2-Diazoacetoacetic Acid, an Efficient and Convenient Reagent for the Synthesis of Substituted α-Diazo-β-ketoesters

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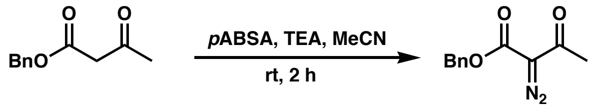
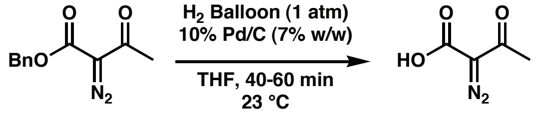
Supporting Information

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). 10% Pd/C was purchased from Aldrich Chemical Company, Inc. (20,569-9). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at 23 °C. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to $CDCl_3$ (δ 7.27). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Multiplicity abbreviations are: s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet, dt = doublet of triplets, td = triplet of doublets, and br = broad. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz), or a Varian Inova 500 (at 125 MHz) and are reported relative to $CDCl_3$ (δ 77.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.



Synthesis of Benzyl-α-diazo-acetoacetate: Triethylamine (15.0 mL, 78 mmol) was added to a solution of benzylacetoacetate (5.0 g, 26.0 mmol) and *p*ABSA (6.87 g, 28.6 mmol) in 65 mL of MeCN at 0 °C and under N_2. The reaction was allowed to warm to rt, and monitored by TLC (3:7 EtOAc:Hexanes). After 2 hours, the reaction was complete. The resulting suspension was filtered, and washed 3x's with MeCN. The filtrate was concentrated in vacuo to 1/3 of the initial volume. The remaining solution was diluted with Et_2O, washed 2x with H_2O, and then with brine. The organic layer was dried over Na_2SO_4, and concentrated in vacuo. The product was purified by passing it through a 3 in. column (SiO_2) using 1:4 EtOAc:Hexanes to remove *p*ABSA byproduct, and thus affording 5.05g (90% yield) of the diazo product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.28 (s, 2H), 2.50 (s, 3H).



4

General Procedure for the Hydrogenolysis of Benzyl Diazoacetoacetate: 10% Pd/C (17.5 mg, 7% w/w) was added to a solution of the benzyl ester (250 mg, 1.15 mmol) in THF (11.5 mL) at 23 °C The N_2 atmosphere was evacuated and backfilled with H_2 (balloon) 4x. The reaction was complete within 40-60 minutes as monitored by TLC (4:6 EtOAc:Hexanes).[1] Once finished, the reaction mixture was passed through a short pad of celite (Et_2O eluent), and the solvent was concentrated in vacuo to obtain 2-diazoacetoacetic acid (**4**) as a pale yellow solid that was used directly in the esterification step. Compound **4** was ca. 95% pure by ^{1}H NMR. *Note:* A pure (98%) sample of **4** was obtained by crystallization using Et_2O/Heptane and cooling at -20 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H); IR (film) 2932, 2150, 1722, 1601, 1302 cm^{-1}; UV-VIS (MeOH) $\lambda_{max} = 273$ nm; HRMS-EI (*m/z*): calc'd for $[C_4H_4N_2O_3]^+$, 128.0222; found, 128.0227.

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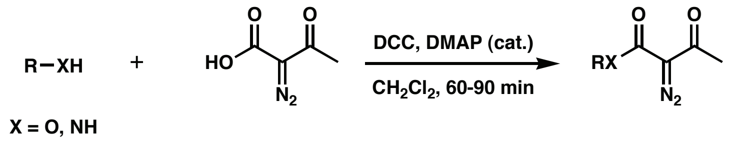
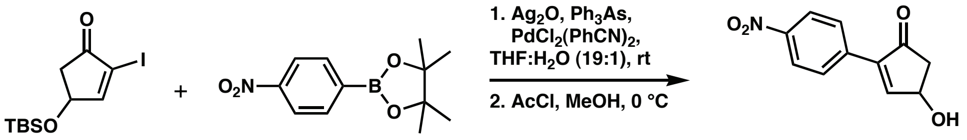
[1] If the hydrogenolysis is stopped after 20 minutes, only a trace of acetoacetic acid is observed by ^{1}H NMR. If the reaction is allowed to continue for 1-2 hours after completion, ca. 15% acetoacetic acid is observed by ^{1}H NMR. Longer times result in complete decomposition.



4

General Procedure for the Esterification Step: To a solution of substrate (0.50 mmol), **4** (1.2 mmol), and DMAP (0.050 mmol) in CH_2Cl_2 (3.3 mL) at 23 °C, was added in one portion DCC (1.0 mmol). *Note: For 1° alcohols, the reaction remained at 23 °C. However, for 2° alcohols, the reaction was heated to 40 °C after the addition of DCC.* The reaction was monitored by TLC, and the reaction was complete in 60-90 minutes. The reaction was filtered through a plug of celite (Et_2O eluent), and the resulting filtrate was partitioned between H_2O and Et_2O. The aqueous layer was extracted 2x with Et_2O. The organic extracts were combined, washed with $NaHCO_3$ (saturated), and then with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The products were purified by flash chromatography.

For the following compounds, "**Entry #**" refers to Table 1 of the publication.



1

Hydroxy enone 1. A flask containing 4-(*tert*-butyldimethylsilyloxy)-2-iodocyclopent-2-enone[2] (400 mg, 1.60 mmol) was charged with *p*-nitrophenyl pinacolato borate[3] (388 mg, 1.15 mmol), silver(I) oxide (800 mg, 3.45 mmol), and Ph_3As (35.2 mg, 0.120 mmol) at 23 °C under N_2. THF (5.5 mL) and H_2O (290 μL) was added, followed by addition of $PdCl_2(PhCN)_2$ (22.1 mg, 0.0580 mmol). The reaction was stirred for 15 minutes at 23 °C, at which point TLC (5:95 EtOAc:Hexanes) indicated the reaction was complete. The reaction was passed through a pad of celite (EtOAc eluent), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (7:93 EtOAc:Hexanes) to afford 405 mg (95% yield) of the Suzuki product.

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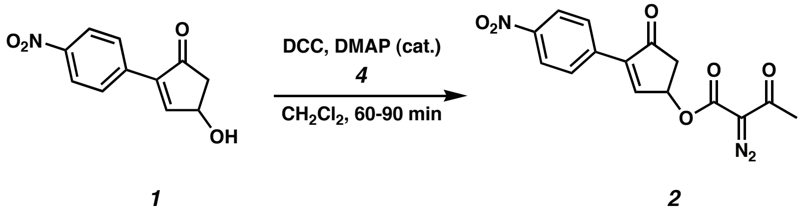
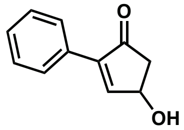
[2] Reul, F. S.; Braun, M. P.; Johnson, C. R. *Org. Synth.* **1996**, *75*, 69-72.

[3] Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, *68*, 3729-3732.

This product (125 mg, 0.370 mmol) was then added to a solution of AcCl (130 μL, 1.90 mmol) in MeOH (7.5 mL) at 0 °C and under N_2. The reaction continued to stir for 20 minutes, upon which TLC (4:6 EtOAc:Hexanes) showed consumption of the Suzuki product. The reaction was diluted with brine and EtOAc. The layers were separated, and the aqueous layer was washed 2x with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. TBSOH is removed azeotropically with toluene to afford pure **1** (99% yield). R_f = 0.20 (1:1 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25-8.20 (m, 2H), 7.91-7.87 (m, 2H), 7.82 (d, *J* = 2.4 Hz, 1H), 5.15 (m, 1H), 3.05 (dd, *J* = 18.9, 6.6 Hz, 1H), 2.60 (dd, *J* = 18.6, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 159.3, 147.8, 142.1, 136.7, 128.4, 123.7, 67.7, 45.7; IR (film) 3415, 1711, 1516, 1348 cm^{-1}; HRMS-EI (*m/z*): calc'd for $[C_{11}H_9NO_4]^+$, 219.0532; found, 219.0506.

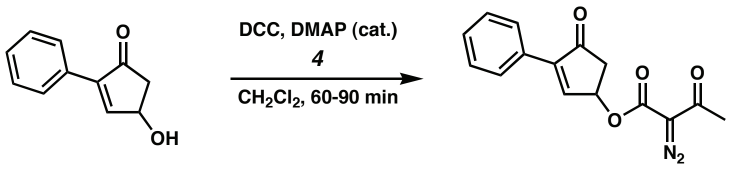


Diazoester 2 (Entry 1). See General Esterification Procedure. Product was purified by flash chromatography (1:1 EtOAc:Hexanes). R_f = 0.30 (3:7 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (m, 2H), 7.97-7.93 (m, 2H), 7.87 (d, *J* = 2.7 Hz, 1H), 6.09 (dt, *J* = 6.6, 2.7 Hz, 1H), 3.18 (dd, *J* = 18.9, 6.6 Hz, 1H), 2.70 (dd, *J* = 18.9, 2.1 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 189.4, 160.9, 153.8, 148.3, 144.4, 135.9, 128.6, 124.0, 70.4, 42.3, 28.3; IR (film) 2145, 1717, 1519, 1350, 1317 cm^{-1}; HRMS-EI (*m/z*): calc'd for $[C_{15}H_{11}N_3O_6]^+$, 329.0648; found, 329.0647.



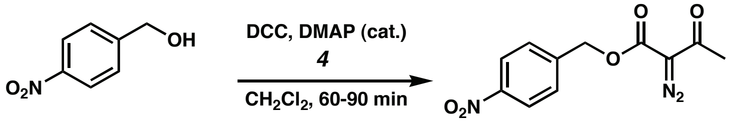
5

Hydoxy enone 5. This compound was prepared in the same manner as **1**, using phenyl boronic acid as the coupling partner. It was also made via a known route, see: D'Auria, M. *Heterocycles* **2000**, *52*, 185-194.

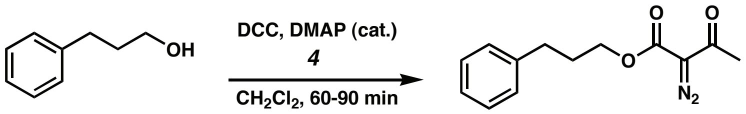


5 **6**

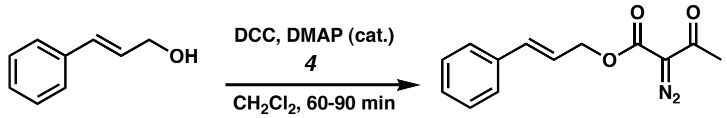
Diazoester 6 (Entry 2). See General Esterification Procedure. Product was purified by flash chromatography (15:85 EtOAc:Hexanes). R_f = 0.40 (3:7 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H), 7.68 (d, *J* = 2.7 Hz, 1H), 7.42-7.40 (m, 2H), 6.05 (dt, *J* = 6.6, 2.4 Hz, 1H), 3.10 (dd, *J* = 18.6, 6.6 Hz, 1H), 2.66 (dd, *J* = 18.6, 1.8 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 189.6, 160.9, 150.8, 146.3, 129.7, 129.6, 128.5, 127.6, 70.7, 42.4, 28.3; IR (film) 2144, 1716, 1654, 1313 cm^{-1}; HRMS-FAB (*m/z*): calc'd for $[C_{15}H_{13}N_2O_4]^+$, 285.0875; found, 285.0869.



Diazoester (Entry 3)[4]. See General Esterification Procedure. Product was purified by flash chromatography (1:4 EtOAc:Hexanes). R_f = 0.40 (3:7 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 5.35 (s, 2H), 2.47 (s, 2H); IR (film) 2148, 1711, 1344 cm^{-1}.



Diazoester (Entry 4). See General Esterification Procedure. Product was purified by flash chromatography (1:5 EtOAc:Hexanes). R_f = 0.45 (3:7 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.23-7.16 (m, 2H), 4.27 (t, *J* = 6.3 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.08-2.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 161.2, 140.6, 128.4, 128.2, 126.1, 64.6, 32.0, 30.0, 28.1; IR (film) 2141, 1716, 1660, 1314 cm^{-1}; HRMS-EI (*m/z*): calc'd for $[C_{13}H_{15}N_2O_3]^+$, 247.1083; found, 247.1089.



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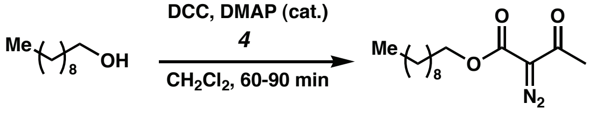
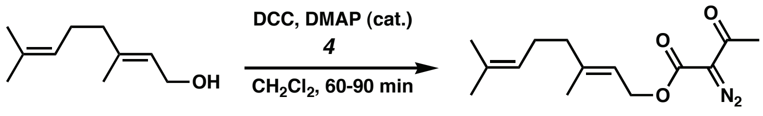
[4] Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936-2939.

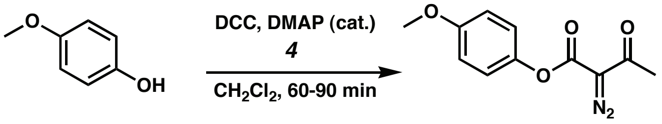
Diazoester (Entry 5). See General Esterification Procedure. Product was purified by flash chromatography (15:85 EtOAc:Hexanes). R_f = 0.50 (2:8 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.28 (m, 5H), 6.70 (d, *J* = 15.6 Hz, 1H), 6.31 (dt, *J* = 15.6, 6.6 Hz, 1H), 4.90 (dd, *J* = 6.6, 1.5 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 161.1, 135.7, 135.3, 128.6, 128.3, 126.6, 122.2, 65.8, 28.2; IR (film) 2140, 1716, 1659, 1316 cm^{-1}; HRMS-EI (*m/z*): calc'd for $[C_{13}H_{12}N_2O_3]^+$, 244.0848; found, 244.0839.



Diazoester (Entry 6). See General Esterification Procedure. Product was purified by flash chromatography (5:95 EtOAc:Hexanes). R_f = 0.50 (2:8 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (t, *J* = 6.6 Hz, 2H), 2.49 (s, 3H), 1.71-1.66 (m, 2H), 1.33-1.27 (m, 14H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 161.5, 65.5, 31.8, 29.43, 29.40, 29.2, 29.1, 28.6, 28.2, 25.7, 22.6, 14.1; IR (film) 2927, 2856, 2138, 1721, 1663, 1313 cm^{-1}; HRMS-EI (*m/z*): calc'd for $[C_{14}H_{25}N_2O_3]^+$, 269.1865; found, 269.1864.

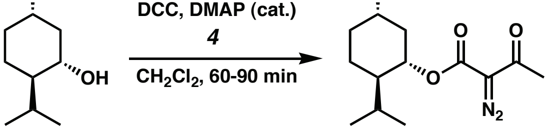


Diazoester (Entry 7). See General Esterification Procedure. Product was purified by flash chromatography (1:9 EtOAc:Hexanes). R_f = 0.50 (2:8 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (dt, *J* = 3.6, 1.2 Hz, 1H), 5.10-5.04 (m, 1H), 4.75 (d, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 2.13-2.05 (m, 4H), 1.74 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 161.4, 143.4, 131.9, 123.5, 117.6, 62.1, 39.4, 28.1, 26.1, 25.6, 17.6, 16.4; IR (film) 2138, 1717, 1662, 1309 cm^{-1}; HRMS-FAB (*m/z*): calc'd for $[C_{14}H_{21}N_2O_3]^+$, 265.1552; found, 265.1548.

