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Supporting Information

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Enantioselective Synthesis of α-Secondary and α-Tertiary Piperazin-2-ones and Piperazines by Catalytic Asymmetric Allylic Alkylation**

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Supporting Information

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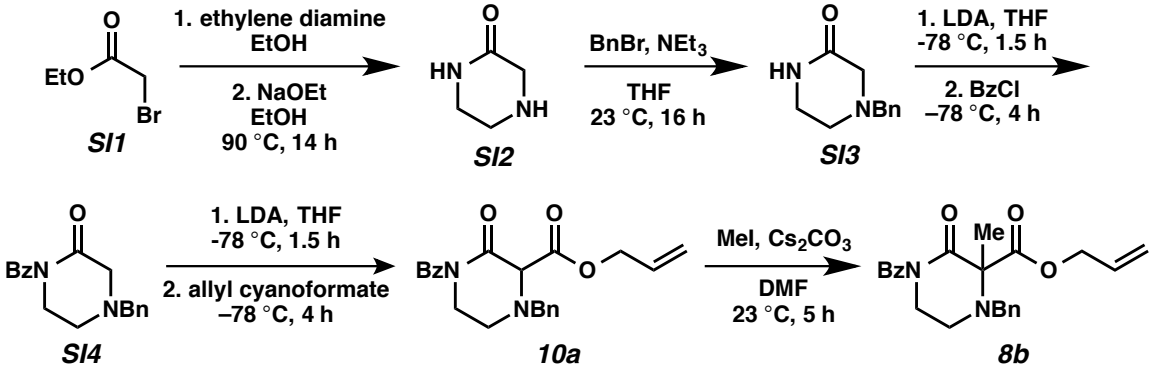
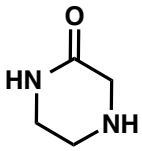
Materials and Methods. Unless otherwise stated, reactions were performed in flame-dried glassware under an inert atmosphere of argon or nitrogen using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF, Et_2O, and CH_2Cl_2 were dried by passage through an activated alumina column under argon. Triethylamine and diisopropylamine were distilled over CaH_2 prior to use. Brine solutions are saturated aqueous solutions of sodium chloride. Allyl Mander's reagents were prepared according to the method of Weber.[1] Allyl 1*H*-imidazole-1-carboxylate reagents were prepared according to the method of Trost.[2] Phosphinooxazoline (PHOX) ligands were prepared by methods described in our previous work.[3] Tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) [$Pd_2(pmdba)_3$] was prepared according to the method of Ibers[4]or Fairlamb.[5] All other reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Stirring was accomplished with Teflon® coated magnetic stir bars. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching or $KMnO_4$ staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer or Varian Mercury 300 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz (126 MHz) or Varian Mercury 300 MHz (75 MHz) spectrometer and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = heptet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for 13C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm) using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent, ee). High-resolution

mass spectra (HRMS) were obtained on an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM: ESI-APCI) ionization mode. Syringe pump additions were performed using a KDS 100 syringe pump from KD Scientific. Preparative HPLC was accomplished using an Agilent 1200 Series HPLC with an Agilent Prep-SIL 30 x 250 mm column. Stereochemistry is assigned by analogy to previous results.[6]

Representative Procedure 1 for the Preparation of 3-Oxopiperazine-2-carboxylates and 1,4-Diazepane-2-carboxylates



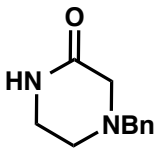
Piperazin-2-one (SI2)



To a solution of ethylene diamine (3.34 mL, 50.0 mmol) in EtOH (39 mL) at 0 °C was added ethyl bromoacetate (**SI1**, 2.76 mL, 25.0 mol) dropwise. The solution was warmed to 23 ºC and allowed to stir overnight open to the air. The resulting white solid was removed by filtration, and the filtrate was transferred to a flame dried flask containing sodium ethoxide (3.74 g, 55.0 mmol) under a nitrogen atmosphere. The solution was then heated to 80 °C and allowed to stir for 16 hours under nitrogen atmosphere. The solution was cooled to room temperature and concentrated. Ketopiperazine (**SI2**) was

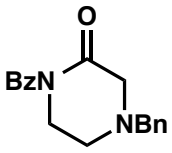
isolated by flash column chromatography (SiO_2, 20% MeOH in CH_2Cl_2 to 25% MeOH in CH_2Cl_2) as a yellow solid. 64% yield. Product identity was confirmed by comparison to previously reported characterization data.

4-Benzylpiperazin-2-one (SI3)



A 25 mL round bottom flask was charged with piperazin-2-one (**SI2**, 3.56 g, 36.3 mmol), triethylamine (8.1 mL, 58.1 mmol), benzyl bromide (3.88 mL, 32.7 mmol), and THF (360 mL) and allowed to stir for 16 hours at 23 ºC. The reaction mixture was then concentrated and taken up in a saturated aqueous $NaHCO_3$ solution. The aqueous solution was extracted with EtOAc (5 x 50 mL) and the organic layers were concentrated to approximately 30 mL at which point **SI3** precipitated from the solution. The solid was collected by filtration and dried. 62% yield. Product identity was confirmed by comparison to previously reported characterization data.

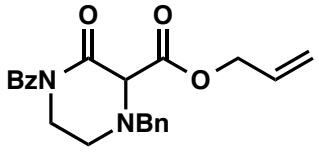
1-Benzoyl-4-benzylpiperazin-2-one (SI4)



Benzyl-protected ketopiperazine (**SI3**, 1.00 g, 5.26 mmol) was dissolved in 20 mL of THF warmed to 60 ºC and added by cannula to a freshly prepared solution of LDA (6.31 mmol, prepared by the addition of 2.53 mL of 2.5 M *n*BuLi solution to a solution of 1.11 mL of diisopropyl amine in 33 mL THF at 0 °C) cooled to –78 °C. The reaction mixture was allowed to stir at –78 °C for 1.5 hours at which point benzoyl chloride (0.79 mL, 8.84 mmol) was added dropwise. The reaction was stirred at –78 °C for another 4 hours at which point full conversion of the starting material was observed by TLC analysis. The reaction mixture was warmed to 23 ºC and poured into 20 mL of H_2O and extracted with EtOAc (4 x 20 mL). The organics were combined, washed once with brine, dried

with $MgSO_4$, and concentrated under reduced pressure. Ketopiperazine **SI4** was isolated by flash column chromatography (SiO_2, 20% EtOAc in hexanes to 25% EtOAc in hexanes) as a pale yellow solid. 83% yield. R_f = 0.5 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.53–7.45 (m, 1H), 7.44–7.28 (m, 7H), 3.89–3.80 (m, 2H), 3.64 (s, 2H), 3.31 (s, 2H), 2.90–2.79 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 169.4, 136.5, 135.9, 131.9, 129.2, 128.7, 128.2, 128.1, 127.9, 61.8, 58.9, 49.3, 45.2; IR (Neat Film, NaCl) 3062, 3027, 2958, 2903, 2809, 1708, 1683, 1600, 1491, 1450, 1401, 1362, 1282, 1237, 1197, 1162, 1136, 1073, 950, 885, 795, 730 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1441, found 295.1446.

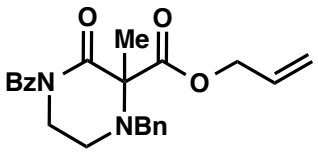
Allyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10a)



Ketopiperazine (**SI4**, 1.40 g, 4.76 mmol) was dissolved in 25 mL of dry THF and added via cannula to a freshly prepared solution of LDA (5.71 mmol) in 23 mL dry THF at –78 °C. The resulting dark red solution was allowed to stir at –78 °C for one hour at which point allyl cyanoformate (58.1 mg, 5.23 mmol) was added neat. After 2.5 hours, the reaction reached completion according to TLC analysis. The reaction mixture was warmed to 23 ºC and poured into 20 mL of H_2O and then extracted with EtOAc (4 x 20 mL). The combined organics were washed once with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Ketopiperazine **10a** was isolated by flash column chromatography (SiO_2, 10% EtOAc in hexanes) as a white solid. 63% yield. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.53 – 7.45 (m, 1H), 7.41 – 7.33 (m, 5H), 7.31 (td, *J* = 8.6, 8.1, 3.9 Hz, 2H) 6.06–5.89 (m, 1H), 5.40 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.31 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 2H), 4.17 (s, 1H), 3.93 (ddd, *J* = 12.5, 8.1, 4.3 Hz, 1H), 3.84 (d, *J* = 13.4 Hz, 1H), 3.81–3.70 (m, 2H), 3.32 (ddd, *J* = 12.2, 8.1, 3.9 Hz, 1H), 2.80 (dt, *J* = 12.4, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 167.7, 166.6, 136.5, 135.2, 132.2, 131.4, 129.1, 128.7, 128.4, 128.3, 128.0, 119.7, 69.7, 66.6, 58.8, 45.0, 44.9; IR (Neat Film, NaCl)

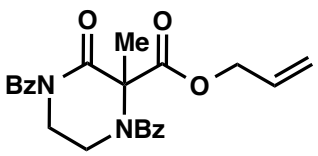
3062, 3029, 2846, 1733, 1690, 1600, 1583, 1494, 1450, 1368, 1281, 1232, 1154, 1091, 1074, 985, 948, 945, 795, 731 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{23}N_2O_4$ $[M+H]^+$: 379.1652, found 379.1664.

Allyl 4-benzoyl-1-benzyl-2-methyl-3-oxopiperazine-2-carboxylate (8b)



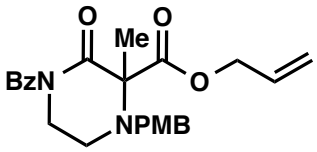
Ketopiperazine (**10a**, 500.0 mg, 1.32 mmol) was dissolved in 8.8 mL of dry DMF along with Cs_2CO_3 (0.75 g, 2.31 mmol) and methyl iodide (90.0 μL, 1.45 mmol) and allowed to stir for 10.5 hours at 23 ºC. The solution was then poured into 10 mL of H_2O and extracted with EtOAc (4 x 10 mL). The combined organics were washed once with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Acylated ketopiperazine **8b** was isolated by flash column chromatography (SiO_2, 15% EtOAc in hexanes to 20% EtOAc in hexanes) as a white solid. 35% yield. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.60 (m, 2H), 7.56–7.45 (m, 1H), 7.44–7.34 (m, 6H), 7.34–7.27 (m, 1H), 6.01 (ddt, *J* = 17.1, 10.4, 6.0 Hz, 1H), 5.50–5.38 (m, 1H), 5.34 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.77 (dt, *J* = 6.0, 1.3 Hz, 2H), 4.01 (d, *J* = 14.0 Hz, 1H), 3.91–3.66 (m, 2H), 3.43 (d, *J* = 14.0 Hz, 1H), 3.15 (ddd, *J* = 13.4, 9.3, 4.2 Hz, 1H), 2.90 (dt, *J* = 12.6, 4.2 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 170.0, 169.3, 137.9, 135.5, 132.0, 131.5, 128.7, 128.6, 128.3, 128.2, 127.8, 119.9, 71.4, 66.6, 54.8, 44.9, 43.0, 20.2; IR (Neat Film, NaCl) 3062, 2943, 2848, 1741, 1685, 1600, 1495, 1449, 1400, 1379, 1315, 1284, 1235, 1150, 1109, 928, 795, 723 cm^{-1}; HRMS (MM: ESI-APCI or EI+) *m/z* calc'd for $C_{23}H_{25}N_2O_4$ $[M+H]^+$: 393.1809, found 393.1792.

Allyl 1,4-dibenzoyl-2-methyl-3-oxopiperazine-2-carboxylate (8a)



Ketopiperazine **8a** was prepared according to representative procedure 1, employing benzoyl chloride instead of benzyl bromide, and was isolated by flash column chromatography (SiO_2, 15% EtOAc in hexanes to 25% EtOAc in hexanes) as a colorless solid. R_f = 0.3 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.54 (m, 2H), 7.54–7.49 (m, 2H), 7.49–7.45 (m, 4H), 7.41 (ddt, *J* = 7.8, 6.5, 1.0 Hz, 2H), 5.98 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.39 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.81–4.70 (m, 2H), 4.20–4.06 (m, 2H), 4.00 (ddd, *J* = 14.1, 5.2, 3.6 Hz, 1H), 3.73–3.63 (m, 1H), 1.99 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 170.2, 169.1, 167.3, 134.7, 134.6, 132.4, 131.7, 130.8, 129.0, 128.5, 127.9, 127.0, 119.0, 69.2, 67.2, 44.6, 44.3, 19.6; IR (Neat Film, NaCl) 3583, 2943, 1762, 1700, 1690, 1647, 1600, 1448, 1405, 1370, 1284, 1255, 1209, 1149, 1123, 991, 942, 789, 725 cm^{-1}; HRMS (MM: ESI-APCI or EI+) *m/z* calc'd for $C_{23}H_{23}N_2O_5$ $[M+H]^+$: 407.1607, found 407.1600.

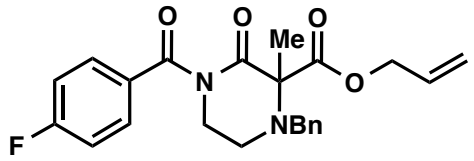
Allyl 4-benzoyl-1-(4-methoxybenzyl)-2-methyl-3-oxopiperazine-2-carboxylate (8c)



Ketopiperazine **8c** was prepared according to representative procedure 1 employing 4-methoxybenzyl chloride instead of benzyl bromide, and was isolated by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 20% EtOAc in hexanes) as a yellow oil. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.58 (m, 2H), 7.54–7.44 (m, 1H), 7.43–7.33 (m, 2H), 7.30–7.21 (m, 2H), 6.94–6.84 (m, 2H), 6.01 (ddt, *J* = 16.4, 10.4, 6.0 Hz, 1H), 5.43 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.34 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.82–4.72 (m, 2H), 3.90 (d, *J* = 13.7 Hz, 1H), 3.82 (s, 3H), 3.80 (t, *J* = 4.0 Hz, 1H), 3.70 (ddd, *J* = 12.5, 9.8, 4.2 Hz, 1H), 3.32 (d, *J* = 13.7 Hz, 1H), 3.10 (ddd, *J* = 13.2, 9.8, 3.7 Hz, 1H), 2.87 (dt, *J* = 12.6, 4.2 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 170.4, 169.4, 159.2, 135.6, 132.0, 131.6, 130.2, 129.6, 128.2, 128.1, 119.8, 114.0, 71.4, 66.5, 55.4, 54.1, 45.2, 42.7, 20.1; IR (Neat Film, NaCl) 3062, 2997, 2949, 2836, 1742, 1687, 1611, 1512, 1465, 1449, 1378, 1285, 1245, 1171, 1150, 1108, 1034, 926, 825

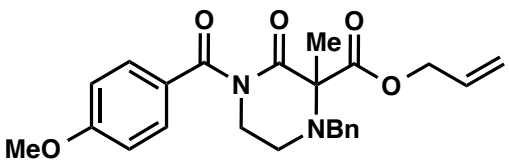
cm^{-1}; HRMS (MM: ESI-APCI or EI+) *m/z* calc'd for $C_{24}H_{27}N_2O_5$ $[M+H]^+$: 423.1914, found 423.1890.

Allyl 1-benzyl-4-(4-fluorobenzoyl)-2-methyl-3-oxopiperazine-2-carboxylate (8d)



Ketopiperazine **8d** was prepared according to representative procedure 1 employing 4-fluoro-benzoyl chloride instead of benzoyl chloride, and was isolated by flash column chromatography (SiO_2, 15% EtOAc in hexanes) as a colorless solid. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.63 (m, 2H), 7.35 (d, *J* = 4.4 Hz, 4H), 7.32–7.27 (m, 1H), 7.10–7.02 (m, 2H), 6.01 (ddt, *J* = 17.1, 10.4, 6.0 Hz, 1H), 5.44 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.36 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.84–4.71 (m, 2H), 4.00 (d, *J* = 14.0 Hz, 1H), 3.83–3.67 (m, 2H), 3.39 (d, *J* = 14.0 Hz, 1H), 3.10 (ddd, *J* = 13.5, 9.6, 4.1 Hz, 1H), 2.88 (dt, *J* = 12.7, 4.1 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 170.4, 169.4, 165.1 (d, $^1J_{CF}$ = 253.3 Hz), 138.3, 131.6 (d, $^4J_{CF}$ = 3.3 Hz), 130.9 (d, $^3J_{CF}$ = 9.1 Hz), 128.7, 128.4, 127.7, 119.9, 115.5 (d, $^2J_{CF}$ = 22.2 Hz), 71.4, 66.5, 54.7, 45.3, 43.0, 20.2; IR (Neat Film, NaCl) 3064, 3028, 3001, 2947, 2902, 2844, 1742, 1689, 1601, 1509, 1454, 1409, 1379, 1316, 1283, 1235, 1150, 1110, 996, 928, 849, 765 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{24}FN_2O_4$ $[M+H]^+$: 411.1715, found 411.1726.

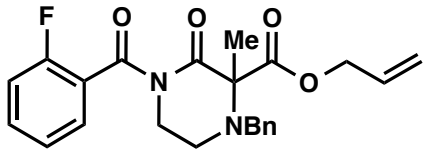
Allyl 1-benzyl-4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-2-carboxylate (8e)



Ketopiperazine **8e** was prepared according to representative procedure 1 employing 4-methoxy-benzoyl chloride instead of benzoyl chloride, and was isolated by flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a white solid. R_f = 0.4 (30% EtOAc

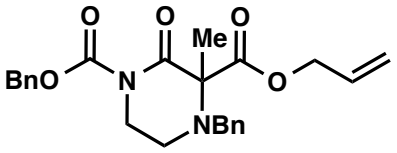
in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.65 (m, 2H), 7.39–7.32 (m, 4H), 7.29 (ddt, *J* = 8.6, 5.5, 2.9 Hz, 1H), 6.91–6.83 (m, 2H), 6.02 (ddt, *J* = 16.4, 10.4, 6.0 Hz, 1H), 5.44 (dq, *J* = 17.2, 1.3 Hz, 1H), 5.34 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.77 (dt, *J* = 5.9, 1.2 Hz, 2H), 3.98 (d, *J* = 14.0 Hz, 1H), 3.85 (s, 3H), 3.78–3.67 (m, 2H), 3.38 (d, *J* = 14.0 Hz, 1H), 3.11 (ddd, *J* = 13.2, 8.4, 5.0 Hz, 1H), 2.87 (dt, *J* = 12.6, 4.1 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 170.1, 169.6, 163.1, 138.4, 131.7, 131.0, 128.7, 128.4, 127.6, 127.4, 119.8, 113.6, 71.3, 66.5, 55.5, 54.8, 45.3, 43.0, 20.2; IR (Neat Film, NaCl) 3583, 2917, 2848, 1740, 1679, 1602, 1511, 1458, 1315, 1256, 1170, 1149, 1109, 1026, 927, 843, 739 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{24}H_{27}N_2O_5$ $[M+H]^+$: 423.1914, found 423.1879.

Allyl 1-benzyl-4-(2-fluorobenzoyl)-2-methyl-3-oxopiperazine-2-carboxylate (8f)



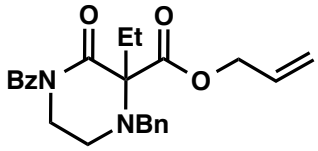
Ketopiperazine **8f** was prepared according to representative procedure 1 employing 2-fluoro-benzoyl chloride instead of benzoyl chloride, and was isolated by flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a yellow oil. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (td, *J* = 7.4, 1.7 Hz, 1H), 7.43 (dddd, *J* = 8.3, 7.2, 5.2, 1.8 Hz, 1H), 7.38–7.32 (m, 4H), 7.32–7.26 (m, 1H), 7.20 (td, *J* = 7.6, 1.0 Hz, 1H), 7.04 (ddd, *J* = 10.1, 8.3, 0.8 Hz, 1H), 6.04–5.87 (m, 1H), 5.37 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.28 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.83–4.60 (m, 2H), 3.99 (dt, *J* = 12.6, 4.0 Hz, 1H), 3.89 (d, *J* = 14.0 Hz, 1H), 3.67 (ddd, *J* = 12.7, 9.5, 4.3 Hz, 1H), 3.37 (d, *J* = 14.0 Hz, 1H), 3.14 (ddd, *J* = 13.0, 9.5, 3.7 Hz, 1H), 2.86 (dt, *J* = 12.7, 4.4 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 169.4, 168.6, 158.8 (d, $^{1}J_{CF}$ = 250.3 Hz), 138.2, 132.6 (d, $^{4}J_{CF}$ = 8.5 Hz), 131.7, 129.5, 128.7, 128.5, 127.7, 125.4 (d, $^{3}J_{CF}$ = 14.6 Hz), 124.4 (d, $^{5}J_{CF}$ = 3.4 Hz), 119.5, 115.6 (d, $^{2}J_{CF}$ = 21.6 Hz), 71.8, 66.5, 54.5, 44.7, 42.5, 20.3; IR (Neat Film, NaCl) 3066, 3029, 2944, 2847, 1743, 1690, 1614, 1491, 1453, 1379, 1301, 1230, 1146, 928, 755 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{24}FN_2O_4$ $[M+H]^+$: 411.1037, found 411.1715.

3-Allyl 1-benzyl 4-benzyl-3-methyl-2-oxopiperazine-1,3-dicarboxylate (8g)



Ketopiperazine **8g** was prepared according to representative procedure 1 employing benzyl chloroformate instead of benzoyl chloride, and was isolated by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 20% EtOAc in hexanes) as a yellow oil. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.32 (m, 2H), 7.32–7.25 (m, 2H), 7.25–7.21 (m, 5H), 7.21–7.16 (m, 1H), 5.86 (ddt, *J* = 17.1, 10.5, 5.8 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (d, *J* = 2.6 Hz, 2H), 5.18 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.74–4.55 (m, 2H), 3.78 (d, *J* = 14.0 Hz, 1H), 3.70 (dt, *J* = 12.2, 3.9 Hz, 1H), 3.55–3.46 (m, 1H), 3.23 (d, *J* = 14.0 Hz, 1H), 2.97 (ddd, *J* = 13.1, 9.7, 3.7 Hz, 1H), 2.65 (dt, *J* = 12.7, 4.3 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 168.9, 153.6, 138.2, 135.3, 131.7, 128.7, 128.6, 128.5, 128.4, 128.2, 127.6, 119.2, 72.2, 68.9, 66.2, 54.4, 46.2, 42.5, 20.9; IR (Neat Film, NaCl) 2944, 2848, 1779, 1723, 1495, 1456, 1378, 1315, 1283, 1213, 1112, 1021, 995, 781, 739 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{24}H_{27}N_2O_5$ $[M+H]^+$: 423.1914, found 423.1913.

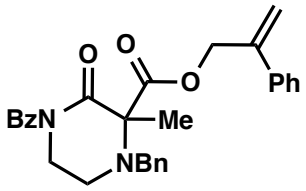
Allyl 4-benzoyl-1-benzyl-2-ethyl-3-oxopiperazine-2-carboxylate (8h)



Ketopiperazine **8h** was prepared according to representative procedure 1 employing ethyl iodide instead of methyl iodide, and was isolated by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 20% EtOAc in hexanes) as a yellow oil. R_f = 0.6 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.63 (m, 2H), 7.53–7.46 (m, 1H), 7.42–7.33 (m, 6H), 7.32–7.27 (m, 1H), 6.04 (ddt, *J* = 17.1, 10.4, 6.0 Hz, 1H), 5.46 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.37 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.84–4.75 (m, 2H), 4.08 (d, *J* = 14.0 Hz, 1H), 3.83 (dt, *J* = 12.6, 2.8 Hz, 1H), 3.69 (td, *J* = 12.2, 3.8 Hz, 1H), 3.29 (d, *J* = 14.0

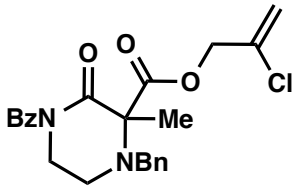
Hz, 1H), 3.17 (td, *J* = 12.1, 3.1 Hz, 1H), 2.95 (ddd, *J* = 12.4, 3.6, 2.5 Hz, 1H), 2.30 (dq, *J* = 14.6, 7.3 Hz, 1H), 2.15 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 169.2, 169.0, 138.2, 135.7, 132.1, 131.7, 128.8, 128.4, 128.3, 128.2, 127.6, 119.9, 75.0, 66.3, 54.5, 44.9, 43.0, 26.1, 8.4; IR (Neat Film, NaCl) 3063, 3030, 2960, 2839, 1744, 1683, 1600, 1495, 1451, 1400, 1377, 1321, 1284, 1225, 1151, 1119, 1082, 987, 962, 940, 796, 738, 720 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{24}H_{27}N_2O_4$ $[M+H]^+$: 407.1965, found 407.1950.

2-Phenylallyl 4-benzoyl-1-benzyl-2-methyl-3-oxopiperazine-2-carboxylate (8l)



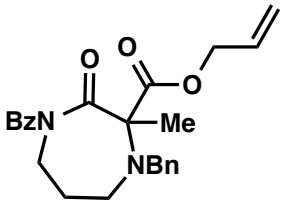
Ketopiperazine **8l** was prepared according to representative procedure 1 starting from **10d** instead of **10a**, and was isolated by flash column chromatography (SiO_2, 15% EtOAc in hexaes) as a yellow oil. R_f = 0.4 (15% EtOAc in hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.56 – 7.44 (m, 3H), 7.42 – 7.35 (m, 4H), 7.35 – 7.30 (m, 3H), 7.30 – 7.26 (m, 1H), 7.23 (d, *J* = 6.9 Hz, 2H), 5.63 (s, 1H), 5.57 – 5.44 (m, 1H), 5.32 (dd, *J* = 12.9, 0.9 Hz, 1H), 5.15 – 4.99 (m, 1H), 3.87 (d, *J* = 14.0 Hz, 1H), 3.69 – 3.56 (m, 2H), 3.12 (d, *J* = 14.0 Hz, 1H), 2.82 (ddd, *J* = 13.8, 9.5, 4.5 Hz, 1H), 2.67 (dt, *J* = 12.7, 3.9 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 170.2, 169.5, 142.5, 138.3, 138.0, 135.6, 131.9, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.5, 126.4, 117.2, 71.3, 67.3, 54.4, 45.1, 42.6, 20.6; IR (Neat Film, NaCl) 3060, 3029, 3001, 2944, 2900, 2845, 1741, 1686, 1600, 1495, 1466, 1449, 1400, 1379, 1316, 1284, 1236, 1150, 1107, 1028, 918, 780, 723 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{29}H_{29}N_2O_4$ $[M+H]^+$: 469.2122, found 469.2122.

2-Chloroallyl 4-benzoyl-1-benzyl-2-methyl-3-oxopiperazine-2-carboxylate (8m)



Ketopiperazine **8m** was prepared according to representative procedure 1 starting from **10c** instead of **10a**, and was isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a yellow oil. R_f = 0.4 (15% EtOAc in hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 2H), 7.54 – 7.48 (m, 1H), 7.44 – 7.38 (m, 2H), 7.38 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 5.59 (dt, *J* = 1.9, 1.0 Hz, 1H), 5.51 (d, *J* = 1.9 Hz, 1H), 4.88 (d, *J* = 14.0 Hz, 1H), 4.80 (d, *J* = 13.3 Hz, 1H), 4.00 (d, *J* = 14.0 Hz, 1H), 3.86 (dt, *J* = 12.4, 3.8 Hz, 1H), 3.73 (ddd, *J* = 12.4, 10.0, 4.1 Hz, 1H), 3.45 (d, *J* = 14.0 Hz, 1H), 3.19 (ddd, *J* = 13.5, 10.0, 3.6 Hz, 1H), 2.91 (dt, *J* = 12.7, 4.1 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 170.1, 169.1, 138.3, 135.7, 135.4, 132.0, 128.7, 128.5, 128.3, 128.2, 127.7, 116.9, 71.6, 67.4, 54.7, 45.2, 43.0, 20.5; IR (Neat Film, NaCl) 3062, 3029, 2946, 2846, 1746, 1686, 1639, 1600, 1495, 1450, 1401, 1379, 1316, 1283, 1234, 1177, 1150, 1105, 1027, 1000, 971, 912, 724 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{24}N_2O_4Cl$ $[M+H]^+$: 427.1419, found 427.1420.

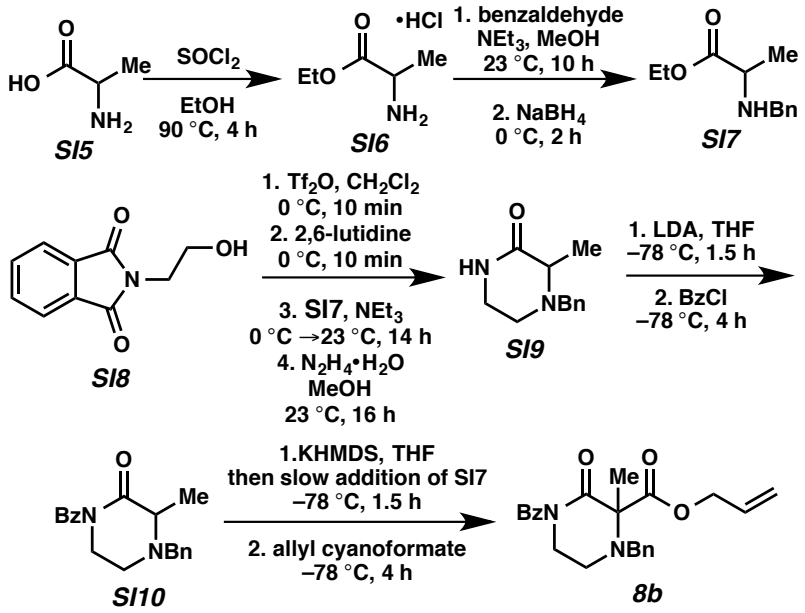
Allyl 4-benzoyl-1-benzyl-2-methyl-3-oxo-1,4-diazepane-2-carboxylate (8o)



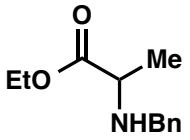
1,4-Diazepane **8o** was prepared according to representative procedure 1 employing 1,3-diaminopropane instead of ethylene diamine, and was isolated by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 20% EtOAc in hexanes) as a colorless solid. R_f = 0.7 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.52 – 7.45 (m, 1H), 7.43–7.30 (m, 5H), 7.28 (m, 2H), 6.00 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.44 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.33 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.87–4.70 (m, 2H), 4.29 (ddd, *J* = 14.4, 8.8, 3.0 Hz, 1H), 3.92 (ddd, *J* = 14.4, 6.1, 3.0 Hz, 1H), 3.77 (d, *J* =

14.2 Hz, 1H), 3.68 (d, J = 14.2 Hz, 1H), 3.44 (ddd, J = 15.4, 10.9, 4.9 Hz, 1H), 2.89 (ddd, J = 15.4, 6.1, 3.0 Hz, 1H), 1.79 (s, 3H), 1.78–1.73 (m, 1H), 1.69–1.62 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 173.7, 170.4, 139.3, 136.2, 131.9, 131.6, 128.6, 128.4, 128.3, 128.1, 127.4, 119.8, 75.1, 66.5, 53.1, 46.8, 42.9, 26.9, 22.7; IR (Neat Film, NaCl) 3062, 3028, 2945, 1742, 1682, 1600, 1494, 1450, 1377, 1357, 1281, 1256, 1139, 1104, 1024, 947, 793, 740, 724 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{24}H_{27}N_2O_4$ $[M+H]^+$: 407.1965, found 407.1966.

Representative Procedure 2 for the Preparation of 3-oxopiperazine-2-carboxylates



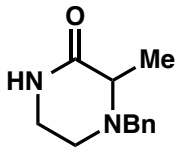
N-Benzylalanine ethyl ester (SI7)



D,L-Alanine **(SI5**, 1.50 g, 16.8 mmol) was dissolved in EtOH (100 mL) and cooled to 0 °C. Thionyl chloride (3.67 mL, 50.5 mmol) was then added dropwise and the resulting solution was heated to reflux for 5 hours. The reaction mixture was then cooled to 23 ºC and excess thionyl chloride and ethanol were removed by rotary evaporation to yield

alanine ethyl ester hydrogen chloride salt (**SI6**) which was used in the following step without further purification. Alanine ester hydrogen chloride salt (**SI6**) was dissolved in MeOH (17 mL). Then triethylamine (2.6 mL, 18.8 mmol) was added and the solution was allowed to stir for 15 minutes at which point benzaldehyde (1.74 mL, 17.1 mmol) was added neat. The resulting solution was allowed to stir for 10 hours open to air. Then the solution was cooled to 0 °C and $NaBH_4$ (1.29 g, 34.1 mmol) was added portionwise. The mixture was allowed to stir overnight. The reaction mixture was then carefully poured into 25 mL of 2 N HCl and was washed with Et_2O (1 x 20 mL). The aqueous layer was then basified with 2 N NaOH and was extracted with CH_2Cl_2 (4 x 40 mL). The organic layers were combined and washed once with brine, dried with $MgSO_4$, and concentrated under reduced pressure to give N-benzylalanine ethyl ester (**SI7**) in a 90% yield from alanine (**SI5**). Product identity was confirmed by comparison to previously reported characterization data.

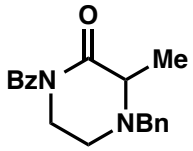
4-Benzyl-3-methylpiperazin-2-one (SI9)



A solution of N-(2-hydroxyethyl)phthalimide (**SI8**, 769 mg, 4.00 mmol) in CH_2Cl_2 (4 mL) under argon atmosphere was cooled to 0 °C. Triflic anhydride (0.81 mL, 4.82 mmol) was added dropwise, and the resulting solution was allowed to stir for 10 minutes at 0°C. Then 2,6-lutidine (560 μL, 4.82 mmol) was added and allowed to stir for another 10 minutes before triethylamine (670 μL, 4.82 mmol) and **SI7** (suspended in 4 mL of CH_2Cl_2) were added sequentially in dropwise fashion. The solution was warmed to 23 ºC and allowed to stir overnight under Ar atmosphere. The reaction mixture was diluted with additional CH_2Cl_2 and washed with 10% aqueous citric acid (2 x 10 mL). The organics were dried with Na_2SO_4 and concentrated. The resulting oil was taken up in MeOH (22 mL), hydrazine hydrate (0.45 mL, 9.20 mmol) was added, and the mixture was allowed to stir overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Ketopiperazine **SI9** was isolated by flash column

chromatography (SiO_2, 3% MeOH in CH_2Cl_2 to 5% MeOH in CH_2Cl_2) as a yellow solid. 54% yield. R_f = 0.5 (10% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 6.02 (br s, 1H), 3.94 (d, *J* = 13.5 Hz, 1H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.36–3.17 (m, 3H), 2.91 (dt, *J* = 12.3, 4.8 Hz, 1H), 2.48 (ddd, *J* = 12.3, 7.4, 4.5 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 138.2, 128.9, 128.5, 127.4, 60.3, 58.3, 45.3, 41.2, 15.5; IR (Neat Film, NaCl) 3203, 3057, 2983, 2953, 2923, 2878, 2819, 1667, 1495, 1451, 1345, 1303, 1147, 1088, 1072, 1051, 1024, 890, 822, 750 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.1335, found 205.1338.

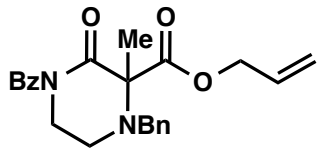
1-Benzoyl-4-benzyl-3-methylpiperazin-2-one (SI10)



Ketopiperazine (**SI9**, 24.7 mg, 1.21 mmol) was dissolved in 6 mL of dry THF and added by cannula to a freshly prepared solution of LDA (1.45 mmol) in 6.1 mL dry THF at –78 °C. The reaction mixture was allowed to stir at –78 °C for 1.5 hours at which point benzoyl chloride (0.18 mL, 1.57 mmol) was added dropwise. The reaction was stirred at –78 °C for another 4 hours at which point full conversion of the starting material was observed by TLC analysis. The reaction mixture was warmed to room temperature and poured into 15 mL of H_2O and extracted with EtOAc (4 x 20 mL). The organics were combined and washed once with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Ketopiperazine **SI10** was isolated by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 15% EtOAc in hexanes) as a colorless solid. 81% yield. R_f = 0.5 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (app d, *J* = 7.3 Hz, 2H), 7.52–7.45 (m, 1H), 7.44–7.33 (m, 6H), 7.34–7.27 (m, 1H), 3.99 (d, *J* = 13.5 Hz, 1H), 3.95–3.83 (m, 1H), 3.77–3.59 (m, 1H), 3.46 (d, *J* = 13.5 Hz, 1H), 3.37 (app q, *J* = 6.1 Hz, 1H), 3.18–3.01 (m, 1H), 2.73–2.51 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 173.5, 136.0, 131.8, 129.9, 129.0, 128.7, 128.3, 128.0, 127.7, 62.3, 58.3, 46.0, 44.7, 15.7; IR (Neat Film, NaCl) 3085, 3062, 3029, 2979, 2942, 2898, 2814, 1693, 1600, 1583, 1455, 1367, 1286, 1228, 1145, 1096, 1075, 1027, 978, 945, 896, 872, 795,

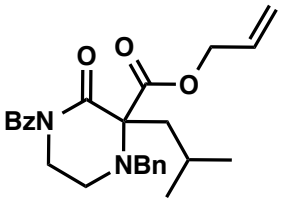
749 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{21}N_2O_2$ $[M+H]^+$: 309.1598, found 309.1599.

Allyl 4-benzoyl-1-benzyl-2-methyl-3-oxopiperazine-2-carboxylate (8b)



To a cooled solution of KHMDS (64.0 g, 3.19 mmol) in THF (20 mL) at –78 ºC was added a solution of ketopiperazine (**SI10**, 89.0 g, 2.90 mmol) in THF (10 mL) over a period of 6.5 hours by syringe pump. The resulting solution was allowed to stir for an additional 30 minutes at which point allyl cyanoformate (39.0 g, 3.48 mmol) was added neat. The reaction mixture was stirred at –78 °C for 2 hours at which point full conversion of the starting material was observed by TLC analysis. The reaction mixture was warmed to 23 ºC, poured into 15 mL of H_2O, and extracted with EtOAc (4 x 20 mL). The organics were combined, washed once with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Ketopiperazine **8b** was isolated by flash column chromatography (SiO_2, 15% EtOAc in hexanes to 20% EtOAc in hexanes) as a light yellow solid. 61% yield. Product identity was confirmed by comparison to characterization data reported above.

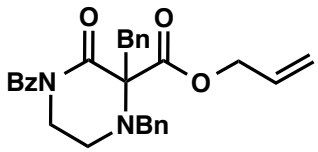
Allyl 4-benzoyl-1-benzyl-2-isobutyl-3-oxopiperazine-2-carboxylate (8i)



Ketopiperazine **8i** was prepared according to representative procedure 2 starting from D,L-leucine instead of D,L-alanine, and was isolated by flash column chromatography (SiO_2, 10% Et_2O in hexanes to 15% Et_2O in hexanes) as a white solid. R_f = 0.4 (20% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.72–7.65 (m, 2H), 7.53–7.46 (m, 1H), 7.41–7.32 (m, 6H), 7.32–7.27 (m, 1H), 6.05 (ddt, *J* = 17.1, 10.4, 6.0 Hz, 1H), 5.46 (dq, *J*

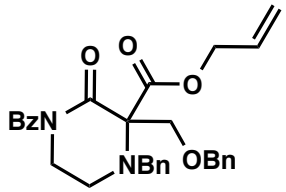
= 17.1, 1.4 Hz, 1H), 5.38 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.85–4.76 (m, 2H), 4.11 (d, *J* = 14.0 Hz, 1H), 3.86–3.71 (m, 2H), 3.23 (d, *J* = 14.0 Hz, 1H), 3.15 (ddd, *J* = 12.4, 10.1, 5.1 Hz, 1H), 2.95 (dt, *J* = 12.4, 3.0 Hz, 1H), 2.28 (dd, *J* = 15.0, 4.3 Hz, 1H), 2.18 (dd, *J* = 15.0, 9.3 Hz, 1H), 2.04 (ddtd, *J* = 10.1, 9.3, 6.7, 4.3 Hz, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 169.0, 168.8, 137.9, 135.6, 132.1, 131.7, 128.8, 128.5, 128.3, 128.1, 127.6, 120.0, 73.8, 66.4, 54.8, 45.0, 43.0, 40.2, 24.7, 23.8, 22.4; IR (Neat Film, NaCl) 3063, 3030, 2958, 2870, 1739, 1687, 1683, 1601, 1495, 1451, 1368, 1317, 1284, 1227, 1151, 1107, 984, 935, 795, 767, 722 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{31}N_2O_4$ $[M+H]^+$: 435.2278, found 435.2291.

Allyl 4-benzoyl-1,2-dibenzyl-3-oxopiperazine-2-carboxylate (8j)



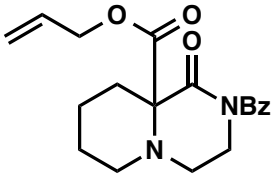
Ketopiperazine **8j** was prepared according to representative procedure 2 starting from D,L-phenylalanine instead of D,L-alanine, and was isolated by flash column chromatography (SiO_2, 15% Et_2O in hexanes) as a white solid. R_f = 0.5 (30% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.44 (m, 3H), 7.40–7.32 (m, 4H), 7.29 (app s, 6H), 7.22 (app d, *J* = 7.1 Hz, 2H), 6.07 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.49 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.39 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.94–4.77 (m, 2H), 4.29 (d, *J* = 13.8 Hz, 1H), 3.77–3.64 (m, 1H), 3.61 (d, *J* = 14.6 Hz, 1H), 3.44 (d, *J* = 14.6 Hz, 1H), 3.32 (d, *J* = 13.8 Hz, 1H), 3.19–3.04 (m, 2H), 2.93–2.82 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 168.9, 168.6, 137.3, 135.9, 135.5, 132.1, 131.6, 131.0, 128.7, 128.7, 128.4, 128.3, 128.1, 127.6, 127.1, 120.0, 75.5, 66.6, 54.5, 44.1, 43.1, 38.7; IR (Neat Film, NaCl) 3086, 3062, 3030, 2845, 1738, 1690, 1601, 1495, 1455, 1403, 1373, 1322, 1283, 1242, 1218, 1102, 1029, 942, 860, 794, 771 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{29}H_{29}N_2O_4$ $[M+H]^+$: 469.2122, found 469.2133.

Allyl 4-benzoyl-1-benzyl-2-[(benzyloxy)methyl]-3-oxopiperazine-2-carboxylate (8k)



Ketopiperazine **8k** was prepared according to representative procedure 2 starting from O-(phenylmethyl)-(L)-serine instead of D,L-alanine, and was isolated by flash column chromatography (SiO_2, 10% EtOAc in hexanes) as a colorless solid. R_f = 0.4 (20% EtOAc in hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 2H), 7.51–7.43 (m, 1H), 7.42–7.36 (m, 4H), 7.36–7.27 (m, 8H), 5.96 (ddt, *J* = 17.1, 10.4, 6.0 Hz, 1H), 5.39 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.35–5.27 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.77–4.64 (m, 3H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.20 (d, *J* = 10.0 Hz, 1H), 4.07 (d, *J* = 10.0 Hz, 1H), 4.03–3.91 (m, 2H), 3.81–3.66 (m, 1H), 3.50 (d, *J* = 14.0 Hz, 1H), 3.18 (ddd, *J* = 12.7, 9.5, 4.2 Hz, 1H), 3.10 (dt, *J* = 12.2, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 168.7, 168.0, 138.3, 137.9, 135.5, 132.0, 131.5, 128.7, 128.6, 128.4, 128.4, 128.1, 127.9, 127.8, 127.6, 119.8, 74.7, 74.0, 71.4, 66.4, 54.4, 44.7, 43.5; IR (Neat Film, NaCl) 3062, 3027, 2938, 2853, 1738, 1687, 1600, 1495, 1452, 1376, 1321, 1284, 1226, 1148, 1099, 1047, 973, 940, 795, 743 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{30}H_{31}N_2O_5$ $[M+H]^+$: 499.2227, found 499.2229.

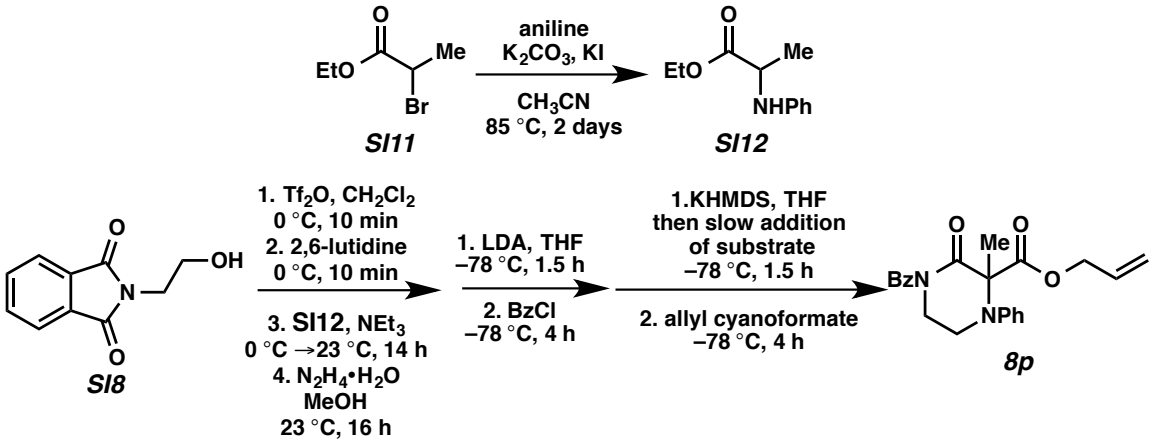
Allyl 2-benzoyl-1-oxooctahydro-9a*H*-pyrido[1,2-*a*]pyrazine-9a-carboxylate (8n)



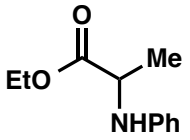
Bicycle **8n** was prepared according to representative procedure 2 starting from pipecolic acid and omitting the benzyl protection operation, and was isolated by flash column chromatography (SiO_2, 15% EtOAc and 1% NEt_3 in hexanes) as a white solid. R_f = 0.3 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.59 (m, 2H), 7.51–7.44 (m, 1H), 7.40–7.33 (m, 2H), 6.00 (ddt, *J* = 17.1, 10.4, 6.0 Hz, 1H), 5.41 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.34 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.76 (dt, *J* = 6.0, 1.4 Hz, 2H), 4.04 (td, *J* = 11.9,

5.5 Hz, 1H), 3.66 (ddd, J = 12.6, 4.7, 2.9 Hz, 1H), 3.49 (ddd, J = 12.9, 11.9, 4.7 Hz, 1H), 3.23–3.07 (m, 1H), 3.07–2.94 (m, 1H), 2.87–2.66 (m, 1H), 2.31–2.15 (m, 1H), 1.88 (m, 1H), 1.75–1.47 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 169.9, 169.8, 135.7, 131.9, 131.4, 128.2, 128.1, 120.0, 70.3, 66.4, 50.0, 47.2, 44.4, 31.3, 24.7, 20.6; IR (Neat Film, NaCl) 2940, 2860, 1721, 1683, 1600, 1449, 1382, 1355, 1283, 1244, 1150, 1124, 987, 940, 726 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{23}N_2O_4$ $[M+H]^+$: 343.1652, found 343.1665.

Procedure for the Preparation of Allyl 4-benzoyl-2-methyl-3-oxo-1-phenylpiperazine-2-carboxylate (8p)

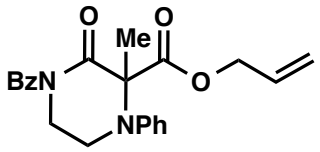


Ethyl phenylalaninate (SI12)



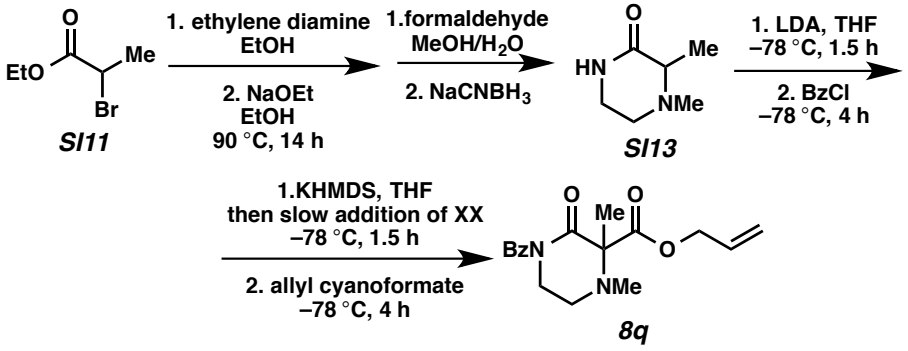
Ethyl 2-bromopropionate (**SI11**, 2 mL, 15.4 mmol) was taken up in acetonitrile (18 mL) along with aniline (1.17 mL, 12.8 mmol), potassium carbonate (3.37 g, 24.4 mmol), and potassium iodide (0.26 g, 0.12 mmol) and heated to reflux for 48 hours. The reaction mixture was filtered and the filtrate concentrated. Ethyl phenylalaninate (**SI12**) was isolated by flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a colorless solid. R_f= 0.6 (30% EtOAc in hexanes). Product identity was confirmed by comparison to previously reported characterization data.

Allyl 4-benzoyl-2-methyl-3-oxo-1-phenylpiperazine-2-carboxylate (8p)

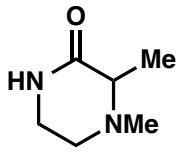


Cyclization, benzoyl protection, and acylation were accomplished as described in representative procedure 2. Ketopiperazine **8p** was isolated by preparative HPLC (SiO_2, 20% EtOAc in hexanes) as a colorless solid. R_f= 0.4 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 2H), 7.55–7.47 (m, 1H), 7.40 (app t, *J* = 7.7 Hz, 2H), 7.35–7.27 (m, 2H), 7.12 (app t, *J* = 7.4 Hz, 1H), 7.10–7.03 (m, 2H), 5.85 (ddt, *J* = 17.2, 10.4, 7.0 Hz, 1H), 5.30 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.25 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.63 (d, *J* = 7.0 Hz, 2H), 4.10 (ddd, *J* = 10.8, 4.7, 2.8 Hz, 1H), 4.05–3.92 (m, 2H), 3.55–3.44 (m, 1H), 1.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 170.5, 169.7, 147.0, 135.4, 132.0, 131.3, 129.1, 128.3, 128.1, 124.6, 123.8, 119.5, 71.9, 66.5, 46.2, 44.9, 21.7; IR (Neat Film, NaCl) 3061, 3028, 2945, 2903, 2862, 1743, 1693, 1599, 1495, 1450, 1398, 1373, 1283, 1179, 1115, 1075, 961, 865, 842, 811, 724 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{23}N_2O_4$ $[M+H]^+$: 379.1652, found 379.1656.

Procedure for the Preparation of Allyl 4-benzoyl-1,2-dimethyl-3-oxopiperazine-2-carboxylate (8q)

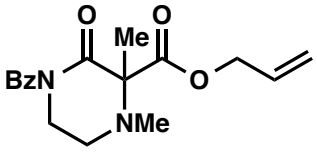


3,4-Dimethylpiperazin-2-one (SI13)



To a solution of ethylene diamine (4.0 mL, 60.0 mmol) in EtOH (23 mL) at 0 °C was added ethyl 2-bromopropionate (**SI11**, 3.89 mL, 30.0 mmol) dropwise. The solution was warmed to 23 ºC and allowed to stir overnight open to air. The resulting white solid was removed by filtration, and the filtrate was transferred to a flame-dried flask containing sodium ethoxide (4.49 g, 66.0 mmol). The solution was then heated to 80 °C and allowed to stir for 16 hours. The solution was cooled to 23 ºC and concentrated. Half of the material was then taken up in 13.2 mL of MeOH. Formaldehyde (37%, 0.88 mL, 10.0 mmmol) was then added and the mixture was allowed to stir for 12 hours at 23 ºC, at which point $NaBH_3CN$ (0.77 g, 12.2 mmol) was added and the mixture was allowed to stir overnight open to air. N-methyl ketopiperazine **SI13** was isolated as a colorless solid by flash chromatography (SiO_2, 5% MeOH in CH_2Cl_2 to 20% MeOH in CH_2Cl_2). 49% yield. R_f = 0.5 (20% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (br s, 1H), 3.43 (td, *J* = 11.0, 10.5, 4.2 Hz, 1H), 3.32–3.10 (m, 1H), 2.87 (dt, *J* = 12.2, 3.9 Hz, 1H), 2.85–2.79 (m, 1H), 2.51 (ddd, *J* = 12.1, 10.0, 4.0 Hz, 1H), 2.36 (s, 3H), 1.36 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 62.6, 50.5, 43.3, 40.7, 15.5; IR (Neat Film, NaCl) 3194, 2986, 2951, 2903, 2846, 2799, 1660, 1495, 1455, 1418, 1354, 1316, 1296, 1249, 1223, 1137, 1097, 1034, 893, 854, 826, 782 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_6H_{13}N_2O$ $[M+H]^+$: 129.1022, found 129.1023.

Allyl 4-benzoyl-1,2-dimethyl-3-oxopiperazine-2-carboxylate (8q)

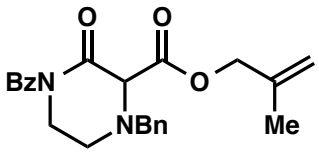


Benzoyl protection of and acylation were carried out as described in representative procedure 2. Ketopiperazine **8q** was isolated by flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a colorless oil. R_f = 0.5 (40% EtOAc in hexanes); ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.68–7.58 (m, 2H), 7.53–7.43 (m, 1H), 7.42–7.32 (m, 2H), 5.97 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.40 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.31 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.79–4.66 (m, 2H), 3.93–3.82 (m, 2H), 3.28 (ddd, *J* = 12.7, 8.4, 5.5 Hz, 1H), 2.94 (app dt, *J* = 12.6, 4.2 Hz, 1H), 2.43 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 170.3, 169.0, 135.5, 132.0, 131.6, 128.2, 128.1, 119.7, 71.2, 66.4, 47.3, 44.6, 39.1, 19.5; IR (Neat Film, NaCl) 3062, 2994, 2950, 2900, 2811, 1742, 1691, 1601, 1450, 1398, 1372, 1315, 1275, 1219, 1153, 1109, 1046, 929, 887, 795, 754, 724 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{20}N_2O_4Na$ $[M+Na]^+$: 339.1315, found 339.1320.

Procedure for the Preparation of 2-Substituted allyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylates

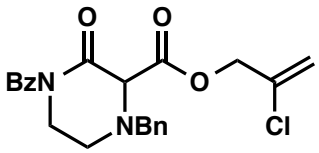
2-Methylallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10b)



LiHMDS (120 mg, 0.61 mmol) was suspended in 1.5 mL of THF and cooled to –78 °C. Then ketopiperazine (**SI4**, 150 mg, 0.51 mmol) dissolved in THF (600 μL) was added dropwise to the LiHMDS solution and allowed to stir at –78 °C for 30 minutes, at which point 2-methylallyl 1*H*-imidazole-1-carboxylate (110 mg, 0.66 mmol) dissolved in 0.5 mL of THF was added dropwise. The reaction mixture was allowed to stir for 6 hours at –78 °C at which point full conversion of the starting material was observed by TLC analysis. The reaction mixture was then warmed to 23 ºC and poured into 5 mL of water. The aqueous layer was extracted with EtOAc (4 x 10 mL), the combined organics washed with brine (1 x 10 mL), and dried with Na_2SO_4. 2-Methylallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (**10b**) was isolated as a yellow oil by flash column chromatography (SiO_2, 20% EtOAc in hexanes). 14% yield. R_f = 0.3 (20% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.58 (m, 2H), 7.49 (tt, *J* = 7.1, 1.2 Hz, 1H), 7.42–7.34 (m, 6H), 7.33–7.27 (m, 1H), 5.03 (d, *J* = 31.1 Hz, 2H), 4.66 (s, 2H), 4.19

(s, 1H), 3.94 (ddd, *J* = 12.6, 8.3, 4.3 Hz, 1H), 3.89–3.78 (m, 2H), 3.76 (ddd, *J* = 12.6, 5.6, 4.0 Hz, 1H), 3.33 (ddd, *J* = 12.4, 8.3, 3.9 Hz, 1H), 2.82 (dt, *J* = 12.4, 4.8 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 167.8, 166.6, 139.2, 136.5, 135.3, 132.2, 129.1, 128.7, 128.4, 128.3, 128.0, 114.5, 69.6, 69.2, 58.7, 44.9, 44.8, 19.8; IR (Neat Film, NaCl) 3062, 3030, 2925, 2853, 1740, 1687, 1600, 1494, 1450, 1402, 1381, 1369, 1282, 1233, 1155, 1074, 1028, 990, 950, 907, 793, 731 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{25}N_2O_4$ $[M+H]^+$: 393.1809, found 393.1809.

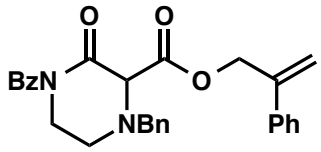
2-Chloroallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10c)



LiHMDS (100 mg, 0.61 mmol) was suspended in 2 mL of THF and cooled to –78 °C. Ketopiperazine (**SI4**, 150 mg, 0.51 mmol) dissolved in THF (2 mL) was then added dropwise and the solution allowed to stir at –78 °C for 30 minutes. 2-Chloroallyl 1*H*-imidazole-1-carboxylate (130 mg, 0.66 mmol) dissolved in 1 mL of THF was then added dropwise. The reaction mixture was allowed to stir for 8 hours at –78 °C and then warmed to 23 ºC and allowed to stir overnight. The reaction mixture was then poured into 10 mL of water, extracted with EtOAc (4 x 15 mL), the combined organics washed with brine (1 x 15 mL), and dried with Na_2SO_4. 2-Chloroallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (**10c**) was isolated as a yellow oil by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 15% EtOAc in hexanes). 46% yield. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.61 (m, 2H), 7.53–7.46 (m, 1H), 7.39 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.38–7.35 (m, 4H), 7.32 (ttd, *J* = 8.7, 4.3, 3.7, 2.4 Hz, 1H), 5.54 (dt, *J* = 2.1, 1.1 Hz, 1H), 5.46 (d, *J* = 1.9 Hz, 1H), 4.80 (s, 2H), 4.21 (s, 1H), 3.94 (ddd, *J* = 12.5, 8.2, 4.3 Hz, 1H), 3.90–3.79 (m, 2H), 3.79–3.73 (m, 1H), 3.33 (ddd, *J* = 12.3, 8.1, 3.9 Hz, 1H), 2.89–2.76 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 167.3, 166.3, 136.3, 135.2, 135.0, 132.3, 129.1, 128.8, 128.4, 128.3, 128.1, 116.5, 69.5, 67.2, 58.8, 44.9, 44.9; IR (Neat Film, NaCl) 3060, 3030, 2949, 2898, 2830, 1744, 1689, 1599, 1491, 1448, 1381, 1280, 1232, 1178, 1138, 1074, 1026, 982, 906, 841, 795,

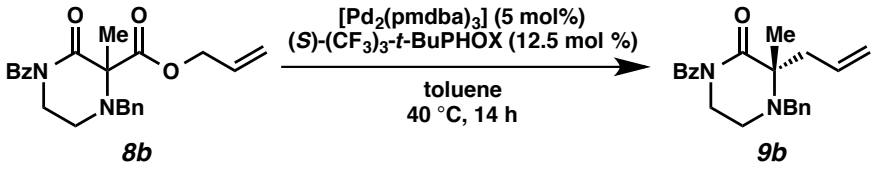
730 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{22}ClN_2O_4$ $[M+H]^+$: 413.1263, found 413.1261.

2-Phenylallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10d)

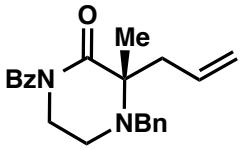


LiHMDS (140 mg, 0.83 mmol) was suspended in 3 mL of THF and cooled to –78 °C. Ketopiperazine (**SI4**, 200 mg, 0.69 mmol) dissolved in THF (3 mL) was then added dropwise to the LiHMDS solution and allowed to stir at –78 °C for 30 minutes. 2-Phenylallyl 1*H*-imidazole-1-carboxylate (210 mg, 0.90 mmol) dissolved in 1 mL of THF was then added dropwise. The reaction mixture was allowed to stir for 12 hours at –78 °C and then warmed to 23 ºC and poured into 10 mL of water. The aqueous layer was extracted with EtOAc (4 x 15 mL). The combined organics were washed with brine (1 x 15 mL), and dried with Na_2SO_4. 2-Phenylallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (**10d**) was isolated as a yellow oil by flash column chromatography (SiO_2, 5% EtOAc in hexanes). 21% yield. R_f = 0.4 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.60 (m, 2H), 7.52–7.42 (m, 3H), 7.40–7.35 (m, 2H), 7.35–7.31 (m, 3H), 7.31–7.26 (m, 3H), 7.24–7.17 (m, 2H), 5.64–5.57 (m, 1H), 5.46 (d, *J* = 0.9 Hz, 1H), 5.24–5.10 (m, 2H), 4.13 (s, 1H), 3.87 (ddd, *J* = 12.7, 8.5, 4.4 Hz, 1H), 3.69–3.60 (m, 3H), 3.13 (ddd, *J* = 12.5, 8.5, 3.9 Hz, 1H), 2.71 (dt, *J* = 12.2, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 167.8, 166.5, 142.2, 137.9, 136.5, 135.3, 132.1, 129.0, 128.8, 128.6, 128.4, 128.4, 128.3, 127.9, 126.3, 116.9, 69.5, 67.2, 58.4, 44.9, 44.5; IR (Neat Film, NaCl) 3061, 3027, 2925, 2849, 1738, 1688, 1600, 1495, 1450, 1402, 1369, 1281, 1232, 1154, 1074, 1028, 977, 913, 780, 731 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{28}H_{27}N_2O_4$ $[M+H]^+$: 455.1965, found 455.1965.

Representative Procedure for the Asymmetric Decarboxylative Allylic Alkylation of 3-Oxopiperazine-2-carboxylates, 1,4-Diazepane-2-carboxylates, 1-Oxooctahydro-9a*H*-pyrido[1,2-*a*]pyrazine-9a-carboxylates, and 3-Oxo-1,4-diazaspiro[4.5]decane-2-carboxylates



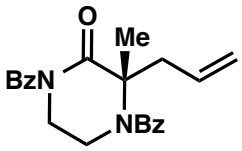
(*S*)-3-Allyl-1-benzoyl-4-benzyl-3-methylpiperazin-2-one (9b)



In a nitrogen-filled glovebox, an oven-dried 20 mL scintillation vial was charged with $[Pd_2(pmdba)_3]$ (27.4 mg, 0.025 mmol, 0.05 equiv) or $[Pd_2(dba)_3]$ (22.9 mg, 0.025 mmol, 0.05 equiv), (*S*)-$(CF_3)_3$-*t*-BuPHOX (37.0 mg, 0.063 mmol, 0.125 equiv), toluene (15 mL or 13 mL if the substrate is an oil), and a magnetic stir bar. The vial was stirred at ambient glovebox temperature (~28 °C) for 30 min and then the substrate (**8b**, 182 mg, 0.50 mmol) was added either as a solid or as a solution in toluene (2 mL). The vial thus charged was sealed and heated to 40 °C. When complete consumption of the starting material was observed by thin layer chromatography, the reaction mixture was removed from the glovebox, concentrated under reduced pressure, and purified by flash chromatography to afford the desired alkylated product. Ketopiperazine **9b** was isolated as a yellow oil by flash column chromatography (SiO_2, 10% Et_2O and 0.2% Me_2NEt in hexanes). 89% yield. R_f = 0.4 (10% EtOAc in hexanes, two developments); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.53 (m, 2H), 7.52–7.45 (m, 1H), 7.44–7.33 (m, 6H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.06 (ddt, *J* = 17.1, 10.3, 7.2 Hz, 1H), 5.24–5.10 (m, 2H), 4.02 (d, *J* = 13.6 Hz, 1H), 3.87 (d, *J* = 12.2 Hz, 1H), 3.60 (td, *J* = 11.9, 4.0 Hz, 1H), 3.43 (d, *J* = 13.3 Hz,

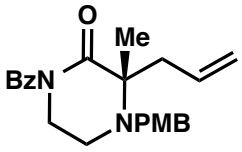
1H), 2.98–2.74 (m, 3H), 2.64 (dd, *J* = 14.9, 6.5 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 174.3, 138.9, 136.3, 134.0, 131.6, 128.7, 128.2, 127.8, 127.5, 118.1, 67.3, 53.0, 45.1, 42.2, 41.5, 18.7; IR (Neat Film, NaCl) 3063, 3029, 2974, 2827, 1701, 1684, 1601, 1494, 1449, 1378, 1363, 1317, 1286, 1223, 1152, 1134, 1027, 993, 912, 794, 724 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$: 349.1911, found 349.1898; $[\alpha]_D^{25.0}$ –58.4 (c 0.97, MeOH, 91% ee).

(*S*)-(2-Allyl-2-methyl-3-oxopiperazine-1,4-diyl)bis(phenylmethanone) (9a)



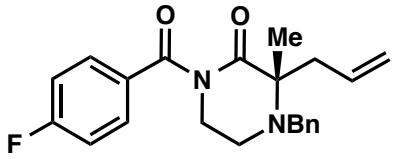
Ketopiperazine **9a** was isolated as an off-white foam by flash column chromatography (SiO_2, 15% EtOAc in hexanes to 25% EtOAc in hexanes). 89% yield. R_f = 0.4 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.54 (m, 2H), 7.54–7.50 (m, 1H), 7.49–7.37 (m, 7H), 5.85 (dddd, *J* = 17.0, 10.1, 8.7, 6.2 Hz, 1H), 5.24 (ddt, *J* = 17.0, 2.3, 1.2 Hz, 1H), 5.20 (dd, *J* = 10.1, 2.1 Hz, 1H), 4.14 (ddd, *J* = 13.1, 5.8, 2.9 Hz, 1H), 3.79 (ddd, *J* = 13.1, 8.9, 2.9 Hz, 1H), 3.71 (ddd, *J* = 14.2, 5.8, 2.9 Hz, 1H), 3.60 (dd, *J* = 13.9, 8.7 Hz, 1H), 3.53 (ddd, *J* = 14.2, 8.9, 2.9 Hz, 1H), 2.88 (ddt, *J* = 13.9, 6.2, 1.2 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 172.5, 171.2, 137.0, 135.6, 133.0, 131.9, 130.2, 128.9, 128.3, 127.6, 126.7, 119.9, 68.4, 46.6, 44.2, 39.4, 24.3; IR (Neat Film, NaCl) 3057, 2978, 2934, 1685, 1643, 1600, 1448, 1405, 1364, 1286, 1210, 1149, 1075, 990, 934, 828, 788, 716 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{23}N_2O_3$ $[M+H]^+$: 363.1703, found 363.1694; $[\alpha]_D^{25.0}$ –15.8 (c 0.78, MeOH, 52% ee).

(*S*)-3-Allyl-1-benzoyl-4-(4-methoxybenzyl)-3-methylpiperazin-2-one (9c)



Ketopiperazine **9c** was isolated as a yellow oil by flash column chromatography (SiO_2, 10% EtOAc in hexanes). 85% yield. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.51–7.43 (m, 1H), 7.42–7.34 (m, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.93–6.85 (m, 2H), 6.05 (ddt, *J* = 17.1, 10.3, 6.9 Hz, 1H), 5.21–5.10 (m, 2H), 3.94 (d, *J* = 13.4 Hz, 1H), 3.85 (dt, *J* = 12.3, 3.4 Hz, 1H), 3.82 (s, 3H), 3.55 (ddd, *J* = 12.2, 10.7, 4.3 Hz, 1H), 3.34 (d, *J* = 13.4 Hz, 1H), 2.88 (dt, *J* = 12.7, 3.8 Hz, 1H), 2.85–2.72 (m, 2H), 2.63 (dd, *J* = 14.9, 6.6 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 174.4, 159.0, 136.3, 134.1, 131.5, 130.8, 129.7, 128.2, 127.7, 118.0, 114.0, 67.2, 55.4, 52.3, 45.2, 41.9, 41.4, 18.6; IR (Neat Film, NaCl) 2938, 2834, 1683, 1611, 1512, 1449, 1377, 1317, 1287, 1245, 1224, 1177, 1153, 1133, 1034, 910, 822 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{27}N_2O_3$ $[M+H]^+$: 379.2016, found 379.1999; $[\alpha]_D^{25.0}$ –75.0 (c 0.86, $CHCl_3$, 90% ee).

