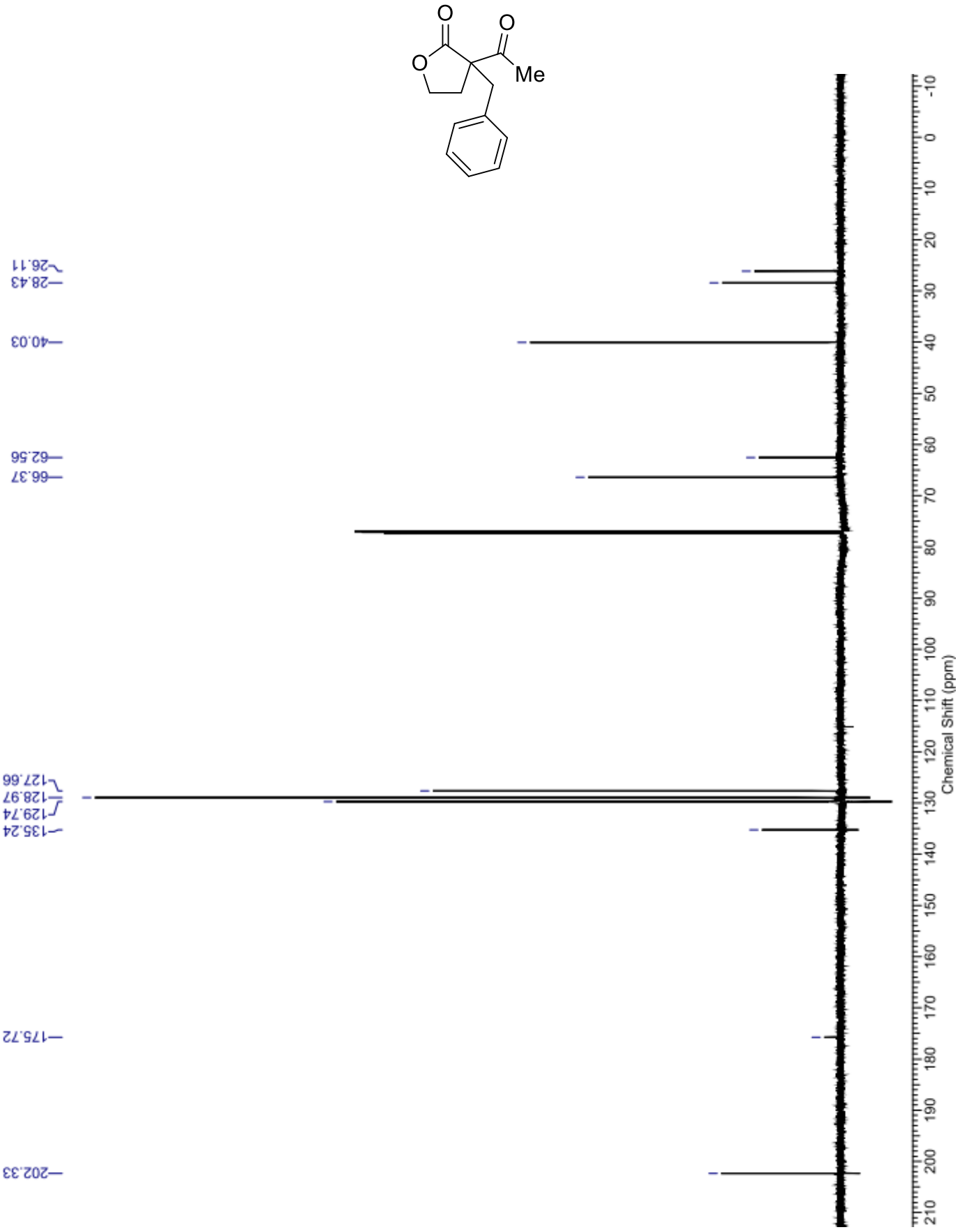

1.74
1.81
1.87
1.87
1.90
2.21
2.23
2.25
2.27
2.65
2.66
2.68
5.07
5.10
5.11
5.12
5.13
5.13
5.52
5.54
5.55
5.58
3.00
5.83
1.99
1.91
0.86
Chemical Shift (ppm)

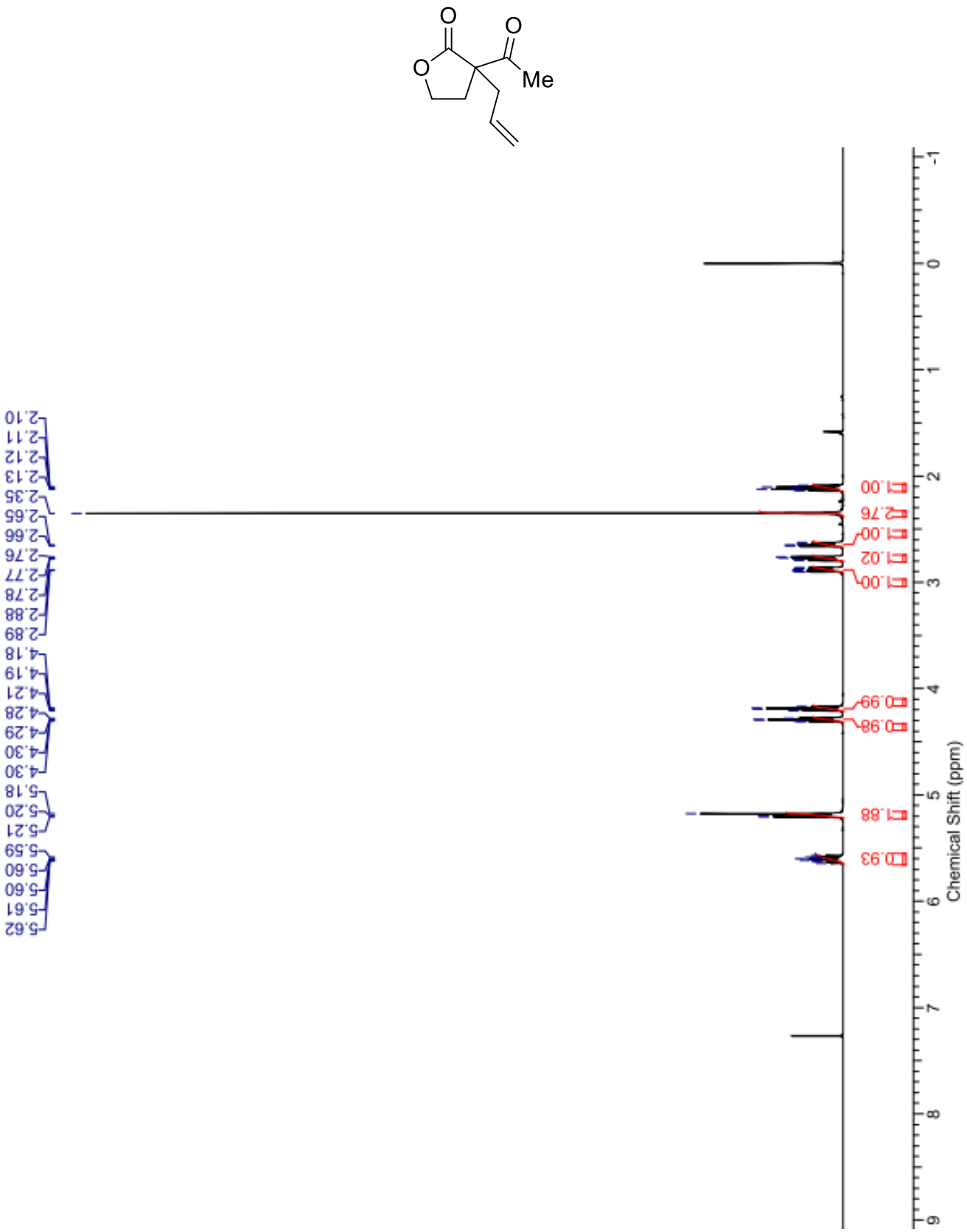

O
O
Me
19.45
26.27
30.39
38.74
39.34
68.62
119.18
132.62
204.04
215.62
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
Chemical Shift (ppm)

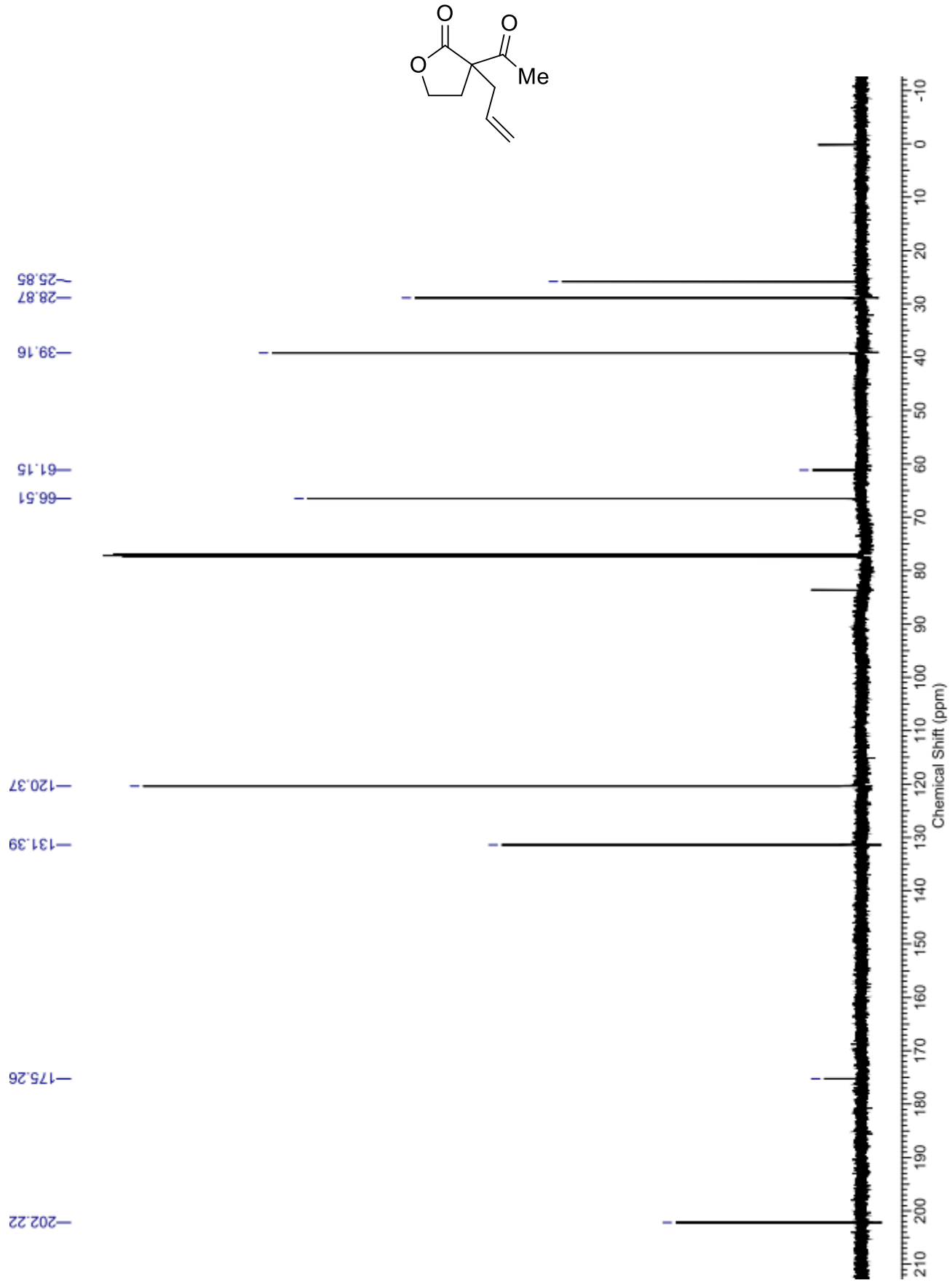

O
O
Me
1.97
1.99
2.00
2.01
2.22
2.23
2.53
2.57
2.57
2.77
2.82
2.82
4.00
2.98
2.11
1.08
1.05
1.07
-1
0
1
2
3
4
5
6
7
8
9
Chemical Shift (ppm)

