Development of (Trimethylsilyl)Ethyl Ester Protected Enolates and Applications in Palladium–Catalyzed Enantioselective Allylic Alkylation: Intermolecular Cross-Coupling of Functionalized Electrophiles

Corey M. Reeves, Douglas C. Behenna and Brian M. Stoltz*

The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

stoltz@caltech.edu

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Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[1] Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 300 MHz and 500 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or C_6HD_5 (δ 7.16 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm) or C_6HD_5 (δ 128.06 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, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer at 282 MHz, and are reported relative to the external standard F_3CCO_2H (δ –76.53 ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR 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). Analytical HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak (AD-H or AS) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral GC analysis was performed with an Agilent 6850 GC

[1] Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518.

utilizing a GTA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

Reagents were purchased from Sigma-Aldrich, Gelest, Strem, or Alfa Aesar and used as received unless otherwise stated. 2-(trimethylsilyl)ethyl chloroformate (**2**) was prepared according to a known procedure.[2] Allyl carbonates **5** and **7** were prepared from methyl chloroformate and the corresponding allyl alcohols by adaptation of a known procedure.[3] β-Ketoesters **3a**–**3h** were prepared by adaptation of procedures by Stoltz and co-workers.[4,5] Data reported herein is for new compounds only.

List of Abbreviations: ee – enantiomeric excess, dr – diastereomeric ratio, HPLC – high-performance liquid chromatography, SFC – supercritical fluid chromatography, GC – gas chromatograph, TBAT – tetrabutylammonium triphenyldifluorosilicate, TLC – thin-layer chromatography, THF – tetrahydrofuran, IPA – isopropanol, dba – dibenzylideneacetone, EtOAc – ethyl acetate, LiHMDS – lithium hexamethyldisilazide, Selectfluor – 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), DCM – dichloromethane.

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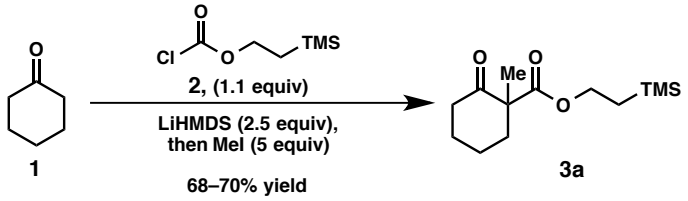
[2] Igarashi, J.; Kobayashi, Y. *Tetrahedron Lett*. **2005**, *46*, 6381.
[3] Dai, Y.; Wu, F.; Zang, Z.; You, H.; Gong, H. *Chem.–Eur. J*. **2012**, *18*, 808.
[4] Hong, A. Y.; Stoltz, B. M. *Angew. Chem., Int. Ed*. **2012**, *51*, 9674.
[5] Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. — Eur. J*. **2011**, *17*, 14199.

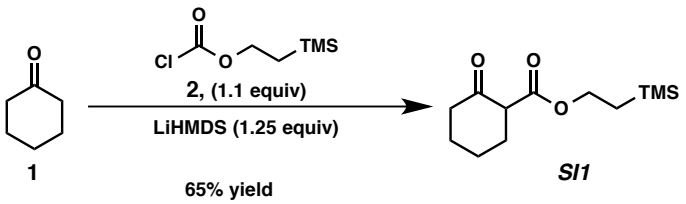
General Procedure for TMSE β-Ketoester Substrate Synthesis



2-(Trimethylsilyl)ethyl 1-methyl-2-oxocyclohexane-1-carboxylate (3a). A flame-dried 1L round bottom flask was charged with 28.02 g (152.83 mmol, 2.5 equiv) of LiHMDS and a magnetic stirring bar in a nitrogen filled glove box. The flask was sealed, removed from the glovebox, fitted with a N_2 line, and suspended in a dry ice/acetone bath. 300 mL of THF was added slowly to the flask and allowed to stir until the LiHMDS had completely dissolved. 6.00 g (61.13 mmol, 1.0 equiv) of cyclohexanone **1** in 130 mL of THF was added via cannula over 30 min, and the flask was removed from the cooling bath and allowed to warm to 23 °C while continuing to stir. After 30 min, the flask was suspended in a dry ice/acetone bath and 12.15 g (67.24 mmol, 1.1 equiv) of chloroformate **2** in 130 mL of THF was added over 30 min via cannula. This mixture was allowed to warm to 23 °C and stirred for 6 h. The flask was then suspended in a water/ice bath and 21.69 g (152.83 mmol, 2.5 equiv) of methyl iodide was added dropwise. This mixture was allowed to warm to 23 °C and stirred for 6 h, at which time an additional 21.69 g (152.83 mmol, 2.5 equiv) of methyl iodide was added dropwise. The mixture was then stirred at 23 °C until full consumption of starting material and acylated intermediate was observed by TLC analysis. 300 mL of saturated aqueous NH_4Cl was then added slowly to the mixture and stirring continued for 2 h. The mixture was then extracted with EtOAc (100 mL x 3), the collected organic fractions washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, hexanes to 3% EtOAc in hexanes) to give 11.05 g (43.08 mmol) of ketoester **3a** as a pale yellow oil. 70.1% yield. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29–4.12 (m, 2H), 2.57–2.37 (m, 3H), 2.05–1.95 (m, 1H), 1.76–1.57 (m, 3H), 1.48–1.37 (m, 1H), 1.26 (s, 3H), 1.01–0.92 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.3, 173.2, 63.6, 57.1, 40.7, 38.2, 27.5, 22.6, 21.2, 17.3, -1.6; IR (Neat Film, NaCl) 3438, 2952, 2897, 2866, 1717, 1452, 1378,

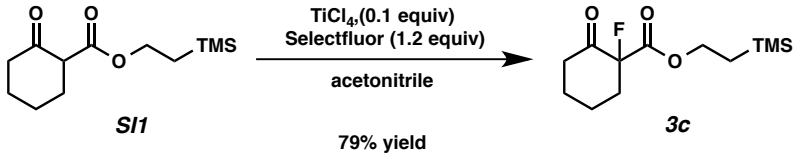
1336, 1251, 1215, 1121, 1084, 1061, 1041, 938, 861, 834, 763 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{25}O_3Si$ $[M + H]^+$: 257.1567; found 257.1556.

Procedures for the Syntheses of TMSE β-Ketoester Intermediate SI1 and Ketoester 3c



2-(Trimethylsilyl)ethyl 1-methyl-2-oxocyclohexane-1-carboxylate (SI1). A flame-dried 500 mL round bottom flask was charged with 4.67 g (25.47 mmol, 1.3 equiv) of LiHMDS and a magnetic stirring bar in a nitrogen filled glove box. The flask was sealed, removed from the glovebox, fitted with a N_2 line, and suspended in a dry ice/acetone bath. 100 mL of THF was added slowly to the flask and allowed to stir until the LiHMDS had been completely dissolved. 2.00 g (20.38 mmol, 1.0 equiv) of cyclohexanone **1** in 50 mL of THF was added via cannula over 30 min, and the flask was removed from the cooling bath and allowed to warm to 23 °C while continuing to stir. After 30 min, the flask was suspended in a dry ice/acetone bath and 4.10 g (22.42 mmol, 1.1 equiv) of chloroformate **2** in 50 mL of THF was added over 30 min via cannula. This mixture was allowed to warm to 23 °C and stirred until full consumption of starting material was observed (ca. 6 h). 100 mL of saturated aqueous NH_4Cl was then added slowly and the mixture stirred for 20 min before being extraced with EtOAc (30 mL x 3). The collected organic fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, hexanes to 2% EtOAc in hexanes), to give 3.20 g (43.08 mmol) of ketoester **SI1** as a colorless oil. 64.6% yield. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.29 (s, 1H), 4.27–4.21 (m, 2H), 2.23 (dtt, *J* = 24.7, 6.3, 1.6 Hz, 4H), 1.76–1.51 (m, 4H), 1.17–0.86 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 171.9, 97.8, 62.4, 29.1, 22.5, 22.4, 21.9, 17.3, -1.5; IR (Neat Film, NaCl) 2952, 2899, 2860, 1742, 1718, 1654,

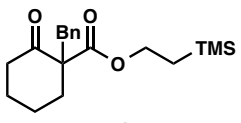
1618, 1453, 1398, 1360, 1297, 1258, 1219, 1175, 1079, 1060, 936, 859, 837 cm^{-1}; HRMS (MM: ESI-APCI–) *m/z* calc'd for $C_{12}H_{21}O_3Si$ $[M - H]^-$: 241.1265; found 241.1270.



2-(Trimethylsilyl)ethyl 1-fluoro-2-oxocyclohexane-1-carboxylate (3c). A flame dried 100 mL round bottom flask was charged with a magnetic stirring bar, 0.35 g **SI1** (1.44 mmol, 1.0 equiv), 5 mL of acetonitrile and cooled to 0 °C. To this mixture was added 0.027 g $TiCl_4$ (0.144 mmol, 0.10 equiv) dropwise over 15 minutes. To this stirring solution was added 0.64 g Selectfluor (1.73 mmol, 1.2 equiv) in 20 mL of acetonitrile over 25 minutes. The mixture was then allowed to warm to 23 °C and stirred for 8 h. A 1:1 mixture of H_2O/EtOAc (20 mL) was added, and the mixture was extracted with EtOAc (20 mL x 3), dried over $MgSO_4$ and adsorbed onto 1 g SiO_2 by concentration *in vacuo*. The crude product was isolated by flash column chromatography (SiO_2, 3% Et_2O in pentane to 12% Et_2O in pentane) to give 0.29 g of **3c** as a colorless oil. 79.0% yield. R_f = 0.2 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41–4.26 (m, 2H), 2.84–2.36 (m, 3H), 2.21–2.04 (m, 1H), 2.00–1.79 (m, 4H), 1.15–0.97 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0 (d, $^4J_{CF}$ = 19.5 Hz), 167.0 (d, $^2J_{CF}$ = 24.6 Hz), 96.4 (d, $^1J_{CF}$ = 197.0 Hz), 65.0, 39.7, 36.0 (d, $^3J_{CF}$ = 21.7 Hz), 26.6 , 21.0 (d, $^5J_{CF}$ = 6.0 Hz), 17.3 , -1.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ –173.70; IR (Neat Film, NaCl) 2953, 1732, 1452, 1287, 1251, 1223, 1157, 1093, 1051, 860, 838 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{21}FO_3SiNa$ $[M + Na]^+$: 283.1136; found 283.1145.

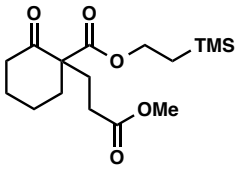
Spectroscopic Data for TMSE β-Ketoester Substrates

2-(Trimethylsilyl)ethyl 1-benzyl-2-oxocyclohexane-1-carboxylate (3b)



Ketoester **3b** was prepared by the general procedure and was isolated by flash column chromatography (SiO_2, hexanes to 5% EtOAc in hexanes) as a colorless oil. 79.4% yield. R_f = 0.3 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.04 (m, 5H), 4.16 (td, *J* = 9.8, 7.1 Hz, 2H), 3.13 (dd, *J* = 125.3, 13.7 Hz, 2H), 2.60–2.35 (m, 2H), 2.05 (ddd, *J* = 12.4, 6.1, 3.0 Hz, 1H), 1.83–1.59 (m, 4H), 1.57–1.40 (m, 1H), 0.92 (ddd, *J* = 8.9, 7.2, 1.0 Hz, 2H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 172.8, 138.3, 132.0, 129.5, 128.2, 65.2, 63.8, 42.9, 42.0, 37.5, 29.2, 24.1, 18.8, 0.0; IR (Neat Film, NaCl) 3029, 2952, 2856, 1713, 1496, 1453, 1439, 1250, 1221, 1177, 1132, 1086, 1053, 988, 932, 860, 838, 765, 744 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{29}O_3Si$ $[M + H]^+$: 333.1880; found 333.1863.

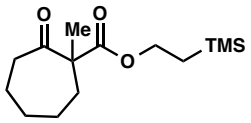
2-(Trimethylsilyl)ethyl 1-(3-methoxy-3-oxopropyl)-2-oxocyclohexane-1-carboxylate (3d)



3d

Ketoester **3d** was prepared according to the general procedure, using methyl acrylate in place of methyl iodide, and isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 81.2% yield. R_f = 0.3 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28–4.08 (m, 2H), 3.62 (s, 3H), 2.41 (dddd, *J* = 14.6, 12.9, 6.5, 2.7 Hz, 4H), 2.27–2.06 (m, 2H), 2.02–1.92 (m, 1H), 1.92–1.84 (m, 1H), 1.76–1.51 (m, 3H), 1.40 (ddd, *J* = 13.5, 12.1, 4.2 Hz, 1H), 1.03–0.91 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 173.5, 171.8, 63.9, 60.0, 51.6, 41.0, 36.3, 29.7, 29.4, 27.5, 22.5, 17.4, -1.6; IR (Neat Film, NaCl) 3432, 2952, 2899, 2866, 1740, 1713, 1437, 1377, 1340, 1308, 1250, 1175, 1137, 1093, 1075, 1062, 1040, 943, 861, 838, 763, 695 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{28}O_5SiNa$ $[M + Na]^+$: 351.1598; found 351.1602.

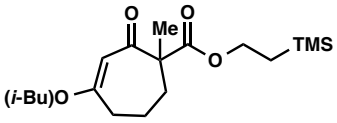
2-(Trimethylsilyl)ethyl 1-methyl-2-oxocycloheptane-1-carboxylate (3e)



3e

Ketoester **3e** was prepared by the general procedure and purified by flash column chromatography (SiO_2, hexanes to 5% EtOAc in hexanes) as a colorless oil. 78% yield. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25–4.14 (m, 2H), 2.78–2.68 (m, 1H), 2.49 (ddd, *J* = 12.2, 8.6, 2.5 Hz, 1H), 2.19–2.10 (m, 1H), 1.88–1.71 (m, 3H), 1.71–1.48 (m, 3H), 1.43–1.34 (m, 1H), 1.33 (s, 3H), 1.06–0.94 (m, 2H), 0.03 (s, 9H);^{13}C NMR (126 MHz, $CDCl_3$) δ 210.5, 173.7, 63.6, 58.8, 42.0, 35.4, 30.1, 25.8, 24.7, 21.5, 17.3, -1.6; IR (Neat Film, NaCl) 2949, 2861, 1736, 1710, 1458, 1378, 1250, 1232, 1152, 1105, 1062, 942, 860, 838 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{26}O_3Si$ [M + Na]$^+$: 293.1543; found 293.1543.

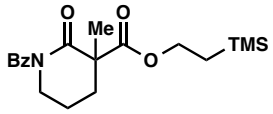
2-(Trimethylsilyl)ethyl 4-isobutyl-1-methyl-2-oxocyclohept-3-ene-1-carboxylate (3f)



3f

Vinylogous ester **3f** was prepared by the general procedure, starting from 3-isobutoxycyclohept-2-en-1-one, and purified by flash column chromatography (SiO_2, hexanes to 10% EtOAc in hexanes) as a colorless oil. 85% yield. R_f = 0.3 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.66–5.53 (m, 1H), 4.32–4.07 (m, 2H), 3.16–3.00 (m, 2H), 2.57 (dddd, *J* = 17.7, 10.1, 3.9, 1.2 Hz, 1H), 2.50–2.37 (m, 1H), 2.20 (ddd, *J* = 17.7, 7.0, 3.6 Hz, 1H), 1.77–1.67 (m, 2H), 1.66 (s, 3H), 1.59–1.41 (m, 2H), 0.88 (ddd, *J* = 10.0, 7.0, 2.1 Hz, 2H), 0.71 (dd, *J* = 6.7, 4.2 Hz, 6H), -0.13 (s, 9H); ^{13}C NMR (126 MHz, C_6D_6) δ 197.1, 173.9, 171.7, 105.6, 74.0, 62.9, 58.9, 33.9, 33.7, 27.6, 24.1, 18.7, 18.7, 17.0, -2.1; IR (Neat Film, NaCl) 2951, 1684, 1452, 1386, 1327, 1281, 1251, 1139, 1053, 859, 839, 718, 693, 658 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{28}H_{33}O_3Si$ [M + H]$^+$: 341.2143; found 341.2139.

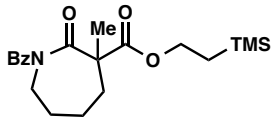
2-(Trimethylsilyl)ethyl 1-benzoyl-3-methyl-2-oxopiperidine-3-carboxylate (3g)



3g

Amide ester **3g** was prepared by the general procedure, starting from *N*-benzoyl-2-piperidone, and purified by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 25% EtOAc in hexanes) as a colorless oil. 89% yield. R_f = 0.3 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H), 7.47 (ddt, *J* = 8.0, 6.9, 1.3 Hz, 1H), 7.41–7.36 (m, 2H), 4.38–4.24 (m, 2H), 3.91–3.82 (m, 1H), 3.78 (dtd, *J* = 12.9, 5.2, 1.4 Hz, 1H), 2.47 (dddd, *J* = 13.8, 5.7, 4.3, 1.4 Hz, 1H), 2.06–1.91 (m, 2H), 1.85–1.74 (m, 1H), 1.46 (s, 3H), 1.14–1.05 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 173.1, 173.0, 135.9, 131.6, 129.0 128.0, 64.4, 52.9, 46.8, 33.7, 22.4, 20.2, 17.5, -1.5; IR (Neat Film, NaCl) 3062, 2953, 2896, 1726, 1703, 1683, 1449, 1389, 1277, 1251, 1192, 1140, 1062, 932, 859, 838, 723, 694 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{27}NO_4SiNa$ $[M + Na]^+$: 384.1602; found 384.1611.

2-(Trimethylsilyl)ethyl 1-benzoyl-3-methyl-2-oxoazepane-3-carboxylate (3h)

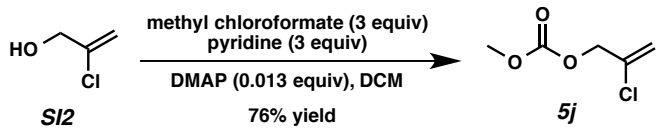


3h

Amide ester **3h** was prepared by the general procedure, starting from 1-benzoylazepan-2-one, and purified by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 25% EtOAc in hexanes) as a colorless oil. 77% yield. R_f = 0.3 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72–7.68 (m, 2H), 7.50–7.45 (m, 1H), 7.39 (ddt, *J* = 8.2, 6.6, 1.1 Hz, 2H), 4.47–4.39 (m, 1H), 4.38–4.31 (m, 2H), 3.15 (ddd, *J* = 15.7, 11.2, 1.2 Hz, 1H), 2.22 (dtd, *J* = 14.8, 3.6, 1.8 Hz, 1H), 2.01–1.90 (m, 2H), 1.89–1.77 (m, 1H), 1.61 (dddt, *J* = 20.7, 12.0, 5.0, 3.2 Hz, 3H), 1.44 (s, 3H), 1.14–1.06 (m, 2H), 0.08 (s, 9H); ^{13}C

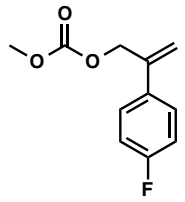
NMR (126 MHz, $CDCl_3$) δ 175.6, 174.9, 173.1, 136.4, 131.5, 128.1, 127.9, 64.3, 55.0, 44.0, 34.4, 27.9, 26.9, 25.0, 17.5, -1.5; IR (Neat Film, NaCl) 2956, 1729, 1661, 1614, 1455, 1383, 1249, 1169, 1115, 860, 838 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{29}NO_4SiNa$ $[M + Na]^+$: 398.1758; found 398.1775.

General Procedure for Allyl Carbonate Substrate Syntheses



2-Chloroallyl methyl carbonate (5j). To a flame-dried 50 mL round bottom flask charged with a magnetic stirring bar, 1.00 g 2-chloroallyl alcohol (**SI2**) (10.8 mmol, 1.0 equiv), 2.56 g of pyridine (32.4 mmol, 3.0 equiv), 0.016 g of dimethylaminopyridine (0.14 mmol, 0.013 equiv) and 22 mL of DCM at 0 °C, was added 3.06 g of methyl chloroformate (32.43 mmol, 3 equiv), dropwise over 10 min. The solution was allowed to warm to 23 °C and stirred for 12 h. The mixture was then diluted with 40 mL of DCM, washed consecutively with 50 mL H_2O and 50 mL brine before being dried over $MgSO_4$ and directly subjected to flash column chromatography (SiO_2, pentane to 5% Et_2O in pentane). 1.23 g of 2-Chloroallyl methyl carbonate was isolated as a colorless oil. 75.6% yield. R_f = 0.6 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (dt, *J* = 2.0, 1.2 Hz, 1H), 5.41 (dt, *J* = 1.8, 0.9 Hz, 1H), 4.68–4.67 (m, 2H), 3.80 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 135.2, 115.2, 69.0, 55.1; IR (Neat Film, NaCl) 3008, 2959, 2255, 1752, 1639, 1444, 1383, 1358, 1265, 1182, 1116, 974, 908, 790, 745 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_5H_8ClO_3$ $[M + H]^+$: 151.0156; found 151.0150.

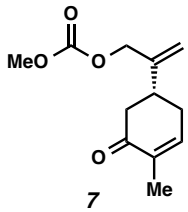
Spectroscopic Data for Allyl Carbonate Substrates



5l

2-(4-Fluorophenyl)allyl methyl carbonate (5l) was prepared by the general procedure from 2-(4-fluorophenyl)allyl alcohol and isolated as a colorless oil by flash column chromatography (SiO_2, pentane to 5% Et_2O in pentane). 87% yield. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.36 (m, 2H), 7.09–6.99 (m, 2H), 5.51 (s, 1H), 5.39 (tt, J = 1.2, 0.5 Hz, 1H), 5.00 (dd, J = 1.3, 0.6 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.65 (d, $^1J_{CF}$ = 247.0 Hz), 155.54, 141.1, 133.85, 127.74 (d, $^3J_{CF}$ = 7.8 Hz), 115.85 (d, $^4J_{CF}$ = 1.4 Hz), 115.41 (d, $^2J_{CF}$ = 21.9 Hz), 69.09 , 54.89; ^{19}F NMR (282 MHz, $CDCl_3$) δ –126.95; IR (Neat Film, NaCl) 3007, 2959, 1893, 1750, 1634, 1603, 1511, 1447, 1372, 1260, 1164, 1102, 969, 918, 839, 791, 742 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{12}FO_3$ $[M + H]^+$: 211.0765; found 211.0772.

(*R*)-Methyl (2-(4-methyl-5-oxocyclohex-3-en-1-yl)allyl) carbonate (7)



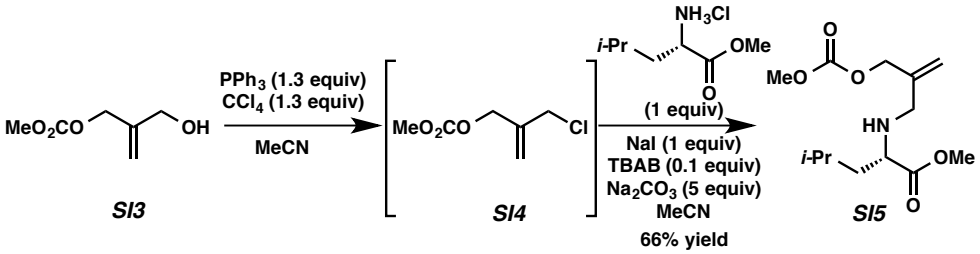
7

Enone carbonate **7** was prepared by the general method from known allylic alcohol (*R*)-5-(3-hydroxyprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (i.e. (*R*)-10-hydroxy carvone)[6] and isolated as a colorless oil by flash column chromatography (SiO_2, 5% EtOAc in henxanes to 20% EtOAc in hexanes). 91% yield. R_f = 0.2 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (ddd, J = 5.9, 2.7, 1.4 Hz, 1H), 5.22 (dt, J = 1.3, 0.7 Hz, 1H), 5.07 (dd, J = 1.4, 0.7 Hz, 1H), 4.64 (ddt, J = 3.8, 1.2, 0.5 Hz, 2H), 3.79 (s, 3H),

[6] Xuan, M.; Paterson, I.; Dalby, S. M. *Org. Lett.* **2012**, *14*, 5492.

2.97–2.74 (m, 1H), 2.63 (ddd, J = 16.1, 3.8, 1.6 Hz, 1H), 2.52 (dddt, J = 18.2, 6.0, 4.5, 1.5 Hz, 1H), 2.39 (dd, J = 16.1, 13.2 Hz, 1H), 2.31 (ddt, J = 18.2, 10.8, 2.5 Hz, 1H), 1.78 (dt, J = 2.6, 1.3 Hz, 3H);^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 155.5, 144.7, 144.0, 135.6, 114.3, 69.1, 54.9, 42.9, 38.2, 31.3, 15.7; IR (Neat Film, NaCl) 2958, 2928, 2893, 1750, 1671, 1444, 1364, 1266, 1107, 984, 954, 913, 791 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{17}O_4$ [M + H]$^+$: 225.1121; found 225.1118.

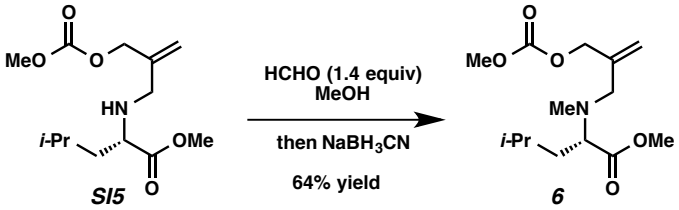
Procedure for the Synthesis Allyl Carbonate 6



Methyl *N*-(2-(((methoxycarbonyl)oxy)methyl)allyl)-*L*-leucinate (SI5). Known hydroxy carbonate **SI3**[7] was prepared by the general method. Following the procedure of Altmann and co-workers,[8] 0.77 g of **SI3** (5.27 mmol, 1.0 equiv) was added to flame-dried round bottom flask charged with a magnetic stirring bar and 0.66 mL of acetonitrile. The solution was cooled to 0 °C and 1.80 g of triphenylphosphine (6.83 mmol, 1.3 equiv) and 0.66 mL of carbontetrachloride (6.85 mmol, 1.3 equiv) were added sequentially. The resulting slurry was allowed to warm to 23 °C and stirred for 2 h before being subjected directly to flash column chromatography. The resulting crude oil, **SI4** was determined to be ca. 95% pure by ^{1}H NMR analysis and used without further purification (yield not determined). Following a known procedure,[9] 0.47 g of crude allylic chloride intermediate **SI4** (2.855 mmol, 1.5 equiv) was combined with 0.28 g of NaI (1.90 mmol, 1.0 equiv), 0.346 g of (*L*)-leucine methyl ester hydrochloride (1.90 mmol, 1.0 equiv), 0.061 g of tetrabutylammonium bromide (0.19 mmol, 0.1 equiv), 1.01 g Na_2CO_3 (9.52 mmol, 5 equiv) and 20 mL acetonitrile in a 50 mL round bottom flask equipped with a

[7] Flegelová, Z.; Pátek, M. *J. Org. Chem.* **1996**, *61*, 6735.
[8] Neuhaus, C. M.; Liniger, M.; Stieger, M.; Altmann, K. -H. *Angew. Chem., Int. Ed.* **2013**, *52*, 5866.
[9] Sun, C. -S.; Lin, Y. -S.; Hou, D. -R. *J. Org. Chem.* **2008**, *73*, 6877.

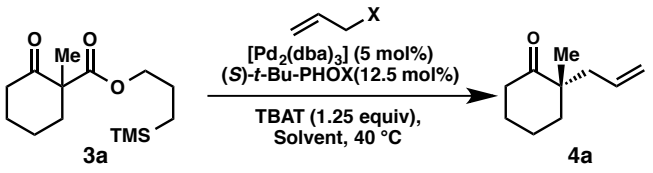
magnetic stirring bar. The flask was fitted with a reflux condenser and the mixture stirred at 82 °C for 14 h. The vessel was then cooled to 23 °C and the mixture diluted with 50 mL Et_2O, washed with H_2O (20 mL x 2), dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 15% EtOAc in hexanes) to give 0.52 g of amino ester **SI5** as a colorless oil. 66.1% yield from crude **SI4**. R_f = 0.2 (40% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23–5.08 (m, 2H), 4.66 (t, *J* = 1.0 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 3.25 (t, *J* = 7.3 Hz, 1H), 3.19 (dd, *J* = 80.0, 13.8 Hz, 1H), 1.74 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.51 (br s, 2H), 1.43 (t, *J* = 7.2 Hz, 2H), 0.89 (dd, *J* = 9.2, 6.6 Hz, 6H);^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 155.7, 141.7, 115.0, 68.9, 59.1, 54.9, 51.7, 50.4, 42.9, 24.9, 22.9, 22.2; IR (Neat Film, NaCl) 2956, 2868, 1750, 1737, 1443, 1368, 1267, 1196, 1151, 980, 943, 792 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{24}NO_5$ [M + H]$^+$: 274.1649; found 274.1659.