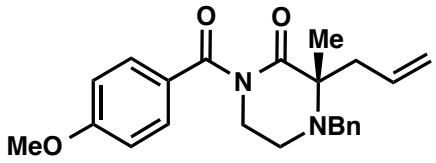
(*S*)-3-Allyl-4-benzyl-1-(4-fluorobenzoyl)-3-methylpiperazin-2-one (9d)



Ketopiperazine **9d** was isolated as a yellow oil by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes). 86% yield. R_f = 0.5 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.1, 5.7 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.0 Hz, 1H), 7.06 (t, *J* = 8.5 Hz, 2H), 6.08 (ddt, *J* = 17.2, 9.9, 6.9 Hz, 1H), 5.17 (t, *J* = 13.8 Hz, 2H), 4.02 (d, *J* = 13.7 Hz, 1H), 3.85 (dt, *J* = 12.1, 3.1 Hz, 1H), 3.57 (td, *J* = 11.4, 4.2 Hz, 1H), 3.41 (d, *J* = 13.7 Hz, 1H), 2.89 (dt, *J* = 12.7, 3.6 Hz, 1H), 2.80 (tt, *J* = 11.0, 5.1 Hz, 2H), 2.72–2.58 (m, 1H), 1.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 173.2, 164.8 (d, $^1J_{CF}$ = 252.5 Hz), 138.9, 134.0, 132.3 (d, $^4J_{CF}$ = 3.3 Hz), 130.5 (d, $^3J_{CF}$ = 9.0 Hz), 128.7, 128.6, 127.5, 118.1, 115.3 (d, $^2J_{CF}$ = 22.1 Hz), 67.3, 53.0, 45.3, 42.2, 41.5, 18.7; IR (Neat Film, NaCl) 3065, 3027, 2976, 2942, 2828, 1681, 1602, 1507, 1453, 1408, 1378, 1318, 1285, 1226, 1152, 1134, 1098, 1028, 994, 913, 843, 769, 738 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for

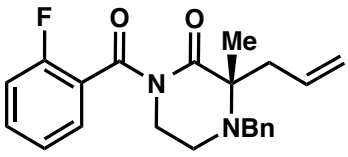
$C_{22}H_{24}FN_2O_2$ $[M+H]^+$: 367.1816, found 367.1799; $[\alpha]_D^{25.0}$ –58.1 (c 1.00, $CHCl_3$, 94% ee).

(*S*)-3-Allyl-4-benzyl-1-(4-methoxybenzoyl)-3-methylpiperazin-2-one (9e)



Ketopiperazine **9e** was isolated as a colorless oil by flash column chromatography (SiO_2, 20% EtOAc in hexanes). 87% yield. R_f = 0.4 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65–7.55 (m, 2H), 7.44–7.26 (m, 5H), 6.93–6.83 (m, 2H), 6.08 (ddt, *J* = 17.1, 10.4, 7.1 Hz, 1H), 5.23–5.10 (m, 2H), 4.02 (d, *J* = 13.7 Hz, 1H), 3.85 (s, 3H), 3.80 (dt, *J* = 12.1, 3.4 Hz, 1H), 3.57 (ddd, *J* = 12.1, 10.5, 4.3 Hz, 1H), 3.41 (d, *J* = 13.7 Hz, 1H), 2.95–2.73 (m, 3H), 2.63 (dd, *J* = 14.9, 6.5 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 173.9, 162.8, 139.0, 134.3, 130.7, 128.6, 128.6, 128.0, 127.4, 117.9, 113.5, 67.1, 55.5, 53.0, 45.3, 42.3, 41.4, 18.7; IR (Neat Film, NaCl) 3066, 2974, 2838, 1676, 1604, 1579, 1511, 1495, 1452, 1419, 1378, 1363, 1317, 1284, 1224, 1170, 1153, 1134, 1027, 993, 913, 838, 801, 770, 738 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{27}N_2O_3$ $[M+H]^+$: 379.2016, found 379.1991; $[\alpha]_D^{25.0}$ –36.5 (c 0.70, $CHCl_3$, 93% ee).

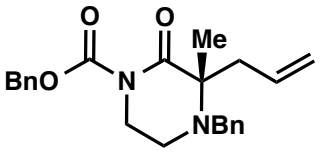
(*S*)-3-Allyl-4-benzyl-1-(2-fluorobenzoyl)-3-methylpiperazin-2-one (9f)



Ketopiperazine **9f** was isolated as a yellow oil by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 20% EtOAc in hexanes). 86% yield. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.59 (m, 1H), 7.50–7.45 (m, 1H), 7.45–7.41 (m, 1H), 7.41–7.37 (m, 2H), 7.38–7.32 (m, 1H), 7.31–7.26 (m, 1H), 7.21 (td, *J* = 7.5, 1.0 Hz, 1H), 7.05 (ddd, *J* = 10.2, 8.3, 0.9 Hz, 1H), 5.96 (ddt, *J* = 17.1, 10.3, 7.0 Hz,

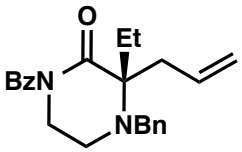
1H), 5.11 (ddt, J = 10.3, 2.1, 1.1 Hz, 1H), 5.07 (dq, J = 17.1, 1.4 Hz, 1H), 3.99 (d, J = 13.7 Hz, 1H), 3.88 (dt, J = 12.5, 3.5 Hz, 1H), 3.60 (ddd, J = 12.5, 10.5, 4.4 Hz, 1H), 3.41 (d, J = 13.7 Hz, 1H), 2.91–2.83 (m, 1H), 2.83–2.75 (m, 2H), 2.59 (dd, J = 14.8, 7.2 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 169.0, 158.5 (d, $^1J_{CF}$ = 249.6), 143.3, 138.9, 133.9, 132.0 (d, $^4J_{CF}$ = 8.4), 129.1 (d, $^6J_{CF}$ = 2.8), 128.5, 127.3, 126.1 (d, $^3J_{CF}$ = 14.9), 124.2 (d, $^5J_{CF}$ = 3.4), 117.7, 115.3 (d, $^2J_{CF}$ = 21.6), 67.2, 52.8, 44.9, 41.9, 41.5, 18.5; IR (Neat Film, NaCl) 3064, 2828, 1701, 1680, 1616, 1493, 1452, 1399, 1377, 1363, 1261, 1158, 1135, 1103, 1028, 992, 914, 857, 820, 756, 740 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{24}FN_2O_2$ $[M+H]^+$: 367.1816, found 367.1824; $[\alpha]_D^{25.0}$ –80.9 (c 1.00, $CHCl_3$, 87% ee).

Benzyl (*S*)-3-allyl-4-benzyl-3-methyl-2-oxopiperazine-1-carboxylate (9g)



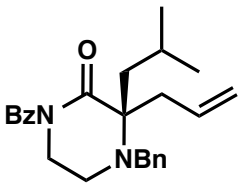
Ketopiperazine **9g** was isolated as a colorless oil by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 20% EtOAc in hexanes). 86% yield. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.26 (m, 10H), 5.96 (ddt, J = 17.3, 10.2, 7.1 Hz, 1H), 5.36–5.19 (m, 2H), 5.16–5.00 (m, 2H), 3.96 (d, J = 13.7 Hz, 1H), 3.63 (dt, J = 11.8, 3.3 Hz, 1H), 3.51 (ddd, J = 11.8, 10.3, 5.0 Hz, 1H), 3.32 (d, J = 13.7 Hz, 1H), 2.85–2.73 (m, 1H), 2.73–2.51 (m, 3H), 1.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 153.6, 138.9, 135.4, 133.6, 128.5, 128.4, 128.2, 128.0, 127.2, 117.8, 68.4, 68.4, 52.7, 46.7, 42.6, 41.6, 18.2; IR (Neat Film, NaCl) 3063, 3029, 2976, 2827, 1775, 1713, 1454, 1377, 1317, 1282, 1221, 1025, 992 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{27}N_2O_3$ $[M+H]^+$: 379.2016, found 379.2016; $[\alpha]_D^{25.0}$ –36.0 (c 1.00, $CHCl_3$, 81% ee).

(*S*)-3-Allyl-1-benzoyl-4-benzyl-3-ethylpiperazin-2-one (9h)



Ketopiperazine **9h** was isolated as a colorless oil by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 20% EtOAc in hexanes). 85% yield. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.53 (m, 2H), 7.53–7.45 (m, 1H), 7.37 (ddd, *J* = 21.1, 8.5, 7.0 Hz, 6H), 7.32–7.26 (m, 1H), 5.99 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.24–5.08 (m, 2H), 3.92 (d, *J* = 13.9 Hz, 1H), 3.79 (d, *J* = 13.9 Hz, 1H), 3.76–3.65 (m, 2H), 3.05 (ddd, *J* = 12.3, 7.9, 4.3 Hz, 1H), 2.94 (dt, *J* = 12.7, 4.5 Hz, 1H), 2.77–2.62 (m, 2H), 2.03 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.85 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ174.8, 173.5, 139.1, 136.6, 134.6, 131.6, 128.7, 128.4, 128.2, 127.8, 127.4, 118.2, 70.2, 52.7, 45.4, 42.6, 40.1, 28.7, 9.7; IR (Neat Film, NaCl) 3062, 3028, 2976, 2837, 1682, 1601, 1583, 1495, 1450, 1401, 1376, 1284, 1221, 1152, 1069, 1027, 1002, 967, 915, 879, 793, 722 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{27}N_2O_2$ $[M+H]^+$: 363.2067, found 363.2078; $[\alpha]_D^{25.0}$ +26.7 (c 1.00, $CHCl_3$, 97% ee).

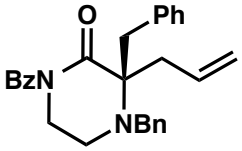
(*S*)-3-Allyl-1-benzoyl-4-benzyl-3-isobutylpiperazin-2-one (9i)



Ketopiperazine **9i** was isolated by flash column chromatography (SiO_2, 8% Et_2O in hexanes to 10% Et_2O in hexanes) as a yellow oil. 69% yield. R_f = 0.6 (20% E_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.52–7.44 (m, 1H), 7.38 (m, 6H), 7.33–7.27 (m, 1H), 5.95 (ddt, *J* = 17.1, 10.1, 7.3 Hz, 1H), 5.26–5.11 (m, 2H), 4.00 (d, *J* = 14.0 Hz, 1H), 3.83–3.73 (m, 2H), 3.71 (d, *J* = 14.0 Hz, 1H), 3.09 (ddd, *J* = 13.4, 9.9, 3.8 Hz, 1H), 2.92 (dt, *J* = 12.7, 3.8 Hz, 1H), 2.79 (dd, *J* = 14.2, 7.0 Hz, 1H), 2.63 (dd, *J* = 14.1, 7.6 Hz, 1H), 2.09–1.91 (m, 2H), 1.80–1.67 (m, 1H), 0.89 (d, *J* = 2.9 Hz, 3H), 0.88

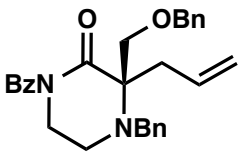
(d, J = 2.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 173.0, 138.8, 136.6, 134.4, 131.6, 128.8, 128.1, 128.1, 127.9, 127.4, 118.2, 68.6, 53.0, 45.5, 43.9, 42.4, 40.0, 24.7, 24.4, 22.5; IR (Neat Film, NaCl) 3062, 3027, 2955, 2868, 1682, 1600, 1495, 1468, 1450, 1399, 1365, 1315, 1284, 1220, 1153, 1113, 1024, 984, 917, 843, 794, 724 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{25}H_{31}N_2O_2$ $[M+H]^+$: 391.2380, found 391.2388; $[\alpha]_D^{25.0}$ +24.6 (c 1.00, $CHCl_3$, 85% ee).

(*R*)-3-Allyl-1-benzoyl-3,4-dibenzylpiperazin-2-one (9j)



Ketopiperazine **9j** was isolated by flash column chromatography (SiO_2, hexanes to 10% EtOAc in hexanes) as a colorless oil. 99% yield. R_f = 0.6 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, J = 7.6, 2.6 Hz, 2H), 7.44–7.34 (m, 2H), 7.34–7.14 (m, 11H), 6.06 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.40–5.06 (m, 2H), 4.14 (d, J = 13.9 Hz, 1H), 3.92 (d, J = 13.9 Hz, 1H), 3.60 (ddd, J = 12.2, 6.0, 3.7 Hz, 1H), 3.49–3.33 (m, 2H), 3.06 (d, J = 14.3 Hz, 1H), 2.97–2.80 (m, 3H), 2.74 (ddd, J = 12.7, 6.0, 3.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 173.1, 137.7, 136.5, 134.2, 131.6, 130.8, 128.6, 128.5, 128.3, 128.1, 127.9, 127.4, 126.8, 118.8, 71.5, 52.8, 45.2, 42.5, 42.1, 41.6; IR (Neat Film, NaCl) 3062, 3029, 2929, 2848, 1683, 1622, 1495, 1450, 1339, 1283, 1223, 1153, 1096, 1028, 993, 918 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{28}H_{29}N_2O_2$ $[M+H]^+$: 425.2224, found 425.2224; $[\alpha]_D^{25.0}$ +31.8 (c 1.00, $CHCl_3$, 97% ee).

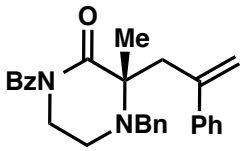
(*R*)-3-Allyl-1-benzoyl-4-benzyl-3-[(benzyloxy)methyl]piperazin-2-one (9k)



Ketopiperazine **9k** was isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 56% yield. R_f = 0.7 (15% EtOAc

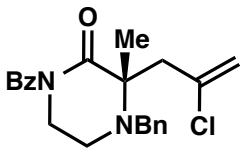
in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.60 (m, 2H), 7.49–7.43 (m, 1H), 7.43–7.26 (m, 12H), 6.00 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.19–5.14 (m, 1H), 5.12 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.06 (d, *J* = 13.6 Hz, 1H), 3.94–3.85 (m, 2H), 3.82 (dt, *J* = 12.2, 3.1 Hz, 1H), 3.70–3.58 (m, 2H), 3.41 (td, *J* = 11.6, 3.1 Hz, 1H), 2.85 (dt, *J* = 12.0, 3.4 Hz, 1H), 2.54 (dd, *J* = 14.4, 7.4 Hz, 1H), 2.43 (dd, *J* = 14.4, 6.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 173.3, 139.2, 137.9, 136.1, 133.4, 131.6, 128.7, 128.6, 128.6, 128.3, 128.0, 127.8, 127.3, 118.6, 75.8, 73.9, 70.3, 52.9, 45.2, 43.9, 37.9; IR (Neat Film, NaCl) 3063, 3029, 2953, 2923, 2862, 1686, 1601, 1495, 1451, 1403, 1373, 1326, 1284, 1246, 1224, 1154, 1111, 1028, 985, 915, 848, 794, 748 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{29}H_{31}N_2O_3$ $[M+H]^+$: 455.2329, found 455.2325; $[\alpha]_D^{25.0}$ –20.3 (c 1.00, $CHCl_3$, 95% ee).

(*S*)-1-Benzoyl-4-benzyl-3-methyl-3-(2-phenylallyl)piperazin-2-one (9l)



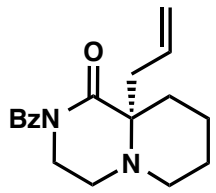
Ketopiperazine **9l** was isolated by flash column chromatography (SiO_2, 5% acetone in hexanes) as a colorless oil. 77% yield. R= 0.4 (15% acetone in hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ7.44 (dd, *J* = 18.2, 7.6 Hz, 3H), 7.39 – 7.19 (m, 12H), 5.38 (s, 1H), 5.29 (s, 1H), 4.04 (d, *J* = 13.3 Hz, 1H), 3.61 (d, *J* = 12.3 Hz, 1H), 3.44 (d, *J* = 15.6 Hz, 1H), 3.34 (d, *J* = 13.1 Hz, 1H), 3.29 (d, *J* = 3.6 Hz, 1H), 2.94 (d, *J* = 15.6 Hz, 1H), 2.80 (d, *J* = 12.6 Hz, 1H), 2.74 – 2.62 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 173.9, 146.1, 142.2, 138.7, 136.6, 131.3, 128.8, 128.5, 128.1, 128.0, 127.7, 127.5, 127.4, 127.3, 117.3, 67.2, 53.4, 44.9, 42.7, 42.2, 19.6; IR (Neat Film, NaCl) 3059, 3027, 2933, 2829, 1682, 1600, 1494, 1449, 1379, 1363, 1317, 1287, 1223, 1146, 1133, 1074, 1028, 967, 945, 908, 850, 794, 778, 726 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{28}H_{29}N_2O_2$ $[M+H]^+$: 425.2224, found 425.2214; $[\alpha]_D^{25.0}$ -73.3 (c 1.00, $CHCl_3$, 96% ee).

(*S*)-1-Benzoyl-4-benzyl-3-(2-chloroallyl)-3-methylpiperazin-2-one (9m)



Ketopiperazine **9m** was isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes) as a colorless oil. 60% yield. R_f = 0.4 (20% EtOAc in hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H), 7.53 – 7.45 (m, 1H), 7.40 (td, *J* = 6.8, 1.3 Hz, 4H), 7.34 (td, *J* = 6.7, 6.2, 1.6 Hz, 2H), 7.31 – 7.27 (m, 1H), 5.27 (t, *J* = 1.1 Hz, 1H), 5.24 (t, *J* = 1.3 Hz, 1H), 4.02 (d, *J* = 13.5 Hz, 1H), 3.80 (dt, *J* = 12.3, 3.1 Hz, 1H), 3.73 (ddd, *J* = 12.3, 11.1, 4.0 Hz, 1H), 3.44 (dt, *J* = 15.7, 1.2 Hz, 1H), 3.38 (d, *J* = 13.5 Hz, 1H), 2.87 (dt, *J* = 12.7, 3.8 Hz, 1H), 2.81 (ddd, *J* = 14.2, 9.9, 2.6 Hz, 2H), 1.49 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 174.0, 139.0, 138.5, 136.5, 131.6, 128.7, 128.6, 128.2, 127.9, 127.5, 115.9, 66.0, 53.5, 45.8, 45.0, 42.5, 18.9; IR (Neat Film, NaCl) 3062, 3029, 2938, 2849, 1682, 1633, 1600, 1495, 1449, 1399, 1378, 1364, 1322, 1287, 1243, 1224, 1210, 1178, 1157, 1135, 1080, 1062, 1030, 997, 968, 944, 879, 850, 794, 725 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{24}N_2O_2Cl$ $[M+H]^+$: 383.1521, found 383.1523. $[\alpha]_D^{25.0}$ -97.0 (c 1.00, $CHCl_3$, 98% ee).

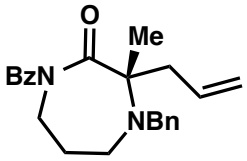
(*S*)-9a-Allyl-2-benzoylhexahydro-2*H*-pyrido[1,2-*a*]pyrazin-1(6*H*)-one (9n)



Bicyclic ketopiperazine **9n** was isolated by flash column chromatography (SiO_2, 15% EtOAc and 1% NEt_3 in hexanes) as a colorless oil. 68% yield. R_f = 0.4 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.49 (m, 2H), 7.50–7.43 (m, 1H), 7.41–7.34 (m, 2H), 5.82 (ddt, *J* = 16.9, 10.1, 7.6, Hz, 1H), 5.25–5.10 (m, 2H), 4.09 (ddd, *J* = 12.7, 9.7, 5.2 Hz, 1H), 3.72 (dt, *J* = 12.7, 4.5 Hz, 1H), 3.39 (ddd, *J* = 13.8, 9.9, 4.8 Hz, 1H), 3.04 (dt, *J* = 13.3, 4.6 Hz, 1H), 3.00–2.90 (m, 1H), 2.75 (ddt, *J* = 21.0, 14.5, 6.9 Hz,

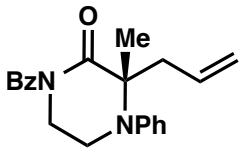
3H), 1.87 (td, *J* = 11.0, 8.9, 3.5 Hz, 1H), 1.76–1.62 (m, 2H), 1.62–1.45 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 174.7, 136.3, 132.8, 131.4, 128.1, 127.5, 118.2, 64.4, 49.4, 44.8, 44.1, 35.9, 29.4, 23.6, 20.4; IR (Neat Film, NaCl) 3071, 2935, 2860, 1681, 1600, 1466, 1448, 1379, 1359, 1315, 1282, 1233, 1206, 1153, 1110, 1036, 997, 918, 795, 724 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{23}N_2O_2$ $[M+H]^+$: 299.1754, found 299.1744; $[\alpha]_D^{25.0}$ +20.9 (c 0.85, $CHCl_3$, 90% ee).

(*S*)-3-Allyl-1-benzoyl-4-benzyl-3-methyl-1,4-diazepan-2-one (9o)



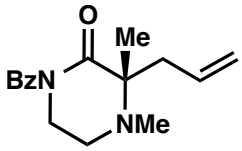
Ketopiperazine **9o** was isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a yellow oil. 89% yield. R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.53 (m, 2H), 7.53–7.44 (m, 1H), 7.44–7.31 (m, 6H), 7.31–7.27 (m, 1H), 6.10–5.92 (m, 1H), 5.28–5.15 (m, 2H), 4.30 (ddd, *J* = 12.0, 8.0, 3.4 Hz, 1H), 4.11 (ddd, *J* = 14.1, 6.5, 3.8 Hz, 1H), 3.98 (d, *J* = 13.8 Hz, 1H), 3.85 (d, *J* = 13.8 Hz, 1H), 2.96 (m, 2H), 2.80 (dd, *J* = 14.7, 7.0 Hz, 1H), 2.69 (dd, *J* = 14.7, 7.4 Hz, 1H), 1.81–1.62 (m, 2H), 1.53 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.5, 175.6, 140.0, 137.0, 133.8, 131.3, 128.5, 128.5, 128.3, 127.7, 127.3, 118.8, 69.8, 52.4, 45.6, 42.7, 42.4, 26.5, 22.0; IR (Neat Film, NaCl) 3063, 3028, 2976, 2941, 2850, 2252, 1682, 1600, 1583, 1494, 1450, 1376, 1353, 1279, 1228, 1210, 1175, 1076, 1023, 966, 918, 872, 848, 790, 737 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{27}N_2O_2$ $[M+H]^+$: 363.2067, found 363.2066; $[\alpha]_D^{25.0}$ +2.0 (c 1.00, $CHCl_3$, 59% ee).

(*S*)-3-Allyl-1-benzoyl-3-methyl-4-phenylpiperazin-2-one (9p)



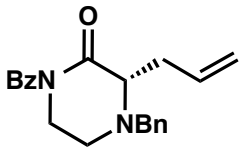
Ketopiperazine **9p** was isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 83% yield. R_f = 0.6 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.55 (m, 2H), 7.48 (tt, *J* = 6.9, 1.3 Hz, 1H), 7.44–7.36 (m, 2H), 7.33 (td, *J* = 7.4, 1.9 Hz, 2H), 7.24–7.12 (m, 3H), 6.24–6.10 (m, 1H), 5.26–5.20 (m, 1H), 5.17 (dq, *J* = 17.2, 1.6 Hz, 1H), 4.11 (ddd, *J* = 12.3, 4.6, 3.5 Hz, 1H), 3.85 (ddd, *J* = 12.4, 9.3, 3.9 Hz, 1H), 3.71–3.55 (m, 1H), 3.47 (dt, *J* = 12.7, 4.2 Hz, 1H), 2.63 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.56 (ddt, *J* = 15.2, 5.6, 1.6 Hz, 1H), 1.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 174.0, 147.9, 136.3, 134.0, 131.6, 128.8, 128.1, 127.8, 126.8, 125.2, 118.6, 68.1, 46.2, 45.3, 42.9, 21.8; IR (Neat Film, NaCl) 3062, 3032, 2975, 2933, 2844, 1683, 1597, 1492, 1449, 1373, 1323, 1284, 1229, 1177, 1128, 1026, 1002, 961, 918, 835, 792, 773, 723 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{23}N_2O_2$ $[M+H]^+$: 335.1754, found 335.1757; $[\alpha]_D^{25.0}$ +25.2 (c 1.00, $CHCl_3$, 94% ee).

(*S*)-3-Allyl-1-benzoyl-3,4-dimethylpiperazin-2-one (9q)



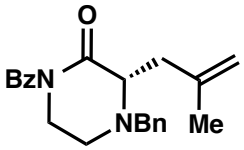
Ketopiperazine **9q** was isolated by flash column chromatography (SiO_2, 5% acetone in hexanes) as a colorless oil. 88% yield. R_f = 0.5 (10% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.50–7.43 (m, 1H), 7.42–7.33 (m, 2H), 5.95–5.79 (m, 1H), 5.14–5.10 (m, 1H), 5.10–5.05 (m, 1H), 3.90 (dt, *J* = 12.3, 3.6 Hz, 1H), 3.73 (ddd, *J* = 12.3, 10.4, 4.7 Hz, 1H), 3.04 (ddd, *J* = 14.2, 10.4, 3.9 Hz, 1H), 2.95 (dt, *J* = 12.8, 4.1 Hz, 1H), 2.73 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.41 (app s, 4H), 1.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 174.5, 136.3, 134.0, 131.6, 128.2, 127.7, 117.7, 66.6, 46.7, 44.7, 40.9, 37.4, 17.3; IR (Neat Film, NaCl) 3072, 2977, 2948, 2849, 2809, 1685, 1600, 1450, 1368, 1318, 1286, 1261, 1217, 1153, 1085, 949, 911, 845, 794, 752, 724 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{21}N_2O_2$ $[M+H]^+$: 273.1598, found 273.1598; $[\alpha]_D^{25.0}$ –66.6 (c 1.00, $CHCl_3$, 82% ee).

(*S*)-3-Allyl-1-benzoyl-4-benzylpiperazin-2-one (11a)



Ketopiperazine **11a** was isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 89% yield. R_f = 0.6 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.54 (m, 2H), 7.53–7.45 (m, 1H), 7.43–7.34 (m, 6H), 7.34–7.28 (m, 1H), 6.12–5.91 (m, 1H), 5.26–5.16 (m, 2H), 4.08 (d, *J* = 13.3 Hz, 1H), 4.02 (ddd, *J* = 12.7, 4.6, 3.7 Hz, 1H), 3.62 (ddd, *J* = 12.7, 9.6, 4.0 Hz, 1H), 3.43 (d, *J* = 13.3 Hz, 1H), 3.39–3.32 (m, 1H), 3.14 (dt, *J* = 12.7, 4.2 Hz, 1H), 2.92–2.80 (m, 1H), 2.80–2.71 (m, 1H), 2.57 (ddd, *J* = 13.0, 9.6, 3.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 172.2, 137.5, 136.0, 134.1, 131.7, 129.0, 128.7, 128.1, 128.0, 127.7, 118.0, 66.8, 58.3, 46.4, 44.0, 34.6; IR (Neat Film, NaCl) 3062, 3028, 2947, 2899, 2811, 1683, 1450, 1283, 1229, 1140, 1072, 1028, 993, 917, 794 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{23}N_2O_2$ $[M+H]^+$: 335.1754, found 335.1758; $[\alpha]_D^{25.0}$ –20.8 (c 1.00, $CHCl_3$, 98% ee).

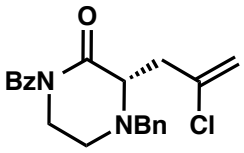
(*S*)-1-Benzoyl-4-benzyl-3-(2-methylallyl)piperazin-2-one (11b)



Ketopiperazine **11b** was isolated as an yellow oil by flash column chromatography (SiO_2, 5% EtOAc in hexanes). 74% yield. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.55 (m, 2H), 7.49 (tt, *J* = 6.9, 1.3, 1H), 7.43–7.37 (m, 2H), 7.35 (d, *J* = 4.8, 4H), 7.32–7.27 (m, 1H), 4.91 (d, *J* = 15.8, 2H), 4.15–3.89 (m, 2H), 3.76–3.59 (m, 1H), 3.59–3.48 (m, 1H), 3.49–3.36 (m, 1H), 3.33–3.10 (m, 1H), 2.95–2.75 (m, 1H), 2.67 (tq, *J* = 16.0, 8.9, 2H), 1.74 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 172.8, 136.0, 131.8, 129.4, 129.1, 129.1, 128.7, 128.2, 128.1, 114.0, 110.1, 65.0, 58.4, 45.3, 38.6, 31.1, 22.6; IR (Neat Film, NaCl) 3067, 3027, 2923, 2852, 1685, 1597, 1512, 1449, 1364, 1318, 1283, 1156, 1133, 1073, 1027, 945, 895, 795, 728 cm^{-1}; HRMS (MM: ESI-APCI) *m/z*

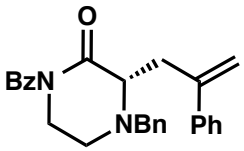
calc'd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$: 349.1911, found 349.1914; $[\alpha]_D^{25.0}$ –18.3 (c 0.27, $CHCl_3$, 97% ee).

(*S*)-1-Benzoyl-4-benzyl-3-(2-chloroallyl)piperazin-2-one (11c)



Ketopiperazine **11c** was isolated as an yellow oil by flash column chromatography (SiO_2, 5% acetone in hexanes). 52% yield. R_f = 0.6 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2H), 7.53–7.46 (m, 1H), 7.44–7.27 (m, 7H), 5.38–5.30 (m, 2H), 4.18–4.04 (m, 1H), 4.04–3.93 (m, 1H), 3.80–3.67 (m, 1H), 3.65–3.45 (m, 2H), 3.16 (ddd, *J* = 27.2, 8.8, 3.8, 2H), 3.01 (dd, *J* = 15.2, 5.4, 1H), 2.65 (ddd, *J* = 12.7, 8.8, 3.6, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 171.5, 138.8, 135.8, 131.9, 129.1, 128.8, 128.3, 128.1, 127.9, 115.8, 110.1, 64.4, 58.5, 45.8, 43.3, 40.0; IR (Neat Film, NaCl) 3062, 3030, 2953, 2816, 1682, 1634, 1601, 1450, 1383, 1366, 1283, 1227, 1162, 1140, 1073, 1022, 910, 795, 746 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{22}N_2O_2$ $[M+H]^+$: 369.1364, found 369.1371; $[\alpha]_D^{25.0}$ –28.9 (c 0.36, $CHCl_3$, 87% ee).

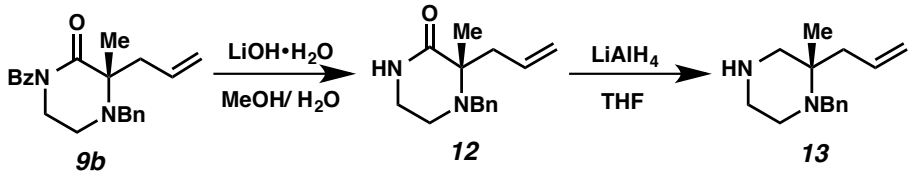
(*S*)-1-Benzoyl-4-benzyl-3-(2-phenylallyl)piperazin-2-one (11d)



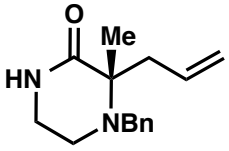
Ketopiperazine **11d** was isolated as an yellow oil by flash column chromatography (SiO_2, 10% EtOAc in hexanes). 72% yield. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.50 (m, 2H), 7.49 (dt, *J* = 7.0, 1.5, 1H), 7.44–7.36 (m, 4H), 7.29 (dtd, *J* = 12.5, 6.7, 2.8, 6H), 7.25–7.19 (m, 2H), 5.35 (d, *J* = 25.9, 2H), 3.93 (ddd, *J* = 12.9, 7.3, 4.5, 2H), 3.53 (ddd, *J* = 12.3, 7.6, 3.8, 1H), 3.43 (dd, *J* = 12.1, 4.1, 2H), 3.23 (qd, *J* = 14.9, 5.8, 2H), 3.12 (ddd, *J* = 13.0, 6.4, 3.9, 1H), 2.58 (ddd, *J* = 12.4, 7.7, 3.8, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 172.7, 145.5, 140.4, 137.6, 135.9, 131.6, 128.8, 128.4, 128.4, 128.1, 127.9, 127.6, 127.4, 126.7, 116.0, 65.3, 58.3, 44.6, 43.1, 37.5;

IR (Neat Film, NaCl) 3059, 3029, 2924, 2852, 1682, 1600, 1494, 1449, 1364, 1283, 1222, 1156, 1073, 1028, 903, 780, 732 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{27}H_{27}N_2O_2$ $[M+H]^+$: 411.2067, found 411.2070; $[\alpha]_D^{25.0}$ –7.3 (c 1.00, $CHCl_3$, 99% ee).

Procedures for Preparation of α-Quaternary Piperazines

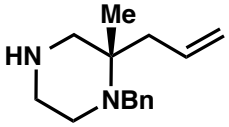


(*S*)-3-Allyl-4-benzyl-3-methylpiperazin-2-one (12)



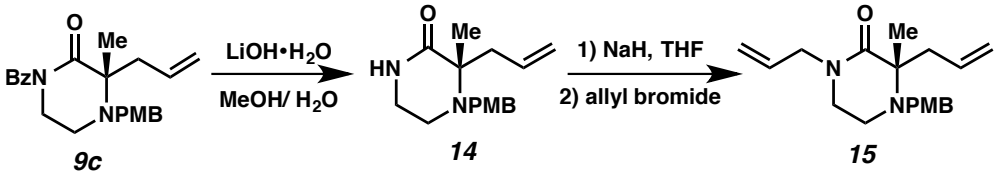
Ketopiperazine **9b** (56.0 mg, 0.16 mmol) was taken up in MeOH (4 mL) and H_2O (4 mL) and stirred with lithium hydroxide monohydrate (10.0 mg, 0.24 mmol) for 16 hours open to air. Reaction mixture was then diluted with EtOAc and washed once with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic layers were combined, washed once with brine, dried with Na_2SO_4, and concentrated under reduced pressure to give **12** as a white solid. 76% yield. R_f = 0.3 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.5, 2H), 7.24 (td, *J* = 6.7, 6.2, 1.6, 2H), 7.21–7.13 (m, 1H), 6.13 (s, 1H), 5.99–5.86 (m, 1H), 5.09–4.99 (m, 2H), 3.92 (d, *J*=13.7, 1H), 3.26 (d, *J* = 13.8, 1H), 3.24–3.18 (m, 1H), 2.99 (dq, *J* = 11.0, 3.3, 1H), 2.83–2.70 (m, 1H), 2.67–2.52 (m, 2H), 2.48 (dd, *J* = 14.6, 7.3, 1H), 1.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 139.7, 134.8, 128.6, 128.5, 127.2, 117.1, 65.7, 52.9, 41.9, 41.8, 41.4, 18.2 ; IR (Neat Film, NaCl) 3435, 3304, 3193, 3077, 2971, 2936, 2809, 1664, 1489, 1451, 1418, 1381, 1361, 1345, 1260, 1202, 1169, 1104, 1085, 1030, 990, 908, 875, 750 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{21}N_2O$ $[M+H]^+$: 245.1648, found 245.1638; $[\alpha]_D^{25.0}$ –32.1 (c 0.90, $CHCl_3$, 91% ee).

(*S*)-2-Allyl-1-benzyl-2-methylpiperazine (13)

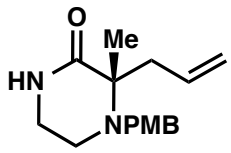


Ketopiperazine **12** (48.0 mg, 0.20 mmol) was taken up in THF (1.0 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (22.0 g, 0.59 mmol) in 1.0 mL of THF. It was allowed to stir under Ar atmosphere at reflux for 16 hours. The reaction mixture was then cooled to 23 ºC and 0.2 mL of water was added dropwise followed by 0.2 mL of 2 N NaOH aqueous solution and 0.6 mL of water. It was allowed to stir for 20 minutes. The reaction mixture was then transferred to a seperatory funnel using 10 mL of EtOAc. The organic layer was washed with a saturated solution of Rochelle's salt (1 x 10 mL) and then the organic layer was washed with brine (1 x 10 mL), dried with Na_2SO_4, and concentrated under reduced pressure to give **13** as a colorless oil. 99% yield. R_f = 0.3 (5% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 5.85 (ddt, *J* = 14.7, 10.2, 7.4 Hz, 1H), 5.06 – 4.97 (m, 2H), 3.56 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 12.4 Hz, 1H), 2.79 (d, *J* = 12.4 Hz, 1H), 2.72 (dt, *J* = 6.8, 2.9 Hz, 2H), 2.55 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.49 (d, *J* = 12.4 Hz, 1H), 2.38 (ddd, *J* = 11.9, 5.7, 4.1 Hz, 1H), 2.33 – 2.22 (m, 1H), 2.08 (dd, *J* = 14.0, 7.4 Hz, 1H), 1.04 (s, 3H); The signal of the NH was not detected; ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 134.9, 128.6, 128.3, 126.7, 117.4, 55.6, 55.5, 53.5, 46.9, 46.8, 29.9; IR (Neat Film, NaCl) 3063, 3025, 2929, 2799, 1494, 1452, 1363, 1313, 1139, 1070, 1028, 991, 910, 822, 727 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{23}N_2$ $[M+H]^+$: 231.1856, found 231.1839; $[\alpha]_D^{25.0}$ –4.6 (c 0.625, $CHCl_3$).

Procedures for the Deprotection and Functionalization of α-Quaternary Piperazin-2-ones

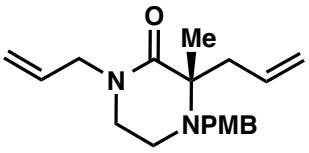


(*S*)-3-Allyl-4-(4-methoxybenzyl)-3-methylpiperazin-2-one (14)



Ketopiperazine **9c** (25.0 mg, 0.07 mmol) was taken up in MeOH (1.5 mL) and H_2O (1.5 mL) and stirred with lithium hydroxide monohydrate (4.0 mg, 0.10 mmol) for 16 hours open to air. Reaction mixture was then diluted with EtOAc and washed once with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the organic layers were combined, washed once with brine, dried with Na_2SO_4, and concentrated under reduced pressure on to silica. Deprotected ketopiperazine **14** was isolated as a white solid by flash column chromatography (SiO_2, 50% EtOAc in hexanes). 93% yield. R_f = 0.3 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.17 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.34 (s, 1H), 6.00 (ddt, *J* = 17.1, 10.3, 7.0 Hz, 1H), 5.24 – 4.98 (m, 2H), 3.92 (d, *J* = 13.5 Hz, 1H), 3.81 (s, 3H), 3.27 (t, *J* = 9.7 Hz, 2H), 3.06 (dq, *J* = 10.8, 3.3 Hz, 1H), 2.83 (dd, *J* = 14.7, 6.5 Hz, 1H), 2.64 (dd, *J* = 8.9, 3.4 Hz, 2H), 2.56 (dd, *J* = 14.6, 7.4 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 158.8, 134.9, 131.6, 129.8, 117.0, 113.8, 65.6, 55.4, 52.2, 41.8, 41.7, 41.3, 18.2; IR (Neat Film, NaCl) 3202, 3073, 2935, 2833, 1667, 1611, 1511, 1488, 1455, 1360, 1344, 1301, 1245, 1168, 1104, 1082, 1034, 989, 909, 824, 799, 731 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{23}N_2O_2$ $[M+H]^+$: 275.1754, found 275.1730; $[\alpha]_D^{25.0}$ –21.3 (c 1.00, $CHCl_3$).

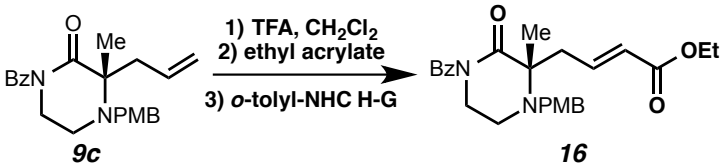
(*S*)-1,3-Diallyl-4-(4-methoxybenzyl)-3-methylpiperazin-2-one (15)



Ketopiperazine **14** (13.0 mg, 0.05 mmol) was taken up in THF (0.5 mL) and stirred with sodium hydride (3.0 mg, 0.07 mmol) for 5 minutes at 0 °C. Then allyl bromide (0.01 mL,

0.07 mmol) was added neat dropwise and the reaction was allowed to stir at 0 °C until TLC analysis indicated full consumption of the starting material. The reaction mixture was warmed to 23 °C and was then diluted with 5 mL od EtOAc and poured into 5 mL of water. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the organic layers were combined, washed once with brine, dried with Na_2SO_4, and concentrated under reduced pressure on to silica. Allylated ketopiperazine **15** was isolated as a colorless oil by flash column chromatography (SiO_2, 20% EtOAc in hexanes). 65% yield. R_f = 0.6 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.92 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.82 – 5.66 (m, 1H), 5.19 – 5.12 (m, 2H), 5.12 – 5.02 (m, 2H), 4.07 (dd, *J* = 15.0, 5.8 Hz, 1H), 3.96 – 3.83 (m, 2H), 3.80 (s, 3H), 3.27 (ddd, *J* = 11.5, 10.0, 5.4 Hz, 1H), 3.22 (d, *J* = 13.4 Hz, 1H), 2.92 (dt, *J* = 11.4, 3.1 Hz, 1H), 2.86 (dd, *J* = 14.6, 6.6 Hz, 1H), 2.63 (tt, *J* = 7.7, 3.9 Hz, 2H), 2.52 (dd, *J* = 14.5, 7.3 Hz, 1H), 1.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 158.8, 135.1, 132.9, 131.6, 129.8, 117.4, 116.9, 113.8, 65.7, 55.4, 52.4, 50.0, 46.7, 41.9, 41.7, 18.2; IR (Neat Film, NaCl) 3072, 2932, 2834, 1716, 1641, 1611, 1512, 1485, 1456, 1381, 1360, 1301, 1246, 1169, 1035, 990, 916, 826, 780, 756 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{27}N_2O_2$ $[M+H]^+$: 315.2067, found 315.2097; $[\alpha]_D^{25.0}$ –16.6 (c 0.62, $CHCl_3$).

Ethyl (*S*,*E*)-4-(4-benzoyl-1-(4-methoxybenzyl)-2-methyl-3-oxopiperazin-2-yl)but-2-enoate (16)

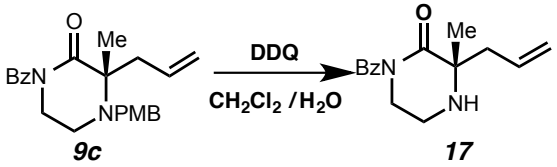


9c *16*

Ketopiperazine **9c** (20.0 mg, 0.05 mmol) was taken up in CH_2Cl_2 (0.5 mL) and stirred with trifluoroacetic acid (5.0 mL, 0.06 mmol) for 5 minutes at 23 °C. Then ethyl acrylate (60.0 mL, 0.53 mmol) was added neat dropwise followed by the addition of the *o*-tolyl-NHC Hoveyda-Grubbs catalyst (3 mg, 0.005 mmol) and the reaction was allowed to stir

at 23 °C for seven days. The reaction mixture was concentrated under reduced pressure directly on to silica. Ketopiperazine **16** was isolated as a colorless oil by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 20% EtOAc in hexanes). 47% yield. R_f = 0.2 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.51 – 7.45 (m, 1H), 7.43 – 7.36 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.15 (dt, *J* = 15.5, 7.3 Hz, 1H), 6.91 – 6.84 (m, 2H), 5.93 – 5.85 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.92 (d, *J* = 13.3 Hz, 1H), 3.88 – 3.82 (m, 1H), 3.81 (s, 3H), 3.58 (ddd, *J* = 12.3, 10.8, 4.4 Hz, 1H), 3.35 (d, *J* = 13.4 Hz, 1H), 3.00 (ddd, *J* = 15.3, 7.3, 1.3 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.79 (ddd, *J* = 12.9, 10.8, 3.6 Hz, 1H), 2.72 (ddd, *J* = 15.3, 7.3, 1.3 Hz, 1H), 1.47 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 174.3, 166.3, 159.1, 144.3, 136.2, 131.7, 130.2, 129.6, 128.3, 127.7, 124.1, 114.1, 67.2, 60.5, 55.4, 52.4, 45.1, 42.0, 39.6, 18.5, 14.5; IR (Neat Film, NaCl) 2976, 2935, 2899, 2827, 1718, 1685, 1653, 1610, 1512, 1448, 1366, 1269, 1245, 1222, 1159, 1035, 977, 934, 821, 727, 694 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{31}N_2O_5$ $[M+Na]^+$: 473.2047, found 473.2046; $[\alpha]_D^{25.0}$ –86.6 (c 0.62, $CHCl_3$).

(*S*)-3-Allyl-1-benzoyl-3-methylpiperazin-2-one (17)



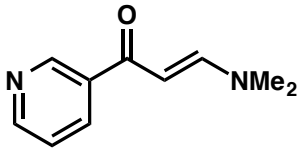
9c *17*

To a 20 mL scintillation vial was added ketopiperazine **9c** (16.0 mg, 0.04 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (19.0 mg, 0.08 mmol), 0.6 mL of CH_2Cl_2, 0.06 mL of H_2O, and a magnetic stir bar. The reaction was allowed to stir for 1.5 hours under ambient conditions at which point there was full conversion of the starting material by TLC. The reaction mixture was poured into 5 mL of saturated sodium bicarbonate and extracted with CH_2Cl_2 (4 x 5 mL). The combined organics were washed once with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Ketopiperazine **14** was isolated as a white solid by flash column chromatography (SiO_2, 5% MeOH in CH_2Cl_2). 75% yield. R_f = 0.4 (10% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ

7.53 (dd, J = 8.3, 1.3 Hz, 2H), 7.51 – 7.44 (m, 1H), 7.43 – 7.35 (m, 2H), 5.86 – 5.71 (m, 1H), 5.27 – 5.16 (m, 2H), 3.90 (dt, J = 12.6, 4.9 Hz, 1H), 3.79 (ddd, J = 12.7, 7.6, 4.9 Hz, 1H), 3.36 – 3.14 (m, 2H), 2.77 (dd, J = 13.7, 6.8 Hz, 1H), 2.32 (dd, J = 13.8, 8.0 Hz, 1H), 1.44 (s, 3H); the signal of the NH was not detected; ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 174.6, 136.2, 132.6, 131.7, 128.3, 127.7, 120.4, 60.6, 48.2, 43.0, 38.6, 25.1; IR (Neat Film, NaCl) 3073, 2968, 2926, 2853, 1682, 1601, 1583, 1463, 1449, 1371, 1313, 1285, 1212, 1177, 1152, 1111, 1071, 1022, 1001, 922, 795, 749, 727 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{19}N_2O_2$ $[M+H]^+$: 259.1441, found 259.1432; $[\alpha]_D^{25.0}$ –71.8 (c 0.87, $CHCl_3$).

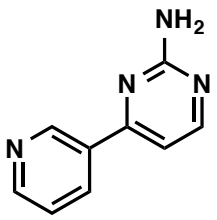
Procedures for Preparation of Imatinib Analogs

(*E*)-3-(Dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (SI14)



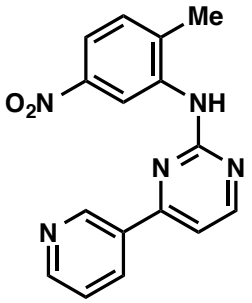
3-Acetylpyridine (2.42 g, 20.0 mmol), *N,N*-dimethylformamide diacetal (3.7 g, 31.0 mmol) and acetic acid (0.2 mL) were added to a 15 mL round-bottom flask equipped with a magnetic stirbar. The reaction was heated to 95 °C for 3 hours. It was then cooled to room temperature and poured into 10 mL of H_2O. The aqueous phase was extracted with CH_2Cl_2 (4 x 15 mL) and the combined organics were washed once with brine, dried with Na_2SO_4, and concentrated to yield **SI14** as a red solid. 97% yield. Product identity was confirmed by comparison to previously reported characterization data.

4-(Pyridin-3-yl)pyrimidin-2-amine (SI15)



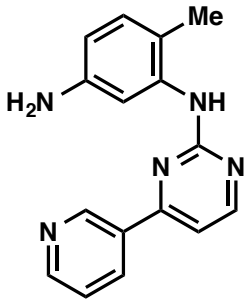
Pyridine **SI14** (2.70 g, 12.5 mmol) was taken up in 12.5 mL of *n*BuOH along with guanidine nitrate (1.53 g, 12.5 mmol) and NaOH (0.50 g, 12.5 mmol). The reaction mixture was refluxed for 20 hours. Upon cooling to room temperature, pyrimidine **SI15** precipitated from the solution and was collected by filtration, washed once with water, and dried under reduced pressure. 76% yield. Product identity was confirmed by comparison to previously reported characterization data.

_N_-(2-Methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (SI16)



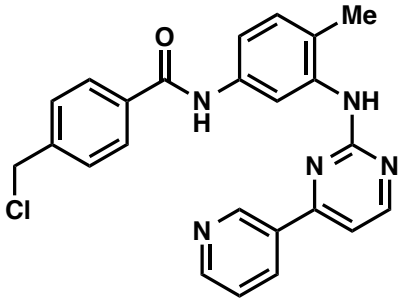
In a 50 mL round-bottom flask [Pd_2dba_3] (80.0 mg, 0.09 mmol), and *rac*-BINAP (130 mg, 0.21 mmol) were combined in 13 mL of dioxane and heated to 100 °C for 30 minutes under argon atmosphere. The resulting catalyst solution was cooled to room temperature and 2-bromo-1-methyl-4-nitrobenzene (376 mg, 1.74 mmol), prepared according to literature procedure,[7] **SI15** (300 mg, 1.74 mmol), and Cs_2CO_3 (1.14 g, 3.48 mmol) suspended in 5 mL of dioxane was then added. The reaction mixture was then heated to 100 °C for 24 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and nitro-arene compound **SI16** was isolated by flash column chromatography (SiO_2, 100% CH_2Cl_2 to 1% MeOH in CH_2Cl_2). 81% yield. Product identity was confirmed by comparison to previously reported characterization data.

6-Methyl-N^1-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (SI17)



In a 100 mL round-bottom flask was added nitro-arene compound **SI16** (190 mg, 0.62 mmol) was dissolved in MeOH (50 mL). Then 40.0 mg of 20% Pd on carbon was added. After sparging the reaction mixture with hydrogen for 15 minutes, the reaction mixture was allowed to stir overnight under one atmosphere of hydrogen. The reaction mixture was carefully filtered through a plug of celite and concentrated to give aniline **SI17**. 99% yield. Product identity was confirmed by comparison to previously reported characterization data.

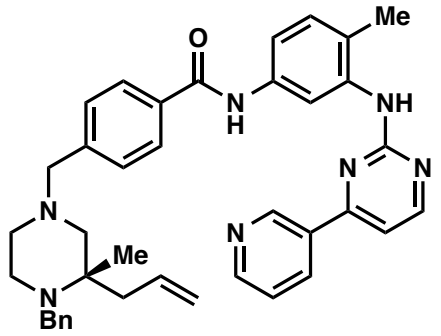
4-(Chloromethyl)-*N*-[4-methyl-3-[(4-(pyridin-3-yl)pyrimidin-2-yl]amino]-phenyl)-benzamide (21)



In a 15 mL round-bottom flask was added aniline **SI17** (115 mg, 0.42 mmol), 4-(chloromethyl)benzoyl chloride (78.0 mg, 0.42 mmol) and triethylamine (120 μL, 0.83 mmol) were taken up in 4.2 mL of THF and allowed to stir for 3 hours at 23 ºC. Reaction mixture was then poured into 5 mL of H_2O and extracted with EtOAc (4 x 10 mL). The combined organics were washed with brine, dried with Na_2SO_4, filtered, and concentrated. Chloride **21** was isolated by flash column chromatography (SiO_2, 100%

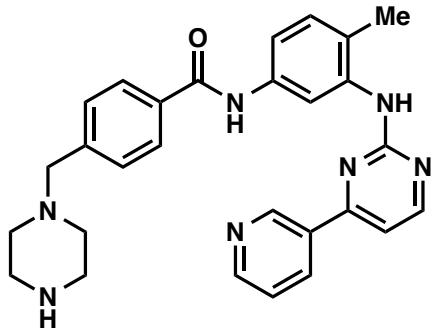
CH_2Cl_2 to 5% MeOH in CH_2Cl_2). 64% yield. Product identity was confirmed by comparison to previously reported characterization data.

(*S*)-4-[(3-Allyl-4-benzyl-3-methylpiperazin-1-yl)methyl]-*N*-(4-methyl-3-[(4-(pyridin-3-yl)pyrimidin-2-yl)amino]phenyl)benzamide (18)



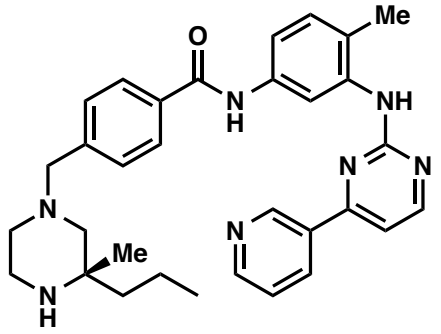
In a 5 mL round-bottom flask chloride **21** (13.0 mg, 0.03 mmol), piperazine **13** (10.0 mg, 0.04 mmol) and Cs_2CO_3 (0.020 g, 0.06 mmol) were taken up in 0.3 mL of dry DMF under Ar atmosphere and allowed to stir for 18 hours at room temperature. Imatinib analog **18** was isolated directly by flash column chromatography (SiO_2, CH_2Cl_2 to 3% MeOH in CH_2Cl_2). 42% yield. R_f= 0.4 (10% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (dd, *J* = 2.2, 0.7 Hz, 1H), 8.70 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.59 (d, *J* = 2.1 Hz, 1H), 8.56 – 8.47 (m, 2H), 8.01 (s, 1H), 7.89 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.44 – 7.38 (m, 1H), 7.38 – 7.26 (m, 4H), 7.25 – 7.14 (m, 2H), 7.04 (s, 1H), 5.93 – 5.71 (m, 1H), 5.11 – 4.92 (m, 2H), 3.66 – 3.41 (m, 3H), 2.95 (s, 2H), 2.88 (s, 2H), 2.79 – 2.60 (m, 1H), 2.61 – 2.39 (m, 3H), 2.35 (s, 3H), 2.10 (dd, *J* = 13.9, 7.6 Hz, 2H), 1.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 162.9, 162.7, 160.7, 159.1, 151.6, 148.6, 137.9, 137.9, 136.8, 135.1, 132.8, 130.9, 129.2, 129.0, 128.6, 128.4, 128.3, 127.1, 126.7, 124.3, 123.9, 117.2, 115.5, 113.3, 108.5, 62.7, 56.2, 54.3, 53.1, 46.5, 36.6, 31.6, 29.8, 17.8; IR (Neat Film, NaCl) 3292, 3054, 2923, 2853, 1666, 1579, 1551, 1528, 1450, 1417, 1265, 1204, 1114, 1021, 801, 751, 703 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{39}H_{42}N_7O$ $[M+H]^+$: 624.3445, found 624.3456; $[\alpha]_D^{25.0}$ +2.3 (c 1.00, $CHCl_3$).

_N_-(4-Methyl-3-[(4-(pyridin-3-yl)pyrimidin-2-yl)amino]phenyl)-4-(piperazin-1-ylmethyl)benzamide (19)



In a 5 mL round bottom flask was added chloride **21** (15.0 mg, 0.04 mmol), piperazine (11.0 mg, 0.13 mmol), Cs_2CO_3 (34.0 mg, 0.11 mmol), and 0.4 mL of dry DMF under Ar atmosphere and allowed to stir for 18 hours at 23 ºC. Des-methyl imatinib (**19**) was isolated directly by flash column chromatography (SiO_2, 1% MeOH in CH_2Cl_2 to 3% MeOH in CH_2Cl_2). 48% yield. Product identity was confirmed by comparison to previously reported characterization data.

(_S_)-_N_-(4-Methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((3-methyl-3-propylpiperazin-1-yl)methyl)benzamide (20)



Ketopiperazine **13** (22.0 mg, 0.10 mmol) was taken up in 3.2 mL of MeOH and 2 mL of glacial acetic acid in a 10 mL round bottom flask. Pd on $CaCO_3$ (5.00 mg) was added. The reaction mixture was then sparged for 15 minutes with H_2 and allowed to stir under H_2 atmosphere for 16 hours. The reaction mixture was then carefully filtered through a plug of celite using MeOH and concentrated. Chloride **21** (41.0 mg, 0.10 mmol) and Cs_2CO_3 (124 mg, 0.38 mmol) were then added along with 1 mL of dry DMF. The

reaction was allowed to stir under Ar atmosphere for 48 hours. Imatinib analog **20** was isolated directly by flash column chromatography (SiO_2, CH_2Cl_2 to 5% MeOH and ~1% NMe_2Et in CH_2Cl_2). 4% yield. R_f= 0.4 (15% MeOH and ~1% NMe_2Et in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.68 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.58 (d, *J* = 1.8 Hz, 1H), 8.54 – 8.42 (m, 2H), 8.03 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.41 (td, *J* = 6.3, 1.2 Hz, 3H), 7.31 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.16 (d, *J* = 5.2 Hz, 1H), 7.06 (s, 1H), 3.65 – 3.47 (m, 2H), 3.15 (t, *J* = 5.3 Hz, 2H), 2.68 (ddt, *J* = 17.2, 11.3, 6.5 Hz, 2H), 2.39 (s, 2H), 2.34 (s, 3H), 1.77 (pd, *J* = 13.1, 4.8 Hz, 2H), 1.38 (s, 4H), 1.21 (dtt, *J* = 12.8, 9.6, 4.6 Hz, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 162.7, 160.5, 159.0, 151.4, 148.5, 141.8, 137.8, 136.5, 134.9, 134.3, 132.6, 130.8, 129.0, 127.2, 124.3, 123.7, 115.4, 113.2, 108.4, 61.9, 59.8, 56.8, 50.7, 39.8, 17.7, 16.4, 14.4; IR (Neat Film, NaCl) 3247, 2960, 2775, 2481, 2212, 1658, 1581, 1532, 1447, 1418, 1318, 1289, 1046, 1019, 910, 801, 731 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{32}H_{38}N_7O$ $[M+H]^+$: 536.3132, found 536.3138; $[\alpha]_D^{25.0}$ –8.4 (c 0.17, $CHCl_3$)

Procedures for the Cell Viability Assay

Human K562 chronic myelogenous leukemia (CML) cells were obtained from the American Type Culture Collection (ATCC). Cells were cultured in RPMI-1640 medium containing 10% fetal bovine serum (FBS) at 37 ^oC in 5% CO_2. MTS assays were performed for cell viability as instructed by the supplier (Promega, Madison, WI). Briefly, cells (10000/well) were seeded in 96-well plates and exposed to compounds in a cell culture incubator in a dose-dependent manner for 48 h. DMSO was used as the vehicle control. Viable cell numbers were determined by tetrazolium conversion to its formazan and absorbance was monitored at 490 nm using an automated ELISA plate reader. Each experiment was performed in quadruplicate. Data are mean ± SD.

References

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[3] (a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc*. **2004**, *126*, 15044–15045. (b) K. Tani, D. C. Behenna, R. M. McFadden, B. M. Stoltz, *Org. Lett*. **2007**, *9*, 2529–2531. (c)M. R. Krout, J. T. Mohr, B. M. Stoltz, *Org. Synth*. **2009**, *86*, 181–193.

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[6] a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045; b) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927; *Angew. Chem.* **2005**, *117*, 7084–7087; c) M. Seto, J. L. Roizen, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2008**, *47*, 6873–6876; *Angew. Chem.* **2008**, *120*, 6979–6982; d) J. Streuff, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem.* **2010**, *2*, 192–196; e) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem*. **2012**, *4*, 130–133; f) C. M. Reeves, C. Eidamshaus, J. Kim, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2013**, *52*, 6718–6721; *Angew. Chem.* **2013**, *125*, 6850–6853.