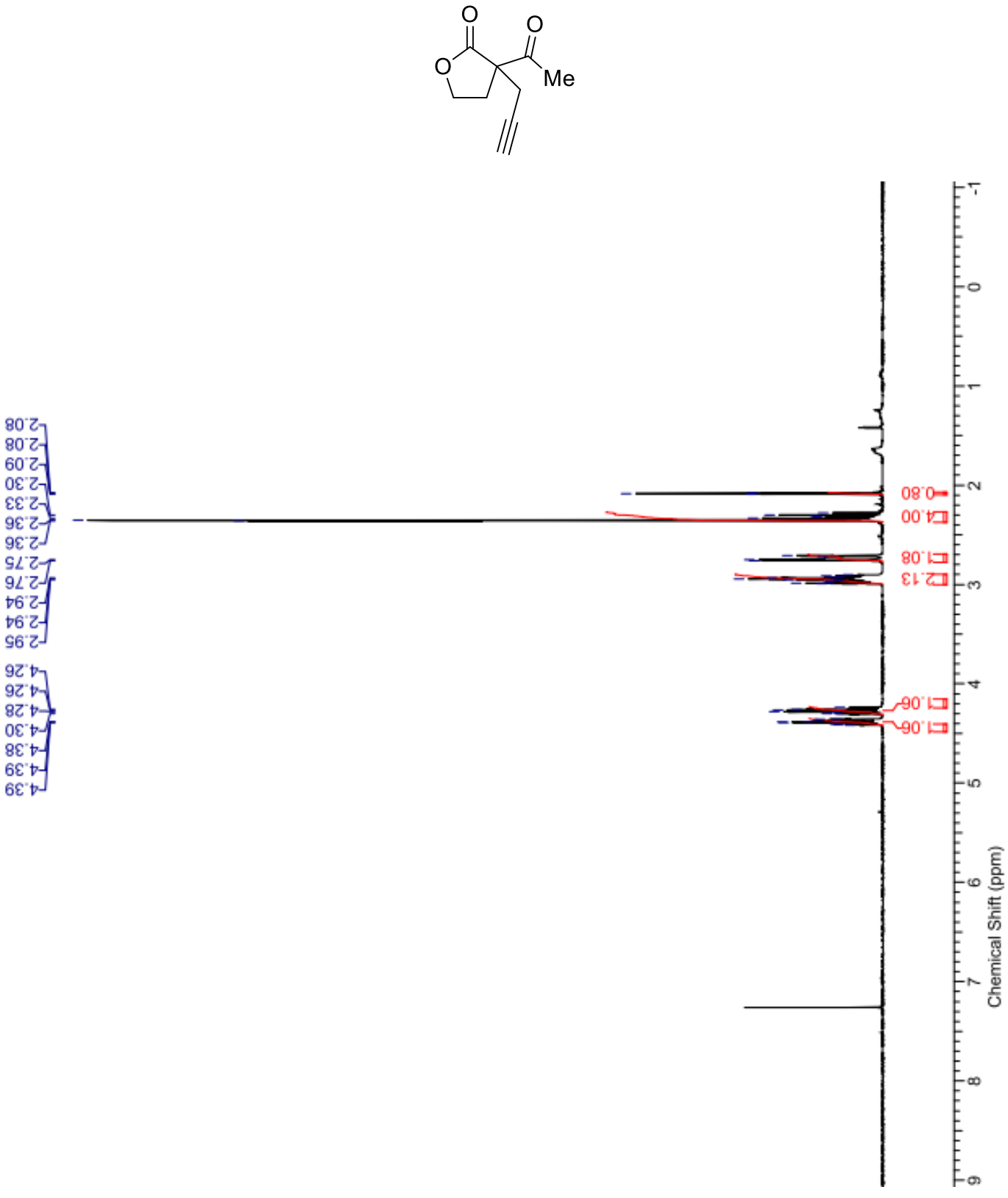

O
O
Me
214.42
202.82
79.43
71.36
67.19
38.63
31.02
26.33
24.45
19.54
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Chemical Shift (ppm)

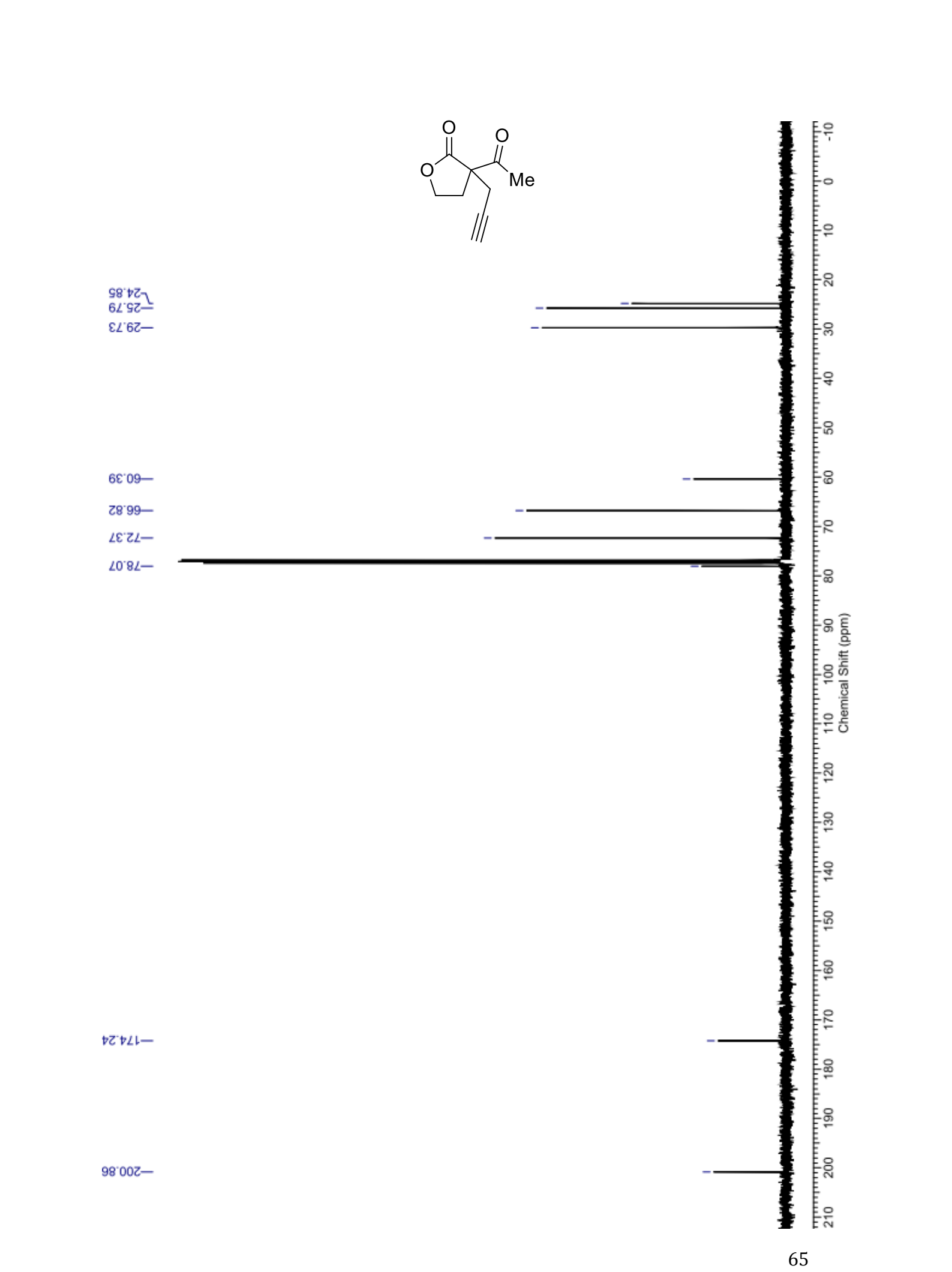

O
O
O
Me
2.10
2.12
2.13
2.42
2.78
2.79
2.80
3.10
3.12
3.42
3.45
3.78
3.78
3.79
3.80
4.04
4.06
4.07
7.16
7.17
7.26
7.27
7.29
7.29
7.30
7.31
1.00
2.72
0.99
1.02
1.00
1.00
0.99
1.83
2.89
Chemical Shift (ppm)

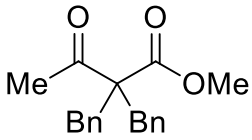

O
O
O
Me
26.11
28.43
40.03
62.56
66.37
127.66
128.97
129.74
135.24
175.72
202.33
Chemical Shift (ppm)

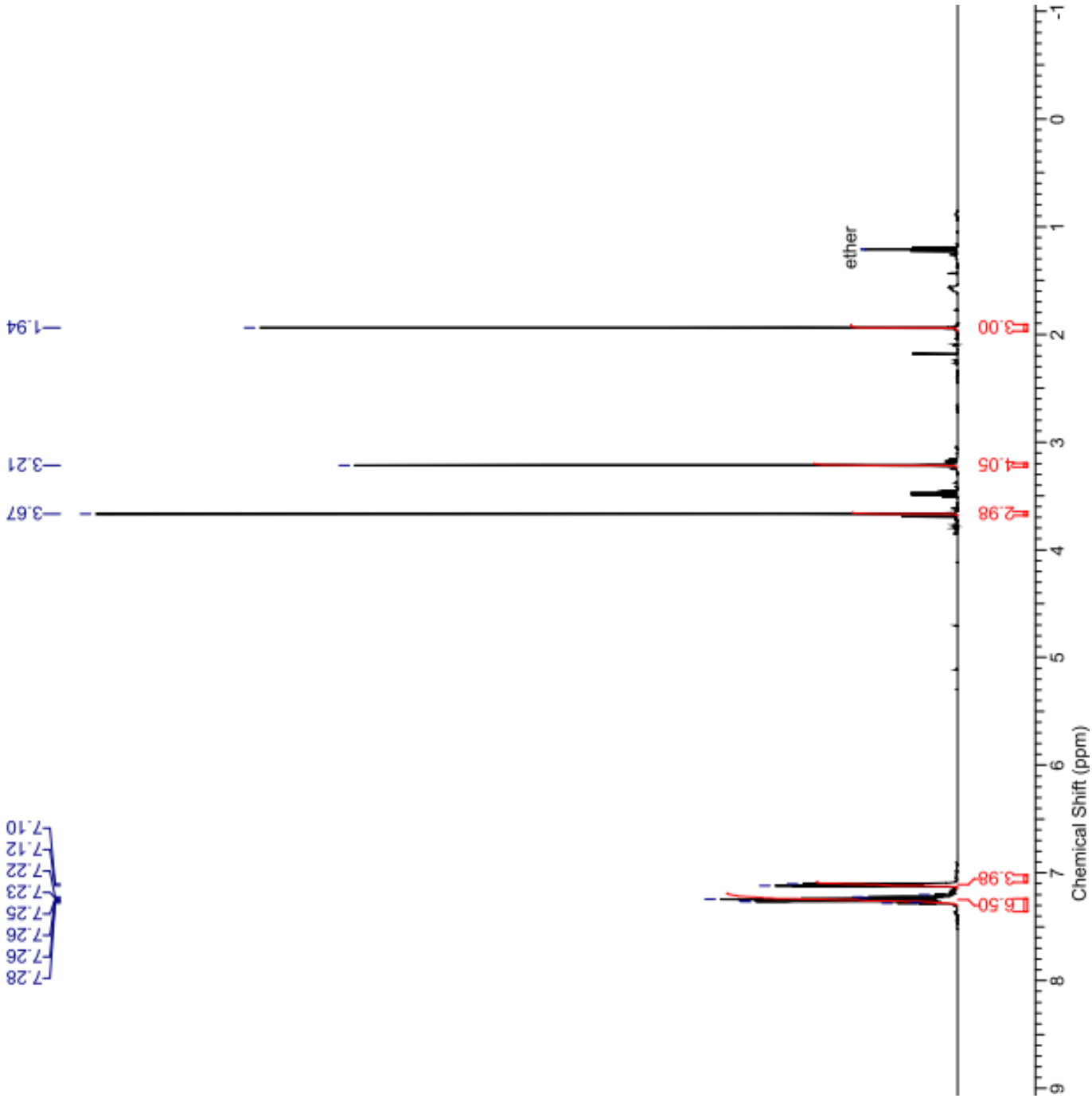

O
O
O
Me
2.10
2.11
2.12
2.13
2.35
2.65
2.66
2.76
2.77
2.78
2.88
2.89
4.18
4.19
4.21
4.28
4.29
4.30
4.30
5.18
5.20
5.21
5.59
5.60
5.60
5.61
5.62
1.00
2.76
1.00
1.02
1.00
0.99
0.98
1.88
0.93
-1
0
1
2
3
4
5
6
7
8
9
Chemical Shift (ppm)