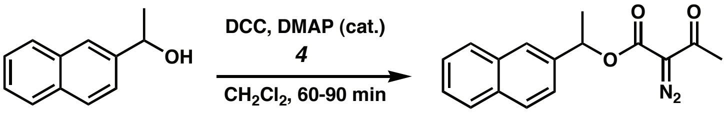


Diazoester (Entry 8). See General Esterification Procedure. Product was purified by flash chromatography (15:85 EtOAc:Hexanes). R_f = 0.20 (2:8 EtOAc:Hexanes); ^{1}H NMR (300 MHz,

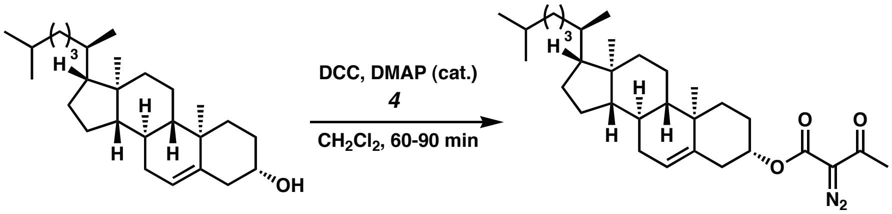
$CDCl_3$) δ 7.28-7.23 (m, 2H), 7.13-7.08 (m, 2H), 4.00 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 160.4, 157.6, 143.0, 122.3, 114.5, 55.6, 28.3; IR (film) 2142, 1732, 1507, 1324, 1191 cm^{-1}; HRMS-FAB (*m/z*): calc'd for $[C_{11}H_{11}N_2O_4]^+$, 235.0179; found, 235.0174.



Diazoester (Entry 9). See General Esterification Procedure. Product was purified by flash chromatography (1:9 EtOAc:Hexanes). All spectroscopic data is identical to that reported by Doyle.[5]



Diazoester (Entry 10). See General Esterification Procedure. Product was purified by flash chromatography (1:9 EtOAc:Hexanes). R_f = 0.20 (1:9 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.83 (m, 4H), 7.55-7.50 (m, 3H), 6.21 (q, *J* = 6.6 Hz, 1H), 2.49 (s, 3H), 1.72 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 160.7, 138.0, 133.1, 133.0, 128.6, 128.0, 127.6, 126.4, 126.3, 125.2, 123.6, 73.8, 28.2, 22.1; IR (film) 2140, 1715, 1658, 1305 cm^{-1}; HRMS-FAB (*m/z*): calc'd for $[C_{16}H_{15}N_2O_3]^+$, 283.1083; found, 283.1079.



Diazoester (Entry 11). See General Esterification Procedure. Product was purified by flash chromatography (5:95 EtOAc:Hexanes). ^{1}H NMR ($CDCl_3$) is identical to that reported by Doyle.[6]

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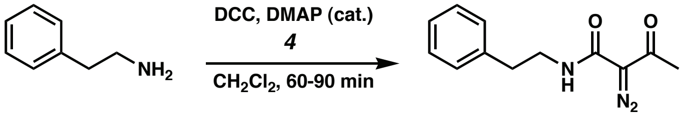
[5] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958-964.



Diazoamide (Entry 12). See General Esterification Procedure. Product was purified by flash chromatography (4:6 EtOAc:Hexanes). R_f = 0.25 (4:6 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.32-7.19 (m, 5H), 3.60 (q, *J* = 6.9 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 160.5, 138.9, 129.0, 128.8, 126.8, 41.4, 36.1, 26.9; IR (film) 3309, 2124, 1667, 1538, 1312 cm^{-1}; HRMS-EI (*m/z*): calc'd for $[C_{12}H_{13}N_3O_2]^+$, 231.1008; found, 231.1007.