Methyl *N*-(2-(((methoxycarbonyl)oxy)methyl)allyl)-*N*-methyl-*L*-leucinate (6). To a 10 mL round bottom flask containing a magnetic stirring bar and a solution of 0.37 g **SI5** (1.35 mmol, 1.0 equiv) in 4 mL of methanol was added 0.056 g of formaldehyde (1.88 mmol, 1.4 equiv) as a 37% solution in H_2O. The mixture was stirred at 23 °C for 12 h at which point 0.11 g sodium cyanoborohydride was carefully added. After an additional 12 h of stirring, the mixture was diluted with H_2O (5 mL), extracted with EtOAc (5 mL x 3), dried over $MgSO_4$, concentrated *in vacuo* and subjected directly to purification by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 25% EtOAc in hexanes) to yield 0.25 g of carbonate **6** as a colorless oil. 63.8% yield. R_f = 0.5 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30–5.07 (m, 2H), 4.63 (t, *J* = 1.0 Hz, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.34 (dd, *J* = 8.3, 7.0 Hz, 1H), 3.18 (dd, *J* = 75.0, 13.8 Hz, 2H), 2.22 (s, 3H), 1.73–1.61 (m, 1H), 1.61–1.46 (m, 2H), 0.90 (dd, *J* = 17.5, 6.6 Hz, 6H);^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 155.6, 141.2, 115.4, 68.5, 63.8, 57.3, 54.7, 50.9, 38.4, 37.0,

24.7, 22.9, 21.9; IR (Neat Film, NaCl) 2955, 2870, 2803, 1751, 1658, 1444, 1385, 1368, 1269, 1193, 1157, 1126, 1072, 978, 945, 792 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{26}NO_5$ $[M + H]^+$: 288.1805; found 288.1795.

Optimization of Reaction Parameters (Table S1)



3a 4a

Entry	X	Equiv Allyl	Sovent	ee (%)[a]	Yield (%)[b]
1	Br	1.0	toluene	83	55
2	OTs	1.0	1,4-dioxane	77	43
3	OMs	1.0	1,4-dioxane	84	45
4	OAc	1.0	1,4-dioxane	82	15
5	OCO_2Allyl	1.0	1,4-dioxane	83	78
6	OCO_2Me	1.0	1,4-dioxane	84	78
7	OCO_2Me	0.75	1,4-dioxane	82	51
8	OCO_2Me	1.5	1,4-dioxane	82	74
9	OCO_2Me	2.0	1,4-dioxane	84	73
10	OCO_2Me	1.1	toluene	82	33
11	OCO_2Me	1.1	MTBE	84	65
12	OCO_2Me	1.1	THF	83	83
13	OCO_2Me	1.1	tol/hex	93	45
14[c]	OCO_2Me	1.1	THF	86	81

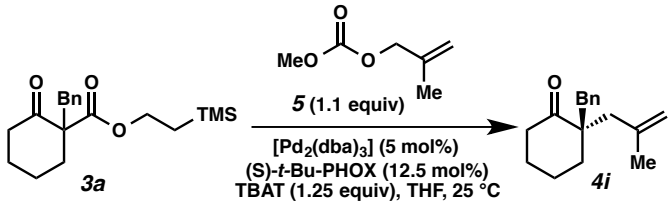
% ee determined by chiral GC analysis of the crude reaction mixture. (b) Yield determined by comparison to tridecane internal standard. (c) Reaction performed at 25 °C.

General Procedure for Optimization Experiments: Inside a nitrogen filled glovebox, an oven-dried 0.5 dram vial was charged with a magnetic stirring bar, 0.0046 g $[Pd_2(dba)_3]$ (0.005 mmol, 0.05 equiv), 0.0047 g (*S*)-*t*-Bu-PHOX (0.0125 mmol, 0.125 equiv), 0.067 g TBAT (0.125 mmol, 1.25 equiv), 0.018 g tridecane (0.10 mmol, 1.0 equiv) and 3.0 mL THF. This mixture was stirred at 25 °C for 30 min at which time 0.026 g of β-ketoester **3a** (0.10 mmol, 1.0 equiv) and 0.013 g of allyl methyl carbonate (0.11

mmol, 1.1 equiv) were added, neat. The vial was capped and stirring continued for 12 h at which time the vial was removed from the glovebox, uncapped and the magnetic stirring bar removed. The reaction mixture was diluted with hexanes (2 mL) and passed through a pipette plug (SiO_2) with 4 mL of hexanes followed by 4 mL of Et_2O. From the combined organic fractions, a sample was prepared and the mixture analyzed by GC.

General Procedure for Pd-Catalyzed Allylic Alkylation

Please note that the absolute configuration for all products **4** has been inferred by analogy to previous studies. For isolated yields, see the main text Table 2 and Figure 2. For respective GC, HPLC or SFC conditions, as well as optical rotation data, please refer to Table S2.

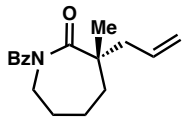


(*S*)-2-benzyl-2-(2-methylallyl)cyclohexan-1-one (**4i**). Inside a nitrogen filled glovebox, an oven-dried 20 mL scintillation vial was charged with a magnetic stirring bar, 0.011 g [$Pd_2(dba)_3$] (0.012 mmol, 0.05 equiv), 0.011 g (*S*)-*t*-Bu-PHOX (0.029 mmol, 0.125 equiv), 0.15 g TBAT (0.28 mmol, 1.25 equiv) and 7 mL THF. This mixture was stirred at 25 °C for 30 min at which time 0.075 g of β-ketoester **3a** (0.23 mmol, 1.0 equiv) and 0.033 g of allyl methyl carbonate (0.25 mmol, 1.1 equiv) were added, neat. The vial was capped and stirring continued for 16 h at which time the vial was removed from the glovebox, uncapped and magnetic stirring bar removed. The reaction mixture was concentrated *in vacuo*. The resulting crude semisolid was purified by flash column chromatography (SiO_2, hexanes to 2% EtOAc in hexanes) to give ketone **4i** as a colorless oil. 89% yield. 89% ee, $[\alpha]_D^{25}$ –20.1 (*c* 1.2, $CHCl_3$); R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2H), 7.22–7.17 (m, 1H), 7.15–7.11 (m, 2H), 4.86 (dd, *J* = 2.0, 1.4 Hz, 1H), 4.69 (dd, *J* = 2.0, 1.0 Hz, 1H), 2.93 (dd, *J* = 114.0, 13.7

Hz, 2H), 2.60–2.49 (m, 1H), 2.44–2.38 (m, 1H), 2.37 (s, 3H), 1.92–1.84 (m, 1H), 1.81–1.69 (m, 2H), 1.67 (dd, J = 1.5, 0.8 Hz, 3H), 1.64–1.56 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.8, 142.2, 137.8, 130.9, 127.9, 126.2, 114.7, 52.5, 43.2, 41.7, 39.7, 35.7, 26.7, 24.6, 20.8; IR (Neat Film, NaCl) 3026, 2935, 2863, 1700, 1448, 1123, 893, 746 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{23}O$ [M + H]$^+$: 243.1743, found 243.1745; SFC conditions: 1% MeOH, 2.5 mL/min, Chiralpak OD–H column, λ = 210 nm, t_R (min): major = 5.79, minor = 6.48.

Spectroscopic Data for Pd-Catalyzed Allylic Alkylation Products

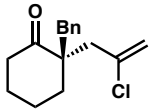
(*S*)-3-Allyl-1-benzoyl-3-methylazepan-2-one (4h)



4h

Lactam **4h** was prepared by the general procedure and isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 25% EtOAc in hexanes) as a colorless oil. 91% yield. 90% ee, $[\alpha]_D^{25}$ –35.2 (*c* 1.7, $CHCl_3$); R_f = 0.2 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H), 7.47–7.42 (m, 1H), 7.39–7.35 (m, 2H), 5.72 (dddd, J = 17.1, 10.3, 7.6, 7.1 Hz, 1H), 5.13–5.06 (m, 2H), 4.13–4.05 (m, 1H), 3.91 (ddd, J = 14.8, 8.8, 2.0 Hz, 1H), 2.40 (dddt, J = 71.6, 13.7, 7.6, 1.2 Hz, 2H), 1.91–1.78 (m, 4H), 1.78–1.67 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.5, 174.7, 137.0, 133.7, 131.0, 128.1, 127.4, 118.7, 47.7, 44.7, 42.6, 35.1, 28.0, 24.9, 23.3; IR (Neat Film, NaCl) 3072, 2830, 1676, 1448, 1279, 1244, 1224, 1148, 1117, 1096, 971, 951, 919, 790, 726, 695 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{21}NO_2$ [M + H]$^+$: 272.1645, found 272.1660; HPLC conditions: 5% IPA, 1.0 mL/min, Chiralpak OJ–H column, λ = 220 nm, t_R (min): major = 5.60, minor = 5.00.

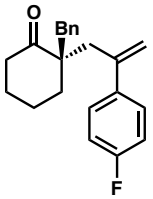
(*R*)-2-Benzyl-2-(2-chloroallyl)cyclohexan-1-one (4j)



4j

Ketone **4j** was prepared according to the general procedure and isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 72% yield. 96% ee, $[\alpha]_D^{25}$ –7.0 (*c* 1.4, $CHCl_3$); R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.16 (m, 2H), 7.20–7.08 (m, 3H), 5.30 (d, *J* = 1.3 Hz, 1H), 5.17 (t, *J* = 1.2 Hz, 1H), 2.99 (dd, *J* = 40.6, 14.1 Hz, 2H), 2.69 (dd, *J* = 56.9, 15.6 Hz, 2H), 2.66–2.34 (m, 2H), 1.97–1.63 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.5, 137.0, 130.7, 128.1, 127.7, 126.5, 116.6, 52.5, 43.9, 41.3, 39.7, 35.1, 26.5, 20.9; IR (Neat Film, NaCl) 2939, 2858, 1705, 1631, 1494, 1452, 1429, 1118, 1088, 889, 701 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{20}ClO$ $[M + H]^+$: 263.1197, found 263.1199; SFC conditions: 3% MeOH, 2.5 mL/min, Chiralpak OD-H column, λ = 210 nm, t_R (min): major = 6.09, minor = 7.04.

(*R*)-2-Benzyl-2-(2-(4-fluorophenyl)allyl)cyclohexan-1-one (4l)

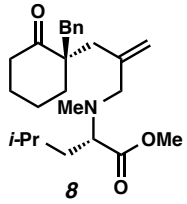


4l

Ketone **4l** was prepared according to the general procedure, and isolated by flash column chromatography (SiO_2, 1% EtOAc in hexanes to 3% EtOAc in hexanes) as a colorless oil. 91% yield. 95% ee, $[\alpha]_D^{25}$ –9.9 (*c* 2.0, $CHCl_3$); R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.12 (m, 5H), 7.11–6.85 (m, 4H), 5.26 (d, *J* = 1.3 Hz, 1H), 5.09 (d, *J* = 1.5 Hz, 1H), 2.86 (dd, *J* = 102.0, 13.7 Hz, 2H), 2.87–2.73 (m, 2H), 2.31 (tt, *J* = 6.2, 2.5 Hz, 2H), 1.83–1.50 (m 6H) ; ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.3 , 162.2 (d, $^1J_{CF}$ = 246.2 Hz), 144.5, 139.2 (d, $^4J_{CF}$ = 3.3 Hz), 137.8, 130.7, 128.2 (d, $^3J_{CF}$ = 7.9 Hz), 127.9, 126.3, 117.6, 115.0 (d, $^2J_{CF}$ = 21.3 Hz), 53.3, 41.7, 40.9, 39.7, 35.1, 26.1, 20.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ –128.24; IR (Neat Film, NaCl) 3027, 2939, 2864, 1703, 1602, 1508, 1453, 1223, 1159, 1126, 905, 841, 750 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z*

calc'd for $C_{22}H_{24}FO$ $[M + H]^+$: 323.1806, found 323.1809; SFC conditions: 10% MeOH, 2.5 mL/min, Chiralpak OJ-H column, λ = 210 nm, t_R (min): major = 8.59, minor = 10.15.

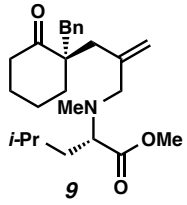
Methyl *N*-(2-(((*R*)-1-benzyl-2-oxocyclohexyl)methyl)allyl)-*N*-methyl-*L*-leucinate (8)



8

Ketone **8** was prepared by the general procedure and isolated by flash column chromatography (SiO_2, 2% EtOAc in hexanes to 5% EtOAc in hexanes) as a colorless oil. 95% yield. >25:1 dr, $[\alpha]_D^{25}$ –20.57 (*c* 1.75, $CHCl_3$); R_f = 0.5 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 7.21–7.16 (m, 1H), 7.15–7.11 (m, 2H), 5.12 (q, *J* = 1.3 Hz, 1H), 4.94–4.88 (m, 1H), 3.67 (s, 3H), 3.33 (t, *J* = 7.6 Hz, 1H), 3.05–2.90 (m, 2H), 2.93 (dd, *J* = 176.8, 13.7 Hz, 2H), 2.67–2.54 (m, 2H), 2.40–2.31 (m, 1H), 2.25 (dd, *J* = 15.1, 1.1 Hz, 1H), 2.20 (s, 3H), 1.90 (ddq, *J* = 8.0, 4.3, 1.9 Hz, 1H), 1.81–1.47 (m, 8H), 0.90 (dd, *J* = 11.9, 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.9, 173.3, 143.0, 138.1, 130.9, 127.8, 126.1, 116.5, 62.9, 61.8, 52.6, 50.8, 41.2, 39.5, 38.9, 38.4, 36.8, 36.5, 26.9, 24.8, 23.0, 22.2, 20.8; IR (Neat Film, NaCl) 2949, 2868, 1732, 1703, 1641, 1452, 1189, 1152, 1122, 1019, 910, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{37}NO_3$ $[M + H]^+$: 400.2836, found 400.2860.

Methyl *N*-(2-(((*S*)-1-benzyl-2-oxocyclohexyl)methyl)allyl)-*N*-methyl-*L*-leucinate (9)

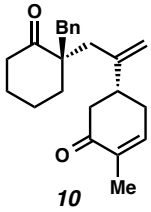


9

Ketone **9** was prepared by the general procedure, using ligand **L3** instead of **L2**, and isolated by flash column chromatography (SiO_2, 2% EtOAc in hexanes to 5% EtOAc in hexanes) as a colorless oil. 95% yield. 1:21 dr, $[\alpha]_D^{25}$ +12.94 (*c* 1.25, $CHCl_3$); R_f = 0.5 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 7.21–7.16 (m, 1H), 7.16–7.12 (m, 2H), 5.11 (d, *J* = 1.5 Hz, 1H), 4.89 (d, *J* = 1.7 Hz, 1H), 3.68 (s,

3H), 3.29 (dd, *J* = 7.7, 7.0 Hz, 1H), 3.03–2.93 (m, 2H), 2.92 (dd, *J* = 197.9, 13.7 Hz, 2H), 2.68–2.58 (m, 2H), 2.34 (dt, *J* = 13.8, 4.9 Hz, 1H), 2.27–2.21 (m, 1H), 2.19 (s, 3H), 1.91 (d, *J* = 12.8 Hz, 1H), 1.85–1.56 (m, 8H), 0.89 (dd, *J* = 12.4, 6.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.8, 173.2, 143.2, 138.2, 131.0, 127.8, 126.1, 116.5, 63.3, 61.6, 52.5, 50.8, 41.1, 39.5, 39.3, 38.2, 36.7, 36.7, 26.9, 24.9, 22.8, 22.5, 20.8; IR (Neat Film, NaCl) 3027, 2950, 2867, 1734, 1702, 1641, 1602, 1495, 1452, 1192, 1154, 1125, 1030, 909, 749, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{37}NO_3$ [M + H]$^+$: 400.2846, found 400.2855.

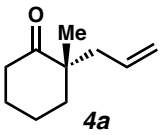
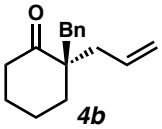
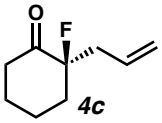
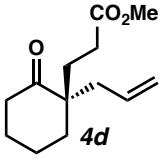
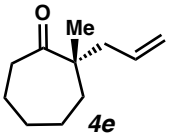
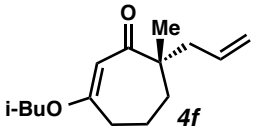
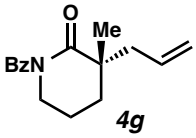
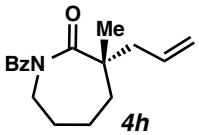
(*R*)-5-(3-((*S*)-1-Benzyl-2-oxocyclohexyl)prop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (10)



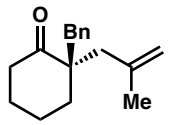
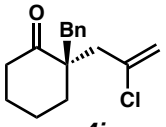
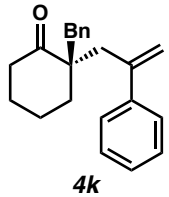
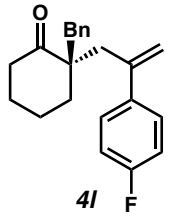
10

Ketone **10** was prepared by the general procedure, at 40 °C, and isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 15% EtOAc in hexanes) as a colorless oil. 87% combined yield (**10** and **11**). Characterization data reported for major diastereomer. 6:1 dr, $[\alpha]_D^{25}$ +49.25 (*c* 0.25, $CHCl_3$); R_f = 0.1 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.18 (m, 3H), 7.12–7.02 (m, 2H), 6.72 (dq, *J* = 4.2, 1.3 Hz, 1H), 4.97–4.91 (m, 1H), 4.82 (d, *J* = 1.2 Hz, 1H), 3.03–2.83 (m, 2H), 2.64–2.49 (m, 2H), 2.49–2.37 (m, 4H), 2.38–2.09 (m, 3H), 1.85–1.78 (m, 2H), 1.77 (dt, *J* = 2.6, 1.3 Hz, 3H), 1.76–1.61 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.7, 199.8, 147.4, 144.7, 137.3, 135.3, 130.6, 128.0, 126.5, 113.1, 52.5, 43.6, 42.2, 41.8, 39.5, 39.4, 35.6, 31.9, 26.7, 20.8, 15.7; IR (Neat Film, NaCl) 2923, 2863, 1702, 1672, 1494, 1450, 1365, 1248, 1109, 901, 750, 703 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{28}O_2Na$ [M + Na]$^+$: 359.1982, found 359.1988.

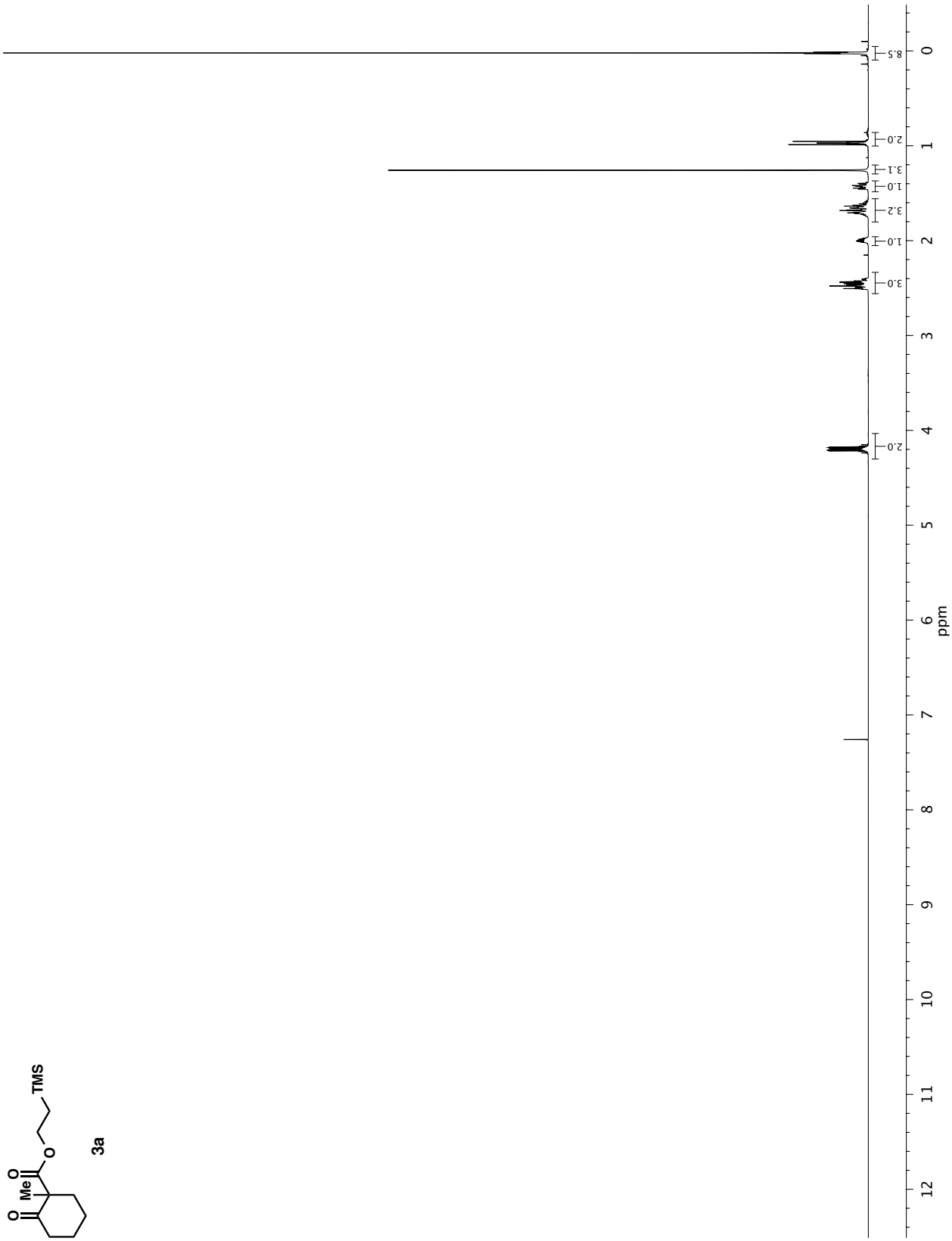
Determination of Enantiomeric Excess and Optical Rotations (Table S2)

entry	compound	analytic conditions	ee (%)	polarimetry
1	 *4a*	GC G-TA, 105 °C, isotherm t_R (min): major 7.80, minor 8.24	86	$[\alpha]_D^{25}$ −11.7 (*c* 0.6, $CHCl_3$)
2	 *4b*	SFC Chiralpak OJ-H, λ = 210 nm 3% IPA/CO_2, 2.5 mL/min, t_R (min): major 5.74, minor 4.71	88	$[\alpha]_D^{25}$ −13.6 (*c* 1.3, $CHCl_3$)
3	 *4c*	GC G-TA, 110 °C, isotherm t_R (min): major 5.039, minor 5.41	91	$[\alpha]_D^{25}$ −68.74 (*c* 1.5, $CHCl_3$)
4	 *4d*	GC G-TA, 120 °C, isotherm t_R (min): major 15.3, minor 22.18	89	$[\alpha]_D^{25}$ 10.51 (*c* 1.6, $CHCl_3$)
5	 *4e*	GC G-TA, 110 °C, isotherm t_R (min): major 6.45, minor 7.23	87	$[\alpha]_D^{25}$ −22.13 (*c* 1.4, $CHCl_3$)
6	 *4f*	HPLC Chiralcel OD-H, λ = 220 nm 1% IPA/hexanes, 1.0 mL/min t_R(min): major 6.12, minor 7.16	92	$[\alpha]_D^{25}$ −65.6 (*c* 1.0, $CHCl_3$)
7	 *4g*	SFC Chiralpak AD-H, λ = 254 nm 5% MeOH/CO_2, 2.5 mL/min, t_R (min): major 5.54, minor 6.23	96	$[\alpha]_D^{25}$ −76.5 (*c* 2.1, $CHCl_3$)
8	 *4h*	HPLC Chiralcel OJ-H, λ = 220 nm 5% IPA/hexanes, 1.0 mL/min t_R(min): major 5.60, minor 5.00	90	$[\alpha]_D^{25}$ −35.2 (*c* 1.7, $CHCl_3$)

Determination of Enantiomeric Excess and Optical Rotations (Table S2 cont.)

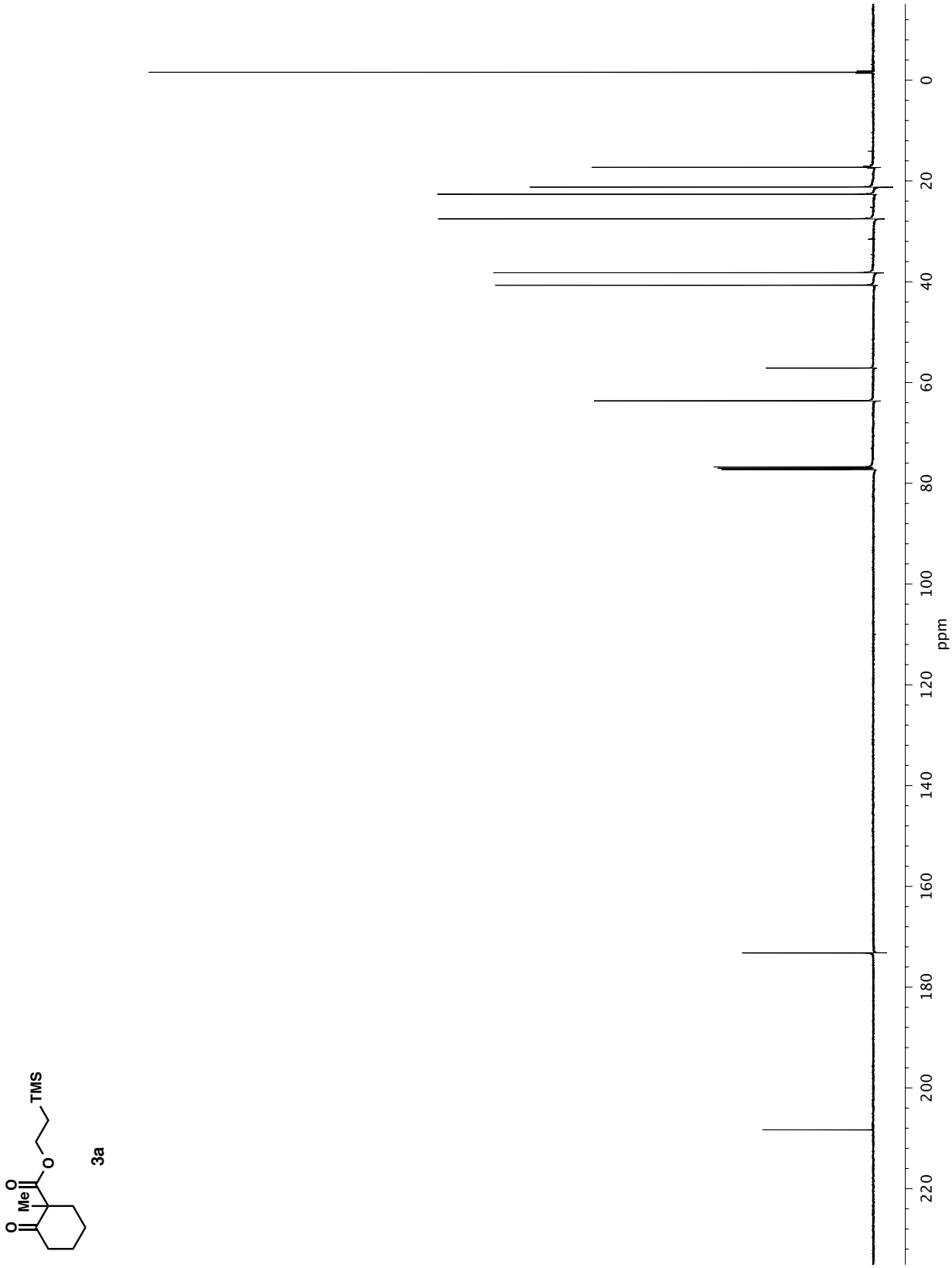
entry		analytic conditions	ee (%)	polarimetry
9	 *4i*	SFC Chiralpak OD-H, λ = 210 nm 1% MeOH/CO_2, 2.5 mL/min, t_R (min): major 5.79, minor 6.48	89	$[\alpha]_D^{25}$ −20.1 (*c* 1.2, $CHCl_3$)
10	 *4j*	SFC Chiralpak OD-H, λ = 210 nm 3% MeOH/CO_2, 2.5 mL/min t_R (min): major 6.09, minor 7.04	96	$[\alpha]_D^{25}$ −7.0 (*c* 1.4, $CHCl_3$)
11	 *4k*	SFC Chiralpak OJ-H, λ= 210 nm 4% IPA/CO_2, 4.0 mL/min t_R (min): major 7.86, minor 8.66	93	$[\alpha]_D^{25}$ −10.5 (*c* 0.8, $CHCl_3$)
12	 *4l*	SFC Chiralcel OJ-H, λ = 210 nm 10% MeOH/CO_2, 2.5 mL/min t_R (min): major 8.59, minor 10.15	95	$[\alpha]_D^{25}$ −9.9 (*c* 2.0, $CHCl_3$)

^{1}H NMR and ^{13}C NMR Spectra

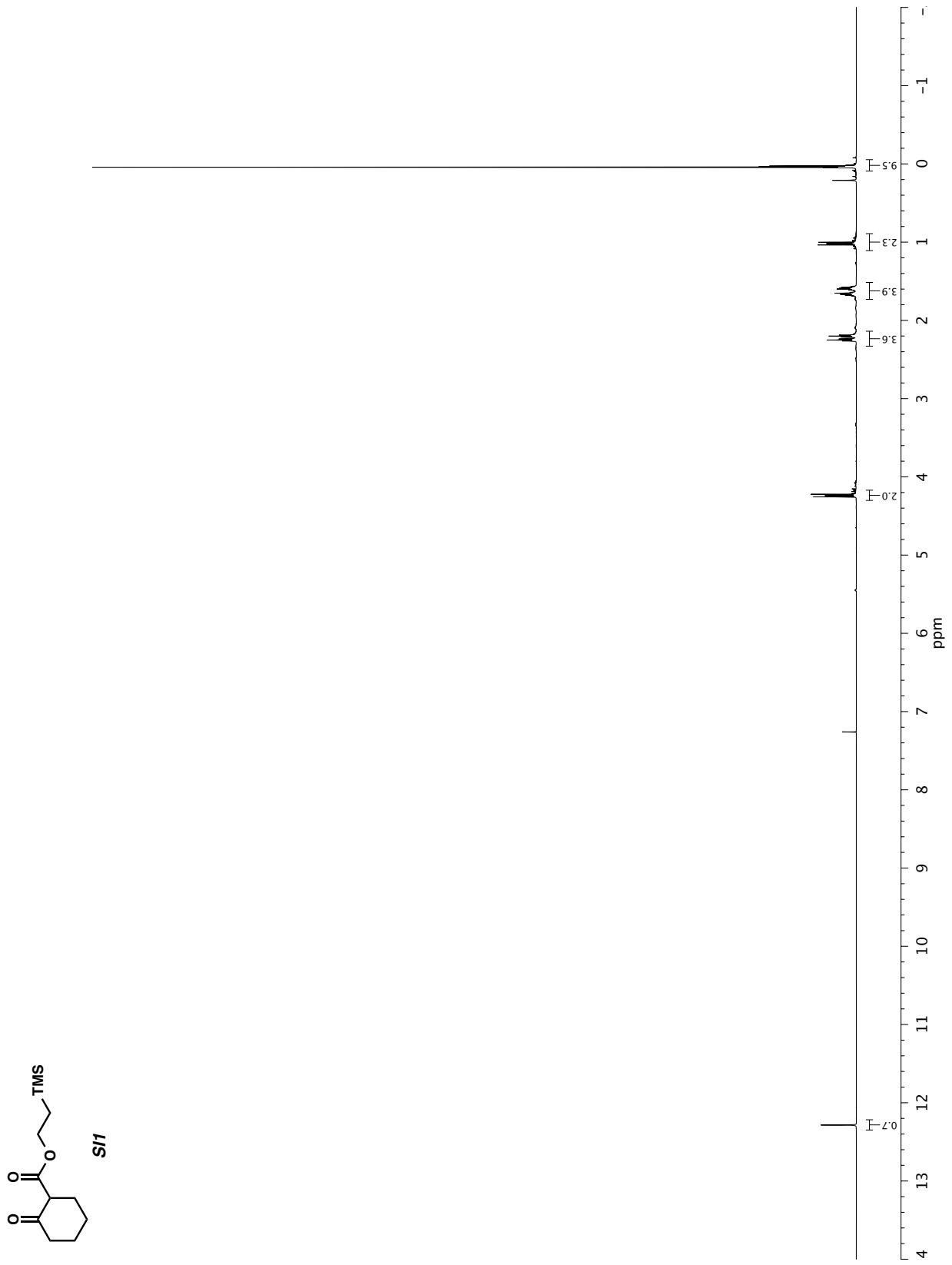


^{1}H NMR (500 MHz, $CDCl_3$) of compound **3a**.