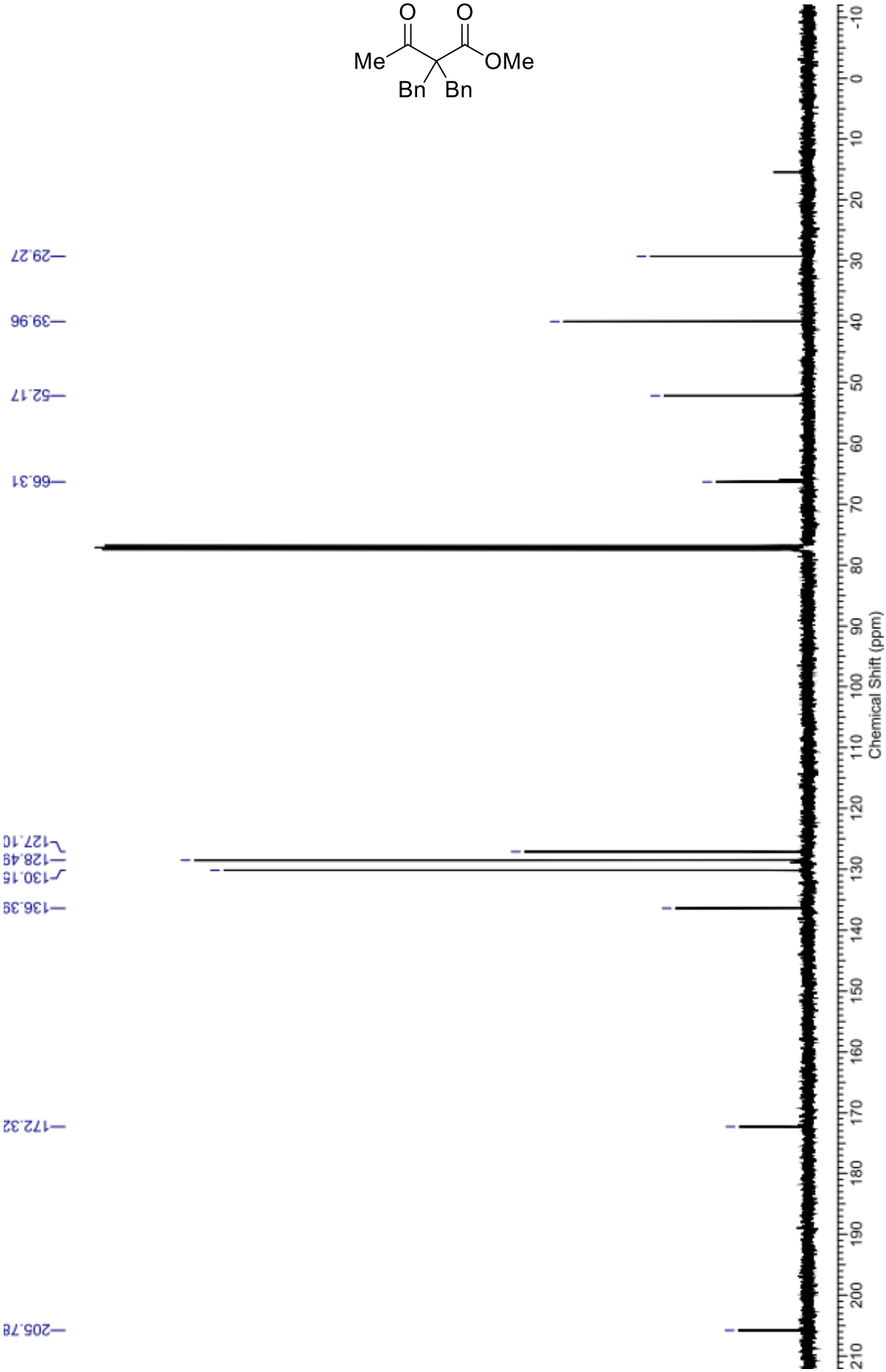

O
O
O
Me
25.85
28.87
39.16
61.15
66.51
120.37
131.39
175.26
202.22
Chemical Shift (ppm)

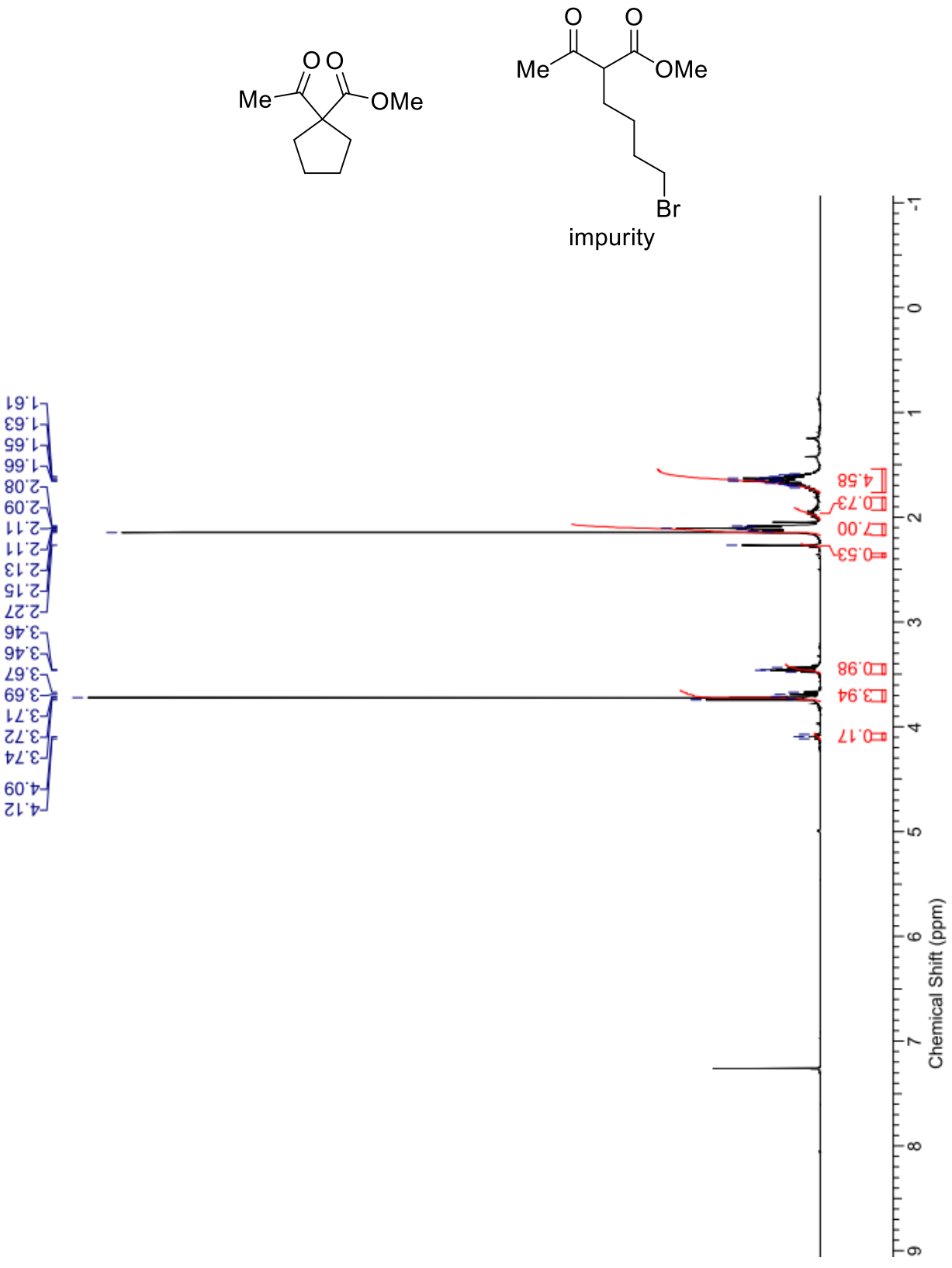

O
O
O
Me
2.08
2.08
2.09
2.30
2.33
2.36
2.36
2.75
2.76
2.94
2.94
2.95
4.26
4.26
4.28
4.30
4.38
4.39
4.39
0.80
4.00
2.08
2.13
1.06
1.06
-1
0
1
2
3
4
5
6
7
8
9
Chemical Shift (ppm)

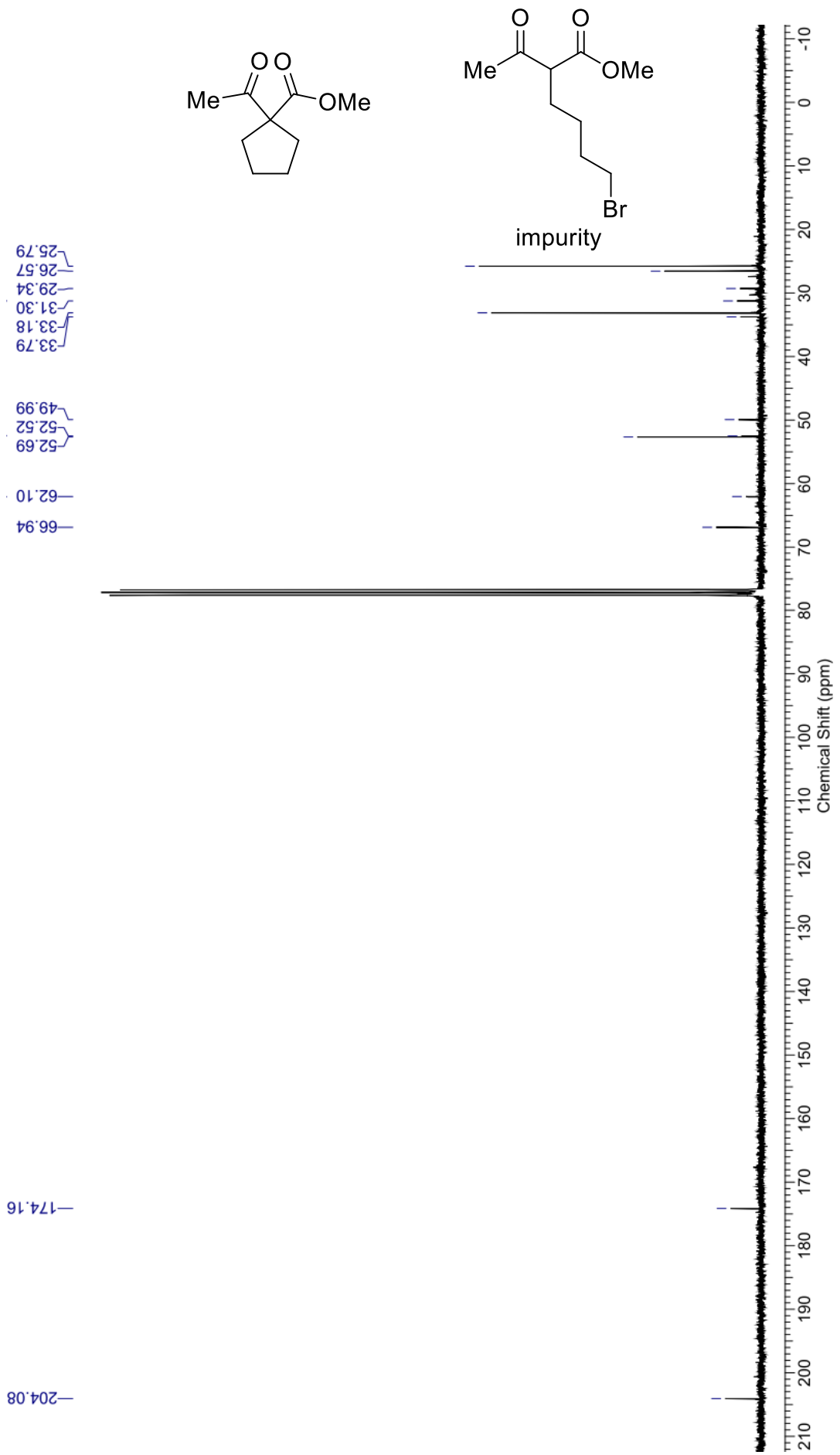

O
O
O
Me
24.85
25.79
29.73
60.39
66.82
72.37
78.07
174.24
200.86
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Chemical Shift (ppm)