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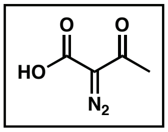
[6] Doyle, M. P.; Davies, S. B.; May, E. J. *J. Org. Chem.* **2001**, *66*, 8112-8119.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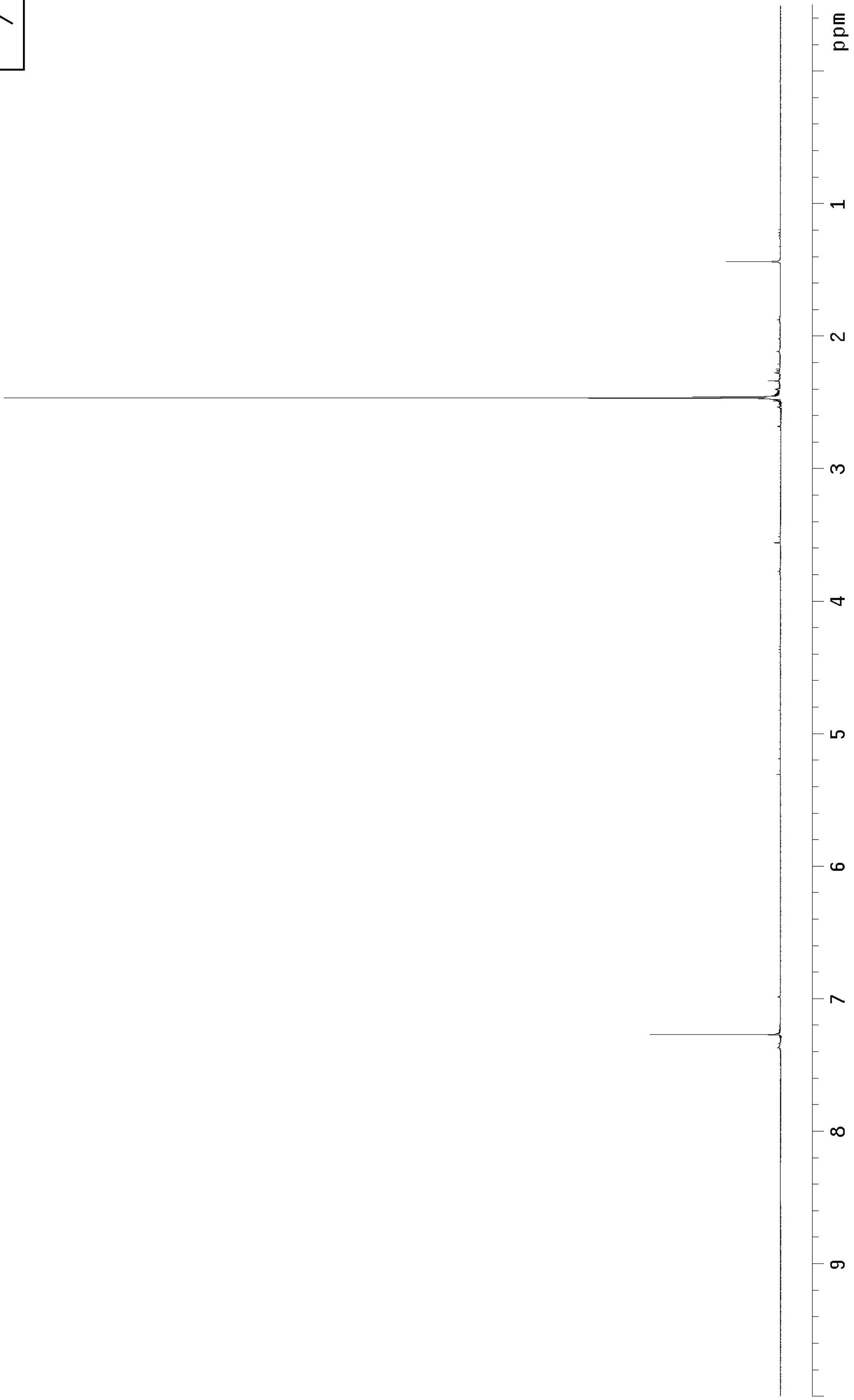
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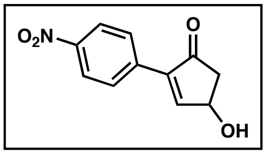
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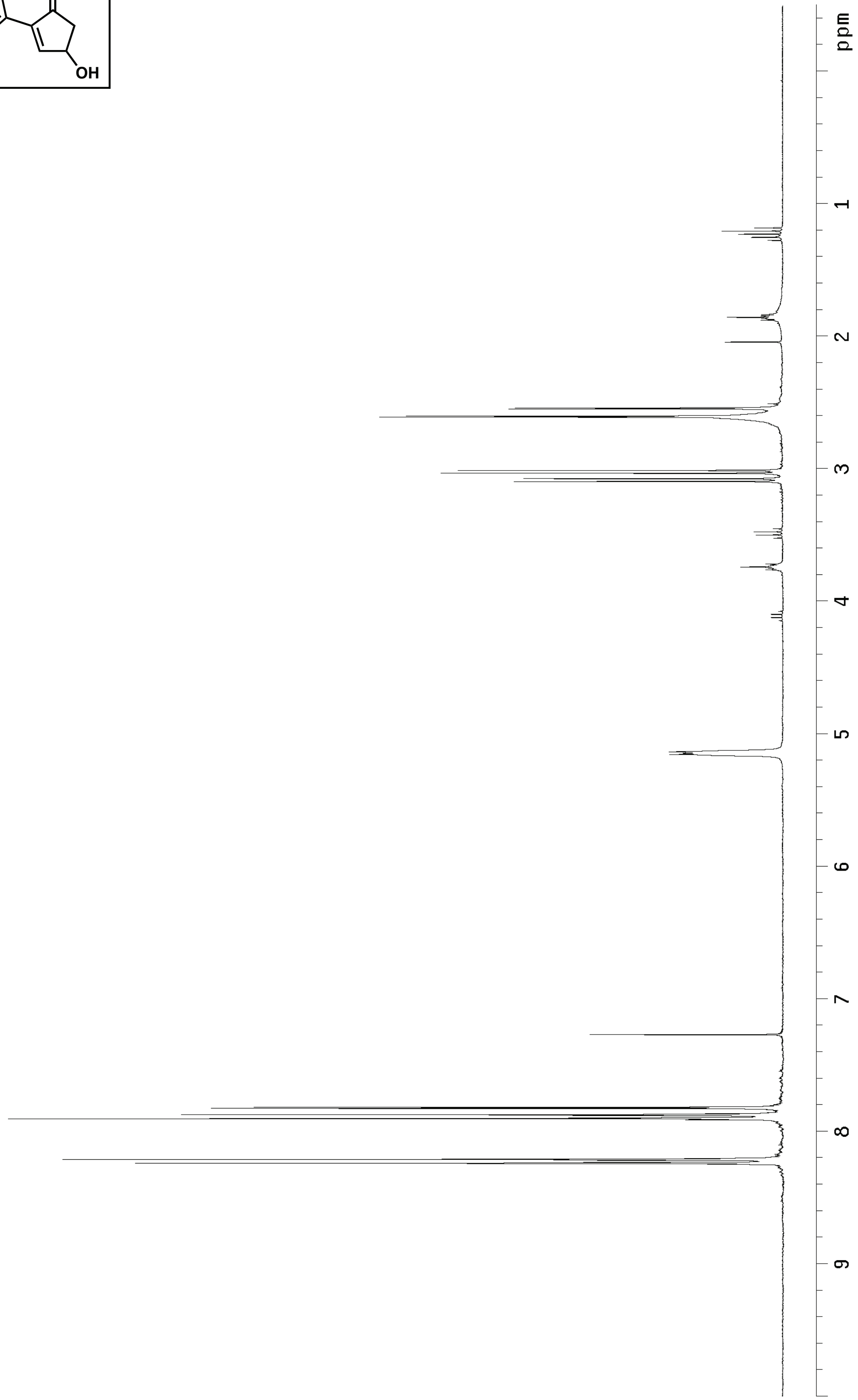
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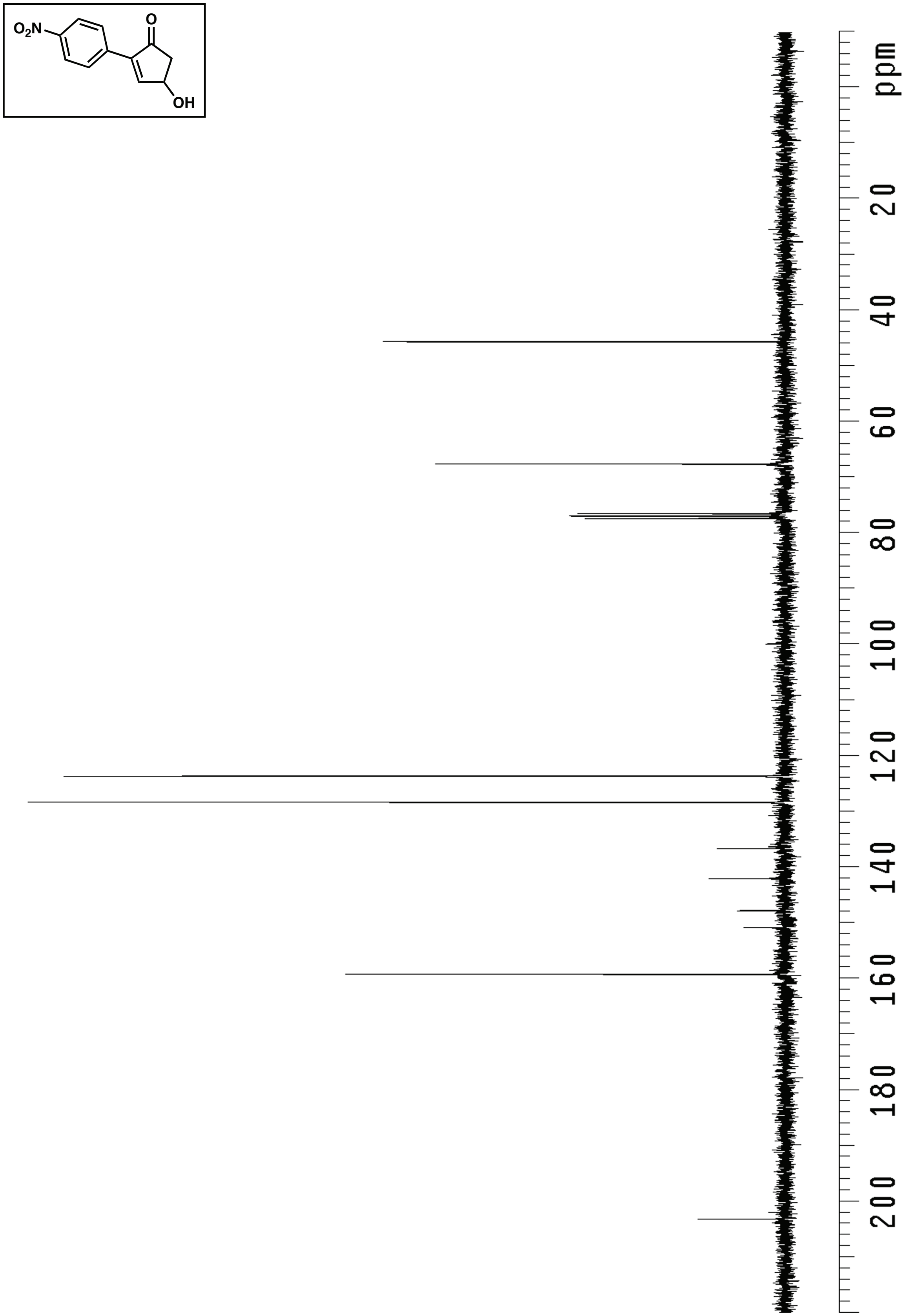
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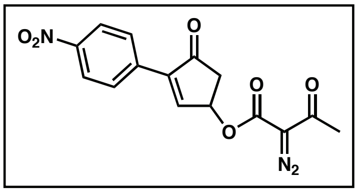