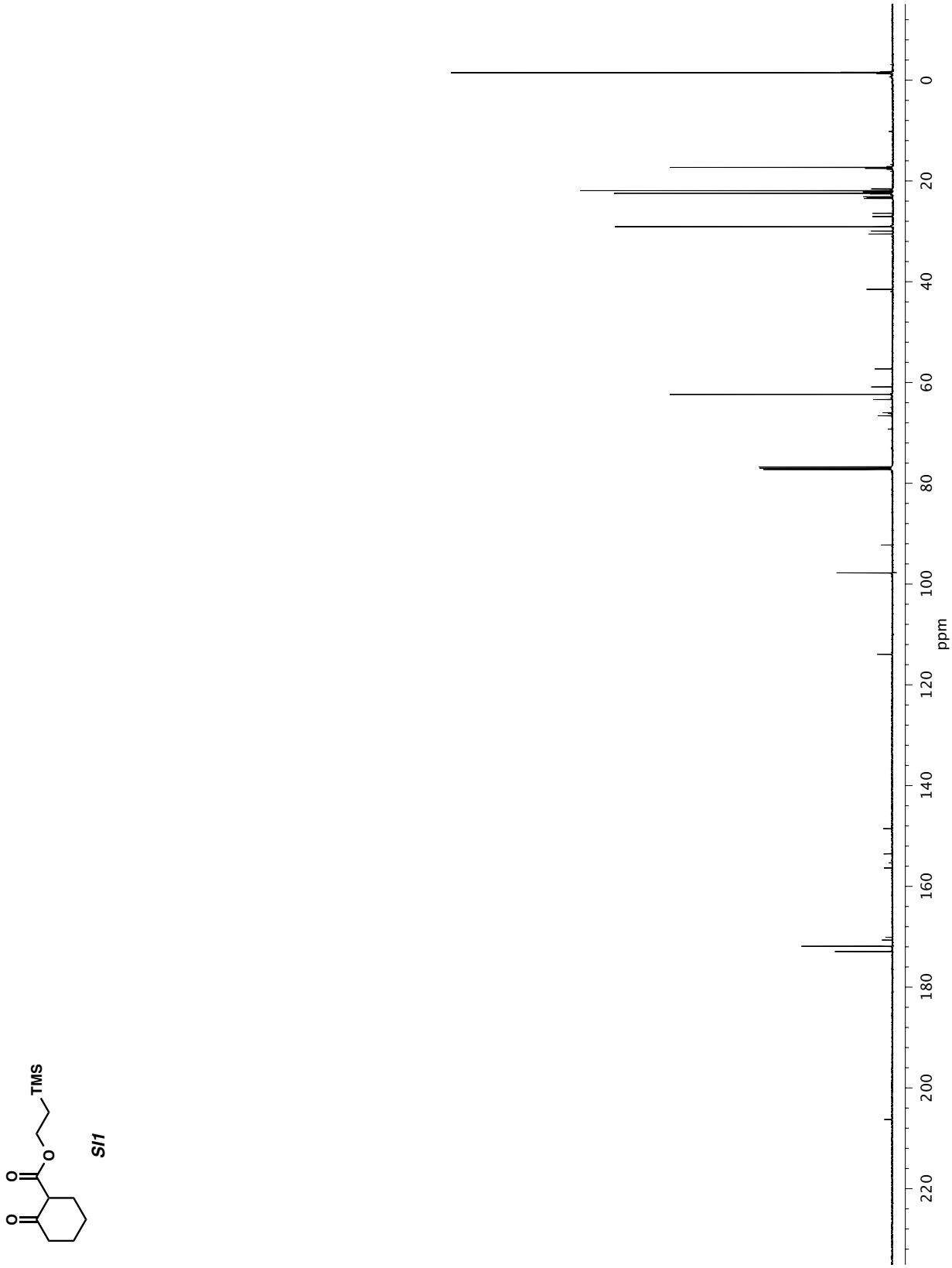
3a



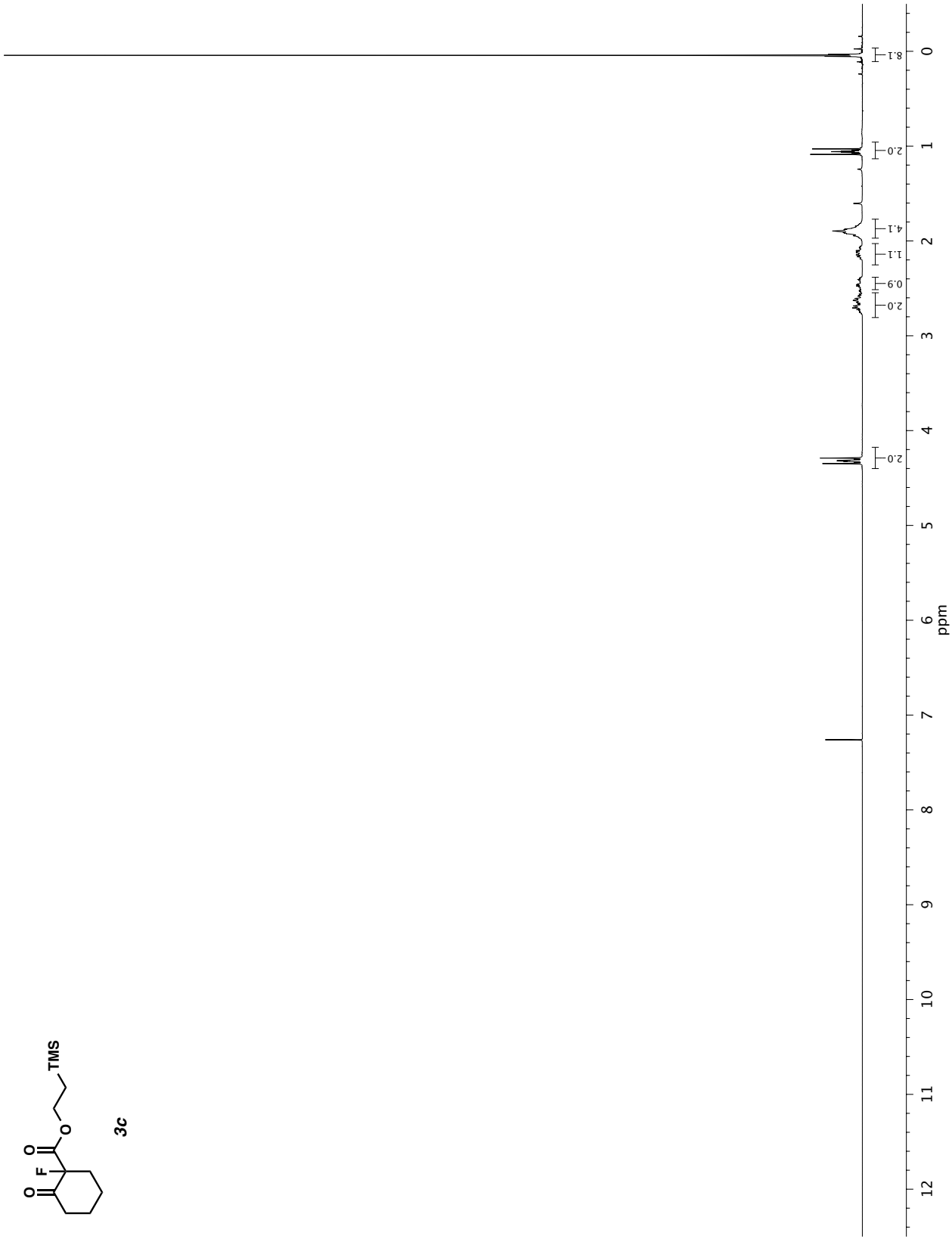
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3a**.



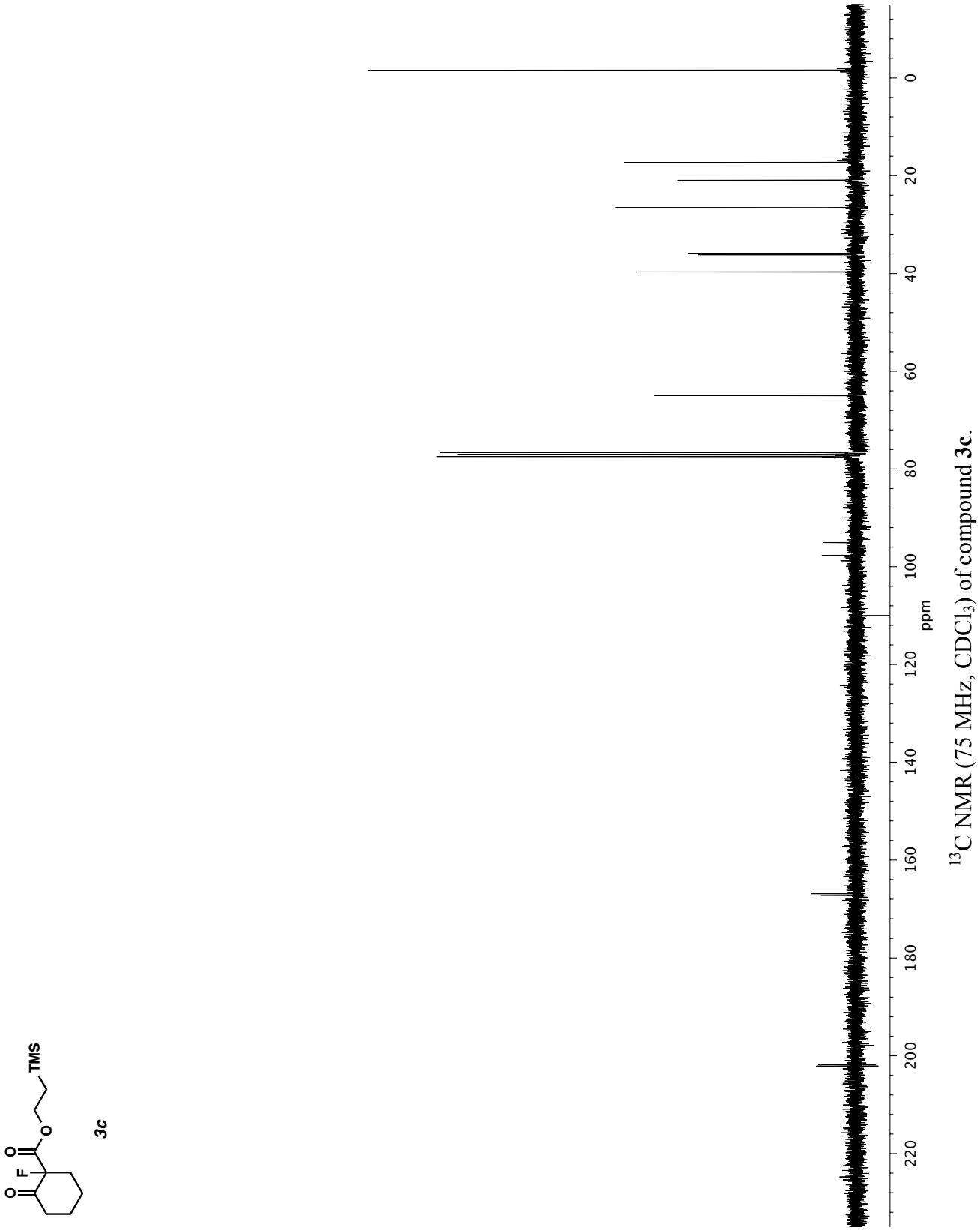
^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI1**.



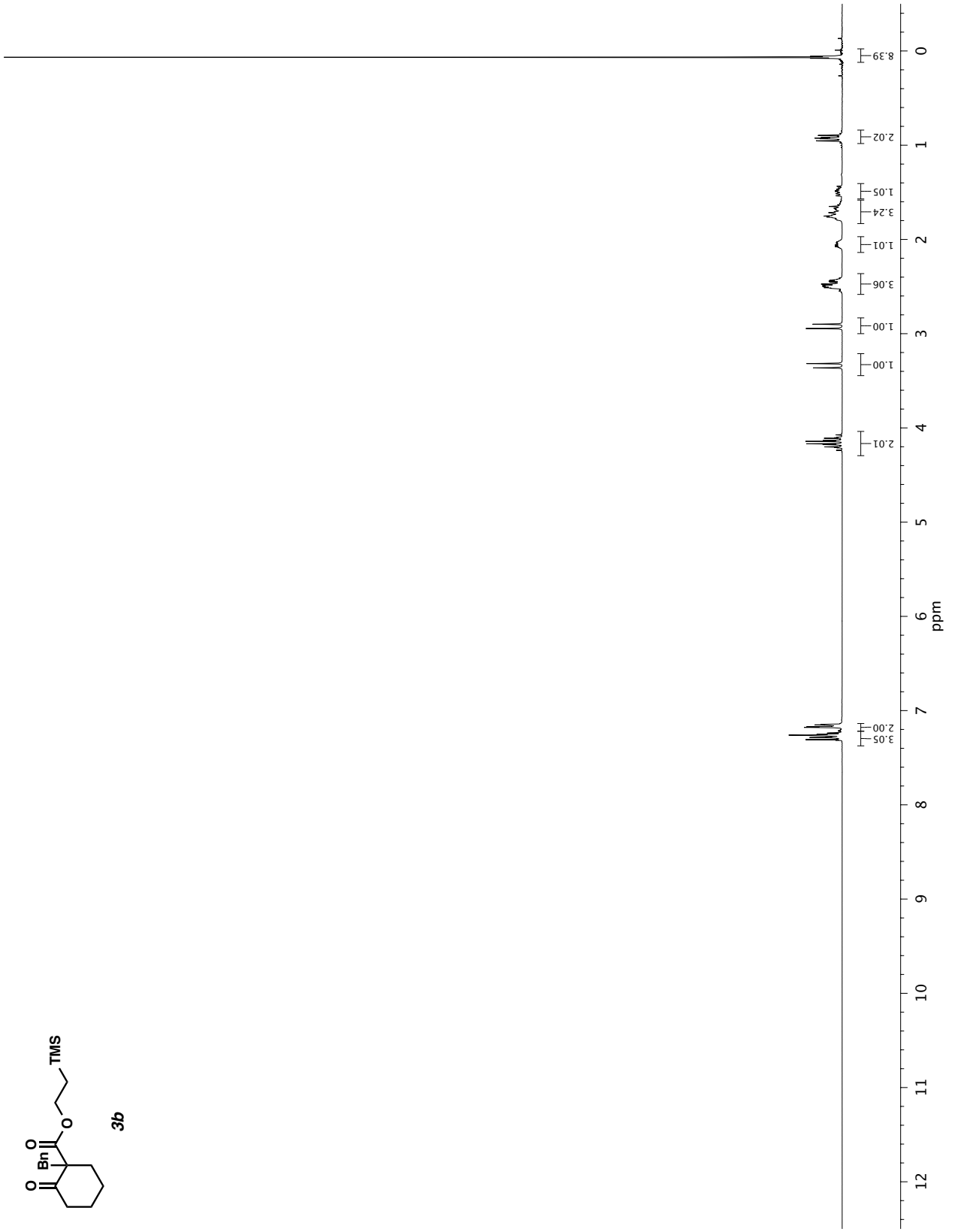
^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI1**.



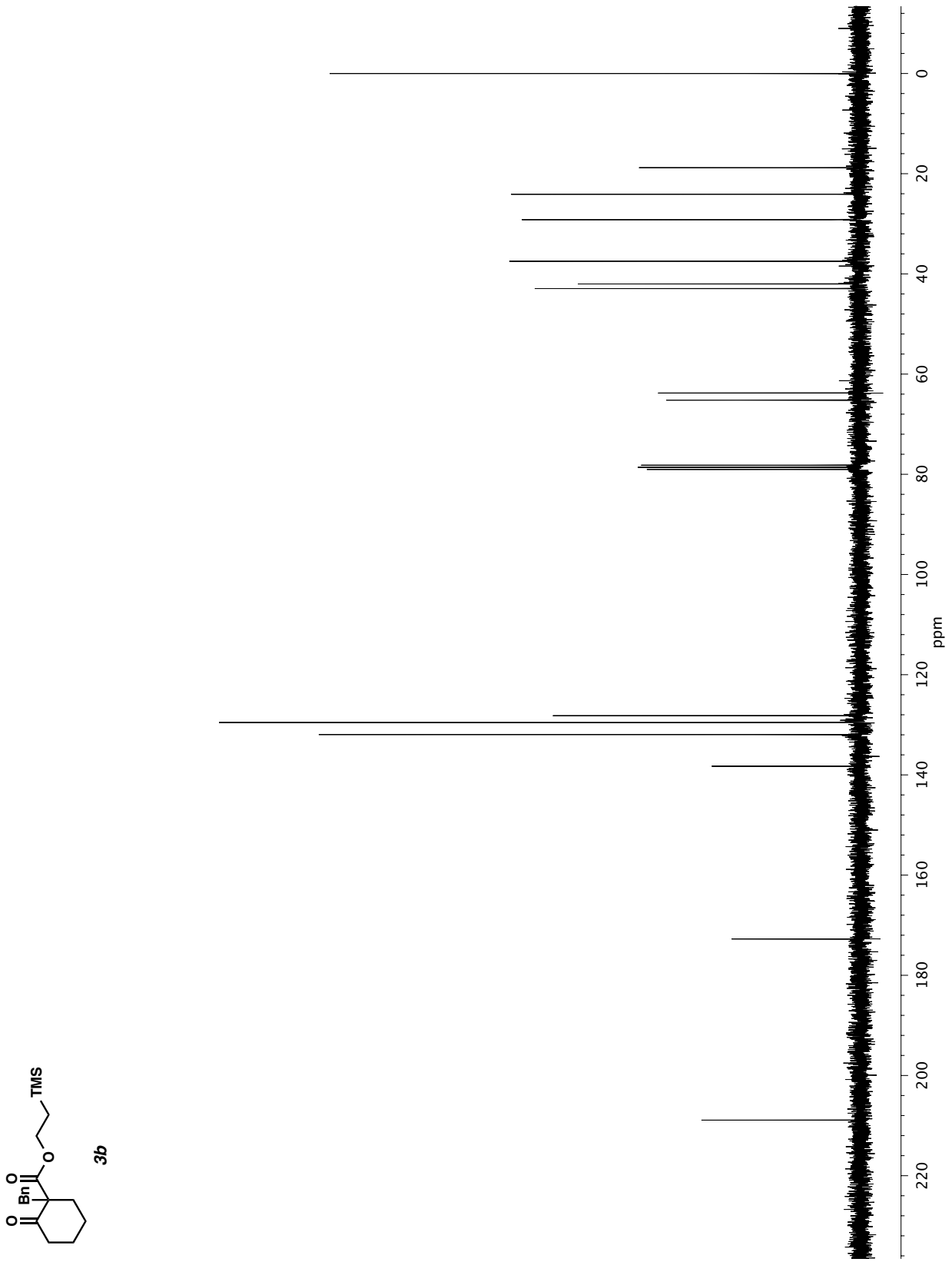
^{1}H NMR (300 MHz, $CDCl_3$) of compound **3c**.



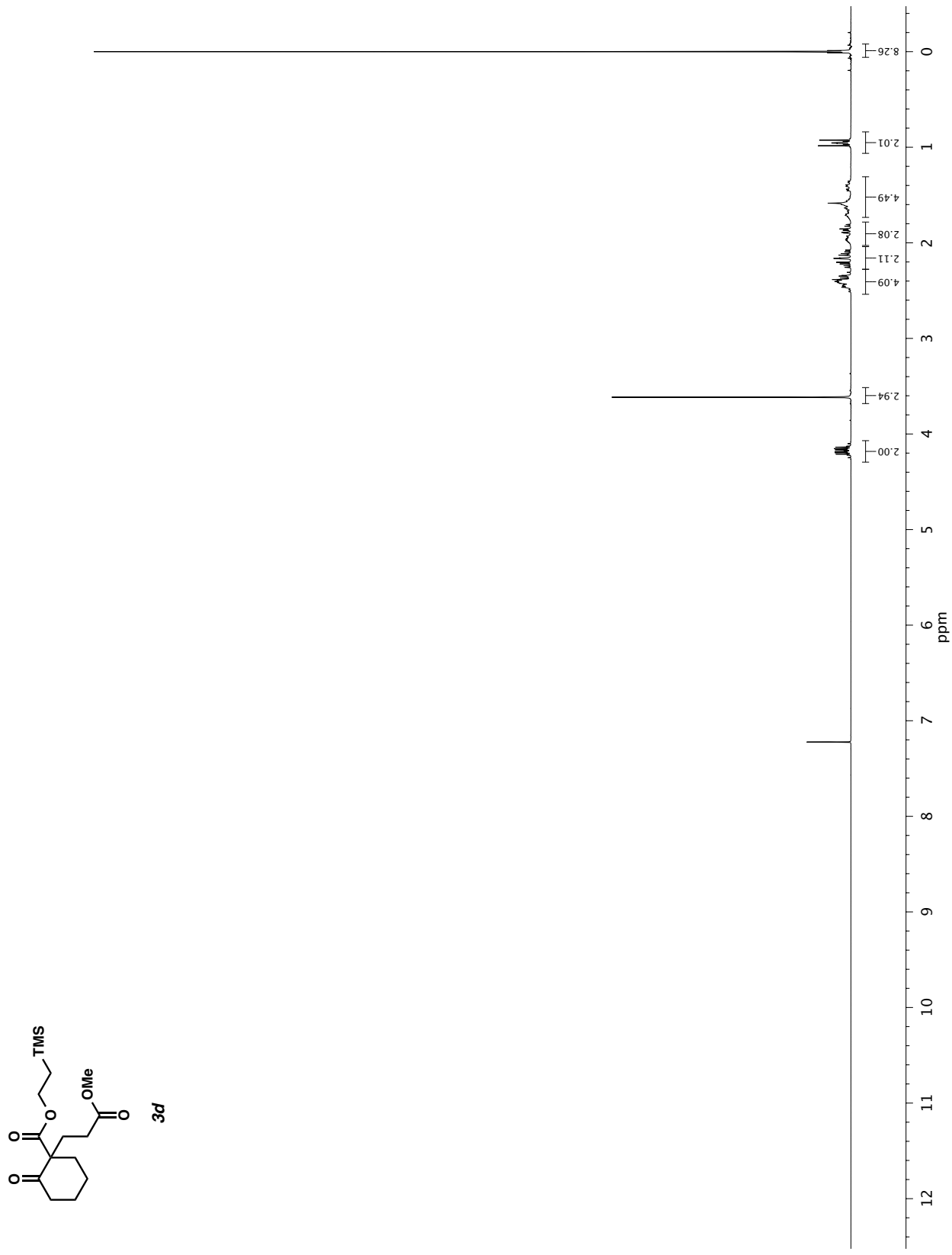
^{13}C NMR (75 MHz, $CDCl_3$) of compound **3c**.



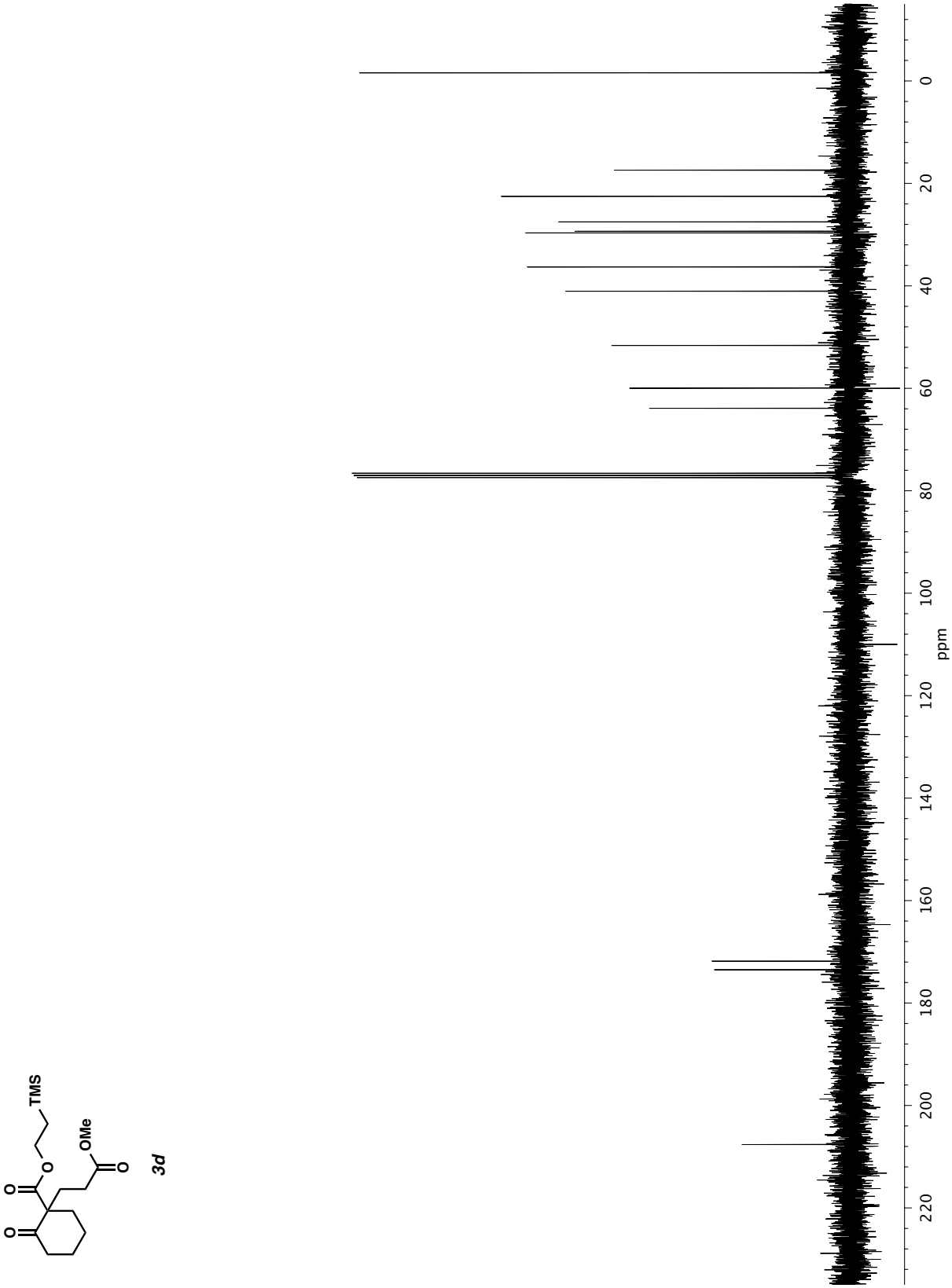
^{1}H NMR (300 MHz, $CDCl_3$) of compound **3b**.