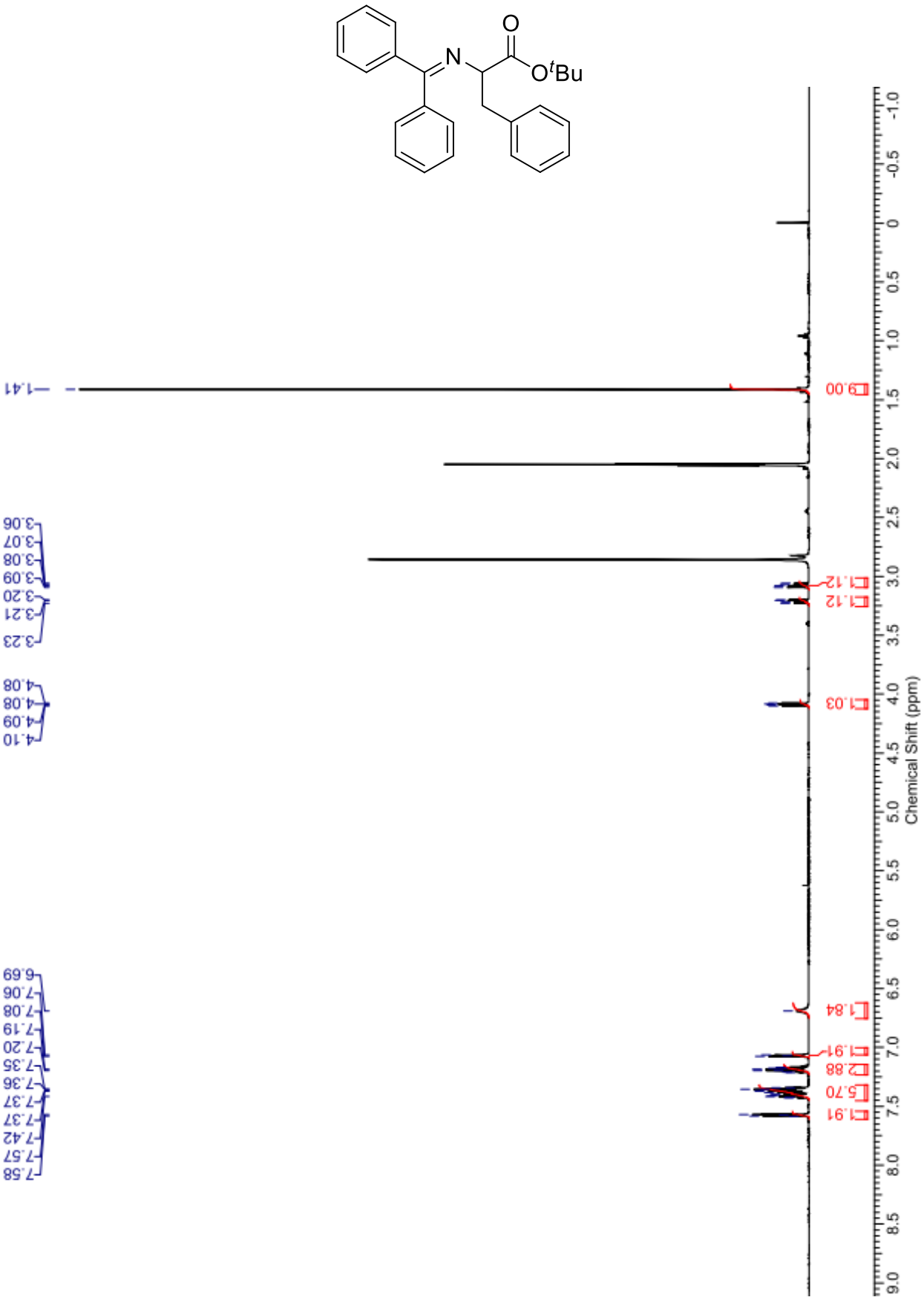

O
O
Me
OMe
Bn
Bn

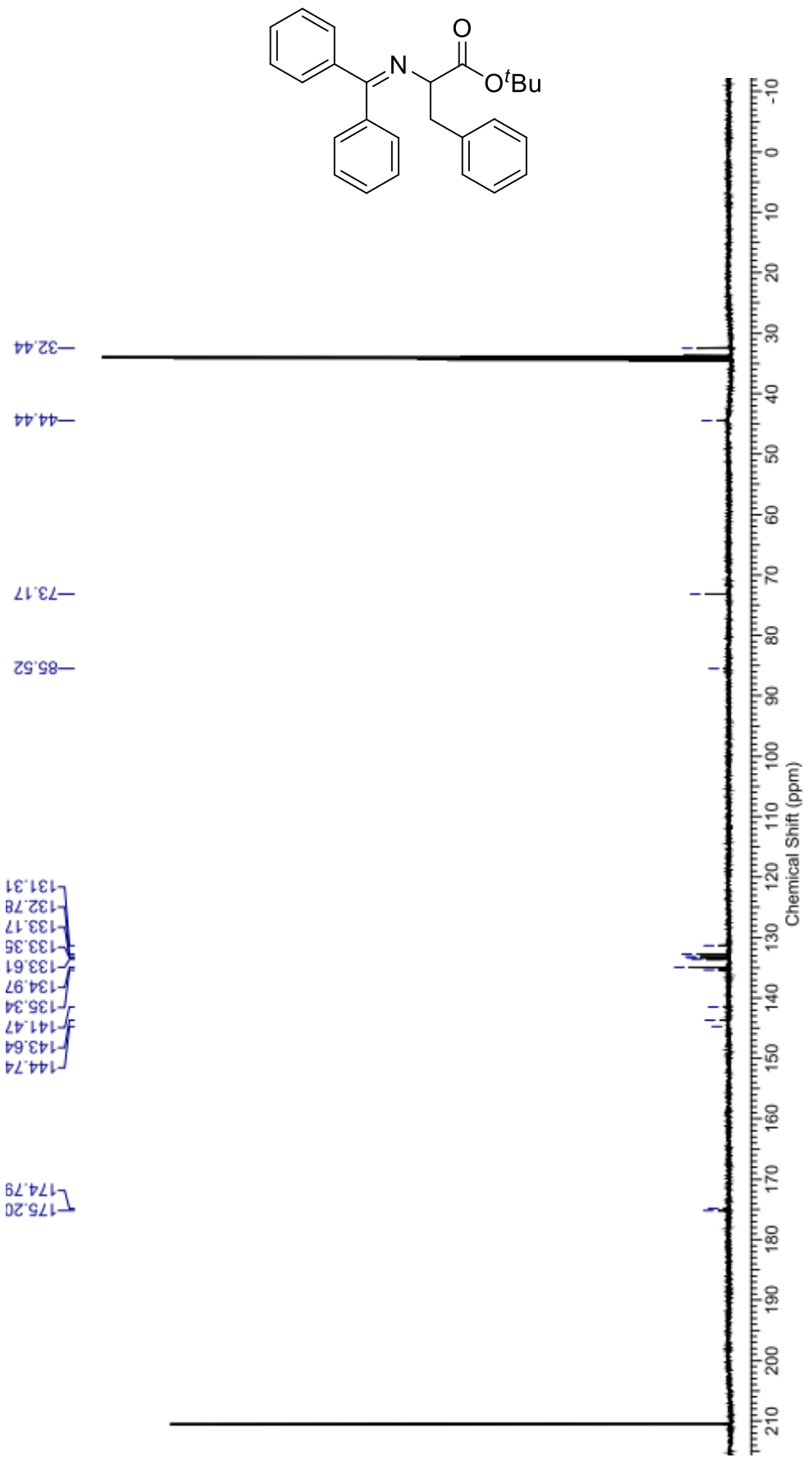

ether
1.94
3.21
3.67
7.10
7.12
7.22
7.23
7.25
7.26
7.26
7.28
3.00
1.05
2.98
3.98
5.50
Chemical Shift (ppm)

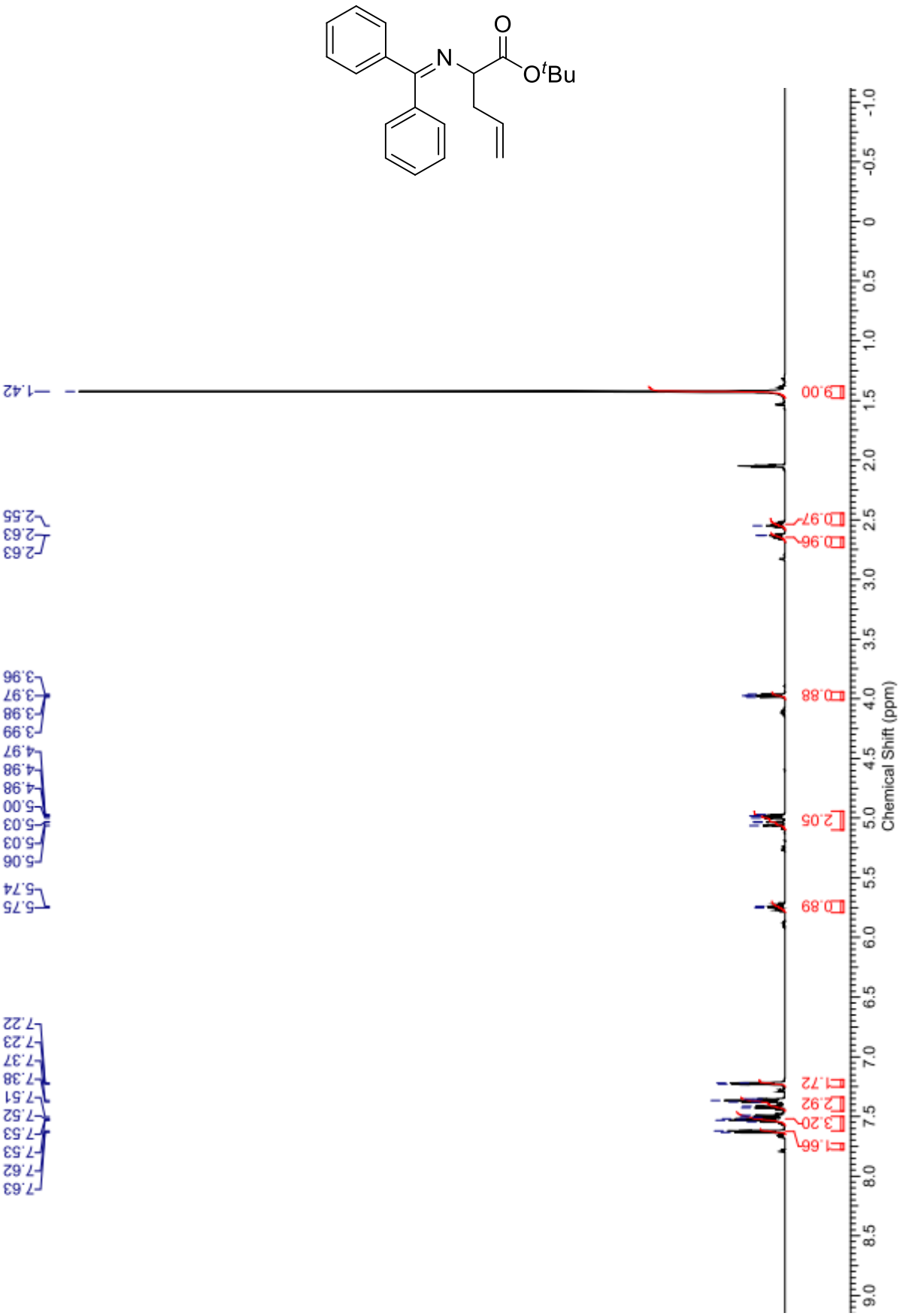

O
O
Me
OMe
Bn
Bn
29.27
39.96
52.17
66.31
127.10
128.49
130.15
136.39
172.32
205.78
Chemical Shift (ppm)

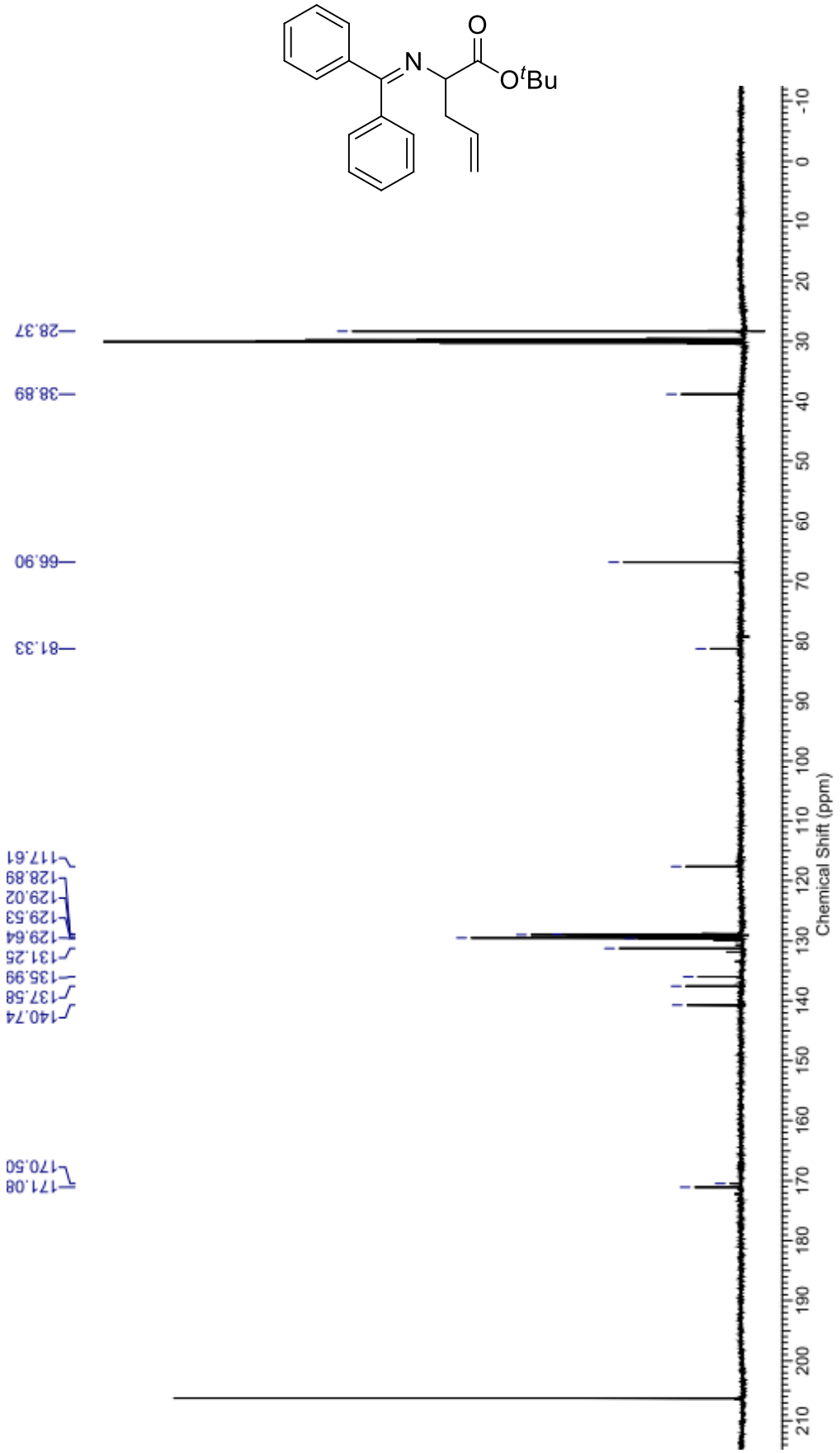

O
O
Me
OMe
O
O
Me
OMe
Br
impurity
1.61
1.63
1.65
1.66
2.08
2.09
2.11
2.11
2.13
2.15
2.27
3.46
3.46
3.67
3.69
3.71
3.72
3.74
4.09
4.12
4.58
0.73
7.00
0.53
0.98
3.94
0.17
-1
0
1
2
3
4
5
6
7
8
9
Chemical Shift (ppm)