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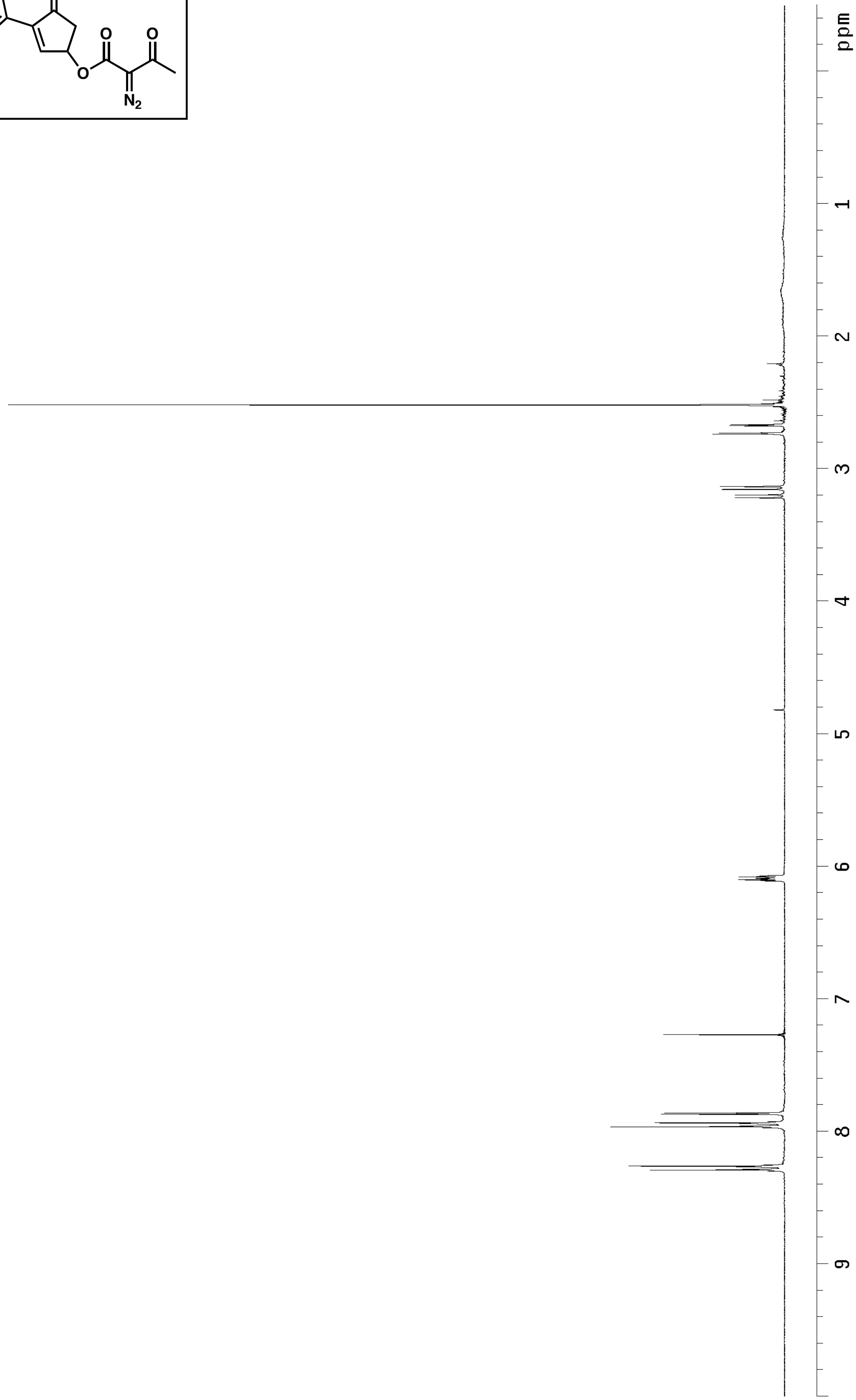
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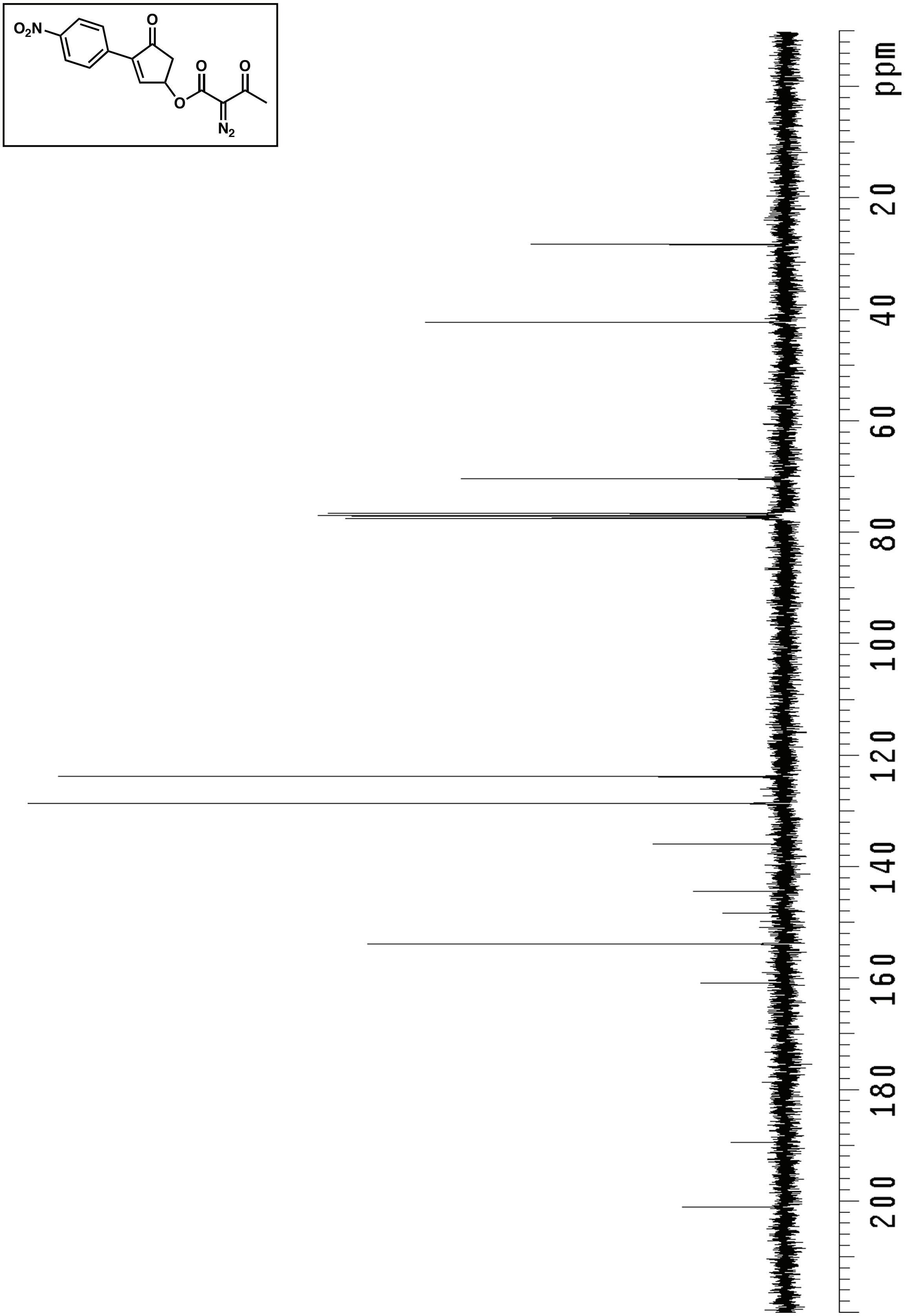
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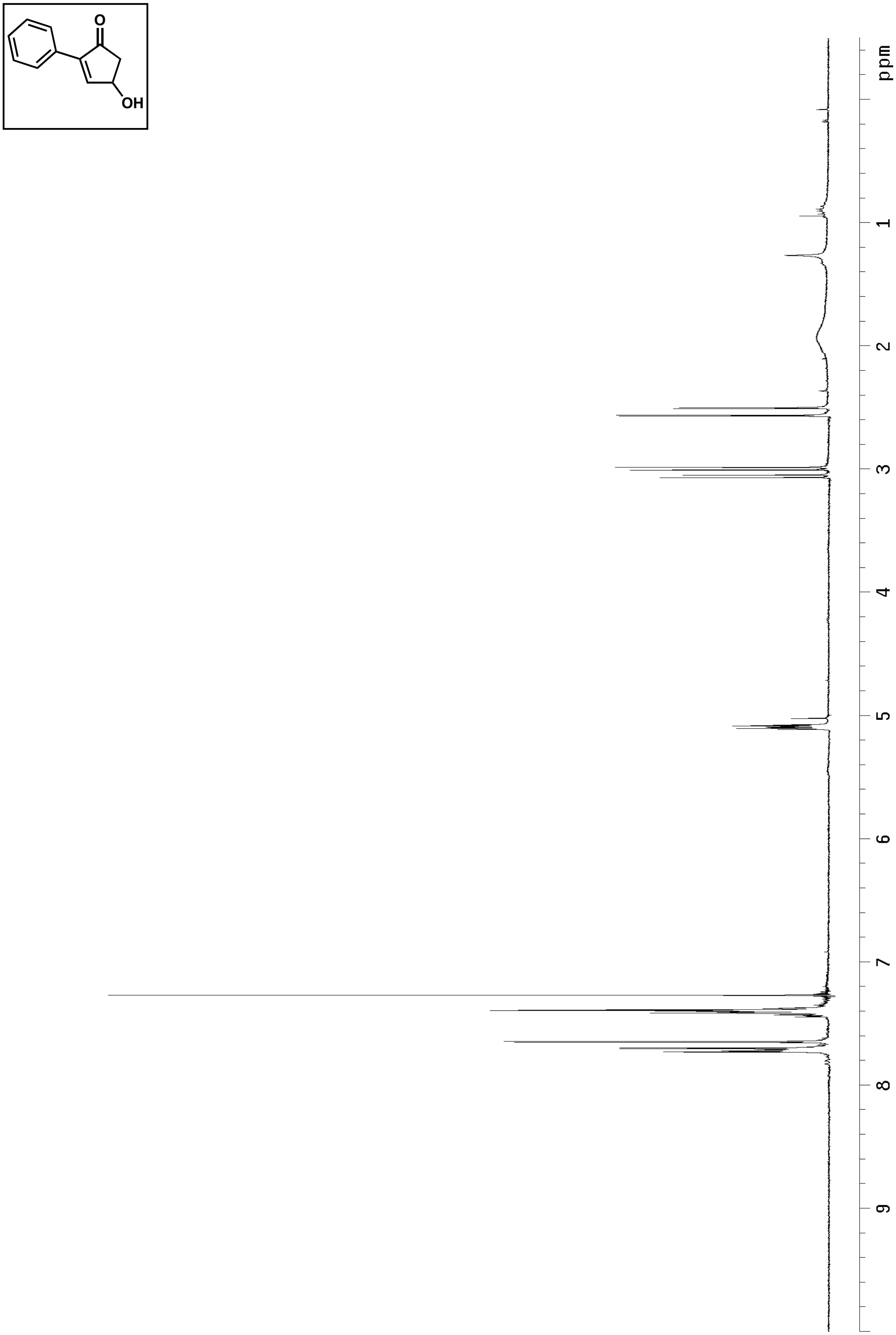
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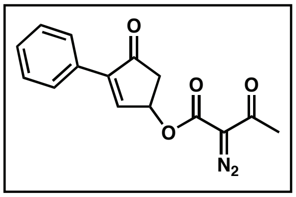
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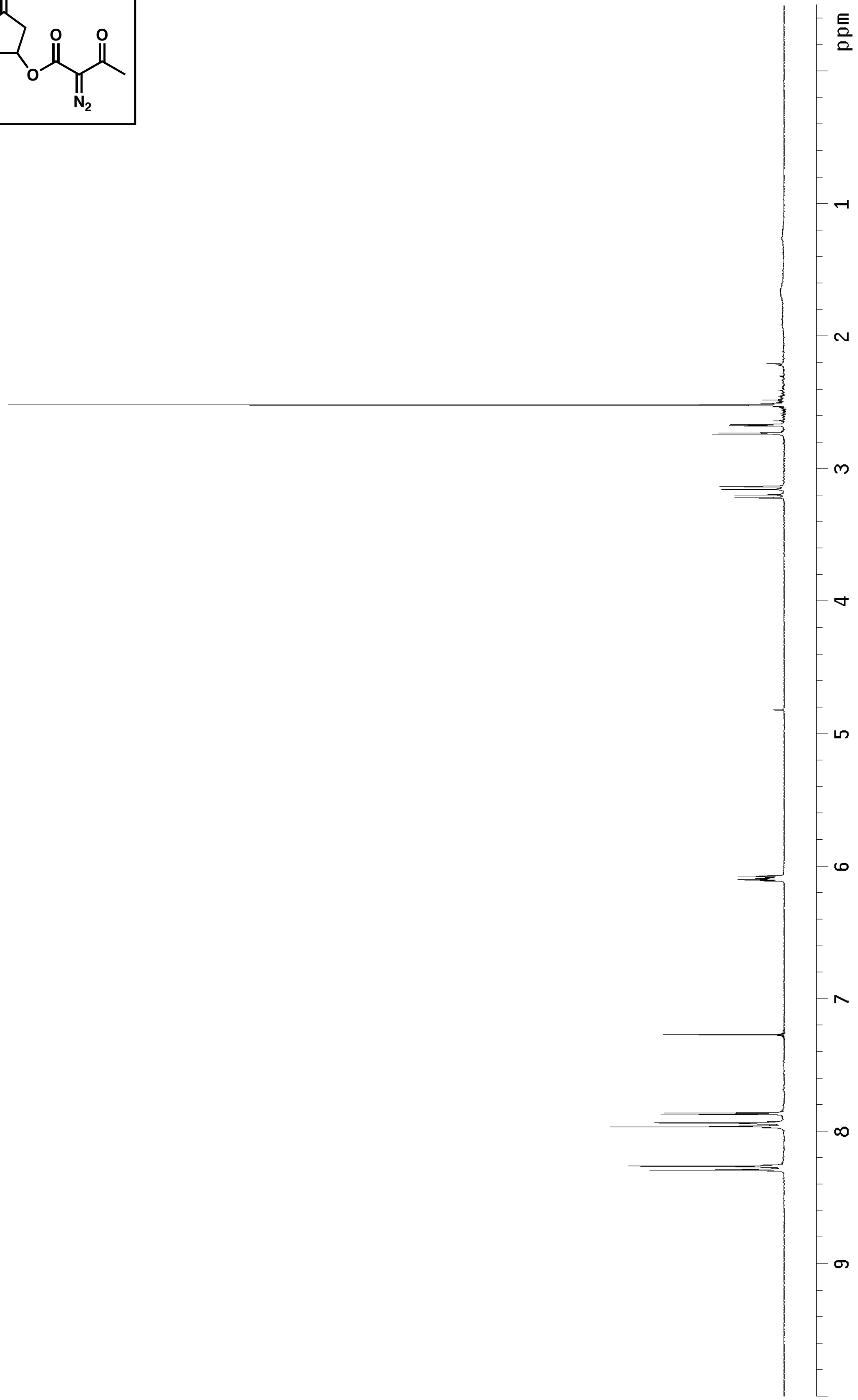
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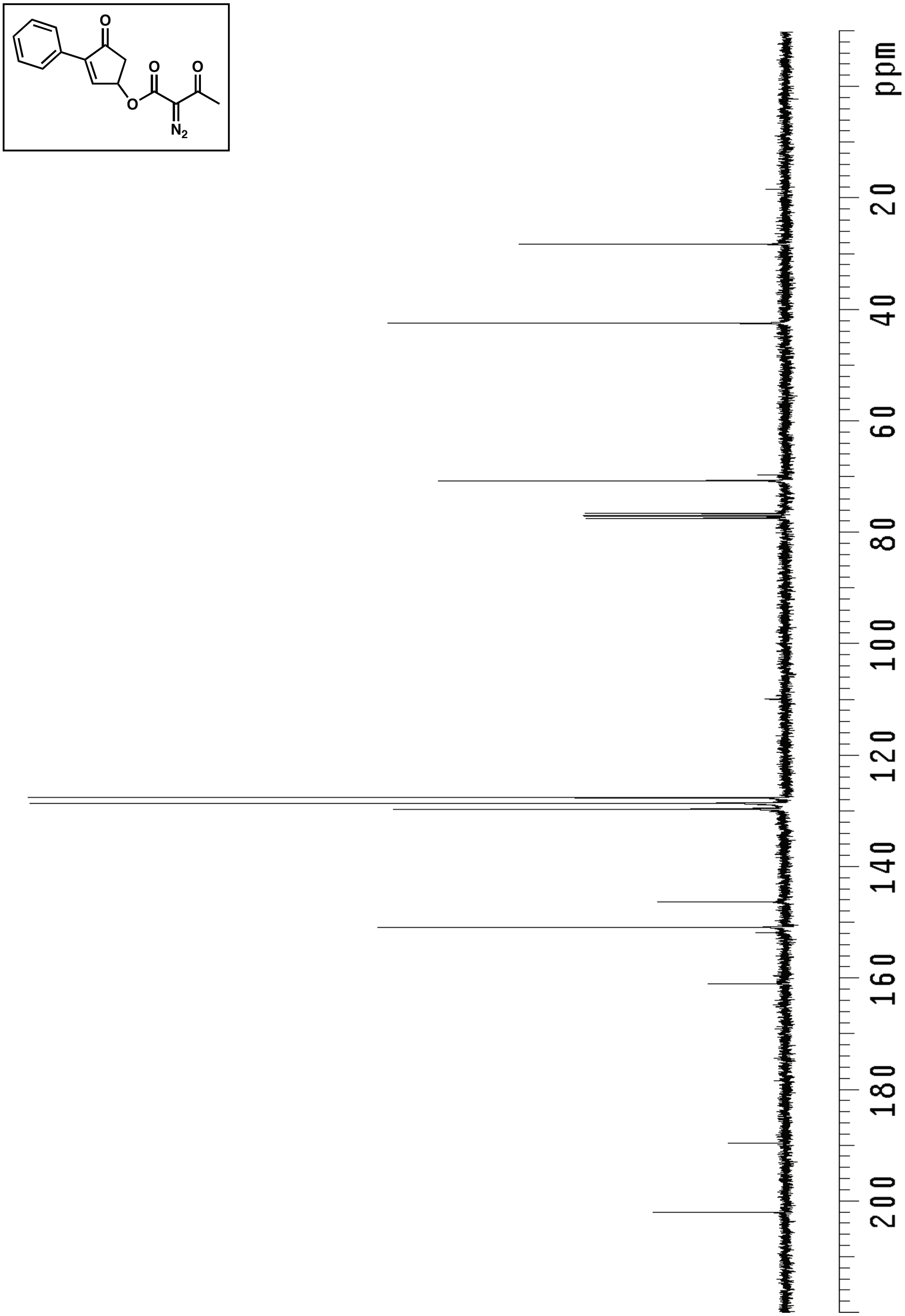
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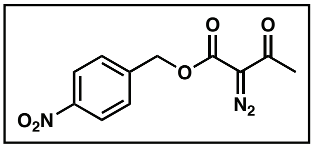