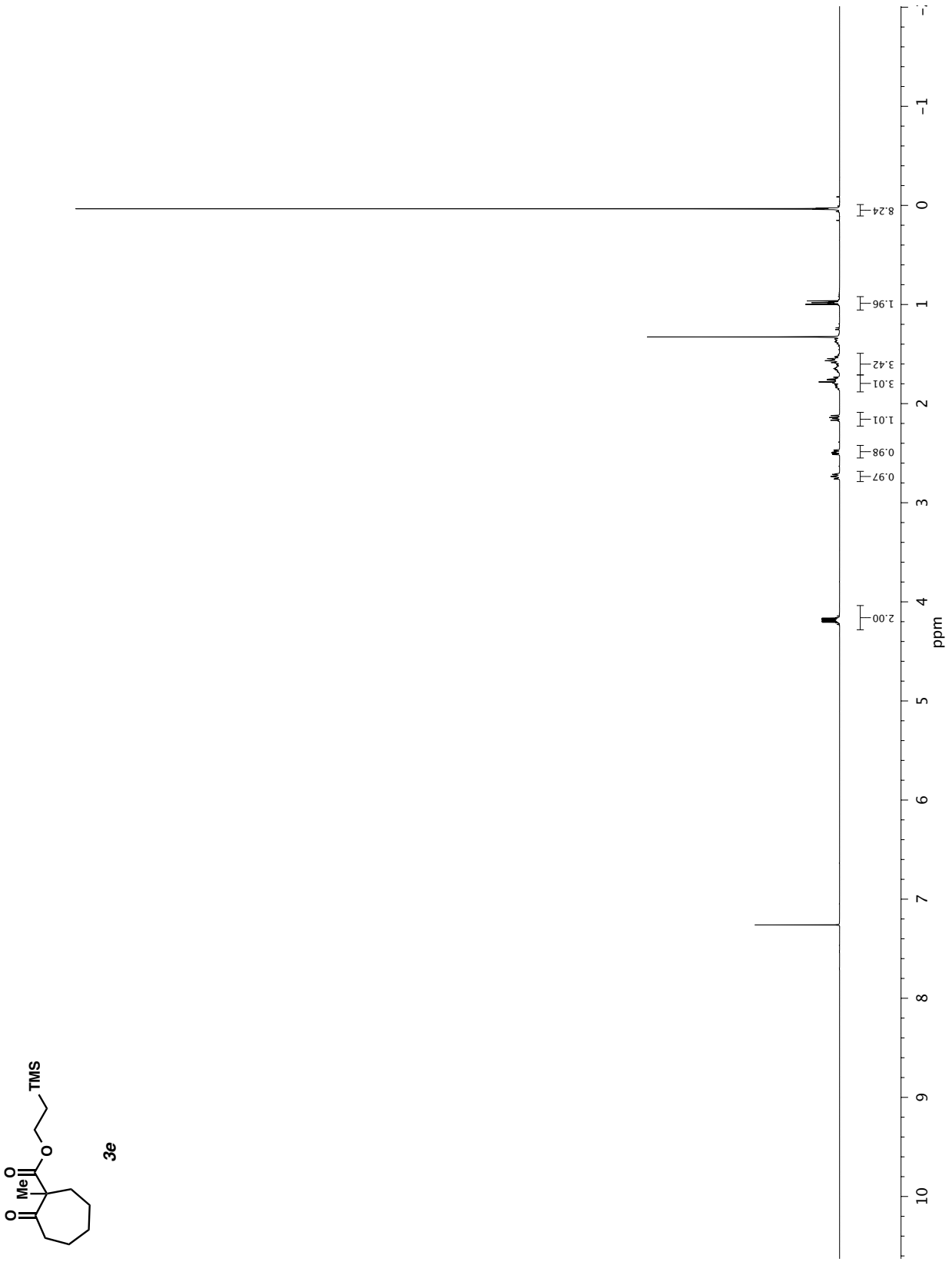
^{13}C NMR (75 MHz, $CDCl_3$) of compound **3b**.



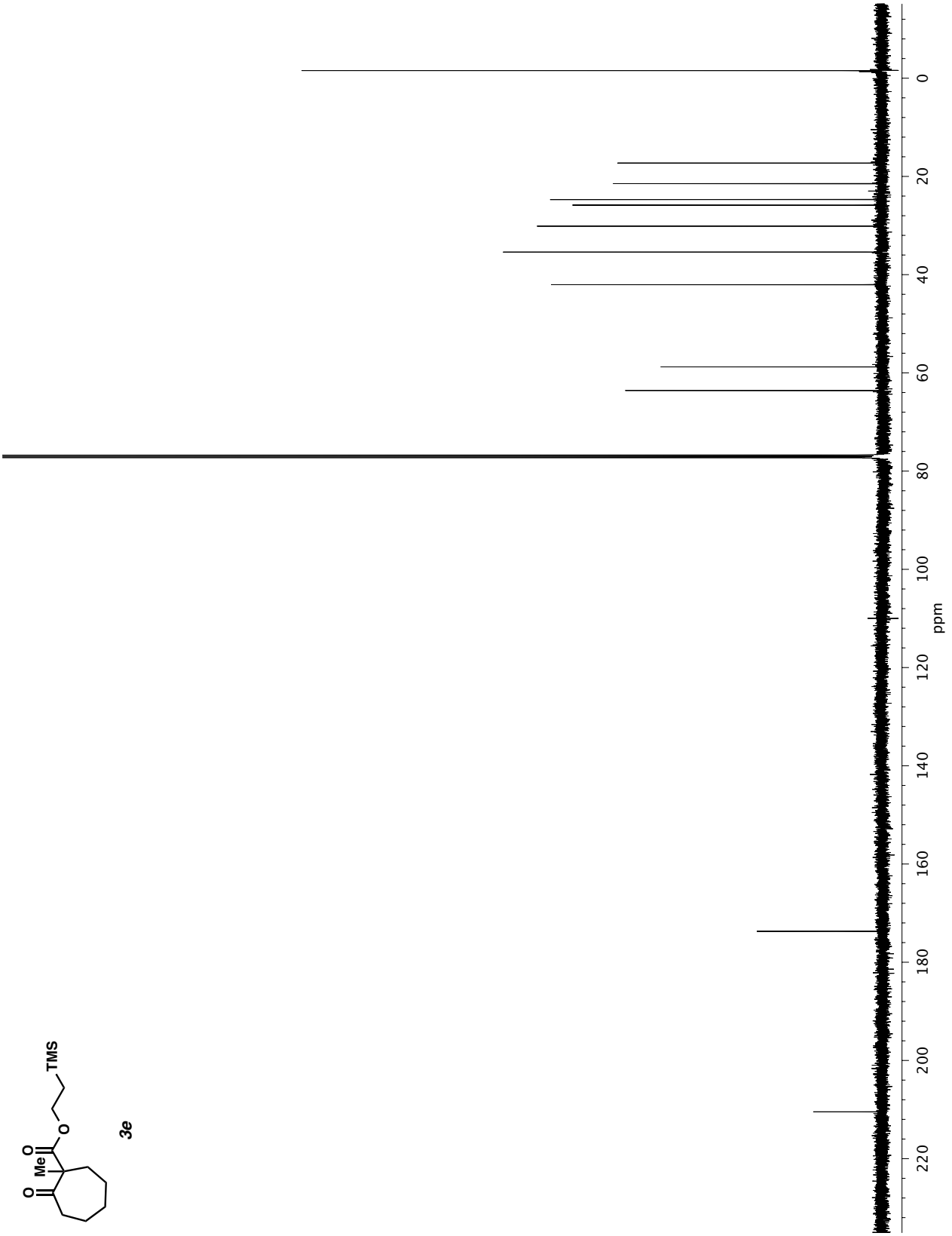
^{1}H NMR (300 MHz, $CDCl_3$) of compound **3d**.



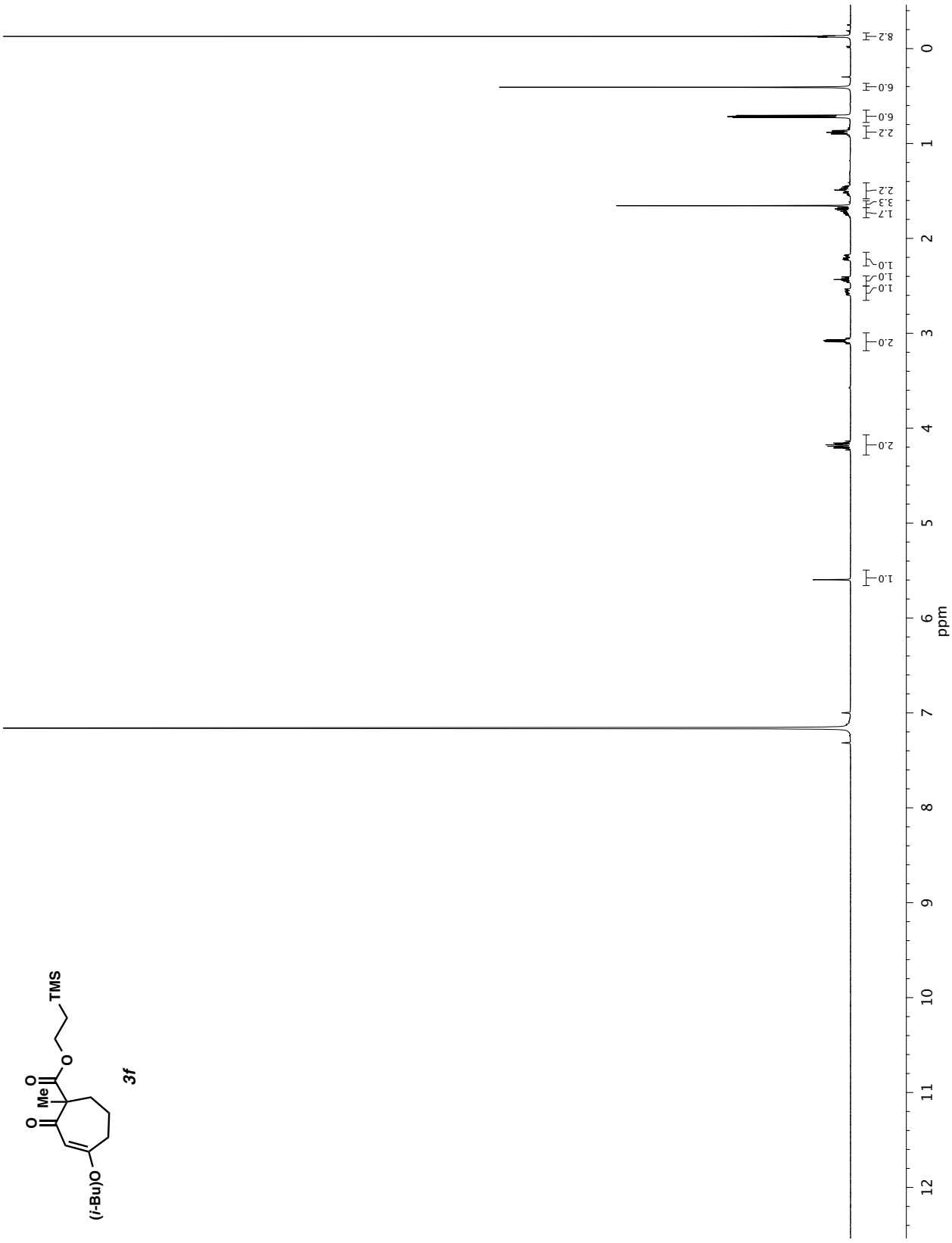
^{13}C NMR (75 MHz, $CDCl_3$) of compound **3d**.



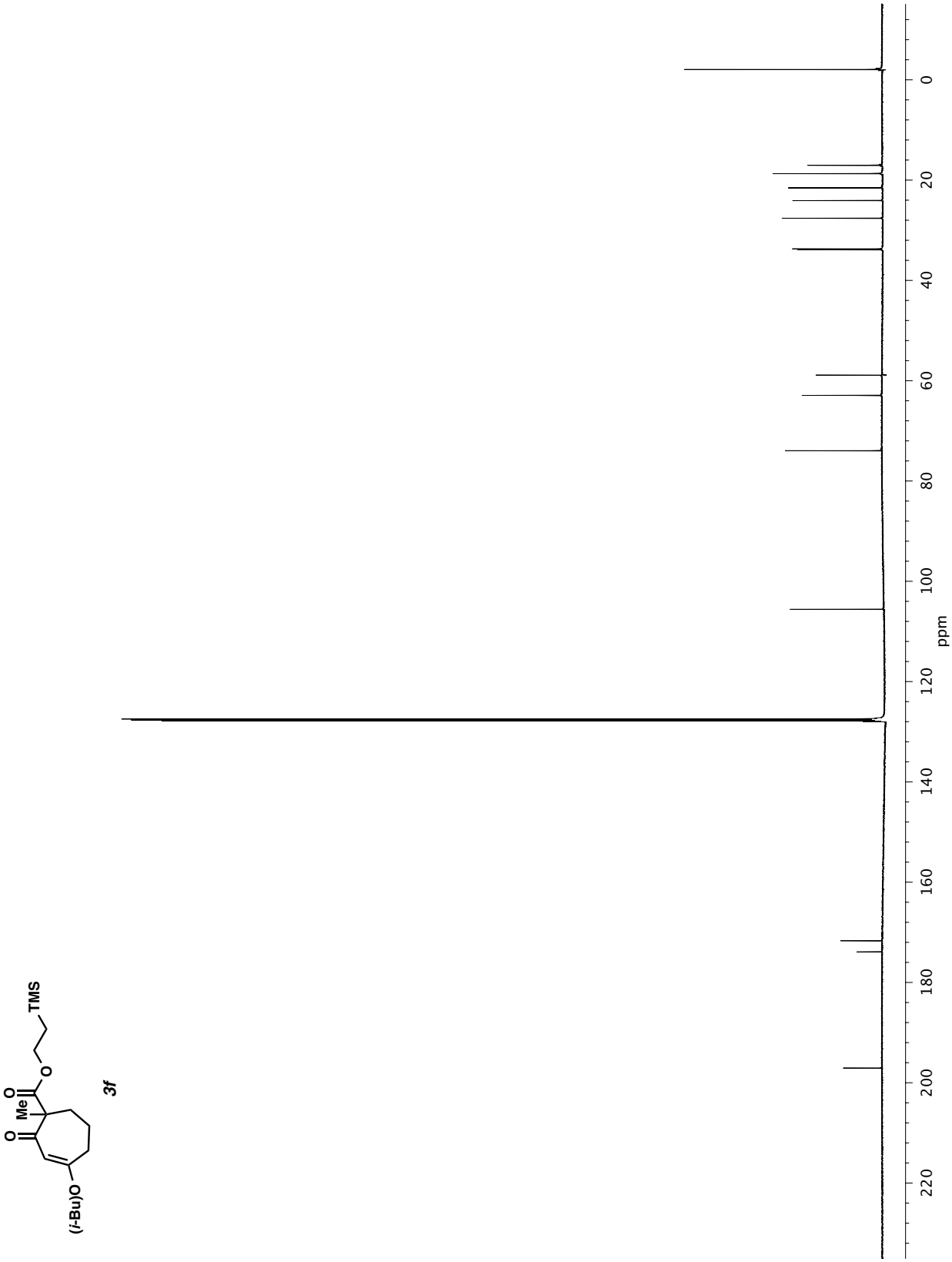
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3e**.



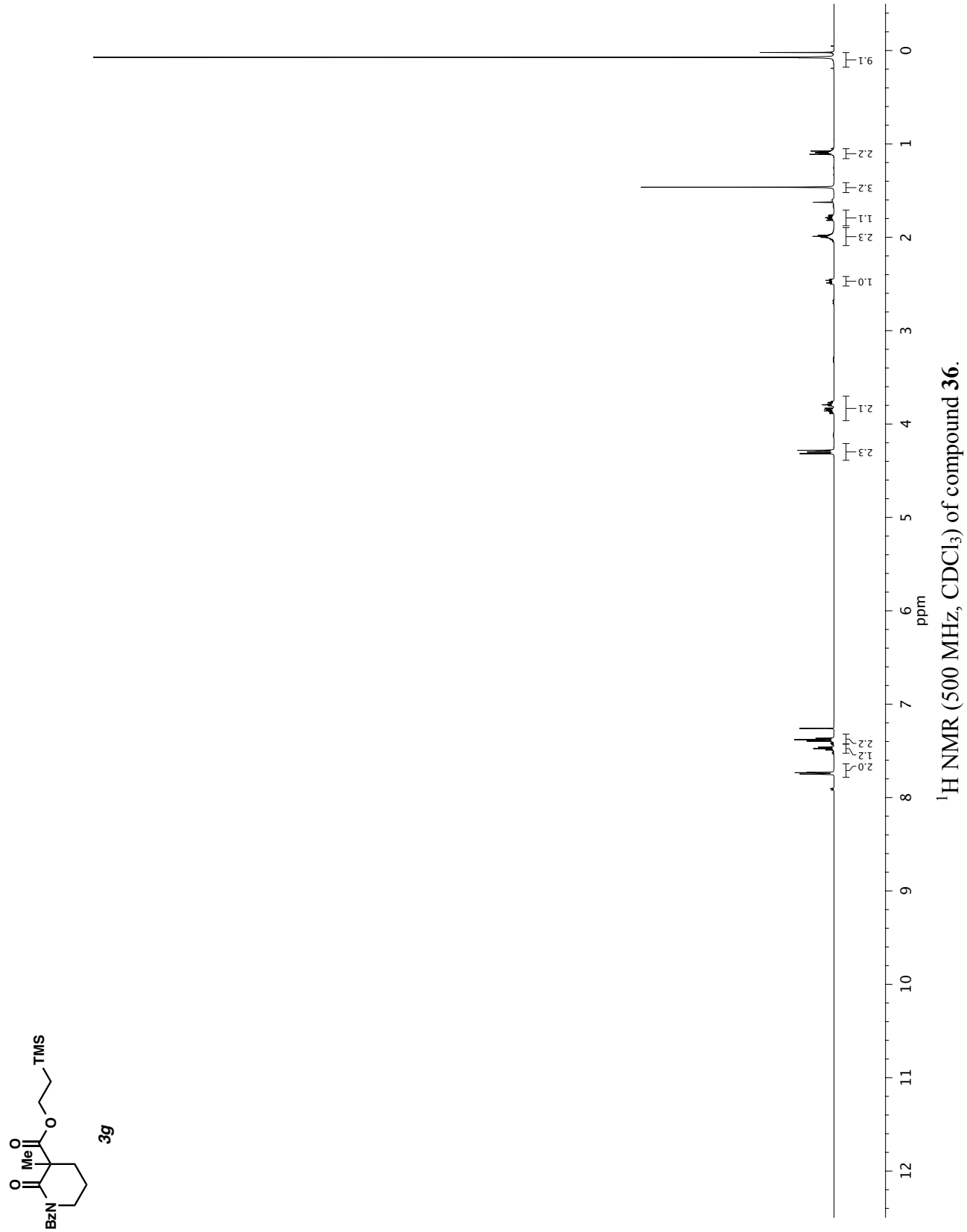
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3e**.



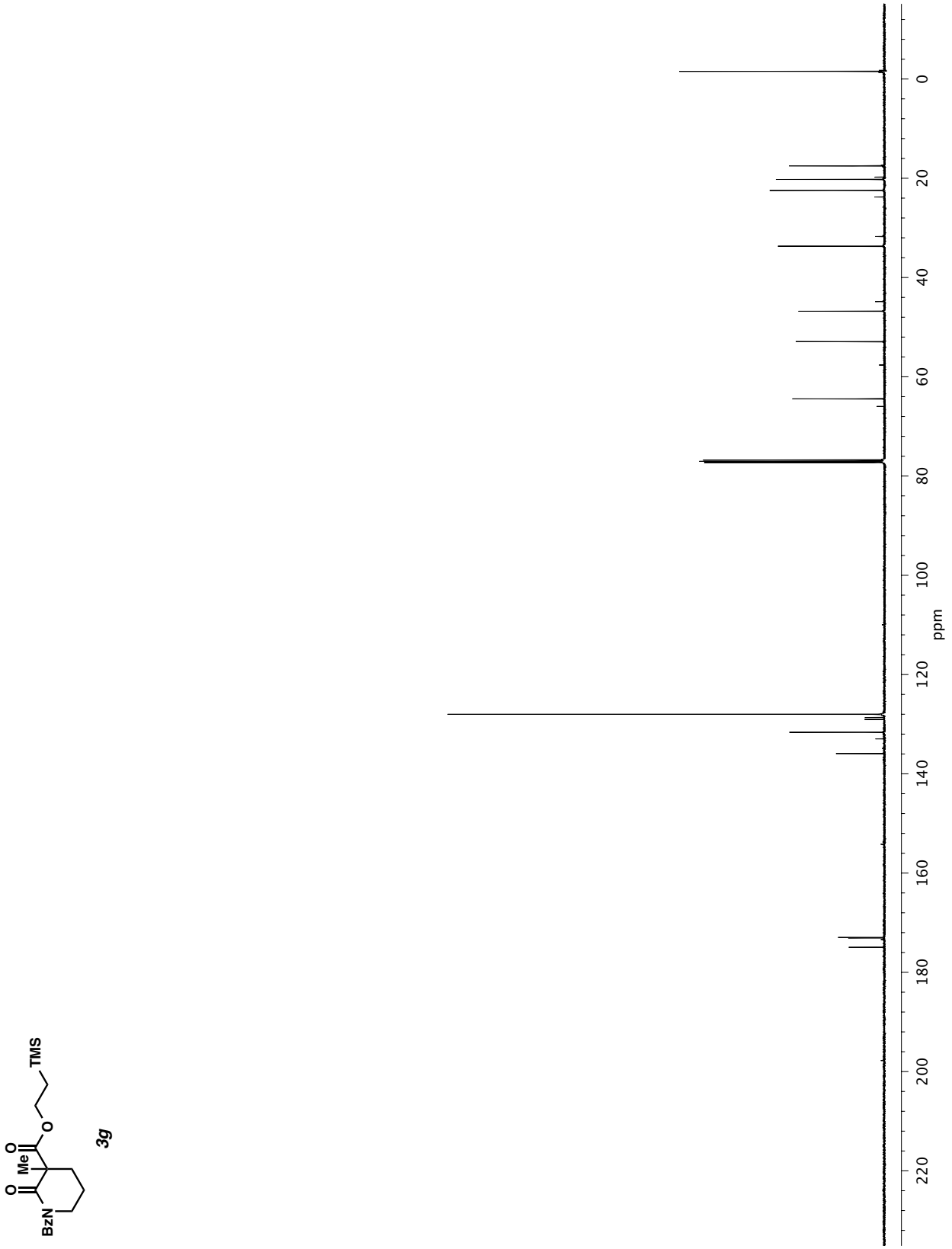
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3f**.



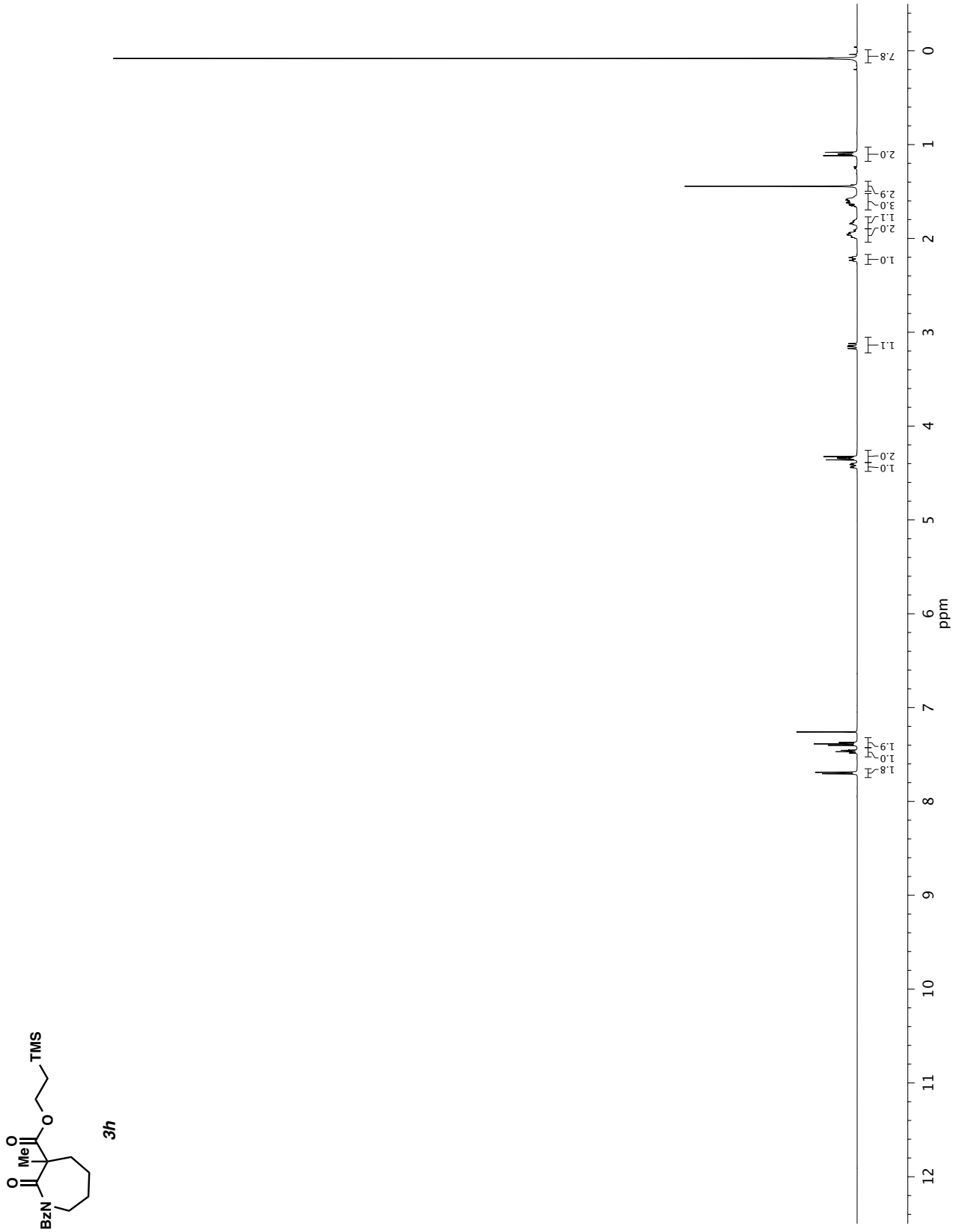
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3f**.



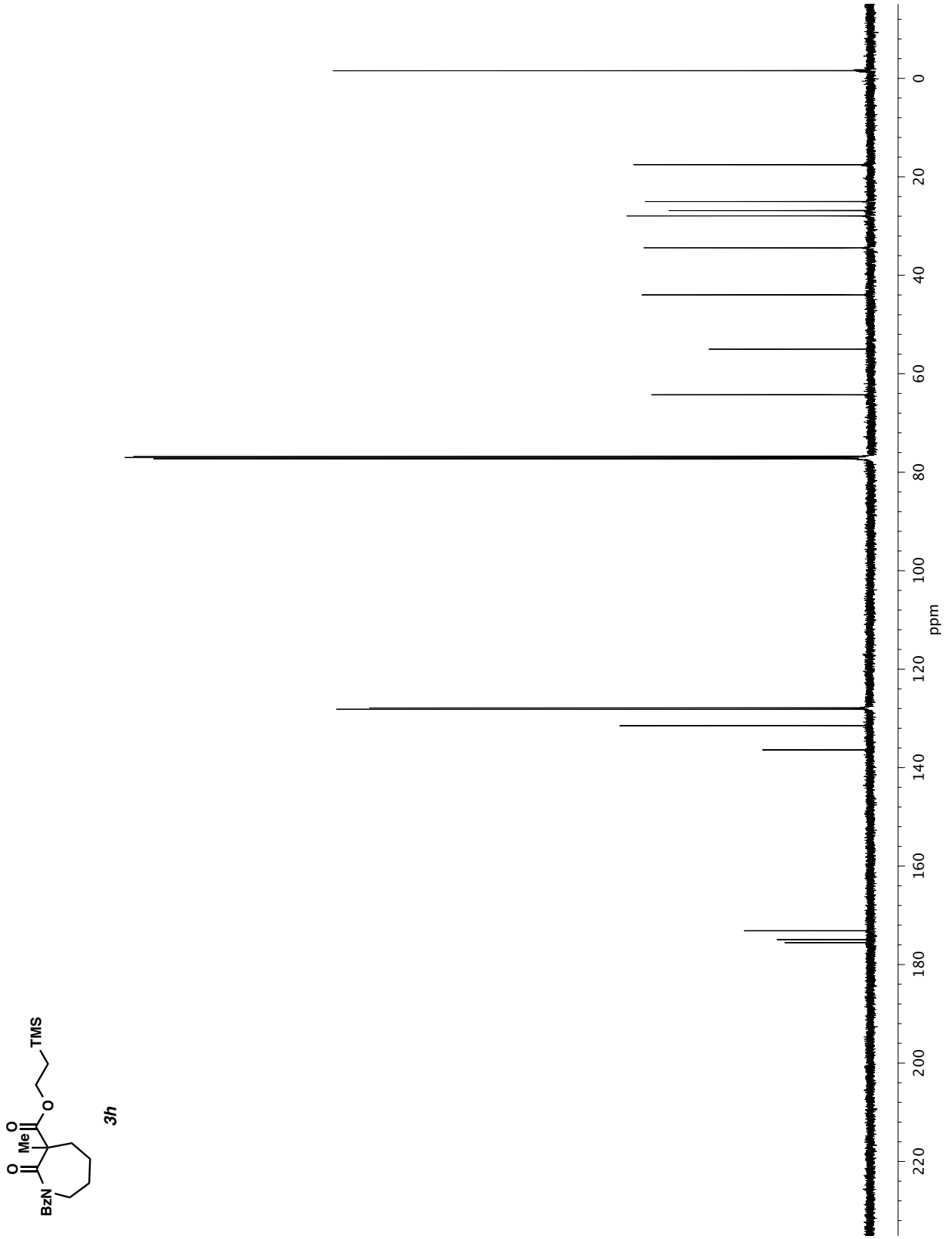
^{1}H NMR (500 MHz, $CDCl_3$) of compound **36**.