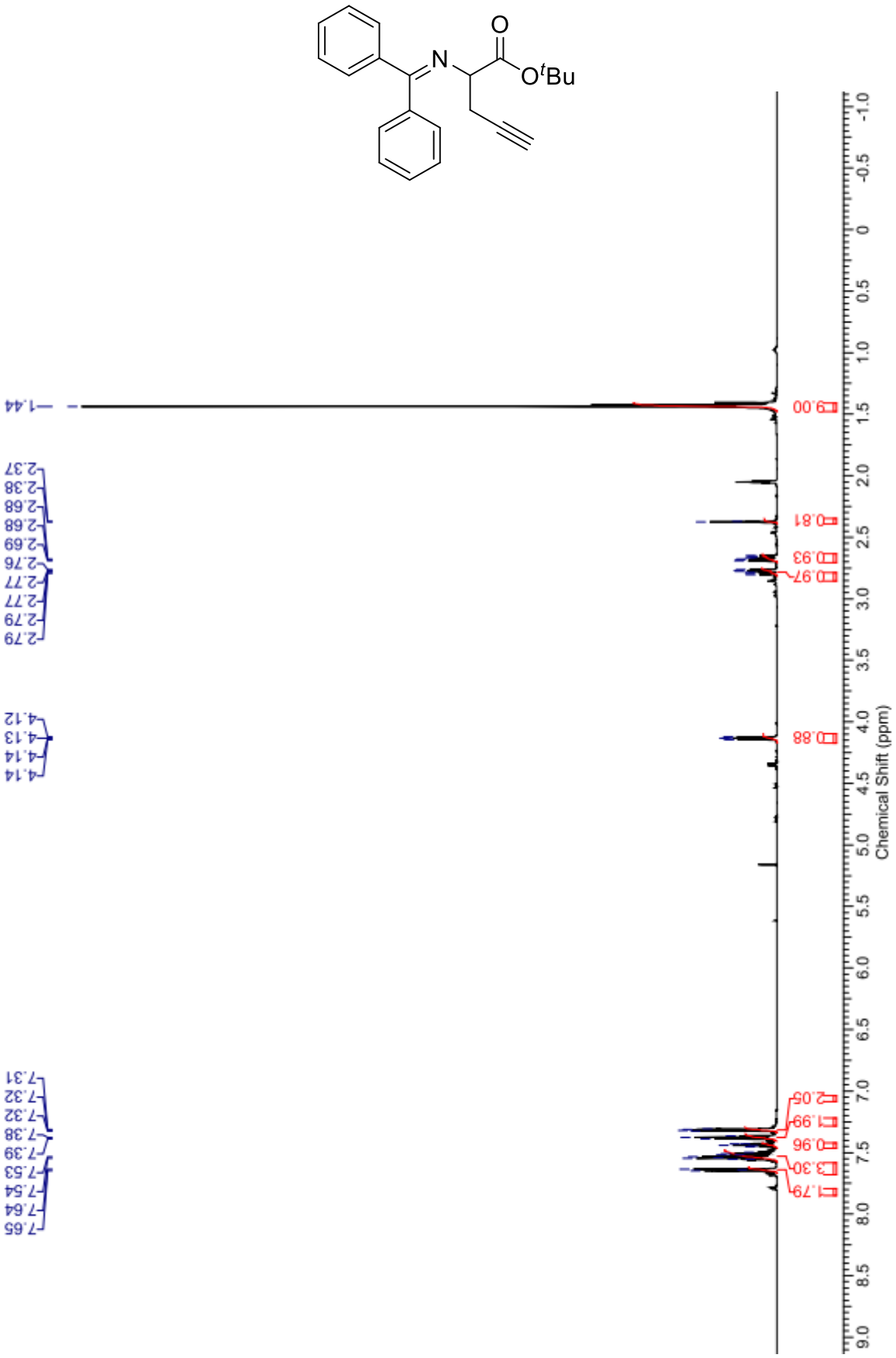

O
O
Me
OMe
O
O
Me
OMe
Br
impurity
25.79
26.57
29.34
31.30
33.18
33.79
49.99
52.52
52.69
62.10
66.94
174.16
204.08
Chemical Shift (ppm)

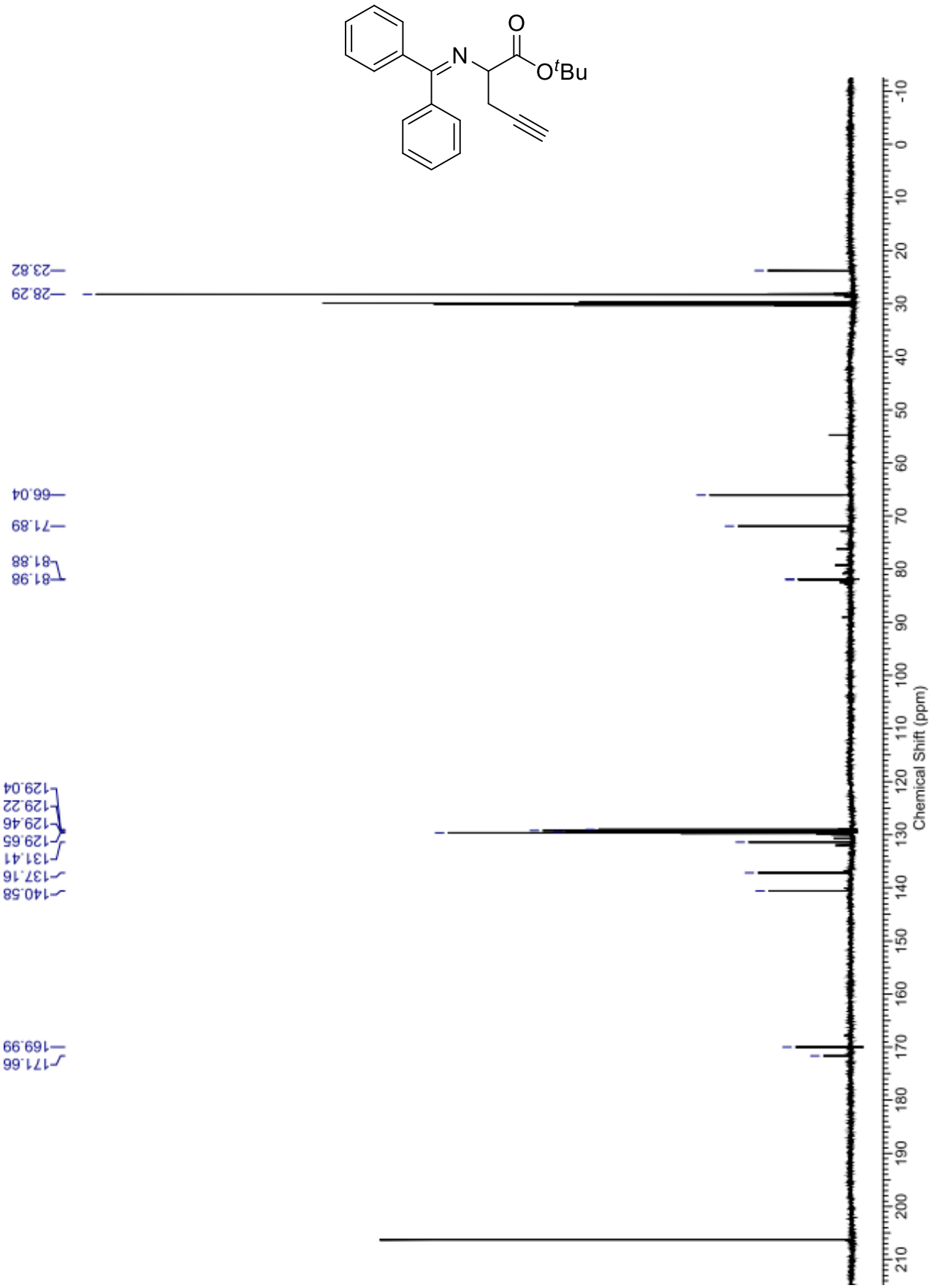

O
N
O^{t}Bu
1.41
3.06
3.07
3.08
3.09
3.20
3.21
3.23
4.08
4.08
4.09
4.10
6.69
7.06
7.08
7.19
7.20
7.35
7.36
7.37
7.37
7.42
7.57
7.58
9.00
1.12
1.12
1.03
1.84
1.91
2.88
5.70
1.91
Chemical Shift (ppm)

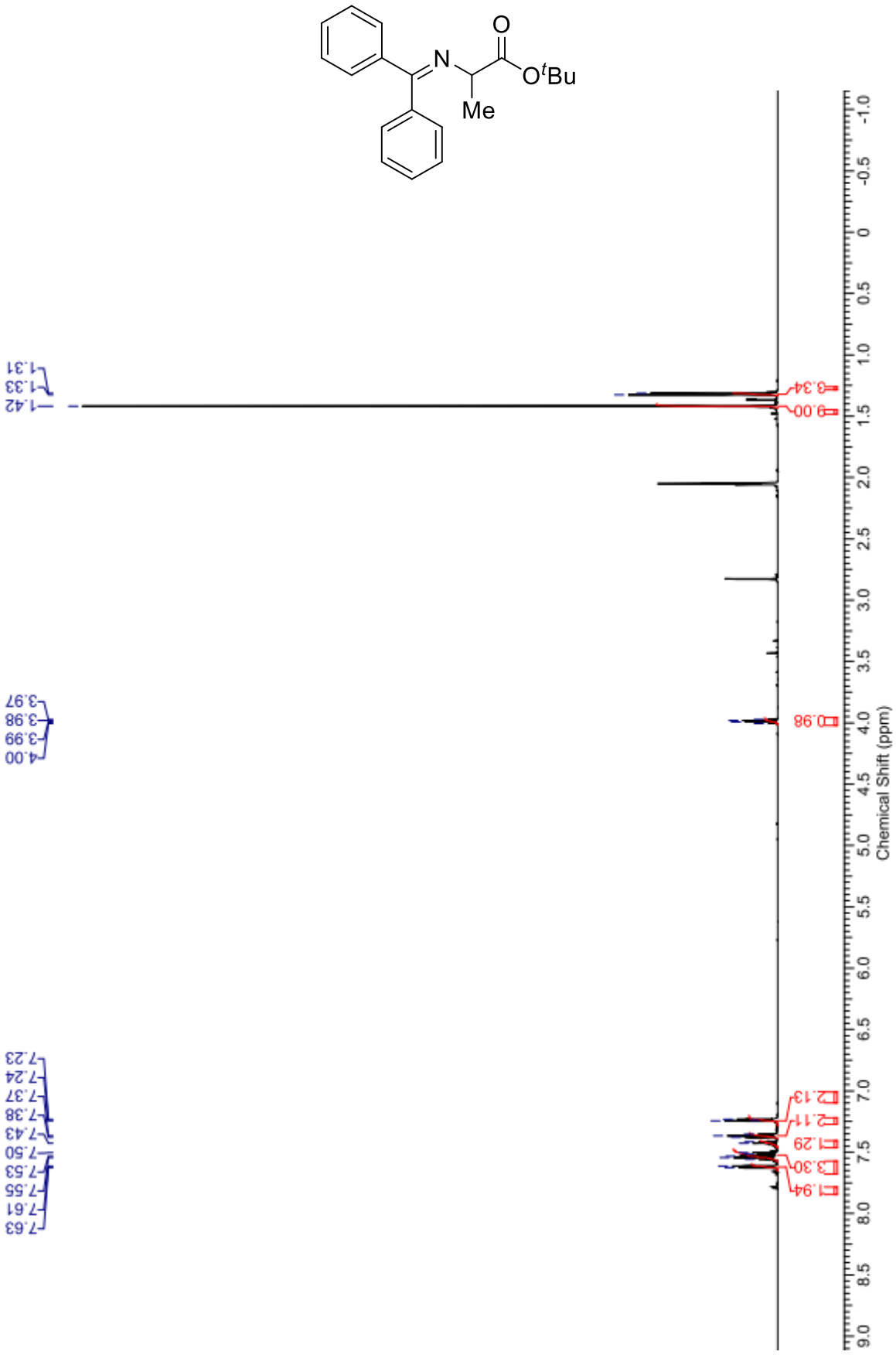

O
N
O^{t}Bu
32.44
44.44
73.17
85.52
131.31
132.78
133.17
133.35
133.61
134.97
135.34
141.47
143.64
144.74
174.79
175.20
Chemical Shift (ppm)