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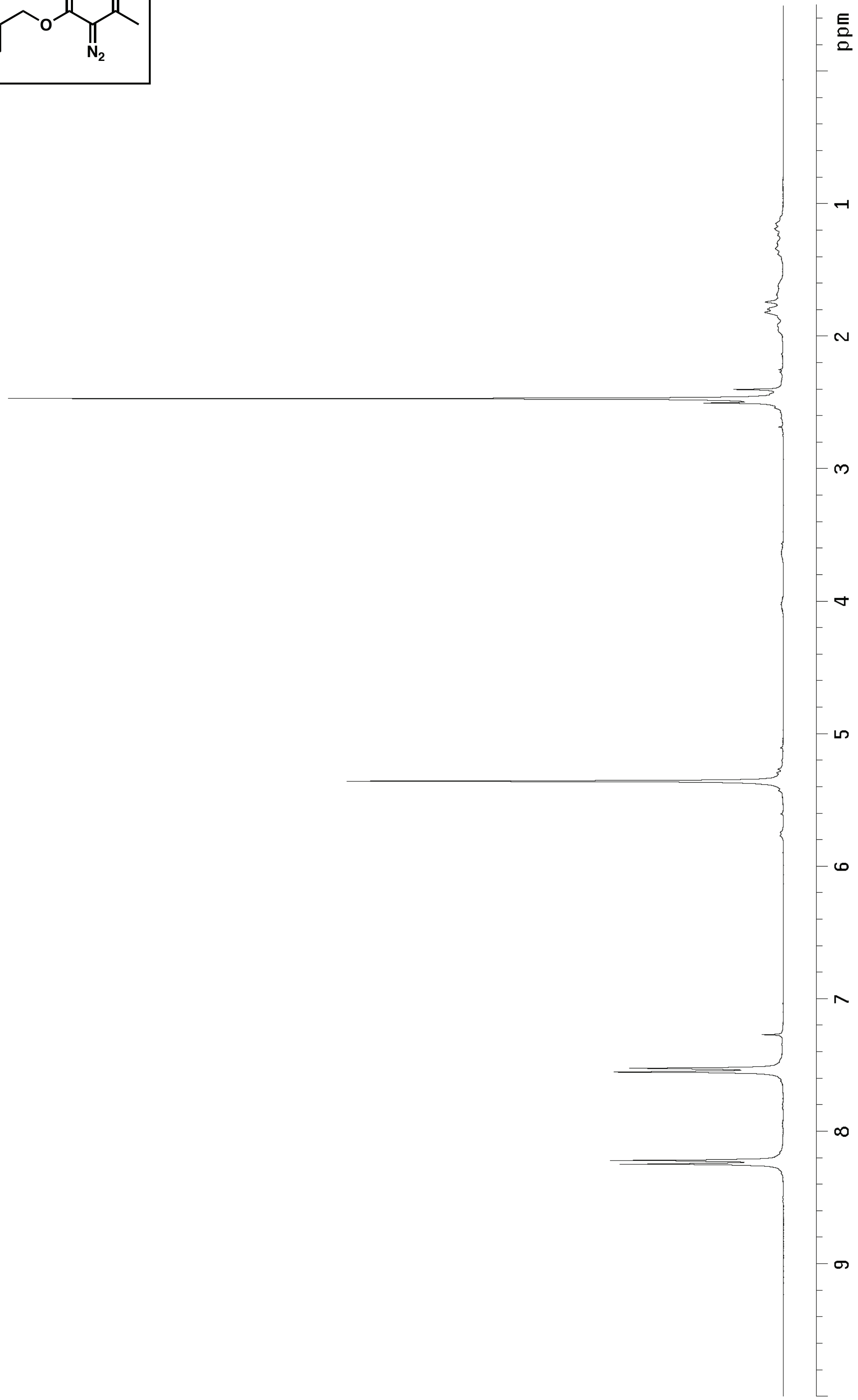
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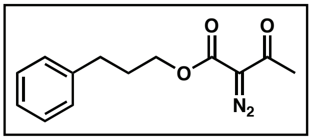
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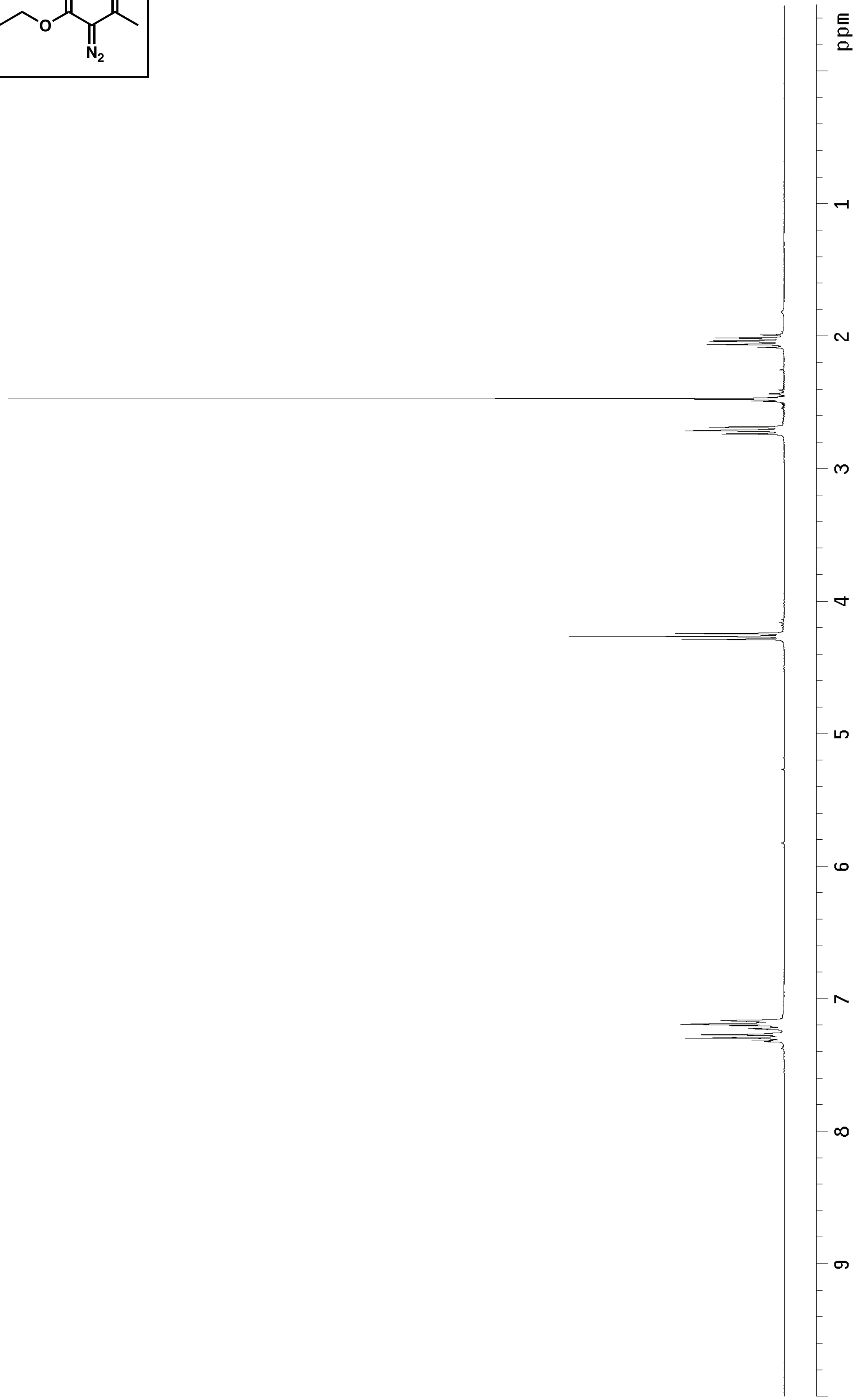
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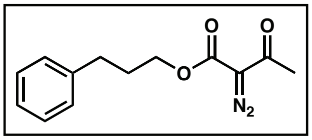
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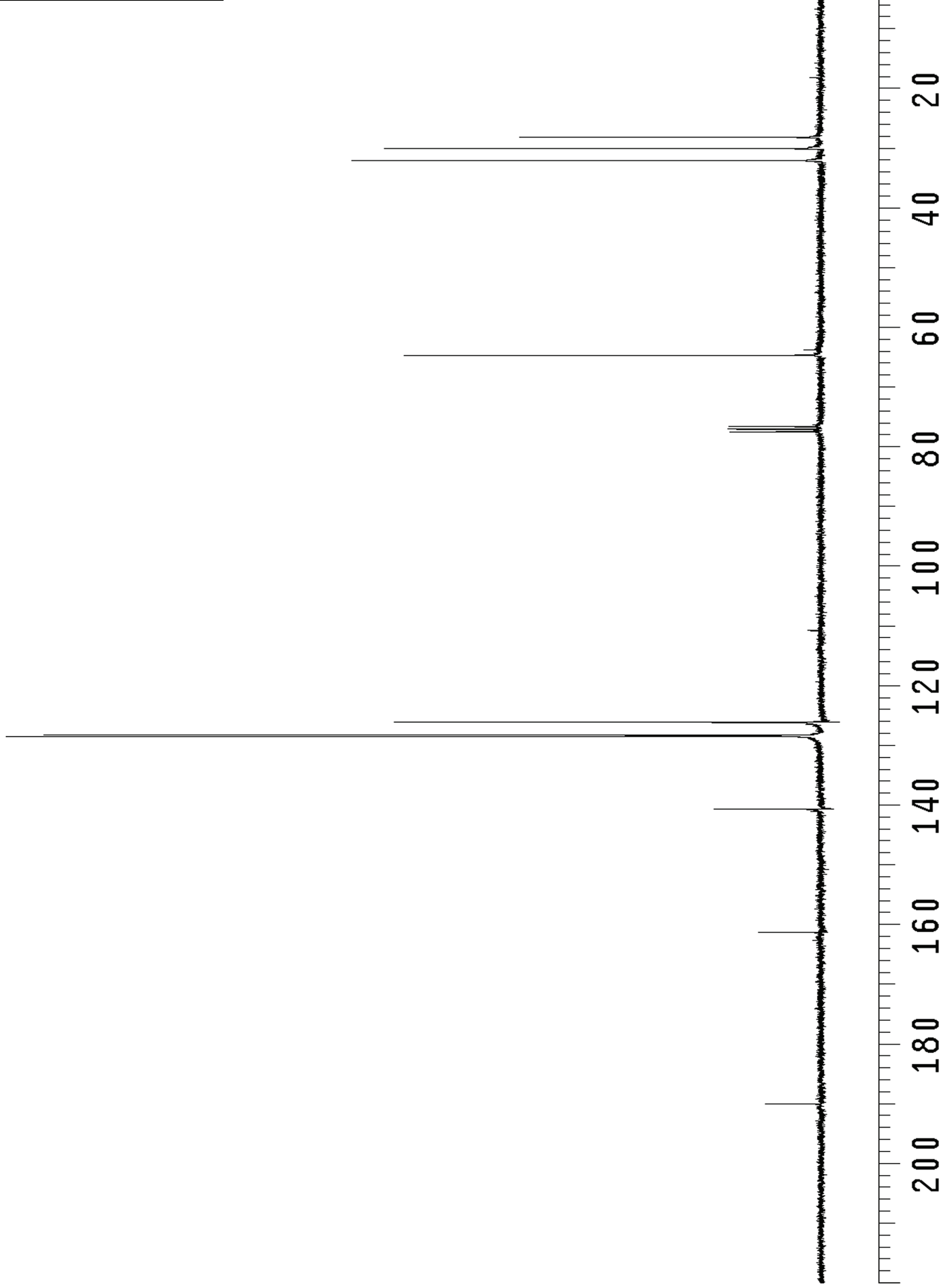
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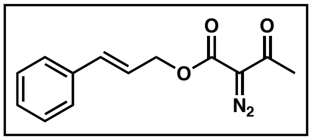
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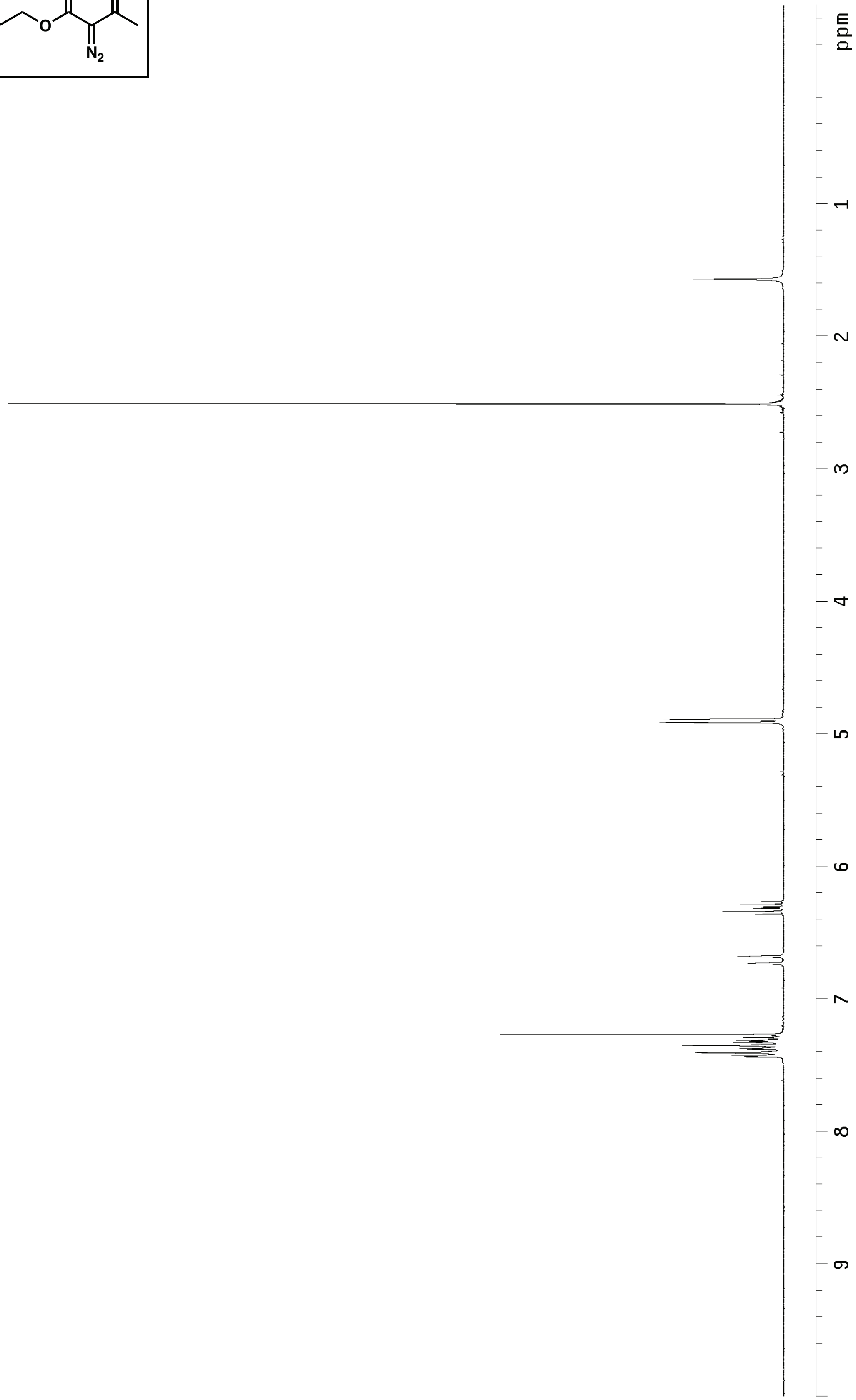