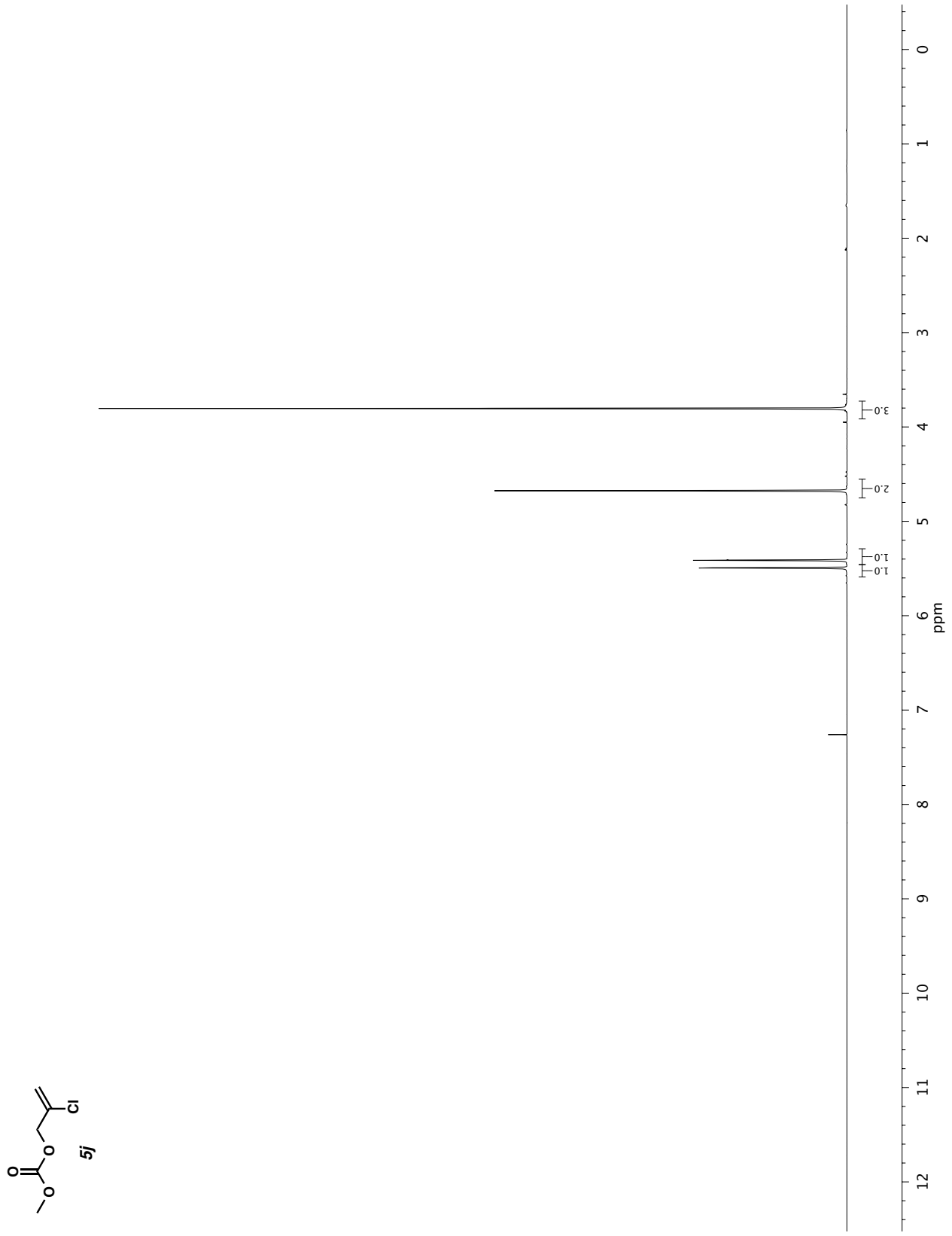
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3g**.



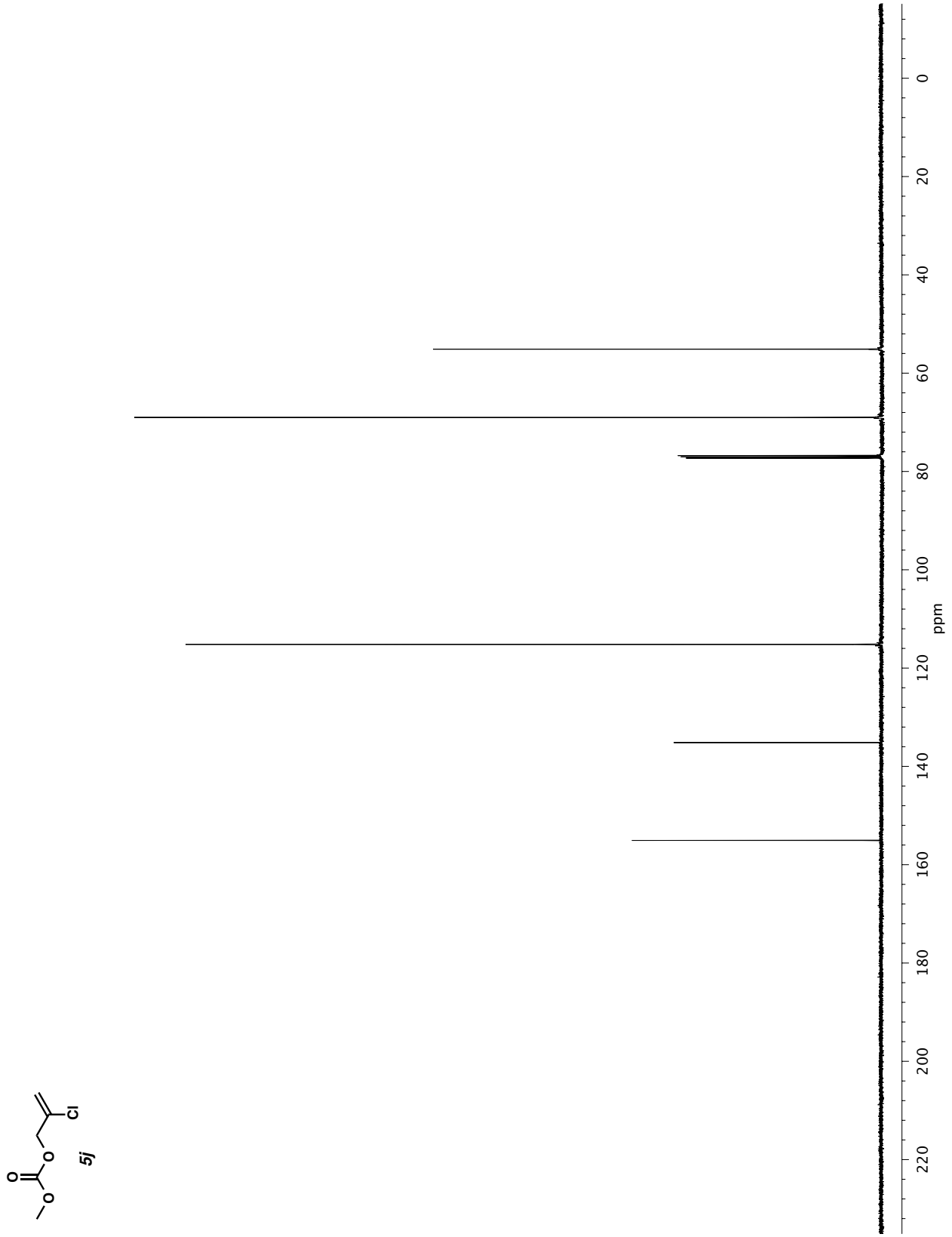
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3h**.



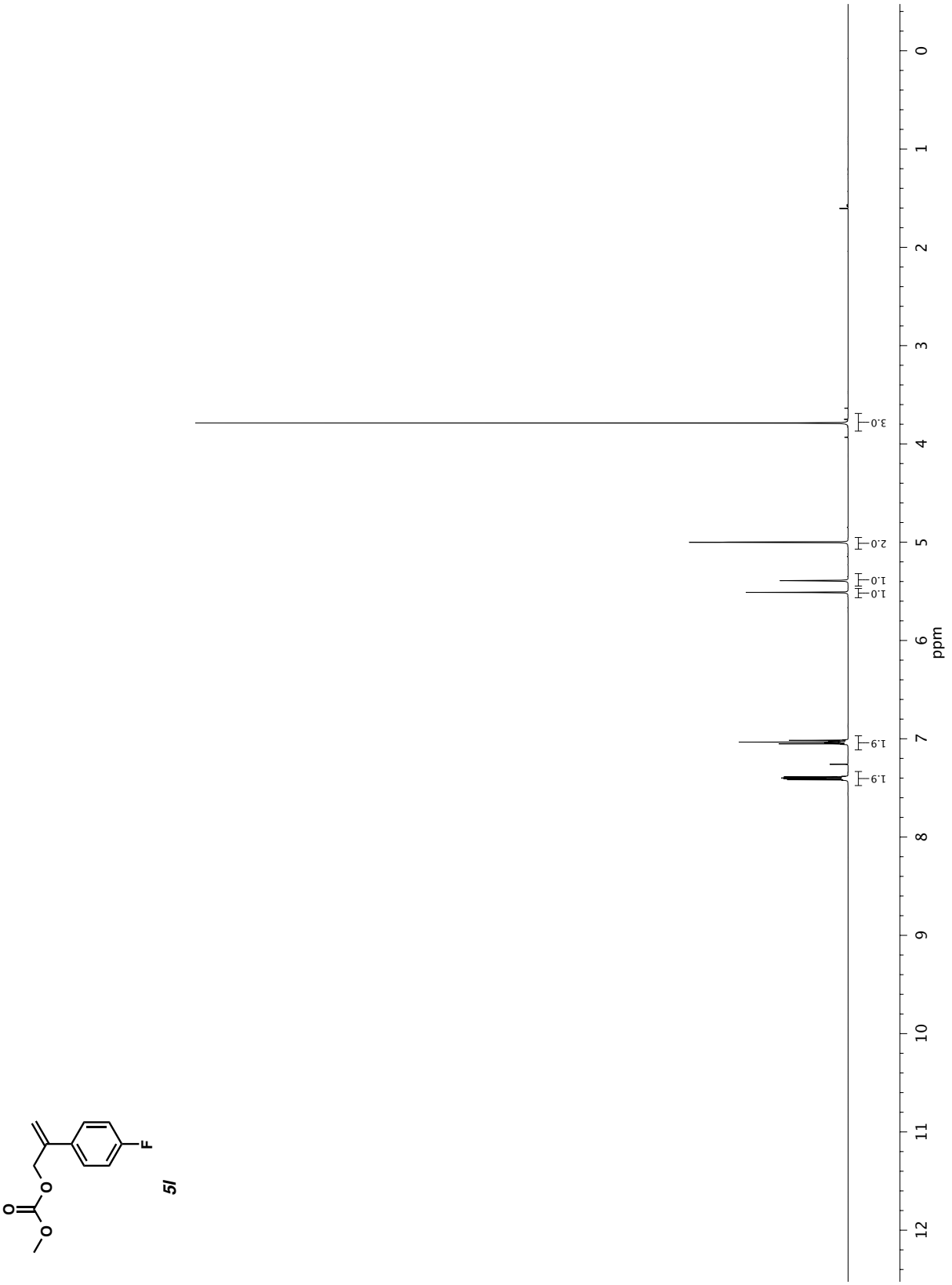
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3h**.



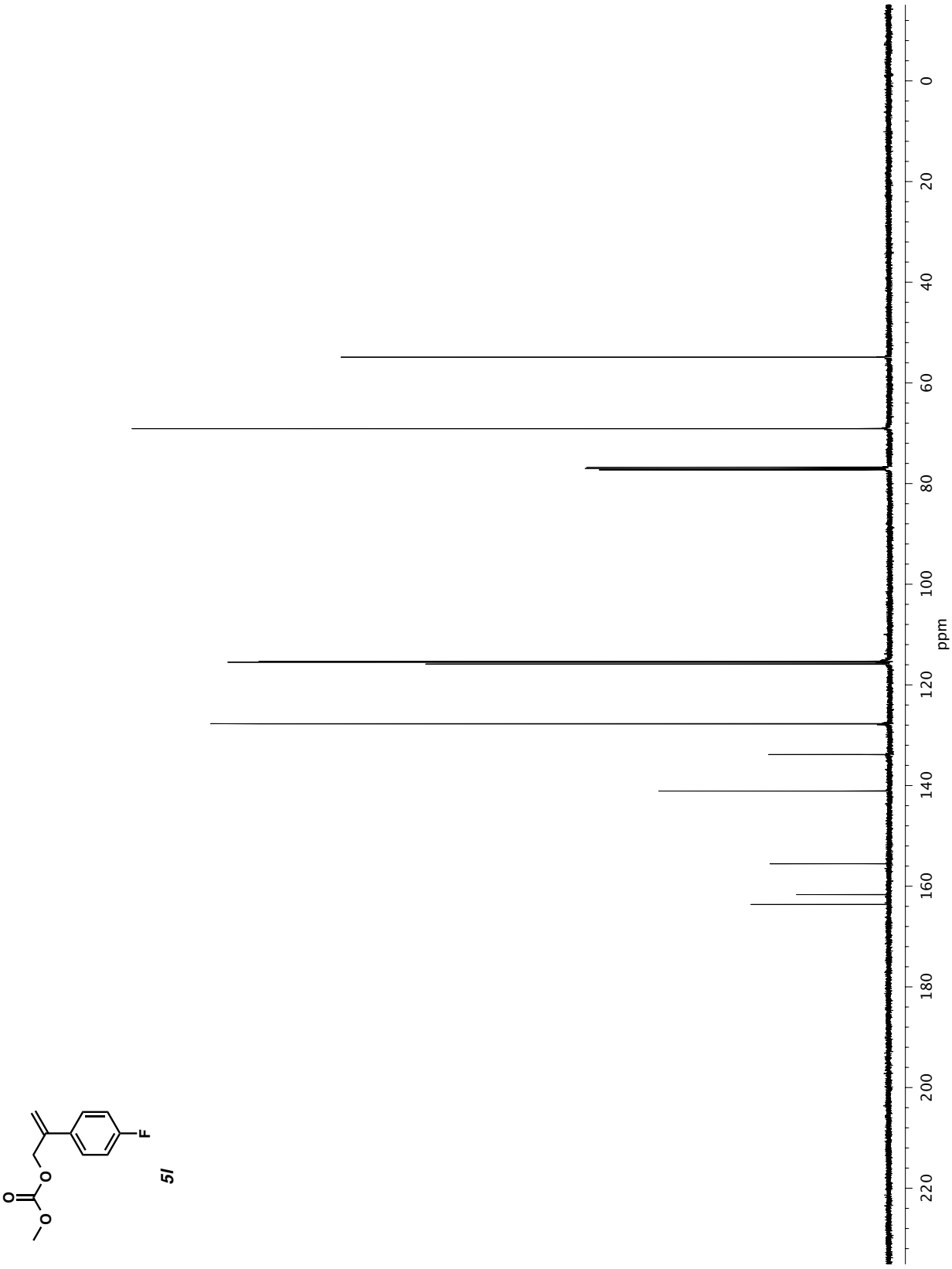
^{1}H NMR (500 MHz, $CDCl_3$) of compound **5j**.



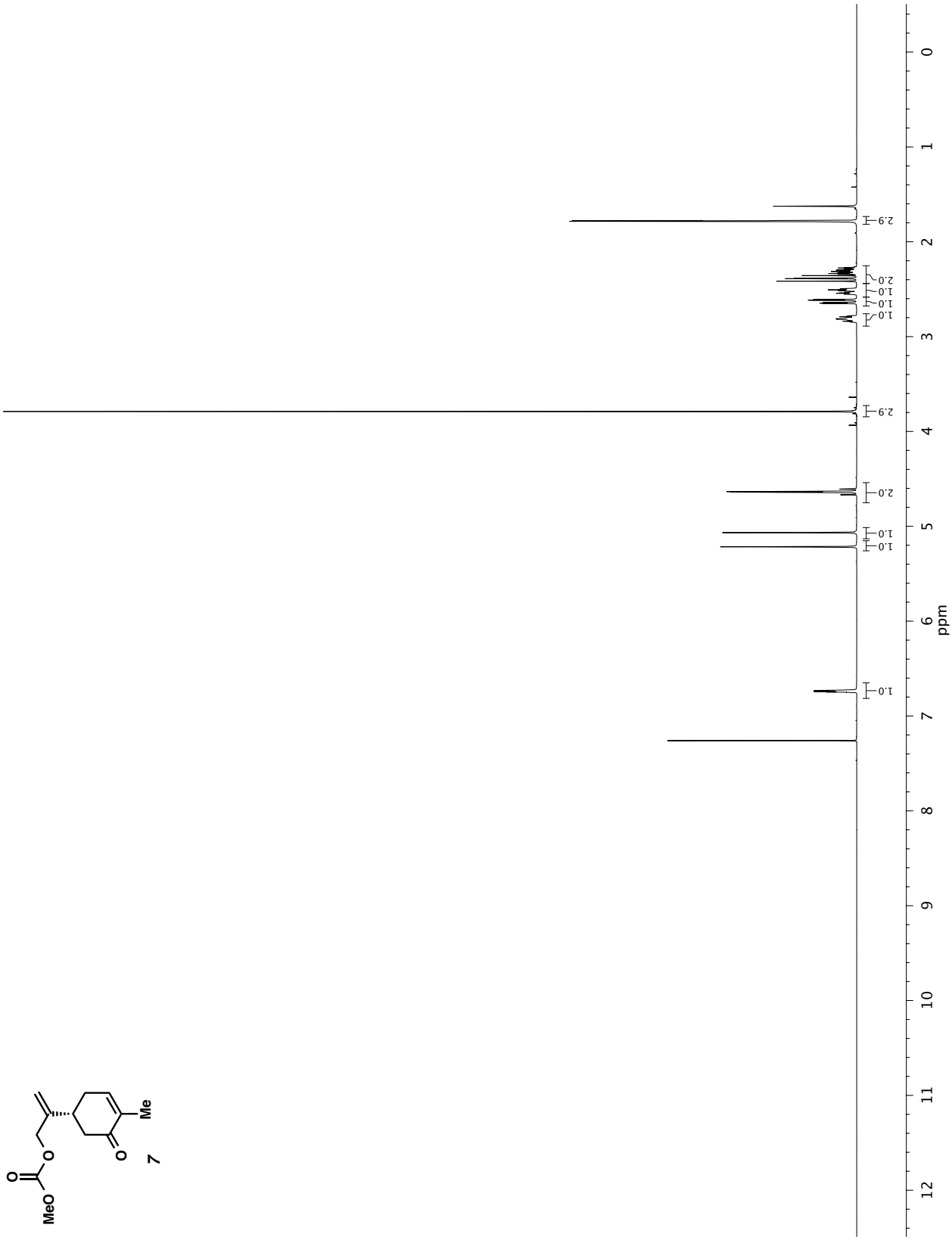
^{13}C NMR (126 MHz, $CDCl_3$) of compound **5j**.



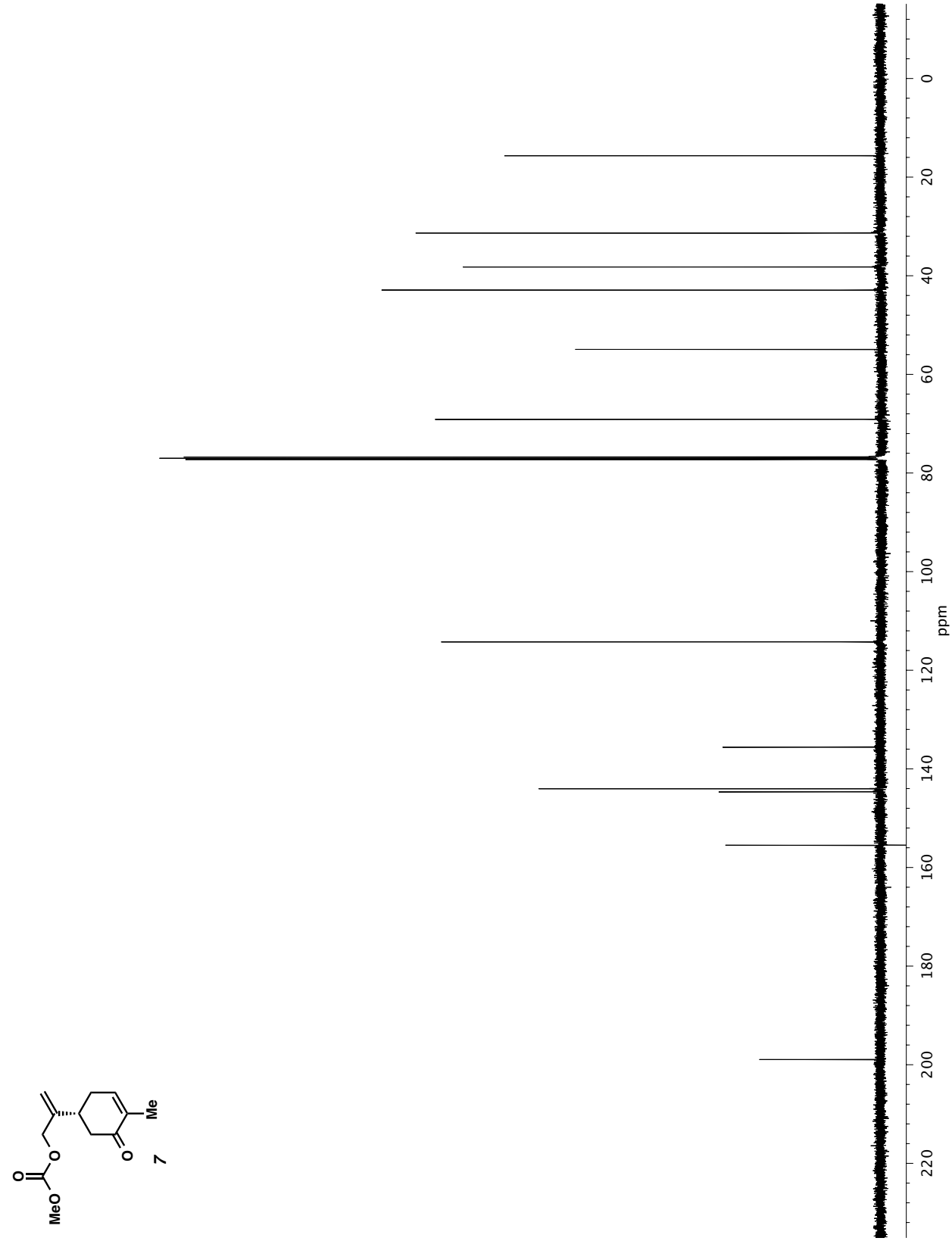
^{1}H NMR (500 MHz, $CDCl_3$) of compound **5l**.



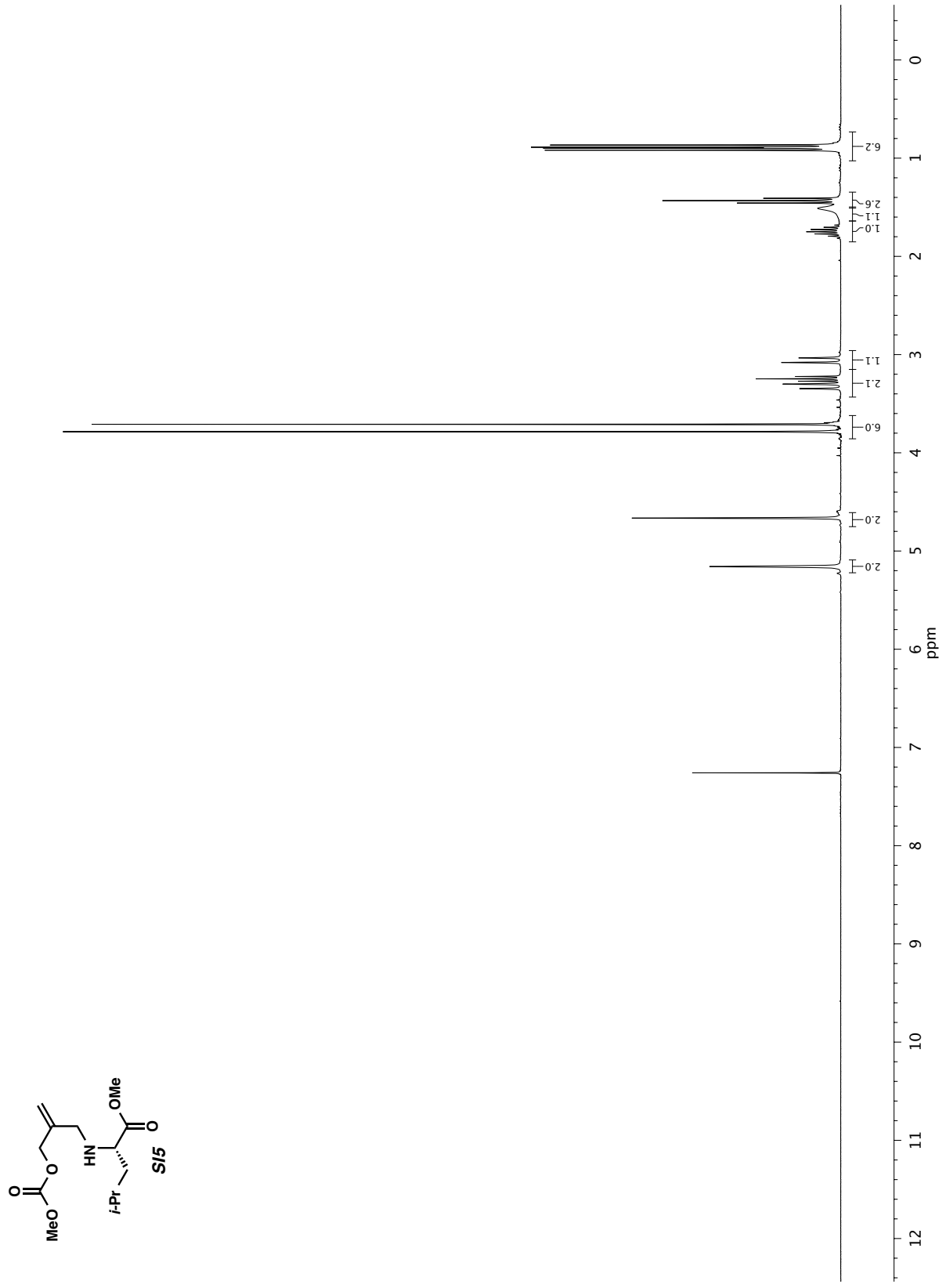
^{13}C NMR (126 MHz, $CDCl_3$) of compound **5l**.



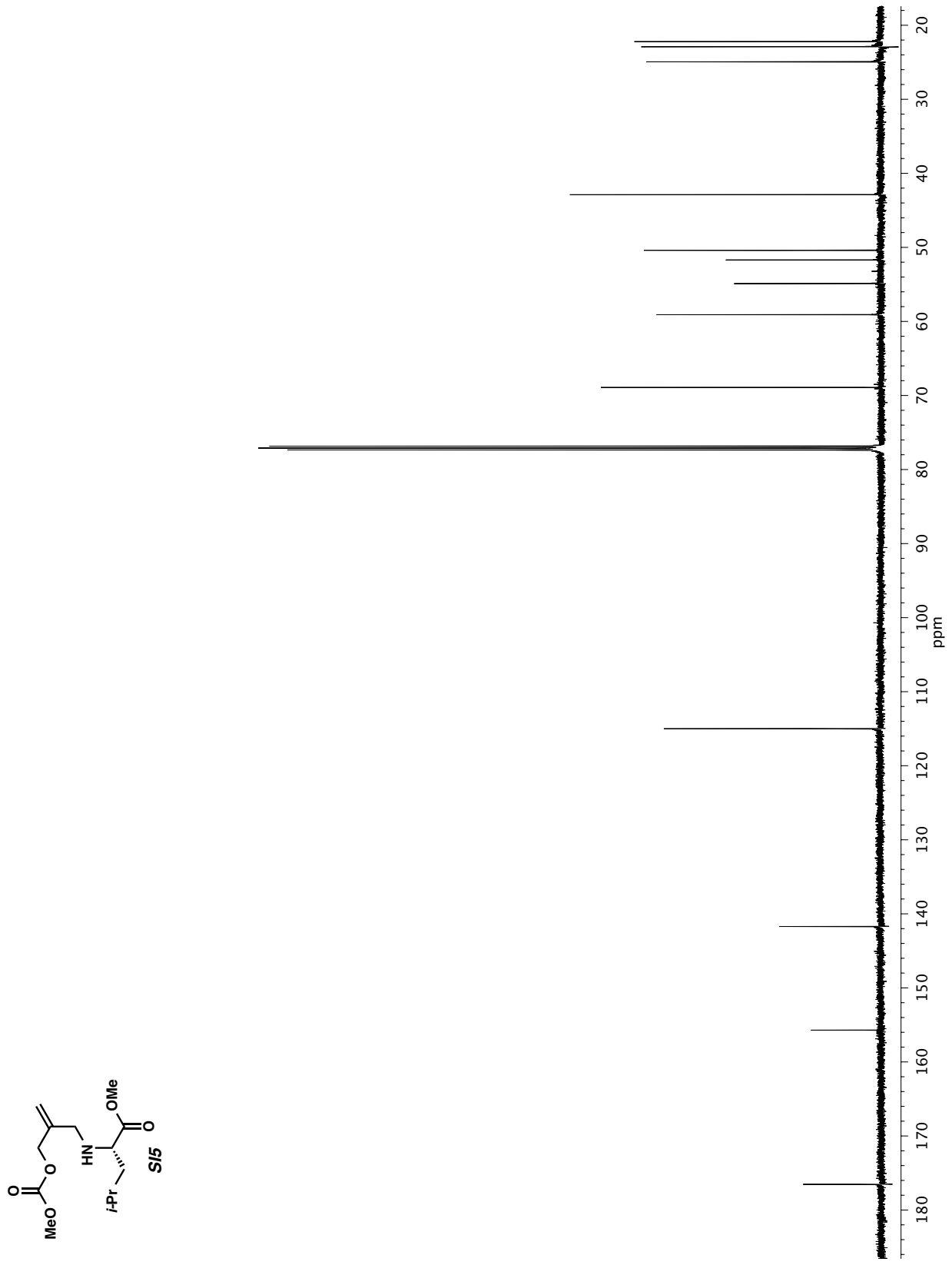
^{1}H NMR (500 MHz, $CDCl_3$) of compound **7**.