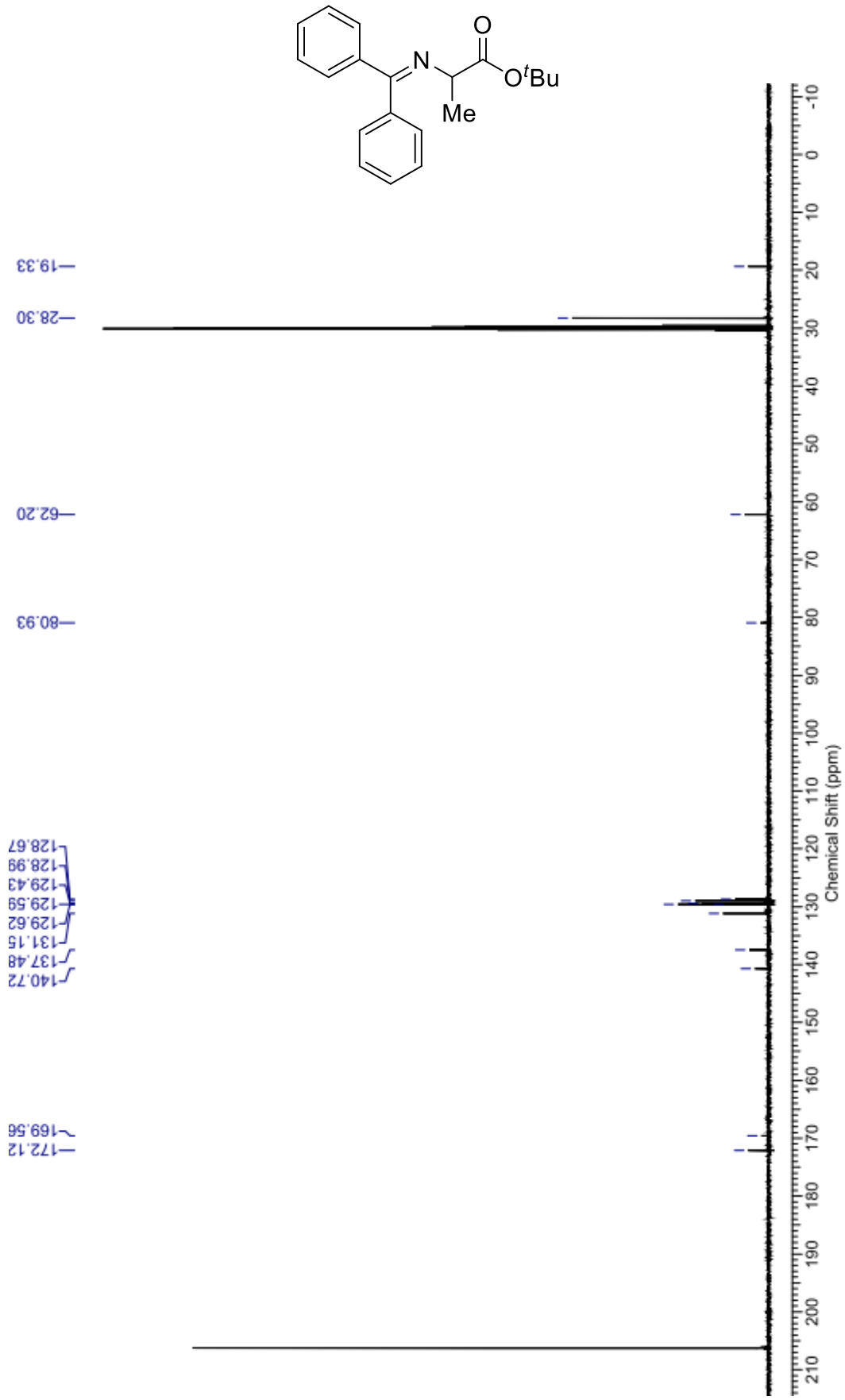

O
N
O^{t}Bu
1.42
2.55
2.63
2.63
3.96
3.97
3.98
3.99
4.97
4.98
4.98
5.00
5.03
5.03
5.06
5.74
5.75
7.22
7.23
7.37
7.38
7.51
7.52
7.53
7.53
7.62
7.63
9.00
0.97
0.96
0.88
2.05
0.89
1.72
2.92
3.20
1.66
Chemical Shift (ppm)

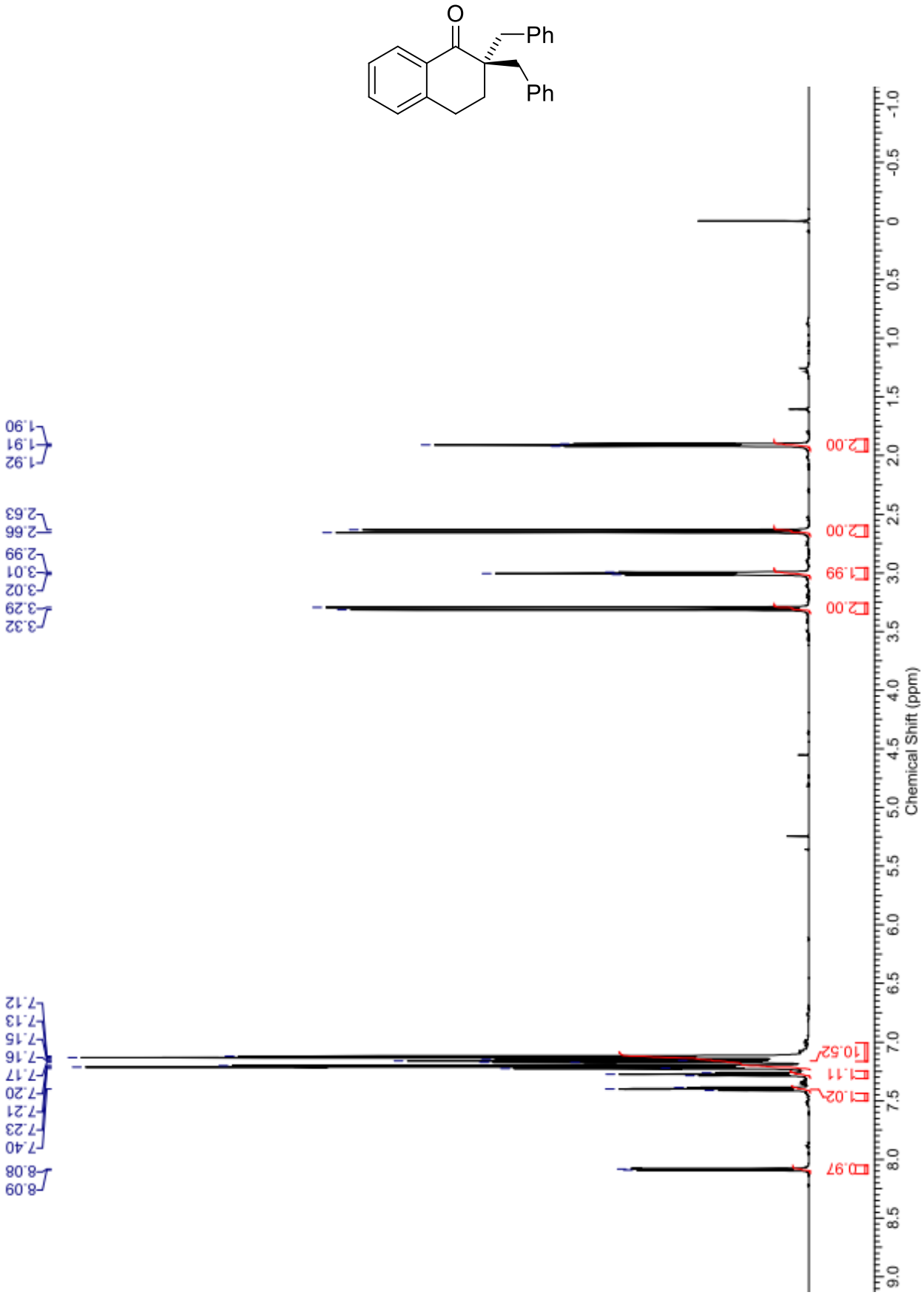

O
N
O^{t}Bu
28.37
38.89
66.90
81.33
117.61
128.89
129.02
129.53
129.64
131.25
135.99
137.58
140.74
170.50
171.08
Chemical Shift (ppm)

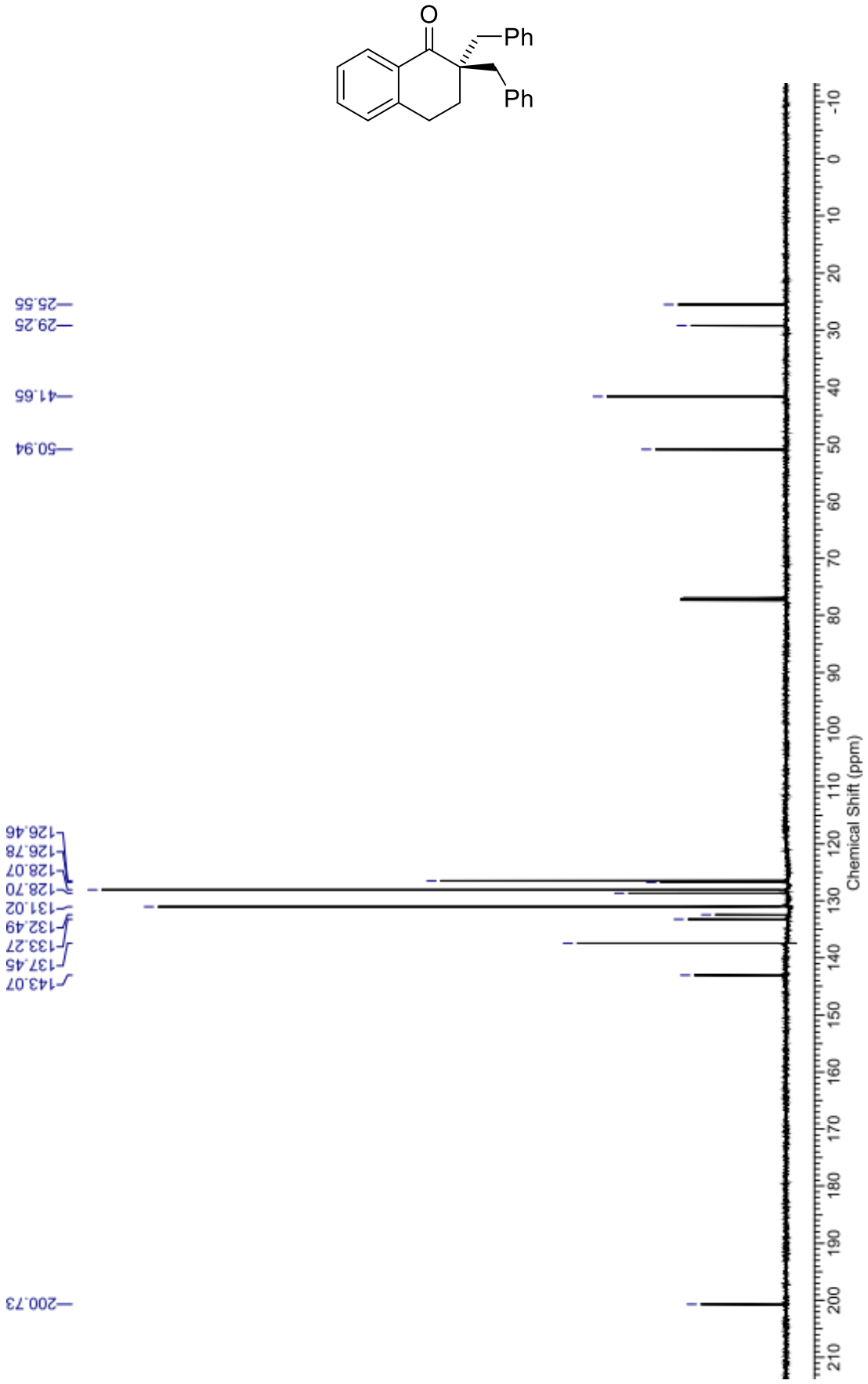

O
N
O
tBu
1.44
2.37
2.38
2.68
2.68
2.69
2.76
2.77
2.77
2.79
2.79
4.12
4.13
4.14
4.14
7.31
7.32
7.32
7.38
7.39
7.53
7.54
7.64
7.65
9.00
0.81
0.93
0.97
0.88
2.05
1.99
0.96
3.30
1.79
Chemical Shift (ppm)

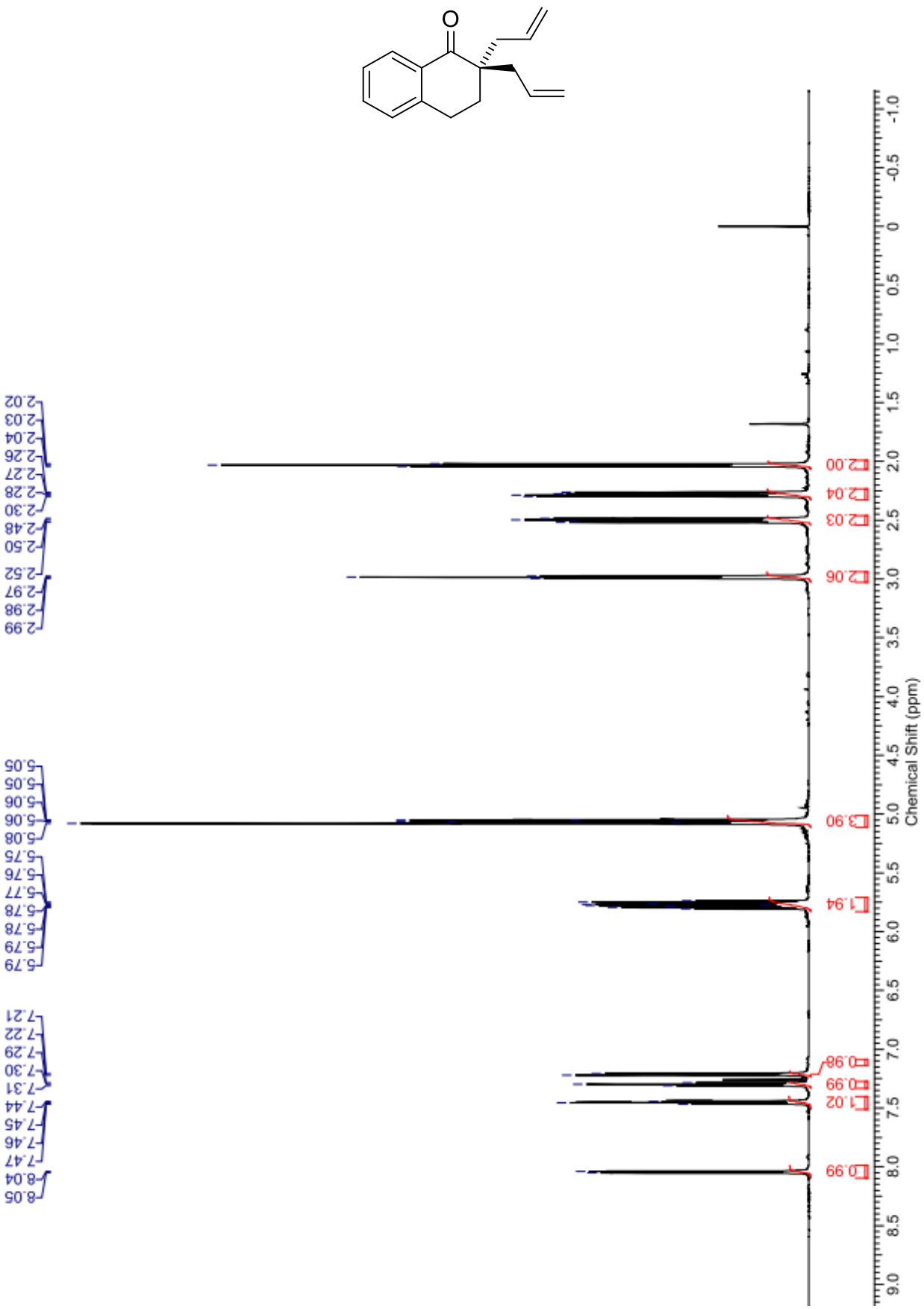

O
N
O^{t}Bu
23.82
28.29
66.04
71.89
81.88
81.98
129.04
129.22
129.46
129.65
131.41
137.16
140.58
169.99
171.66
Chemical Shift (ppm)