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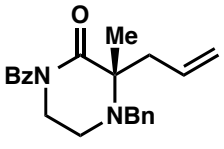
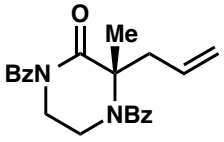
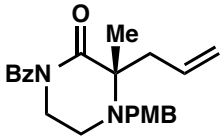
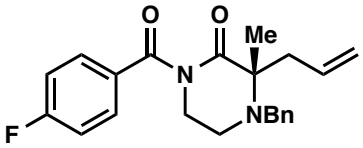
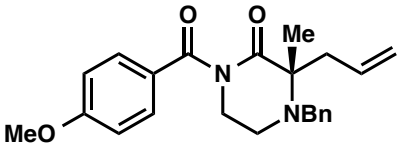
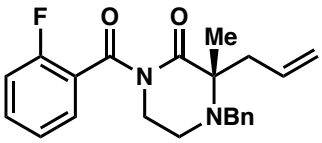
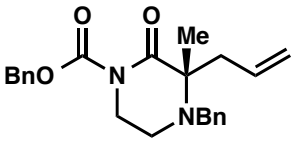
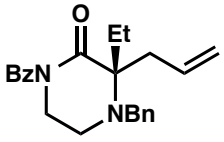
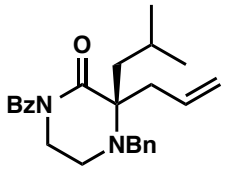
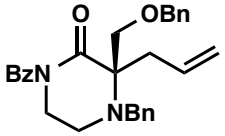
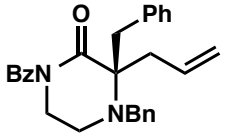
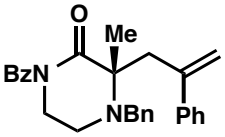
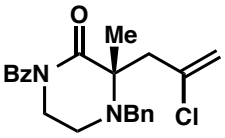
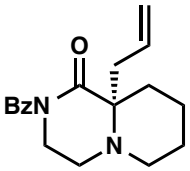
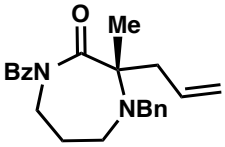
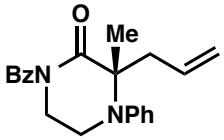
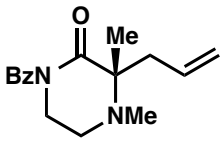
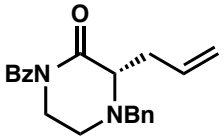
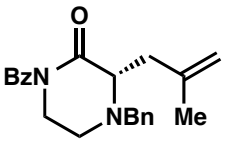
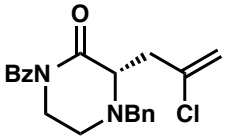
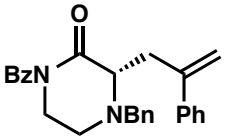
Determination of Enantiomeric Excess

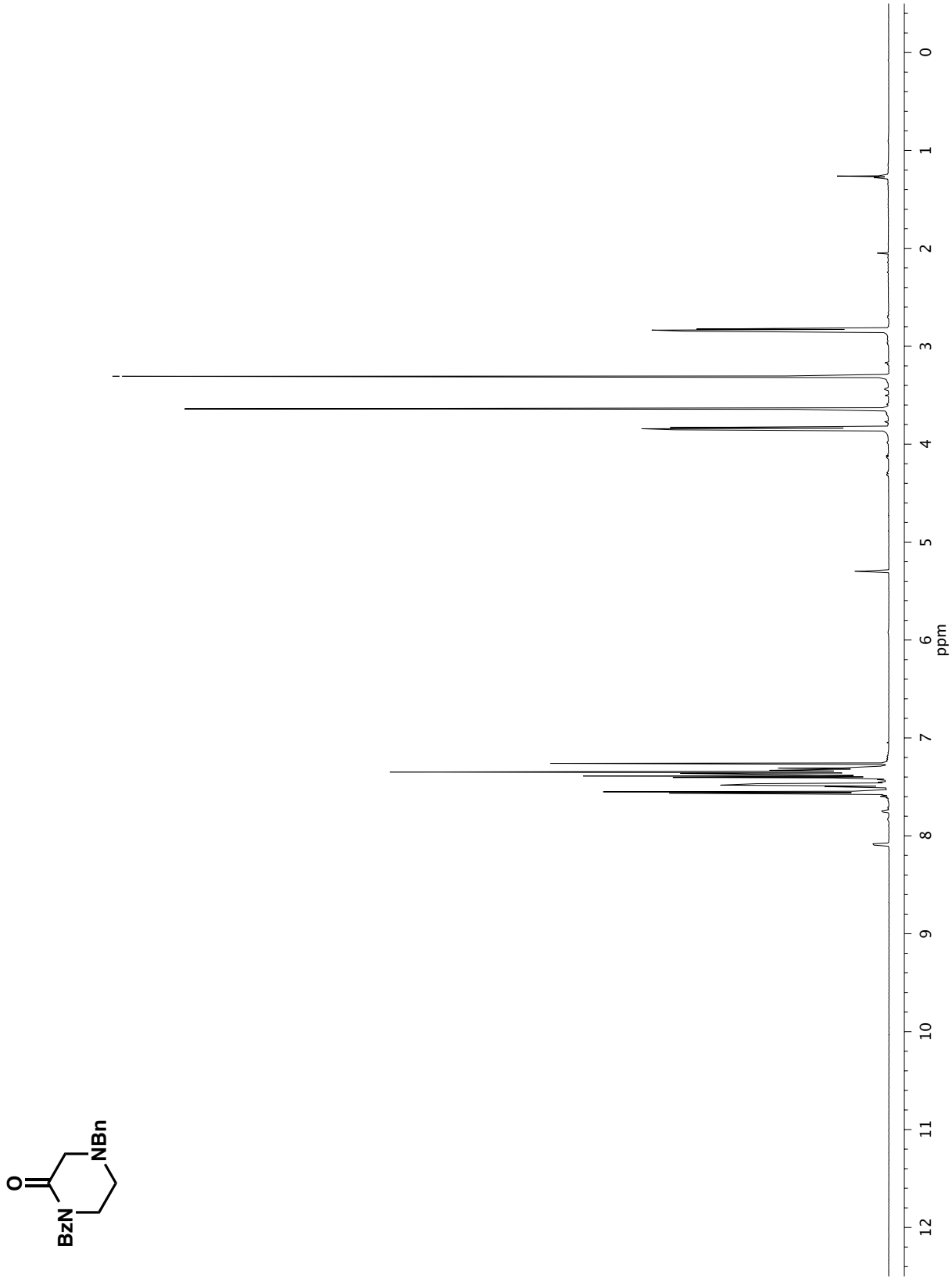
Entry	Compound	Assay Method and Conditions	t_R Major Isomer (min)	t_R Minor Isomer (min)	% ee
1		SFC Chiralcel OD-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	3.63	4.11	91%

Entry	Compound	Assay Method and Conditions	t_R Major Isomer (min)	t_R Minor Isomer (min)	% ee
2		SFC Chiralcel OJ-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	3.40	4.00	52%
3		SFC Chiralpak AD-H 10% MeOH in CO_2 isocratic, 3.0 mL/min 210 nm	6.77	9.00	90%
4		SFC Chiralcel OB-H 3% MeOH in CO_2 isocratic, 2.5 mL/min 210 nm	10.11	9.17	94%
5		SFC Chiralcel OJ-H 10% MeOH in CO_2 isocratic, 3.0 mL/min 210 nm	7.28	5.02	93%
6		SFC Chiralcel OJ-H 10% MeOH in CO_2 isocratic, 3.0 mL/min 210 nm	7.81	4.41	87%
7		SFC Chiralpak AS-H 10% MeOH in CO_2 isocratic, 2.5 mL/min 210 nm	3.66	3.41	81%

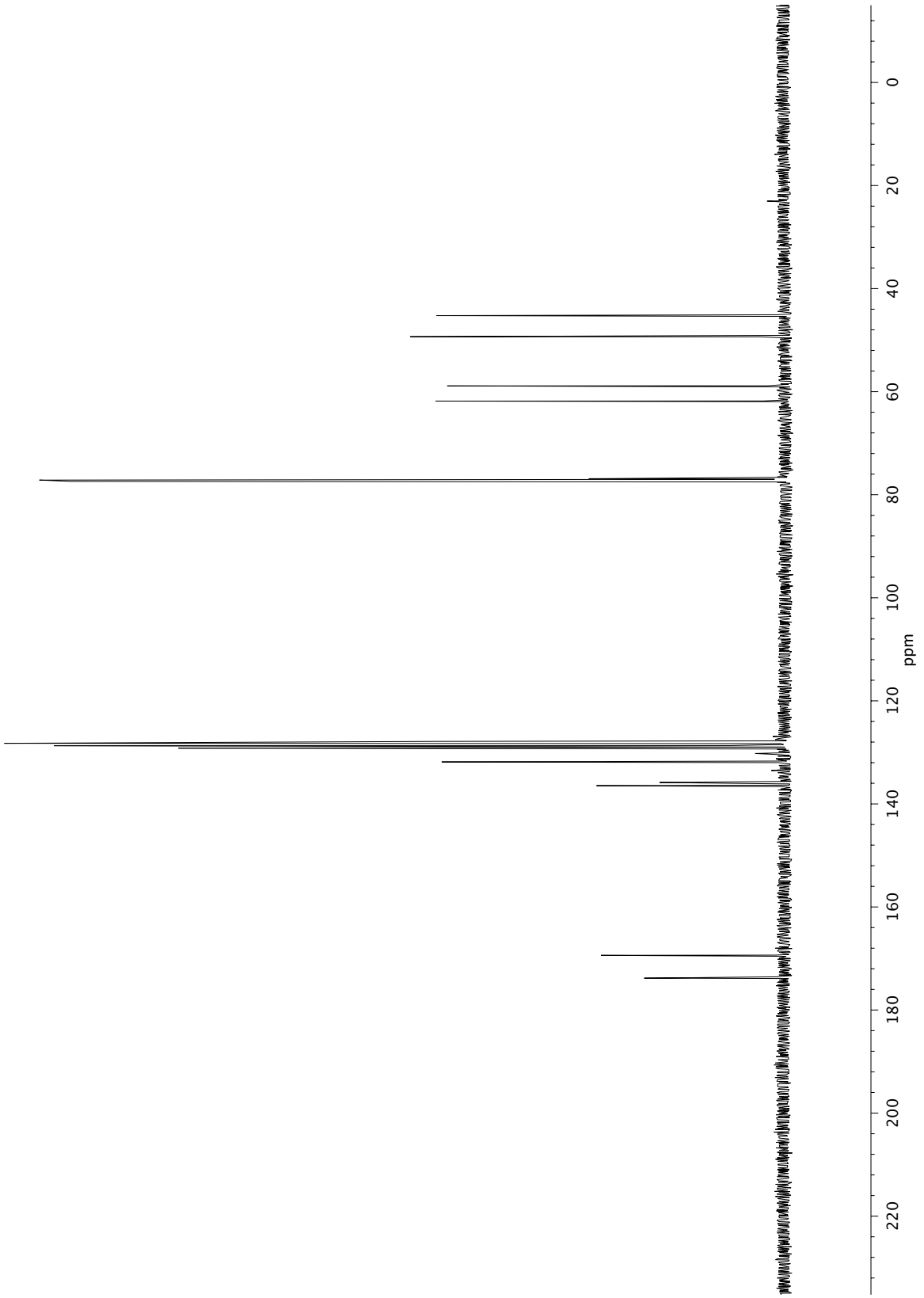
Entry	Compound	Assay Method and Conditions	t_R Major Isomer (min)	t_R Minor Isomer (min)	% ee
8		SFC Chiralcel OJ-H 10% MeOH in CO_2 isocratic, 3.0 mL/min 210 nm	5.36	4.57	97%
9		SFC Chiralcel OJ-H 2% IPA in CO_2 isocratic, 2.5 mL/min 210 nm	3.95	3.43	85%
10		SFC Chiralcel OD-H 1% IPA in CO_2 isocratic, 2.5 mL/min 210 nm	7.71	9.35	95%
11		SFC Chiralcel OJ-H 2% IPA in CO_2 isocratic, 2.5 mL/min 210 nm	10.40	8.74	97%
12		SFC Chiralcel OJ-H 20% IPA in CO_2 isocratic, 2.5 mL/min 210 nm	9.82	8.50	96%
13		SFC Chiralpak AS-H 20% IPA in CO_2 isocratic, 2.5 mL/min 210 nm	3.14	3.84	98%

Entry	Compound	Assay Method and Conditions	t_R Major Isomer (min)	t_R Minor Isomer (min)	% ee
14		SFC Chiralcel OB-H 10% IPA in CO_2 isocratic, 2.5 mL/min 210 nm	6.43	4.82	90%
15		SFC Chiralcel OB-H 5% MeOH in CO_2 isocratic, 2.5 mL/min 210 nm	9.61	11.40	59%
16		SFC Chiralcel OJ-H 2% IPA in CO_2 isocratic, 2.5 mL/min 210 nm	4.55	3.32	93%
17		SFC Chiralpak AS-H 8% IPA in CO_2 isocratic, 2.5 mL/min 210 nm	3.21	2.16	82%
18		SFC Chiralpak AD-H 40% IPA in CO_2 isocratic, 2.5 mL/min 254 nm	6.80	5.07	98%
19		SFC Chiralcel OJ-H 0.2% IPA in CO_2 isocratic, 4.0 mL/min 210 nm	6.45	4.46	97%

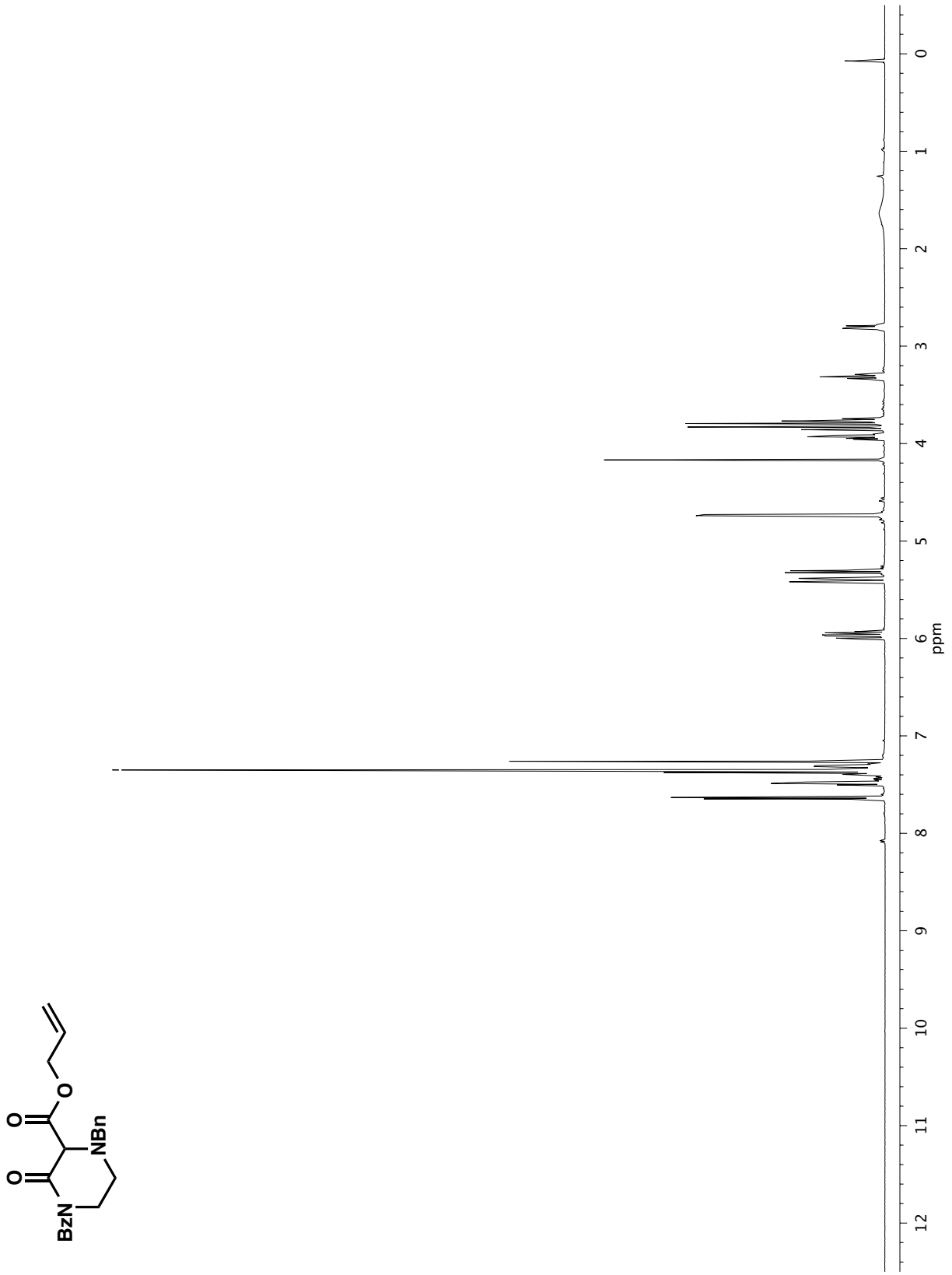
Entry	Compound	Assay Method and Conditions	t_R Major Isomer (min)	t_R Minor Isomer (min)	% ee
20		SFC Chiralpak AD-H 35% IPA in CO_2 isocratic, 3.5 mL/min 210 nm	8.58	7.58	87%
21		SFC Chiralcel OJ-H 25% IPA in CO_2 isocratic, 2.5 mL/min 210 nm	8.12	9.85	99%



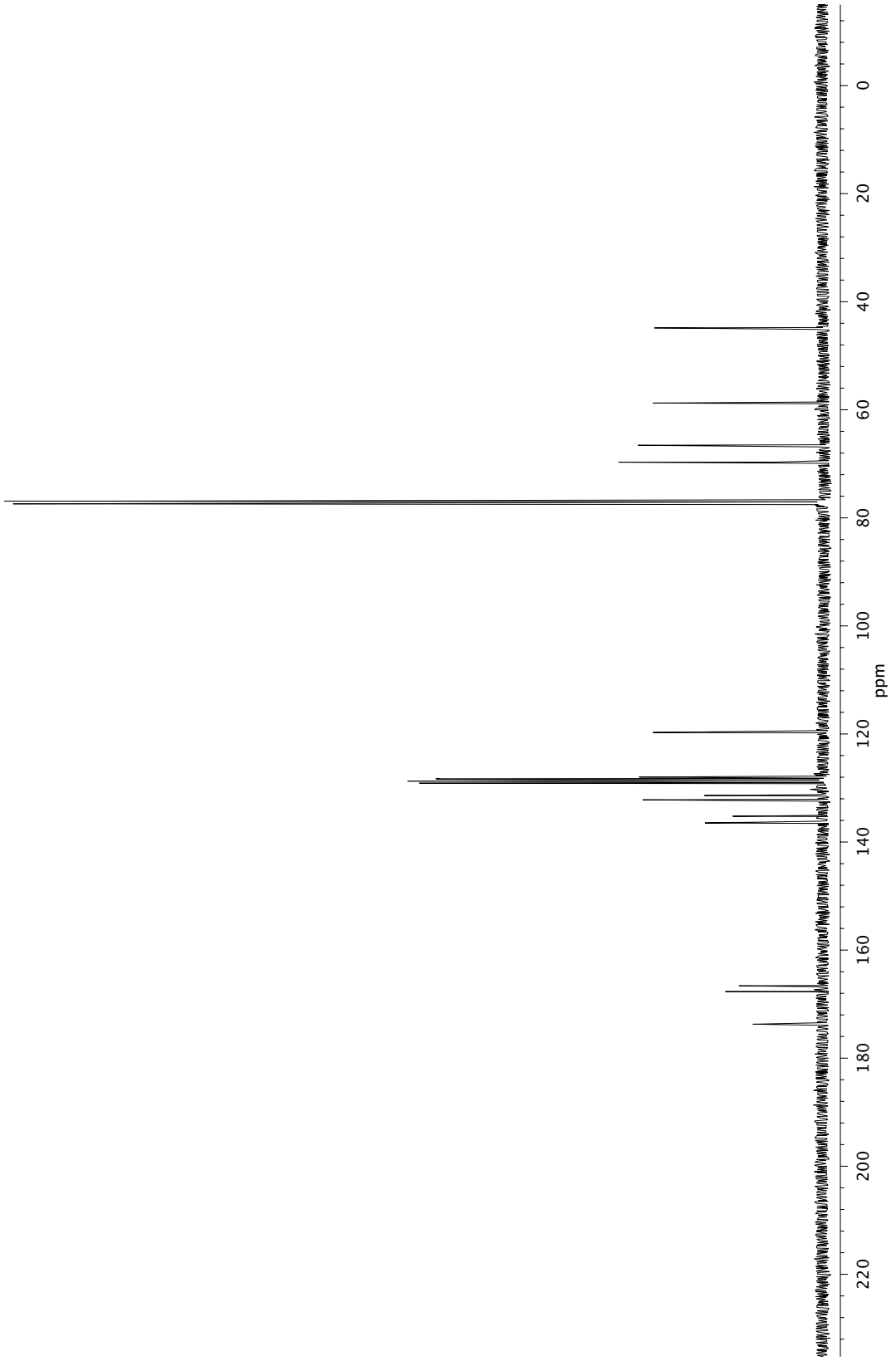
^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI4**.



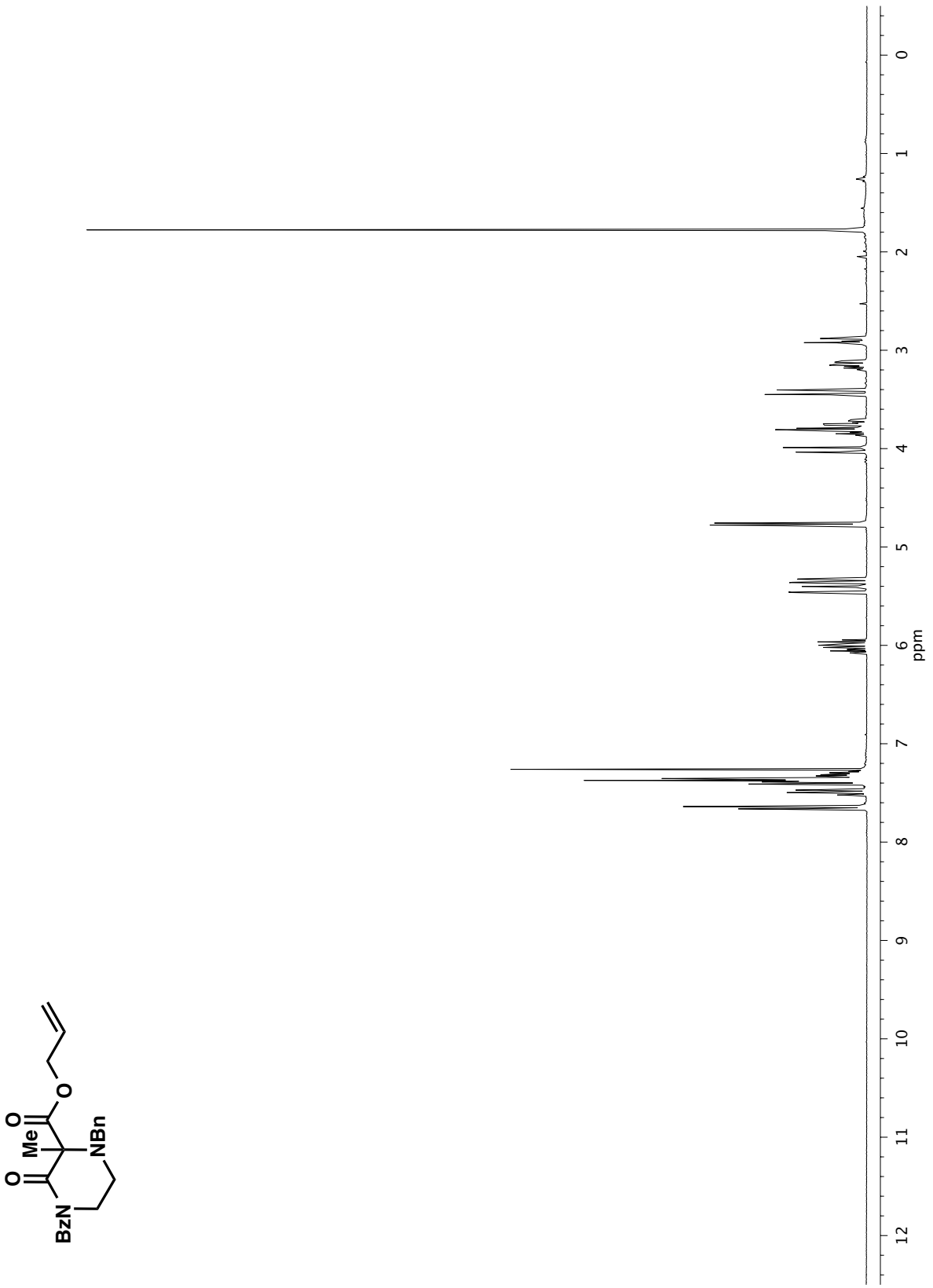
^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI4**.



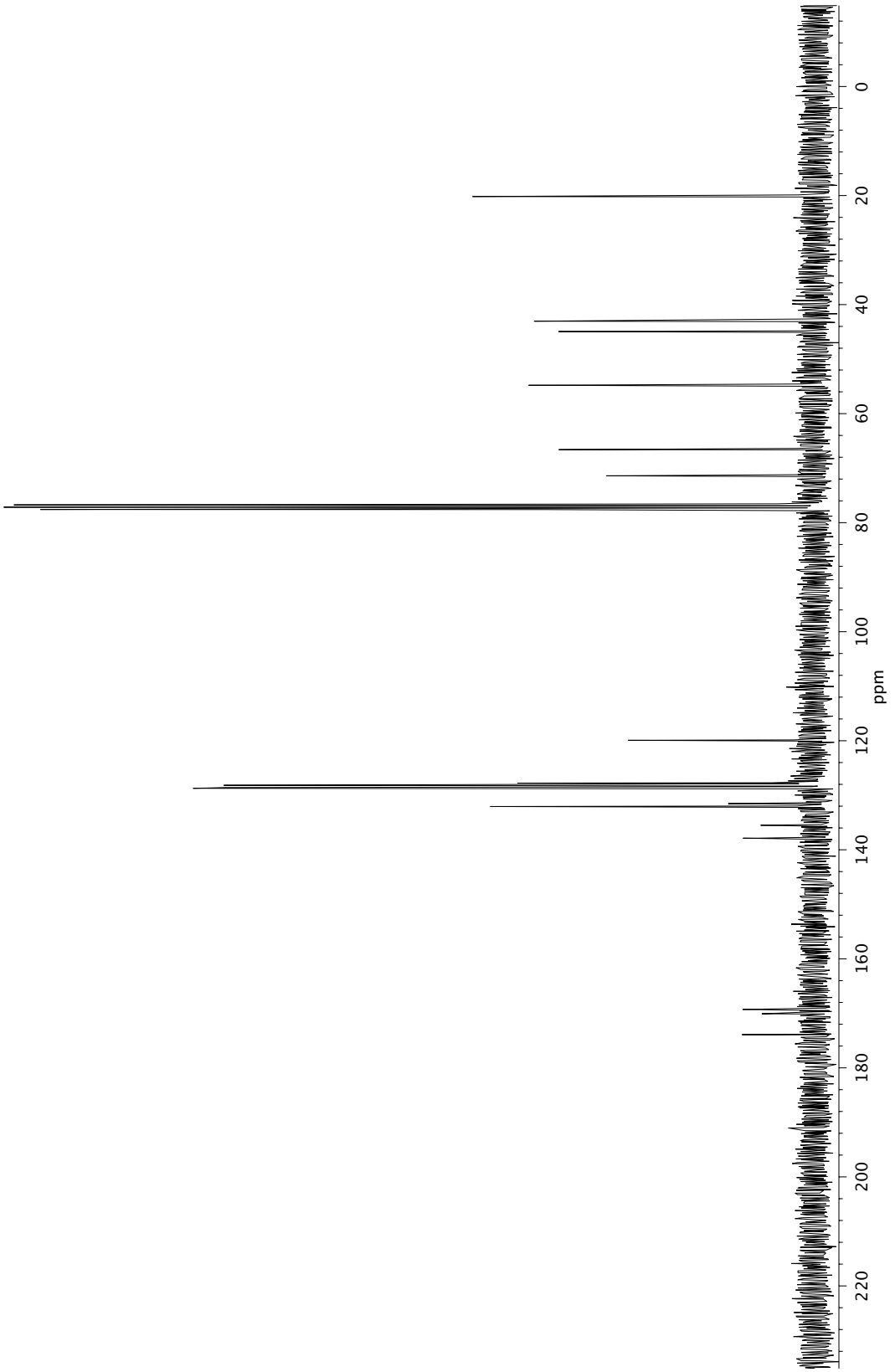
^{1}H NMR (500 MHz, $CDCl_3$) of compound **10a**.



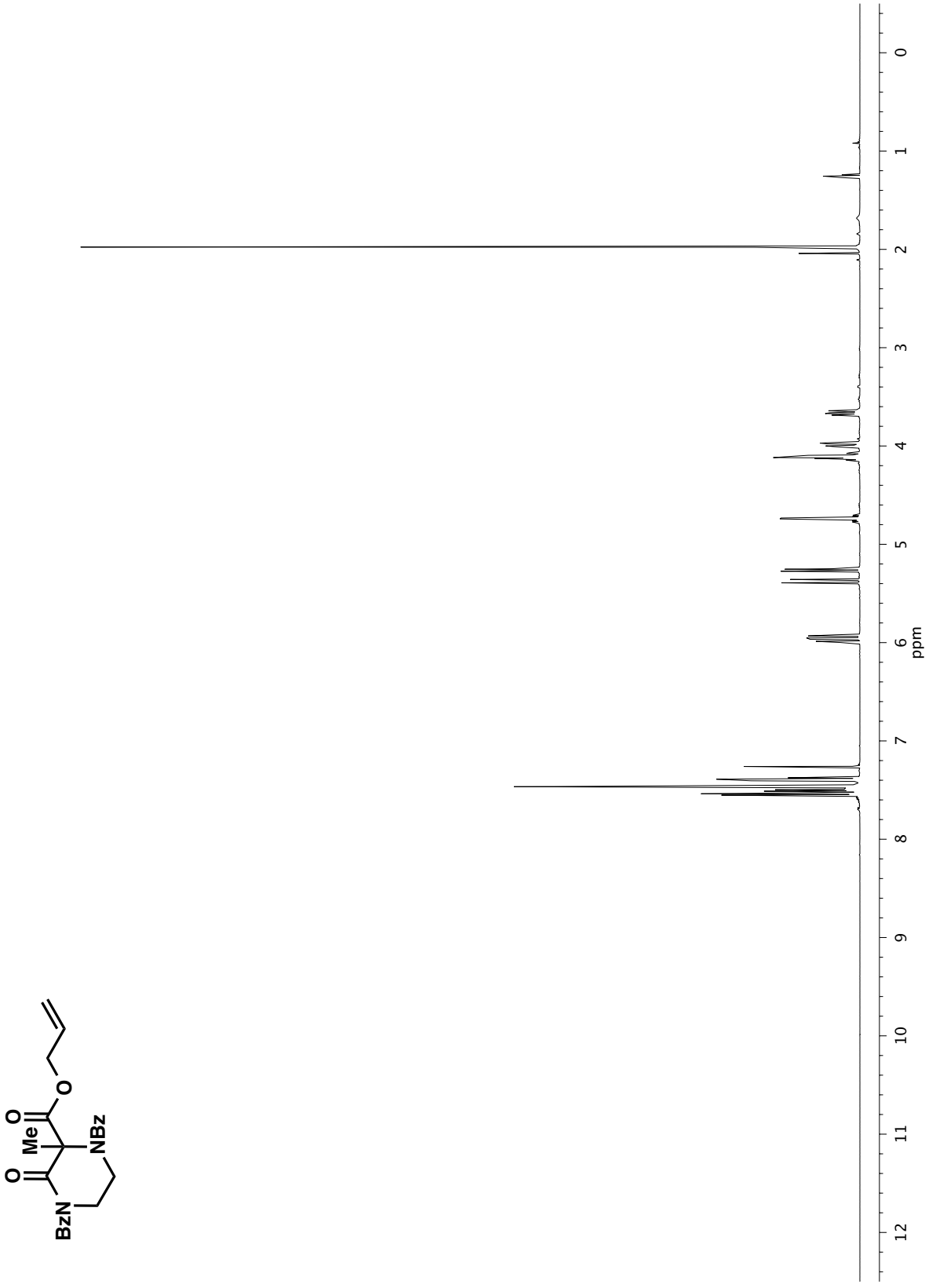
^{13}C NMR (126 MHz, $CDCl_3$) of compound **10a**.



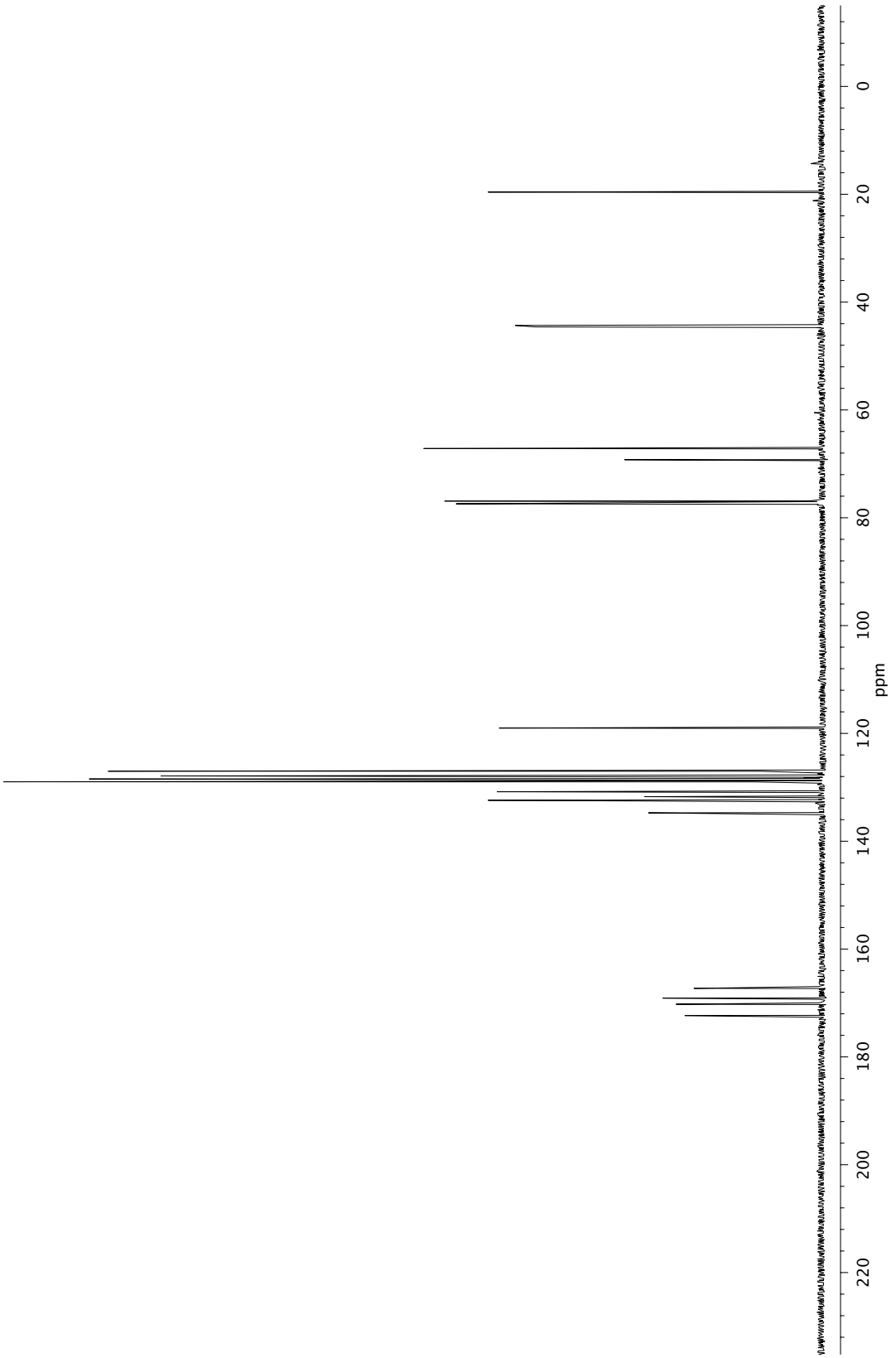
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8b**.



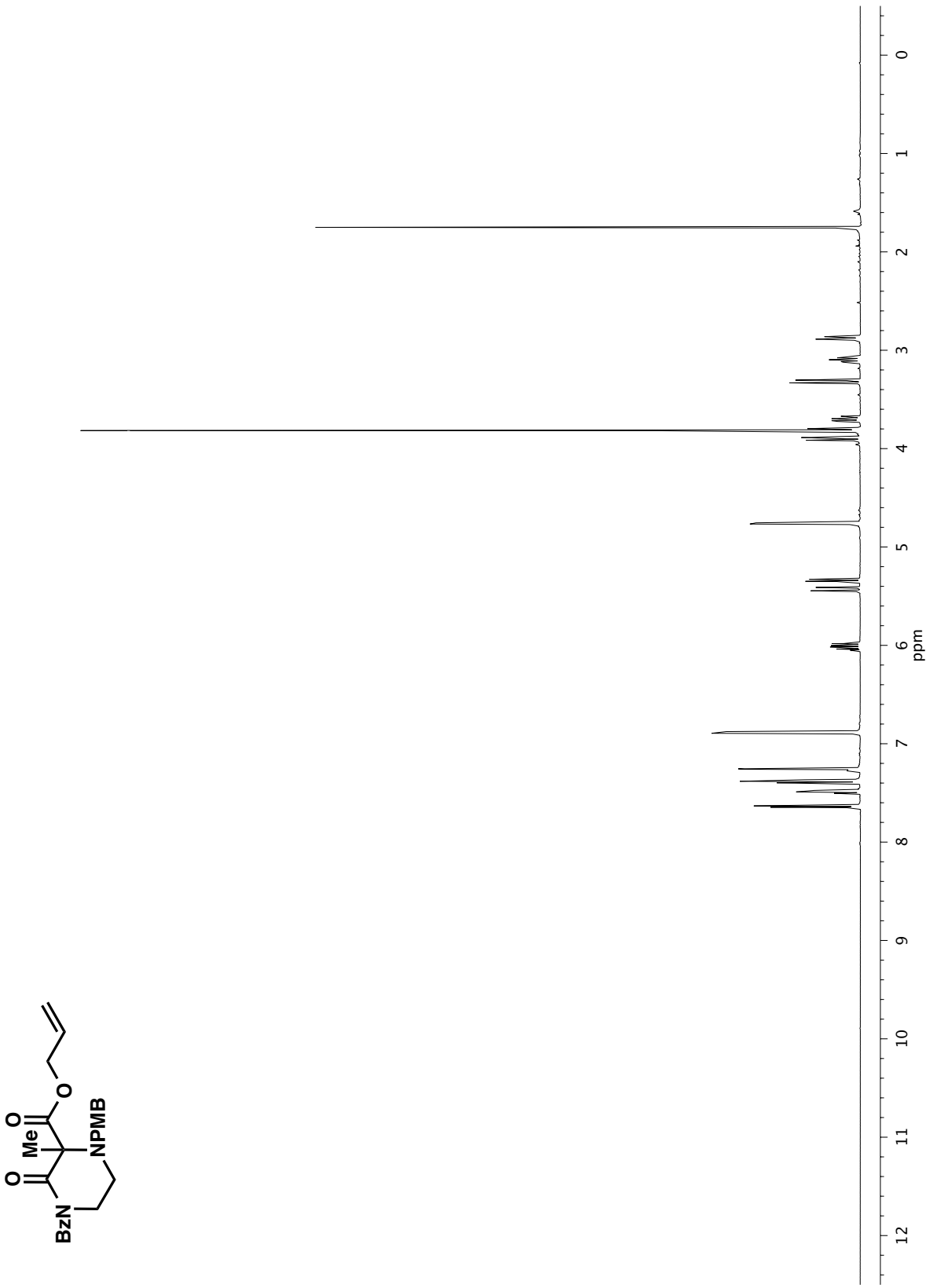
^{13}C NMR (75 MHz, $CDCl_3$) of compound **8b**.



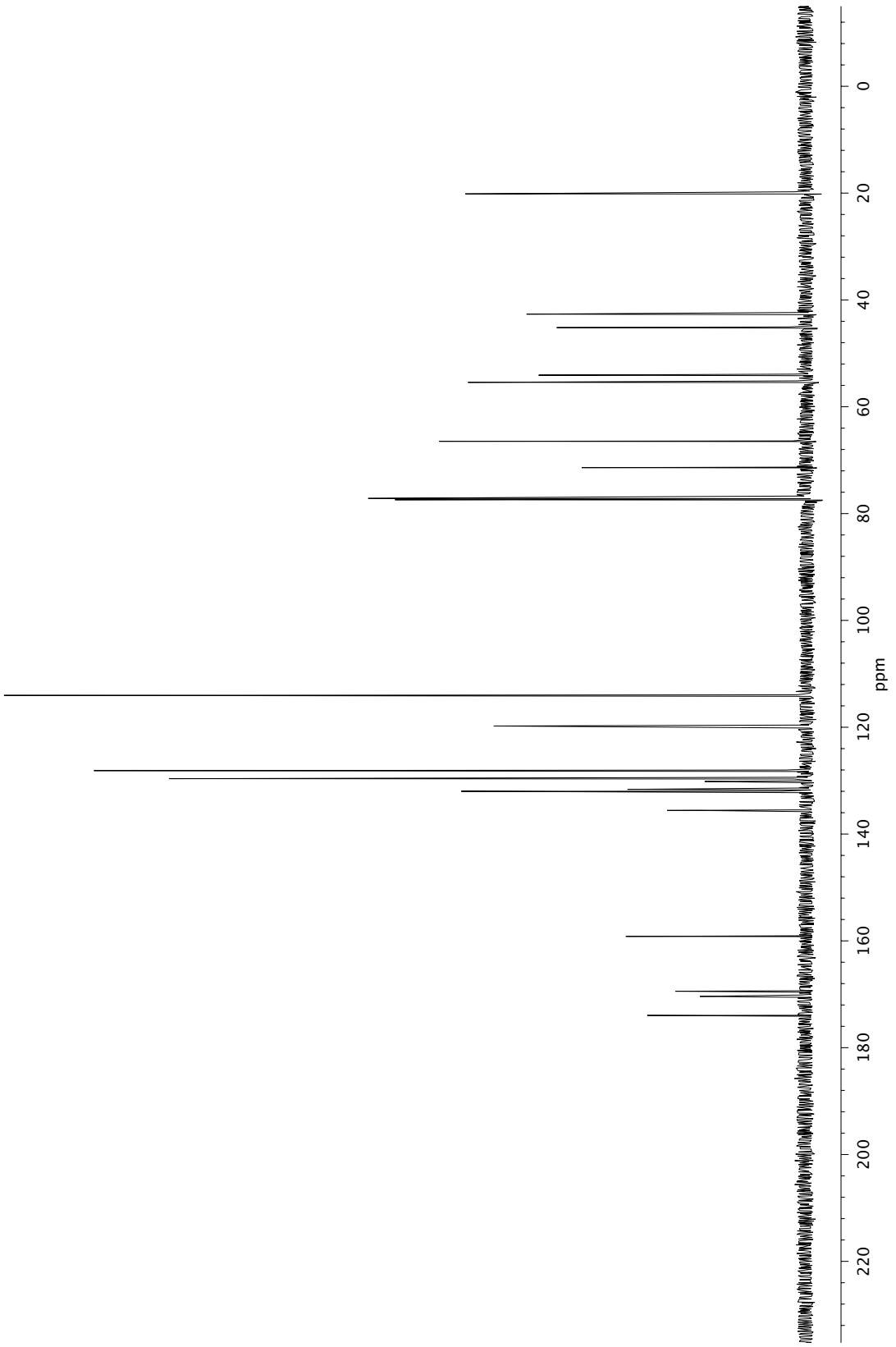
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8a**.



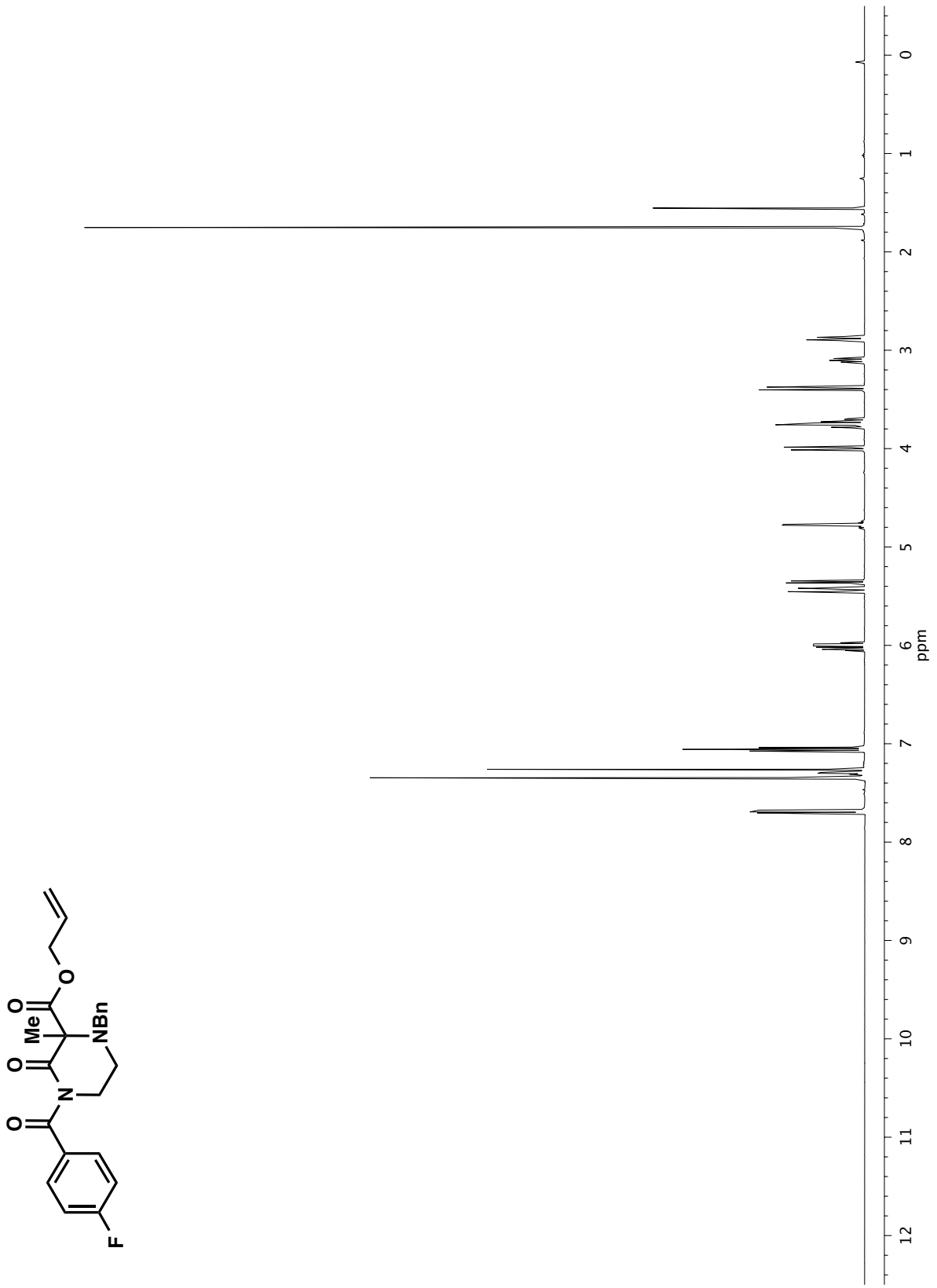
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8a**.



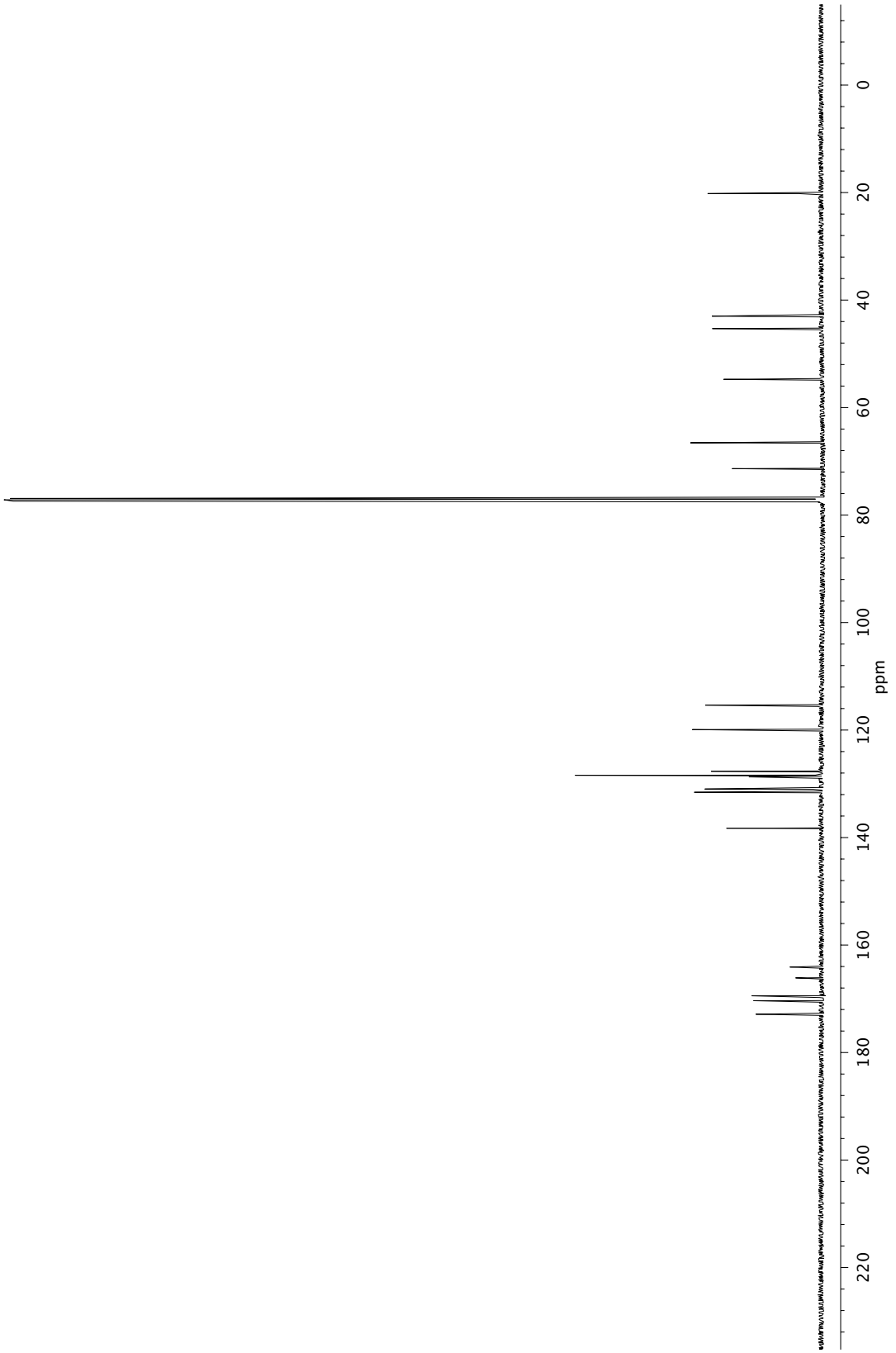
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8c**.



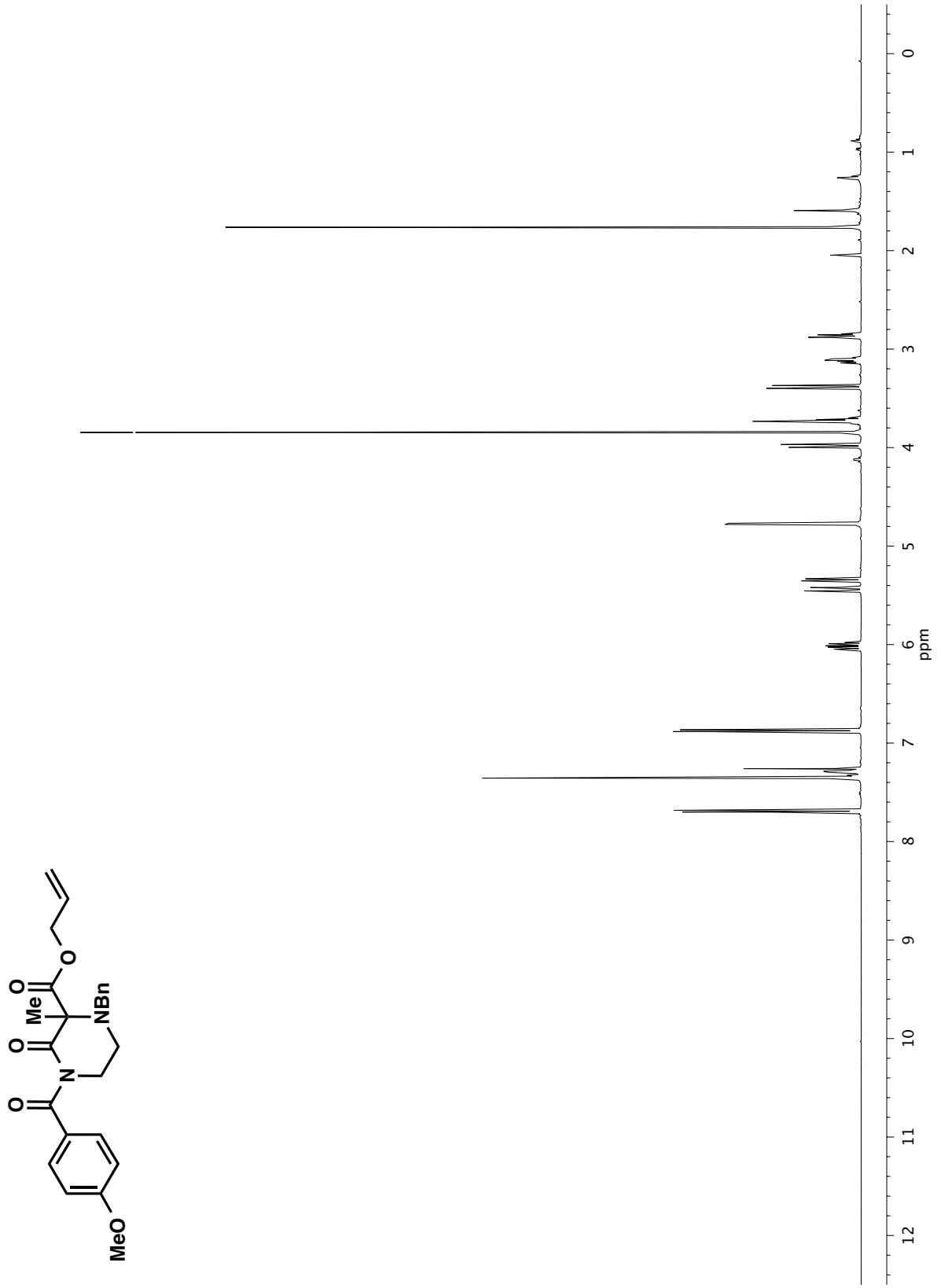
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8c**.



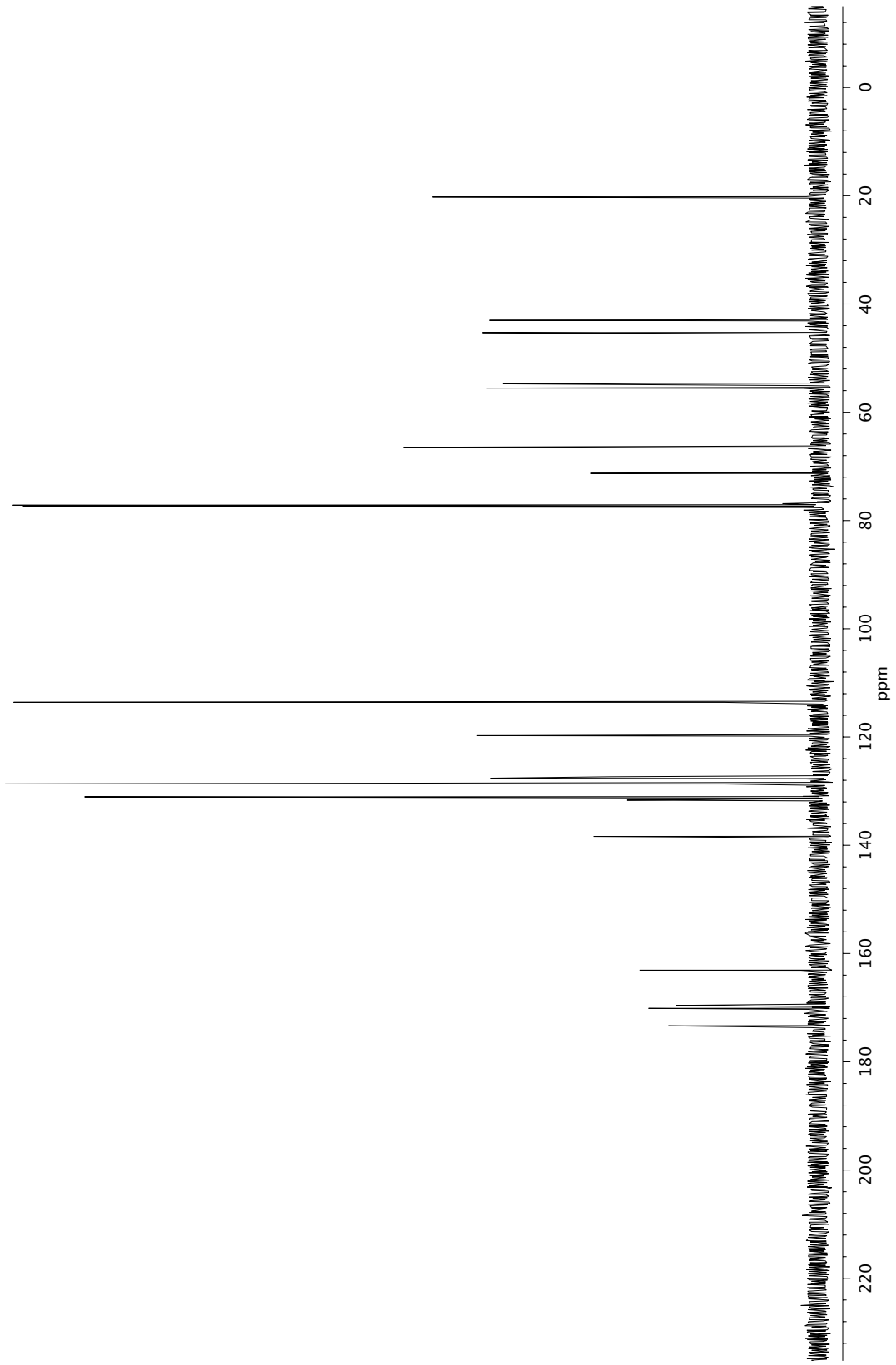
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8d**.



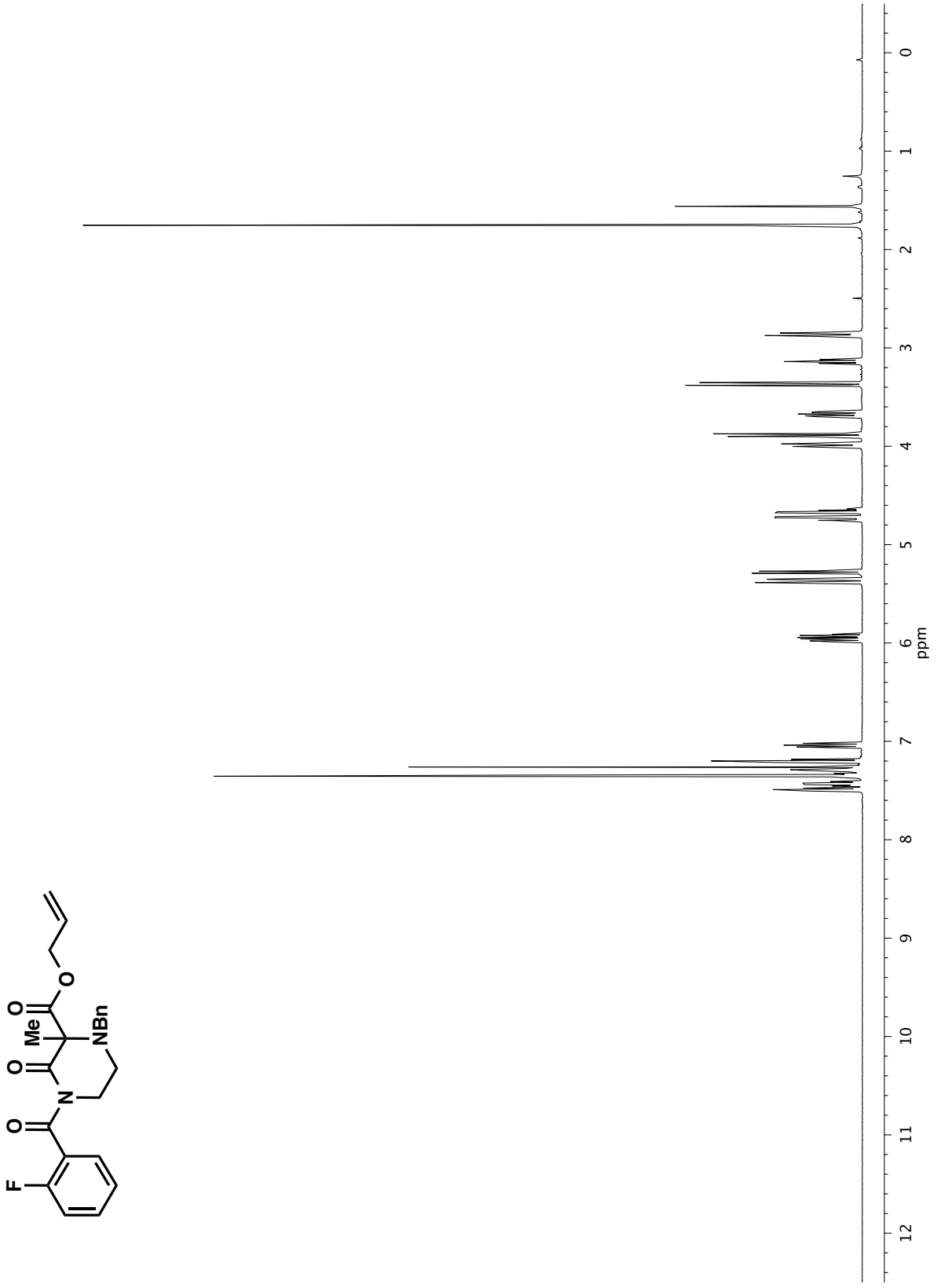
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8d**.



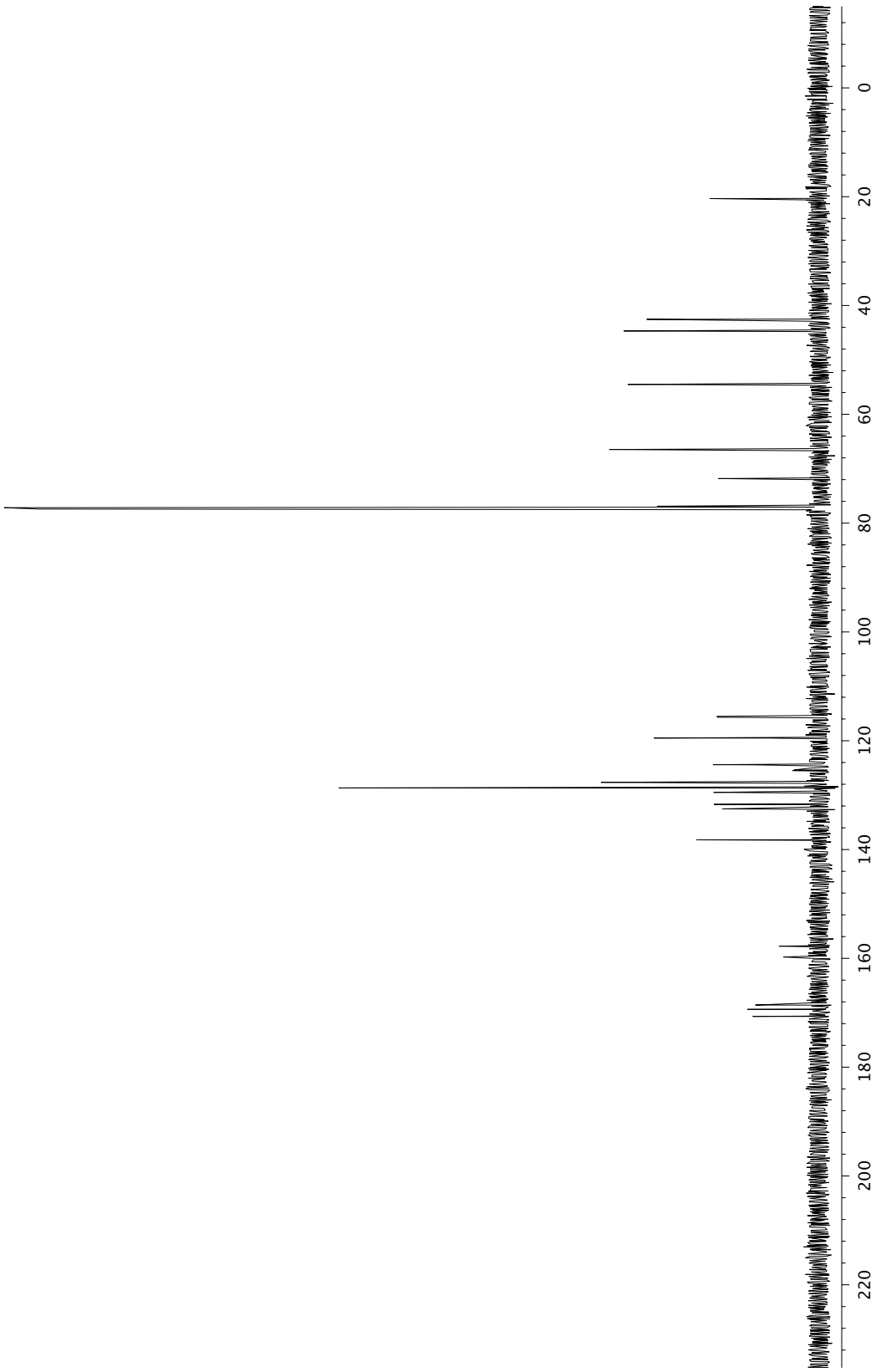
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8e**.



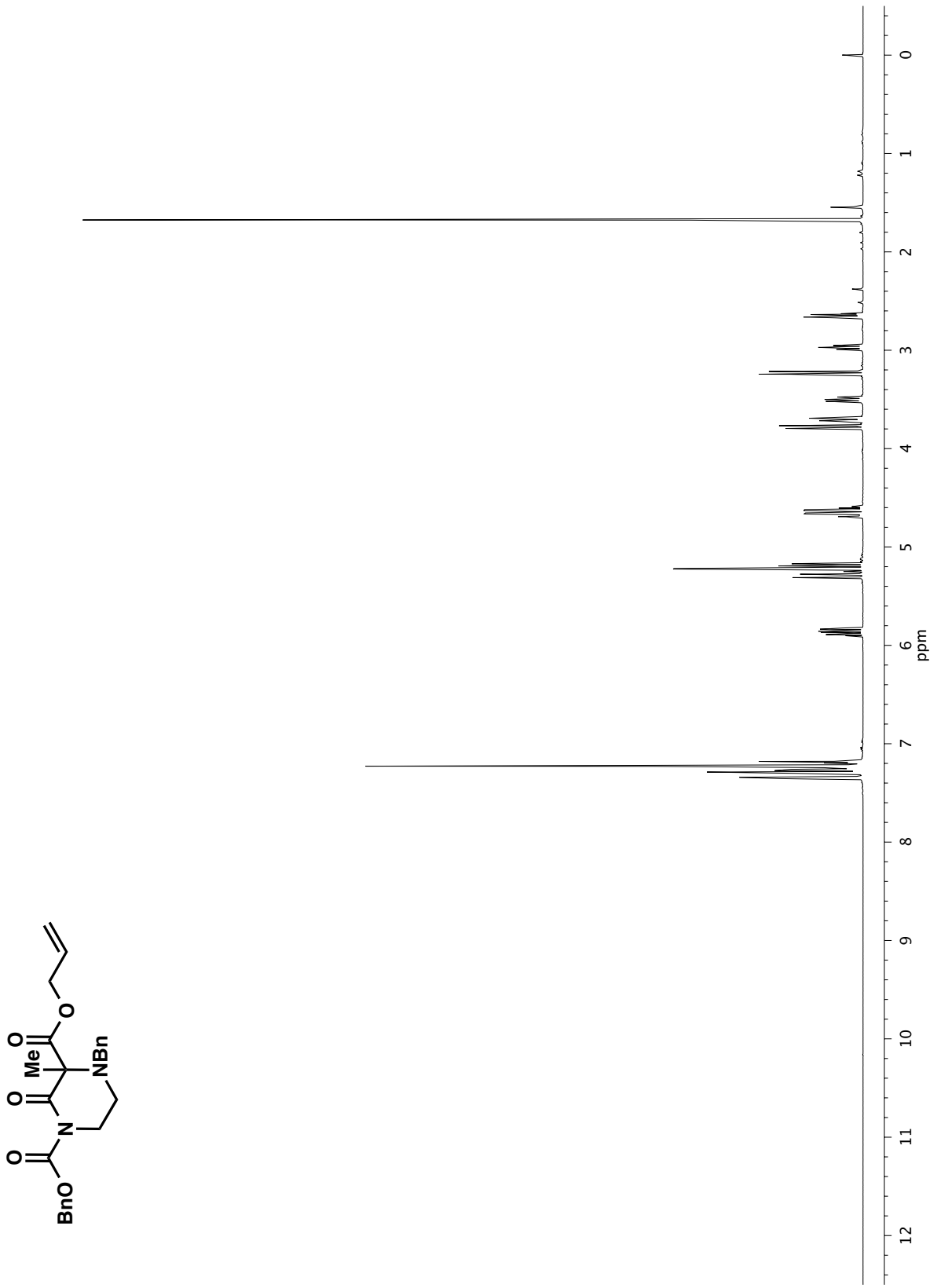
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8e.**



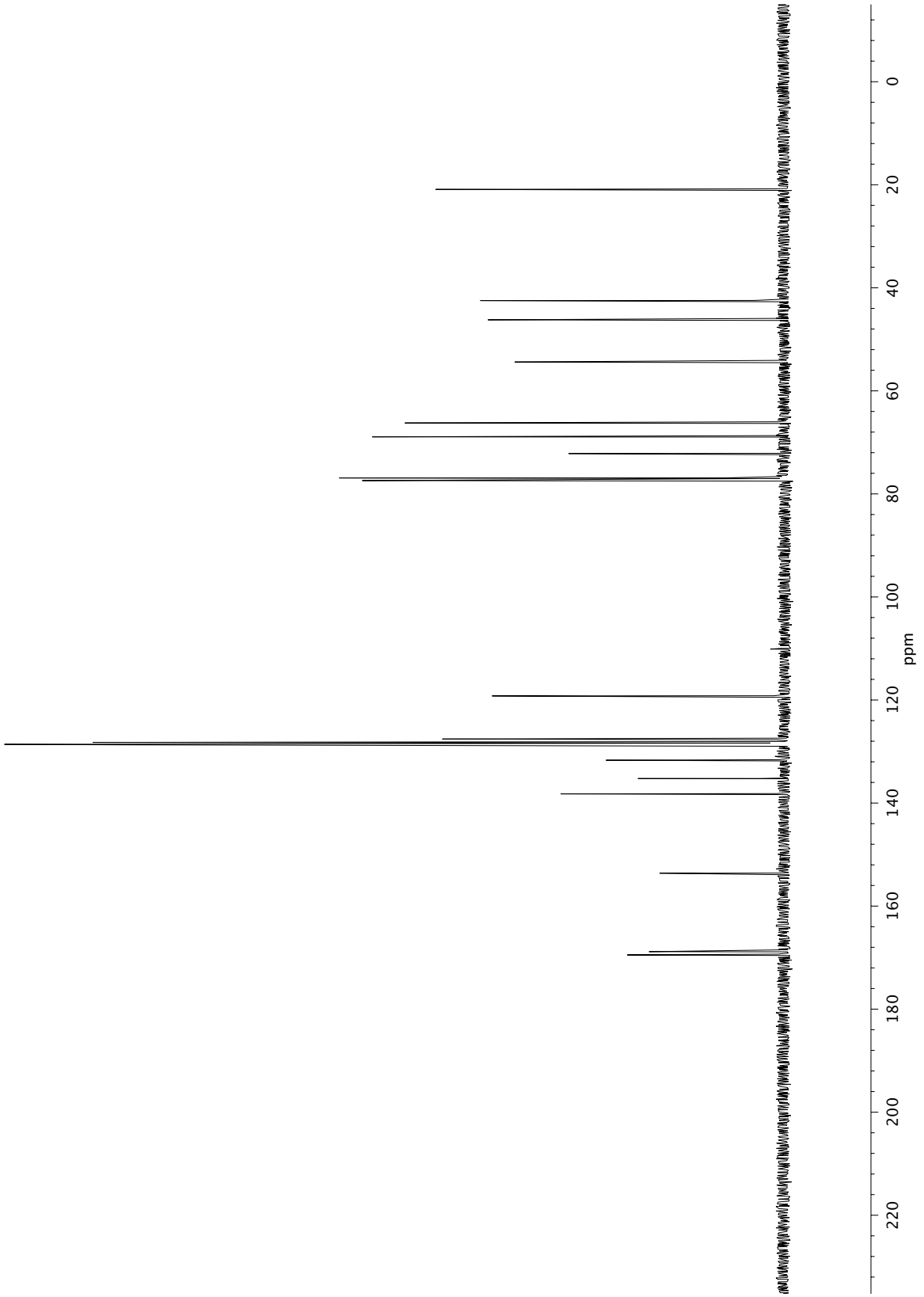
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8f**.