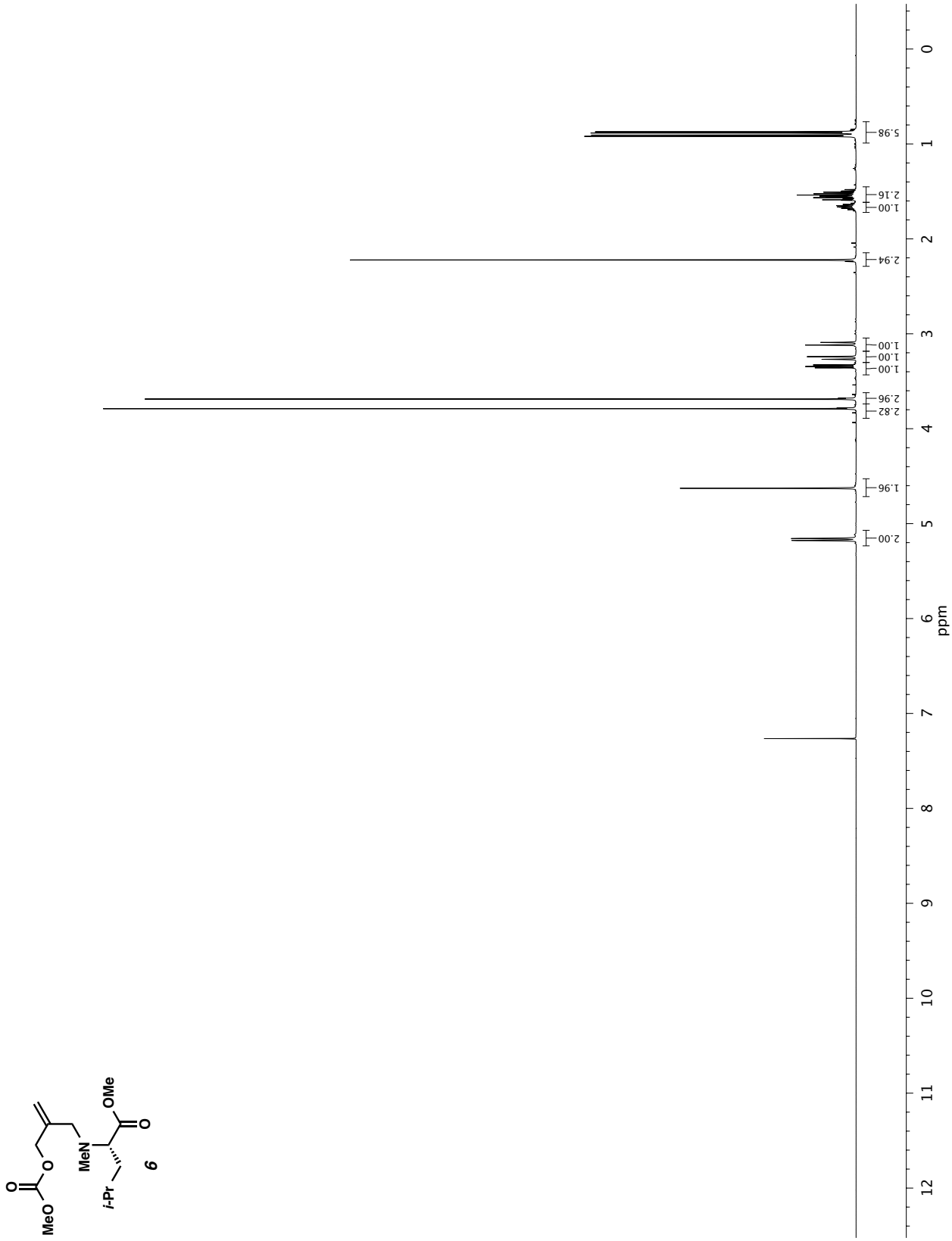
^{13}C NMR (126 MHz, $CDCl_3$) of compound **7**.



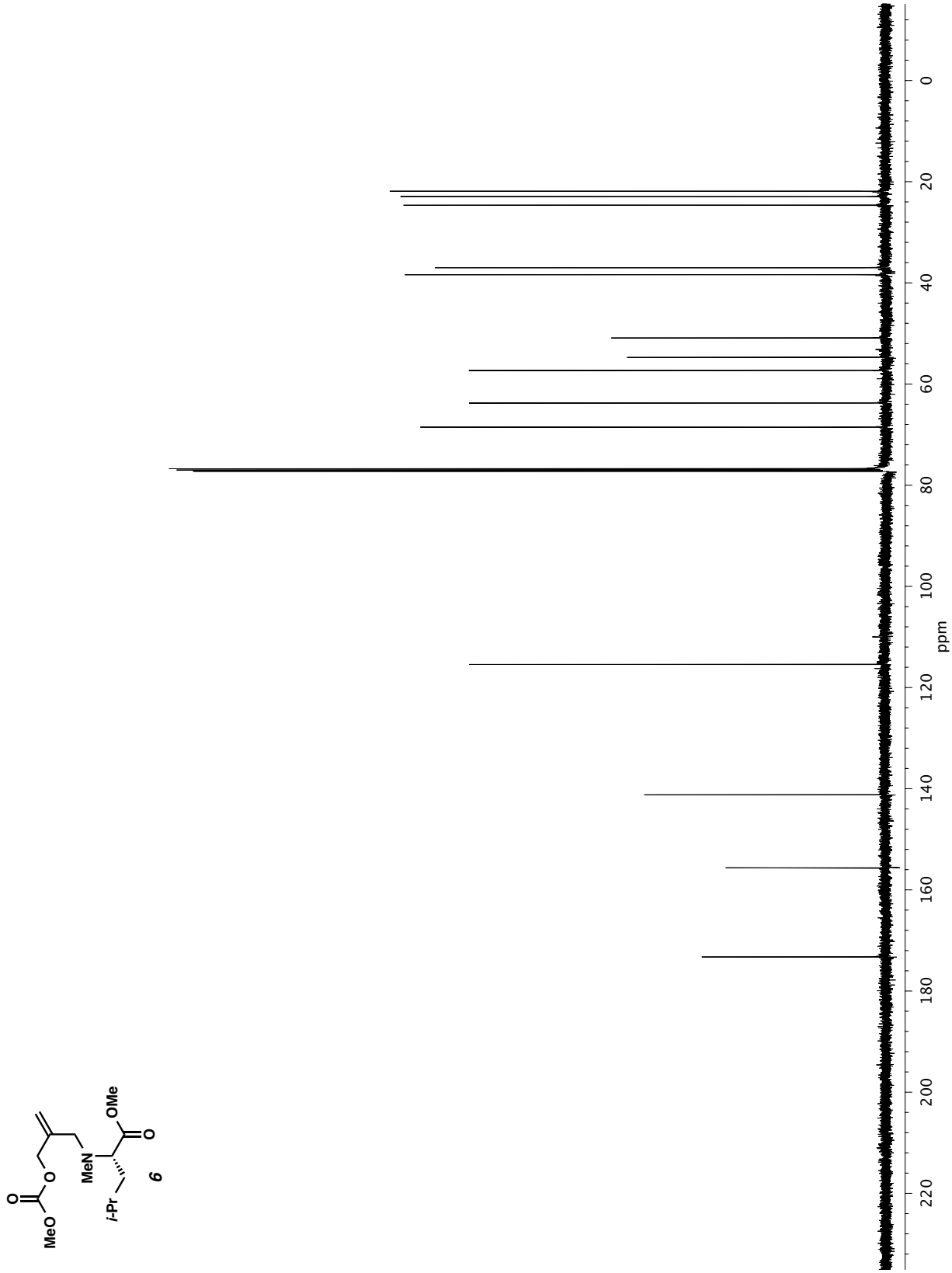
^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI5**.



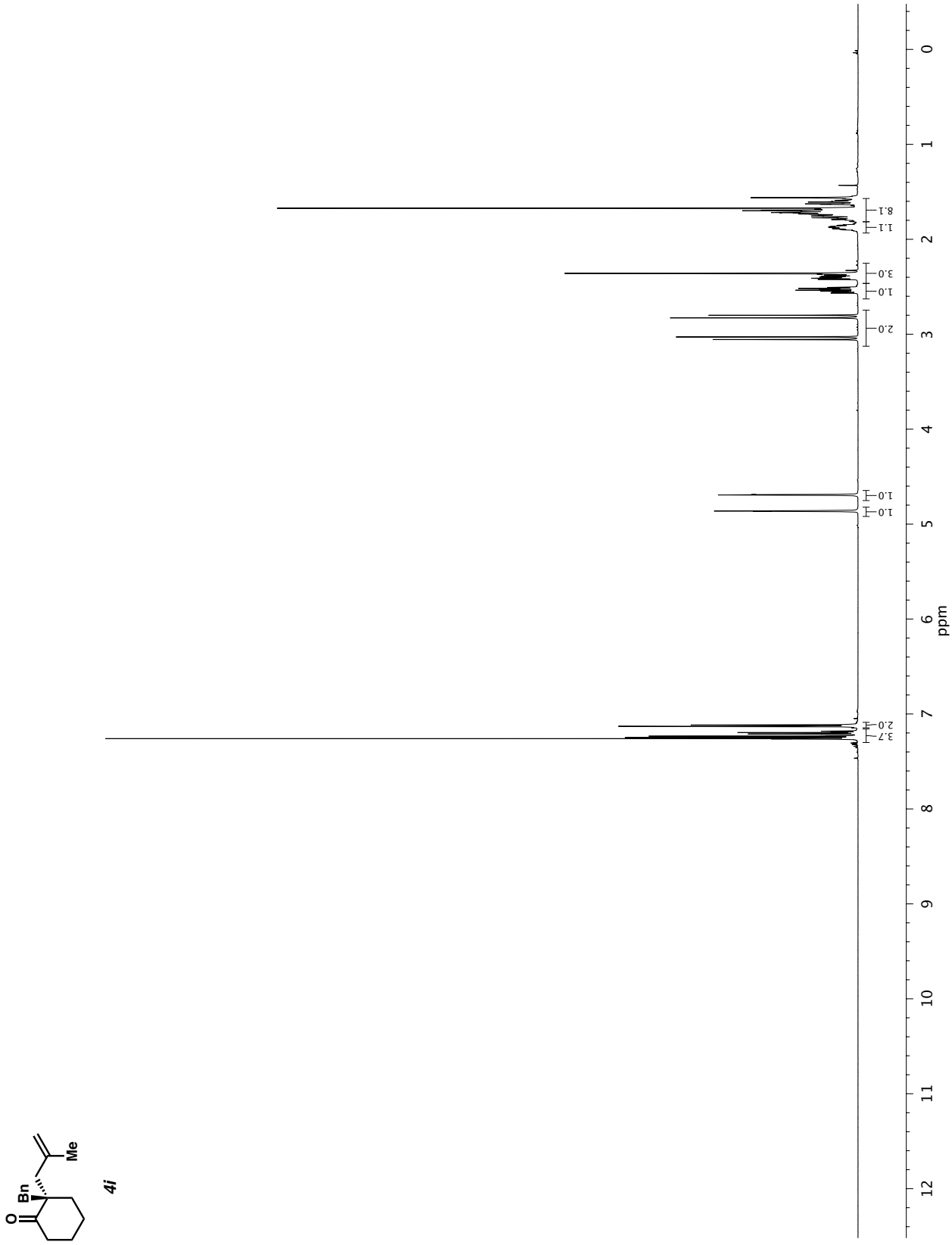
^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI5**.



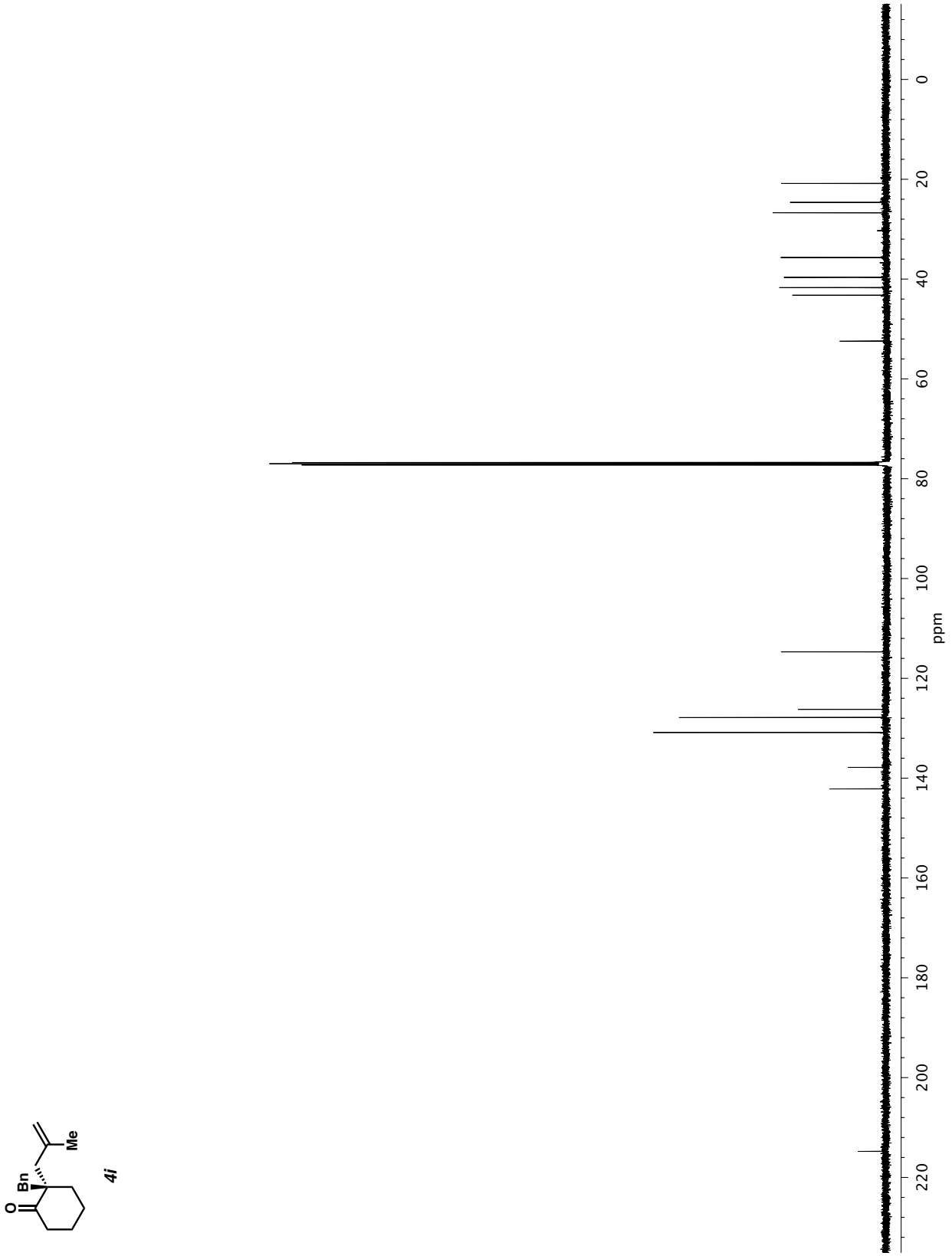
^{1}H NMR (300 MHz, $CDCl_3$) of compound **6**.



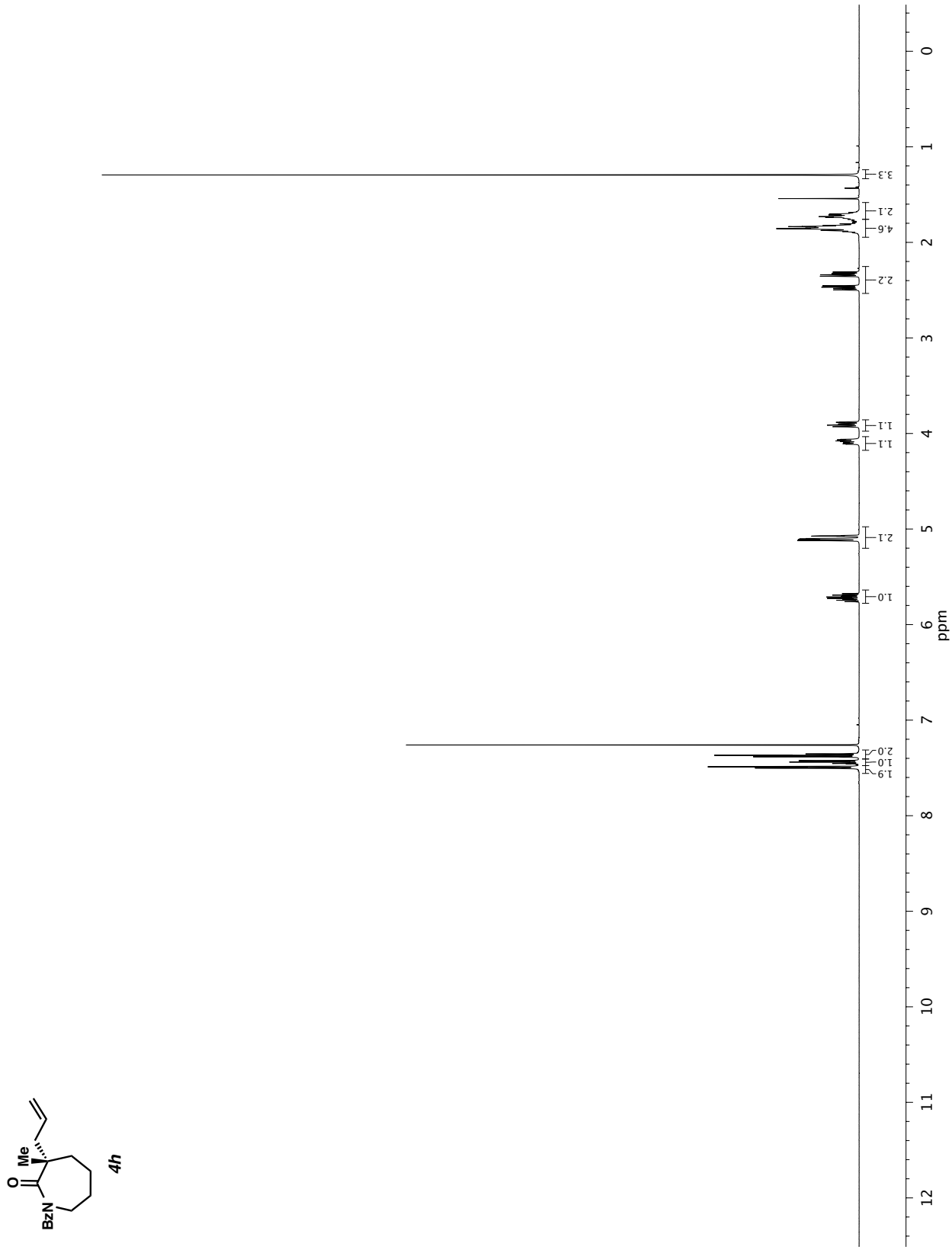
^{13}C NMR (126 MHz, $CDCl_3$) of compound **6**.



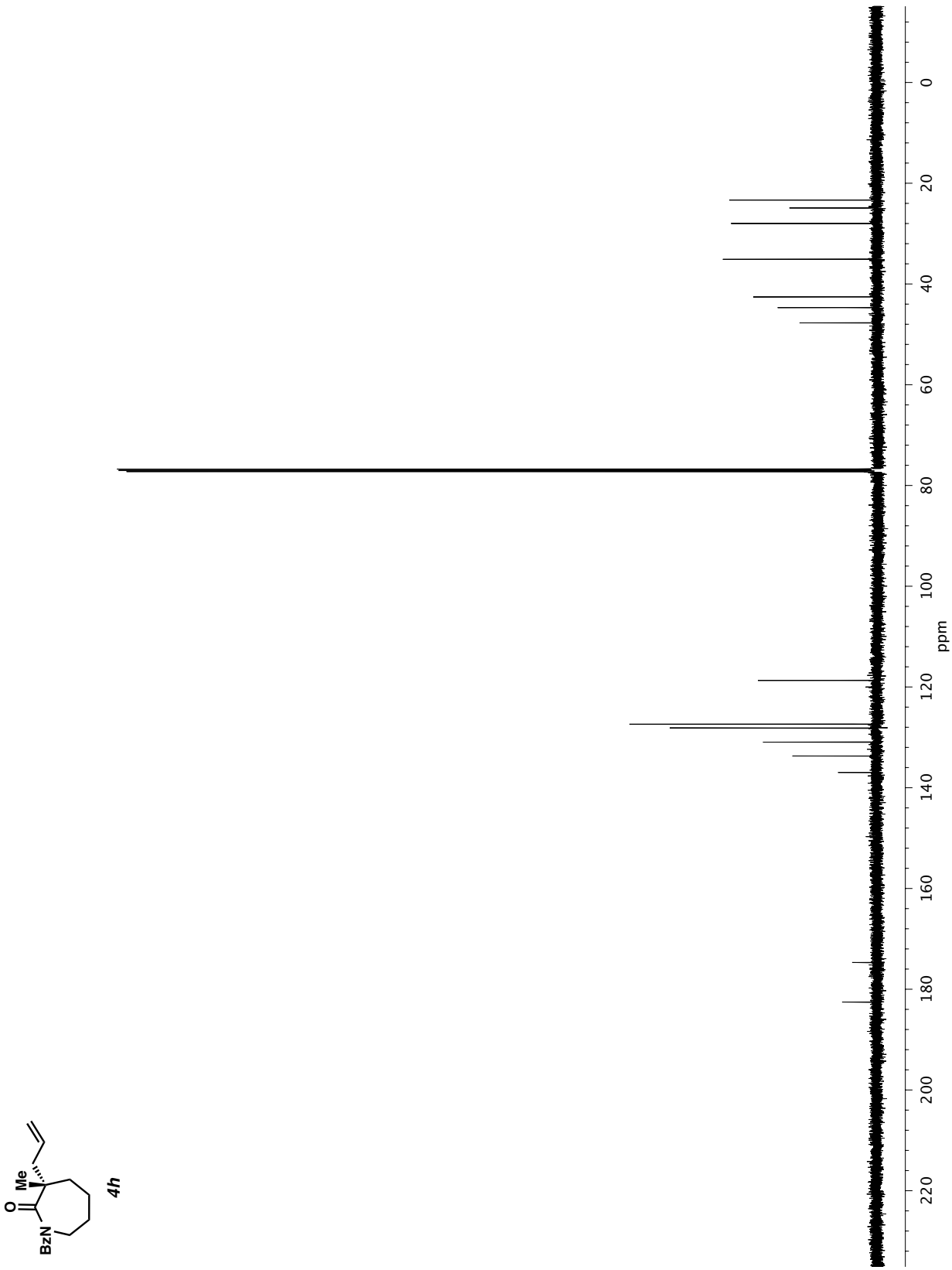
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4i**.



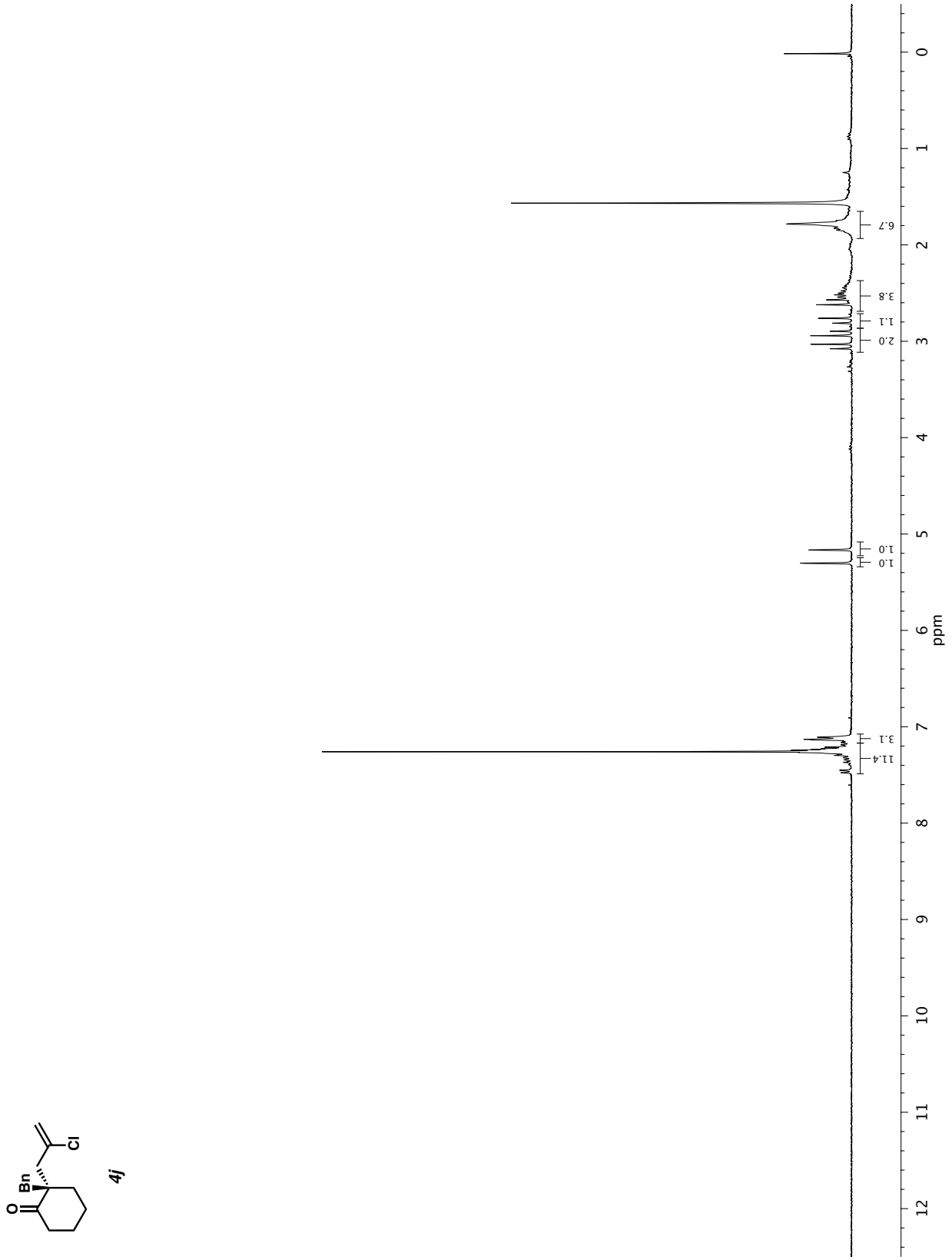
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4i**.