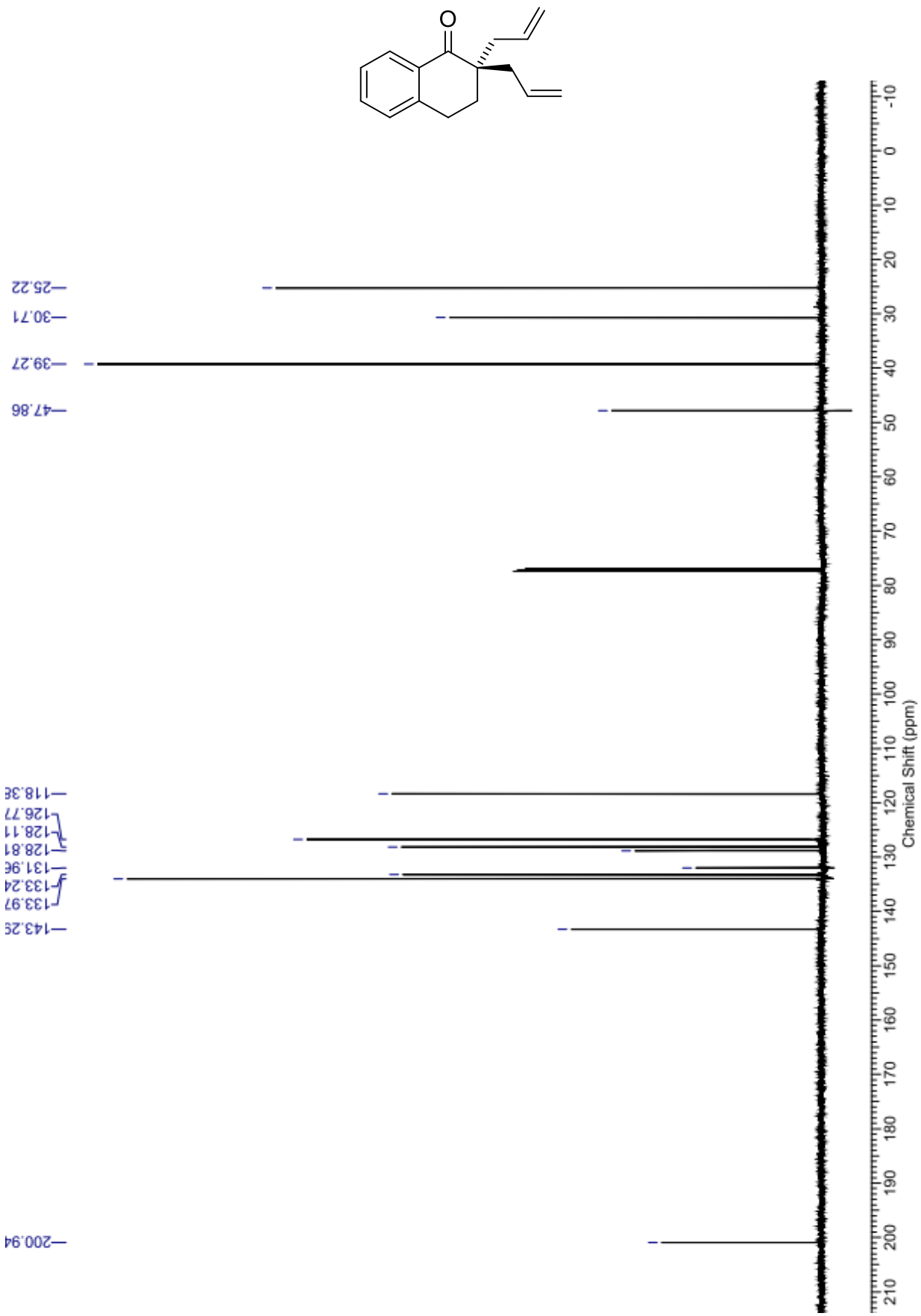

O
N
O^{t}Bu
Me
1.31
1.33
1.42
3.97
3.98
3.99
4.00
7.23
7.24
7.37
7.38
7.43
7.50
7.53
7.55
7.61
7.63
3.34
9.00
0.98
2.13
2.11
1.29
3.30
1.94
Chemical Shift (ppm)

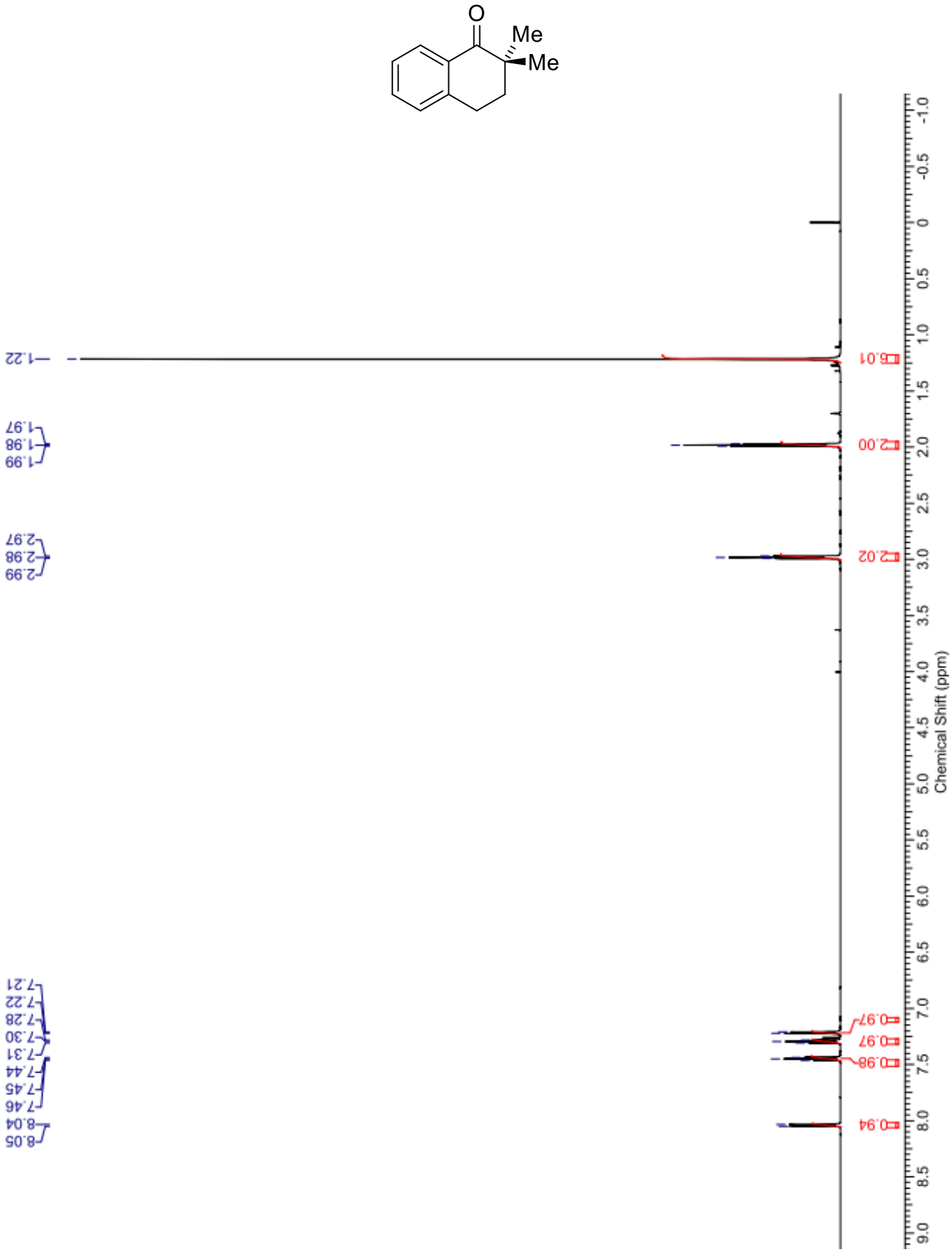

O
N
O^{t}Bu
Me
19.33
28.30
62.20
80.93
128.67
128.99
129.43
129.59
129.62
131.15
137.48
140.72
169.56
172.12
Chemical Shift (ppm)

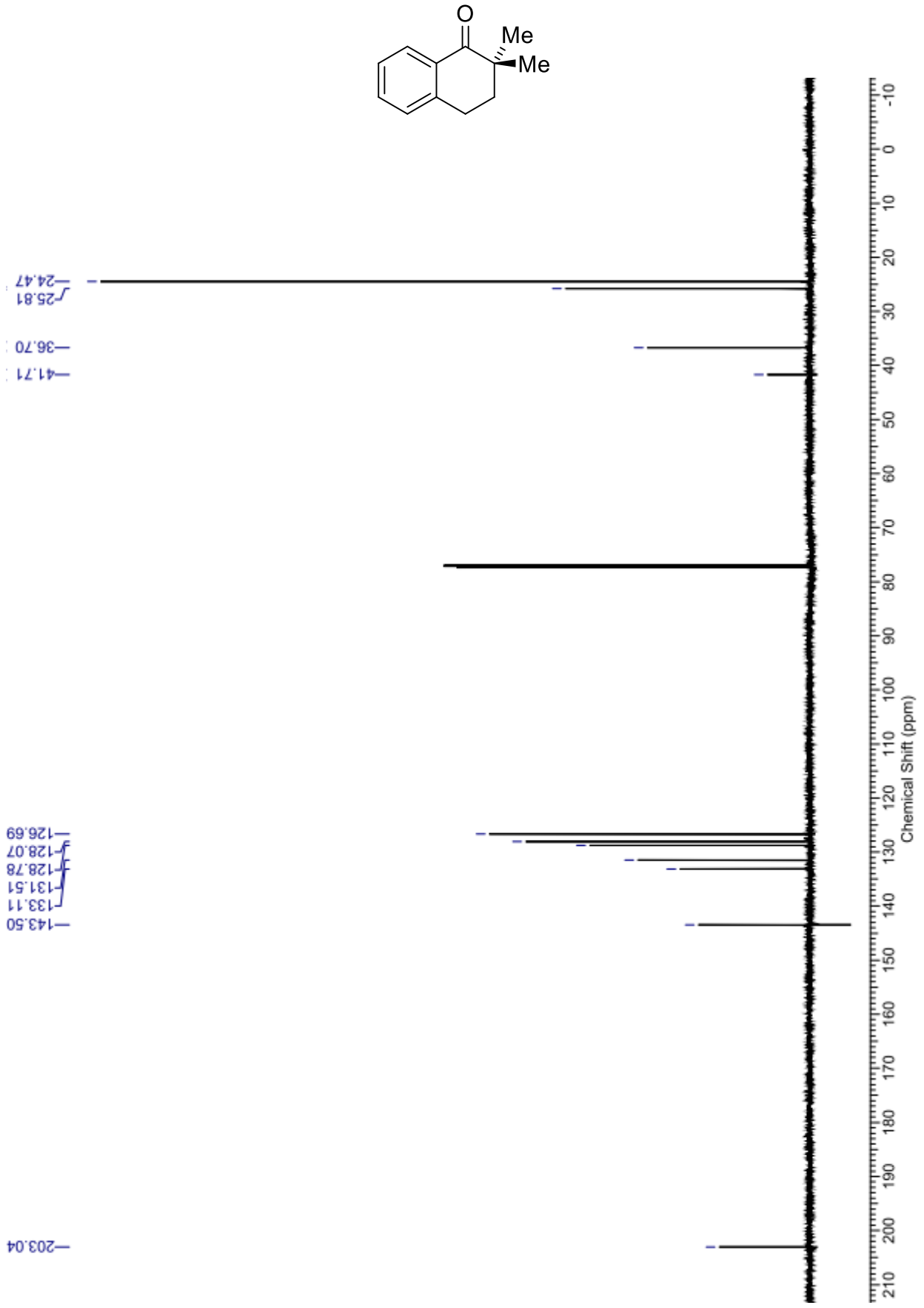

O
Ph
Ph
1.90
1.91
1.92
2.63
2.66
2.99
3.01
3.02
3.29
3.32
7.12
7.13
7.15
7.16
7.17
7.20
7.21
7.23
7.40
8.08
8.09
2.00
2.00
1.99
2.00
10.52
1.11
1.02
0.97
-1.0
-0.5
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
Chemical Shift (ppm)