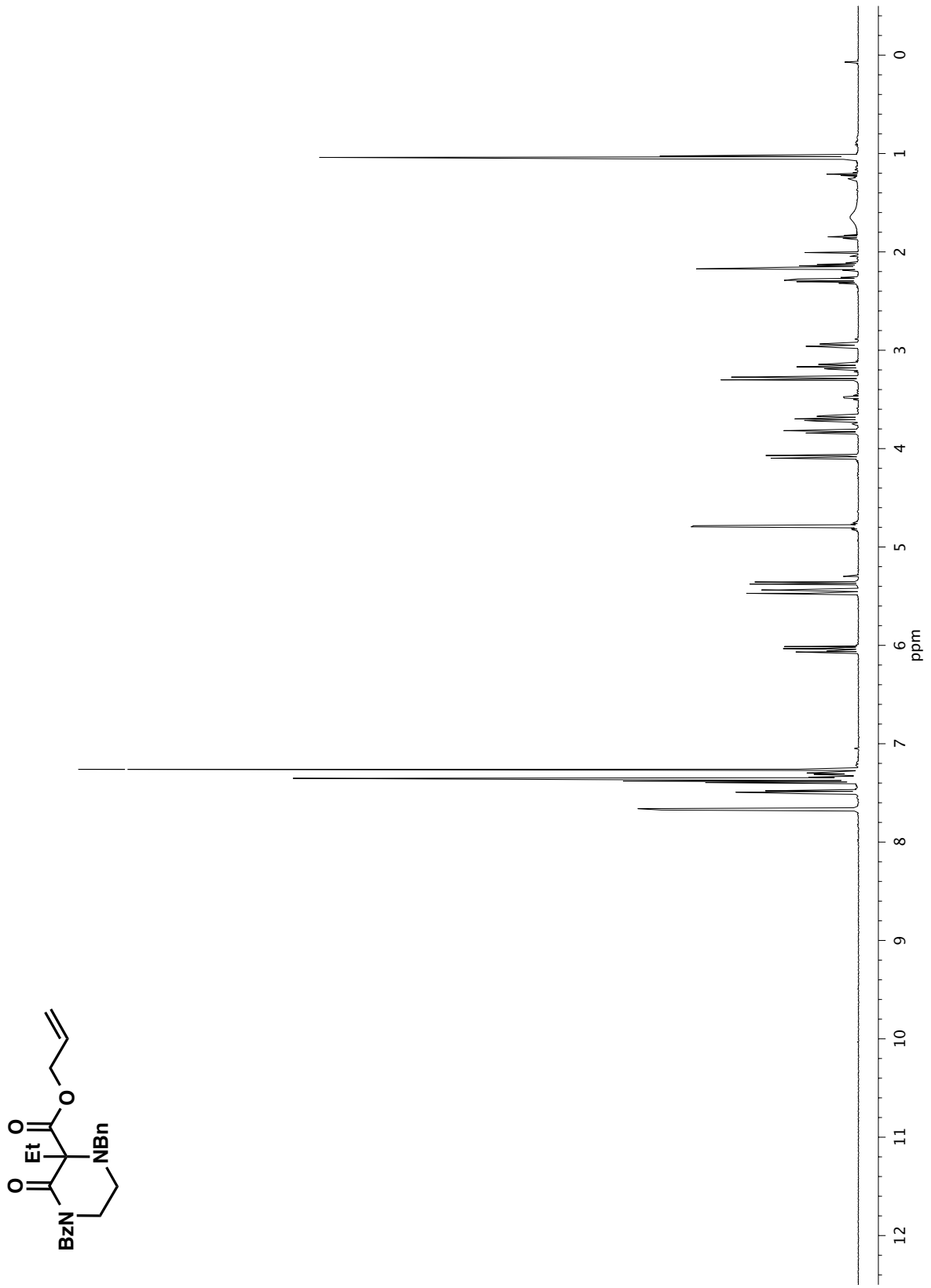
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8f.**



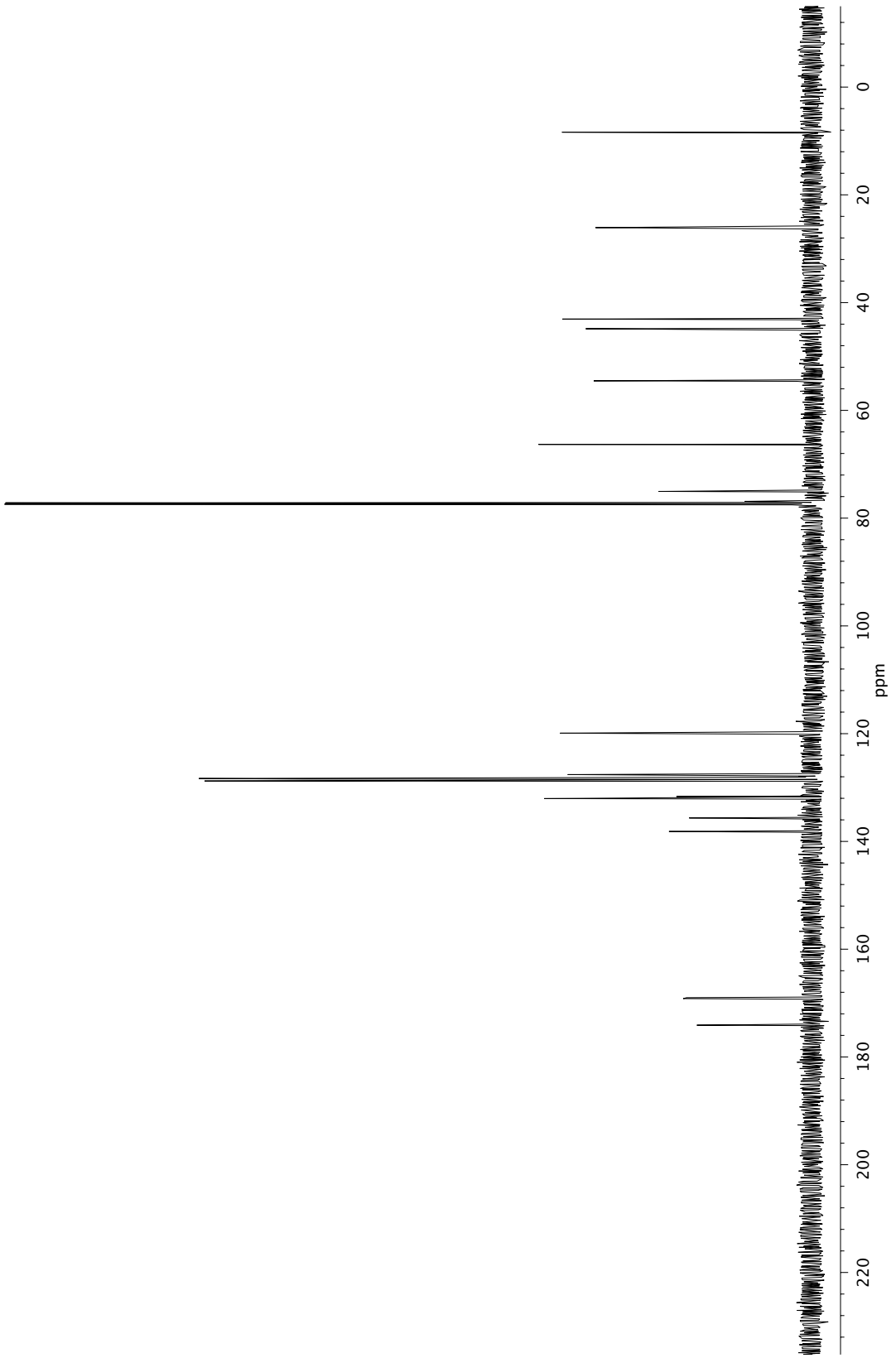
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8g**.



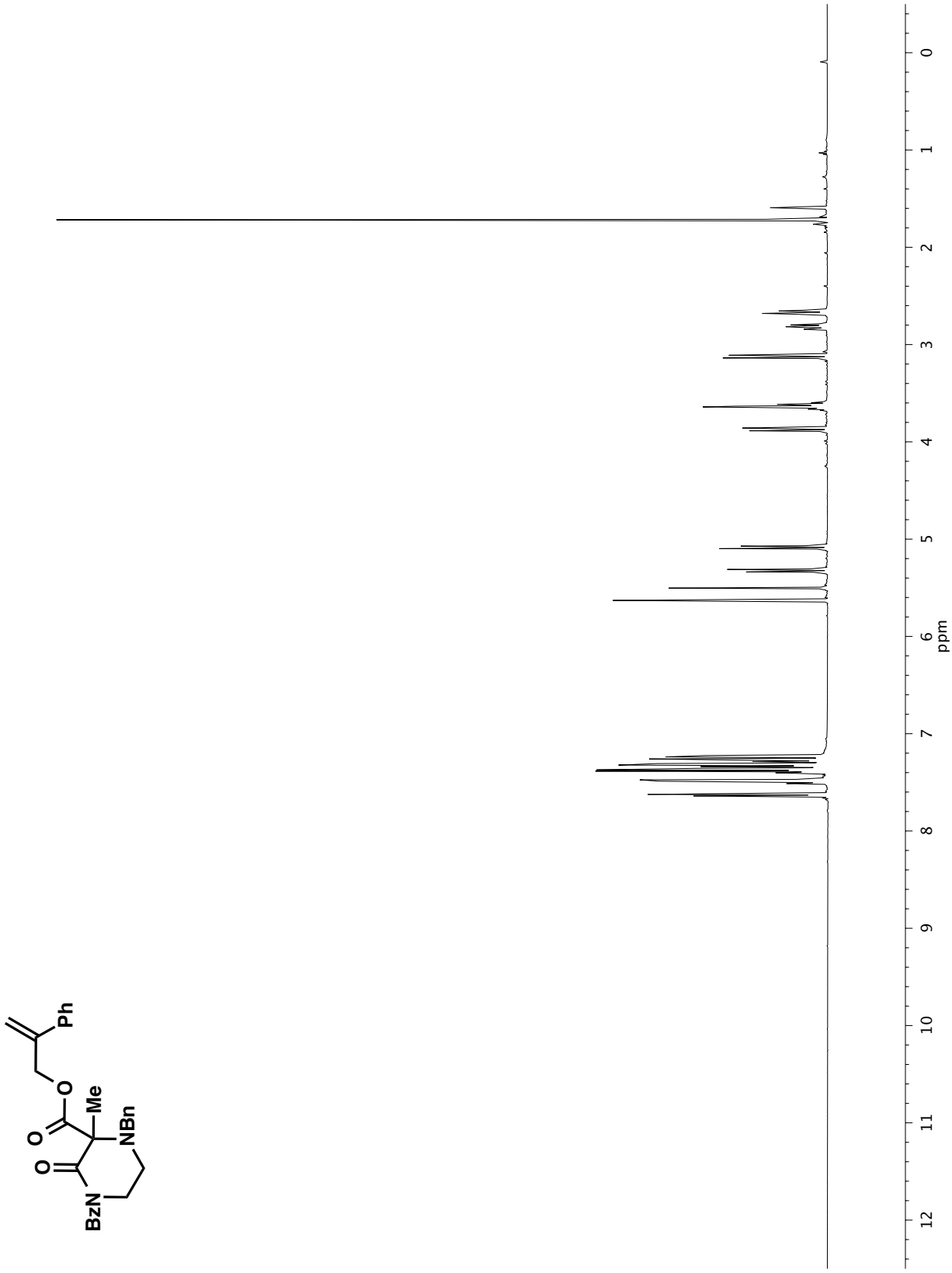
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8g.**



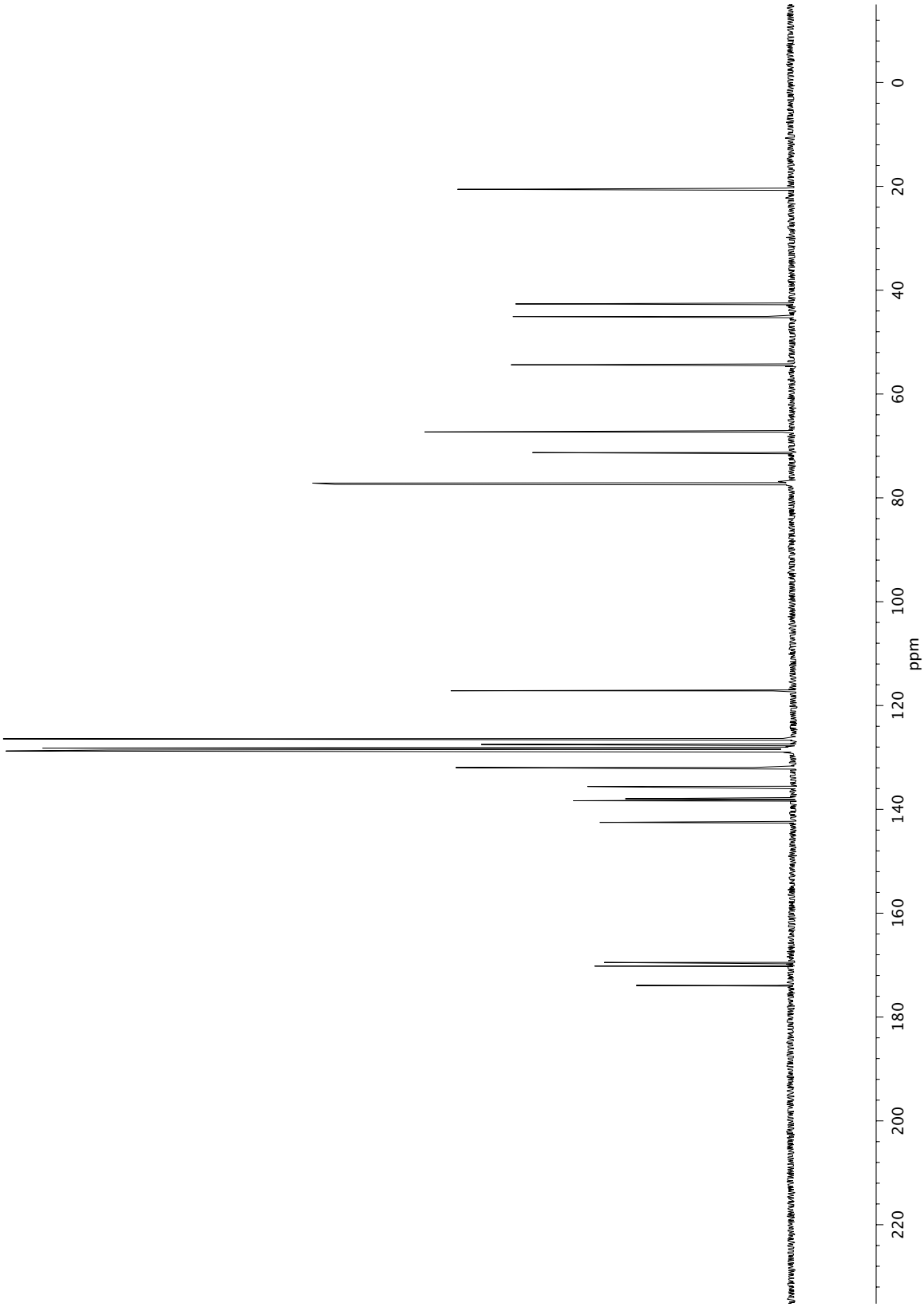
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8h**.



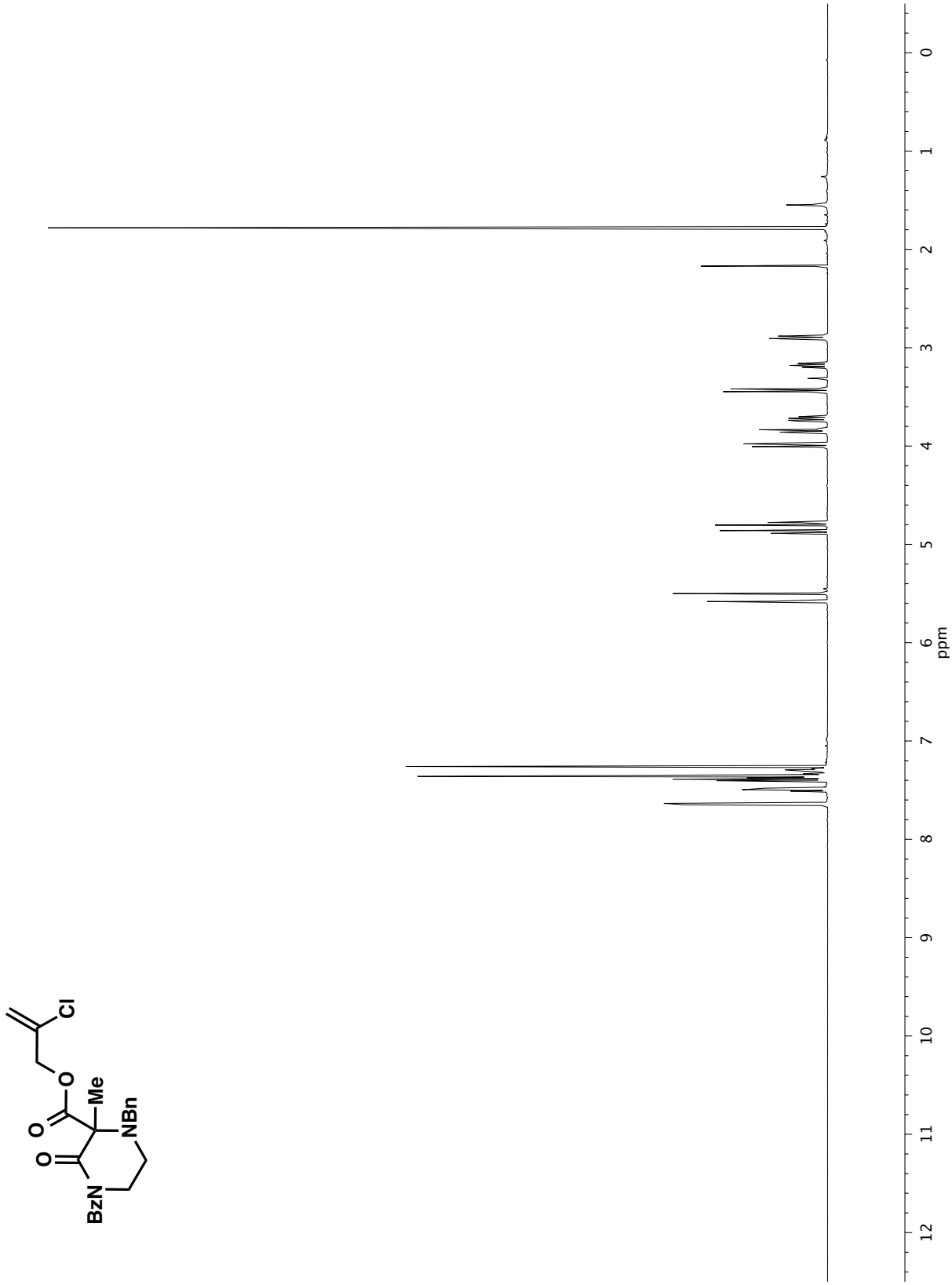
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8h.**



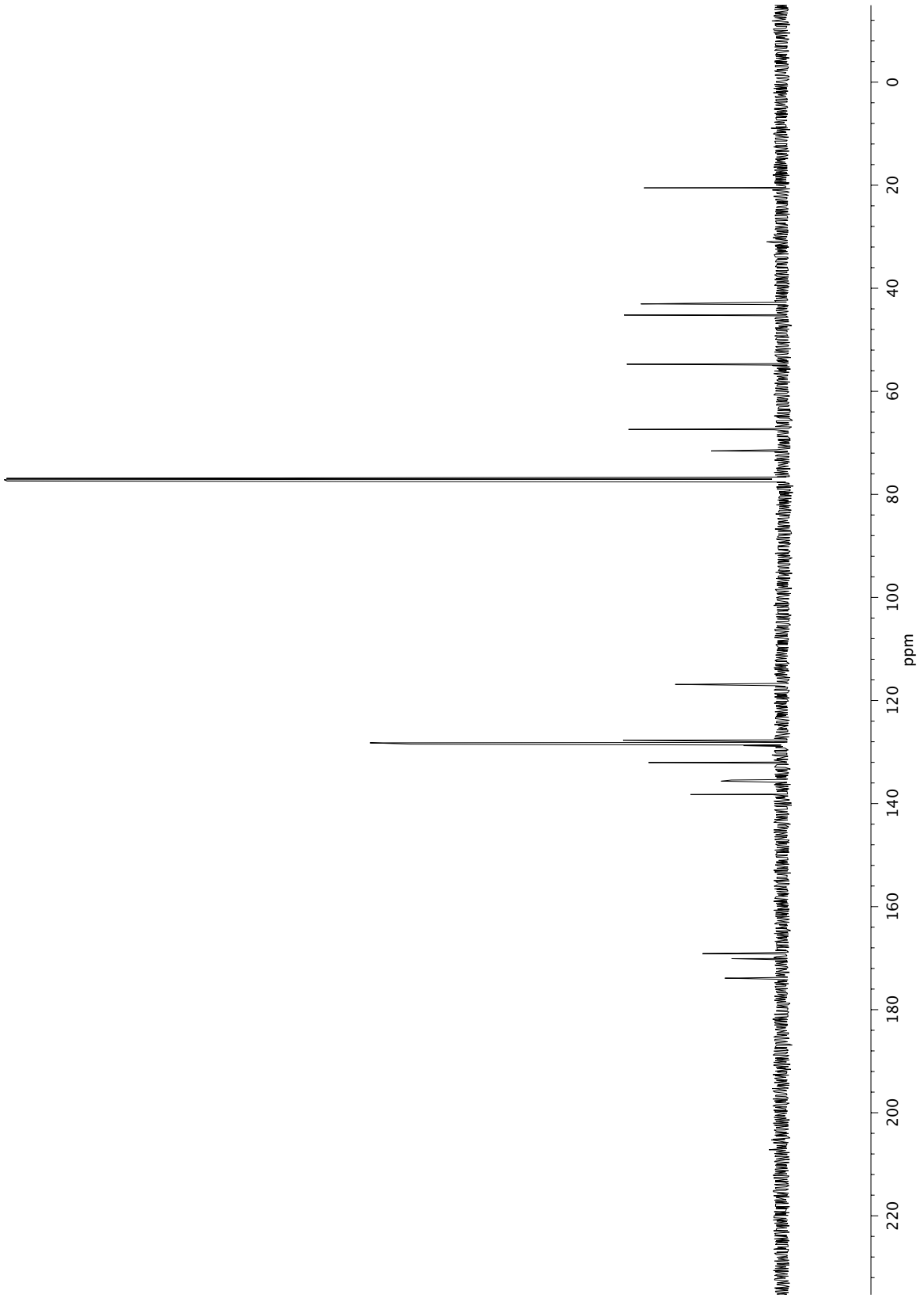
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8l**.



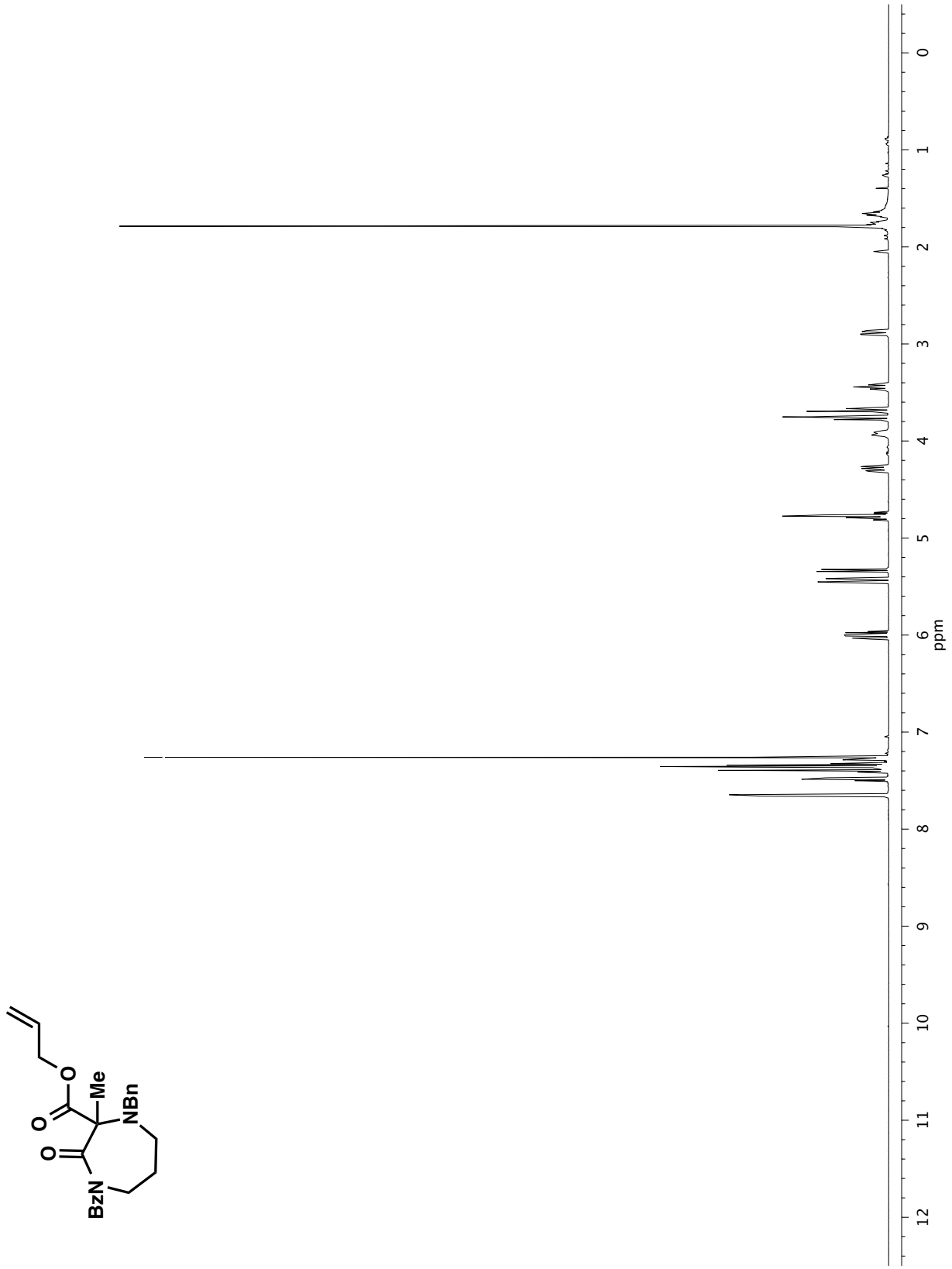
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8l.**



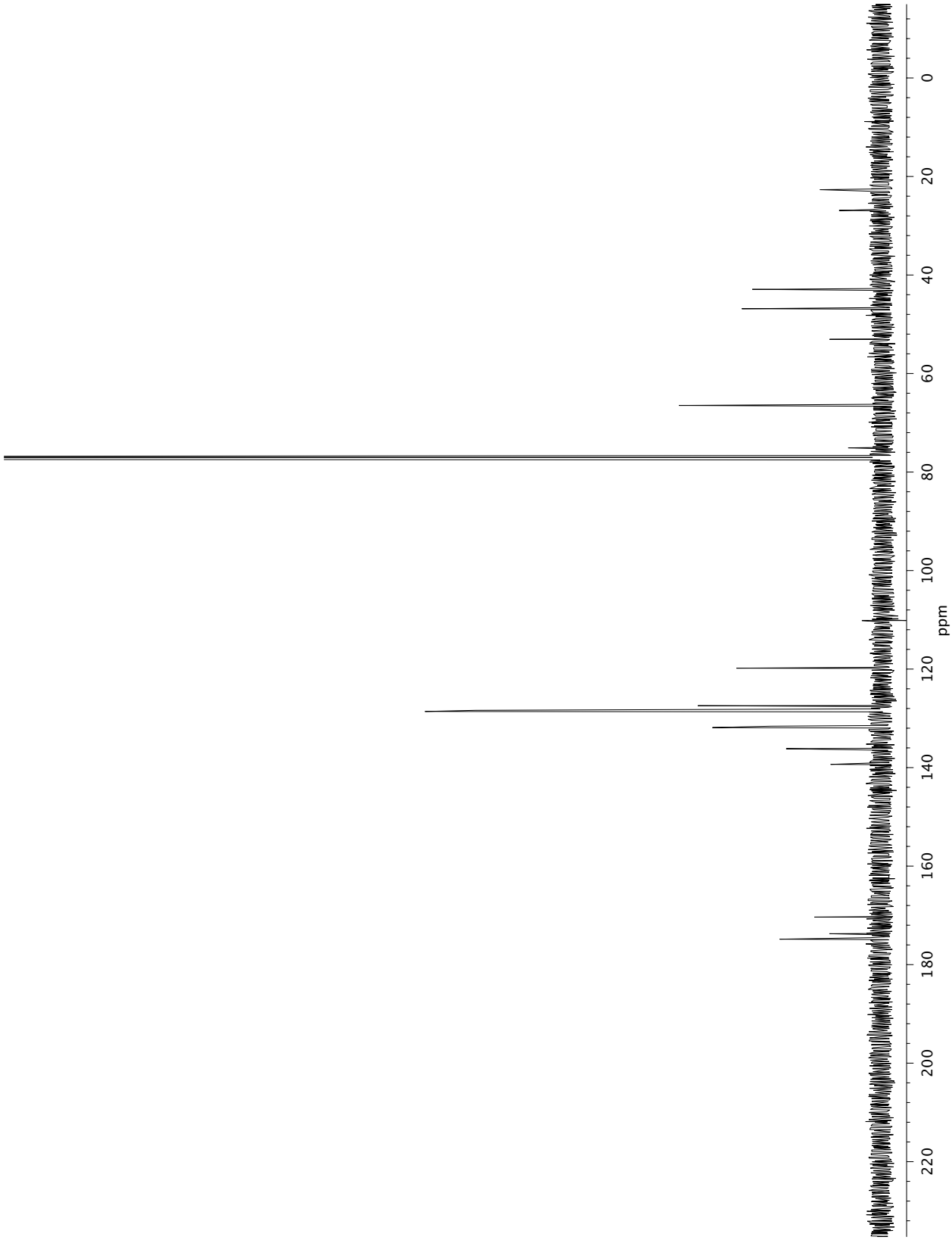
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8m**.



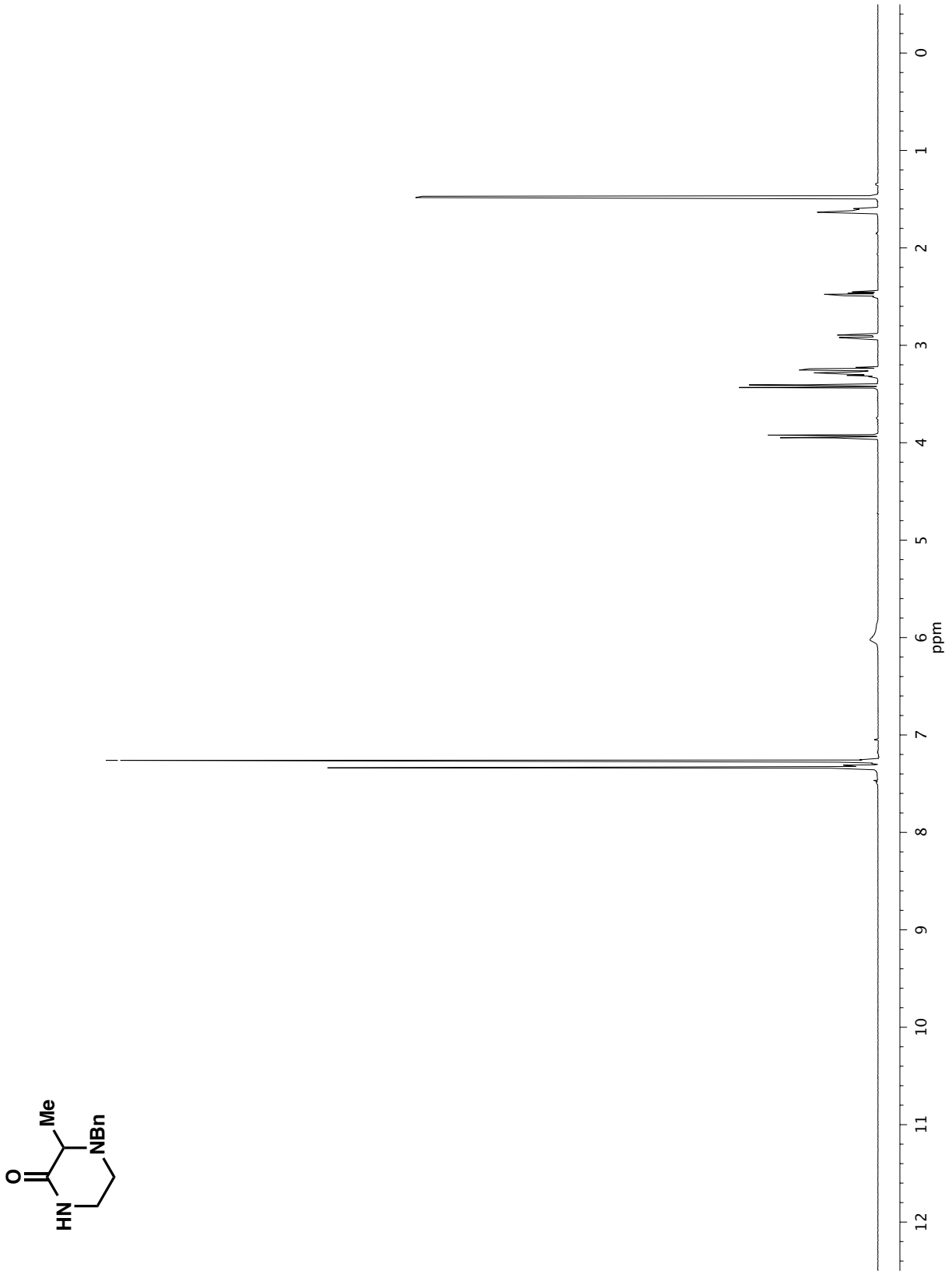
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8m.**



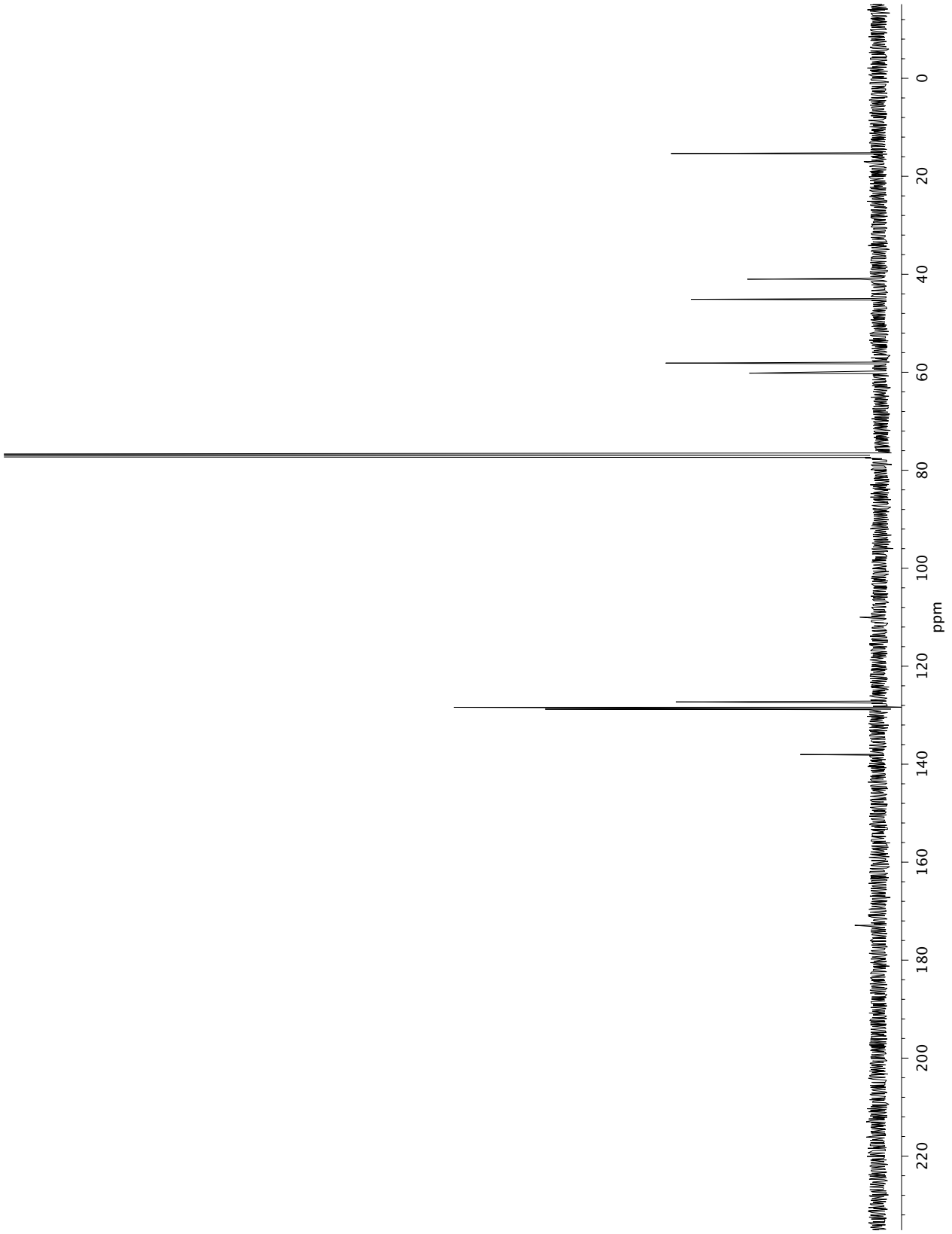
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8o**.



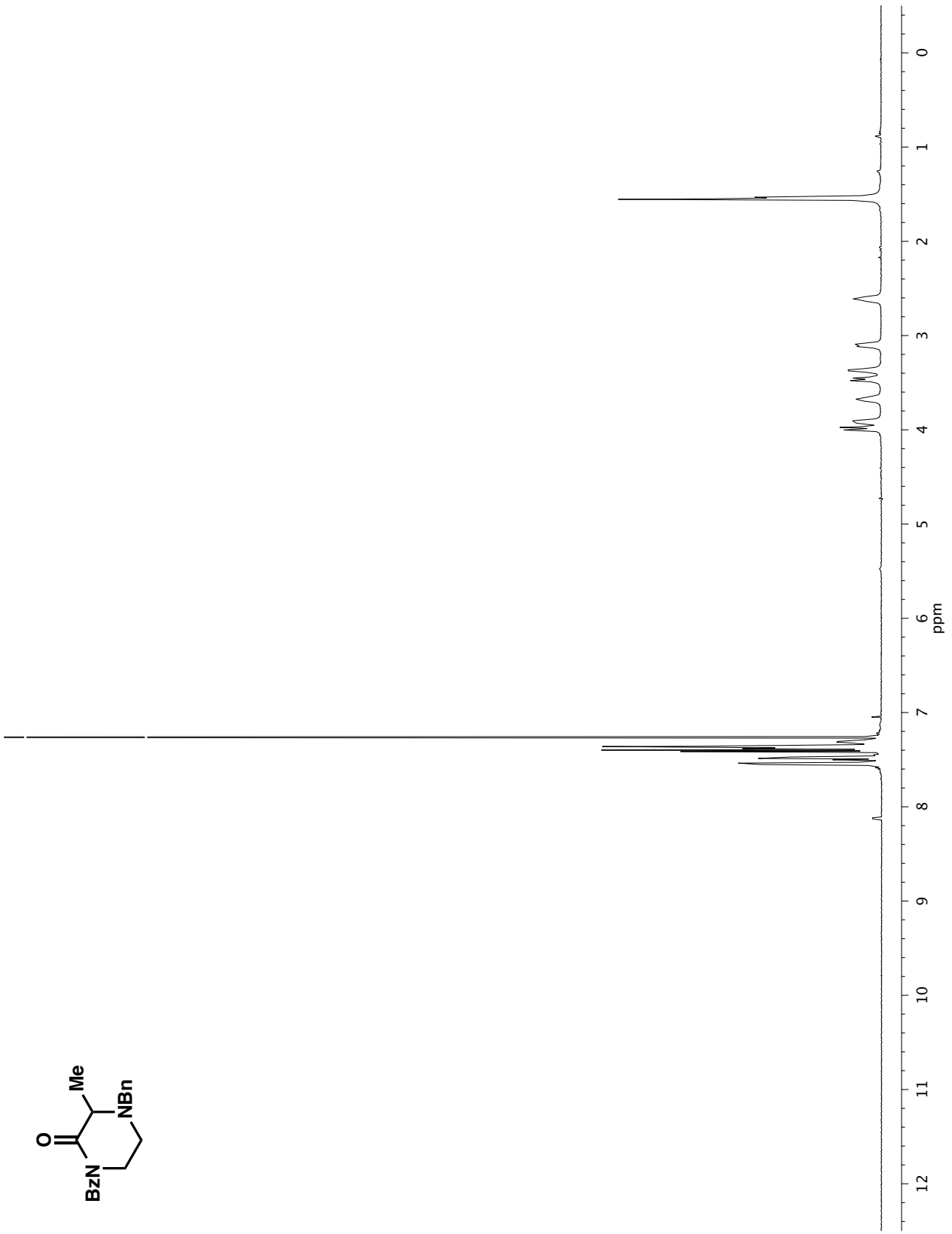
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8o.**



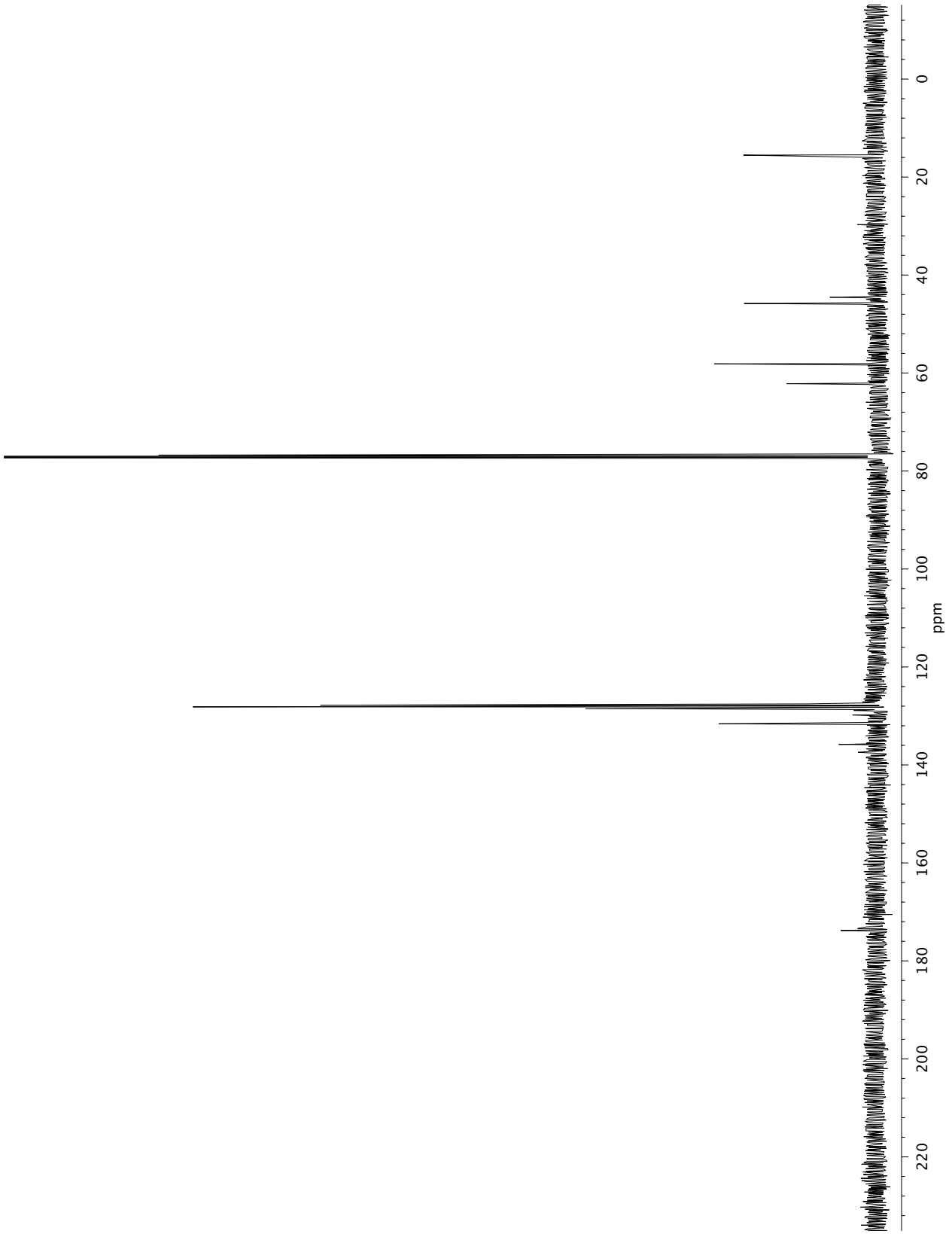
^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI9**.



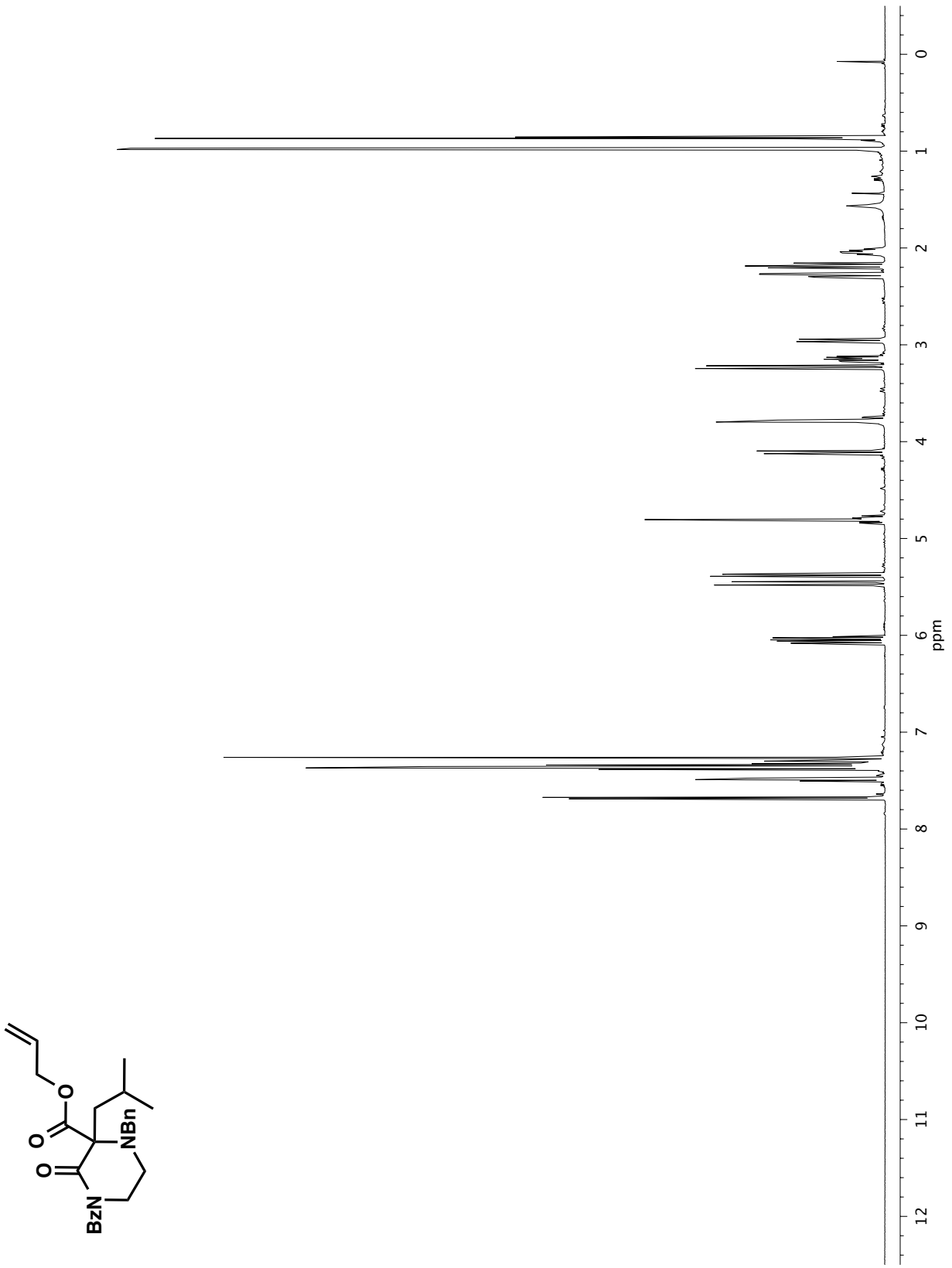
^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI9.**



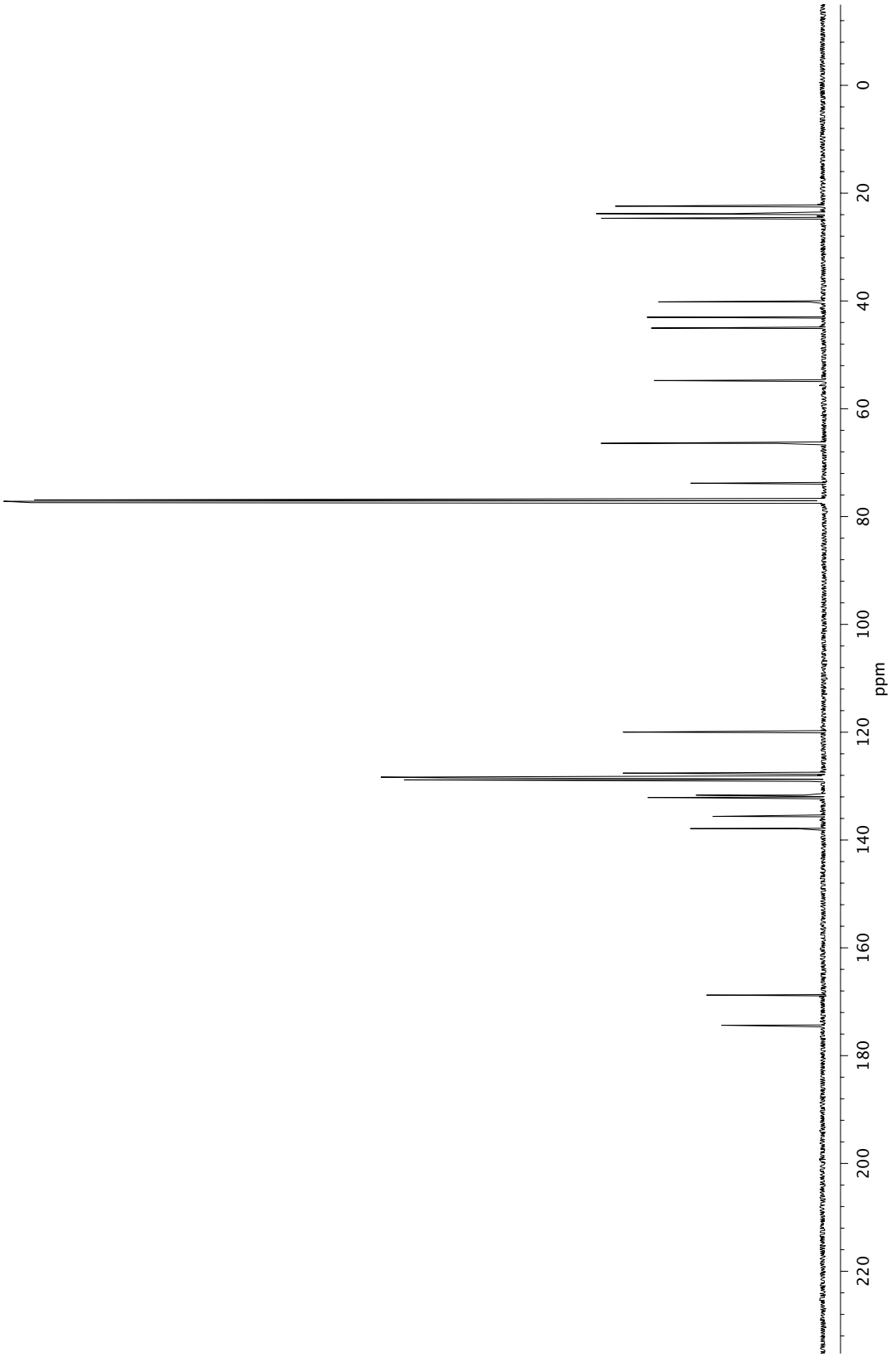
^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI10**.



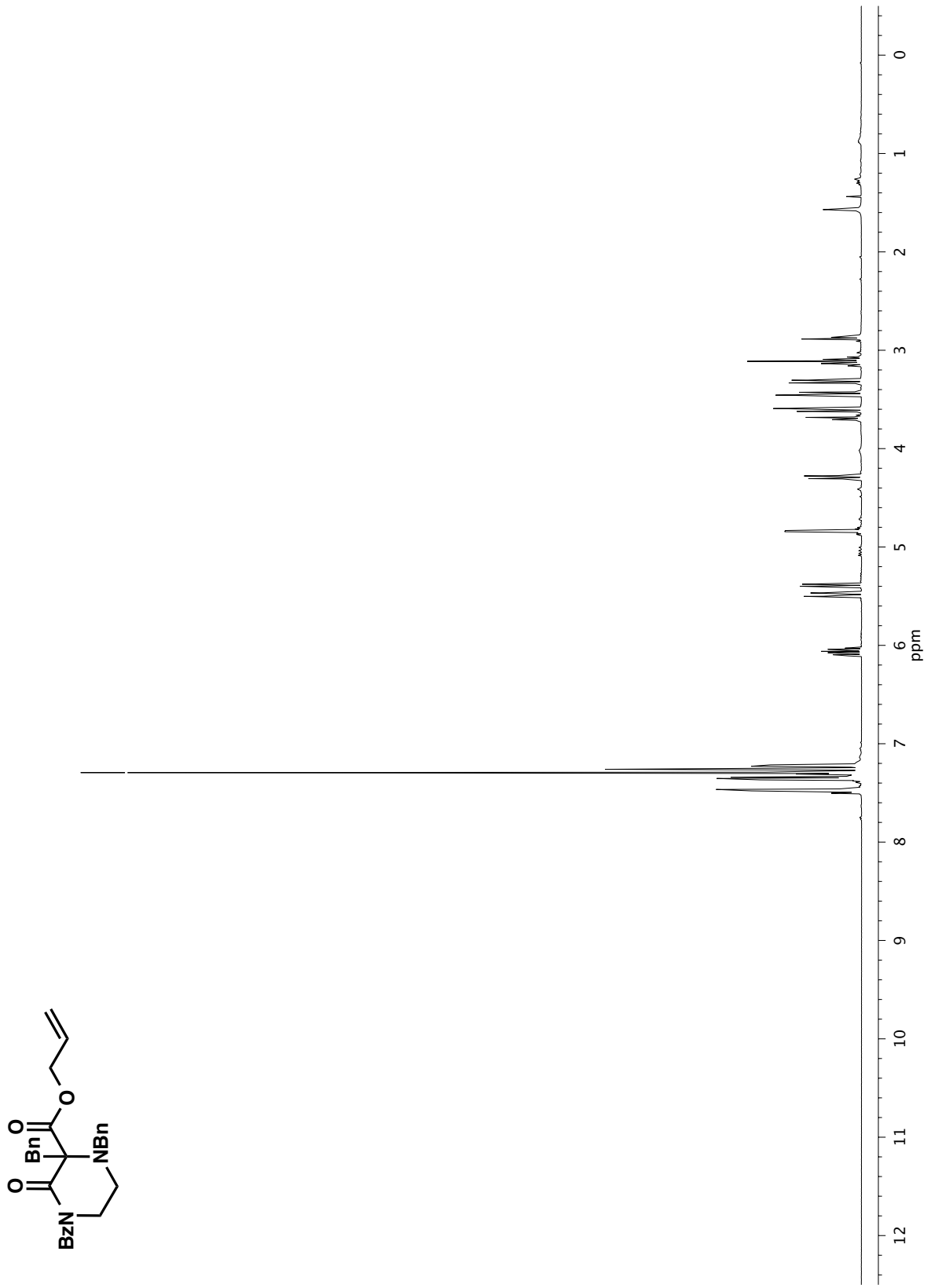
^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI10.**



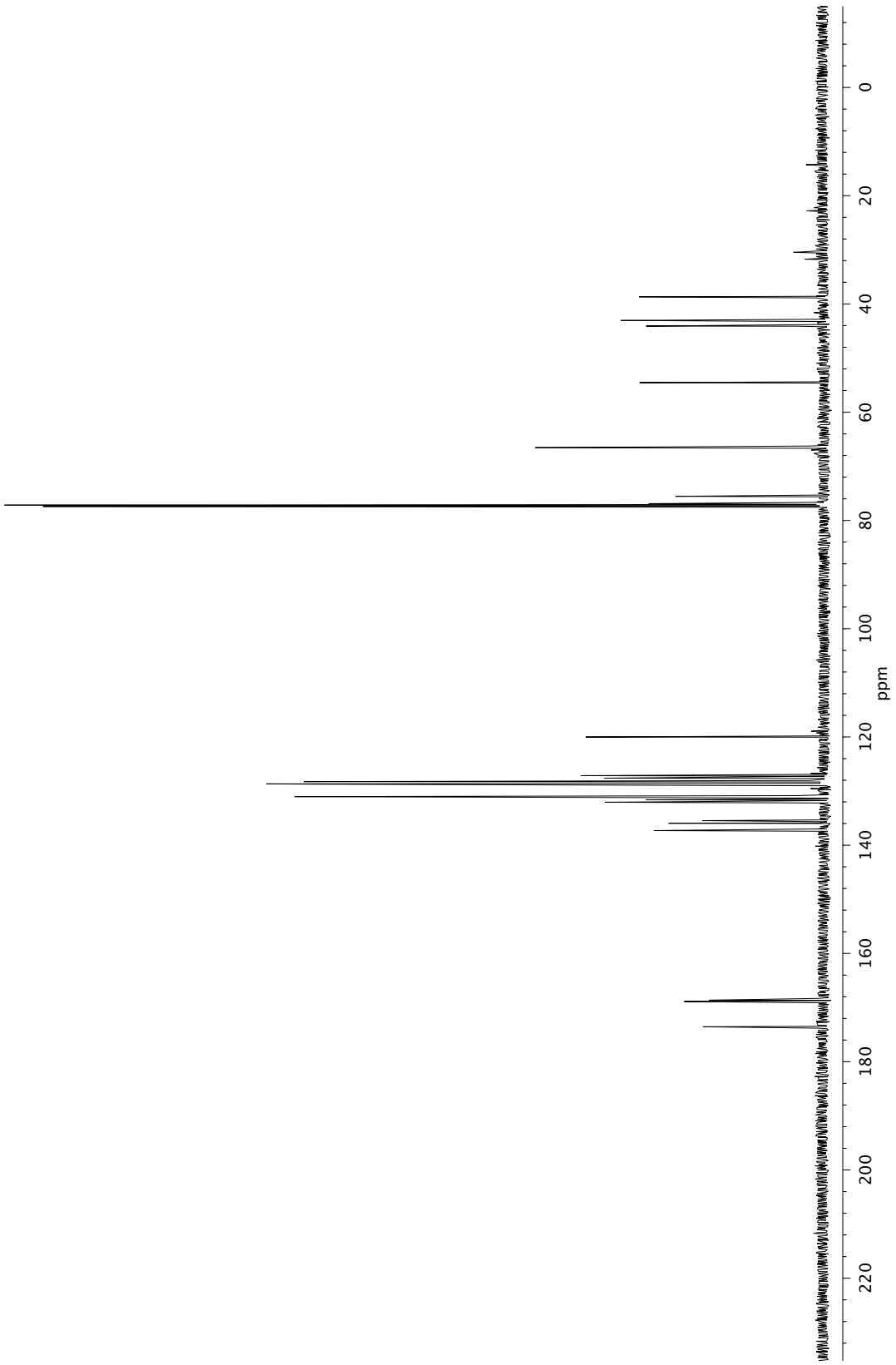
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8i**.



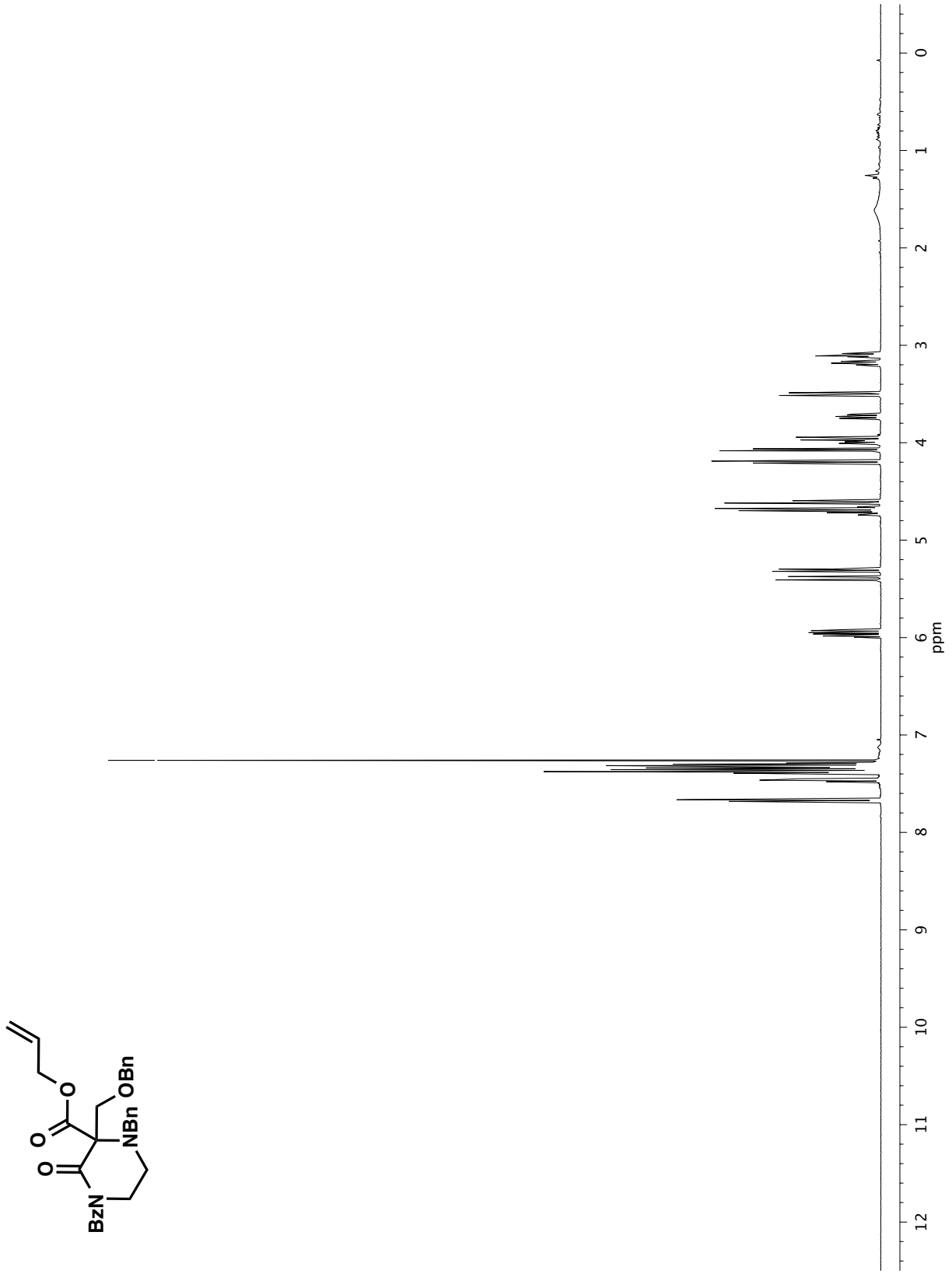
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8i.**



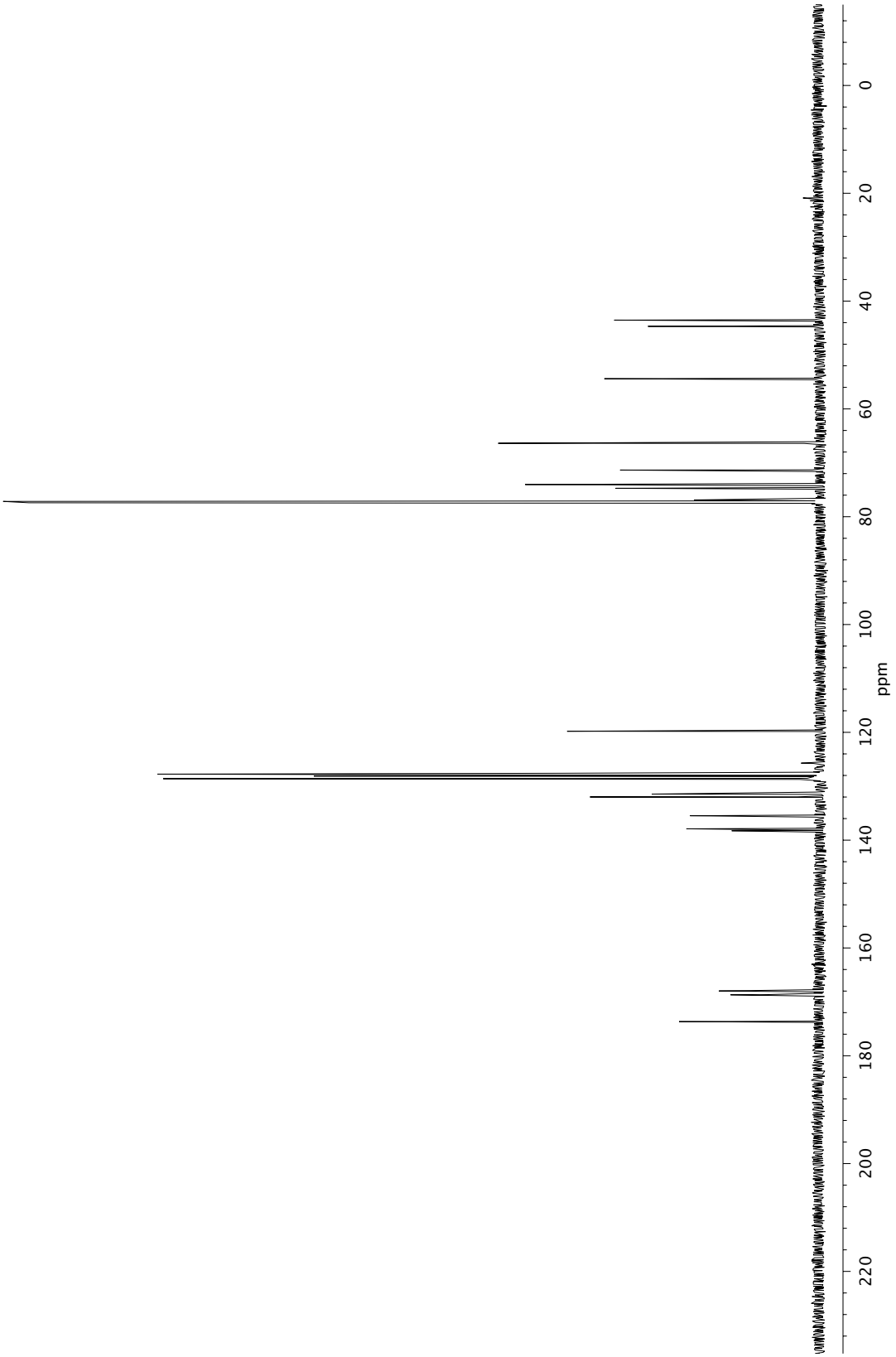
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8j**.