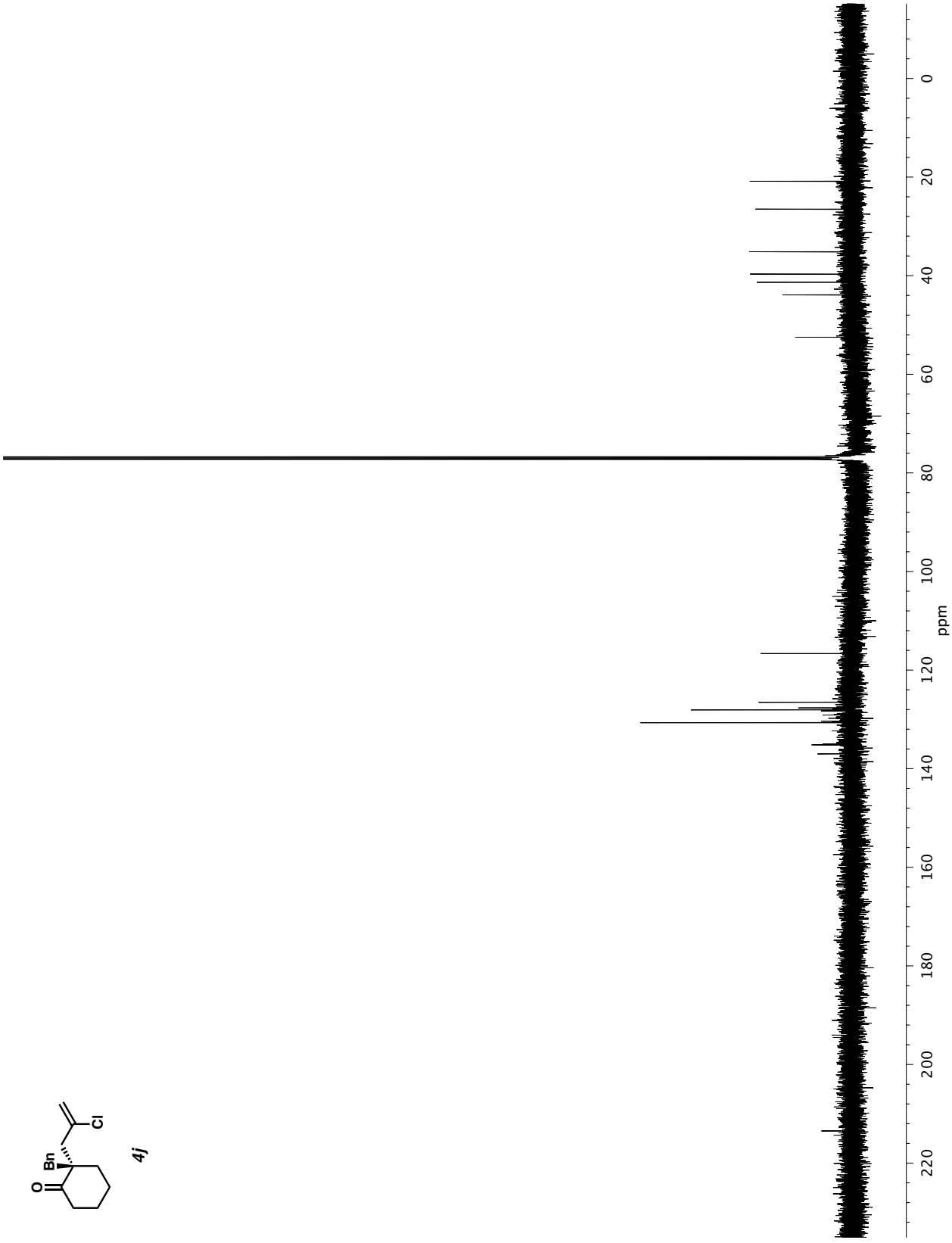
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4h**.



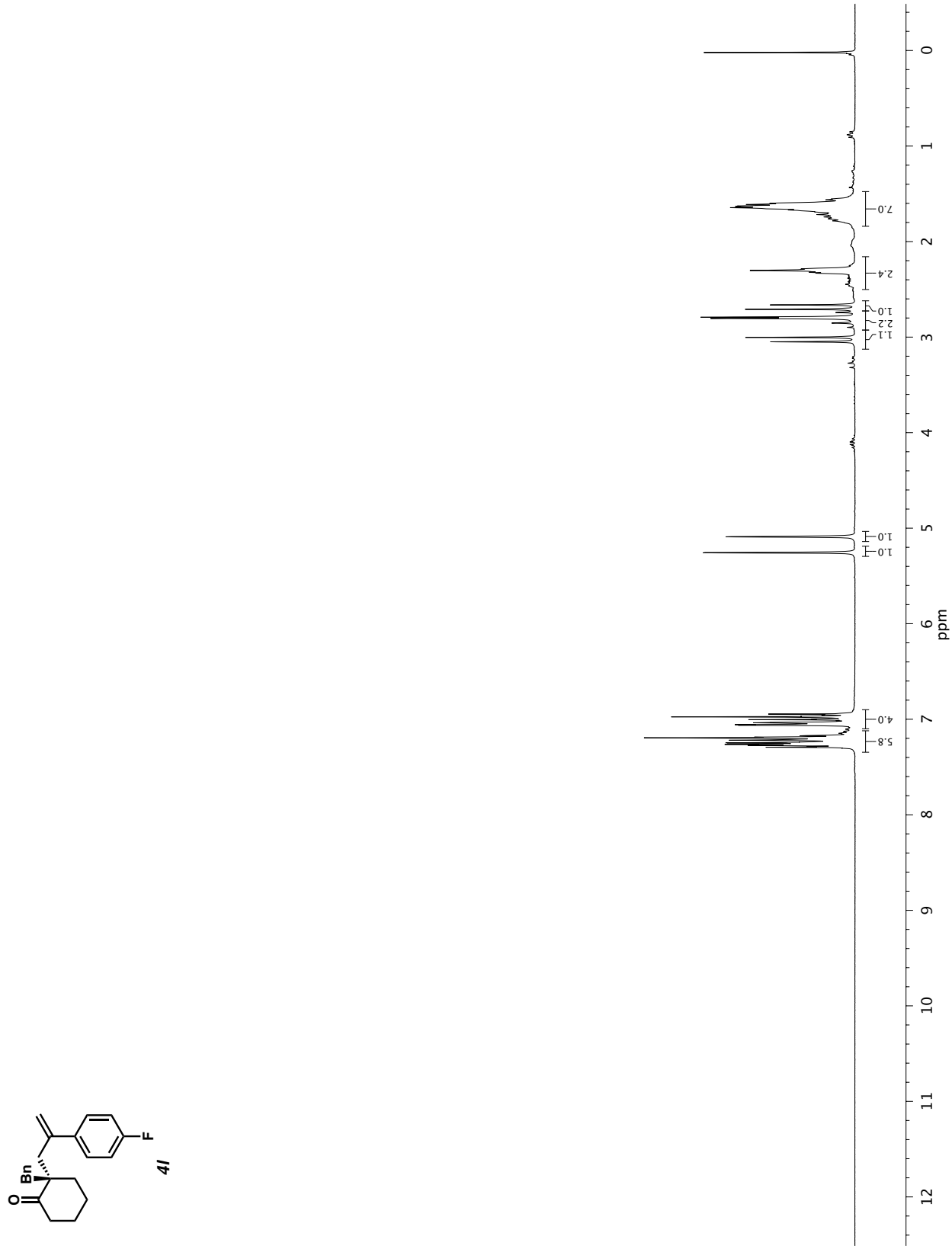
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4h**.



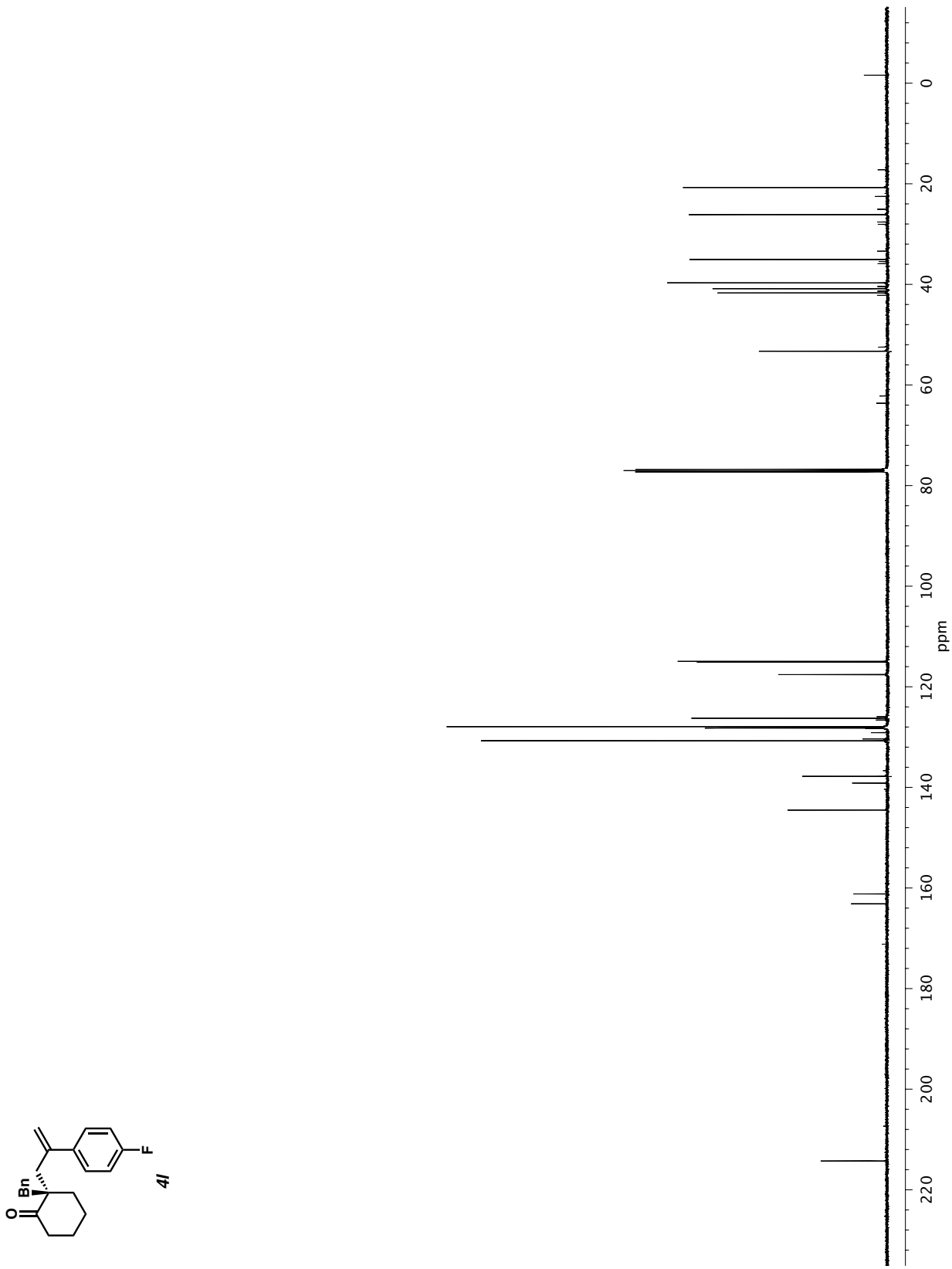
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4j**.



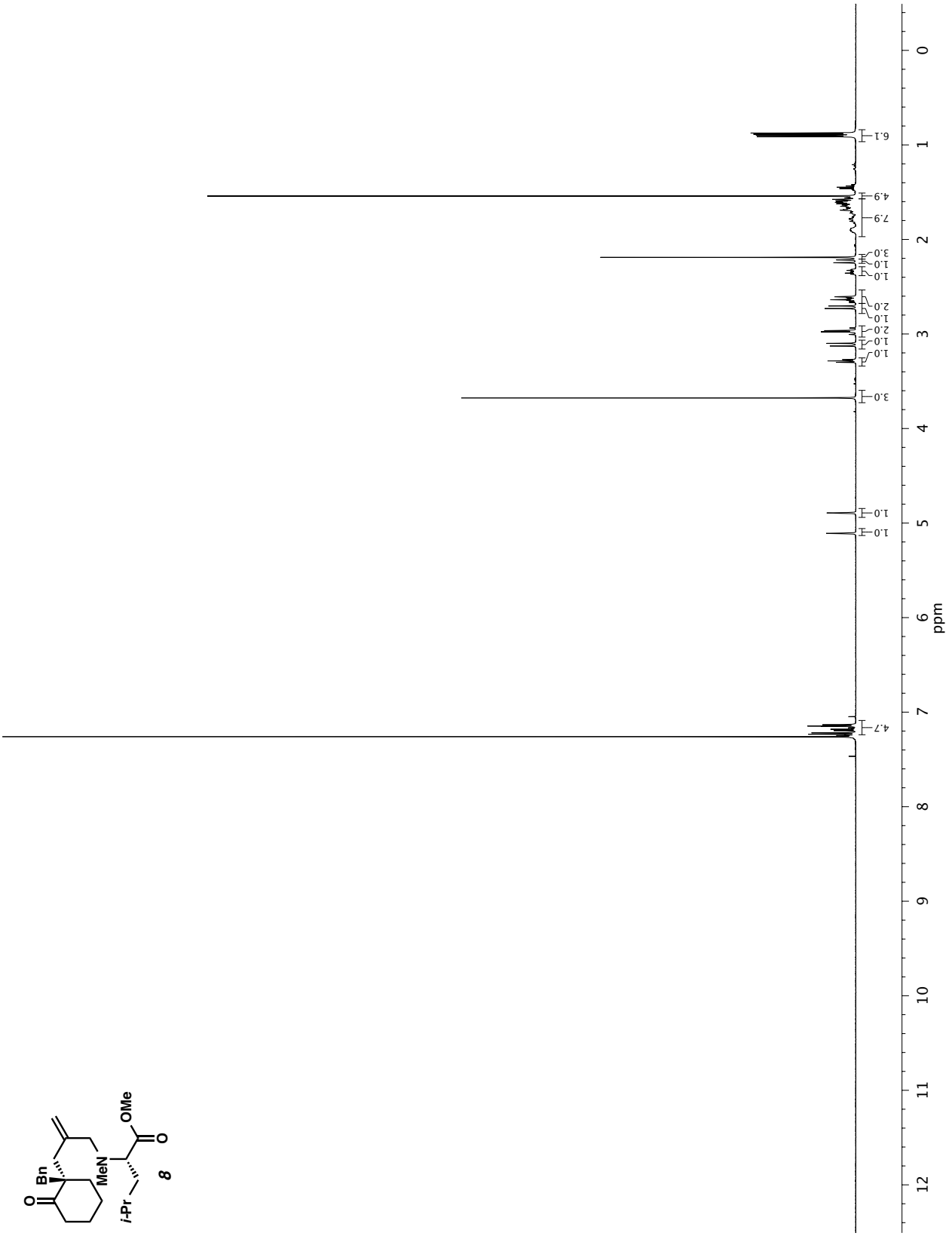
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4j**.



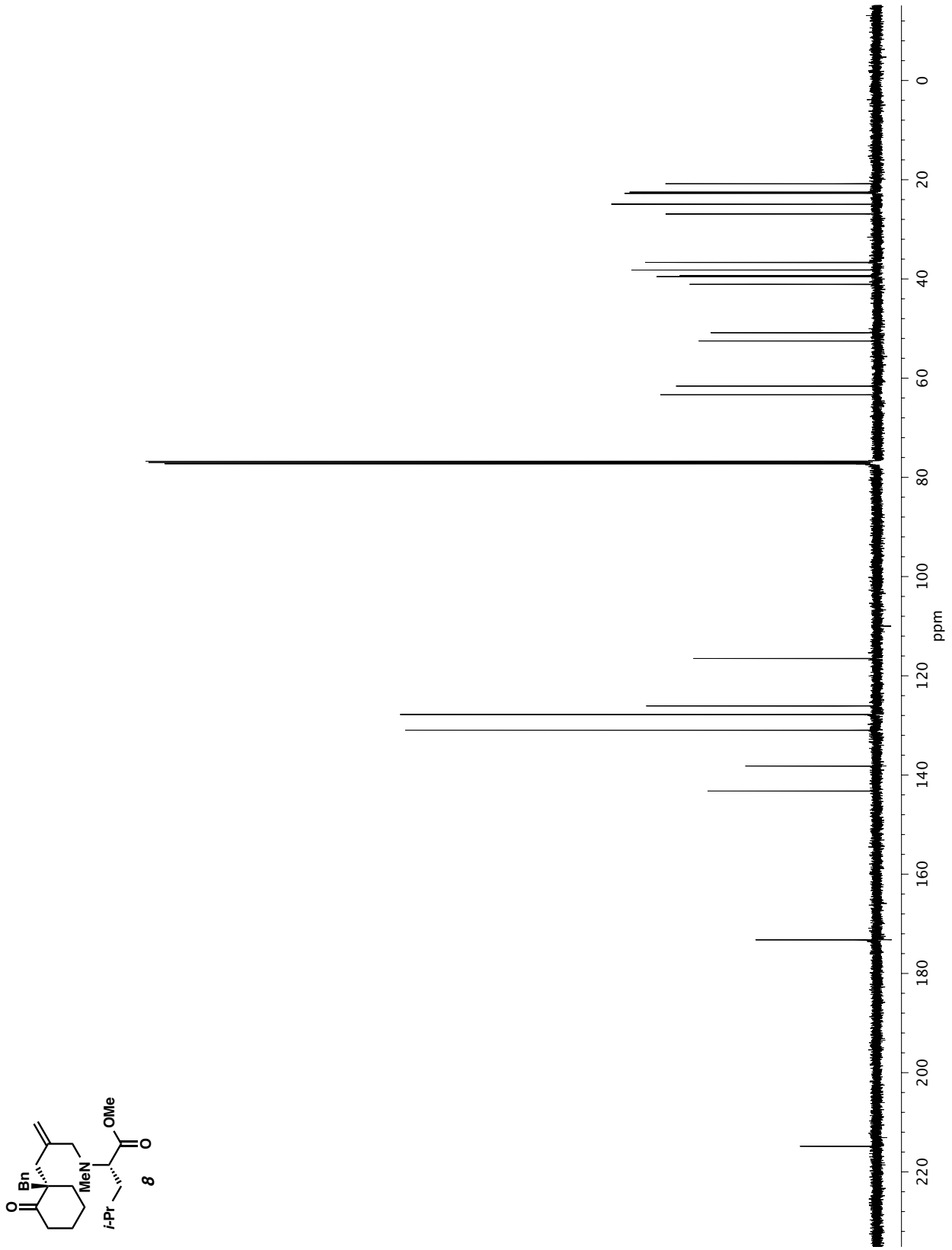
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4l**.



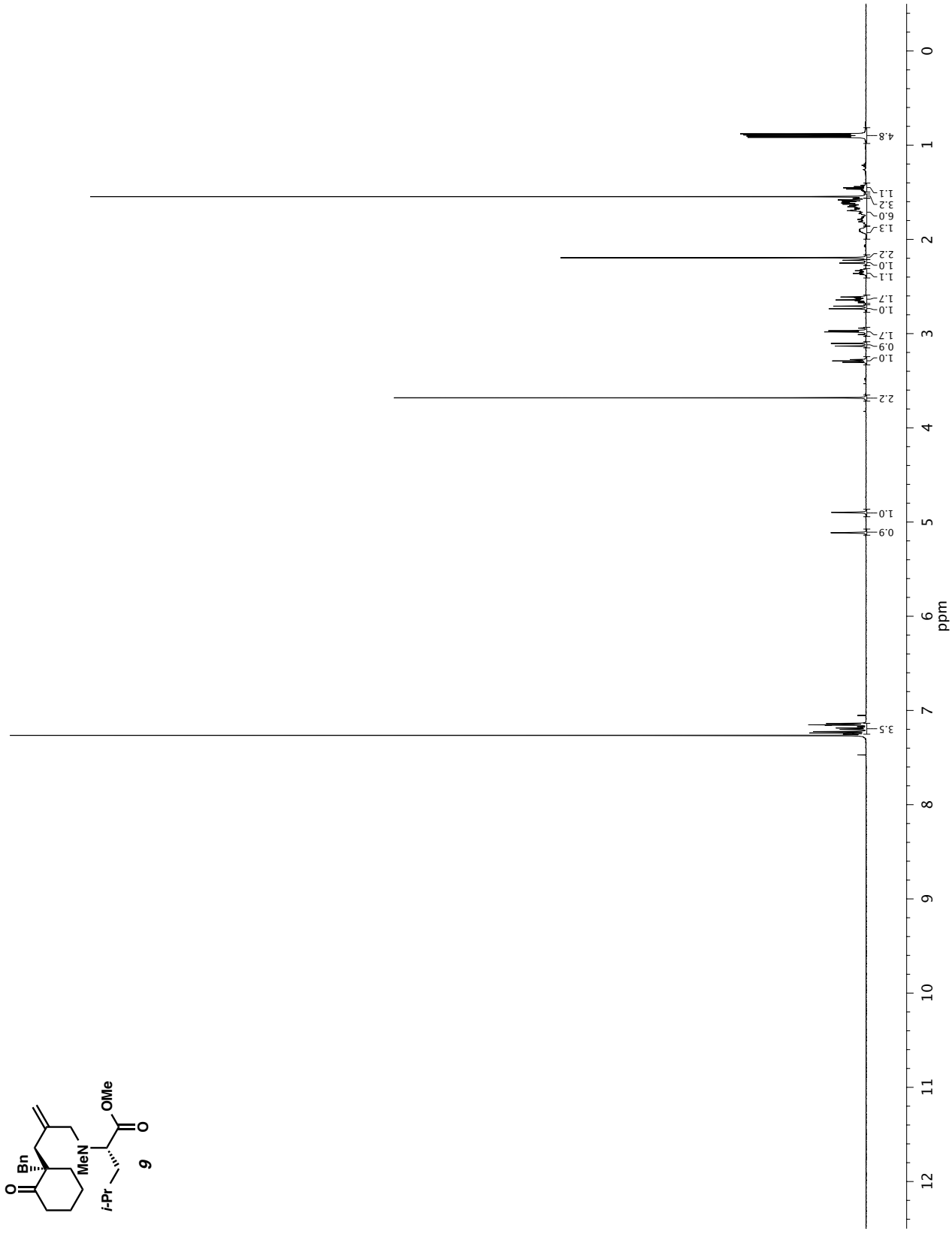
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4l**.



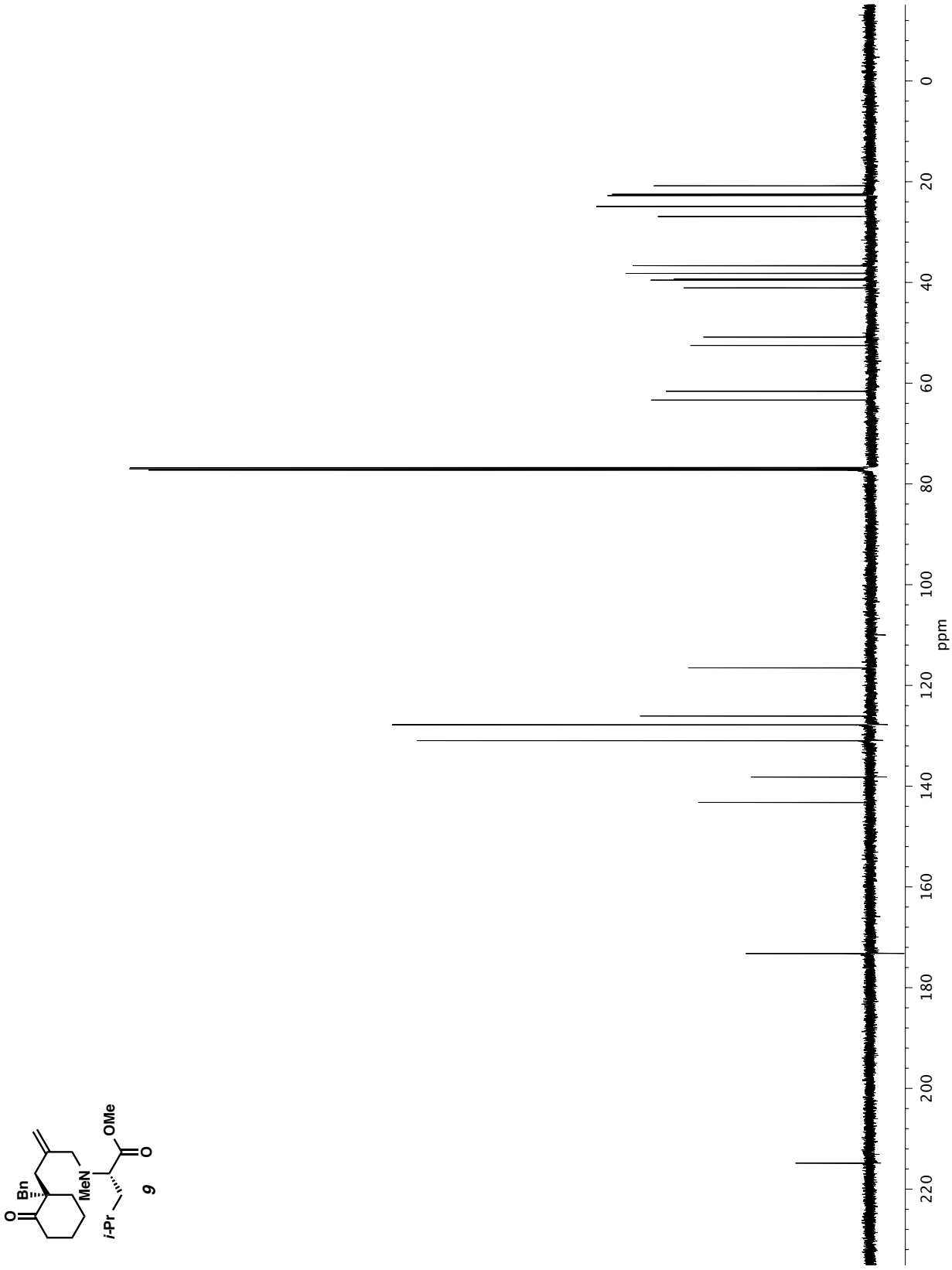
^{1}H NMR (500 MHz, $CDCl_3$) of compound **8**.



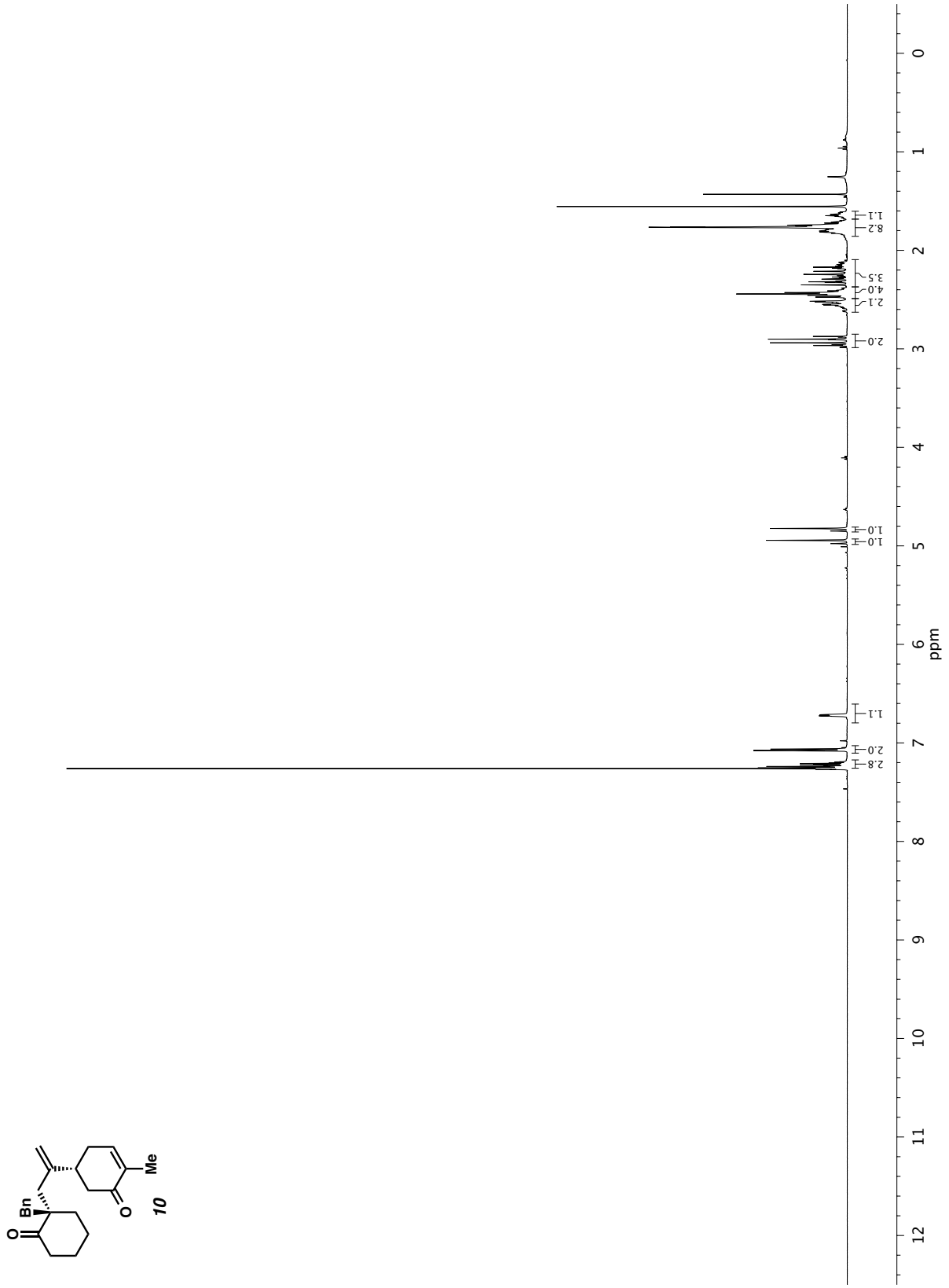
^{13}C NMR (126 MHz, $CDCl_3$) of compound **8**.