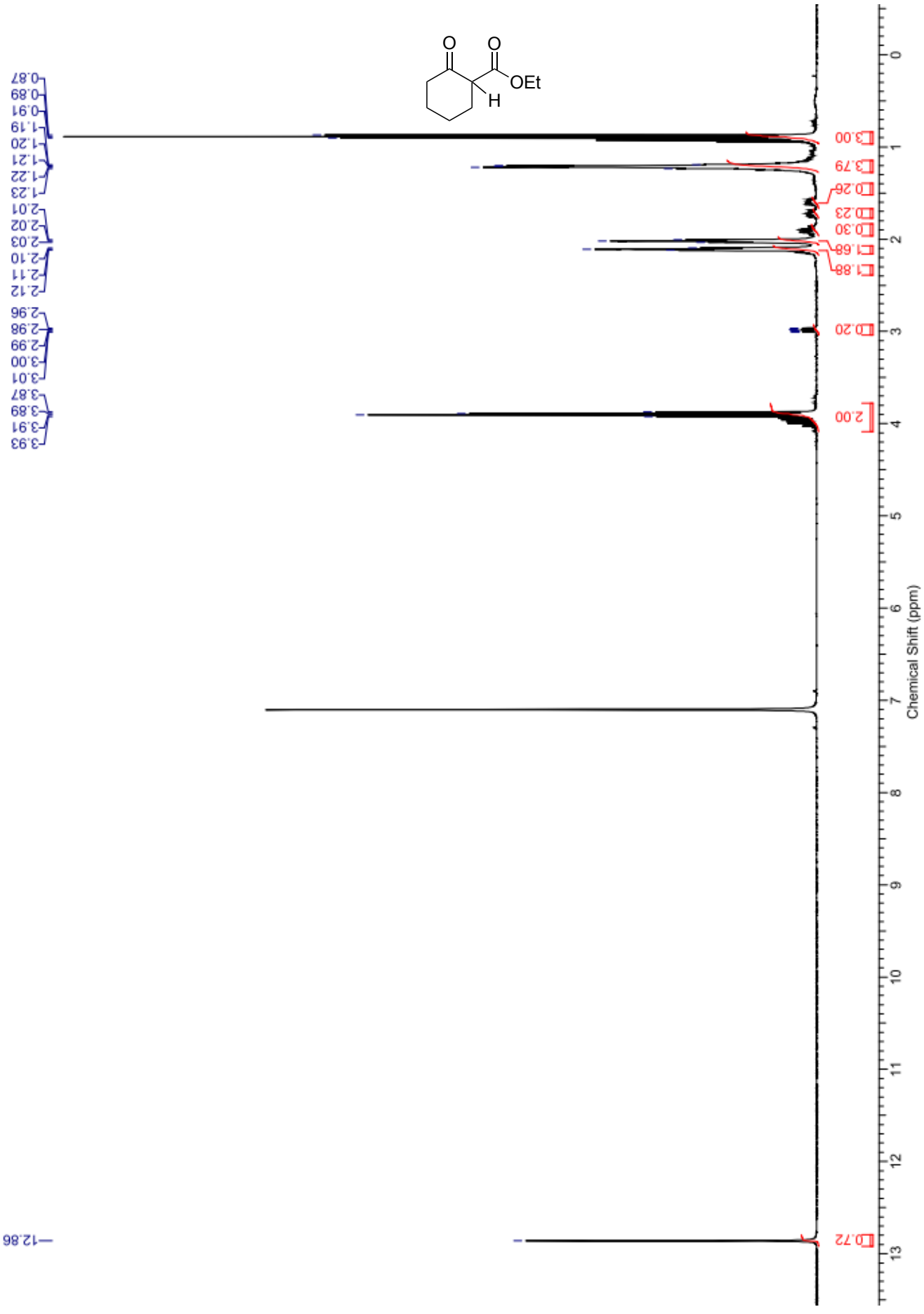

O
Ph
Ph
25.55
29.25
41.65
50.94
126.46
126.78
128.07
128.70
131.02
132.49
133.27
137.45
143.07
200.73
Chemical Shift (ppm)

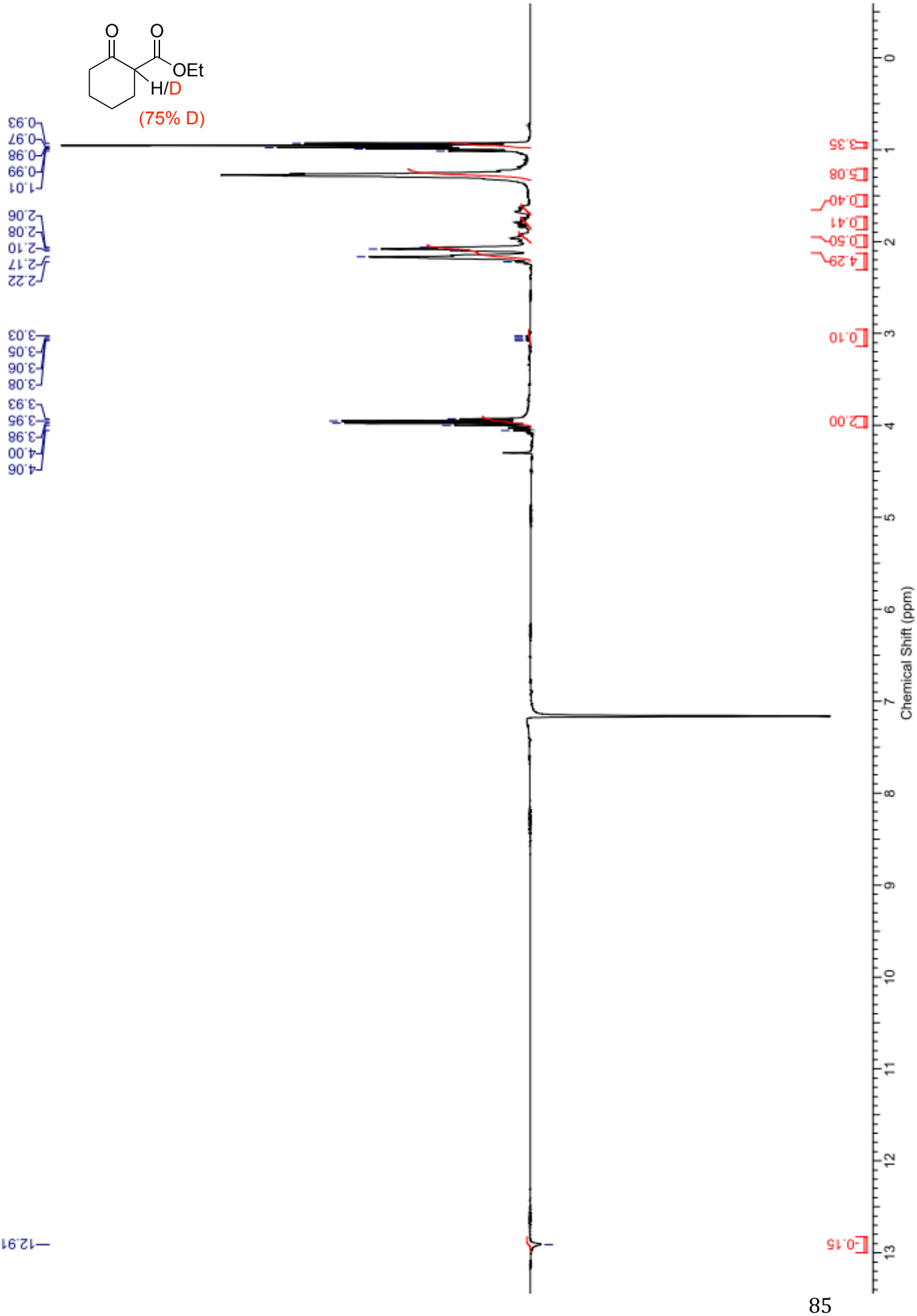

O
2.00
2.04
2.03
2.06
3.90
1.94
0.98
0.99
1.02
0.99
Chemical Shift (ppm)

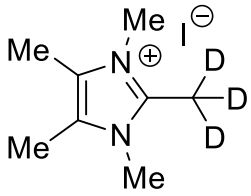

O
25.22
30.71
39.27
47.86
118.36
126.77
128.11
128.81
131.96
133.24
133.97
143.25
200.94
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Chemical Shift (ppm)


O
Me
Me
1.22
1.97
1.98
1.99
2.97
2.98
2.99
7.21
7.22
7.28
7.30
7.31
7.44
7.45
7.46
8.04
8.05
6.01
2.00
2.02
0.97
0.97
0.98
0.94
Chemical Shift (ppm)


O
Me
Me
24.47
25.81
36.70
41.71
126.69
128.07
128.78
131.51
133.11
143.50
203.04
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Chemical Shift (ppm)

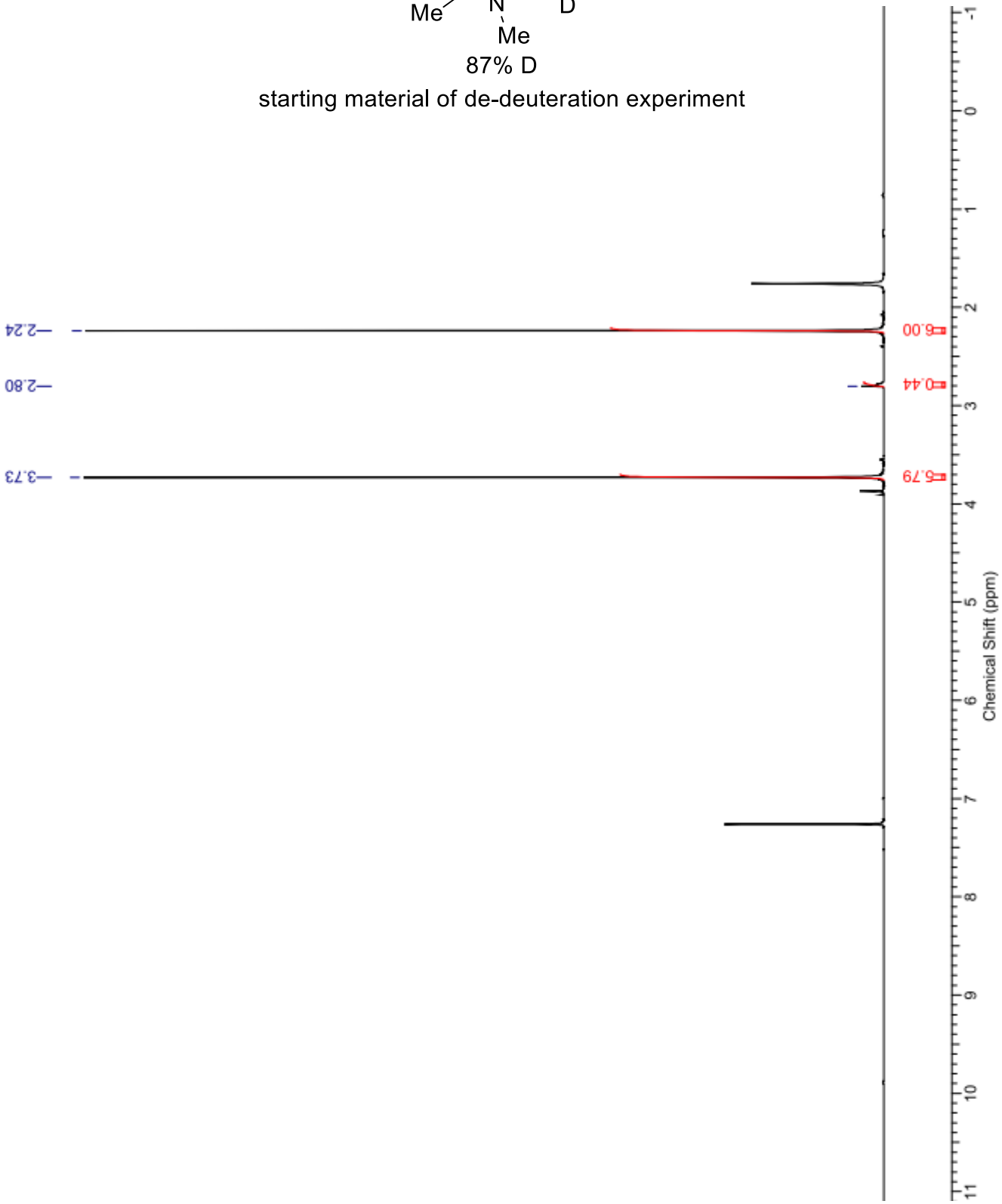

O
O
OEt
H
Chemical Shift (ppm)

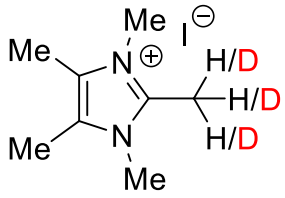

O
O
OEt
H/D
(75% D)
0.93
0.97
0.98
0.99
1.01
2.06
2.08
2.10
2.17
2.22
3.03
3.05
3.06
3.08
3.93
3.95
3.98
4.00
4.06
12.91
3.35
5.08
0.40
0.41
0.50
4.29
0.10
2.00
0.15
Chemical Shift (ppm)



87% D

starting material of de-deuteration experiment





product of de-deuteration experiment