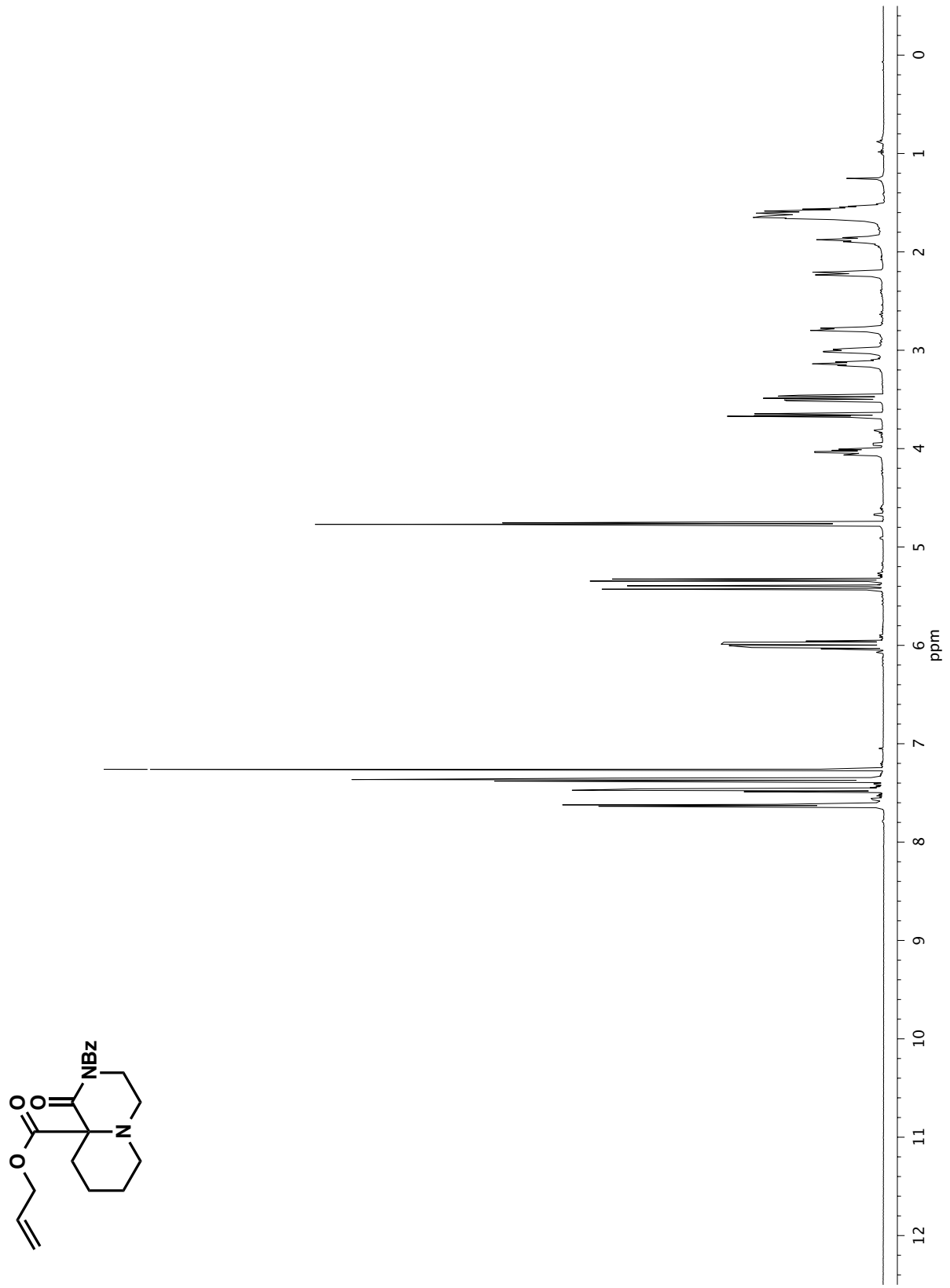
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8j.**



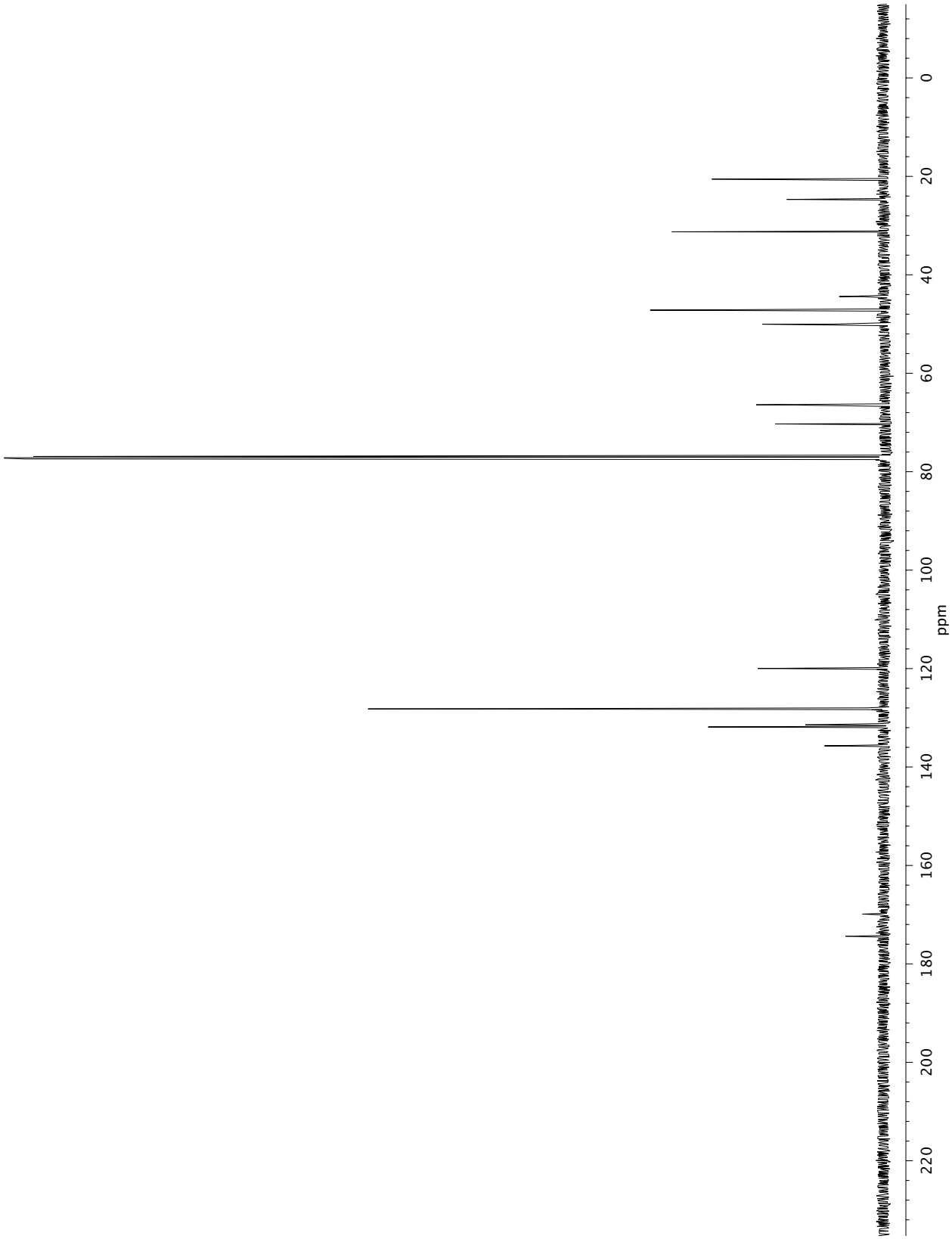
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8k**.



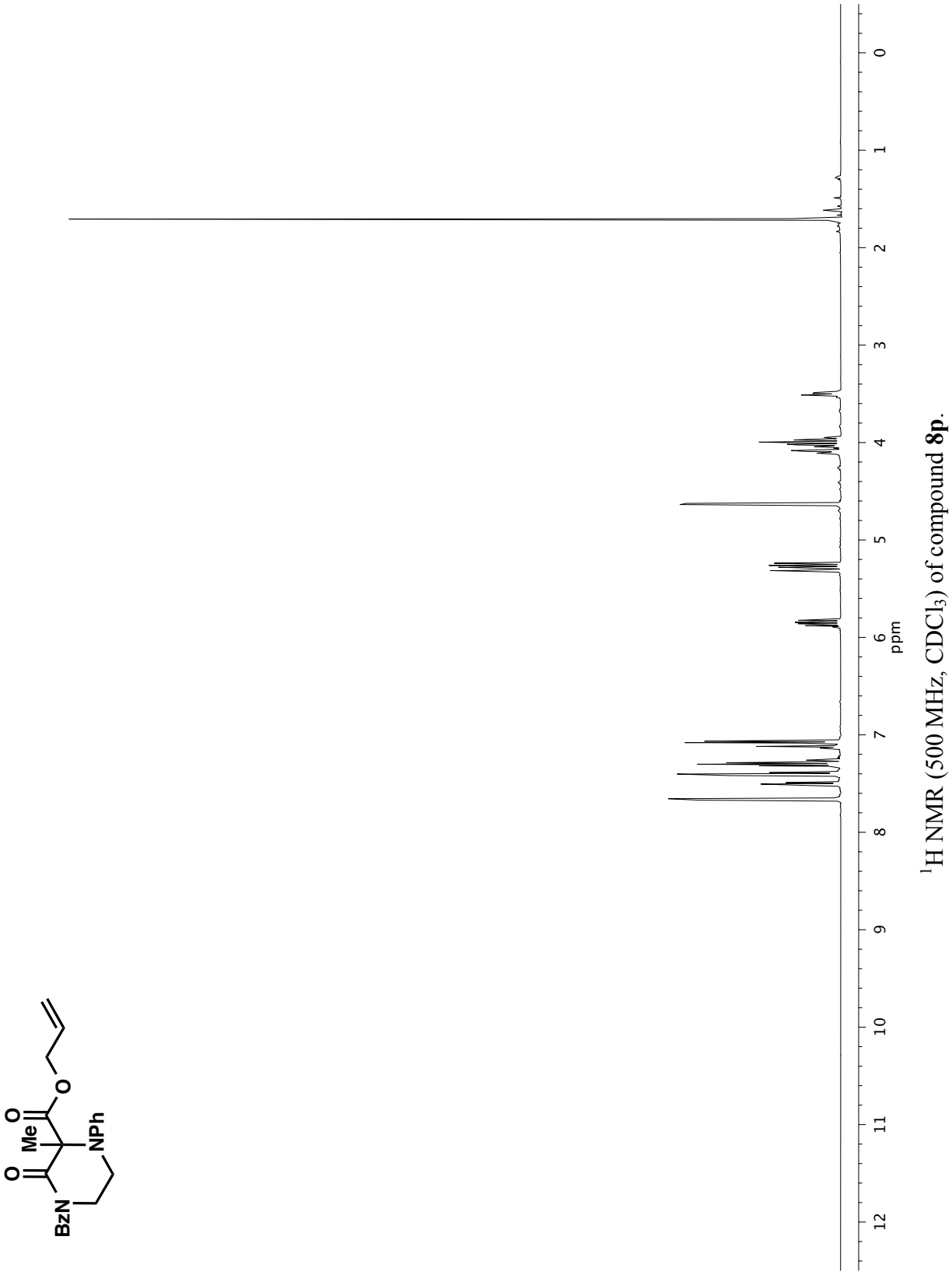
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8k.**



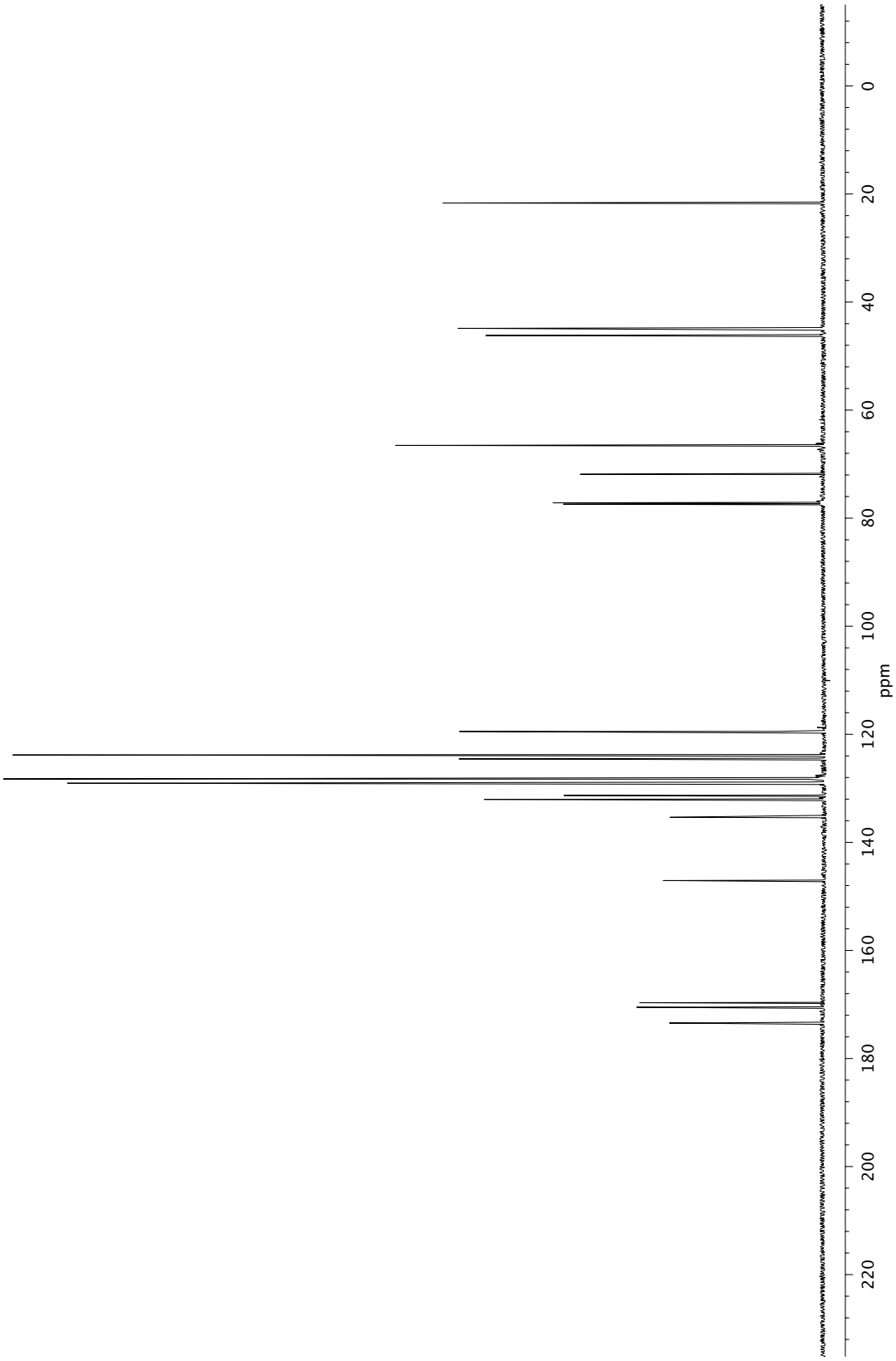
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8n**.



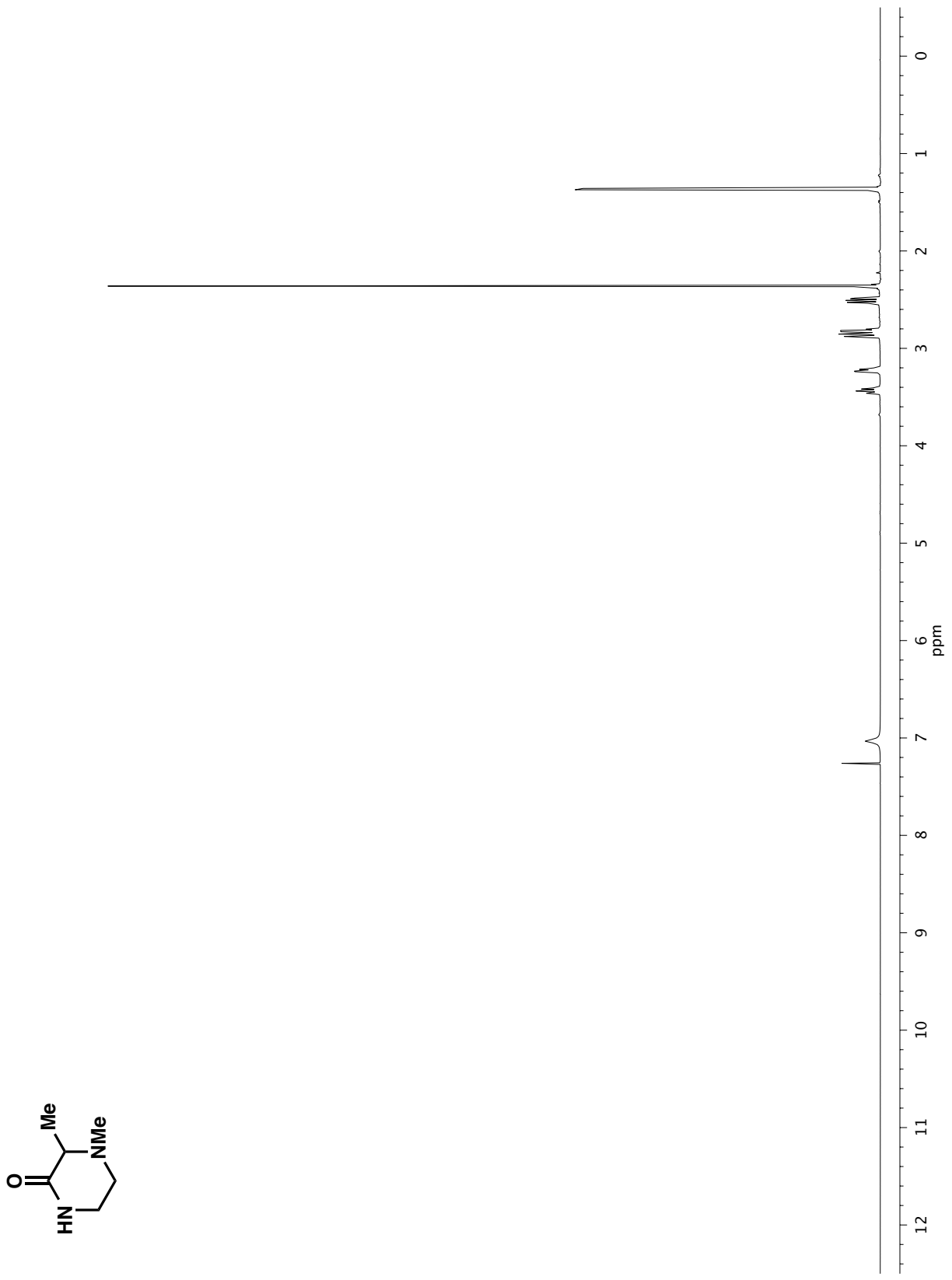
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8n.**



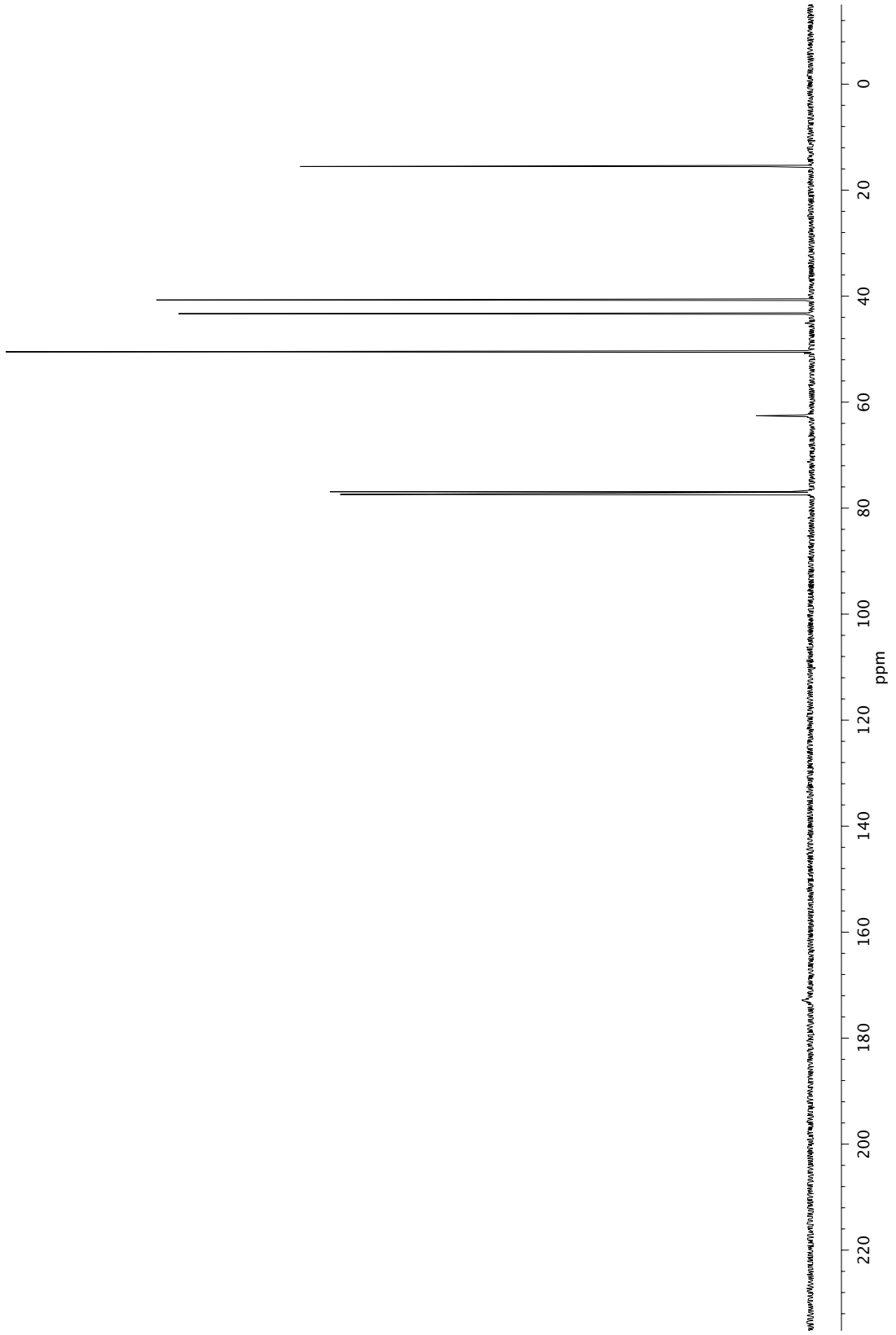
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8p**.



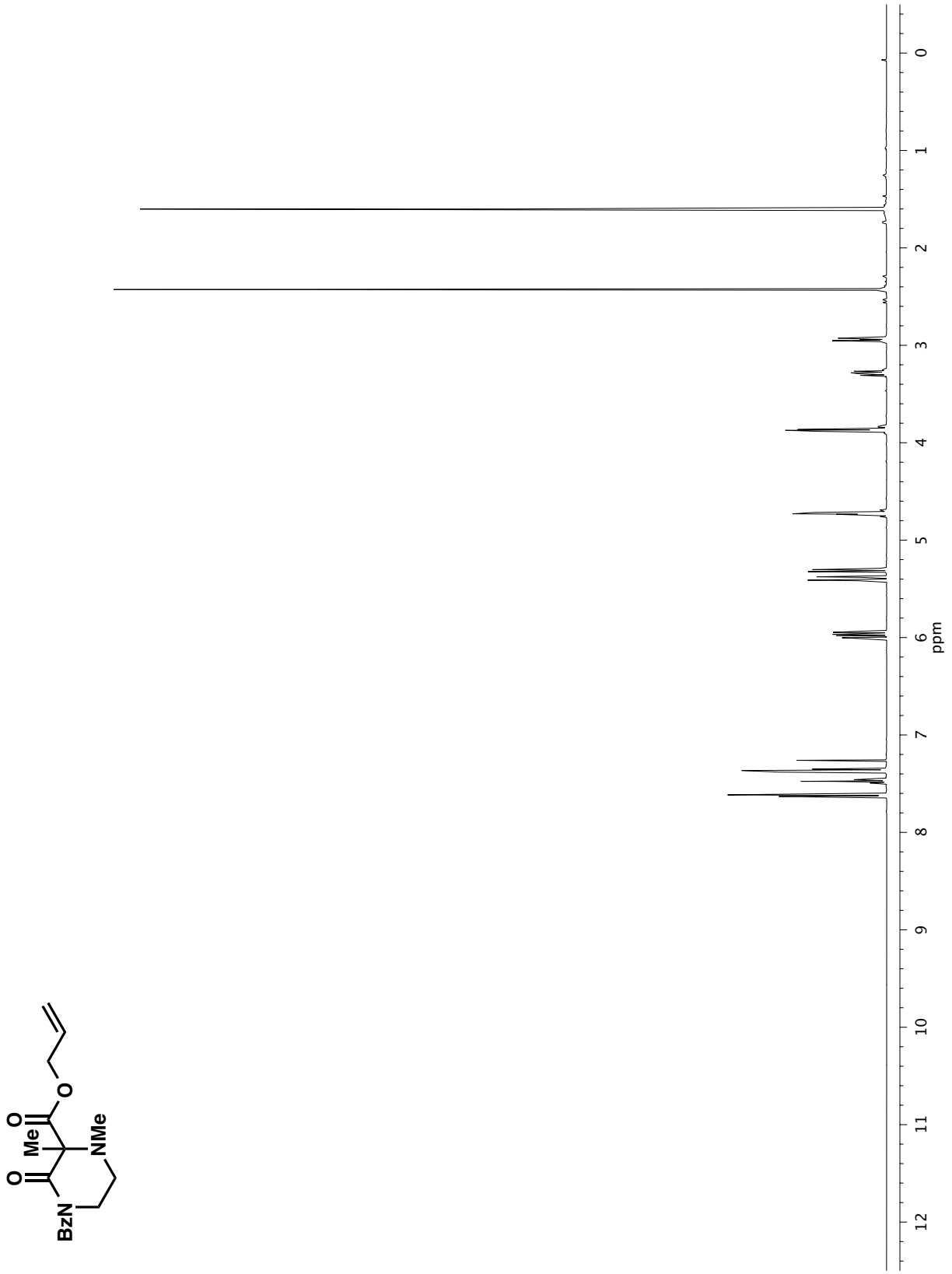
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8p.**



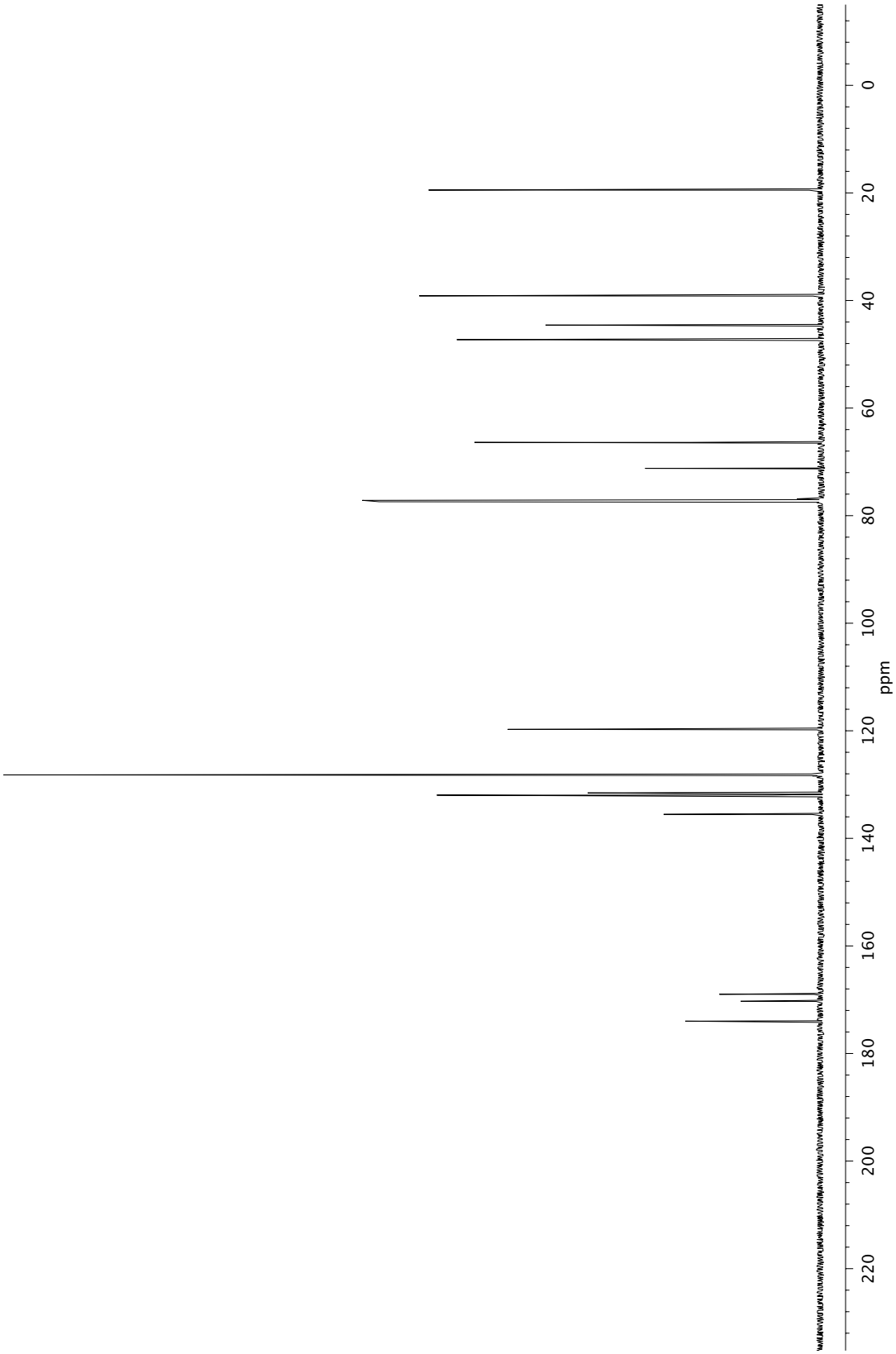
^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI13**.



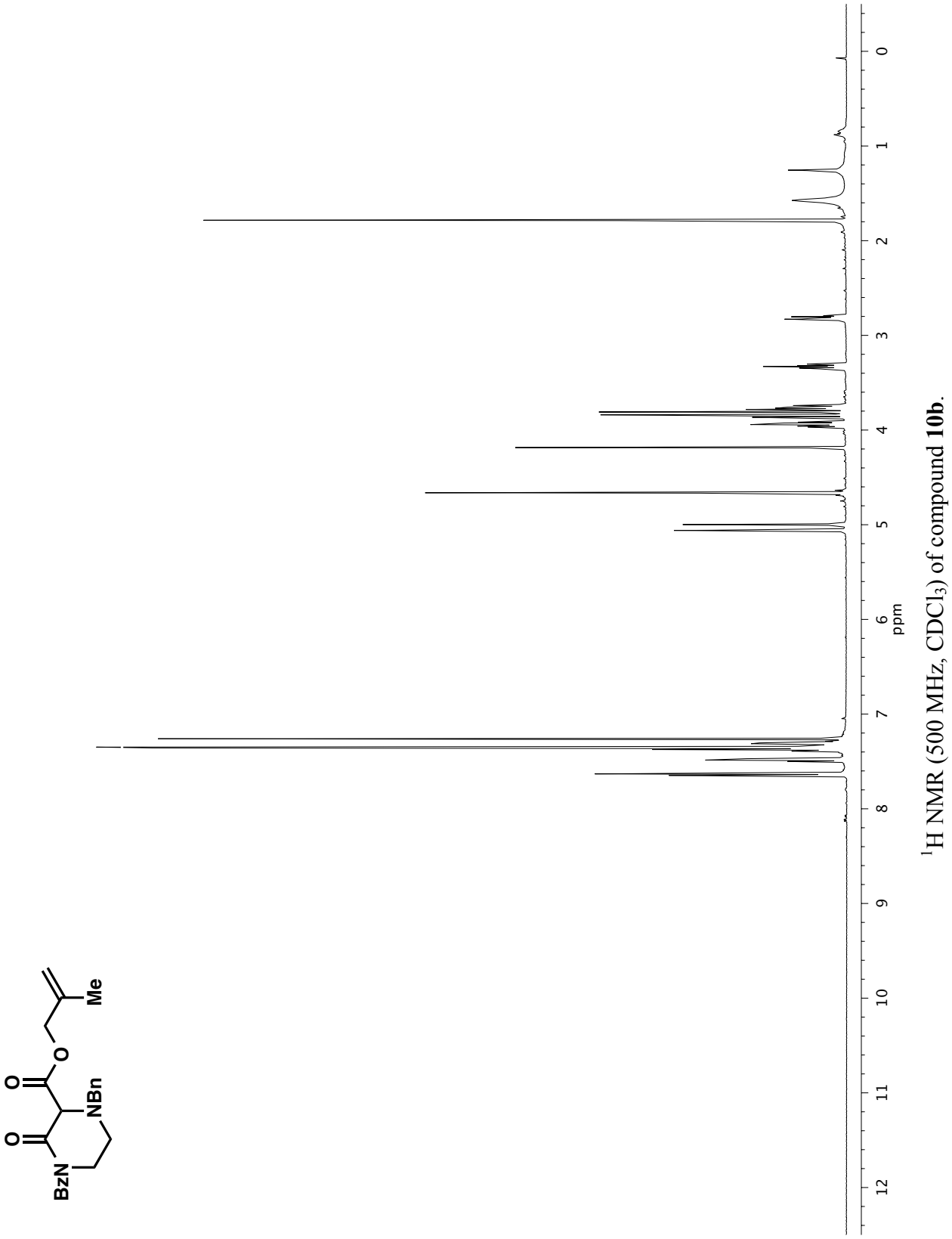
^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI13.**



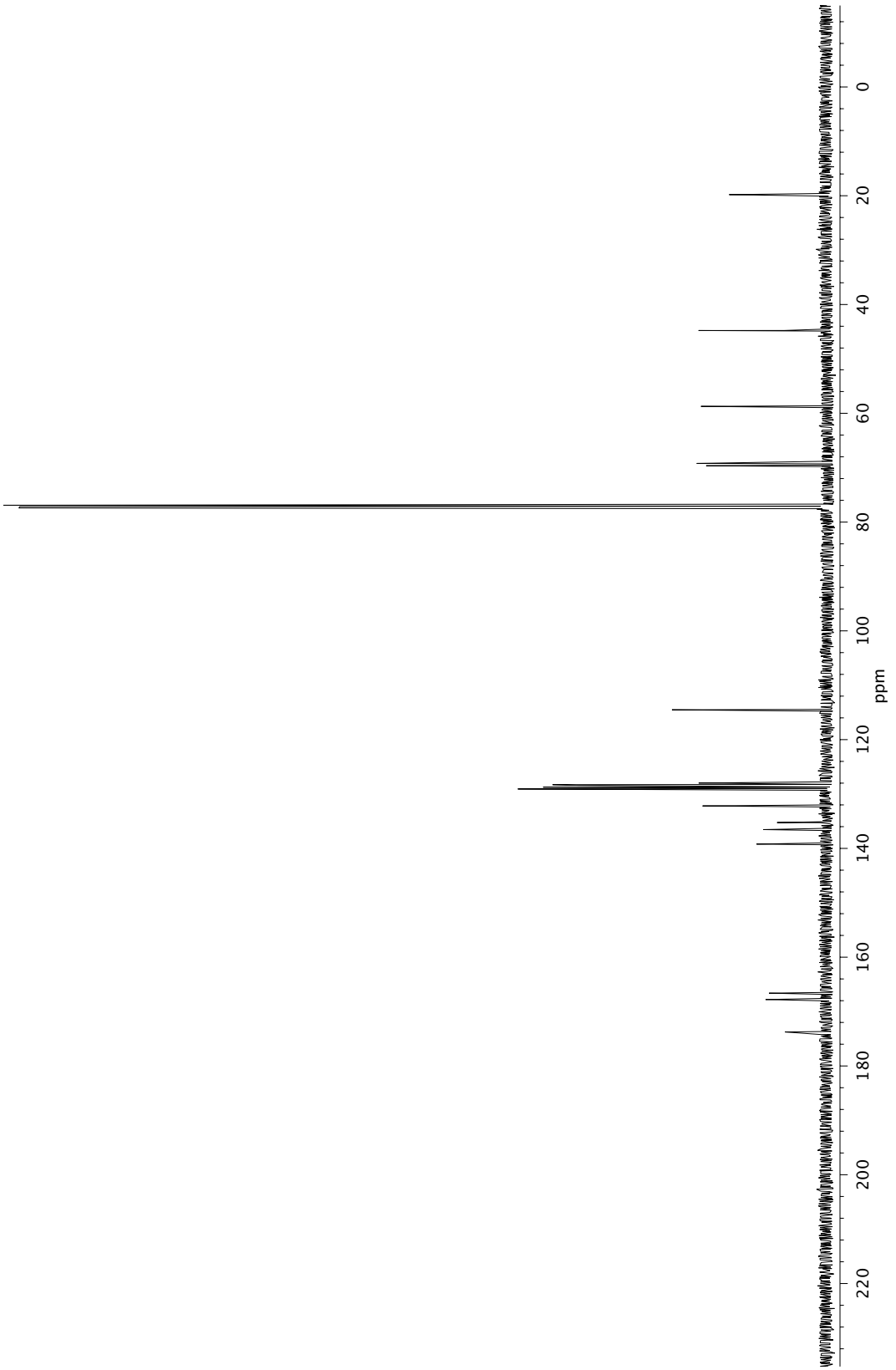
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8q**.



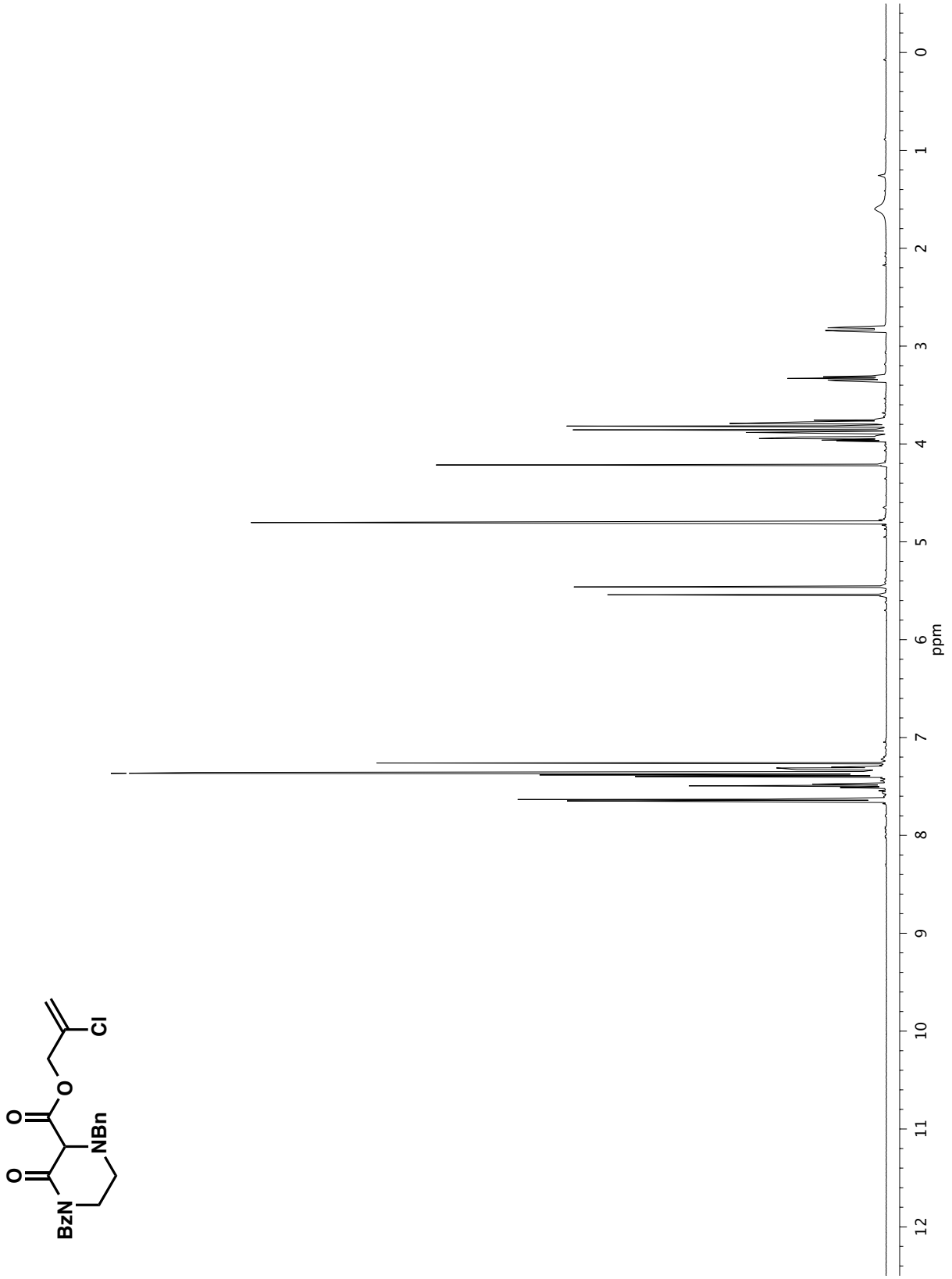
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8q.**



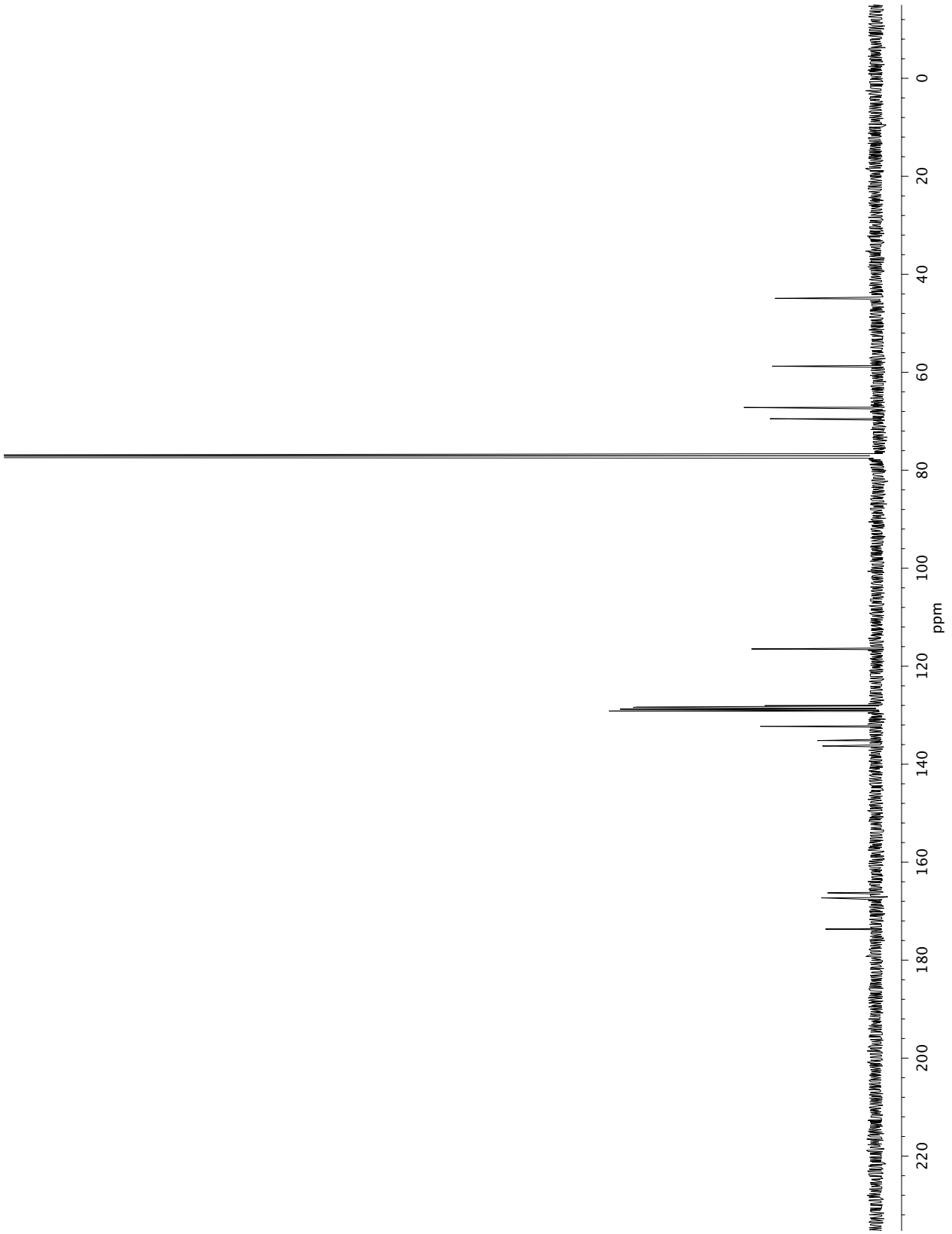
^{1}H NMR (500 MHz, $CDCl_3$) of compound **10b**.



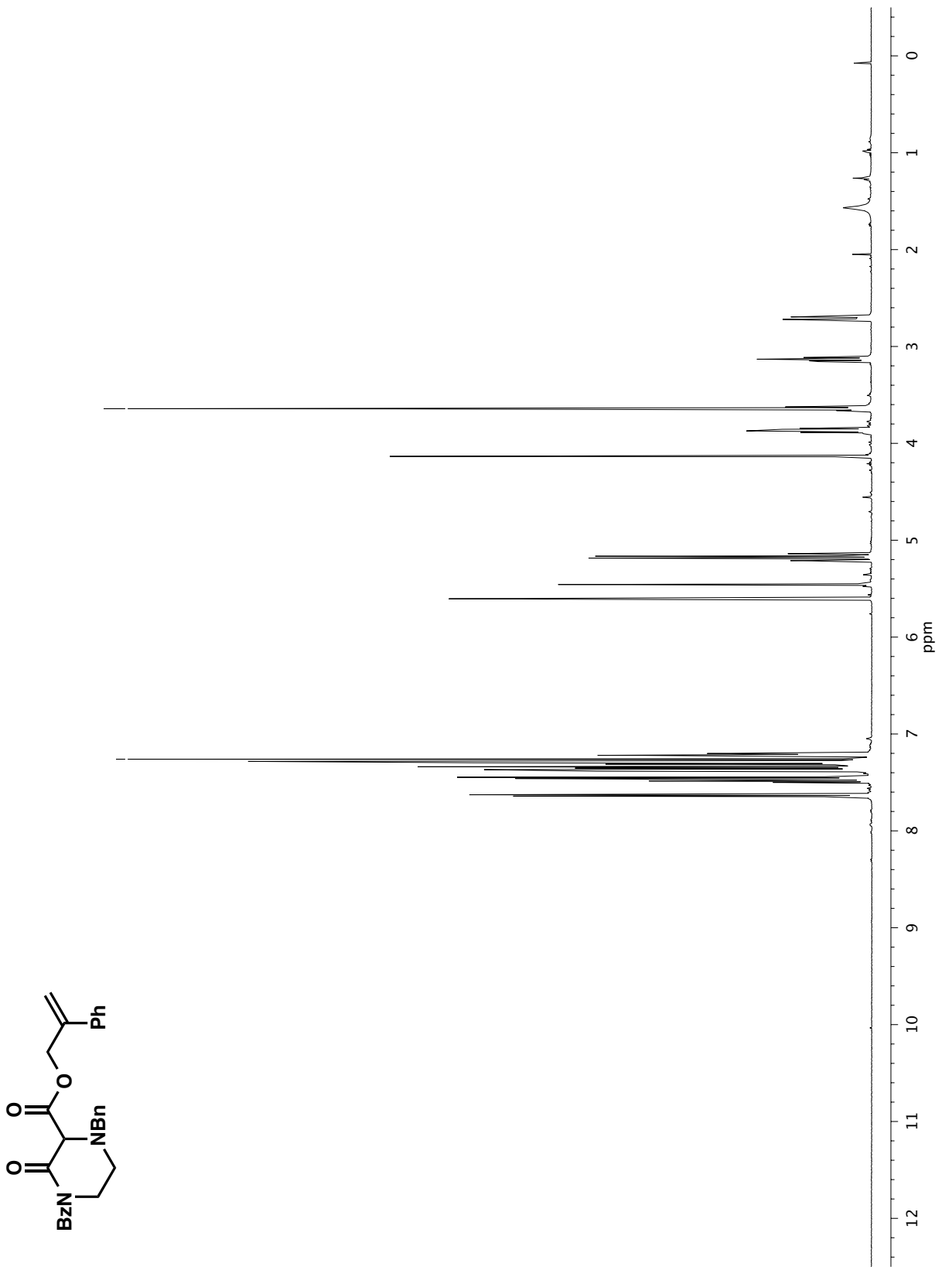
^{13}C NMR (126 MHz, $CDCl_3$) of compound **10b.**



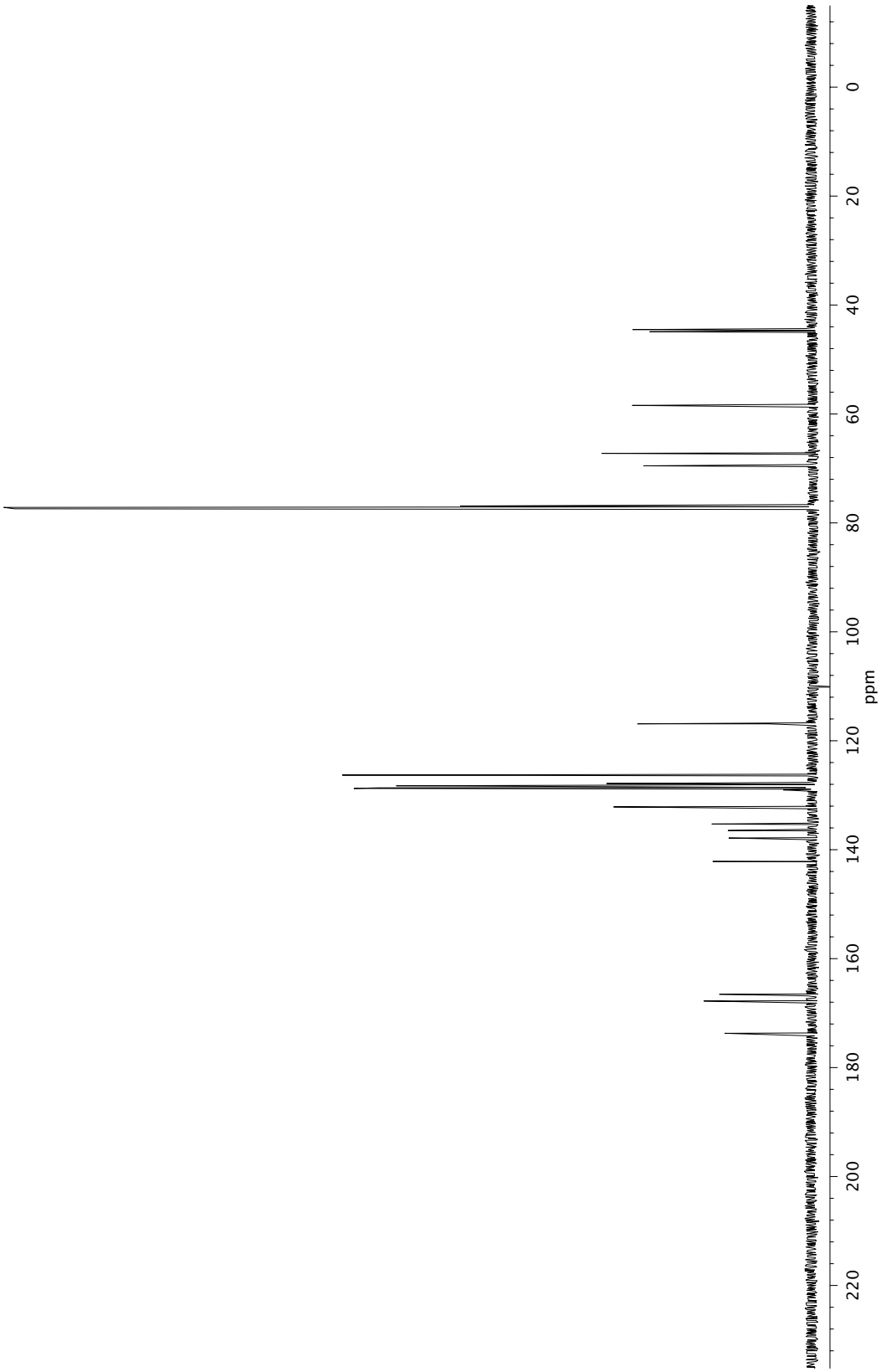
^{1}H NMR (500 MHz, $CDCl_3$) of compound **10c**.



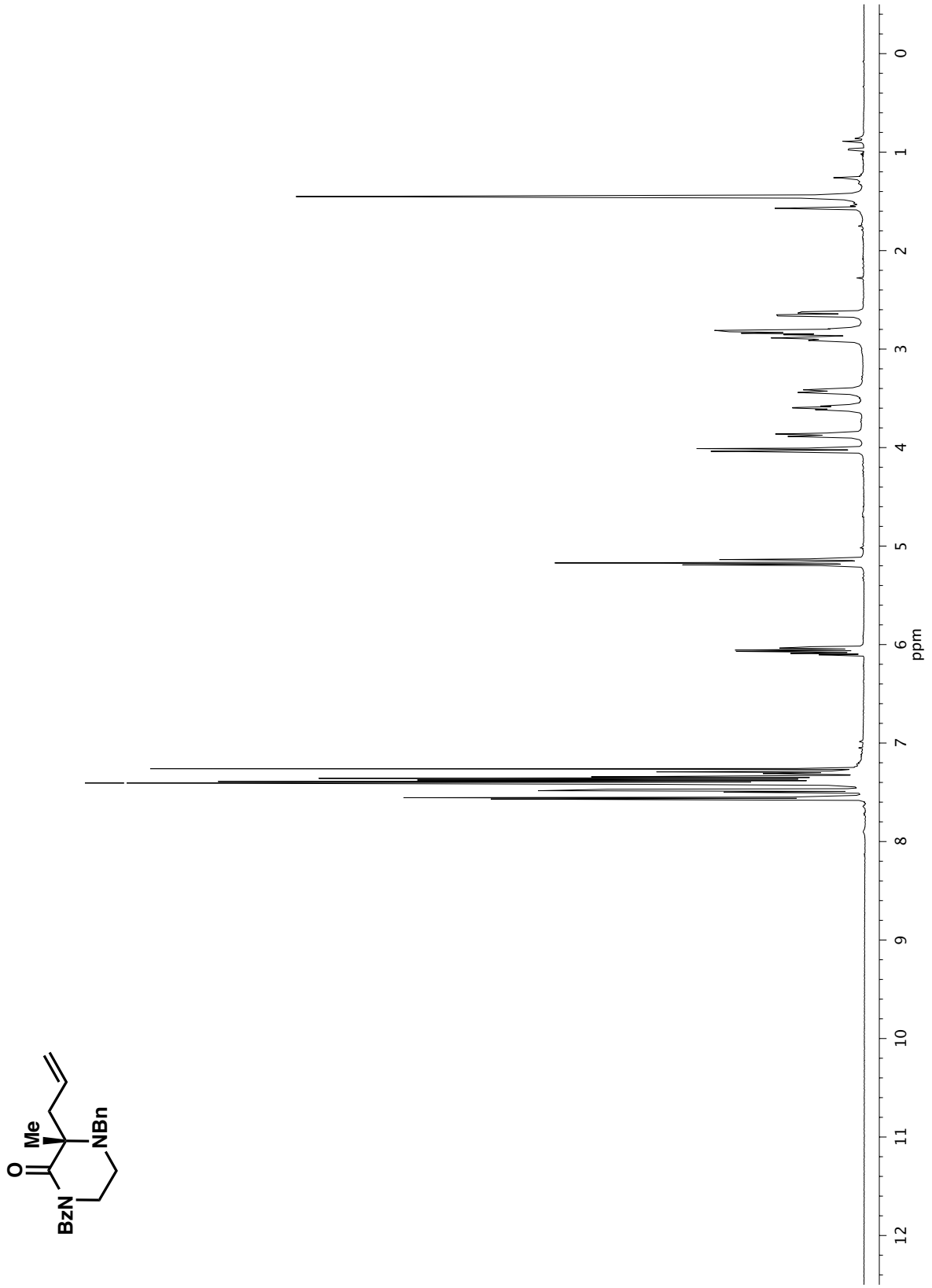
^{13}C NMR (126 MHz, $CDCl_3$) of compound **10c.**



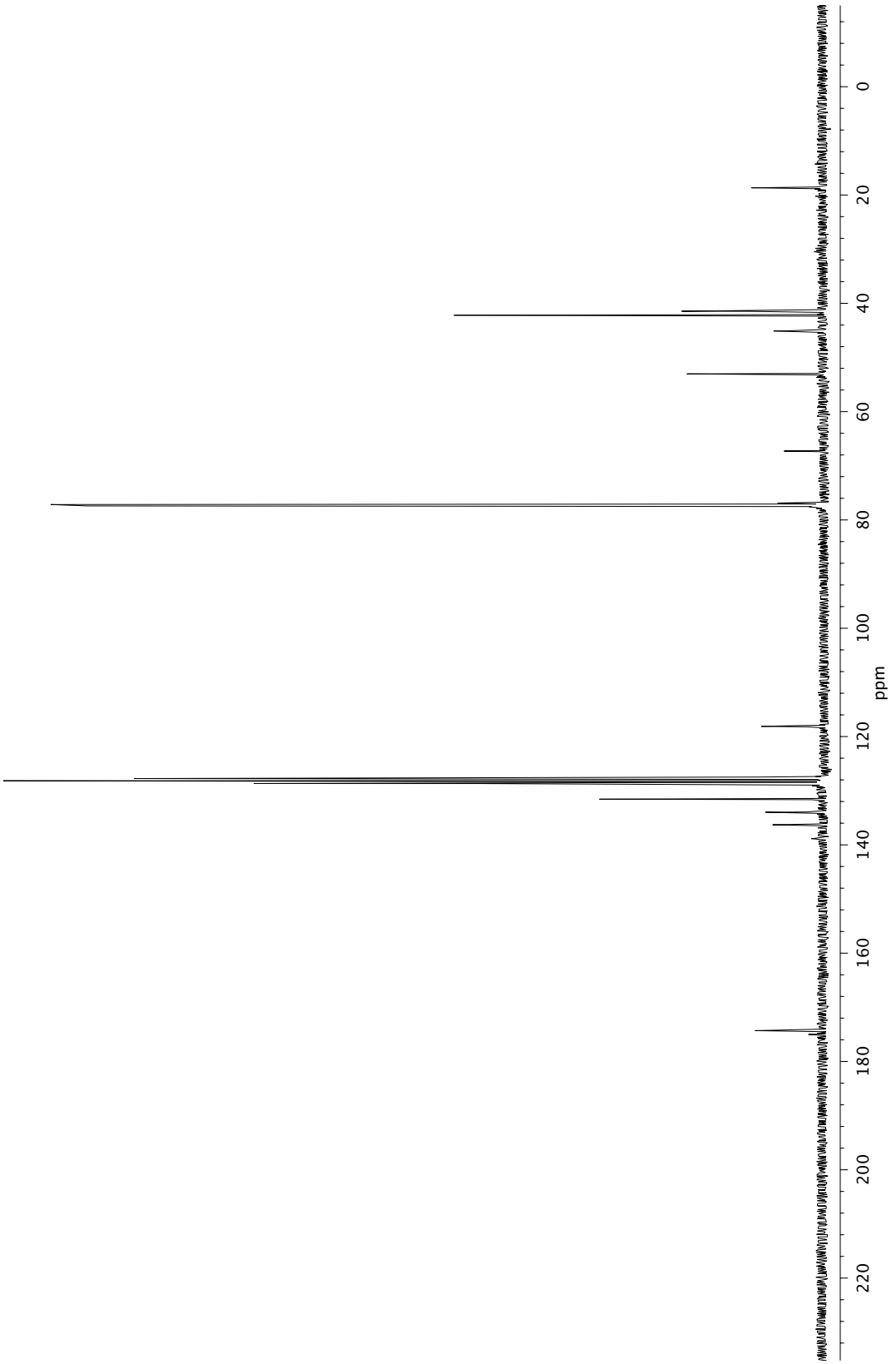
^{1}H NMR (500 MHz, $CDCl_3$) of compound **10d**.



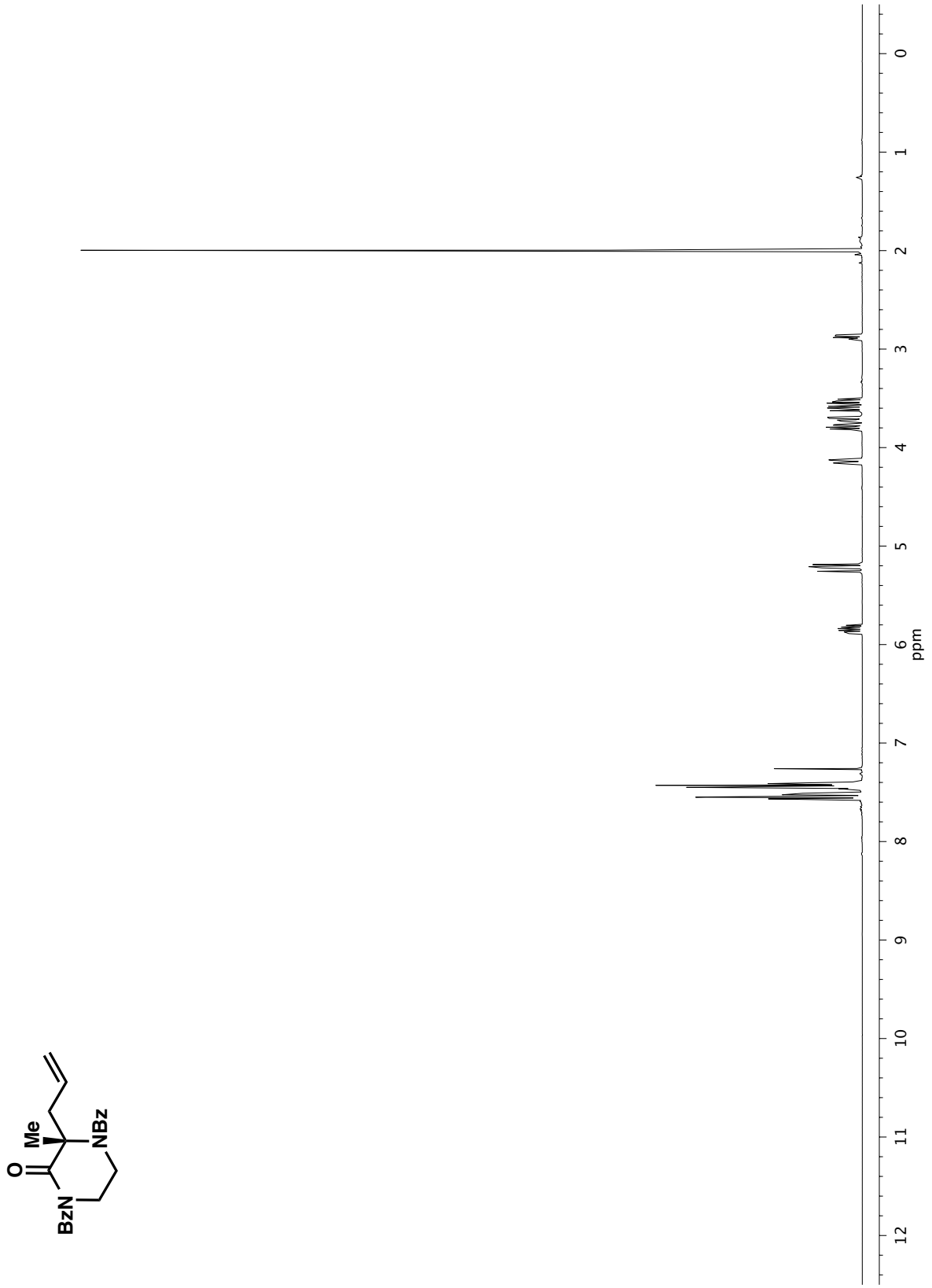
^{13}C NMR (126 MHz, $CDCl_3$) of compound **10d.**



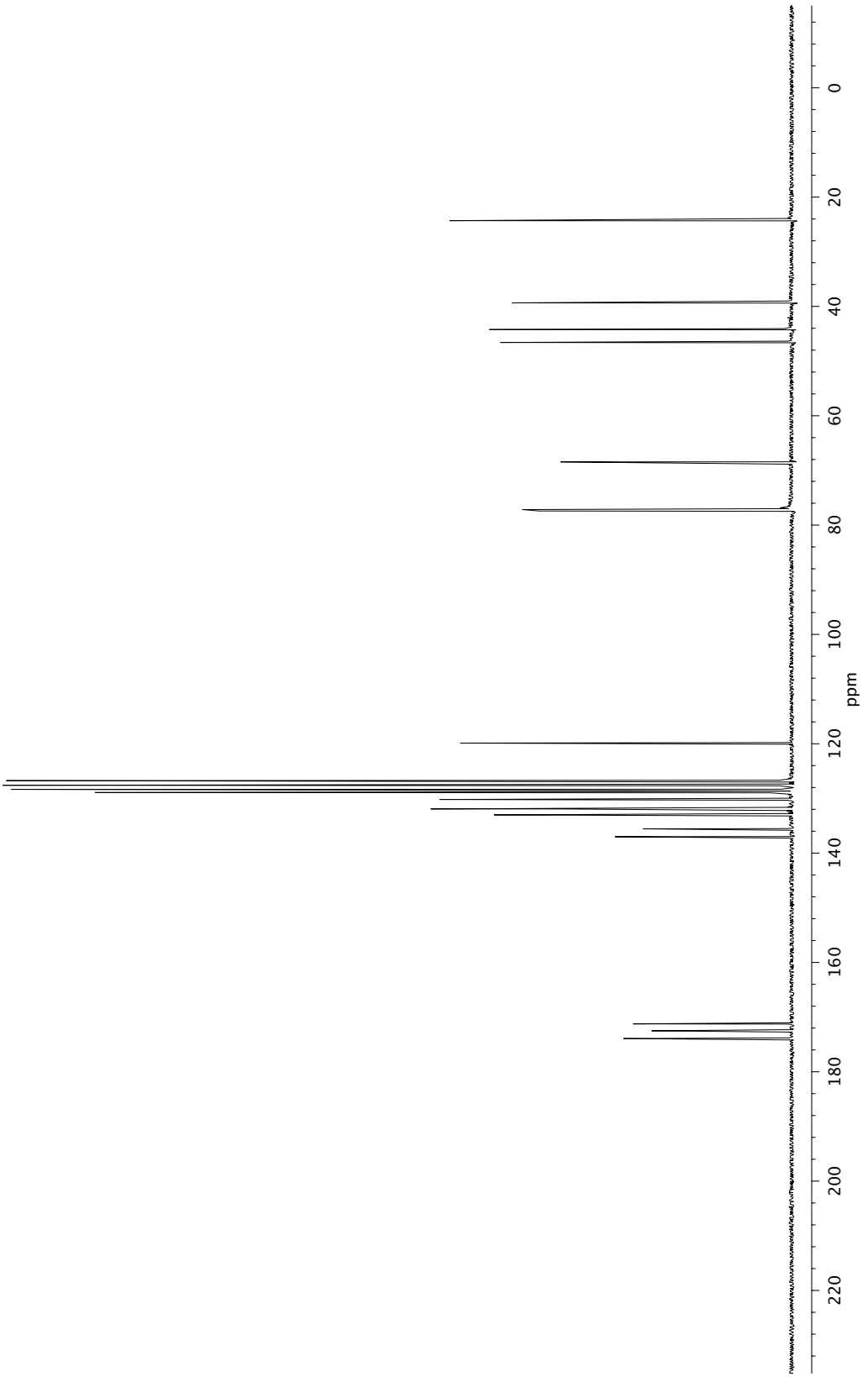
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9b**.