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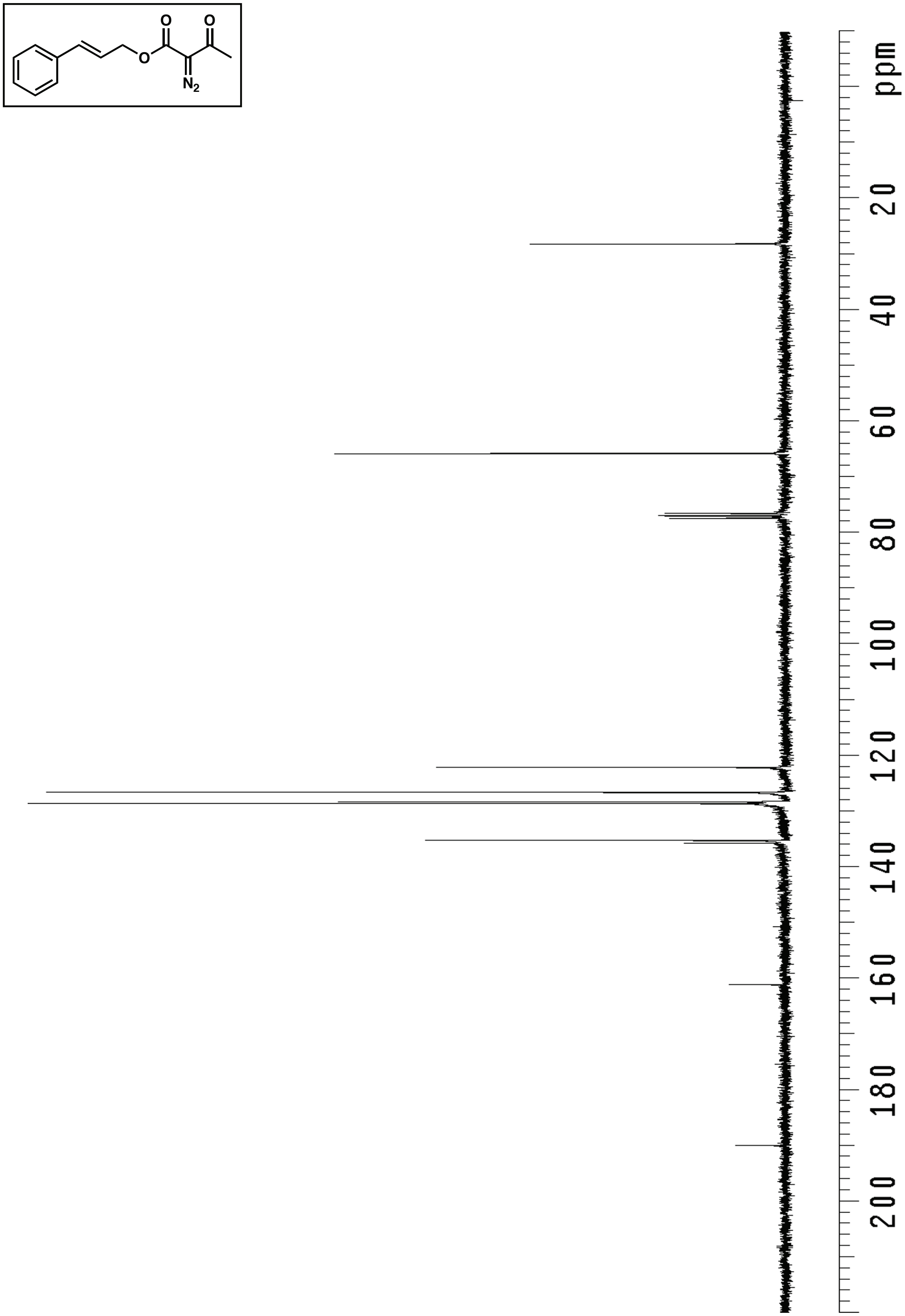
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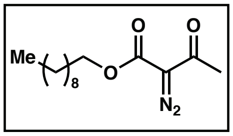
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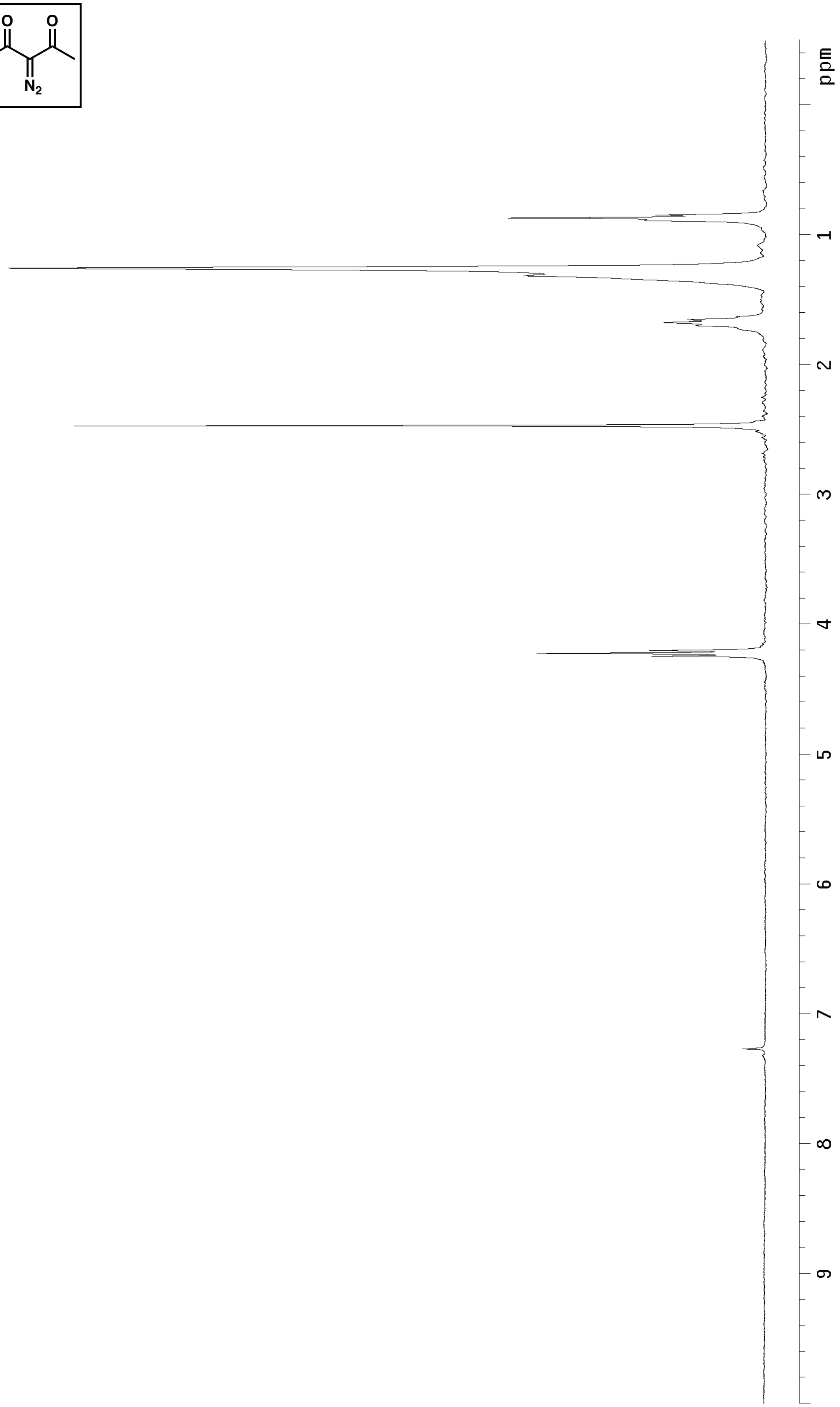
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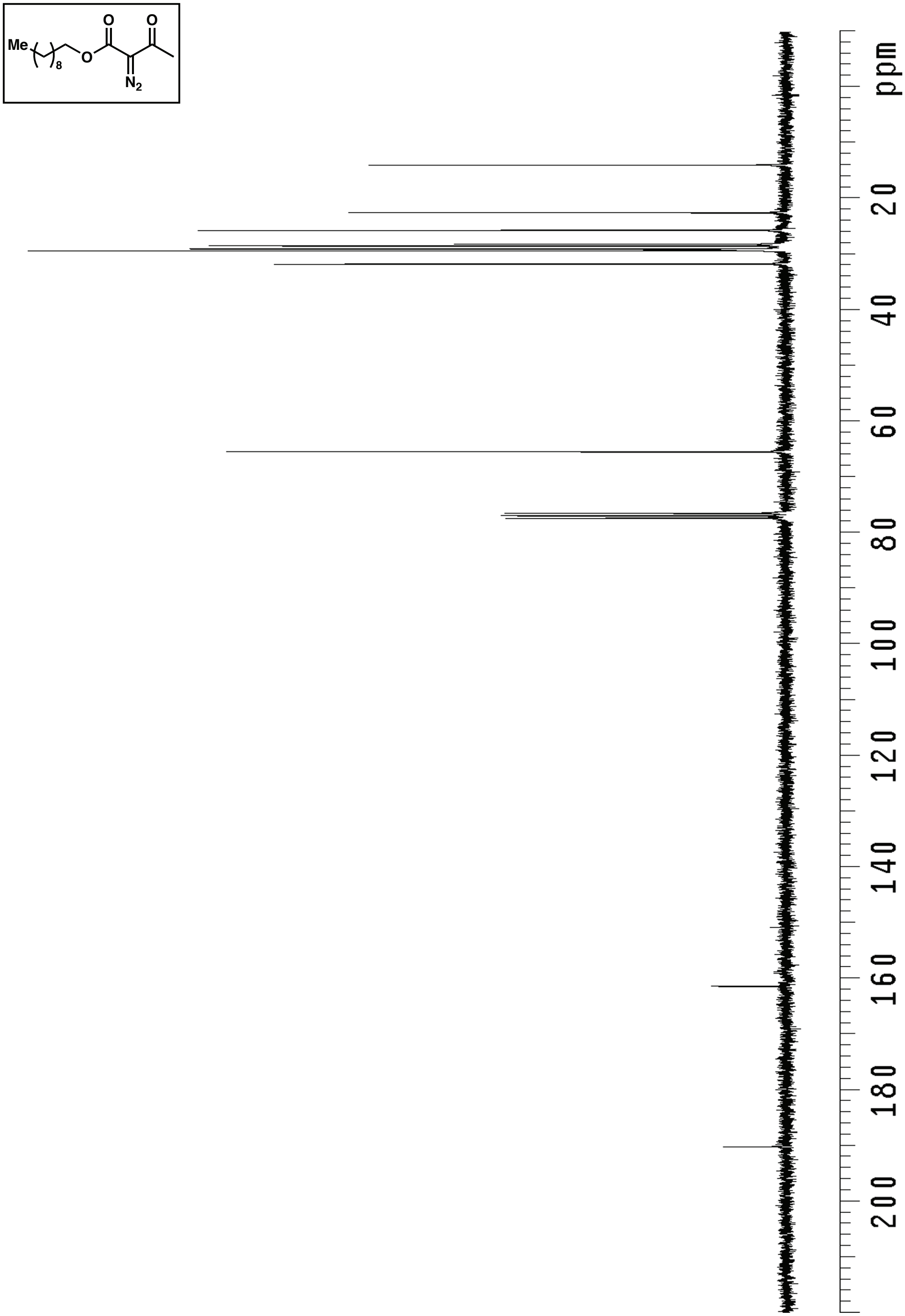
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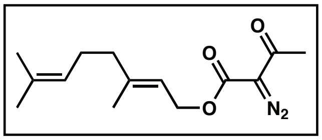
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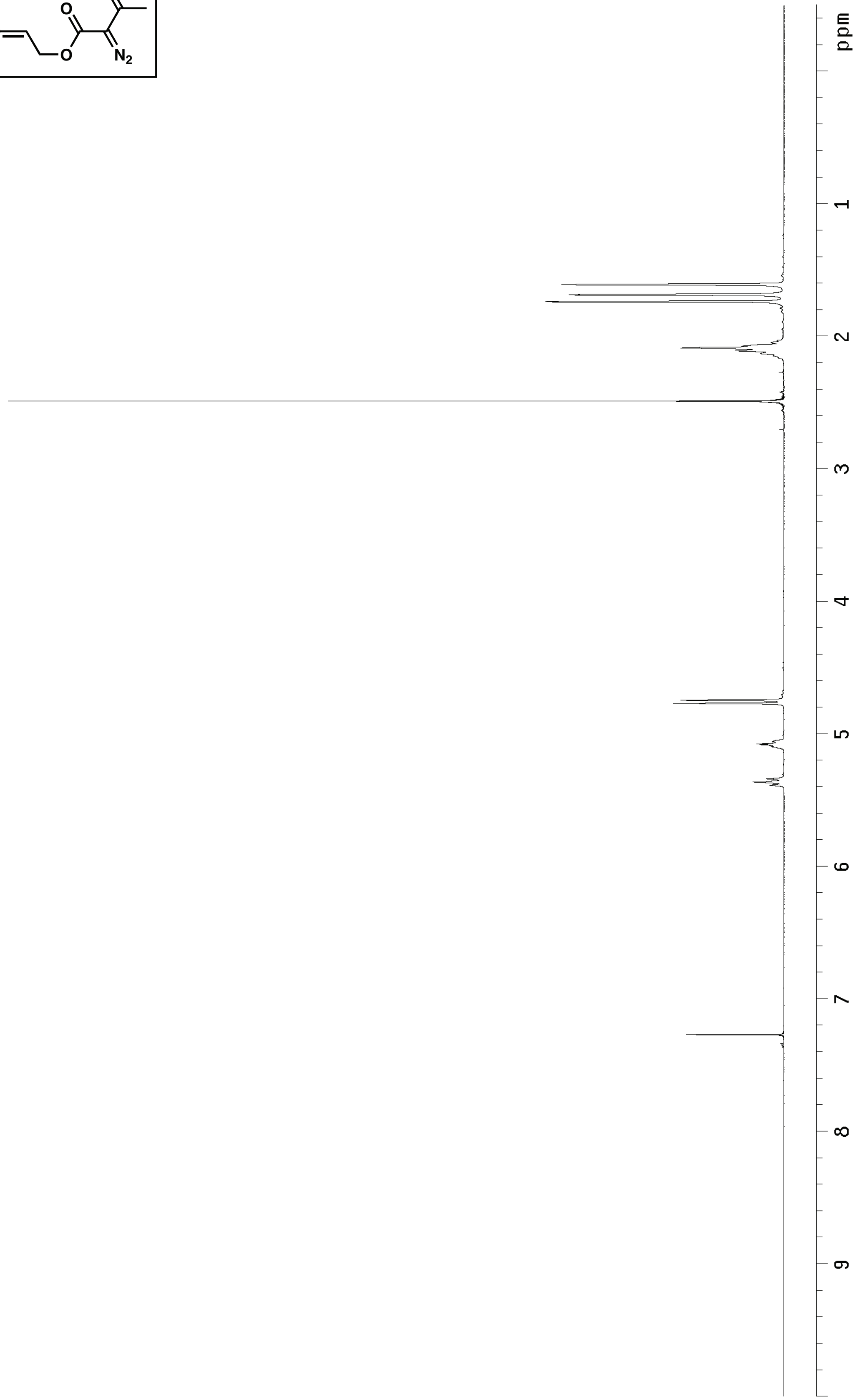
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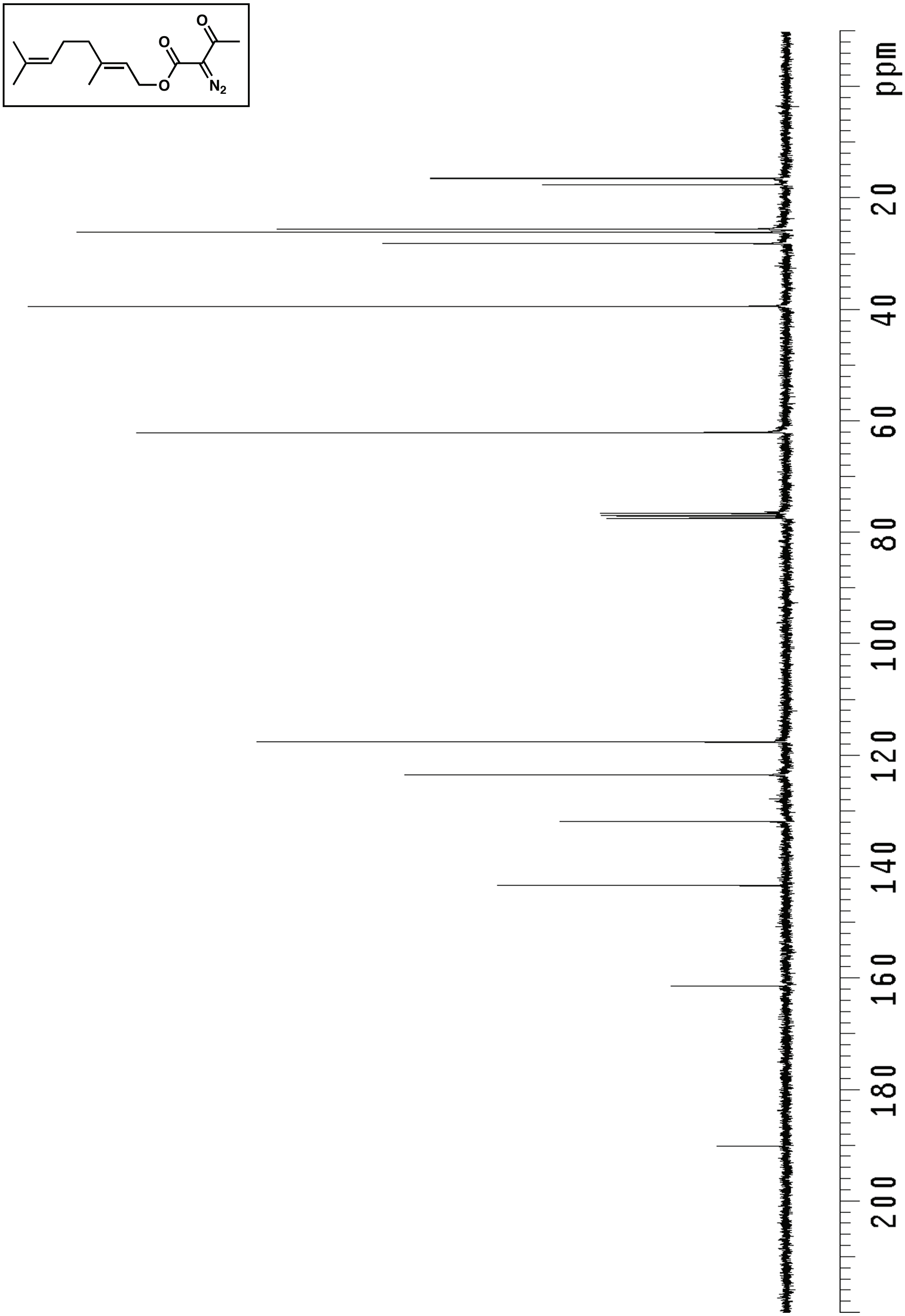