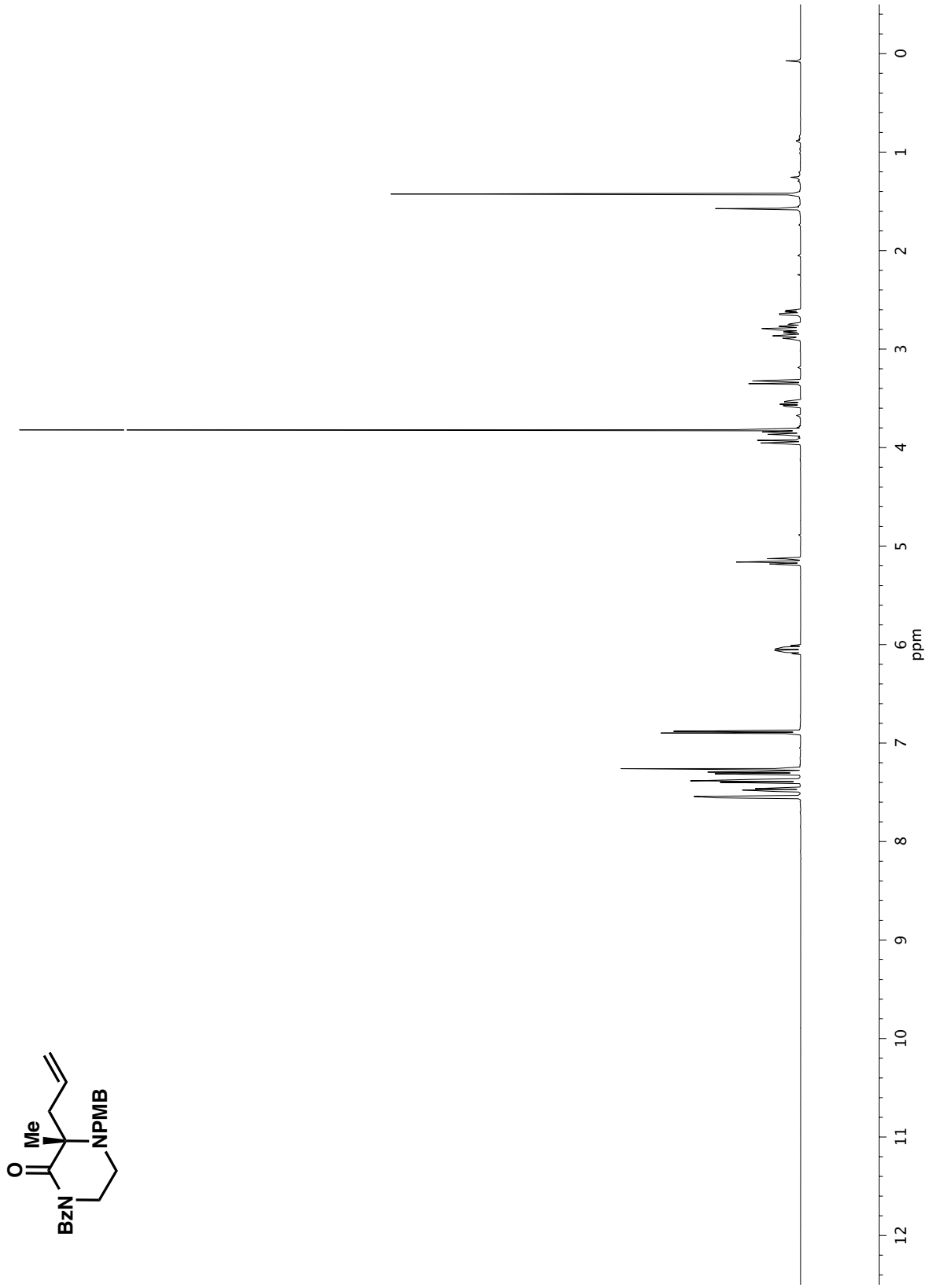
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9b.**



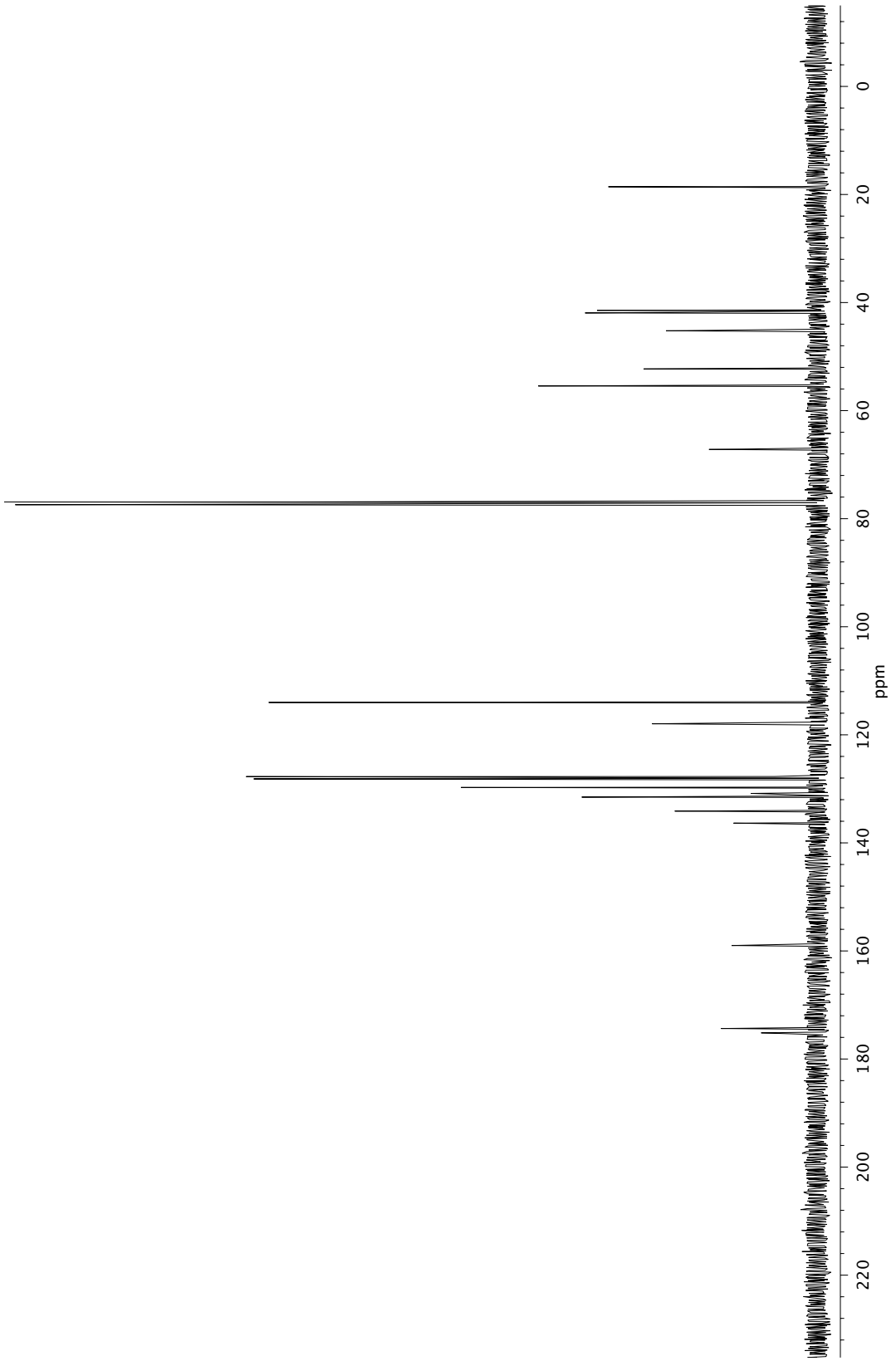
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9a**.



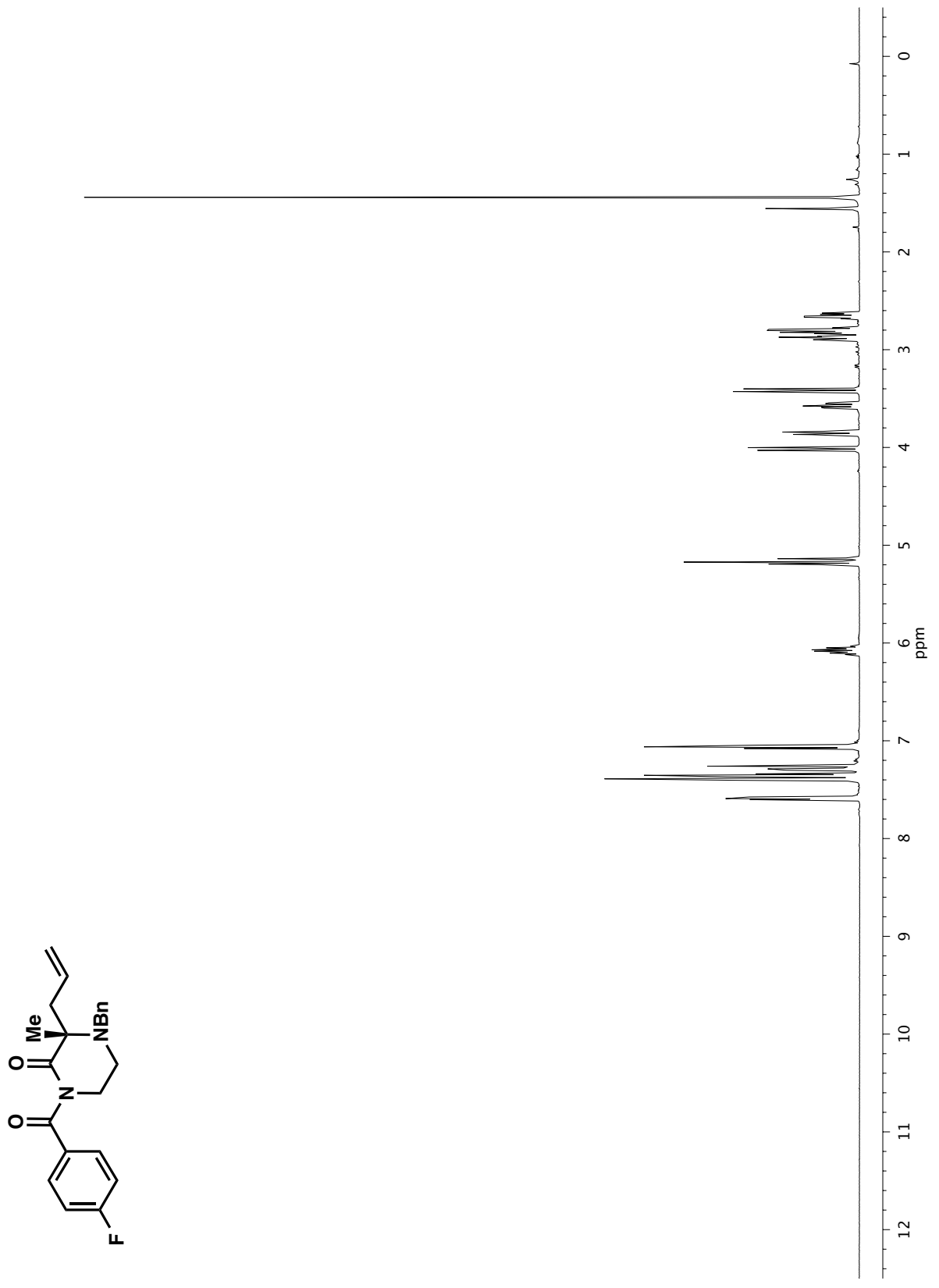
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9a.**



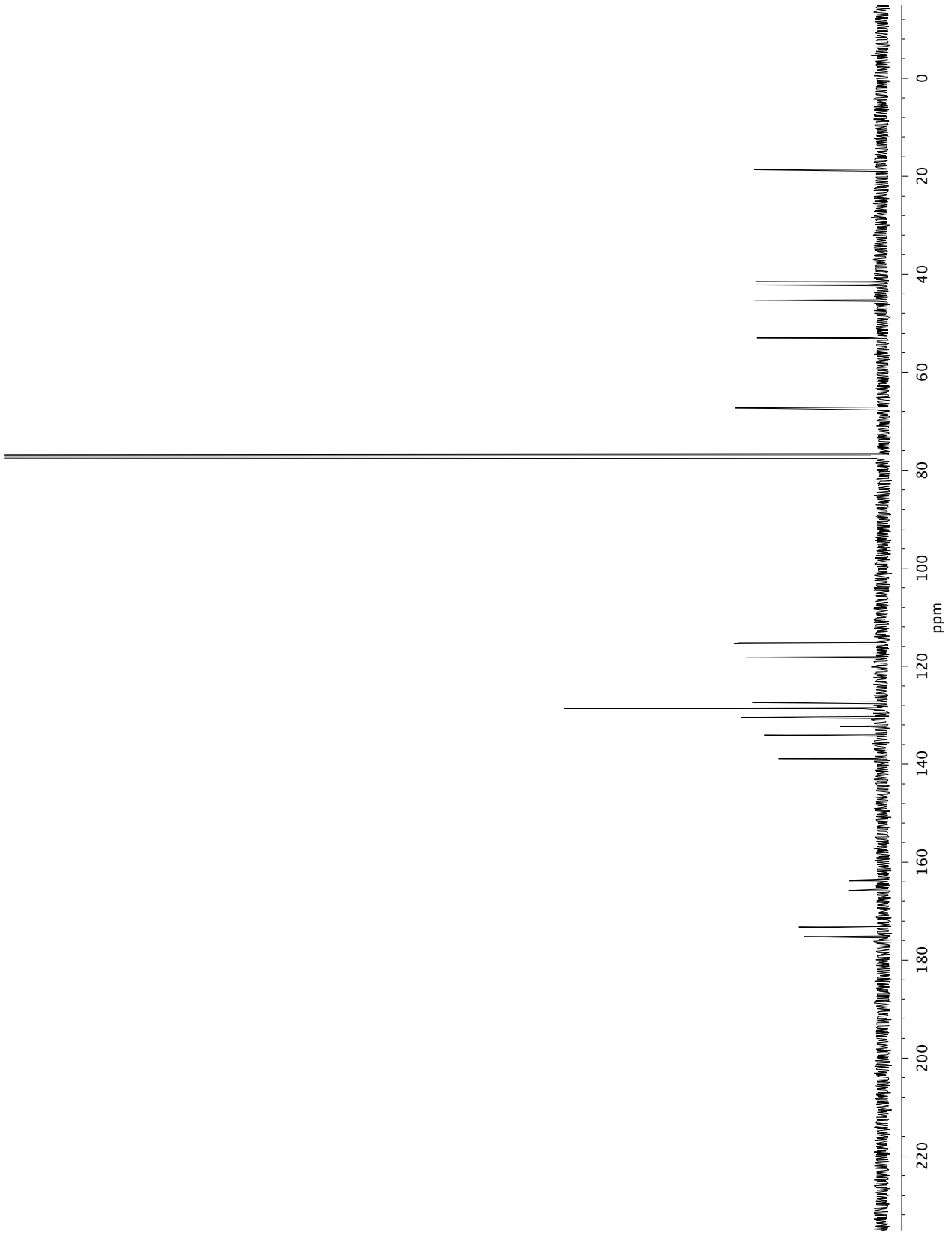
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9c**.



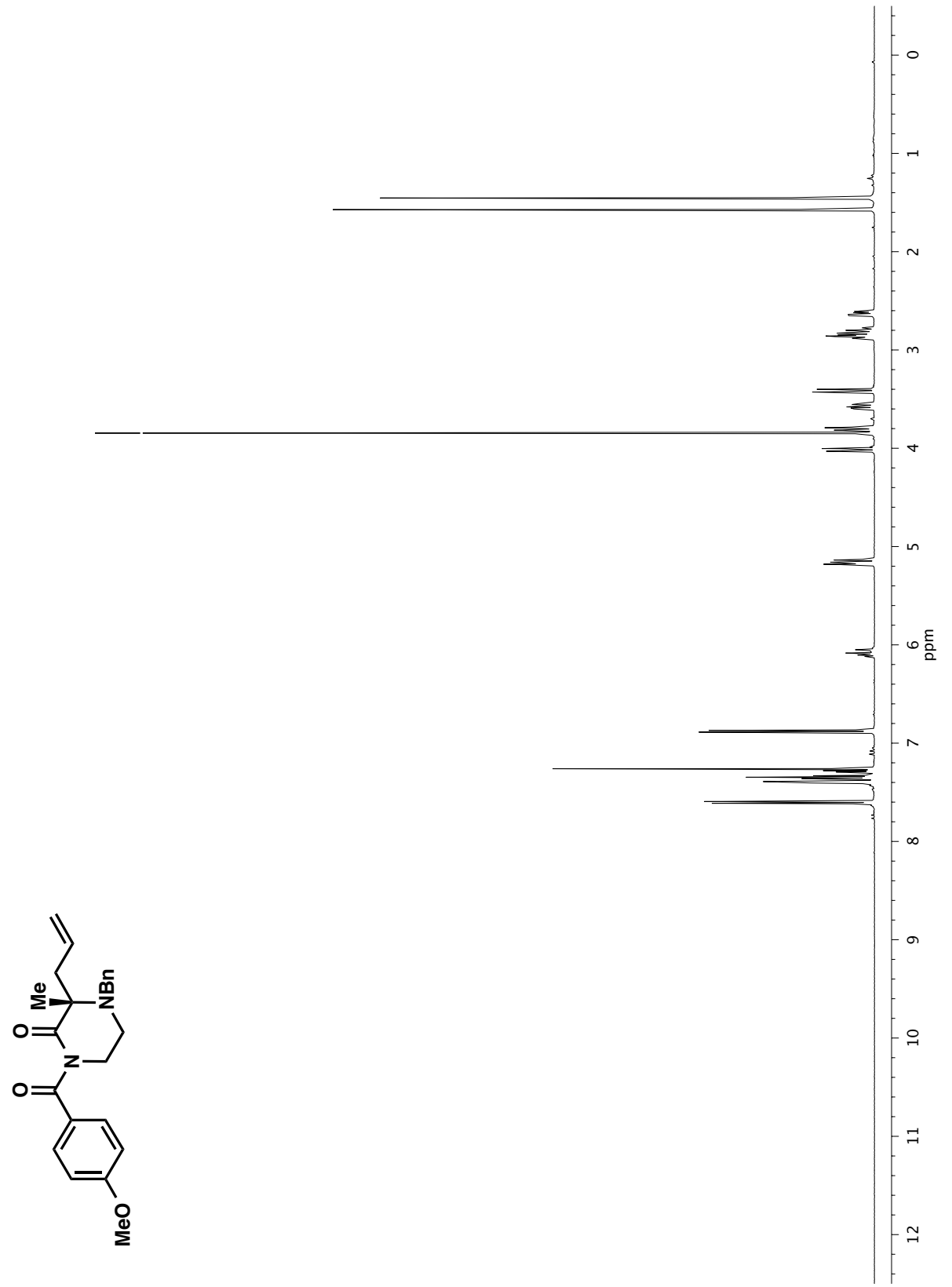
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9c.**



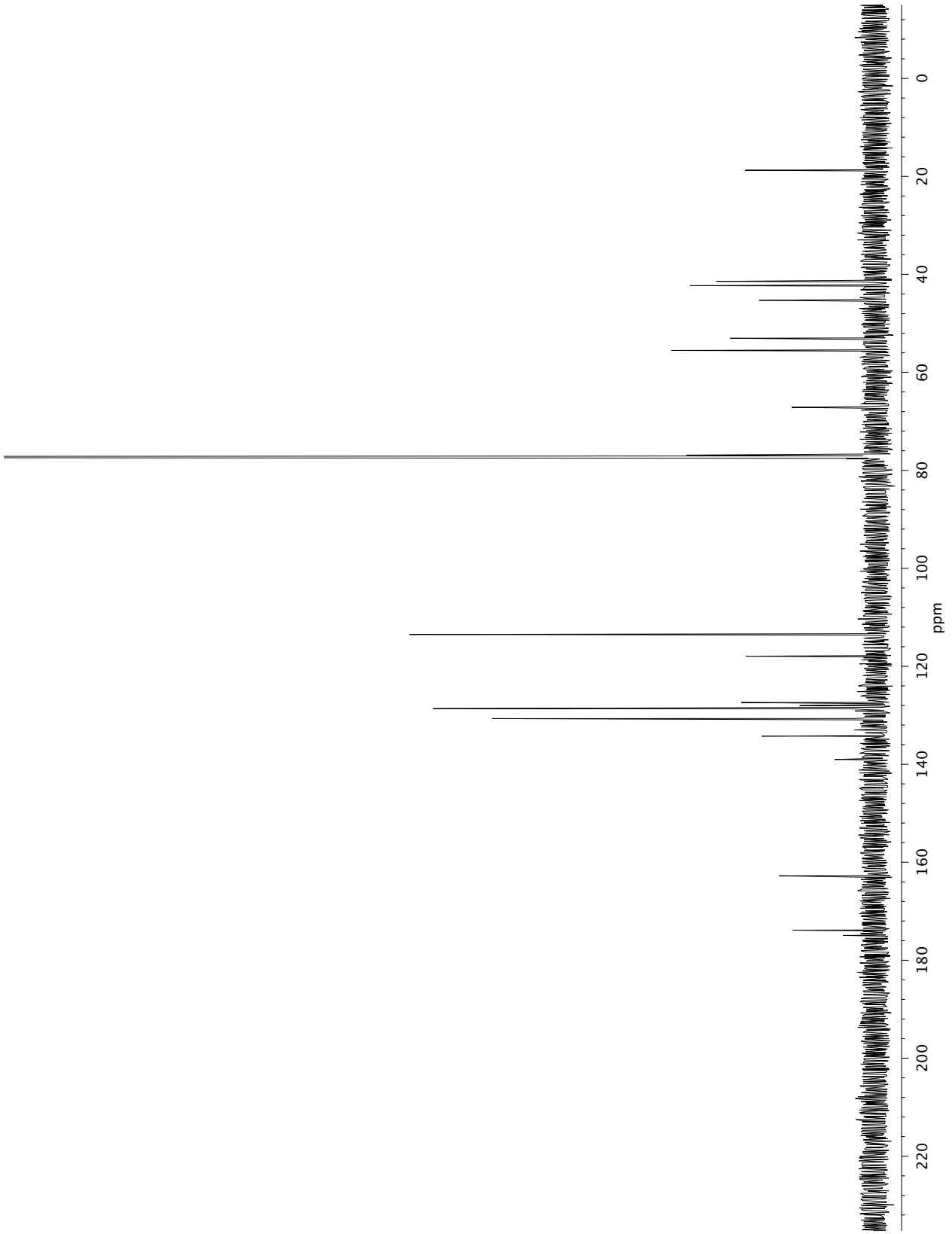
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9d**.



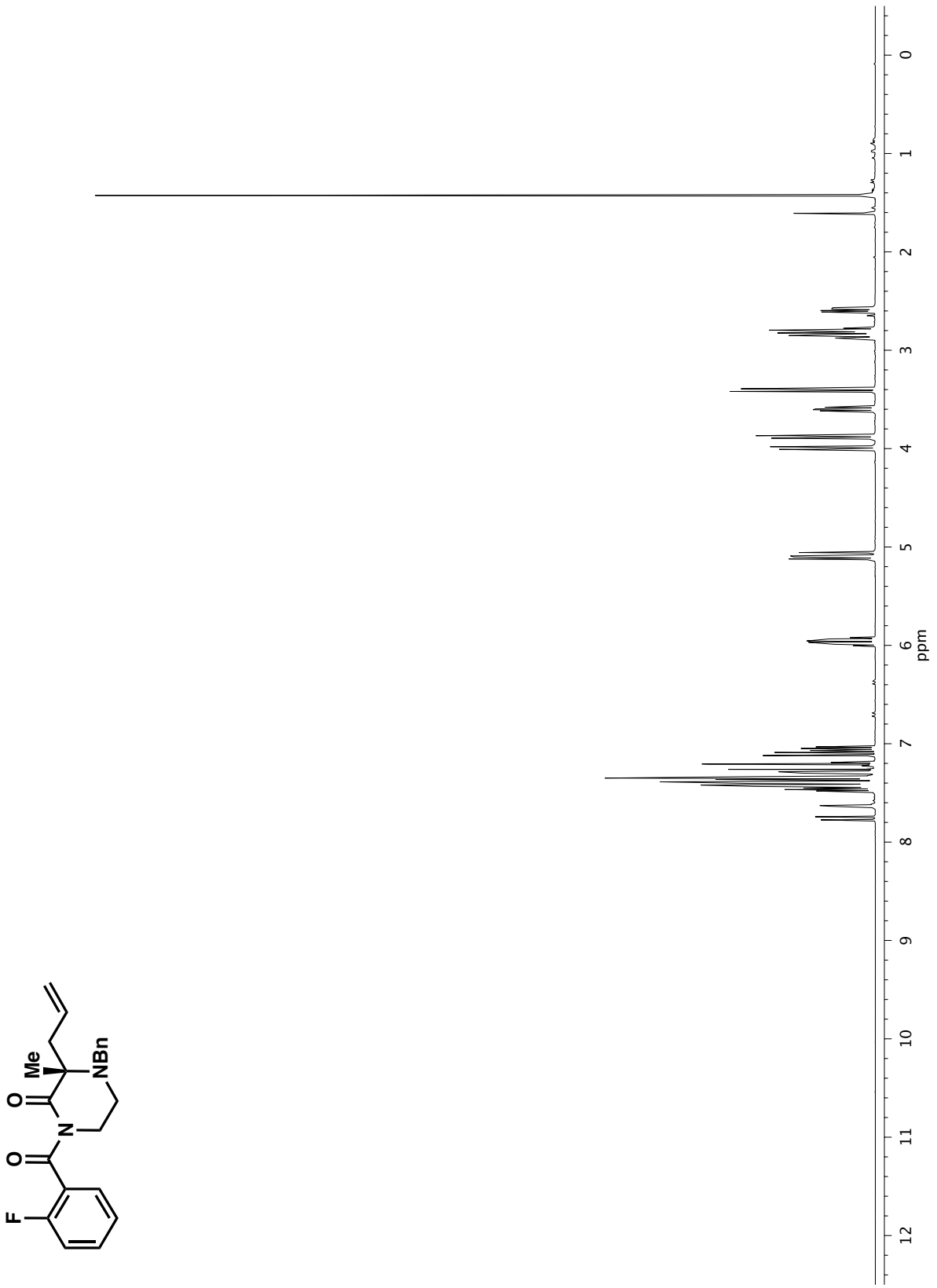
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9d.**



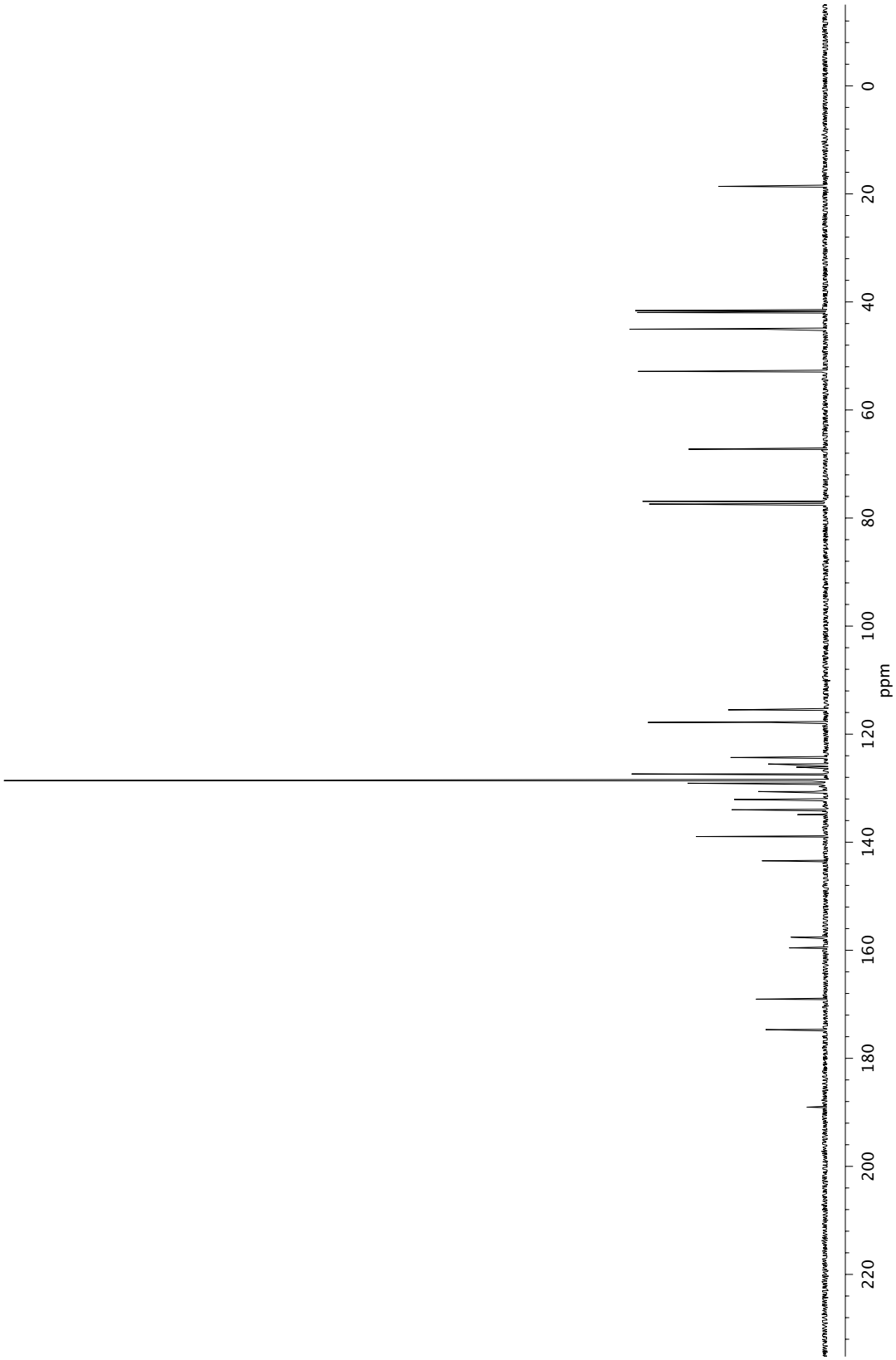
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9e**.



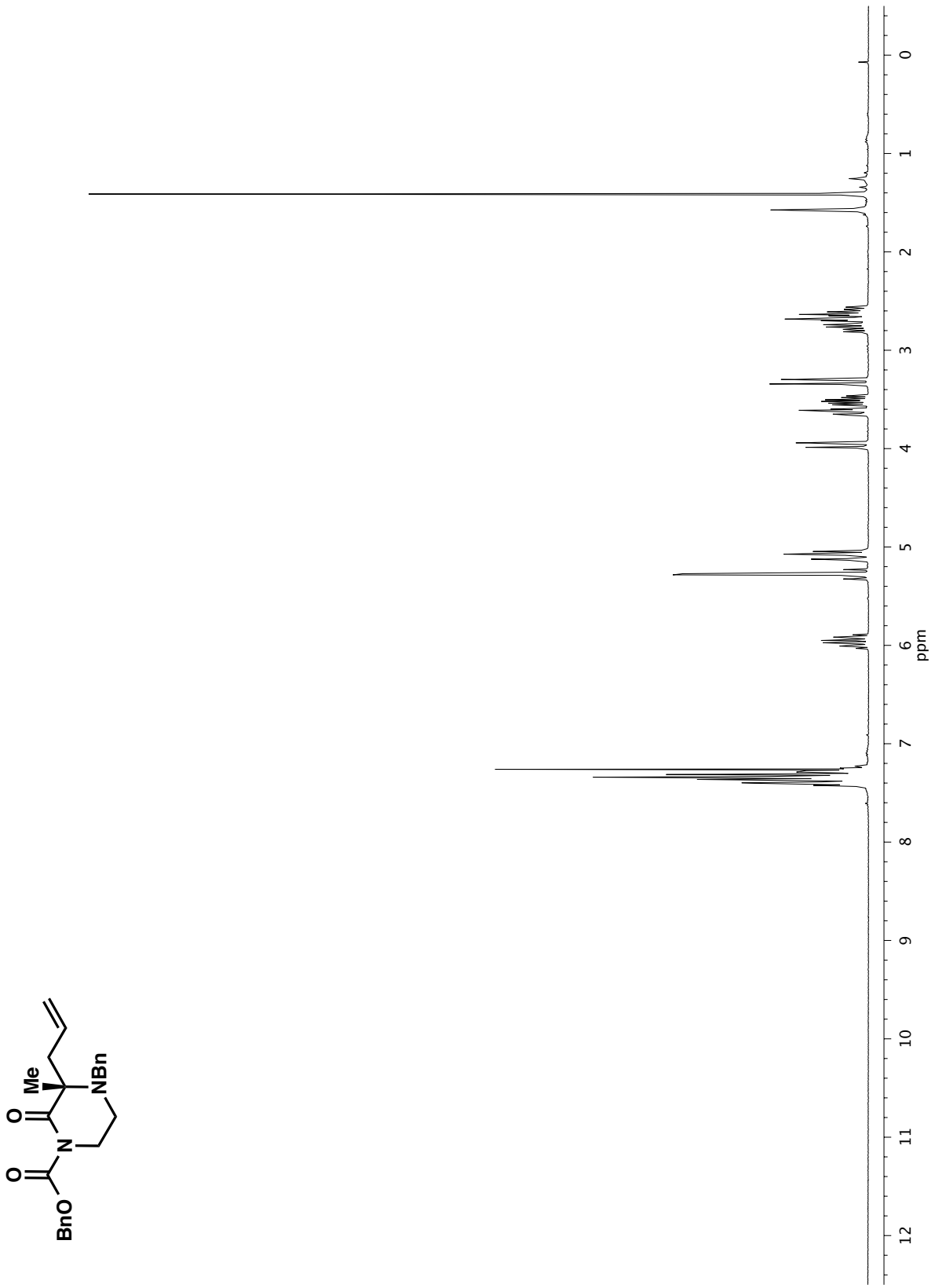
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9e.**



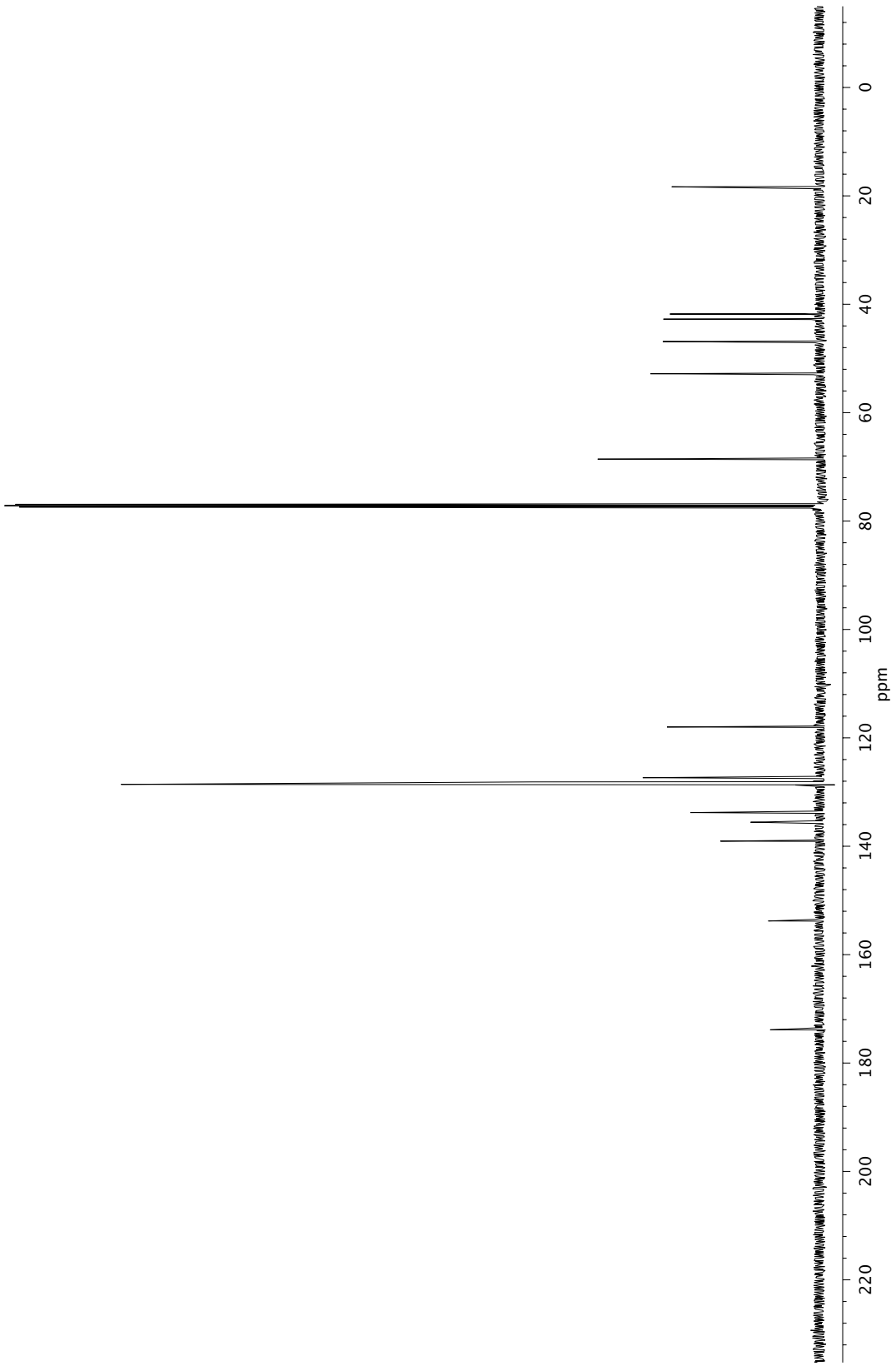
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9f**.



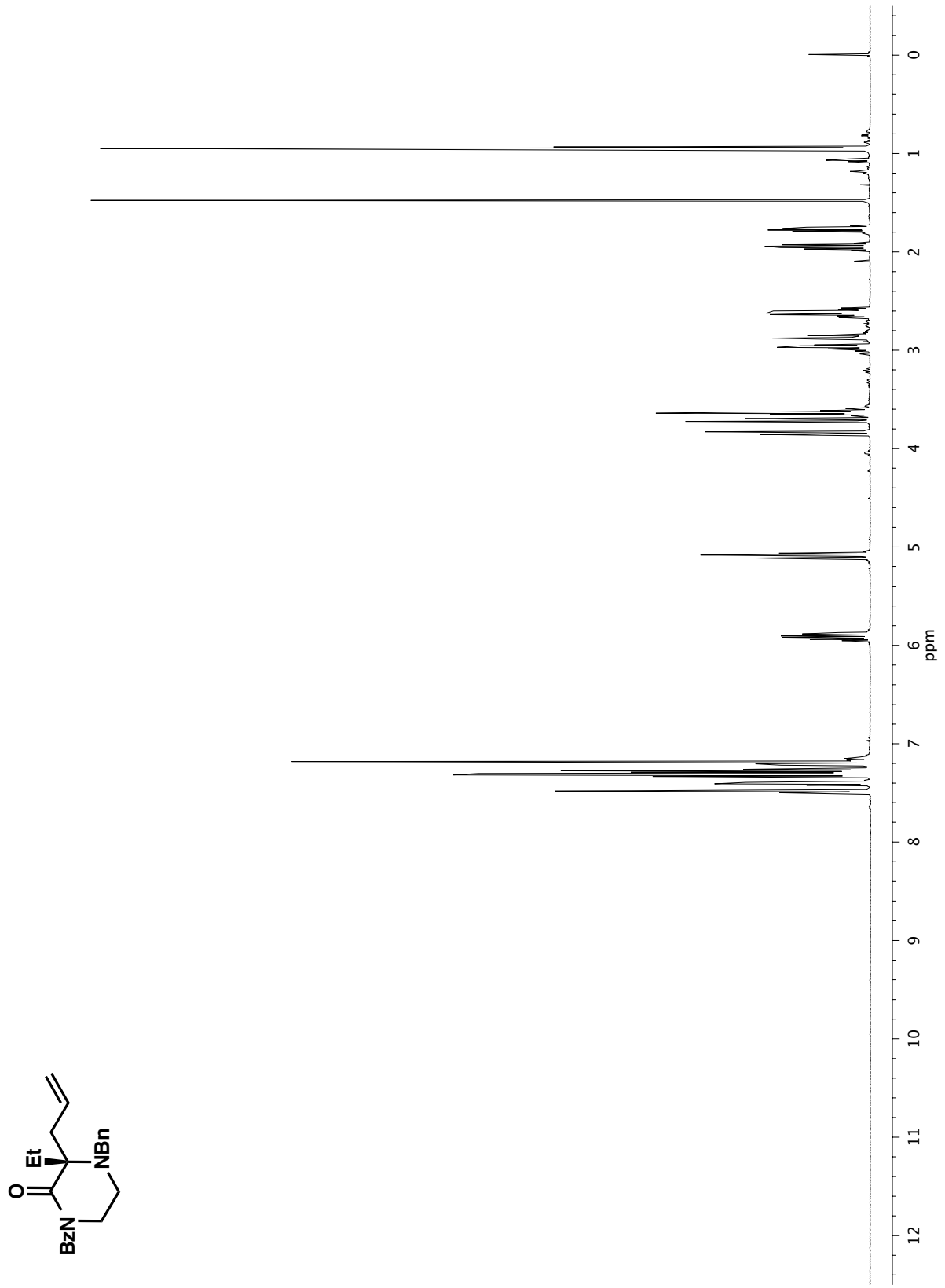
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9f.**



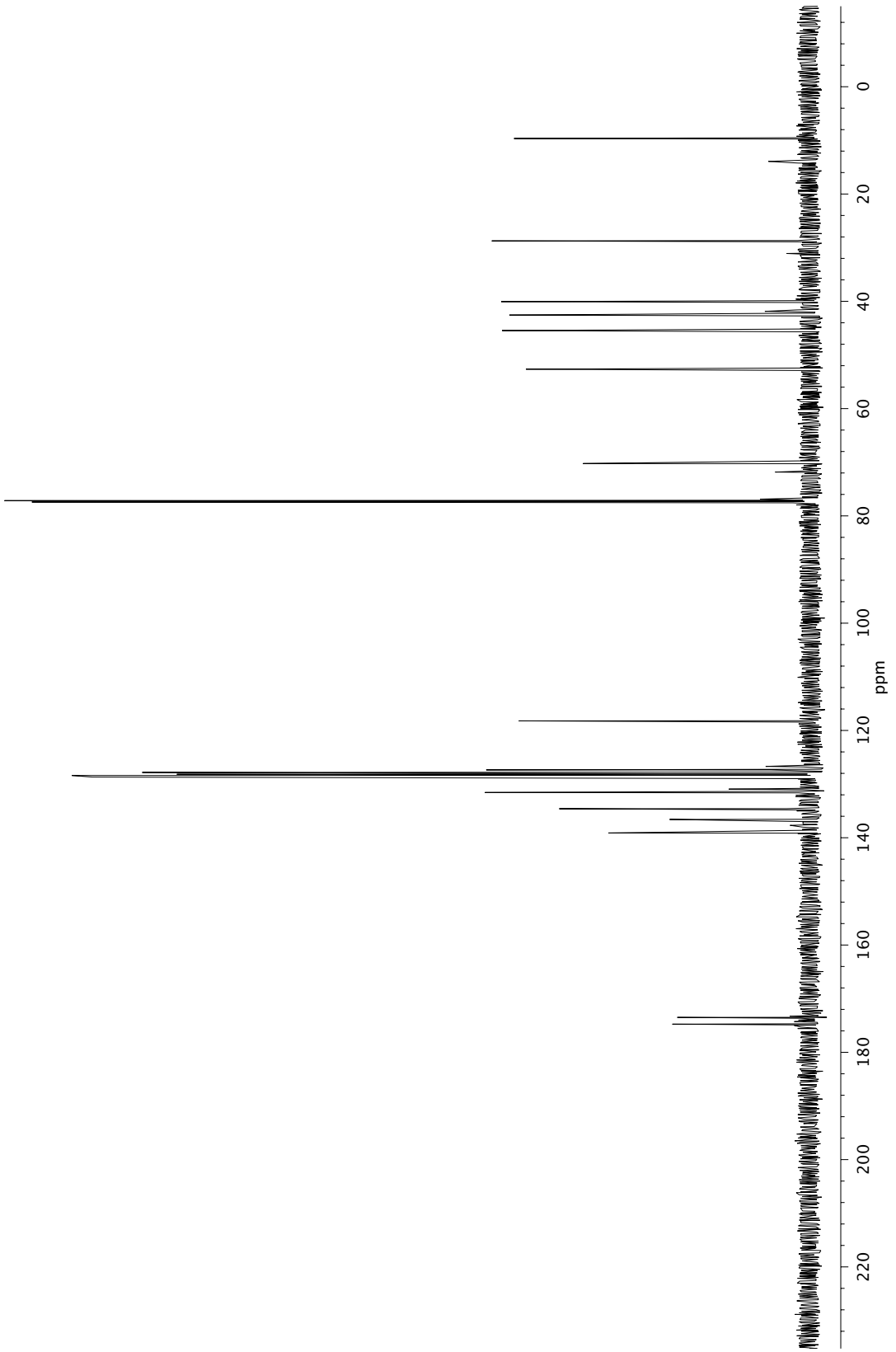
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9g**.



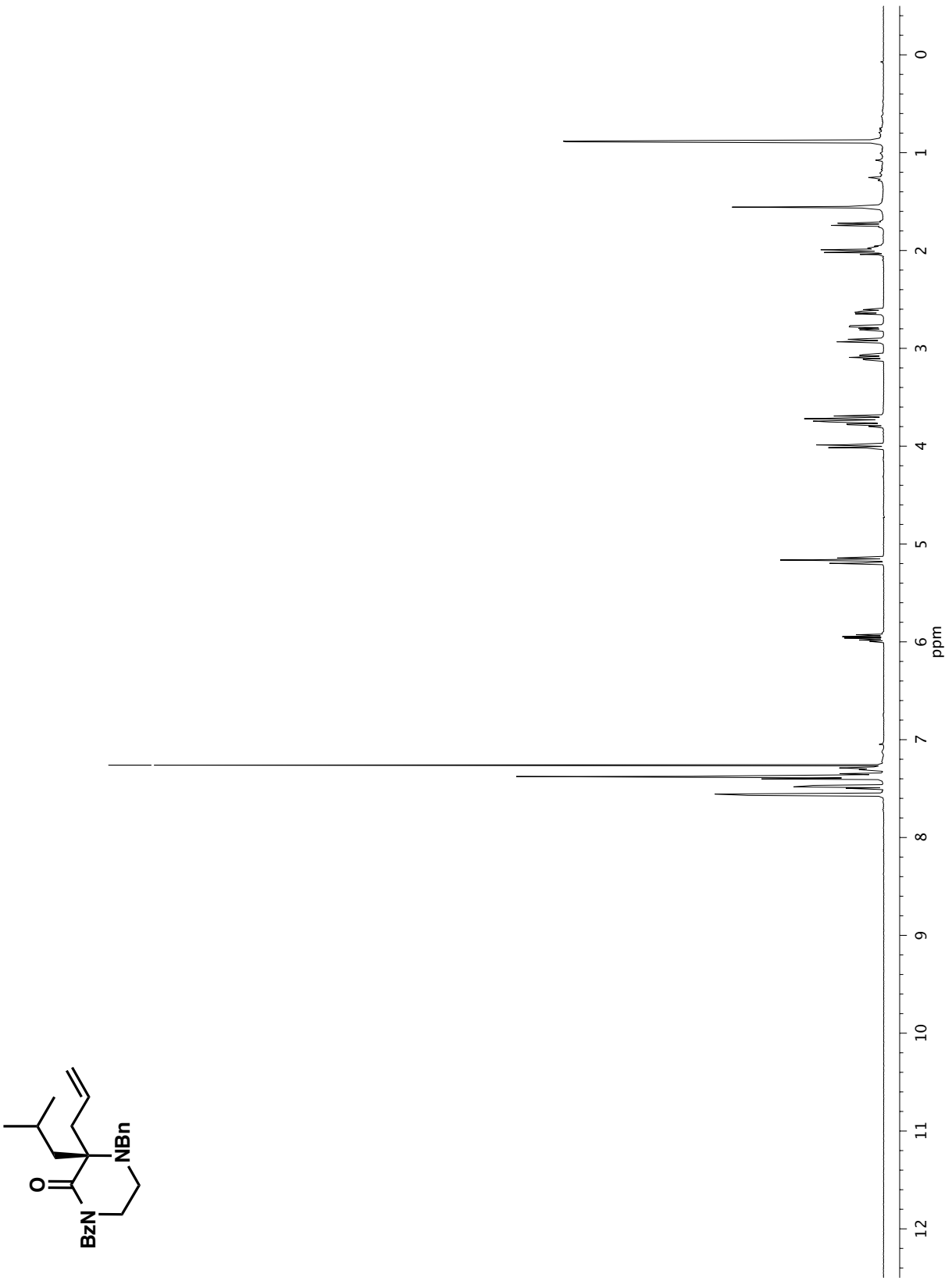
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9g.**



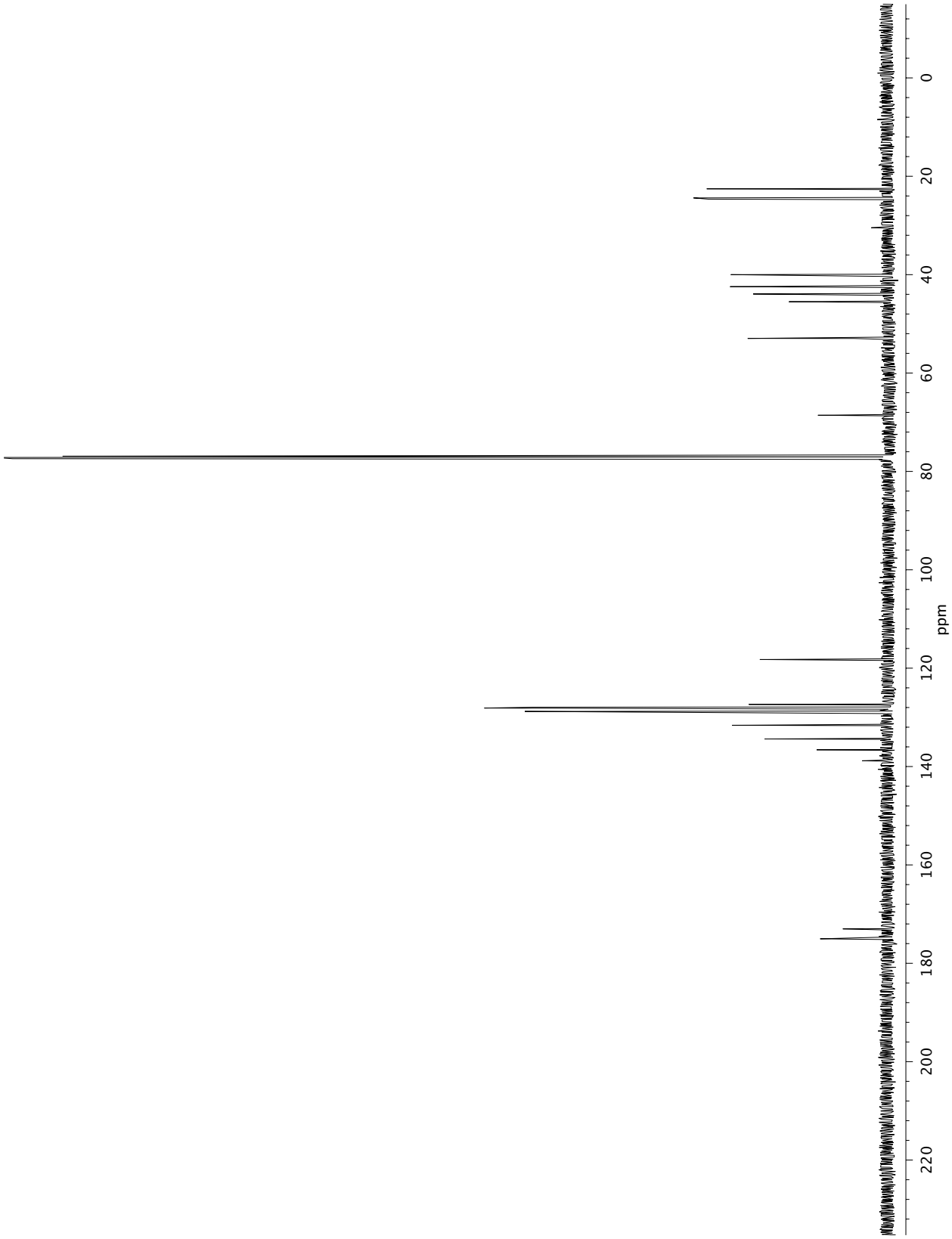
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9h**.



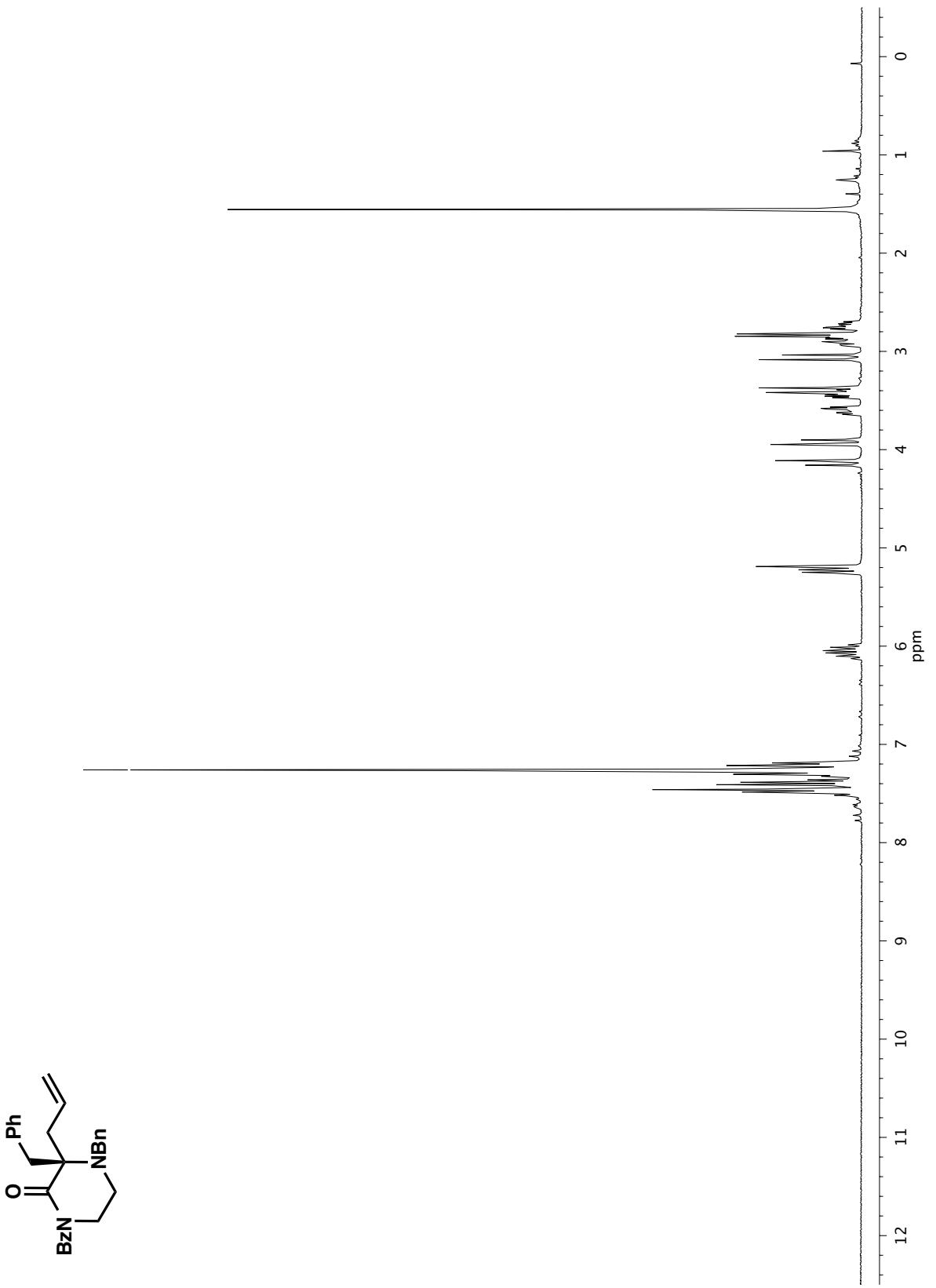
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9h.**



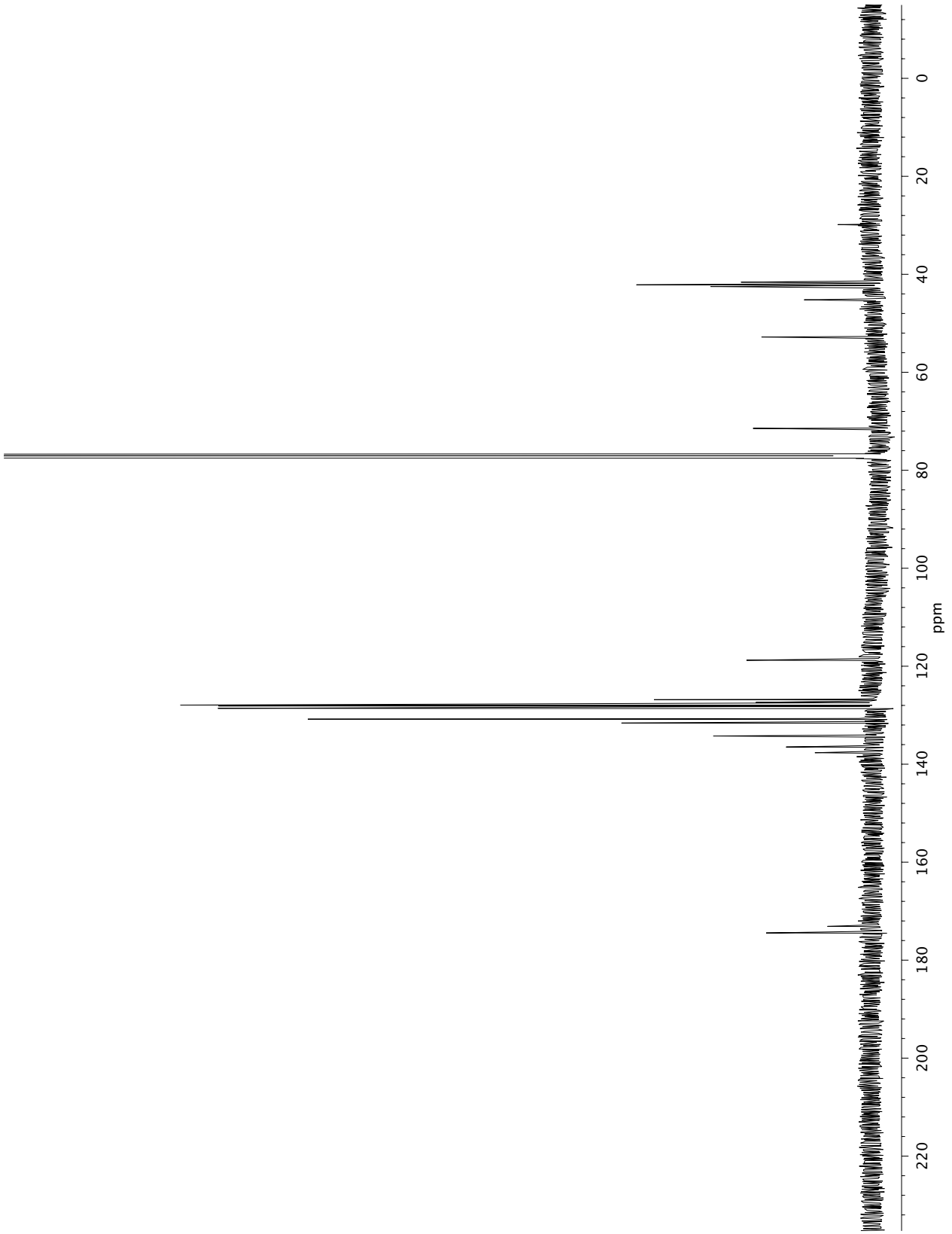
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9i**.



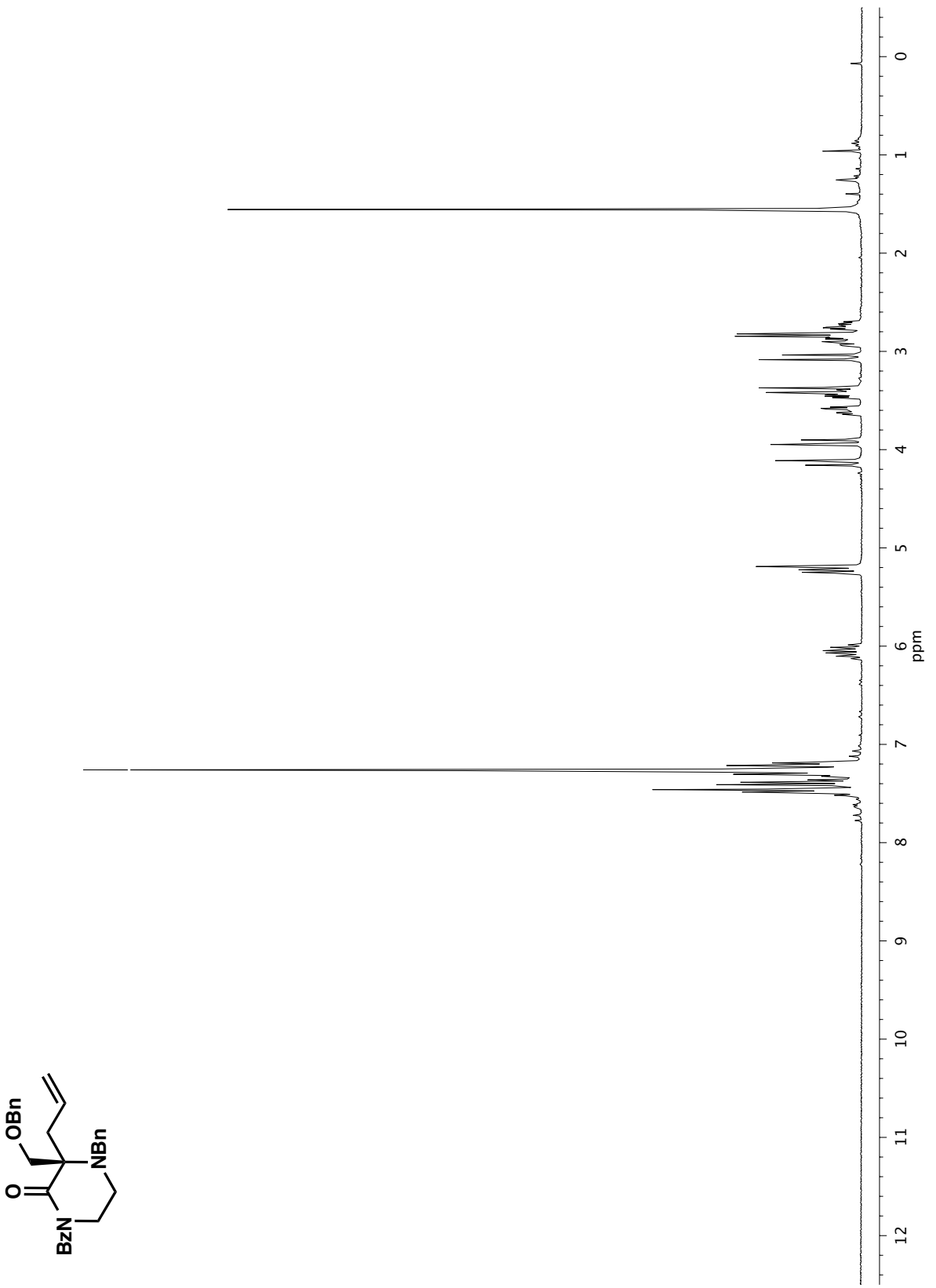
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9i.**



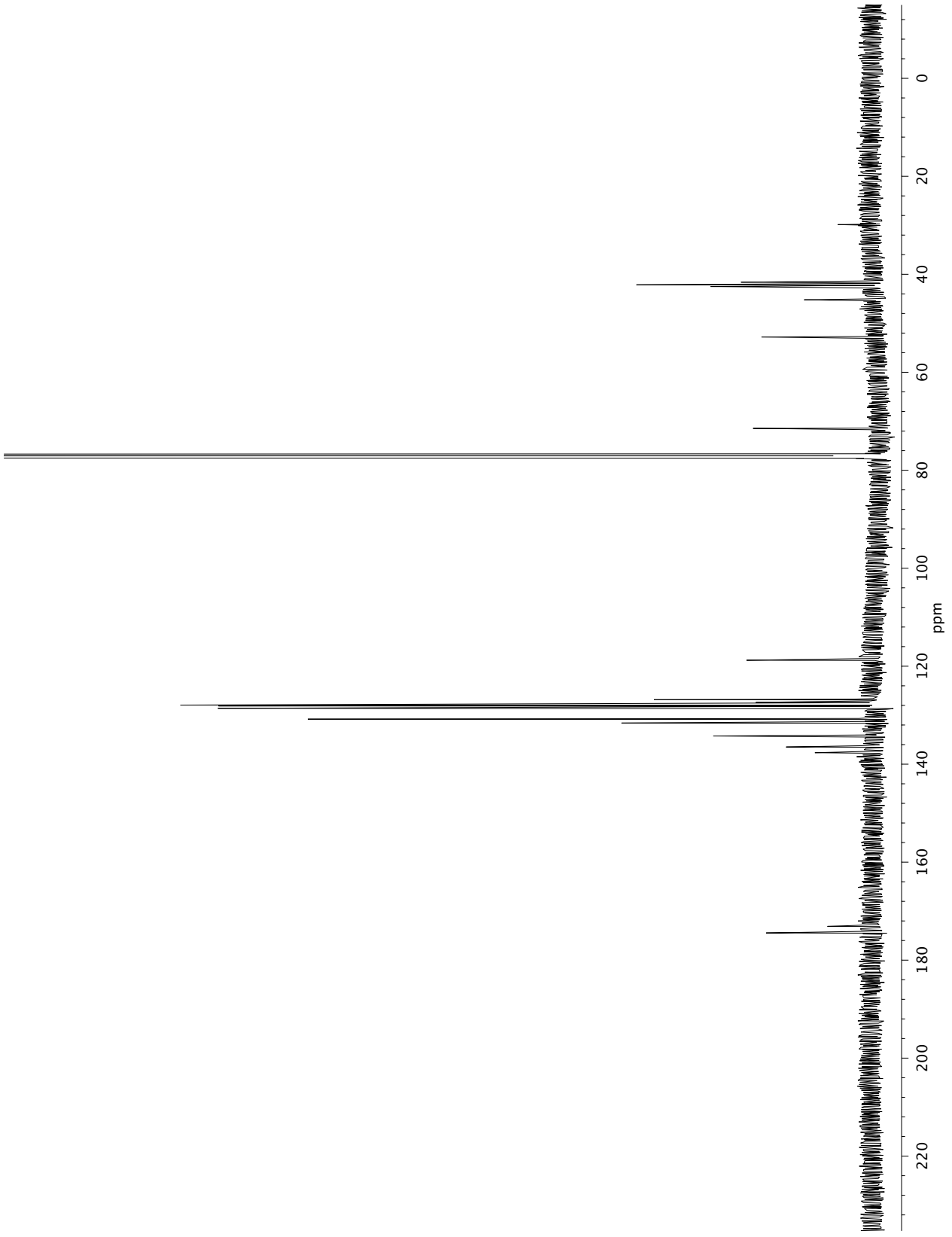
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9j**.



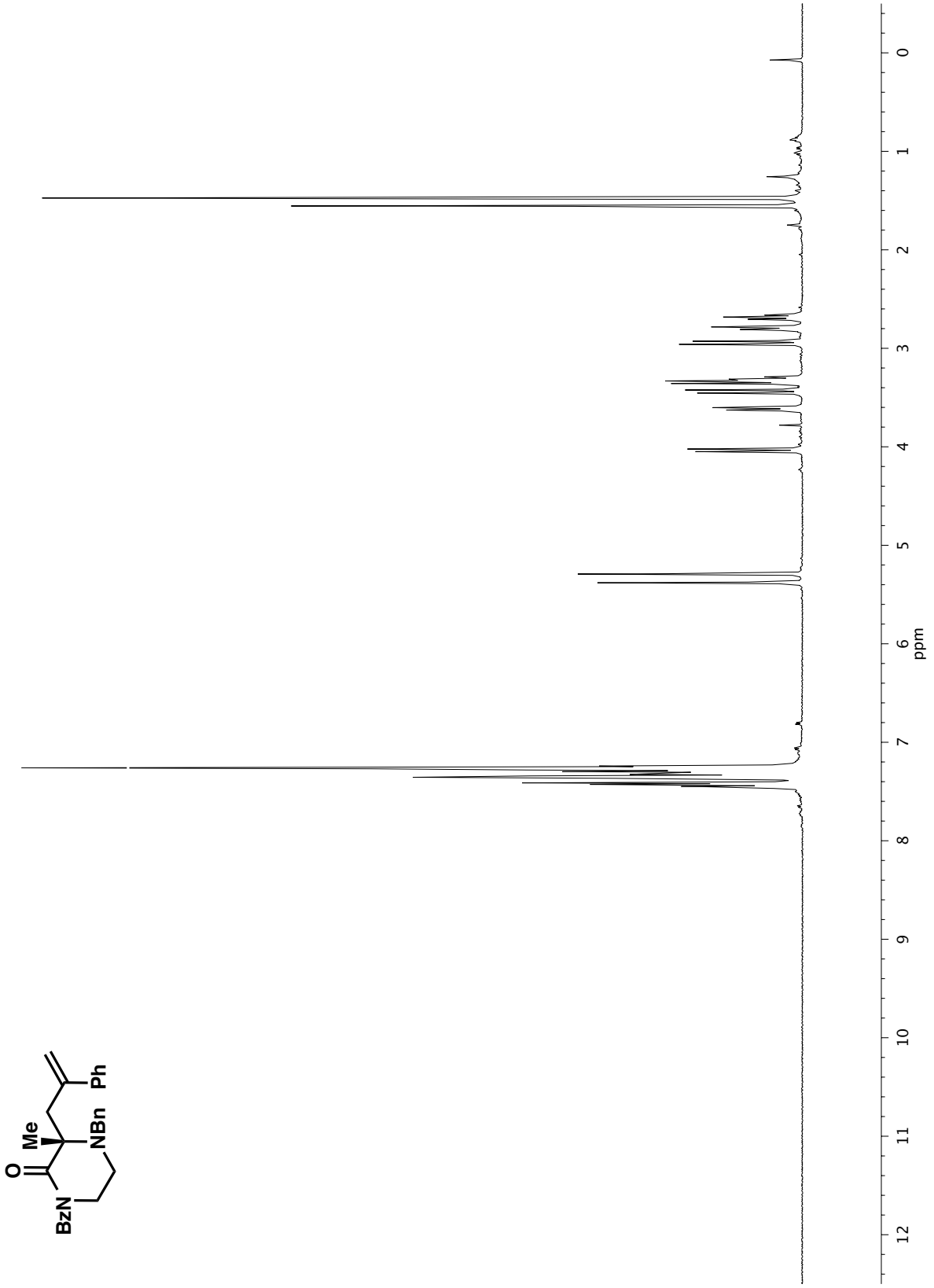
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9j.**



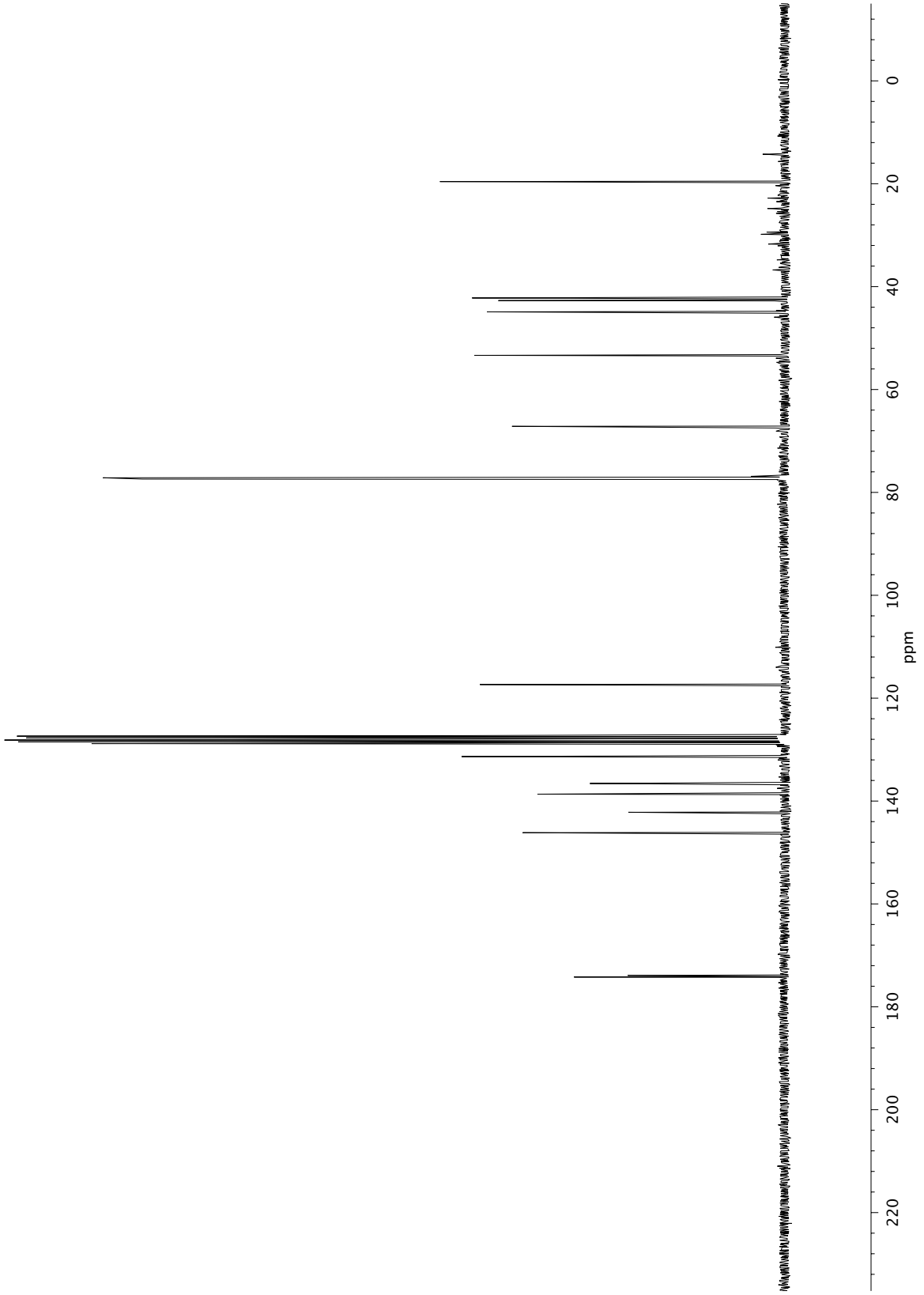
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9k**.



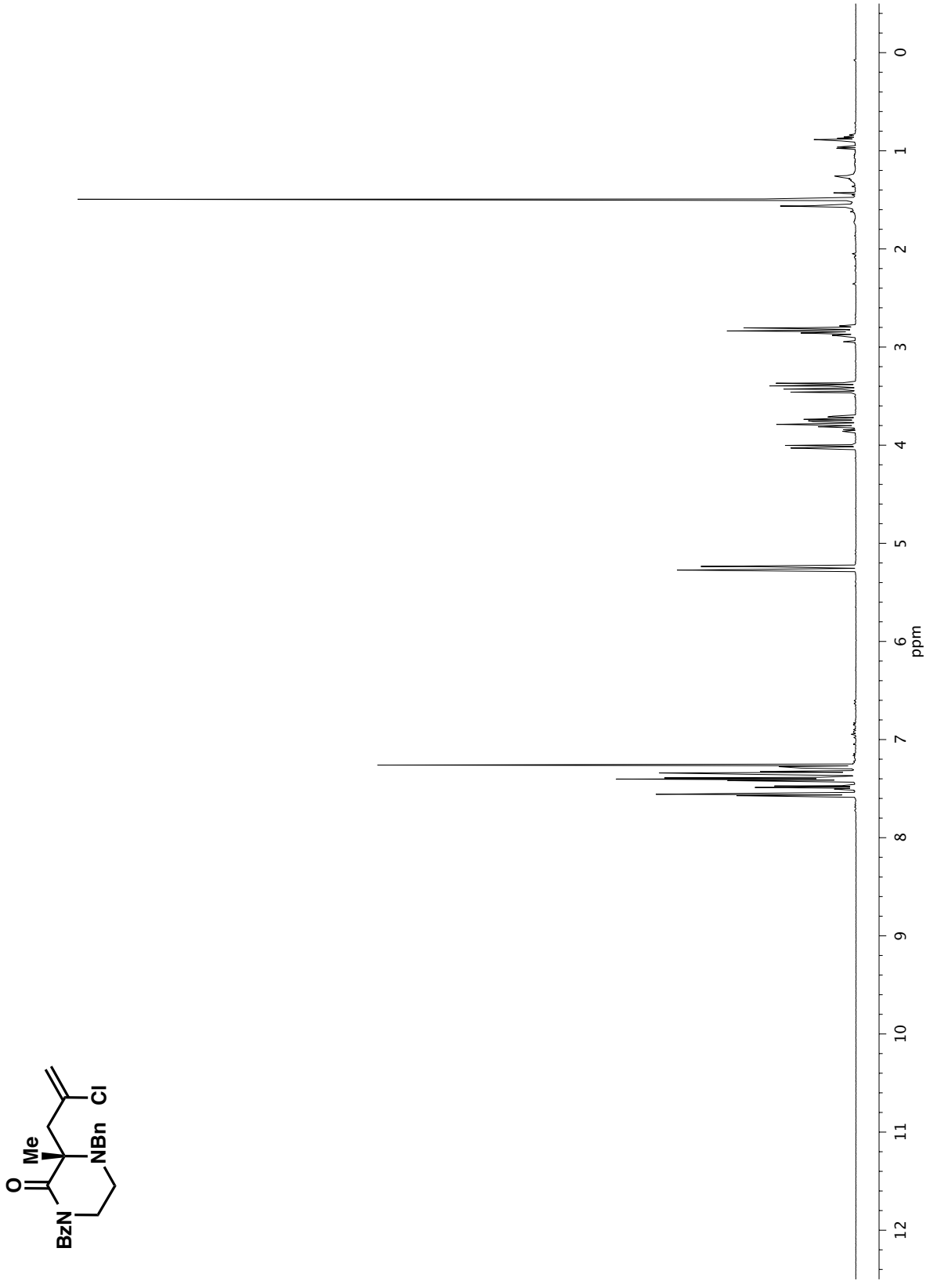
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9k.**



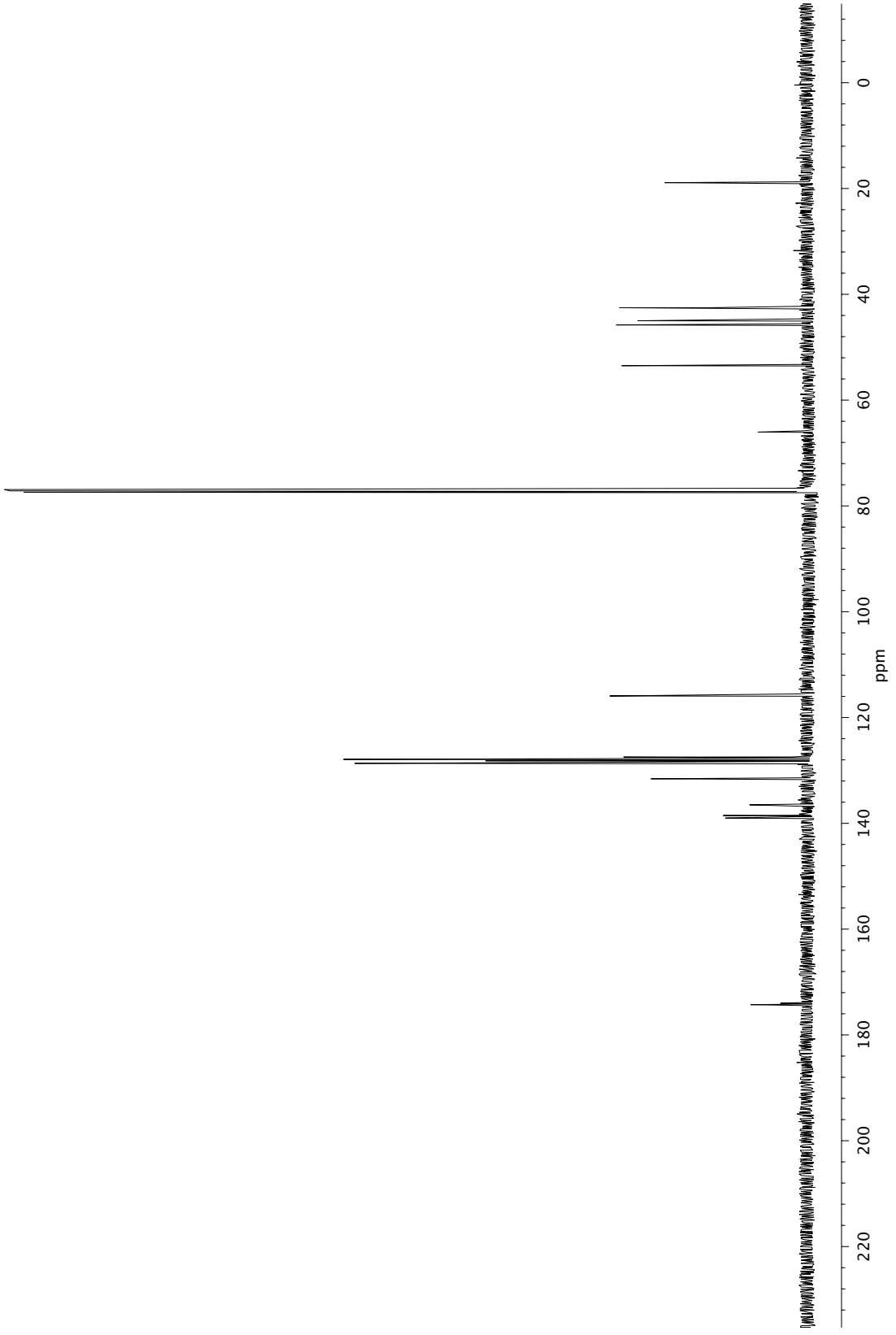
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9l**.



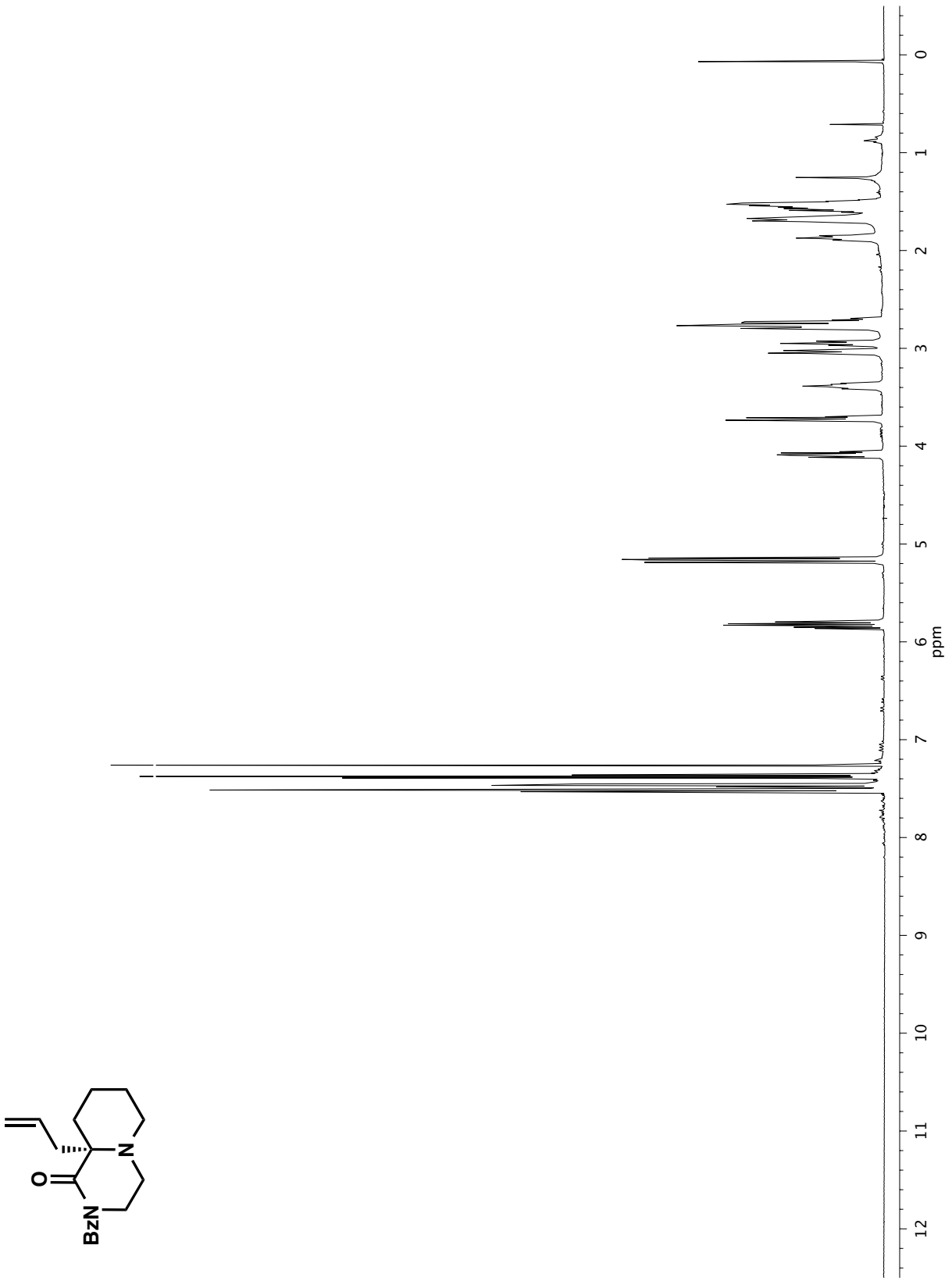
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9l.**



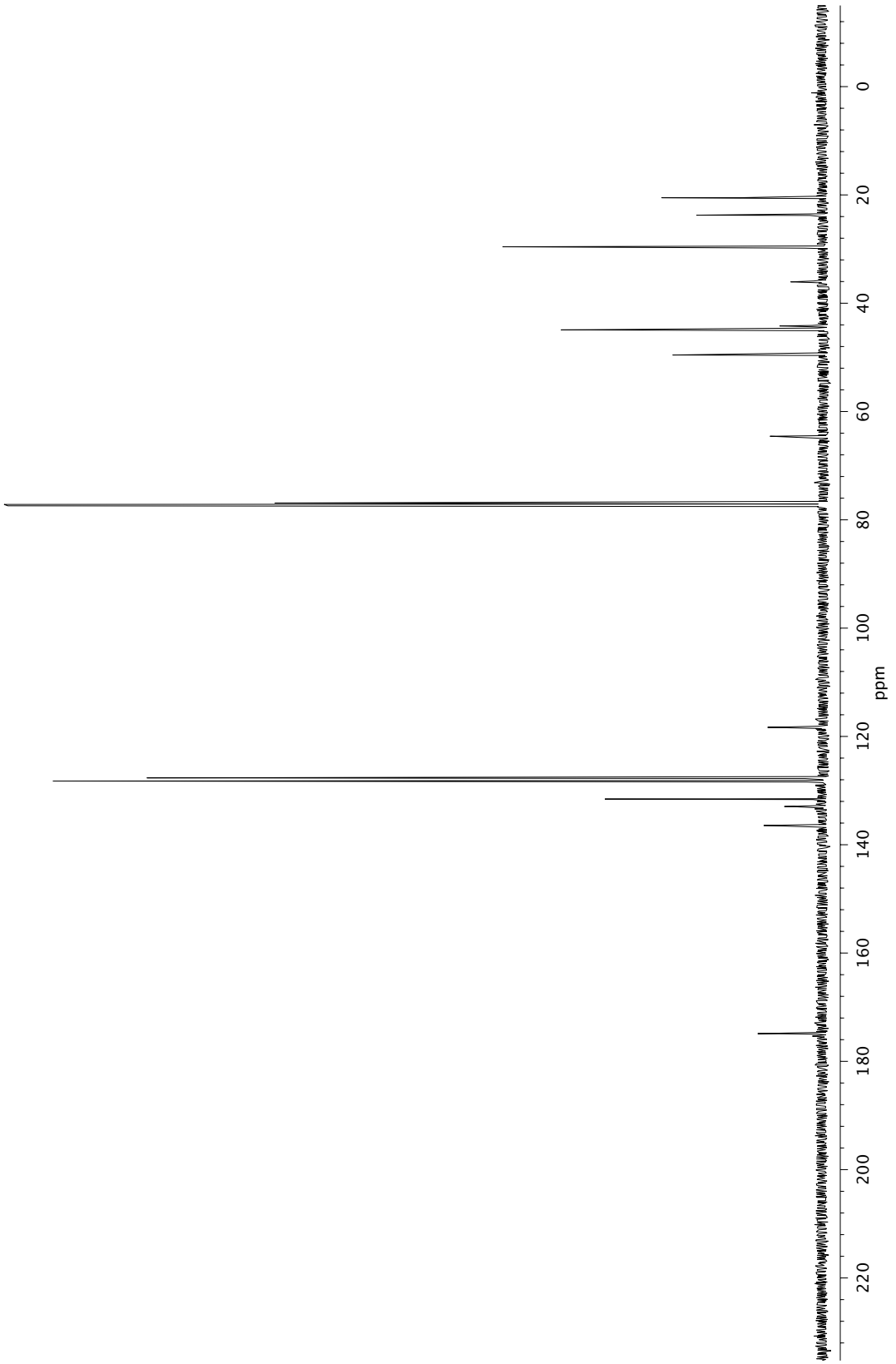
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9m**.



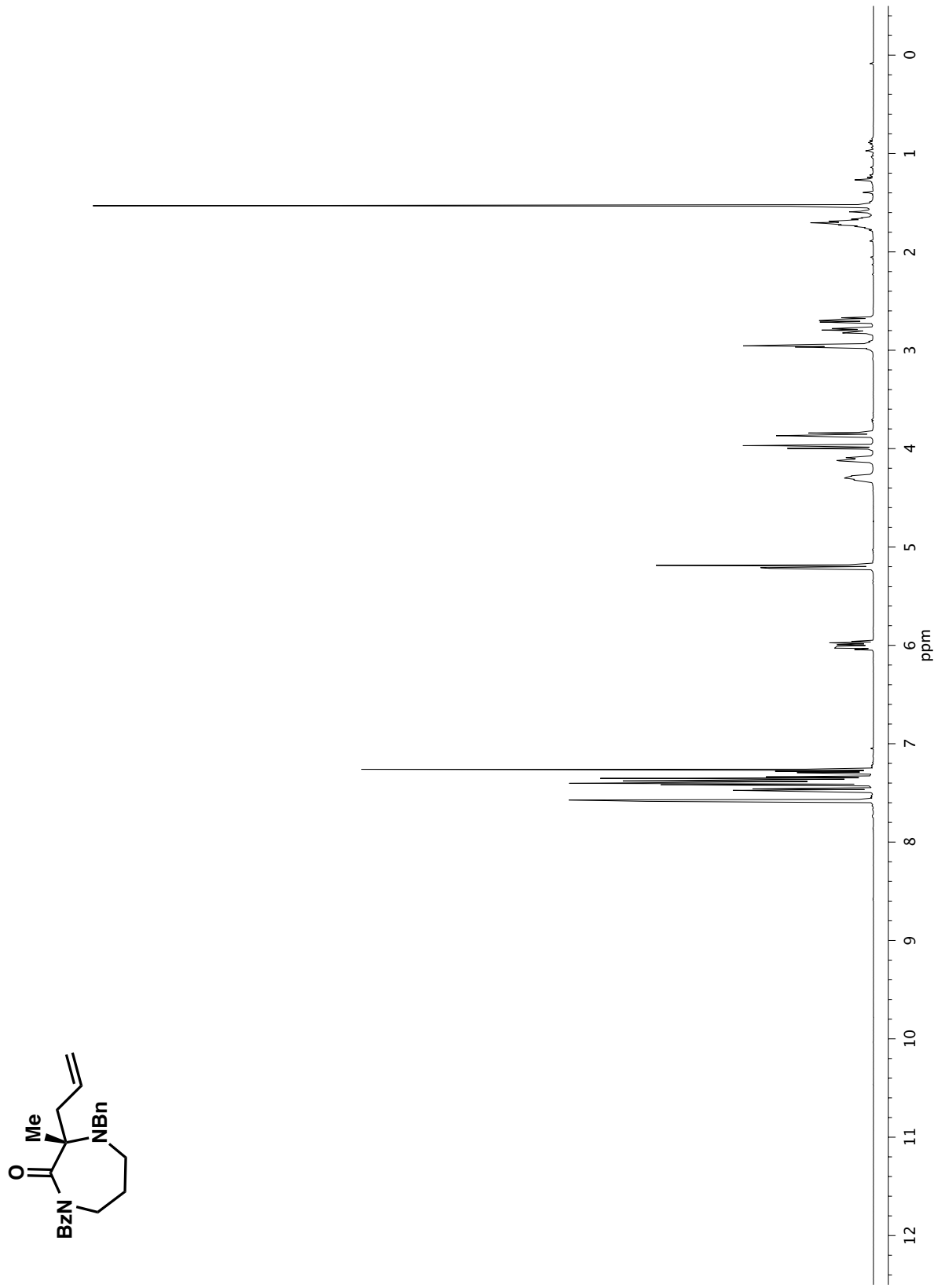
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9m.**



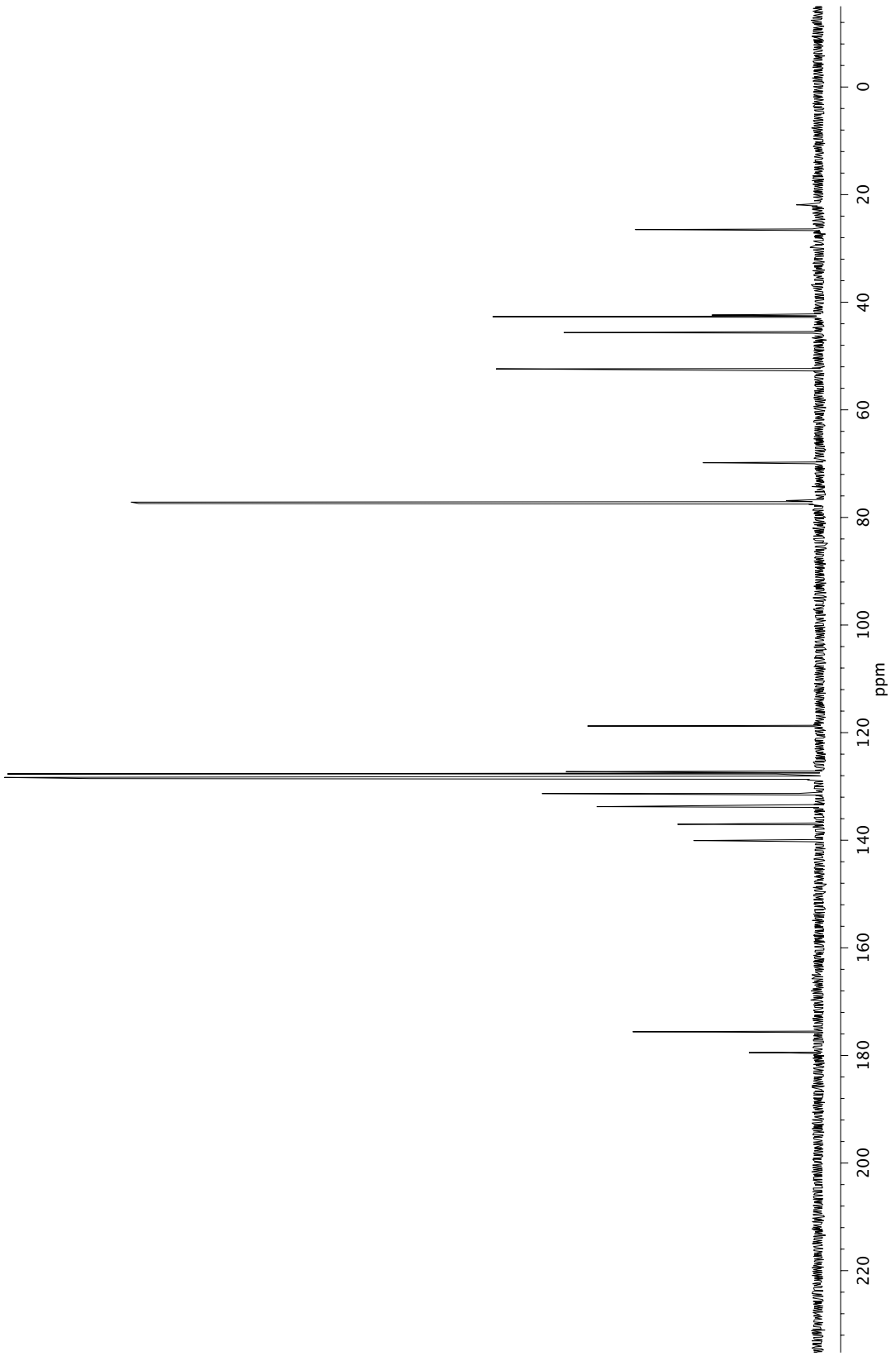
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9n**.



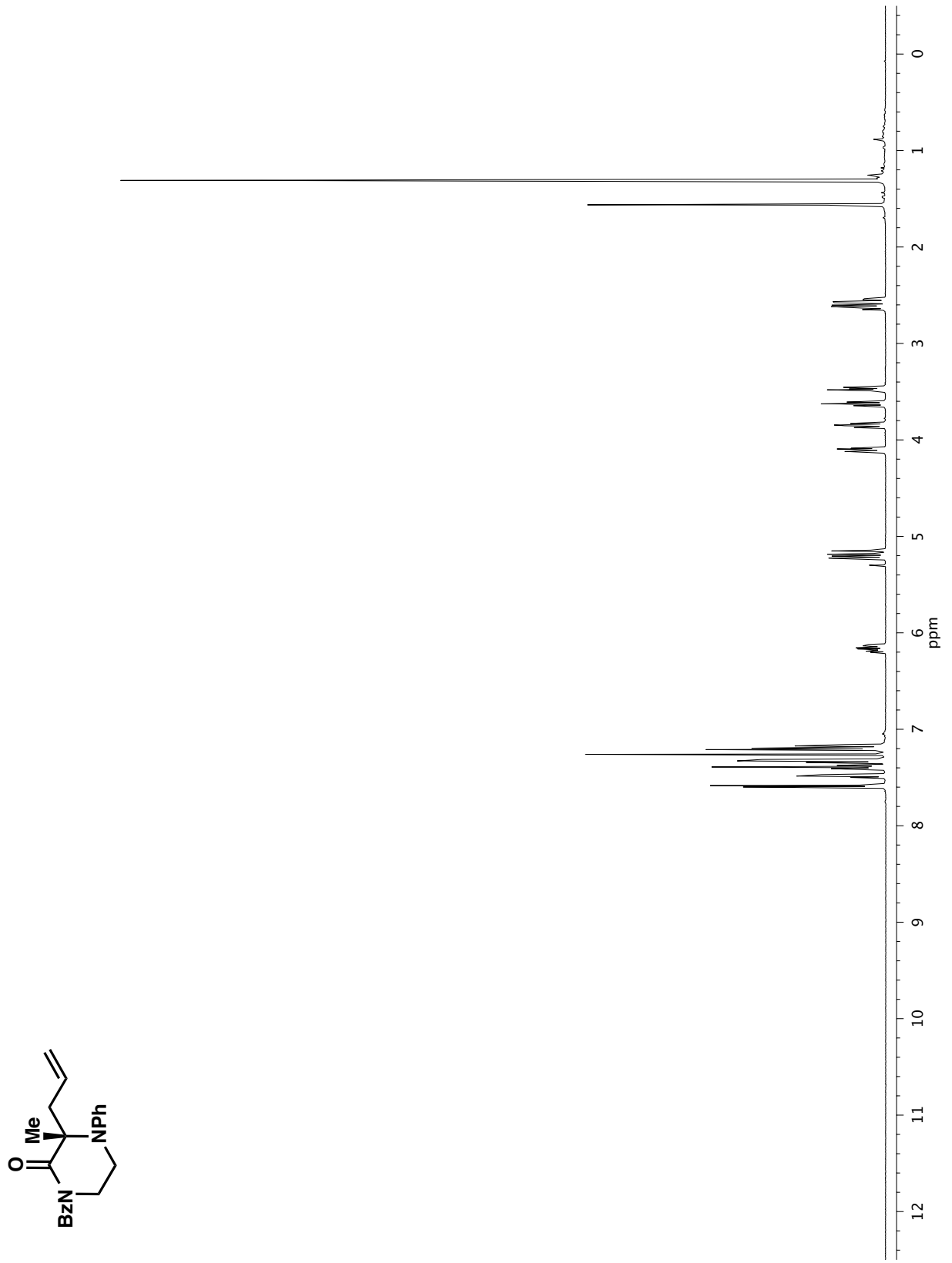
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9n.**



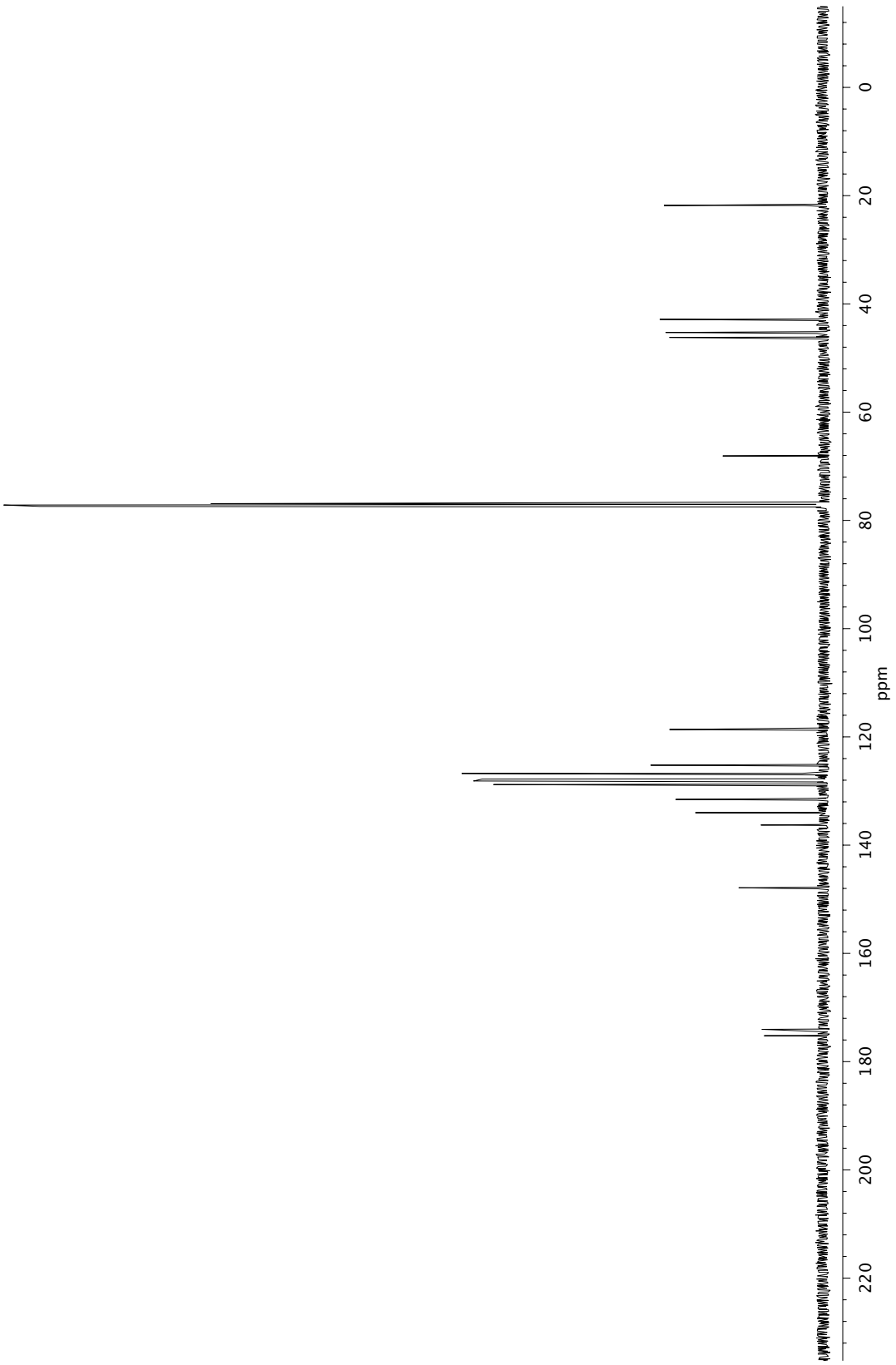
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9o**.



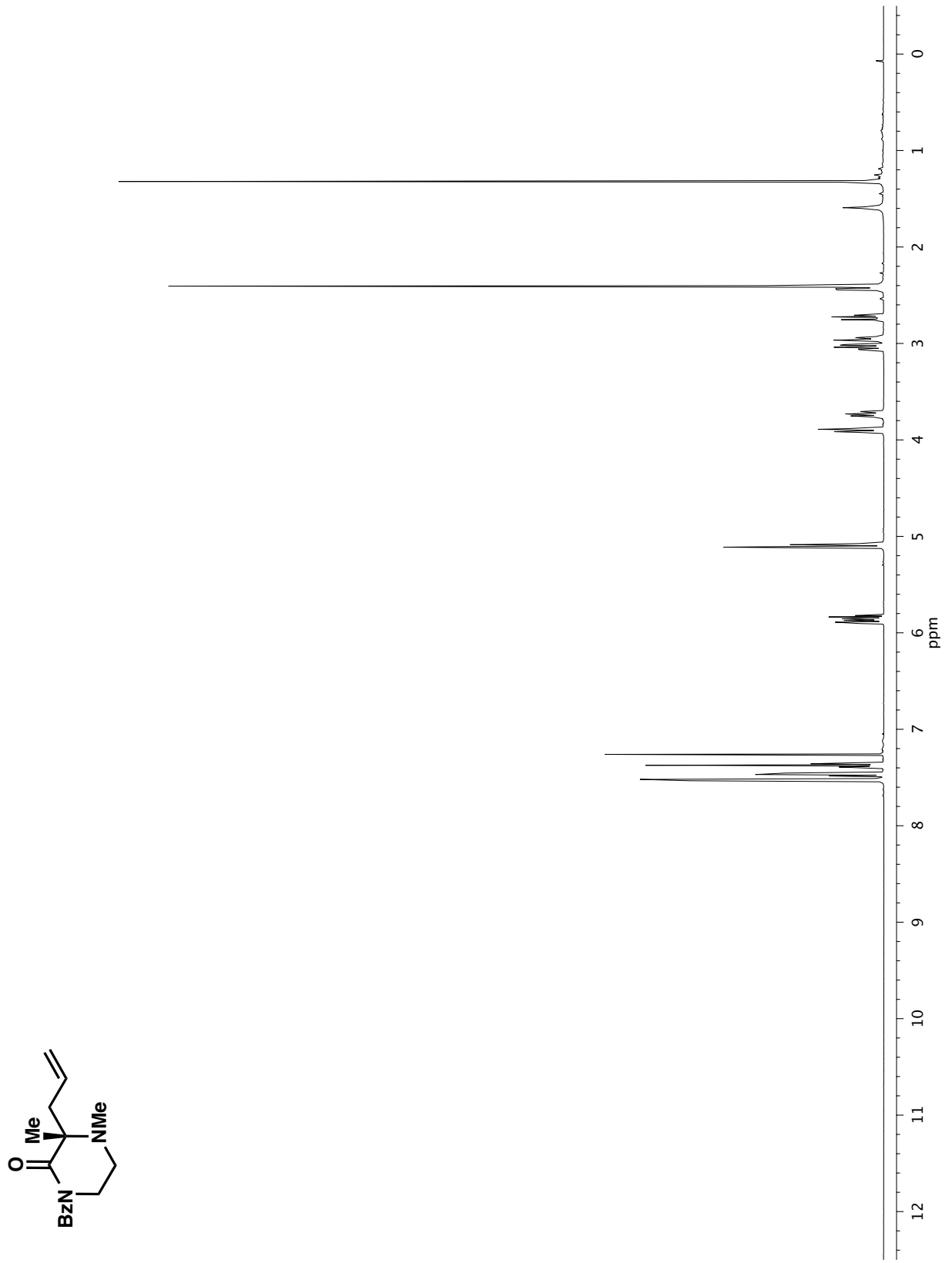
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9o.**



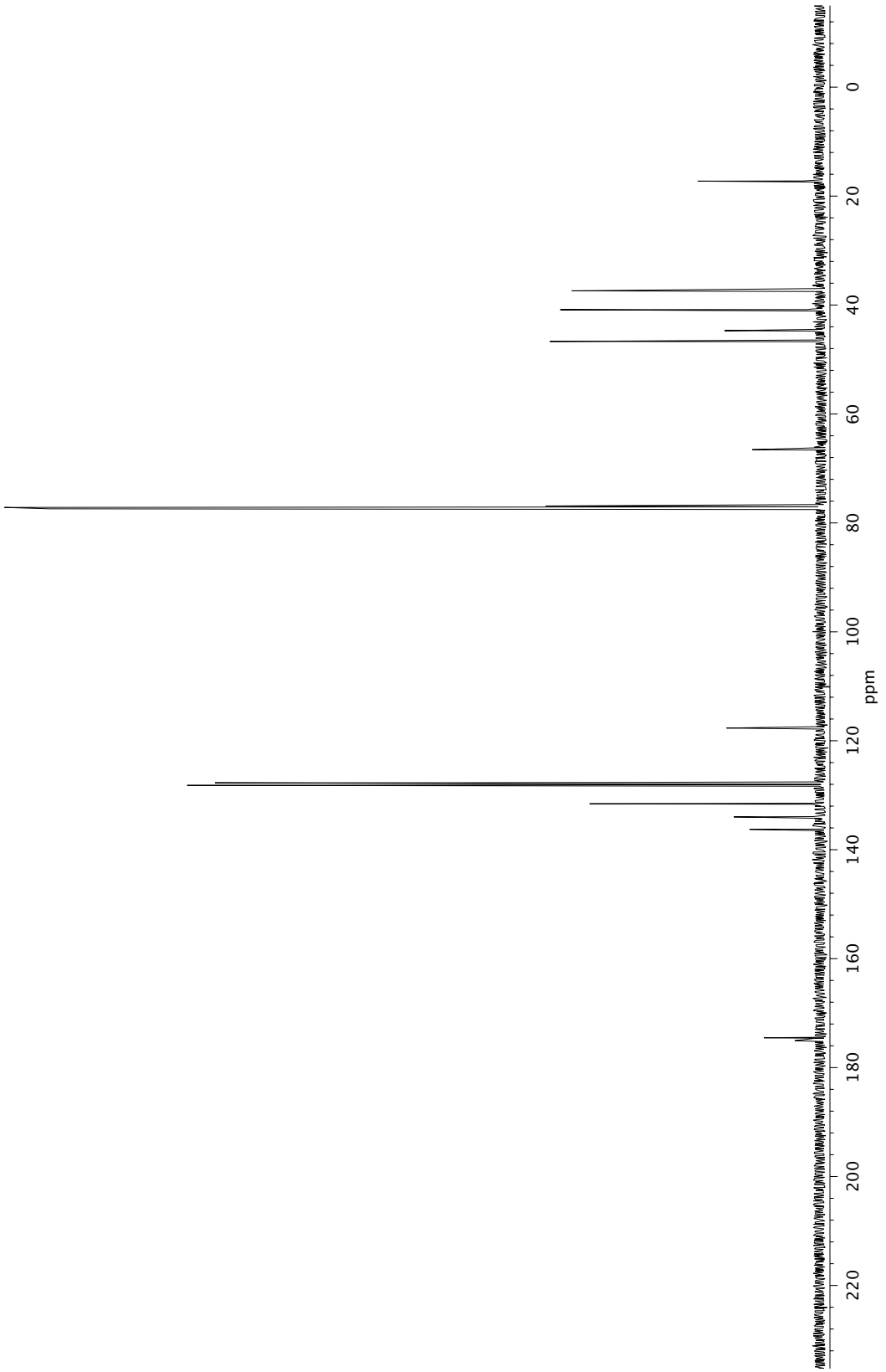
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9p**.



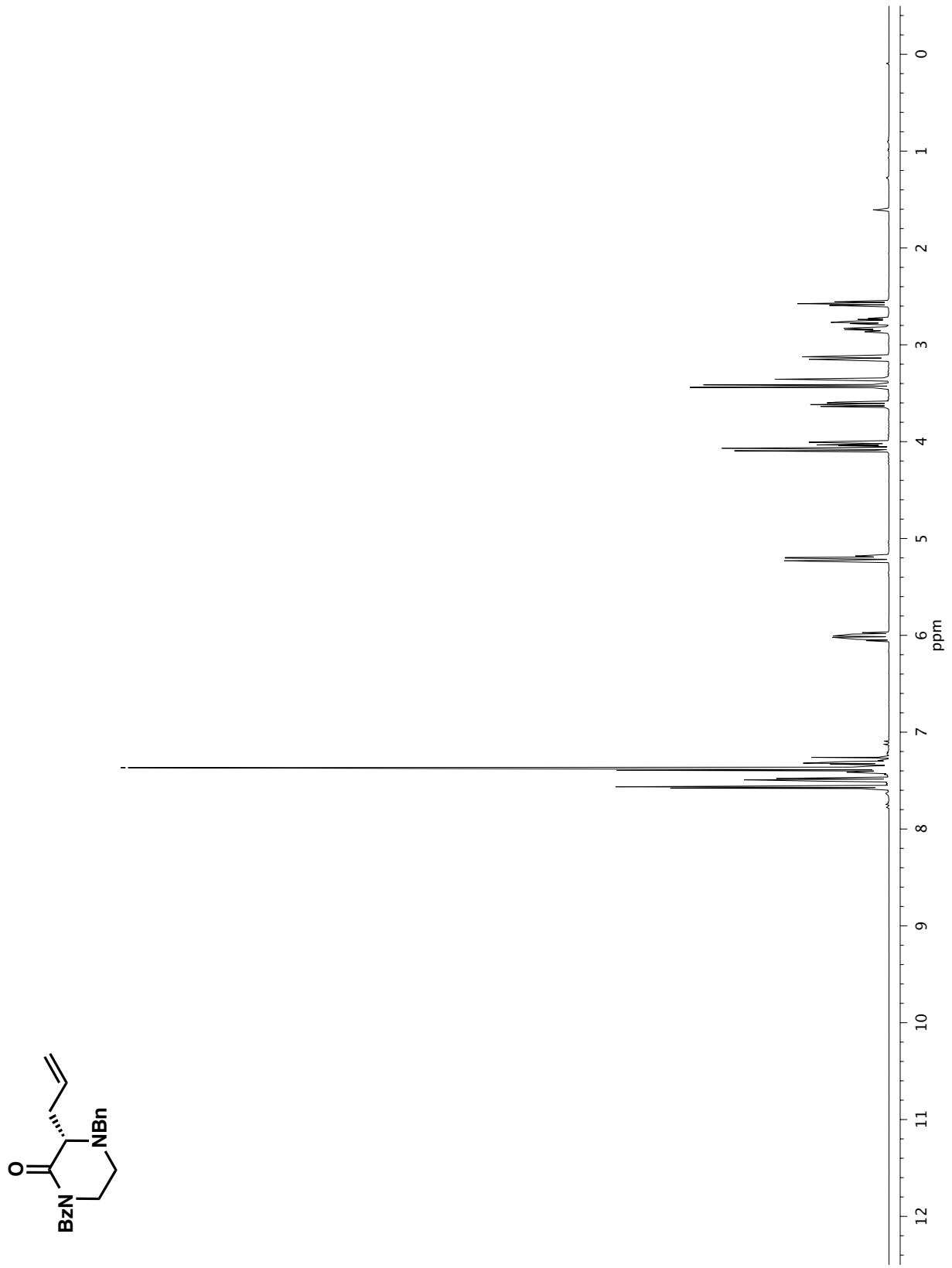
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9p.**



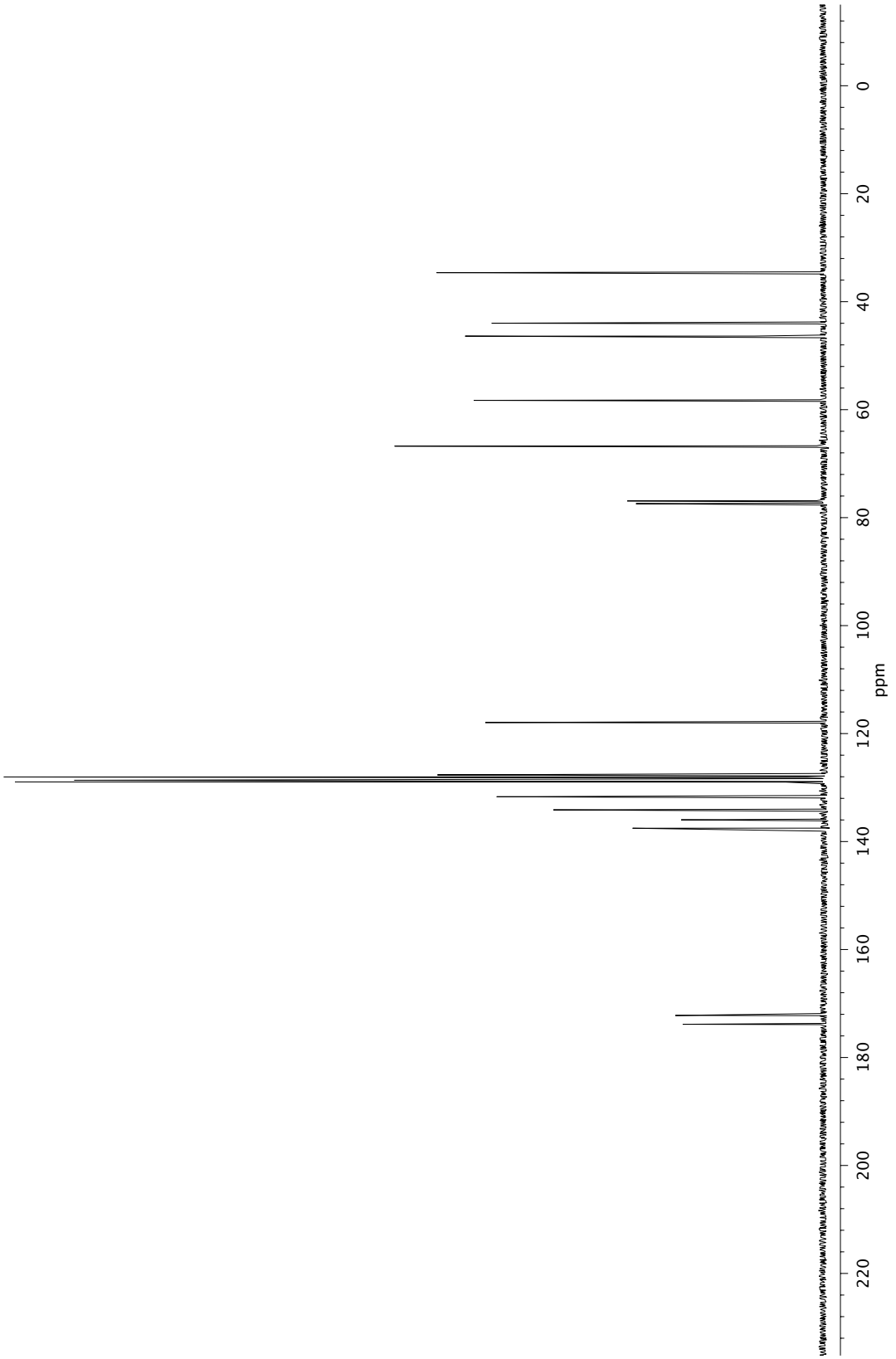
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9q**.



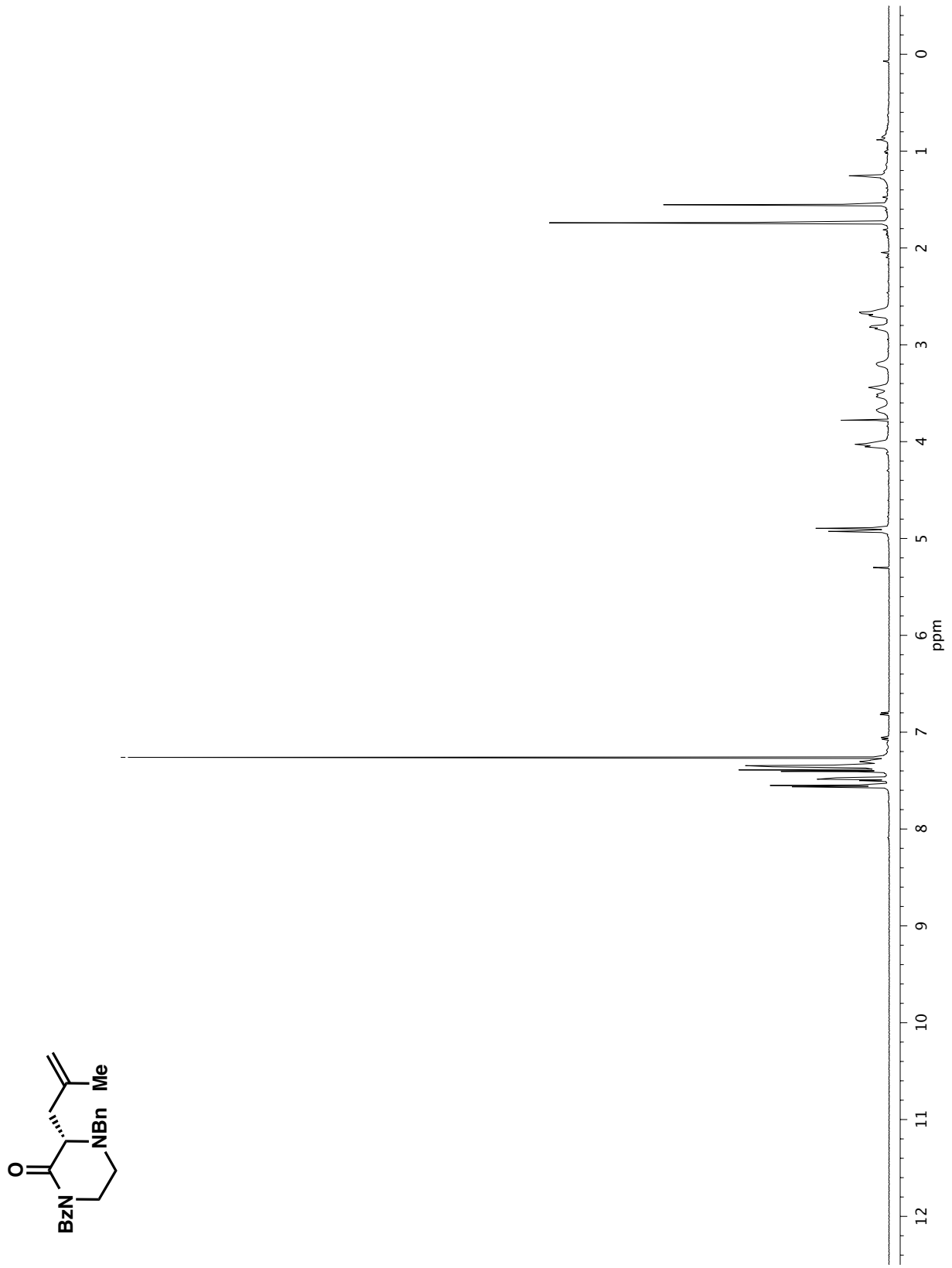
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9q.**



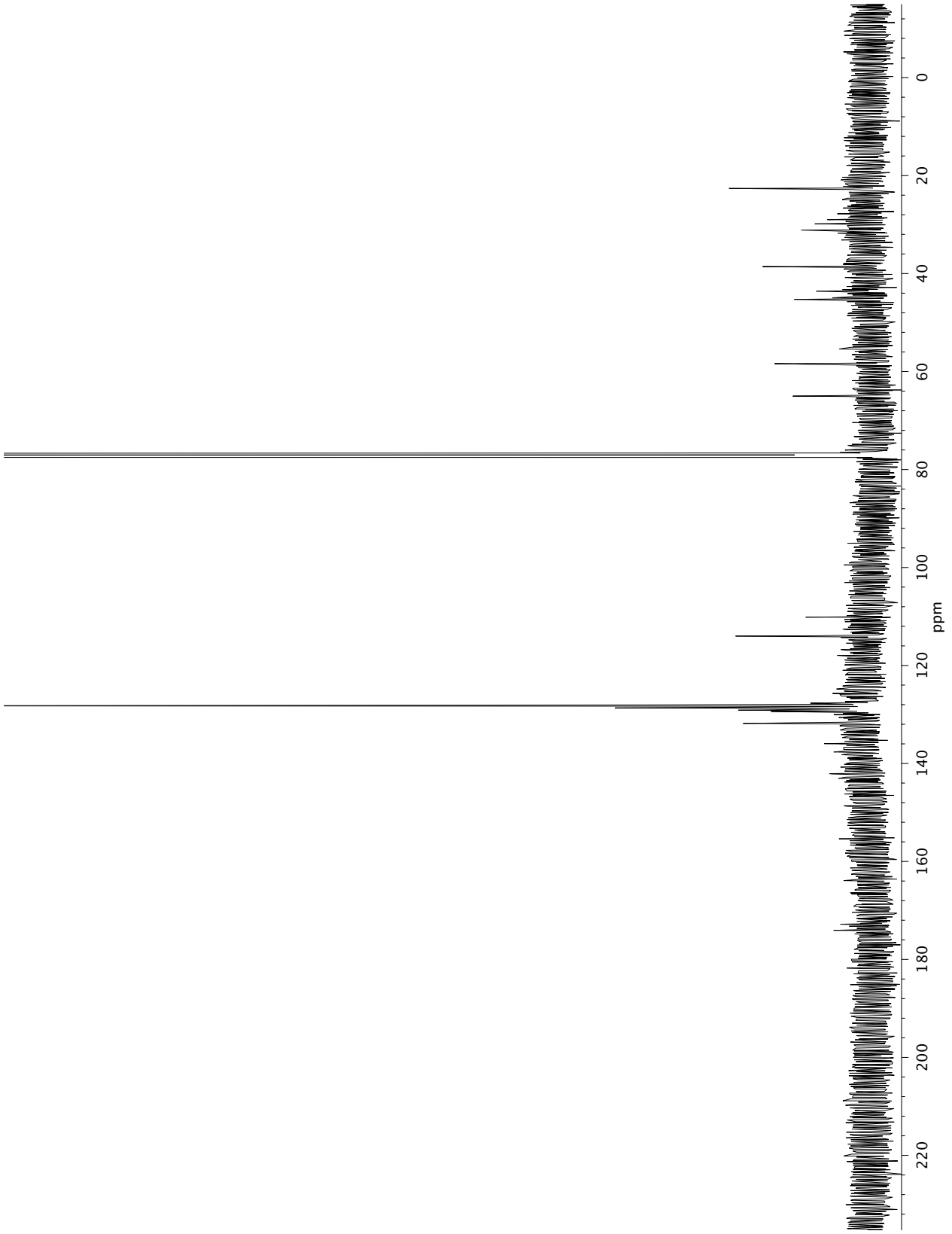
^{1}H NMR (500 MHz, $CDCl_3$) of compound **11a**.



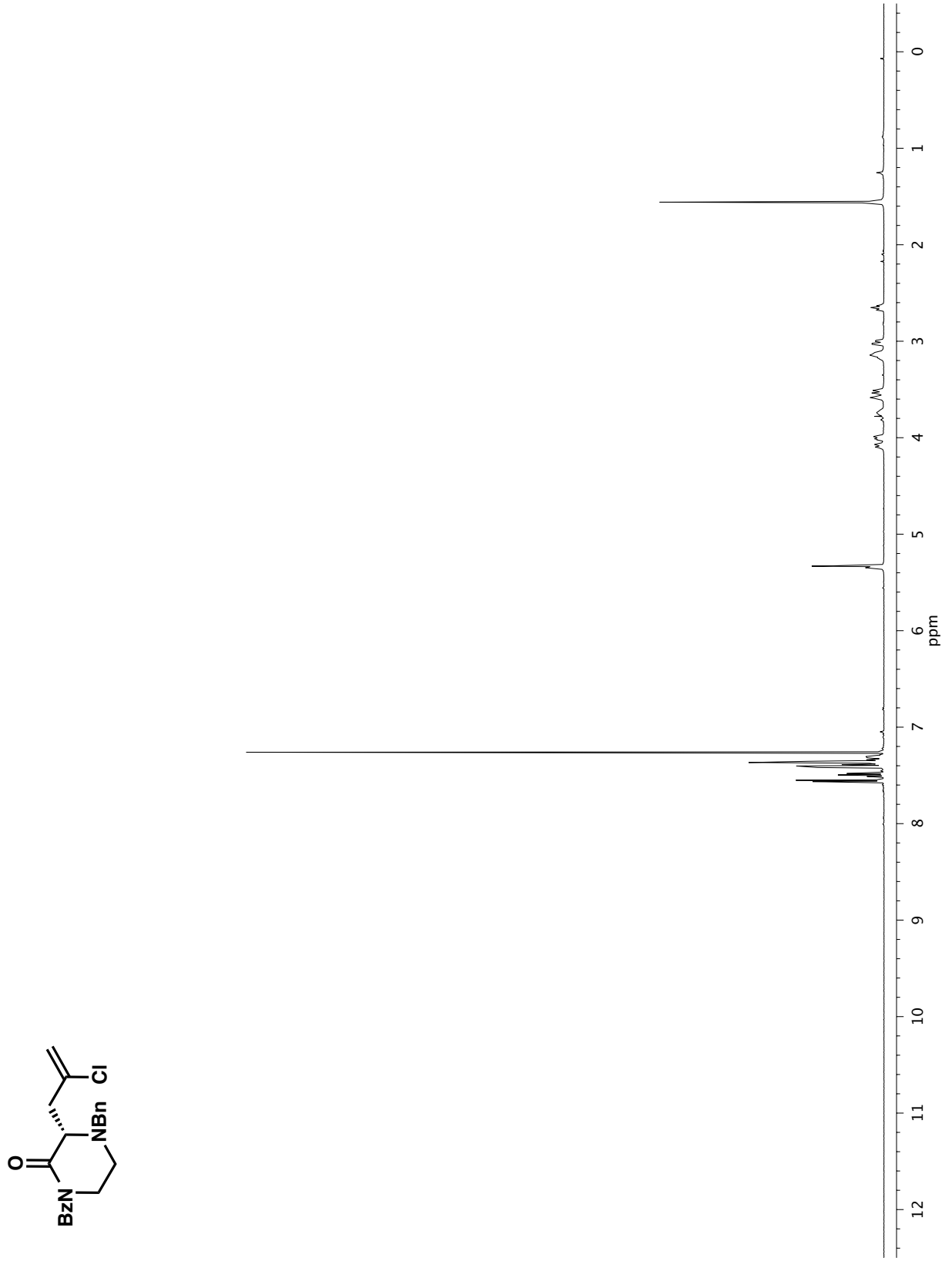
^{13}C NMR (126 MHz, $CDCl_3$) of compound **11a.**



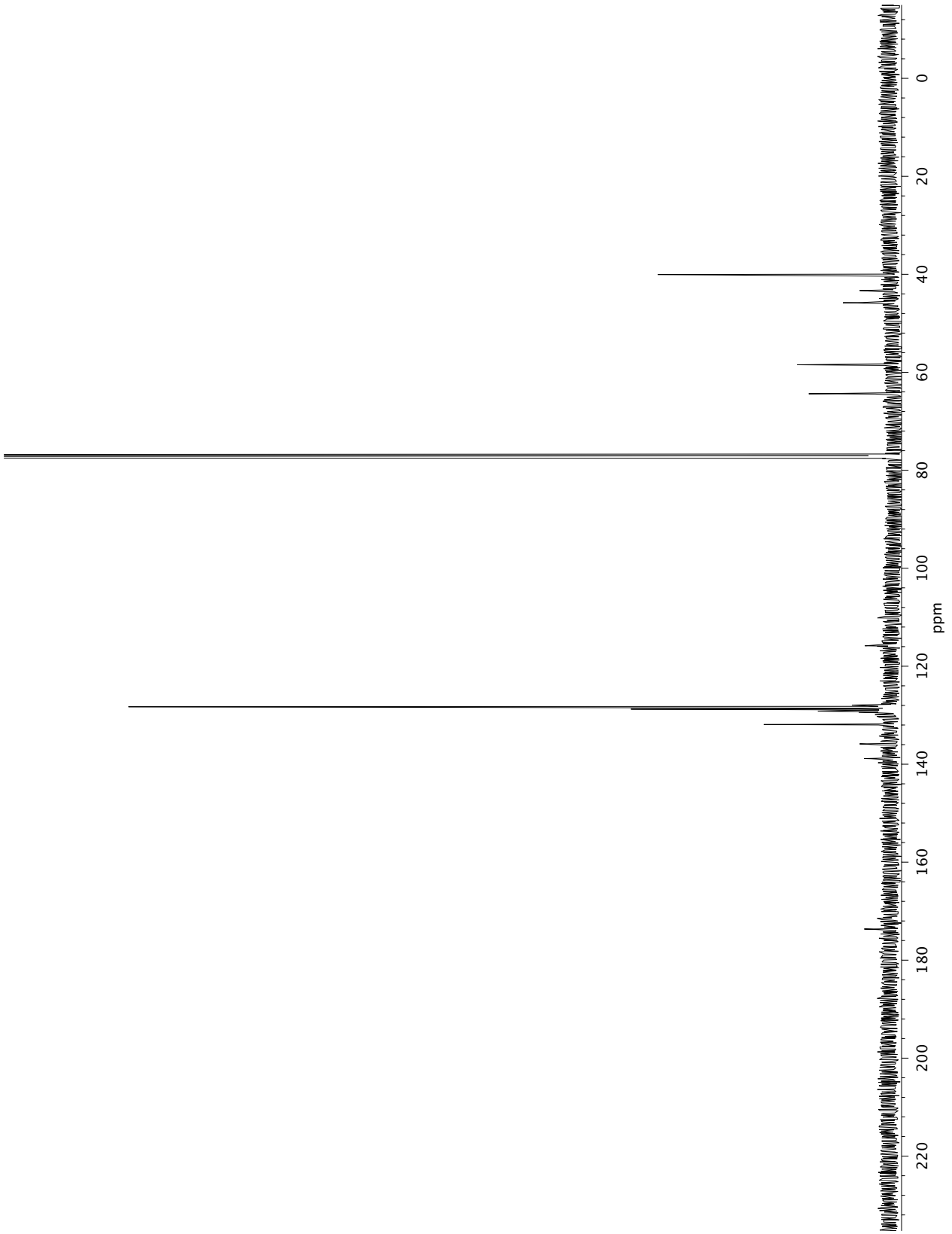
^{1}H NMR (500 MHz, $CDCl_3$) of compound **11b**.