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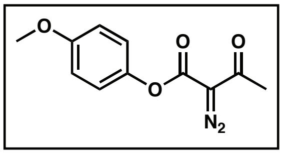
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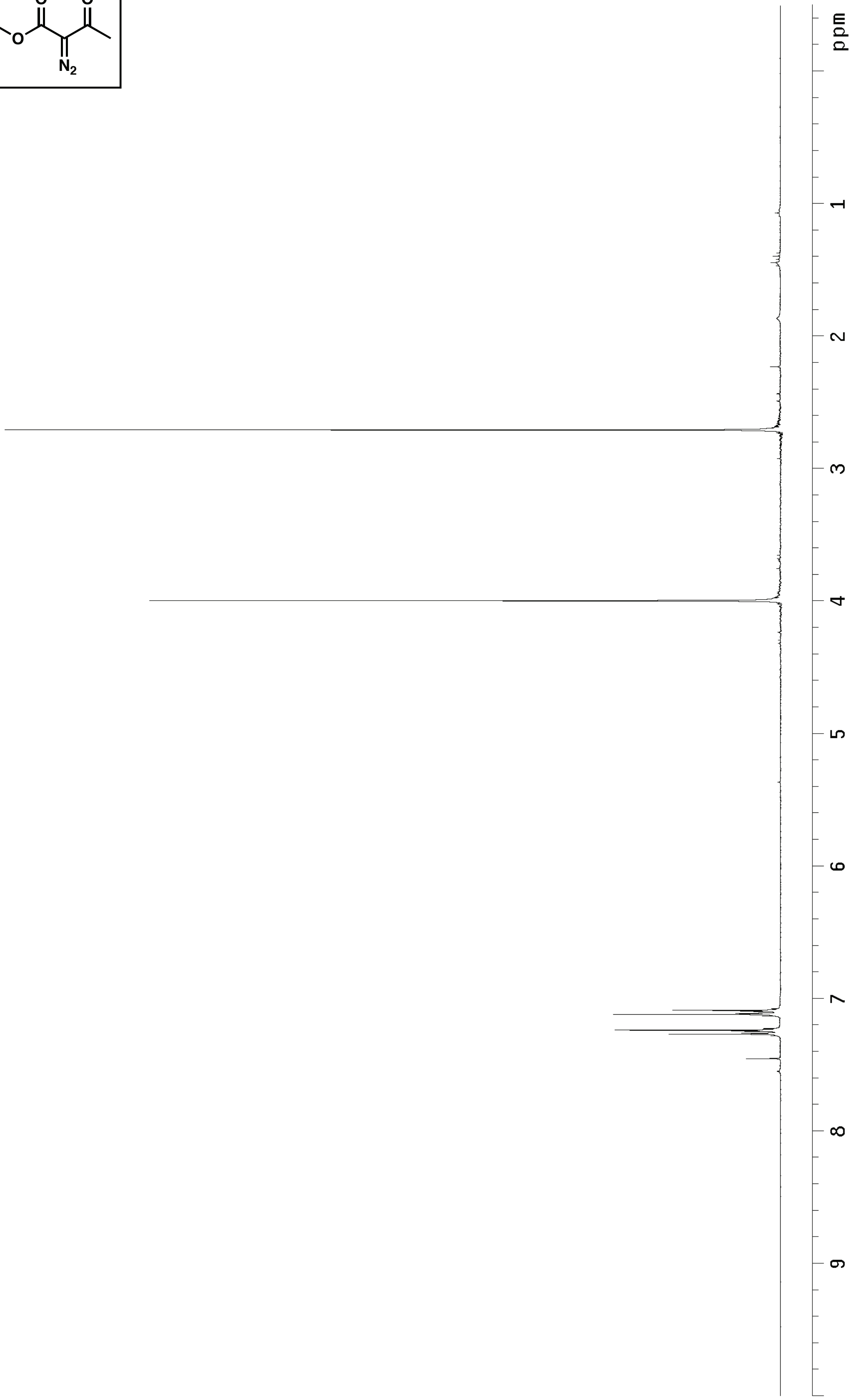
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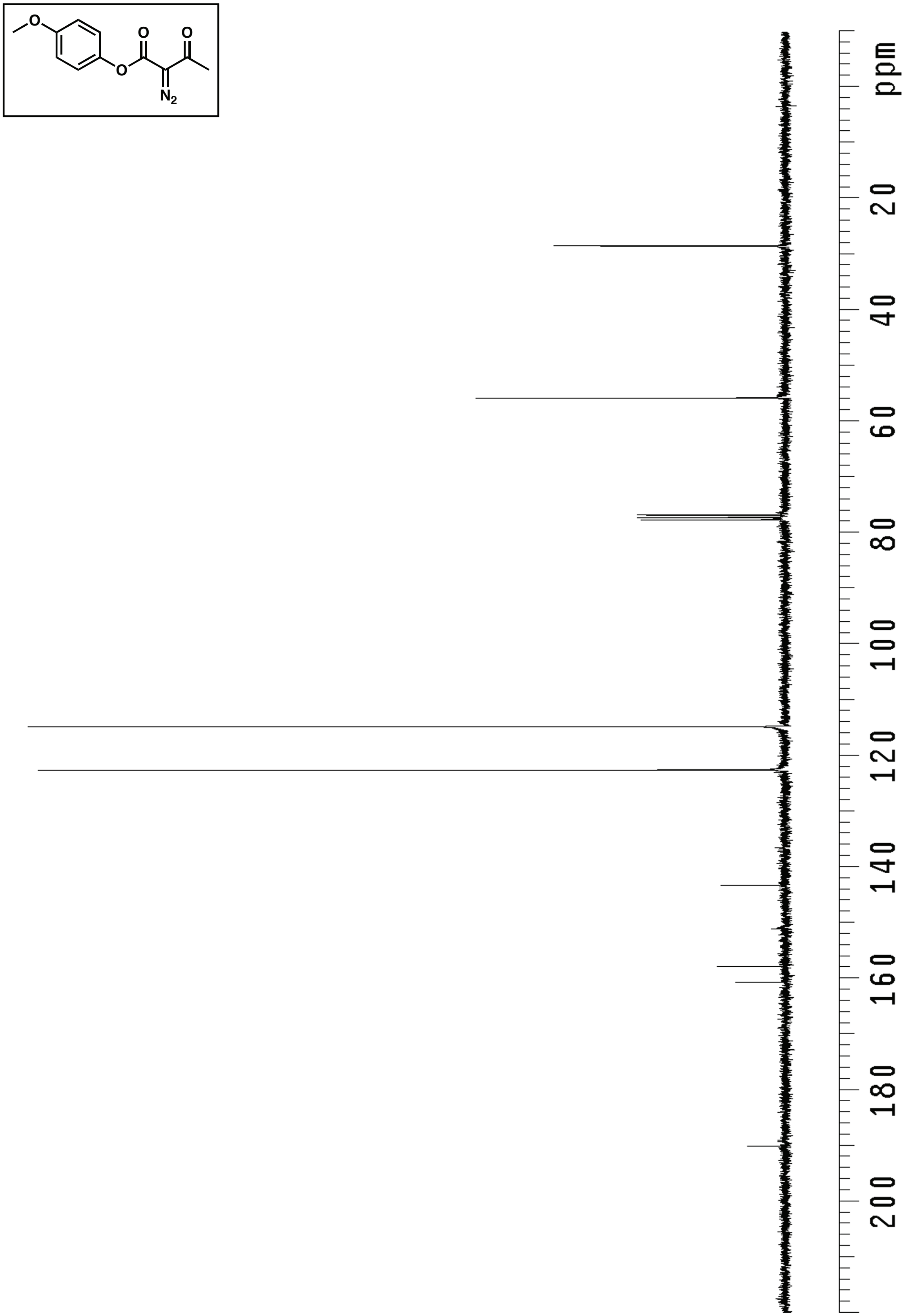
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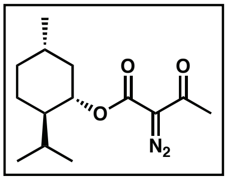
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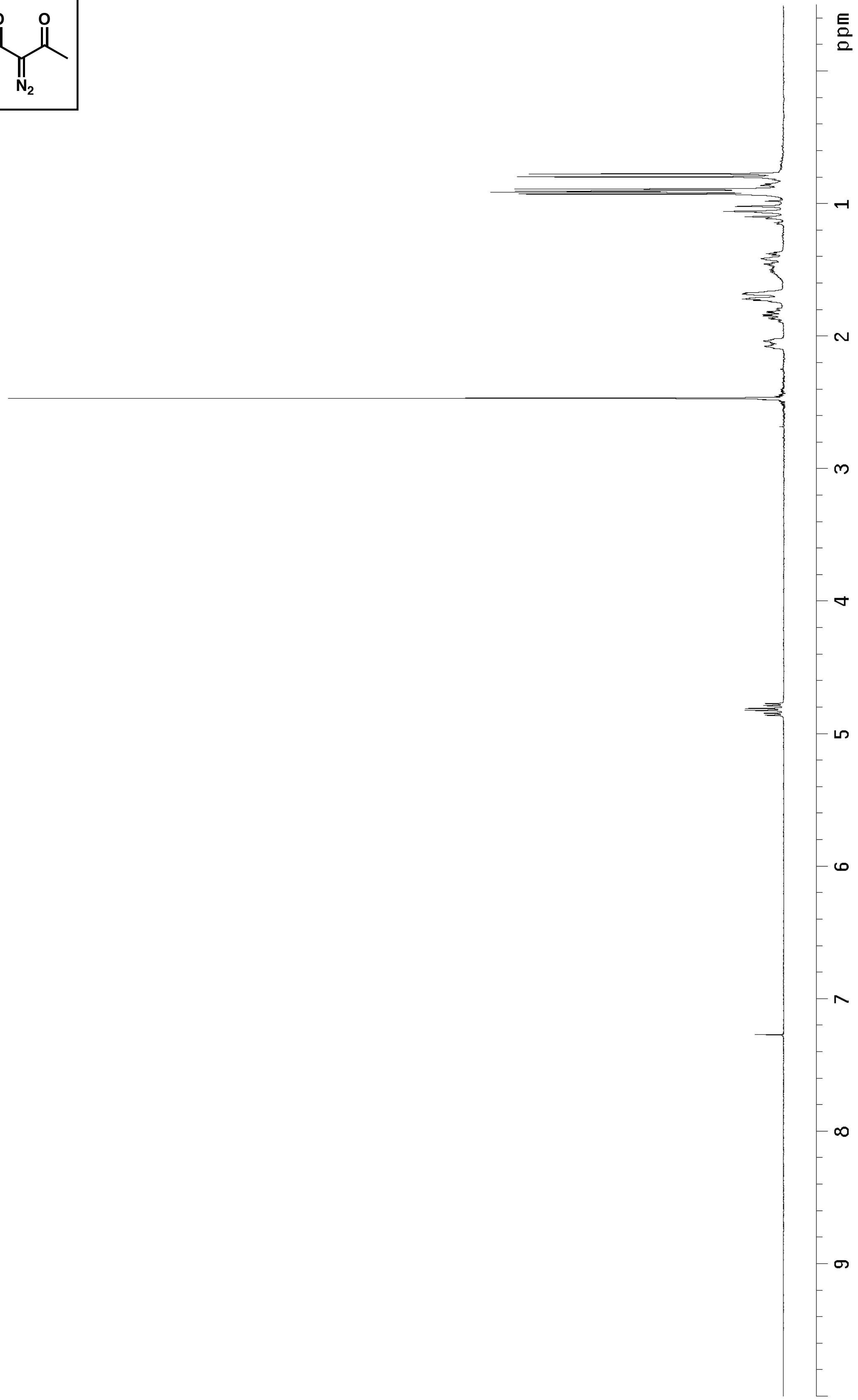
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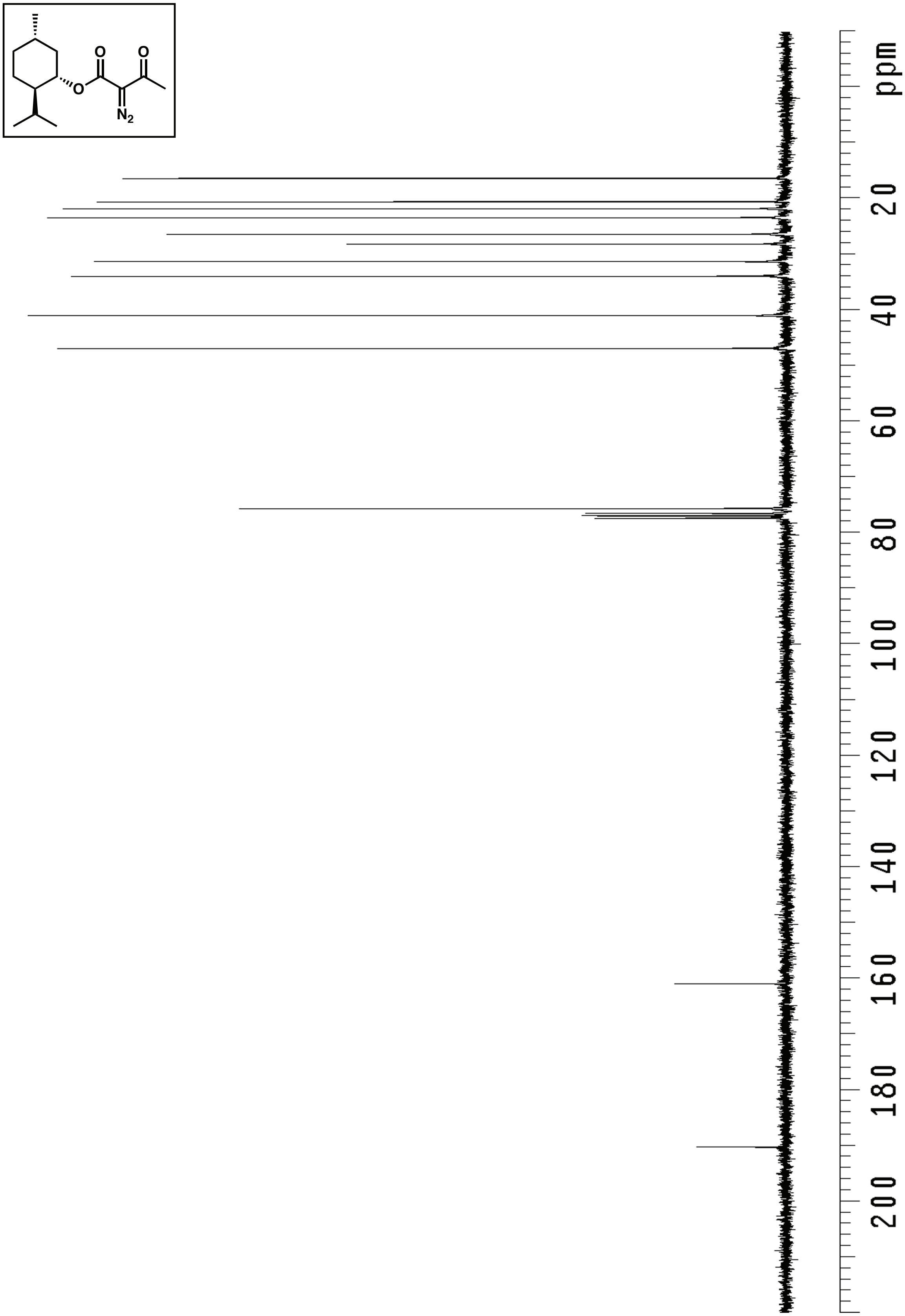
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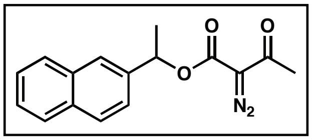