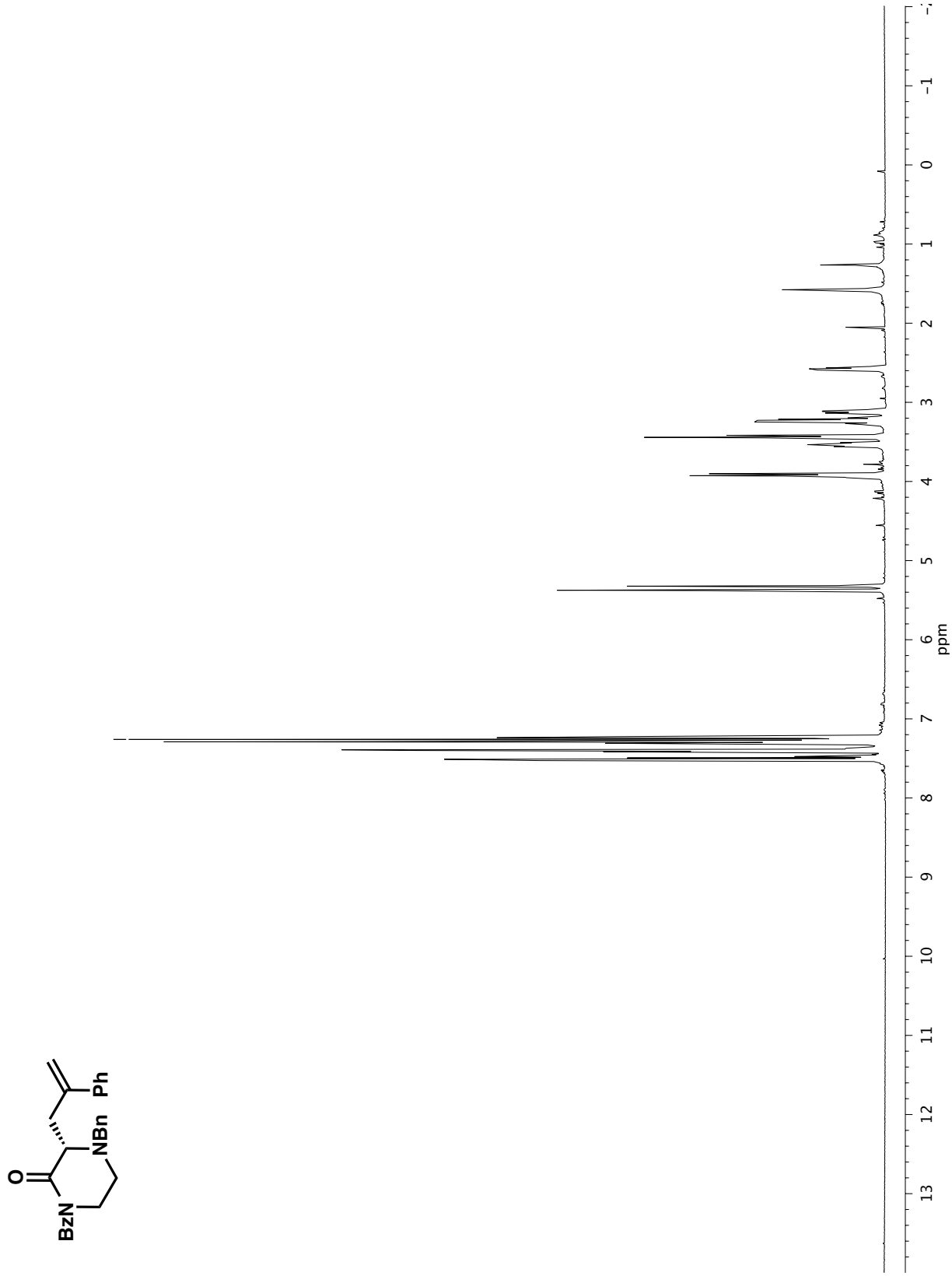
^{13}C NMR (126 MHz, $CDCl_3$) of compound **11b.**



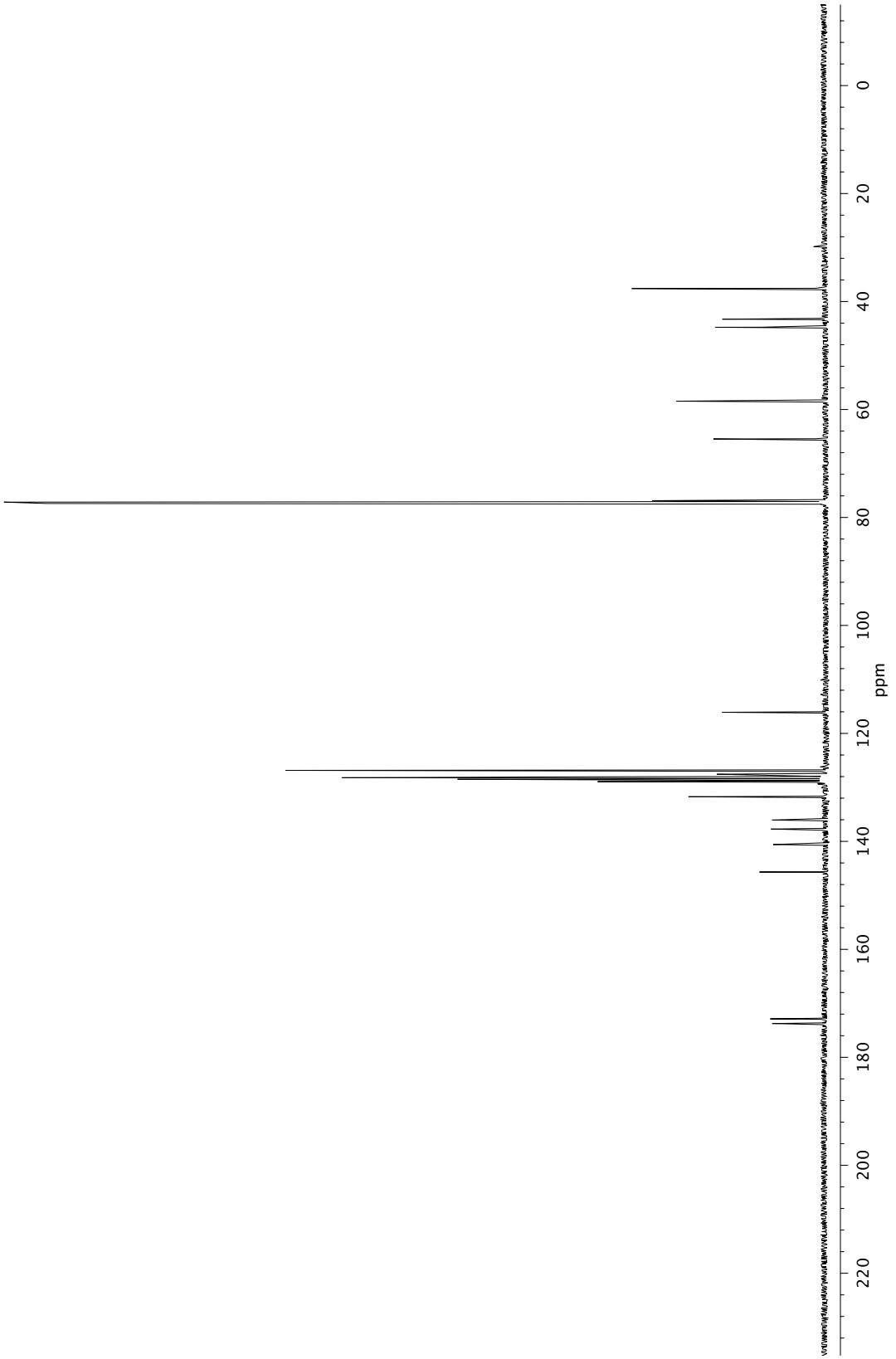
^{1}H NMR (500 MHz, $CDCl_3$) of compound **11c**.



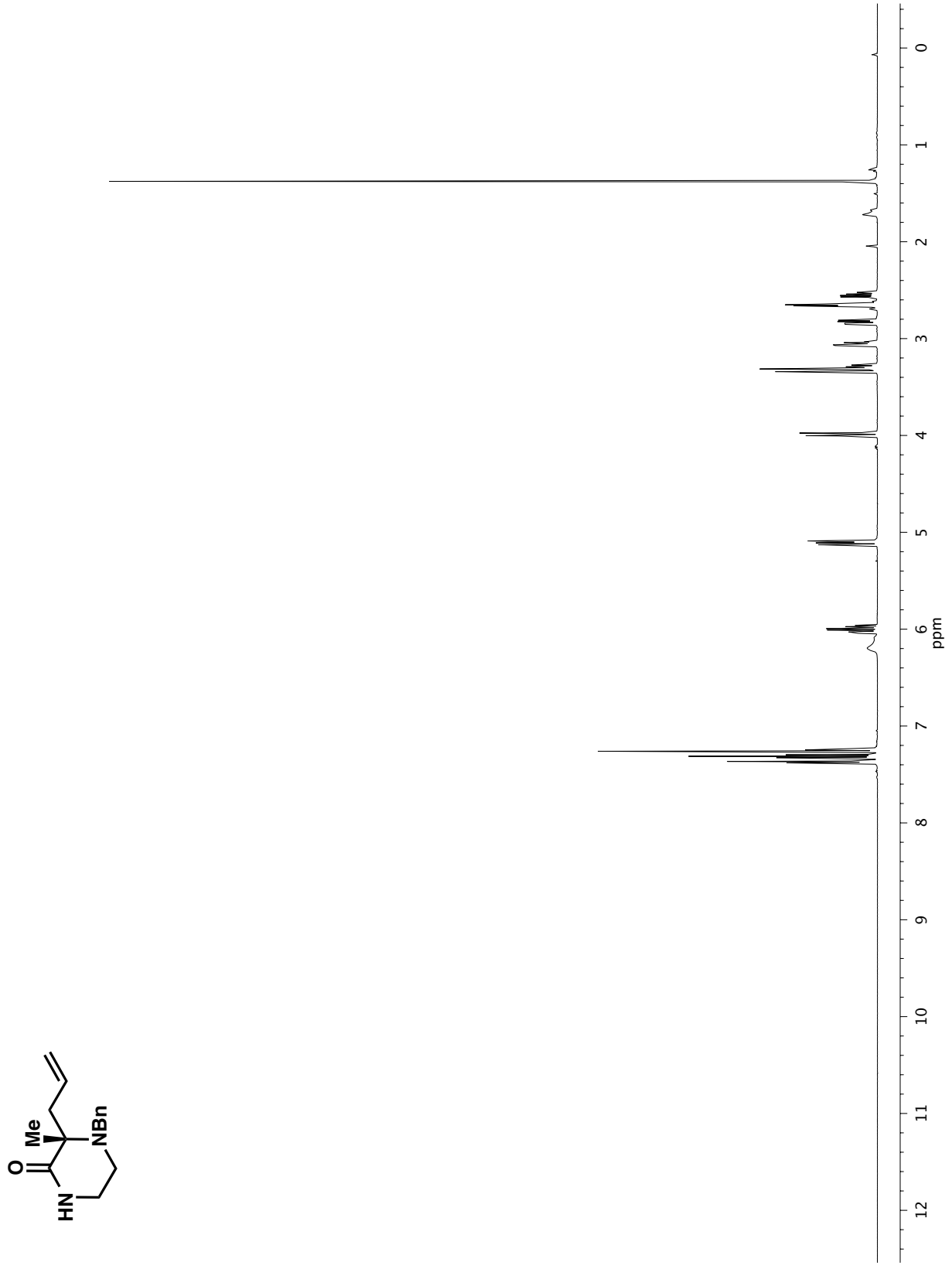
^{13}C NMR (126 MHz, $CDCl_3$) of compound **11c.**



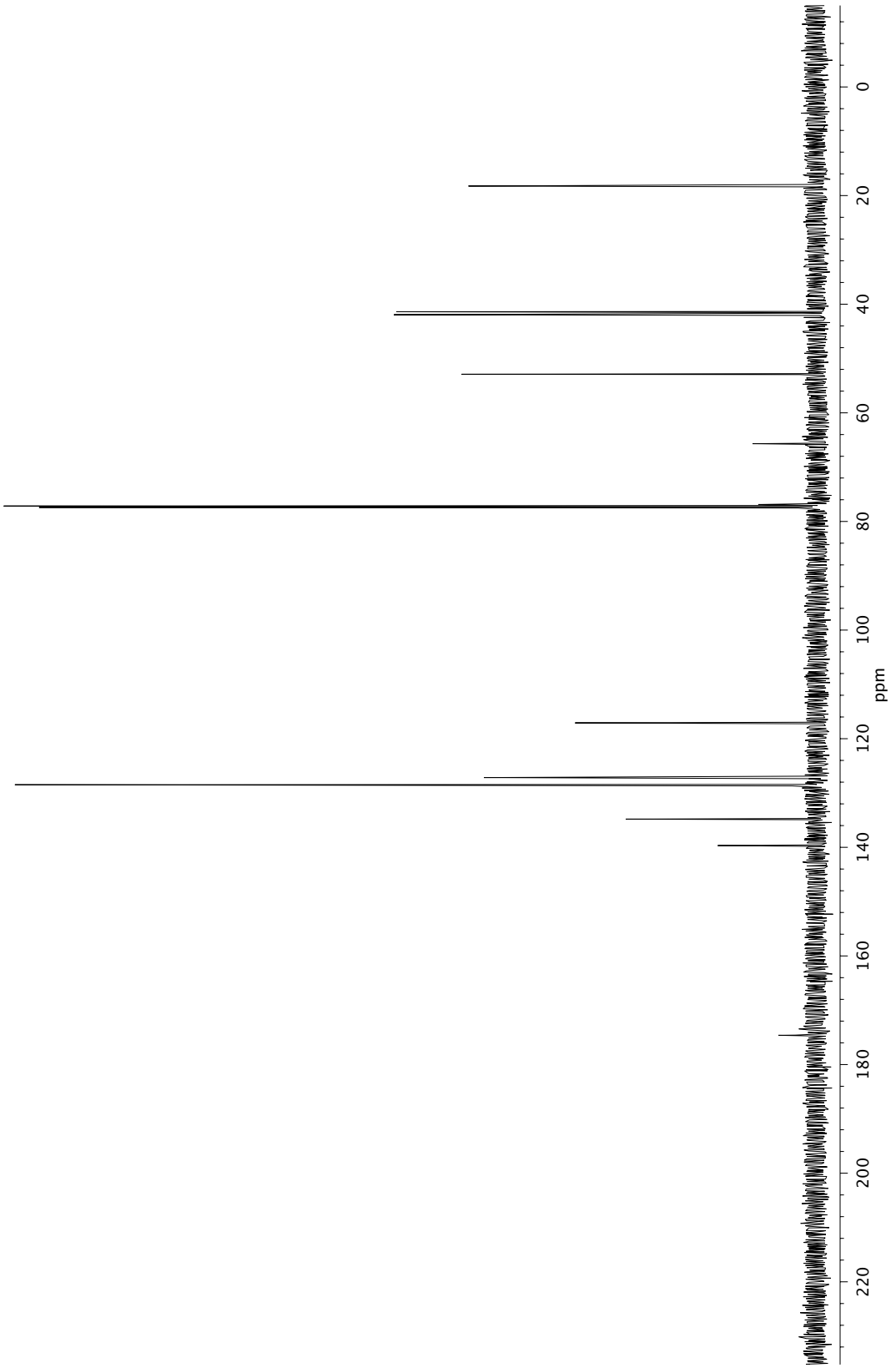
^{1}H NMR (500 MHz, $CDCl_3$) of compound **11d**.



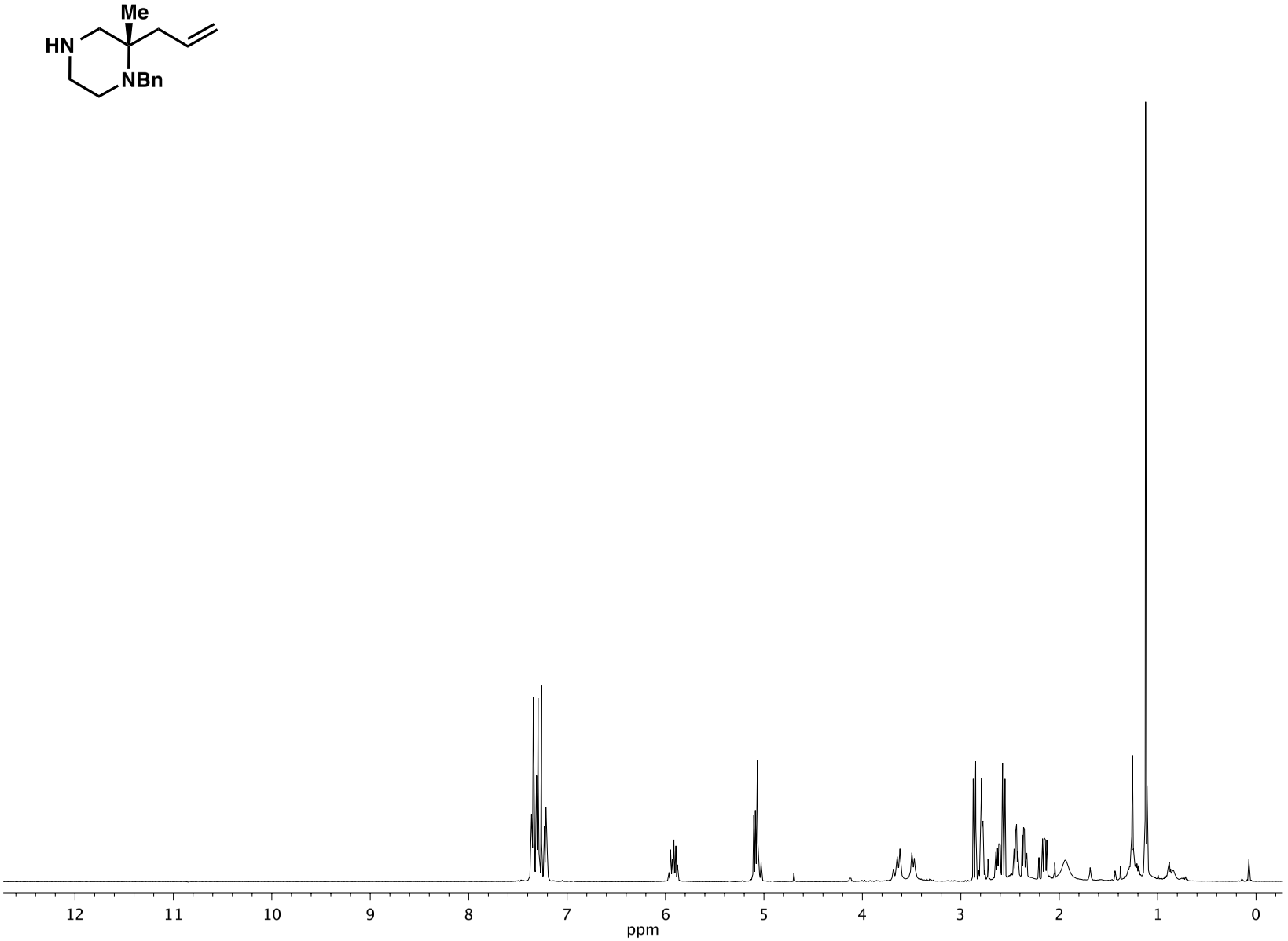
^{13}C NMR (126 MHz, $CDCl_3$) of compound **11d.**



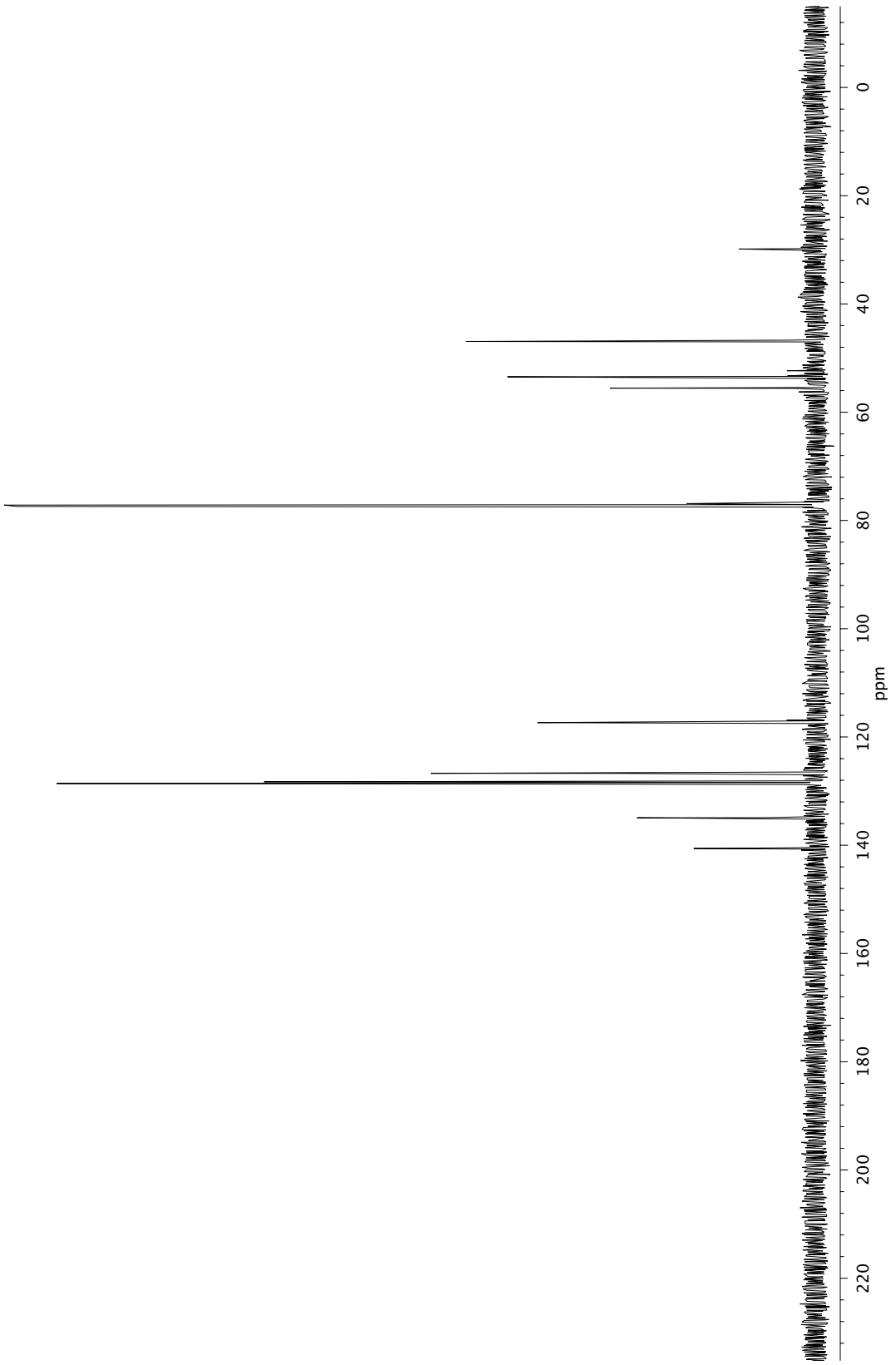
^{1}H NMR (500 MHz, $CDCl_3$) of compound **12**.



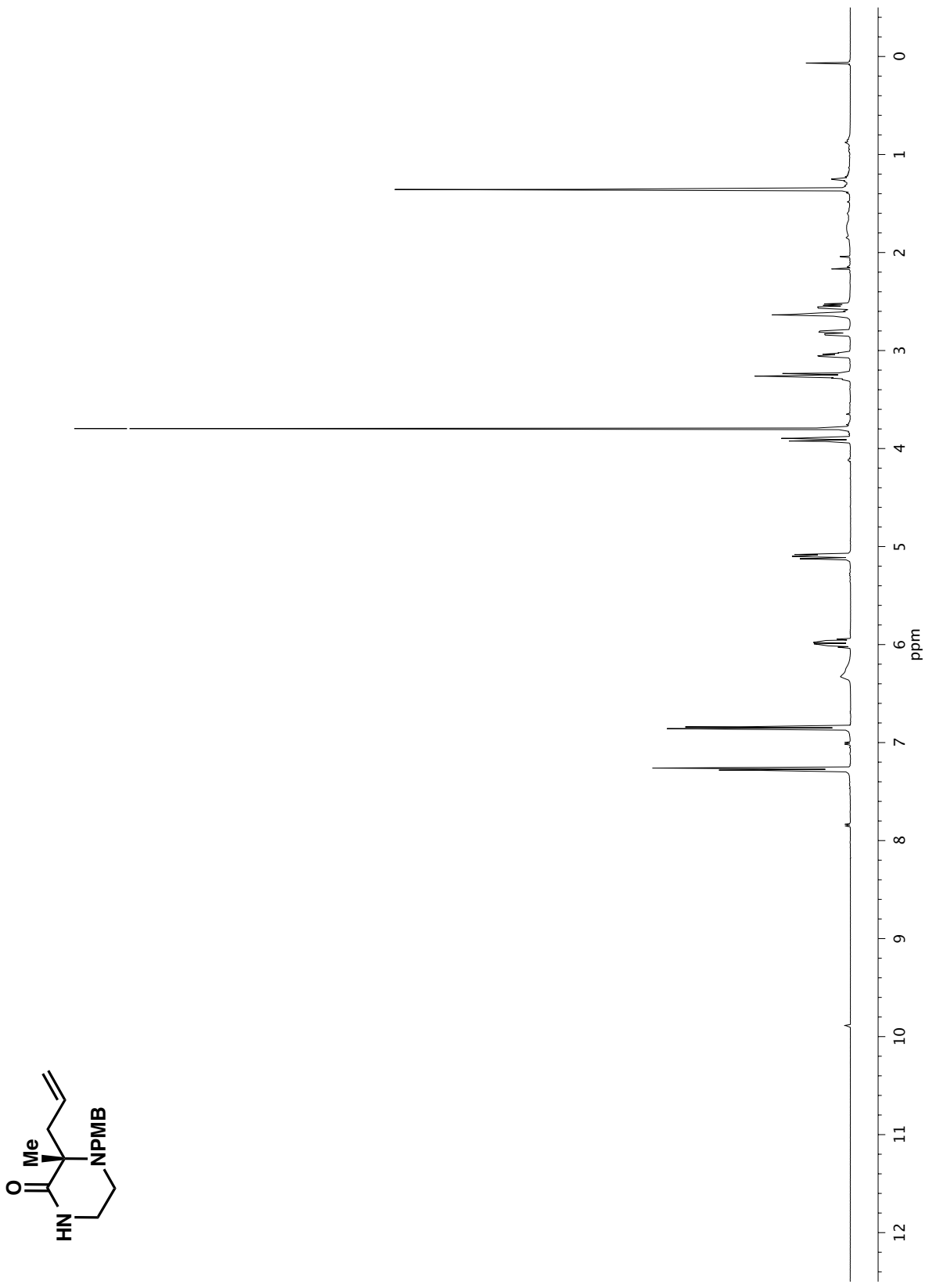
^{13}C NMR (126 MHz, $CDCl_3$) of compound **12.**



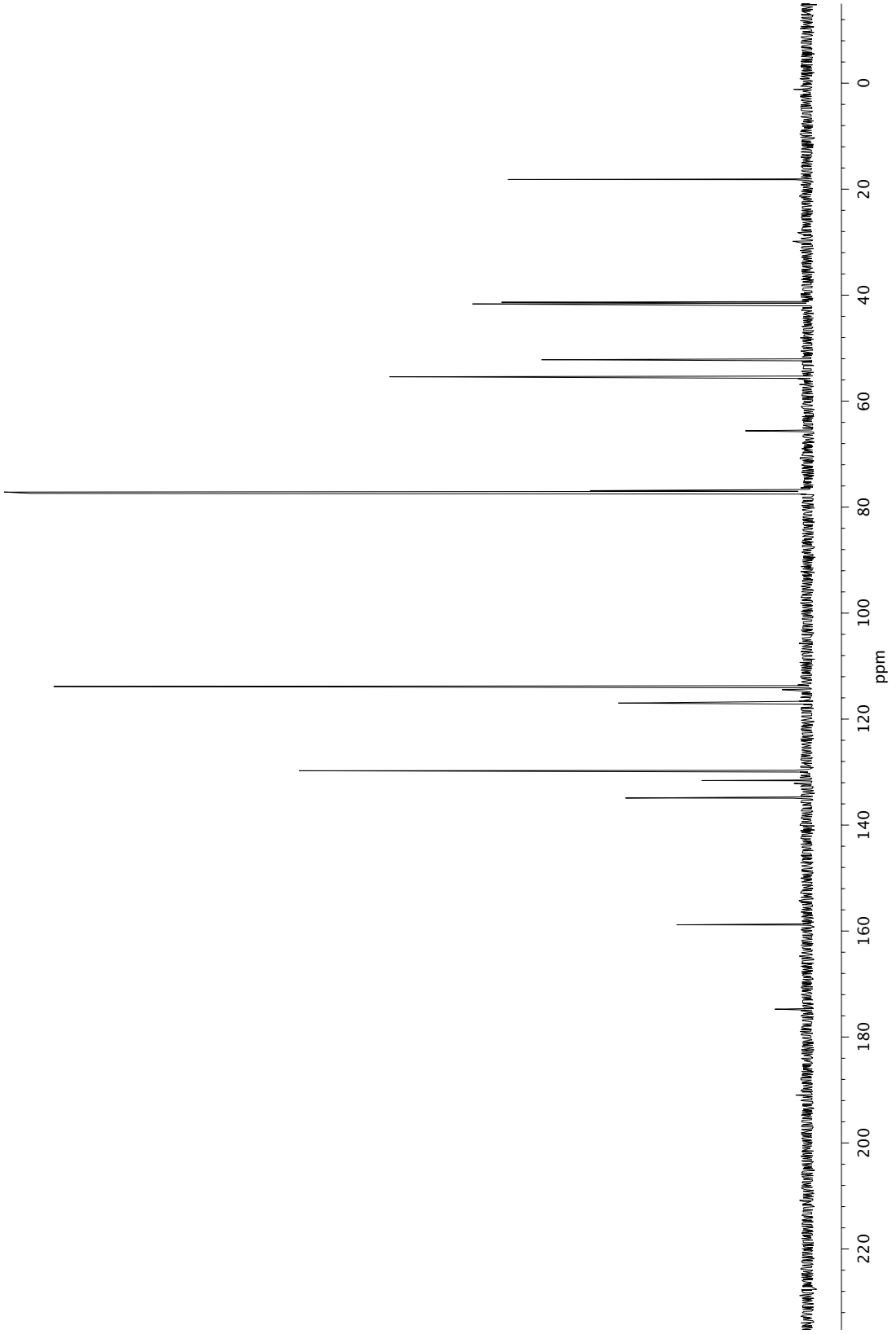
^{1}H NMR (500 MHz, $CDCl_3$) of compound **13**.



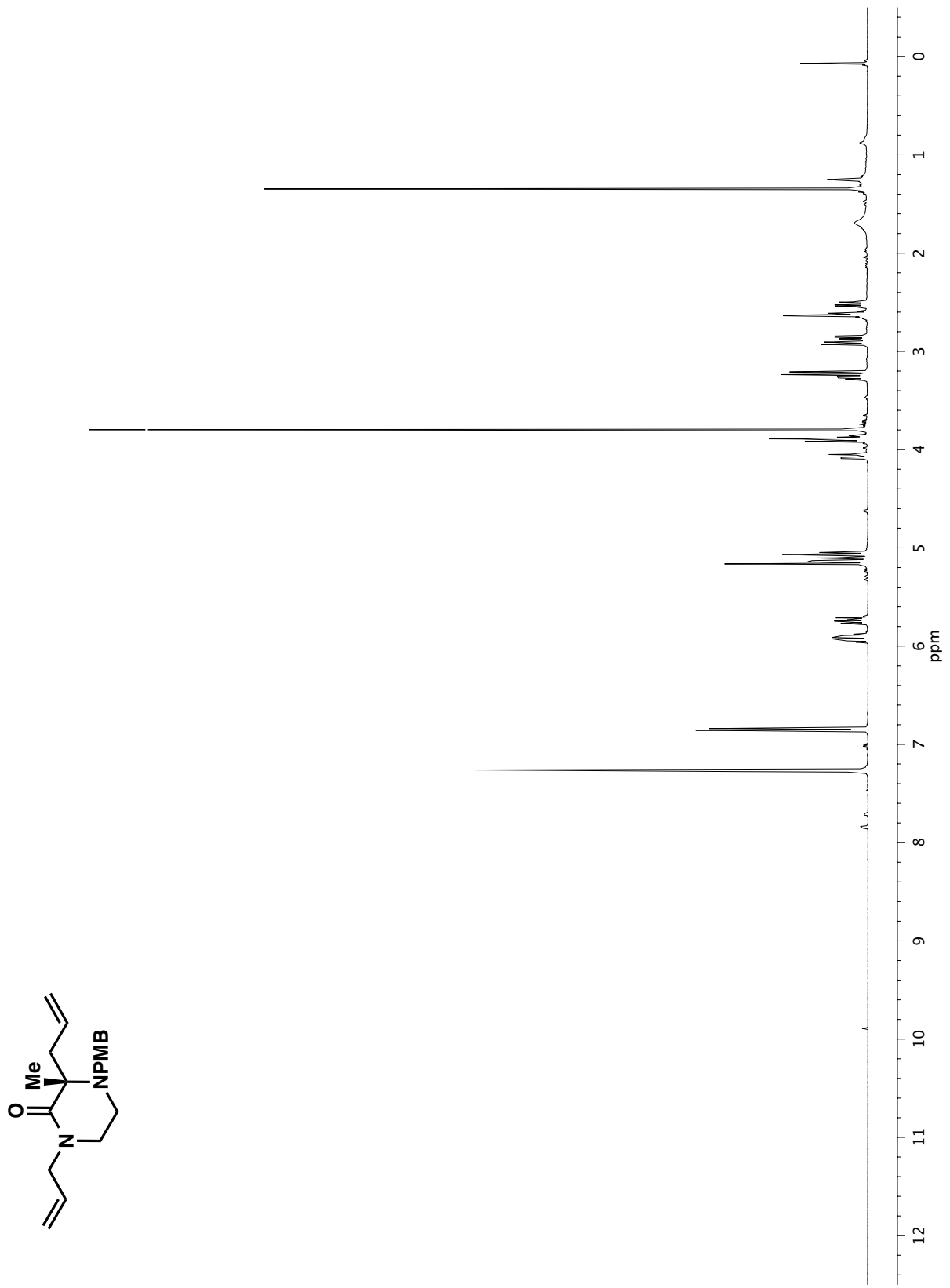
^{13}C NMR (126 MHz, $CDCl_3$) of compound **13.**



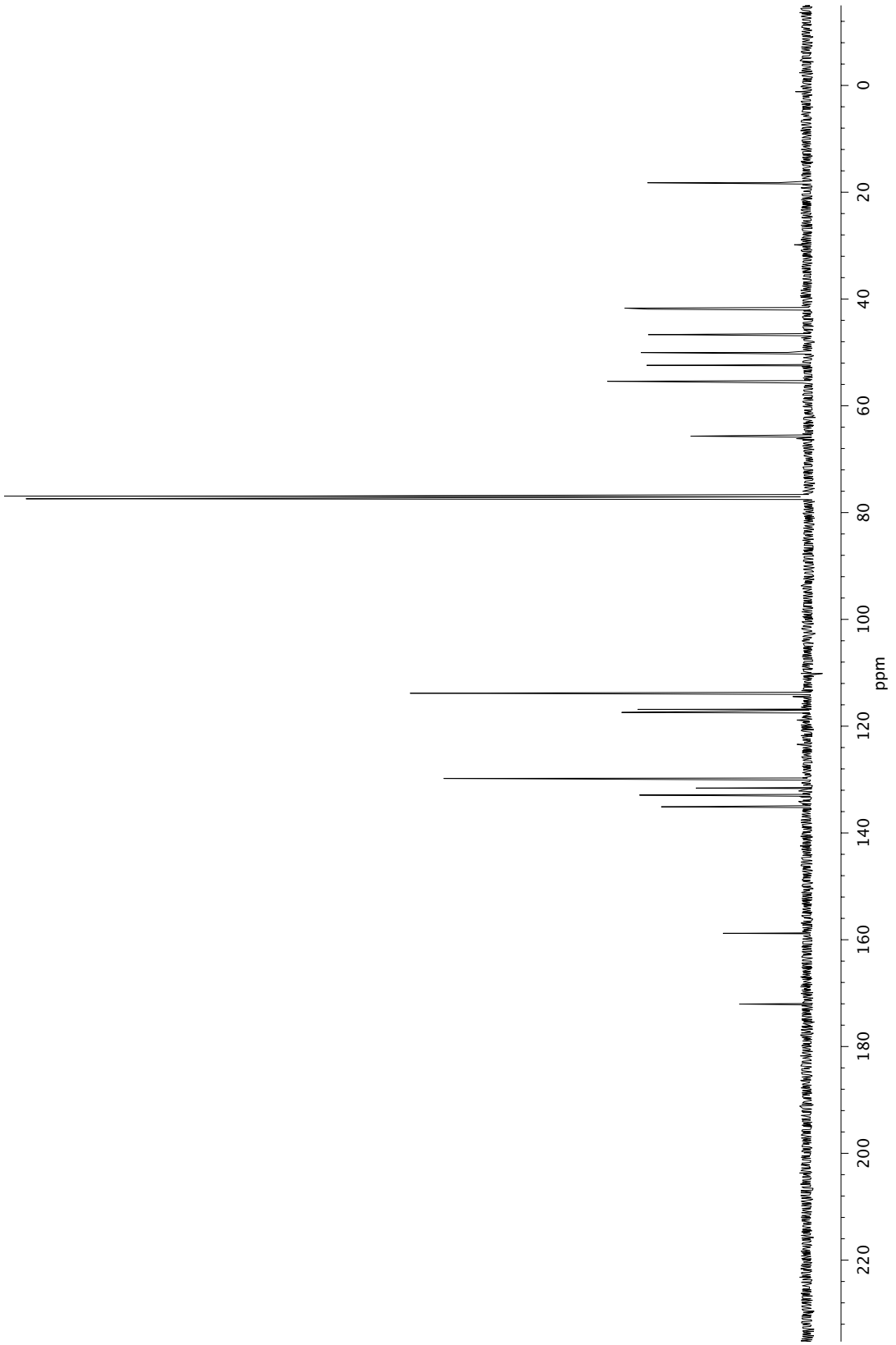
^{1}H NMR (500 MHz, $CDCl_3$) of compound **14**.



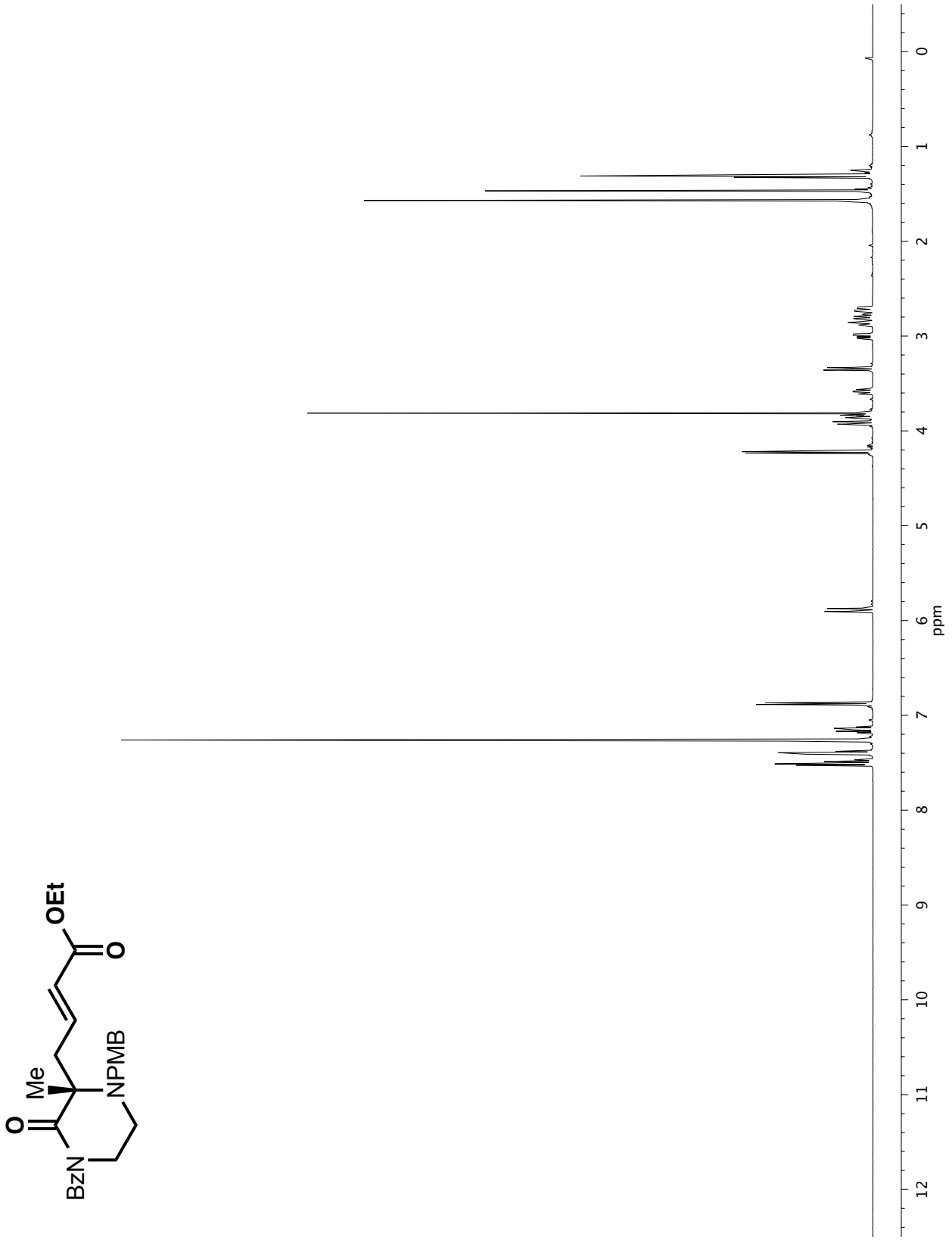
^{13}C NMR (126 MHz, $CDCl_3$) of compound **14.**



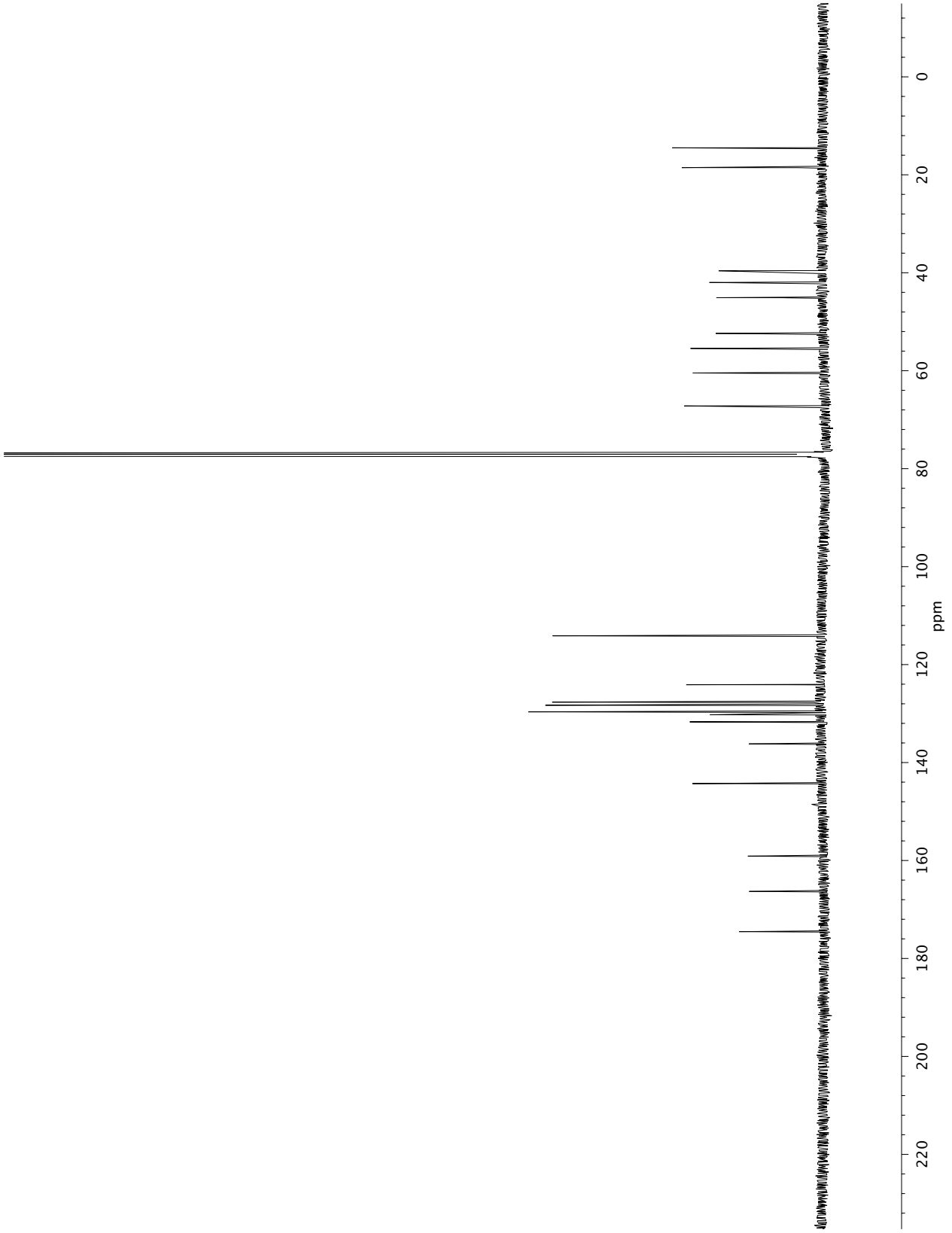
^{1}H NMR (500 MHz, $CDCl_3$) of compound **15**.



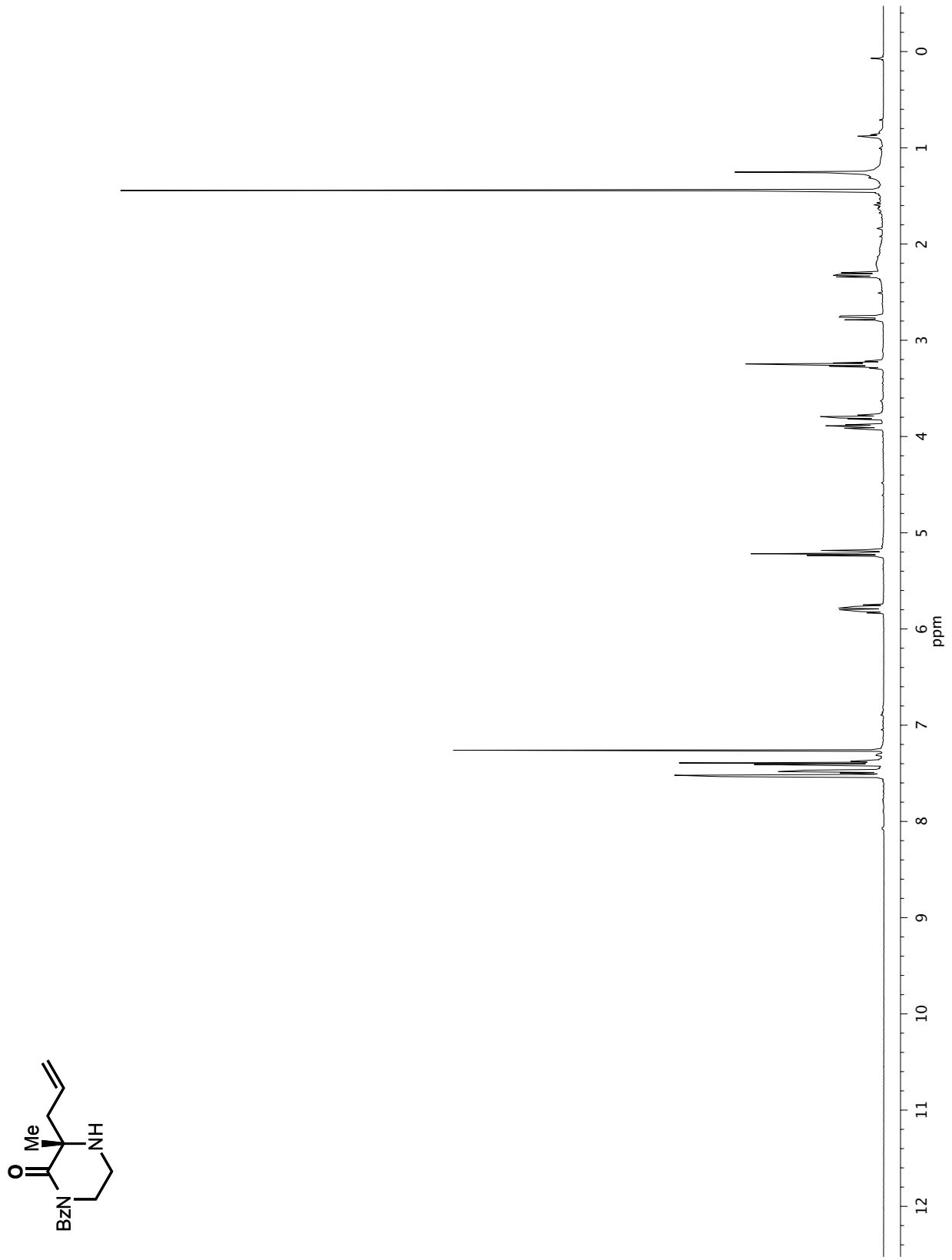
^{13}C NMR (126 MHz, $CDCl_3$) of compound **15.**



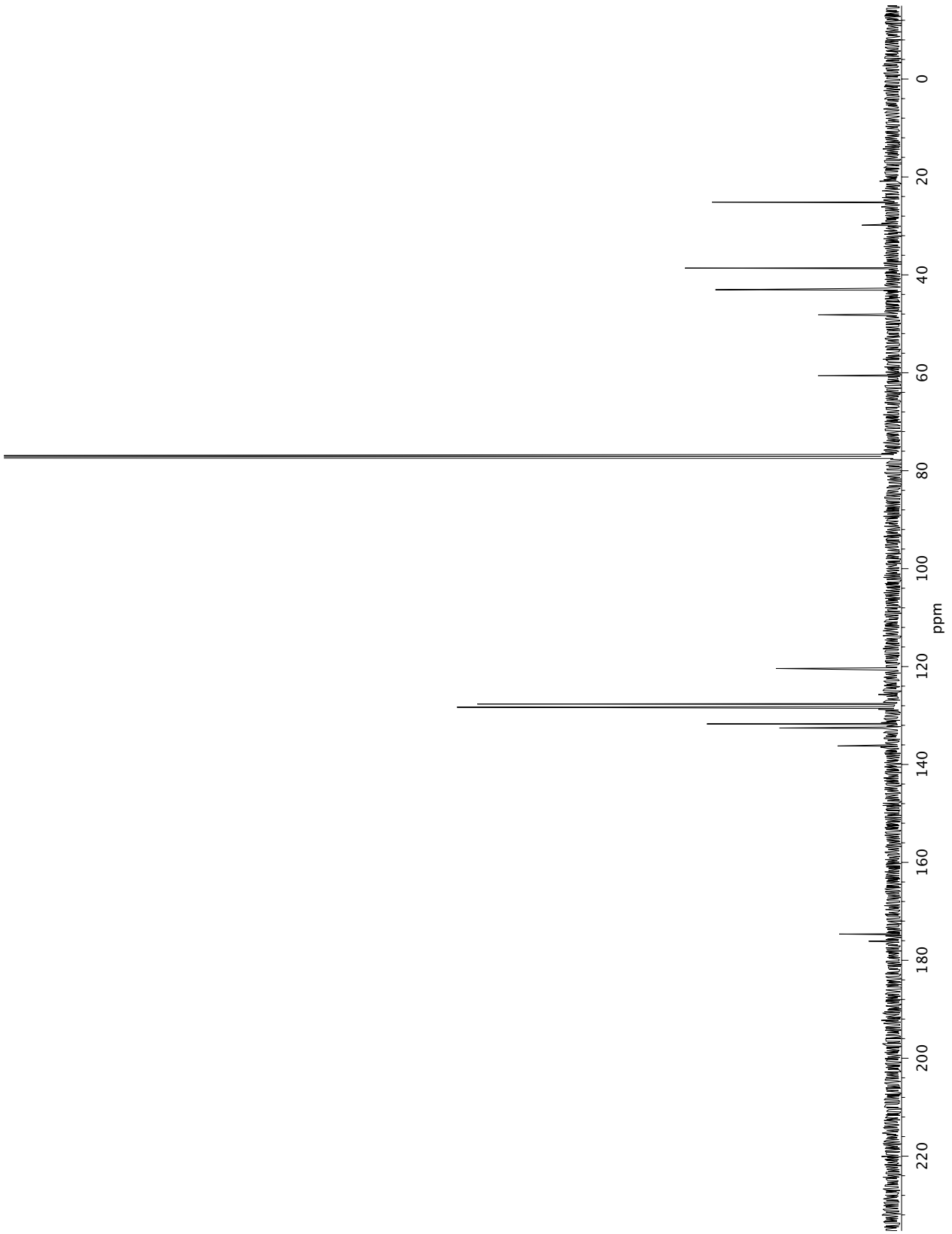
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16**.



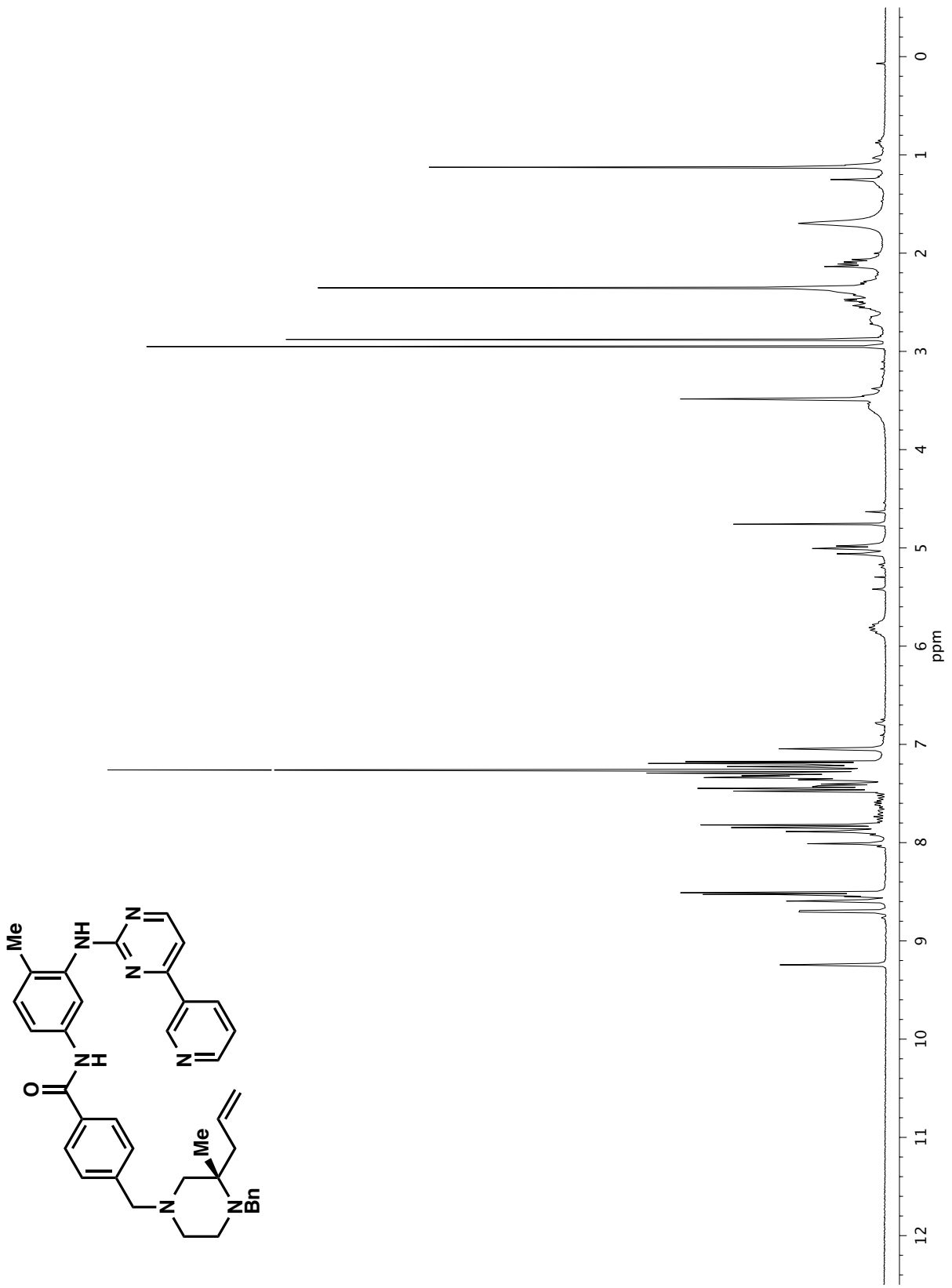
^{13}C NMR (126 MHz, $CDCl_3$) of compound **16.**



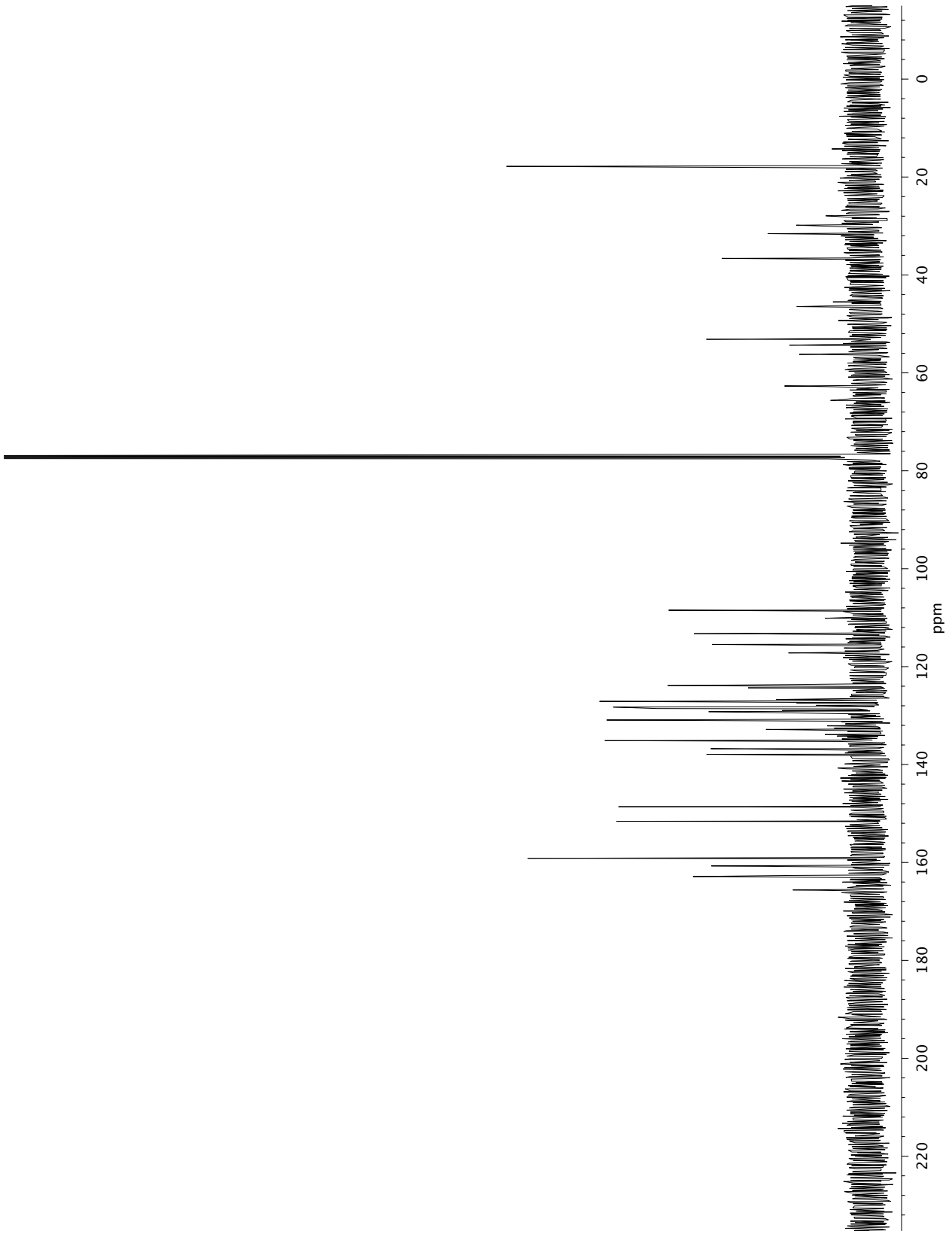
^{1}H NMR (500 MHz, $CDCl_3$) of compound **17.**



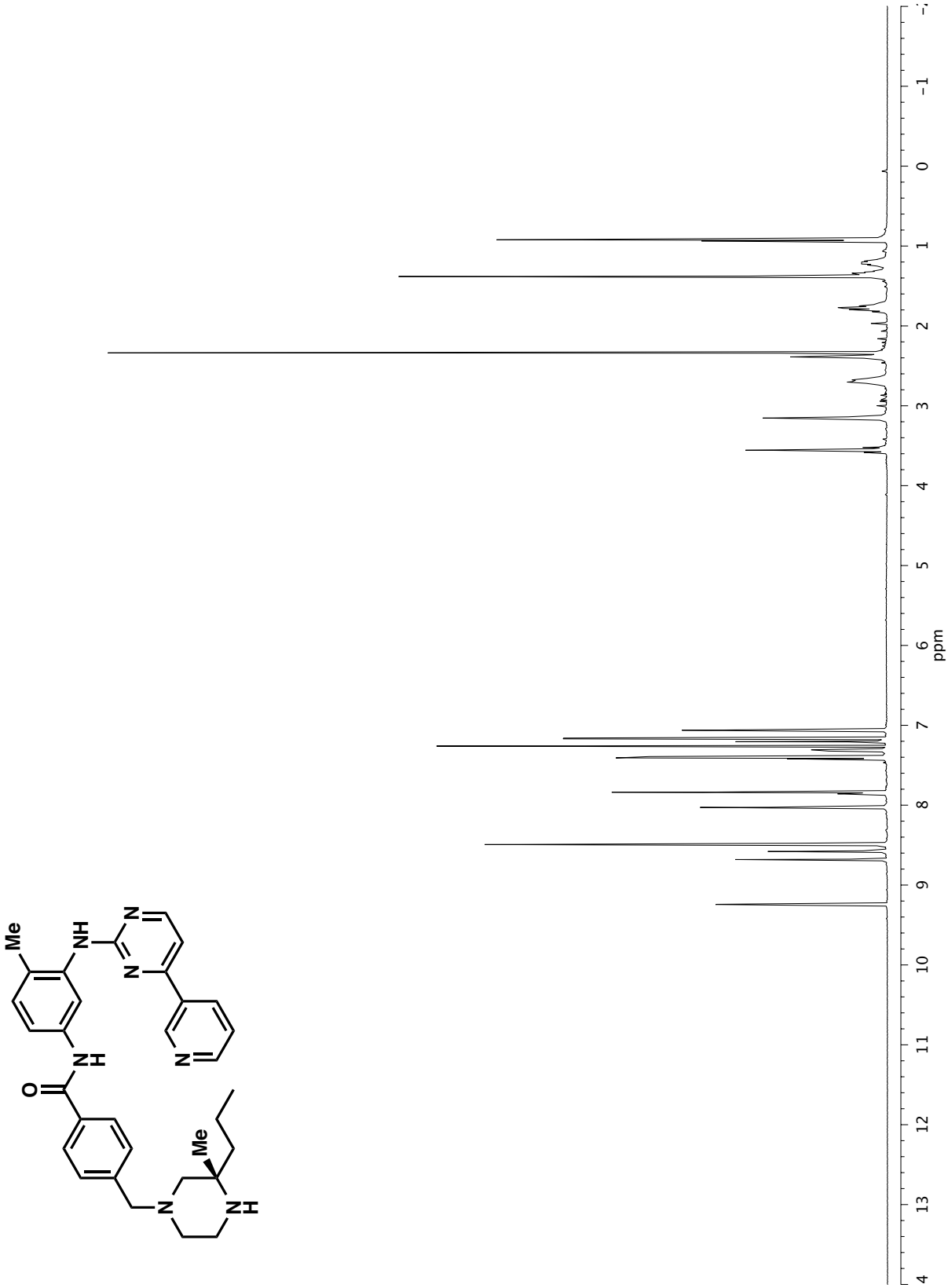
^{13}C NMR (126 MHz, $CDCl_3$) of compound **17.**



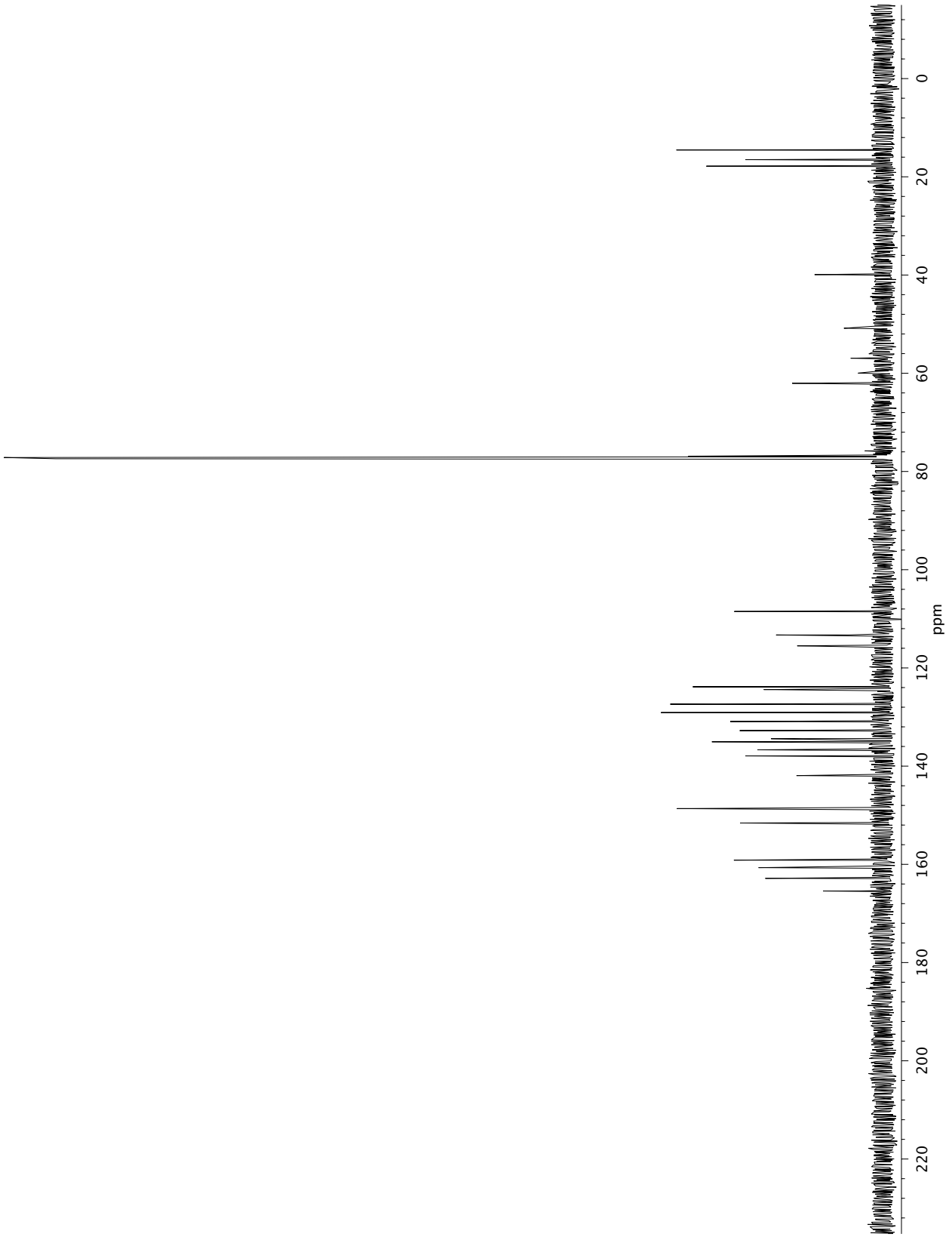
^{1}H NMR (500 MHz, $CDCl_3$) of compound **18**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **18.**



^{1}H NMR (500 MHz, $CDCl_3$) of compound **20**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **20.**