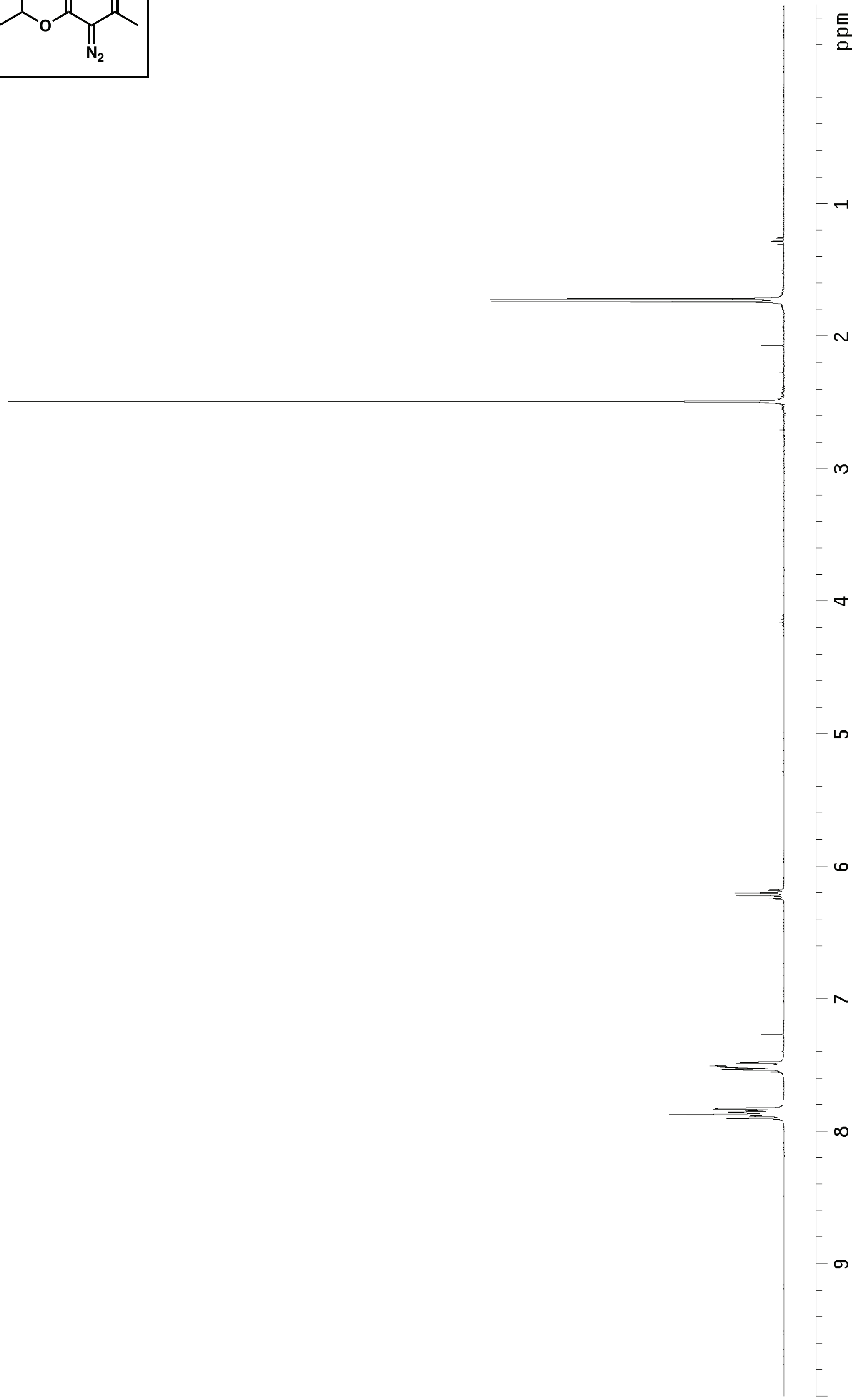
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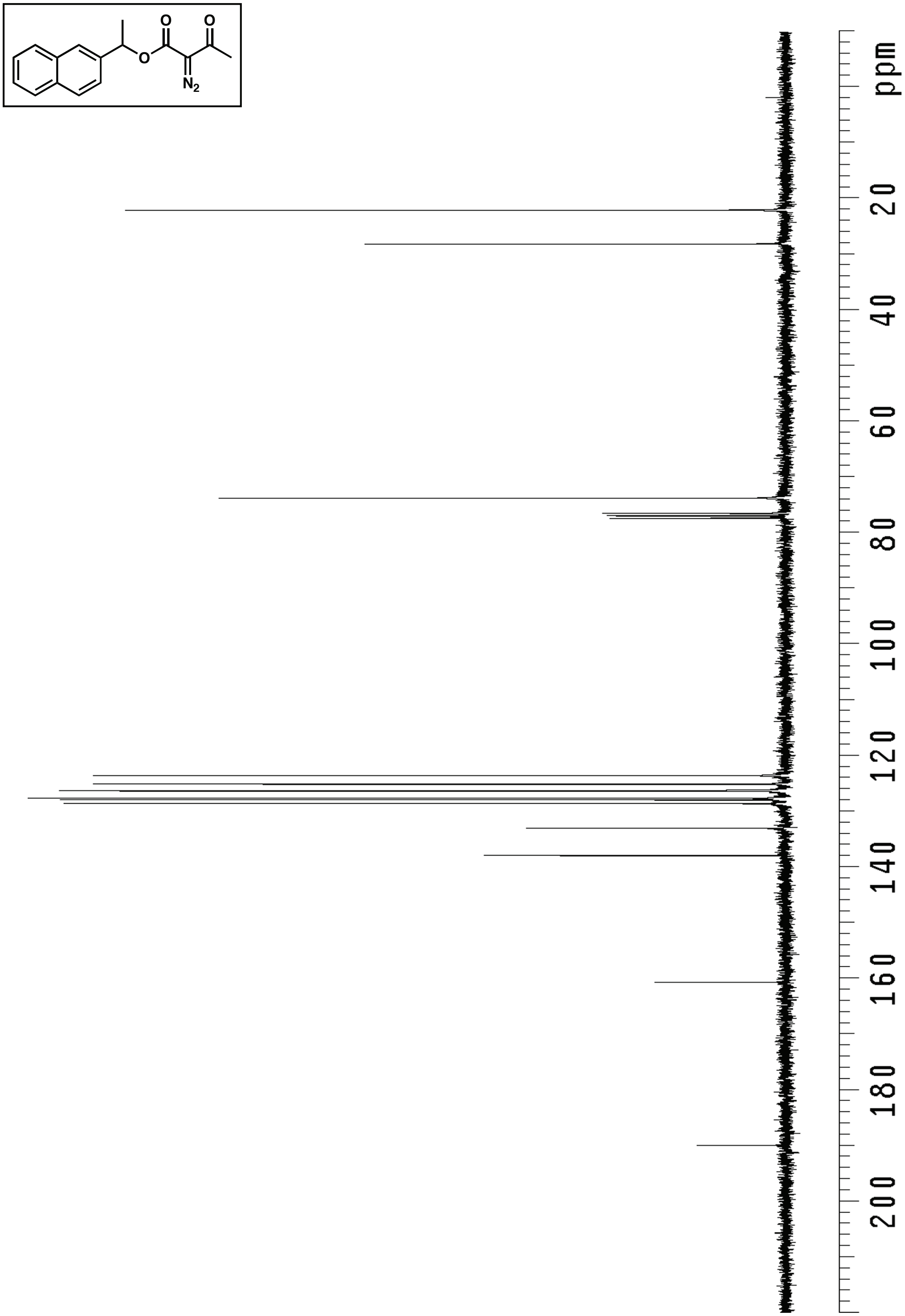
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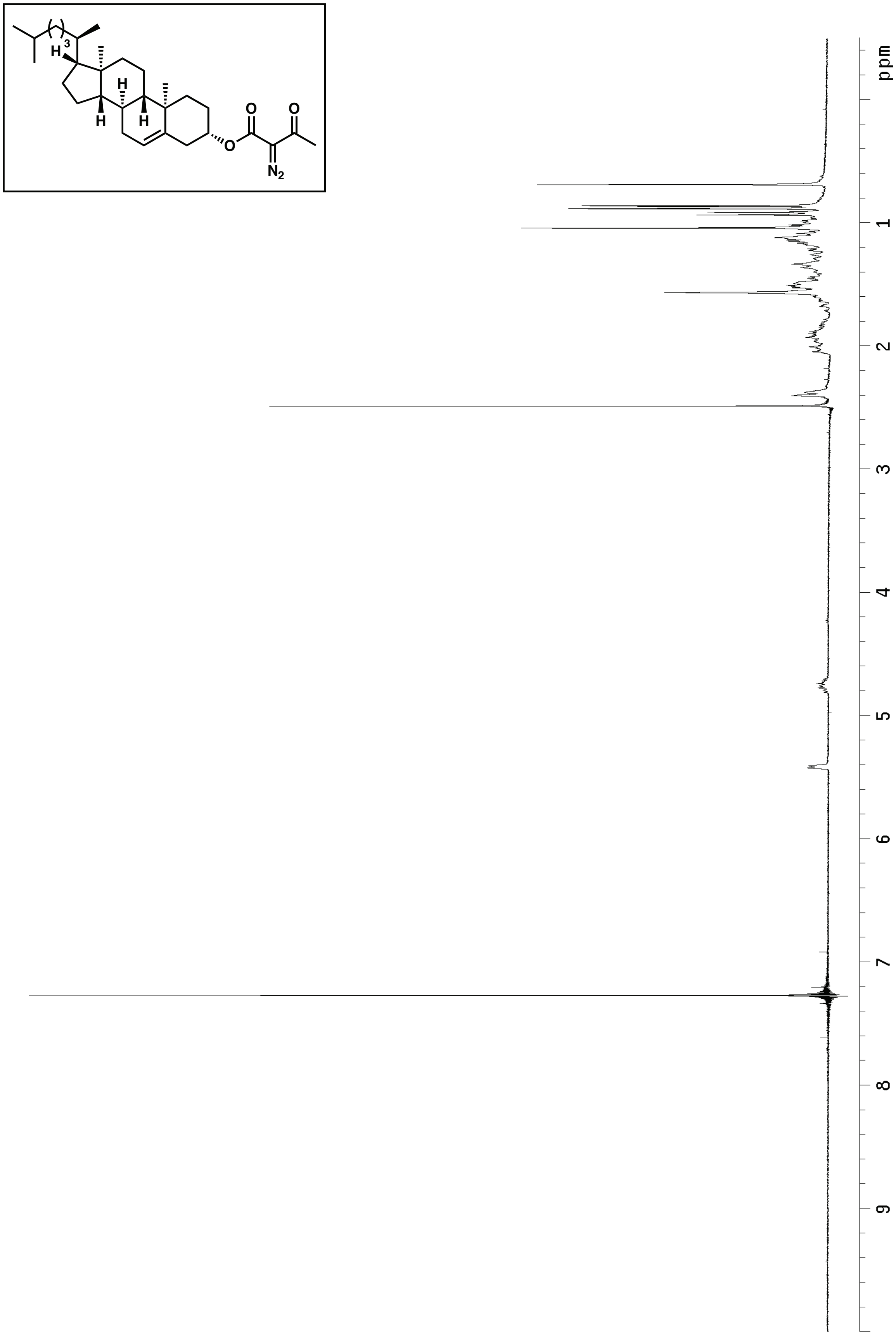
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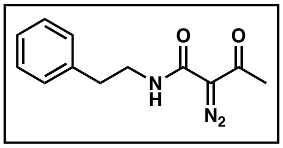
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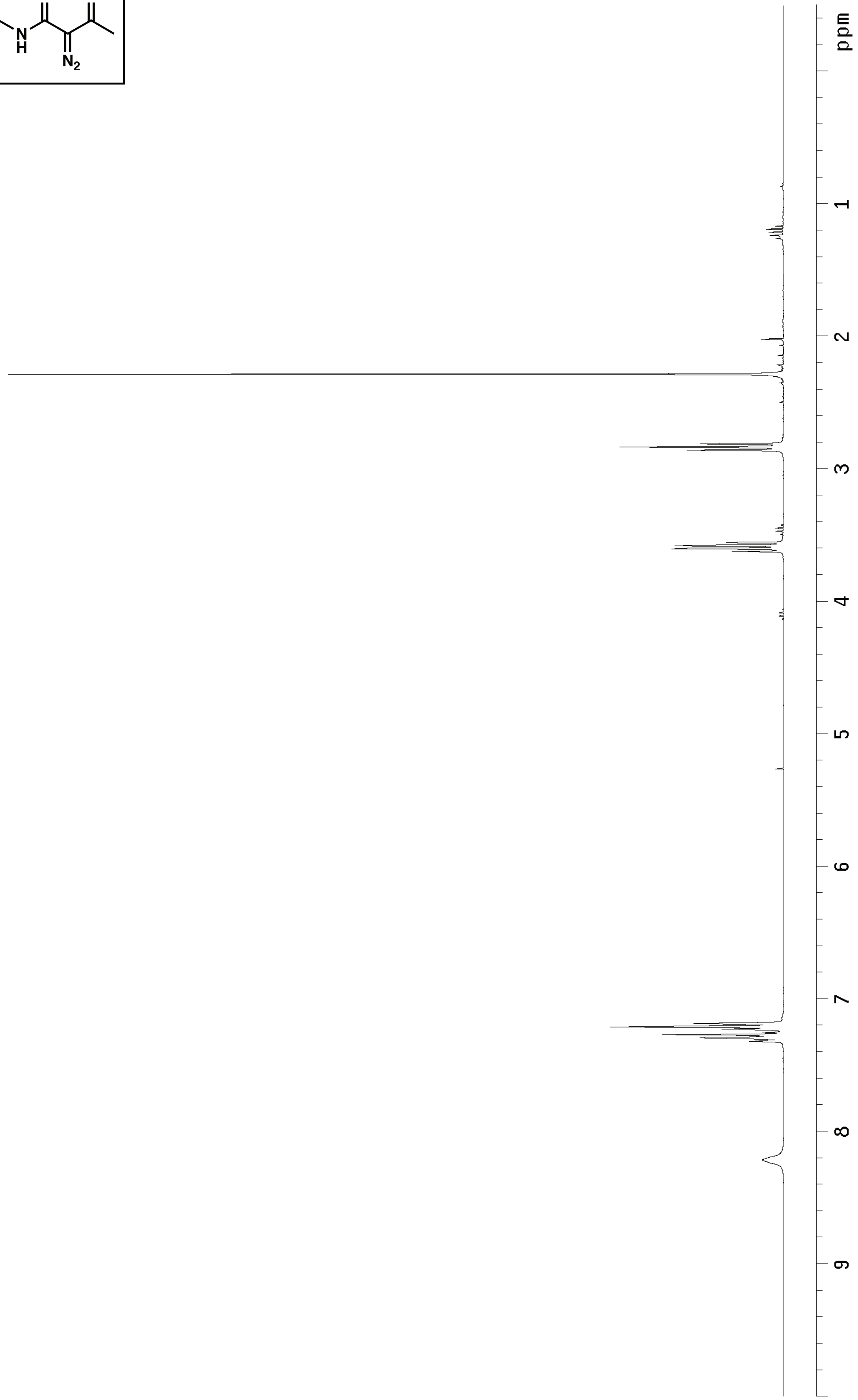
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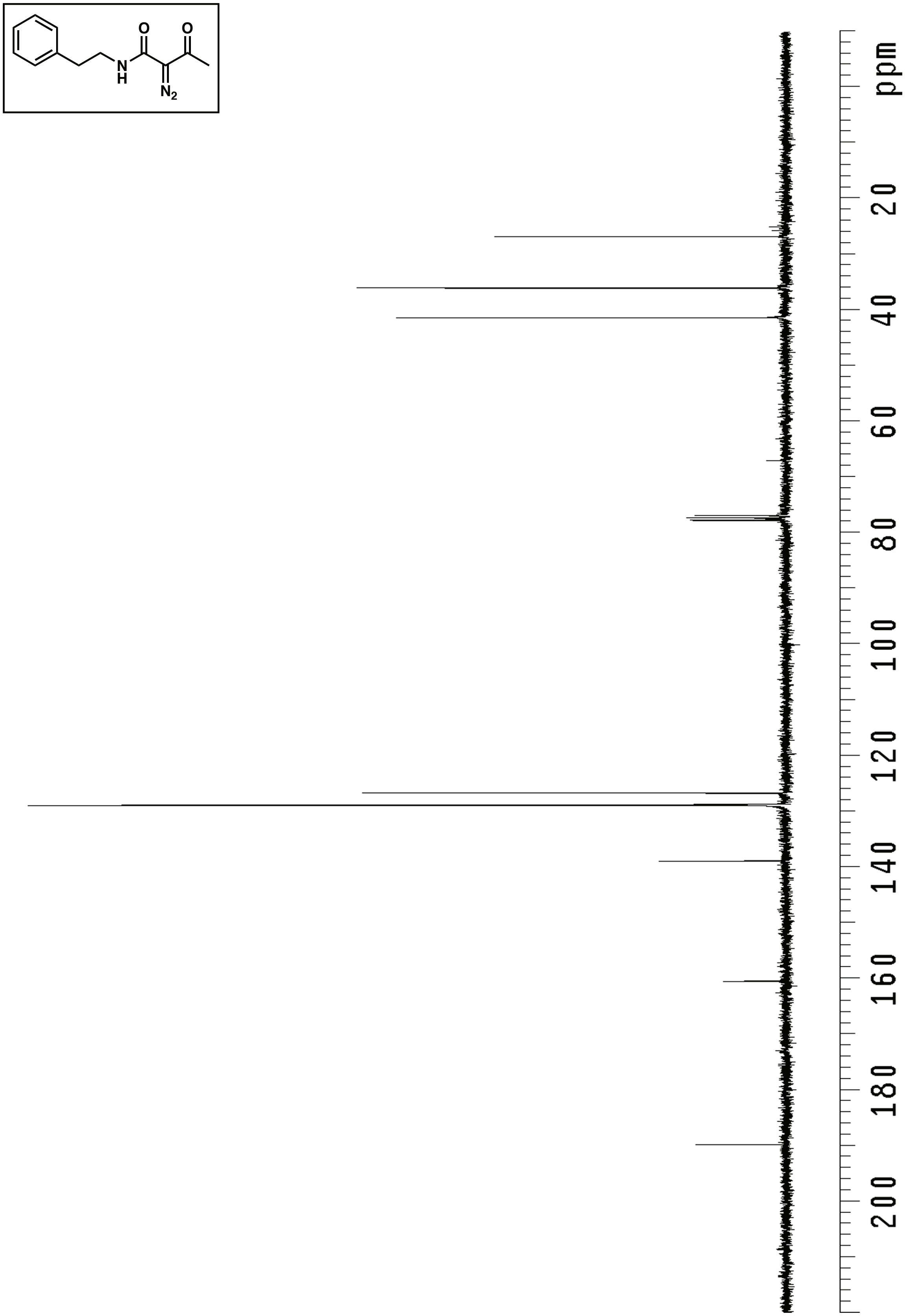
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