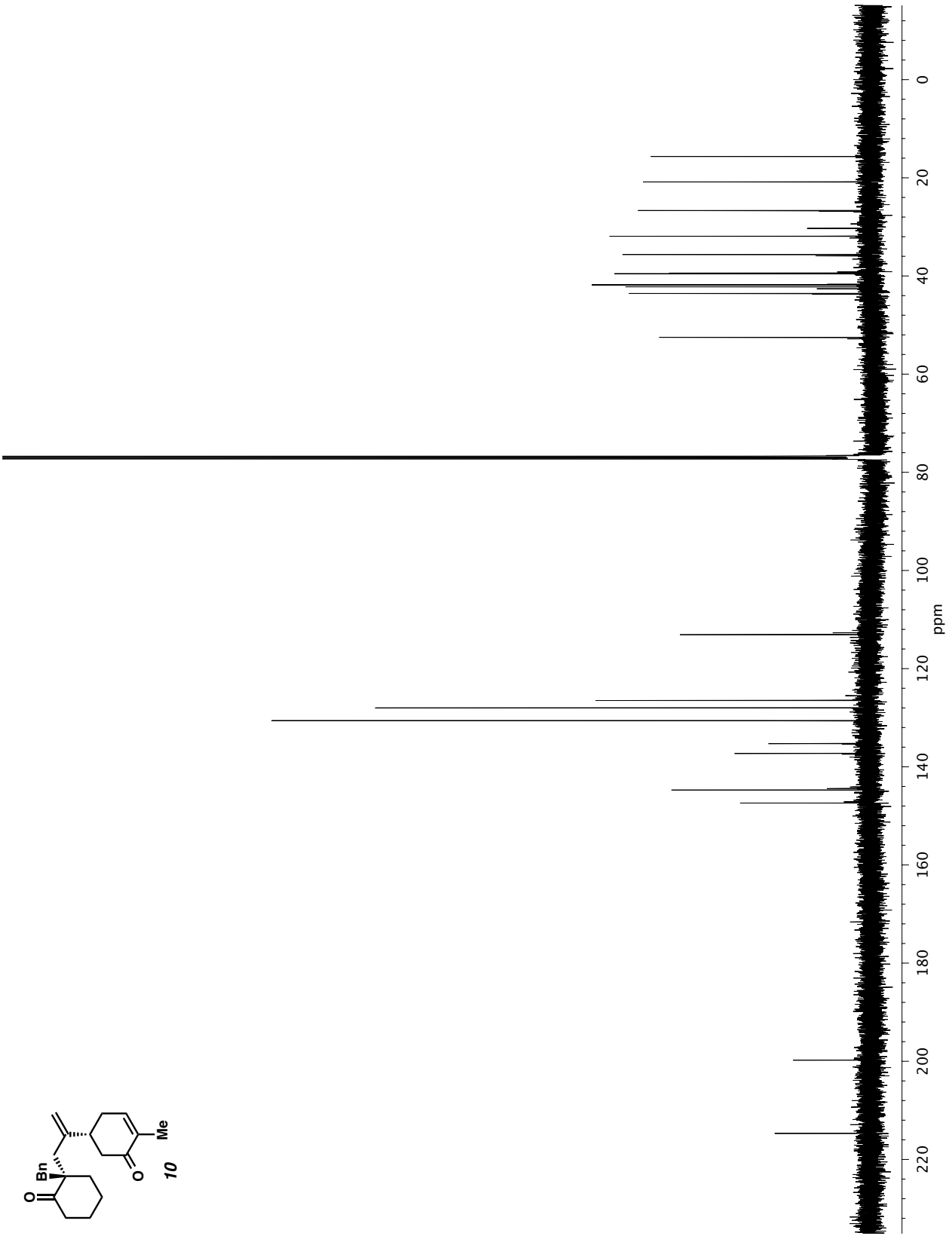
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9**.



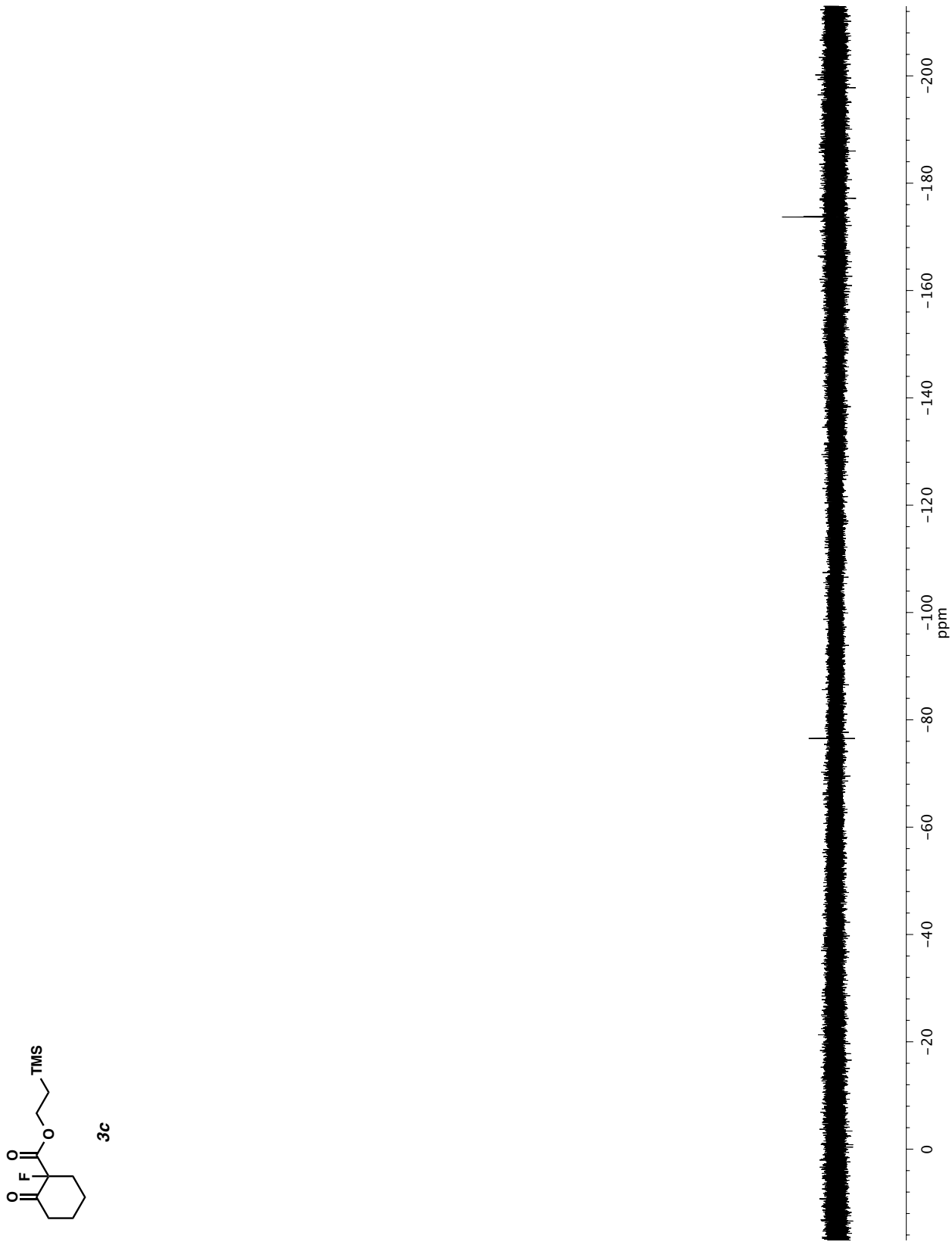
^{13}C NMR (126 MHz, $CDCl_3$) of compound **9**.



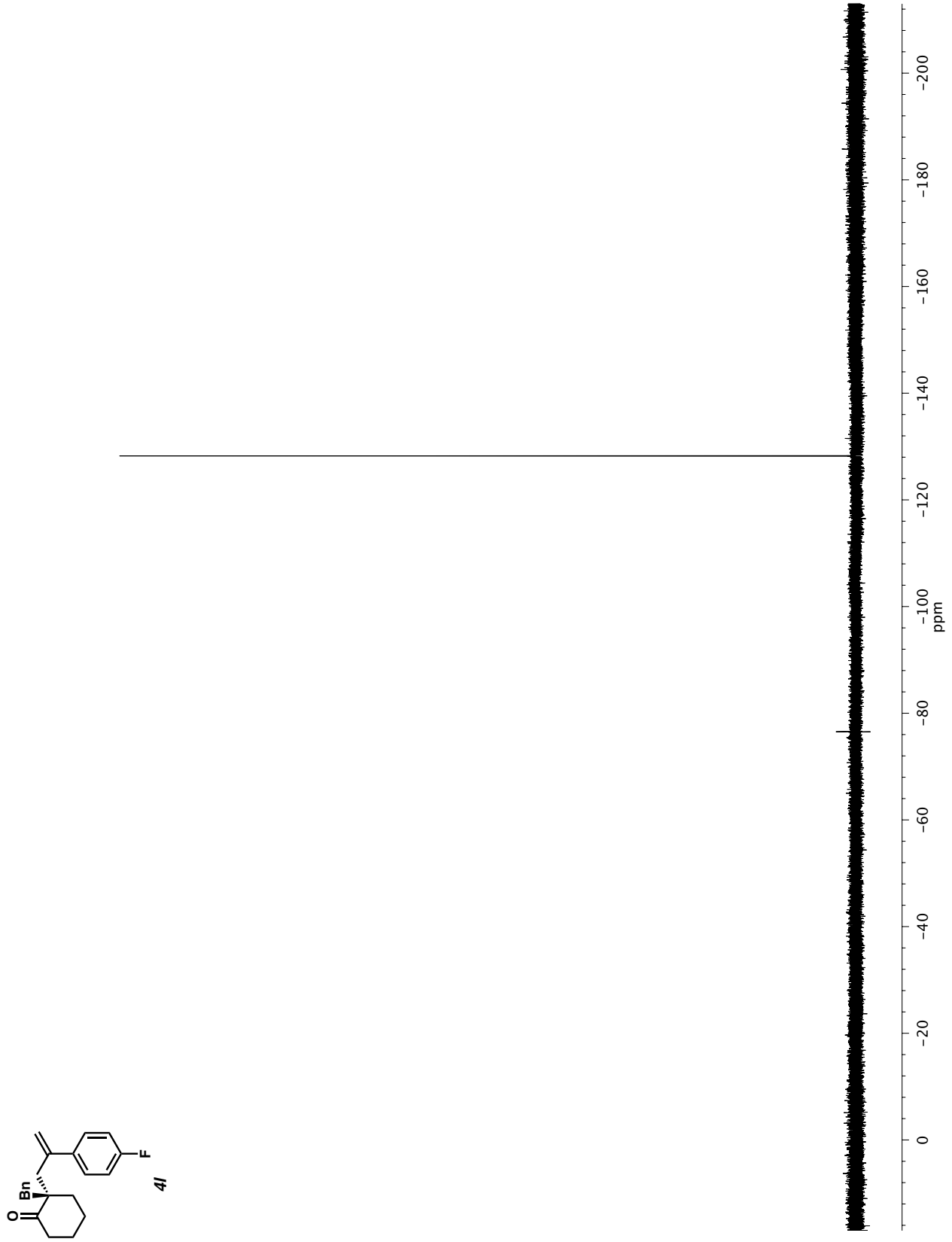
^{1}H NMR (500 MHz, $CDCl_3$) of compound **10**.



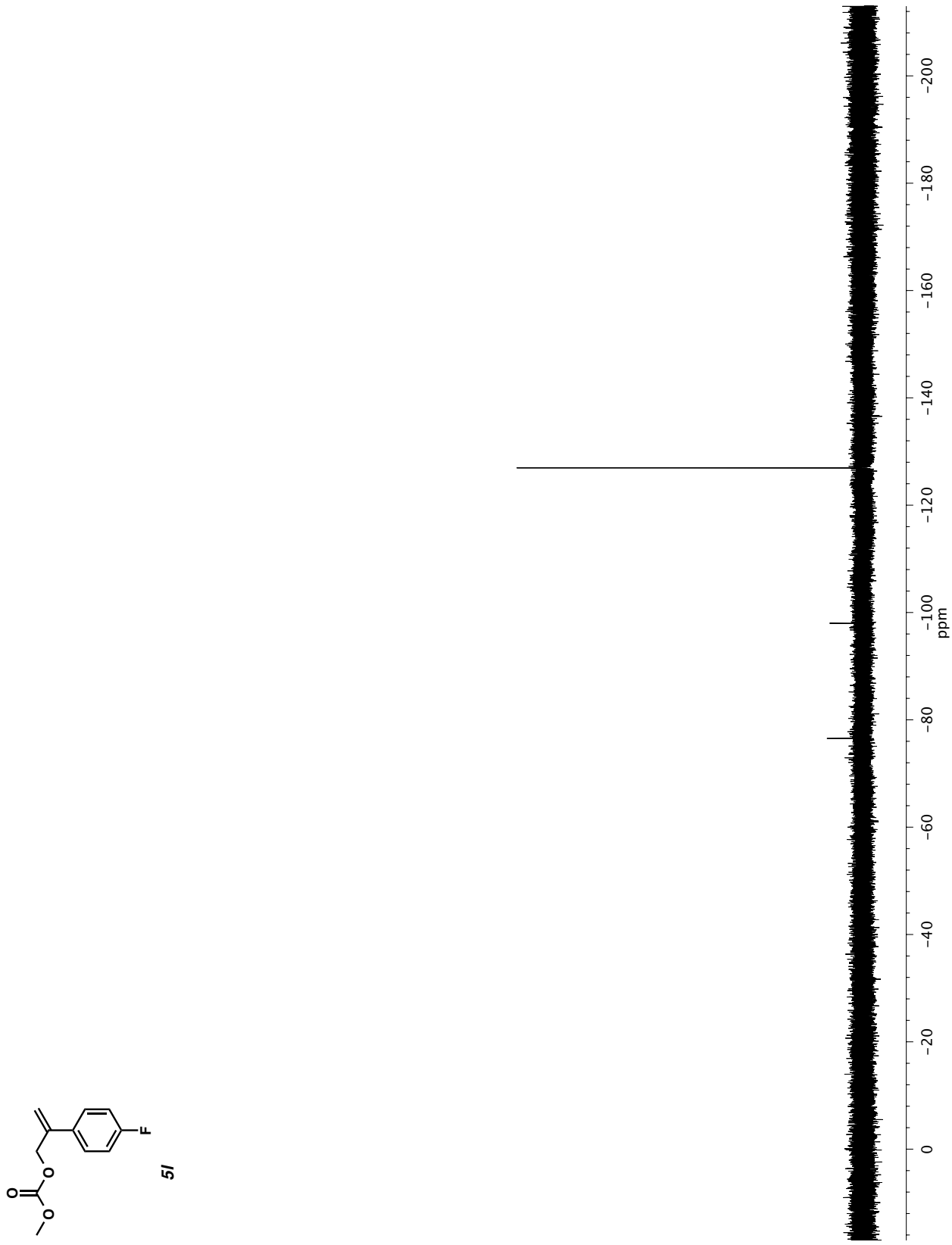
^{13}C NMR (126 MHz, $CDCl_3$) of compound **10**.



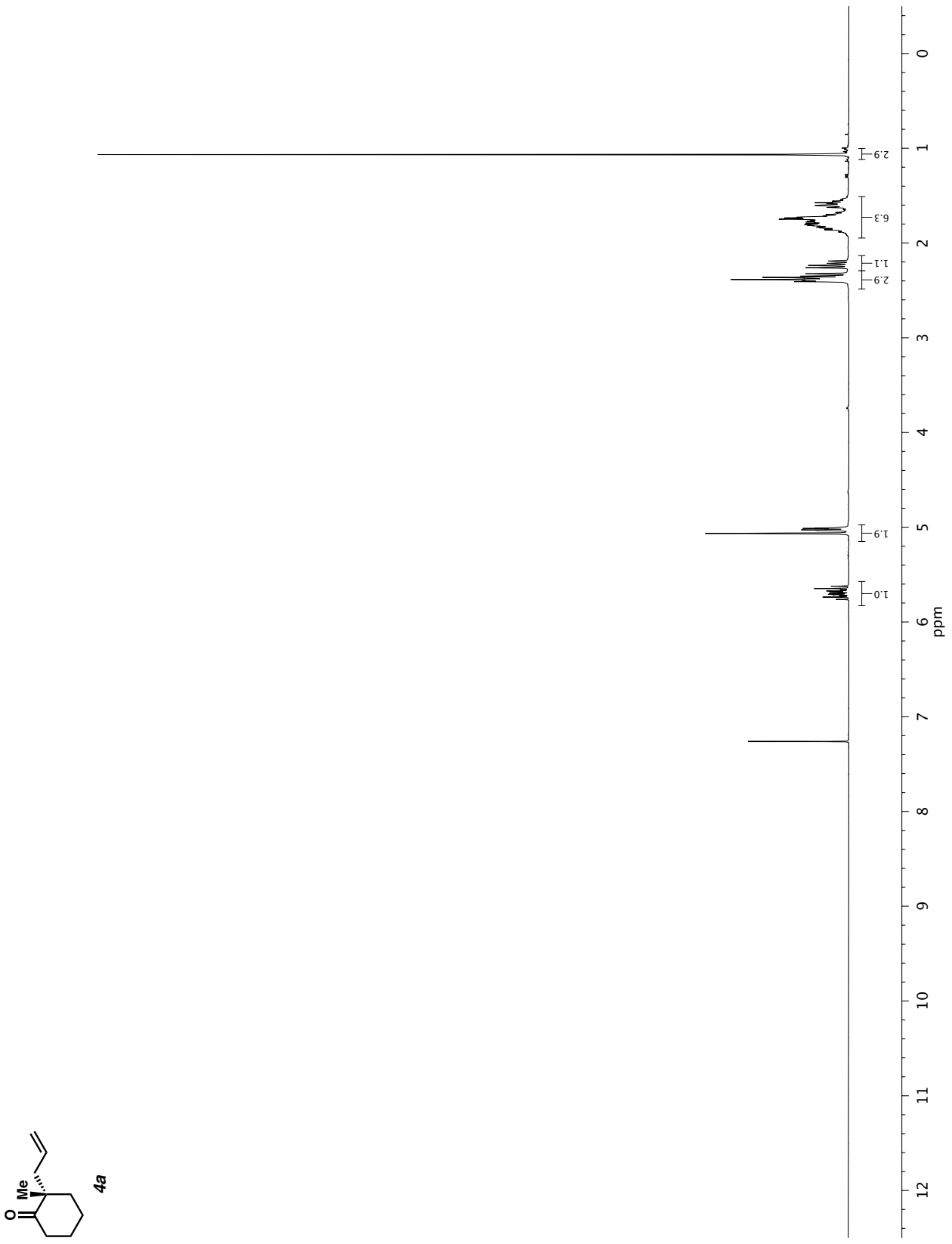
^{19}F NMR (282 MHz, $CDCl_3$) of compound **3c**.



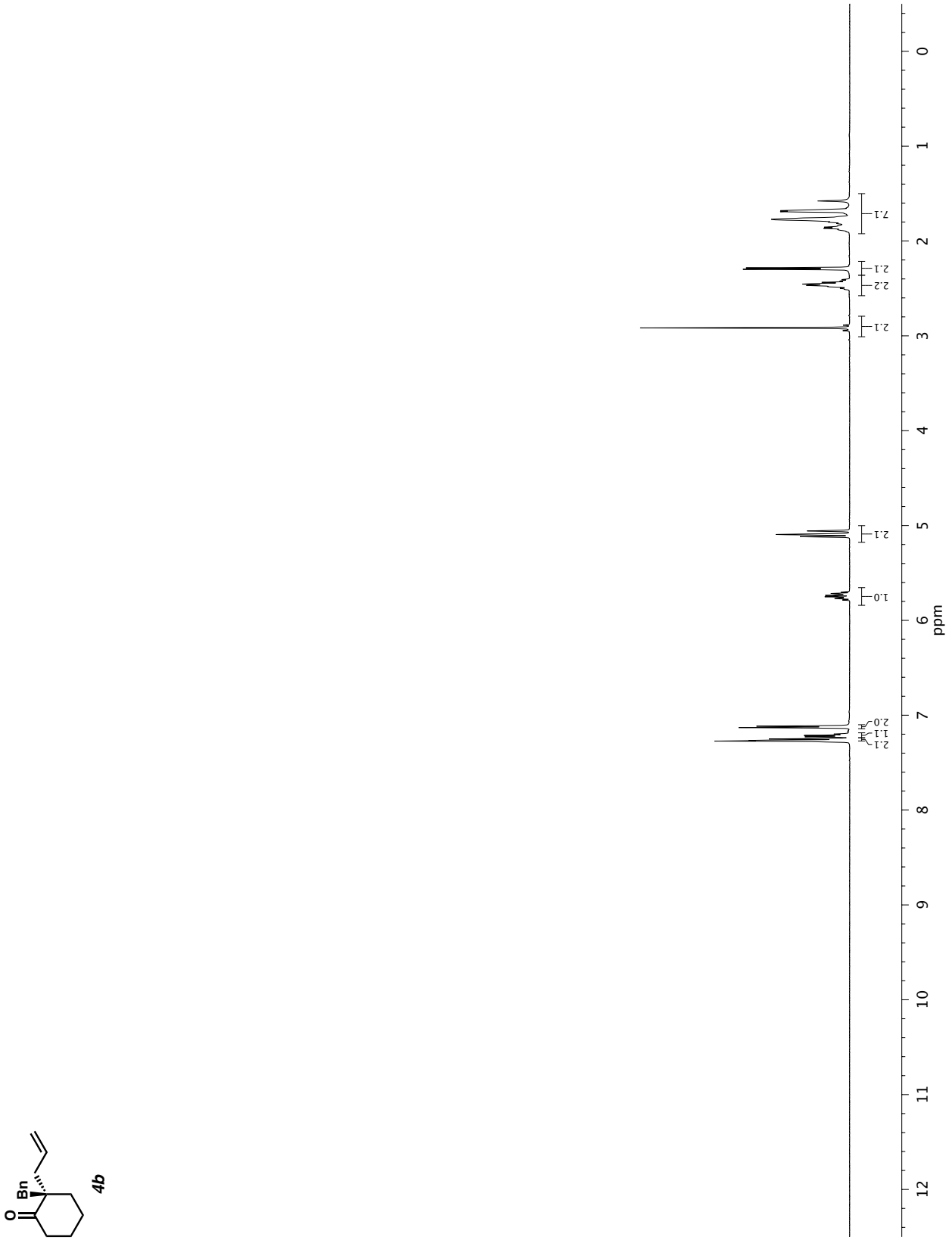
^{19}F NMR (282 MHz, $CDCl_3$) of compound **4l**.



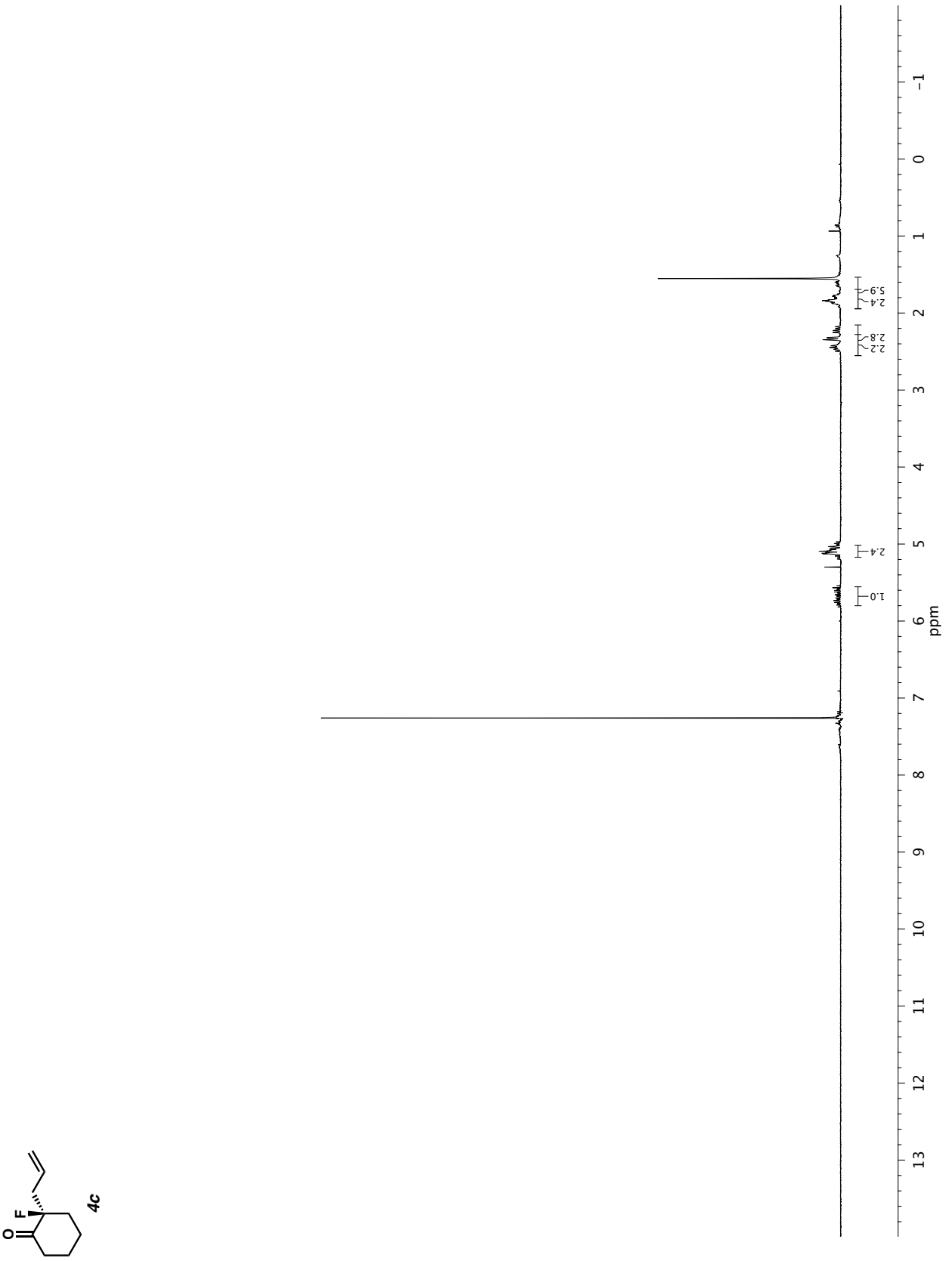
^{19}F NMR (282 MHz, $CDCl_3$) of compound **5l**.



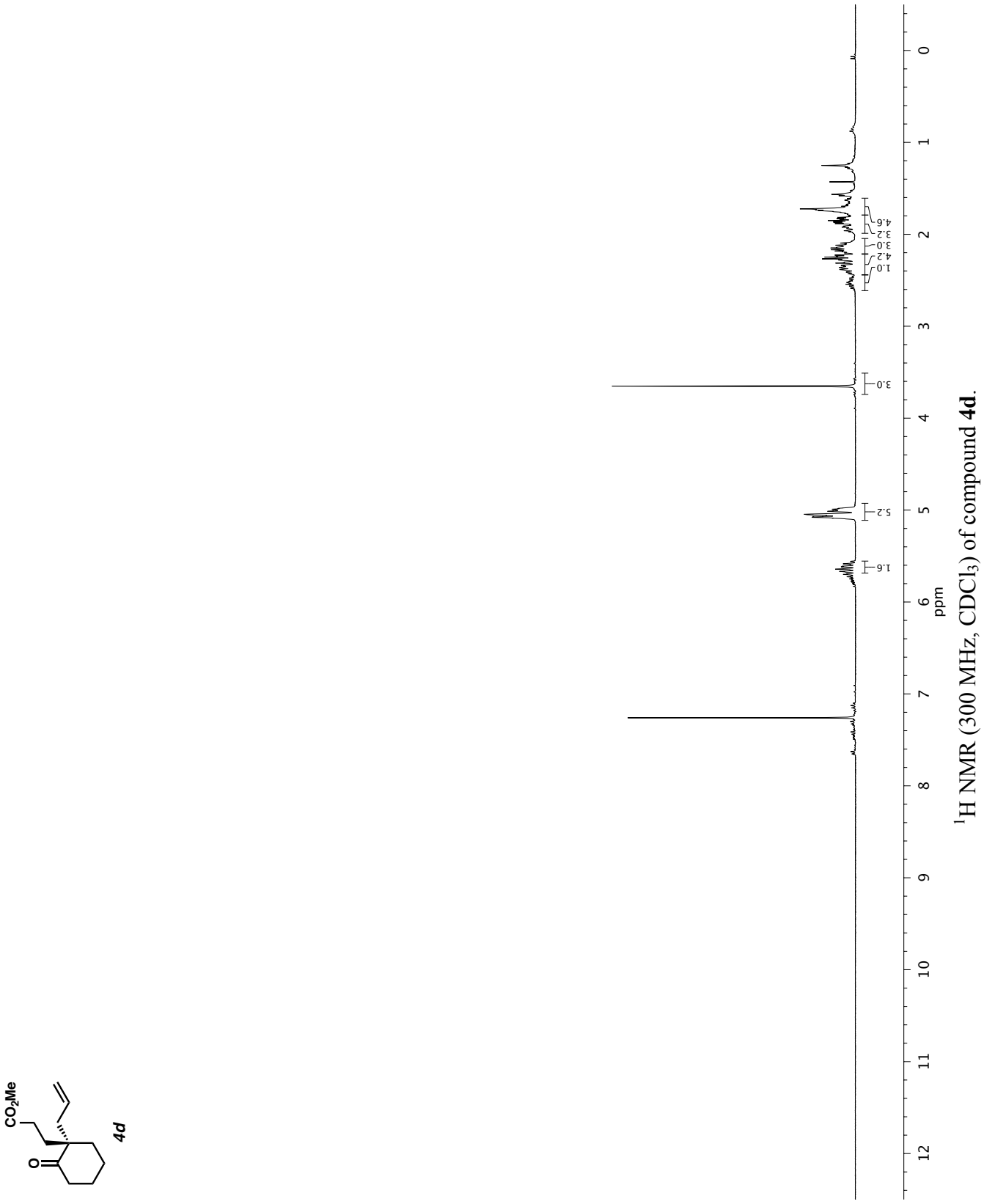
^{1}H NMR (300 MHz, $CDCl_3$) of compound **4a**.



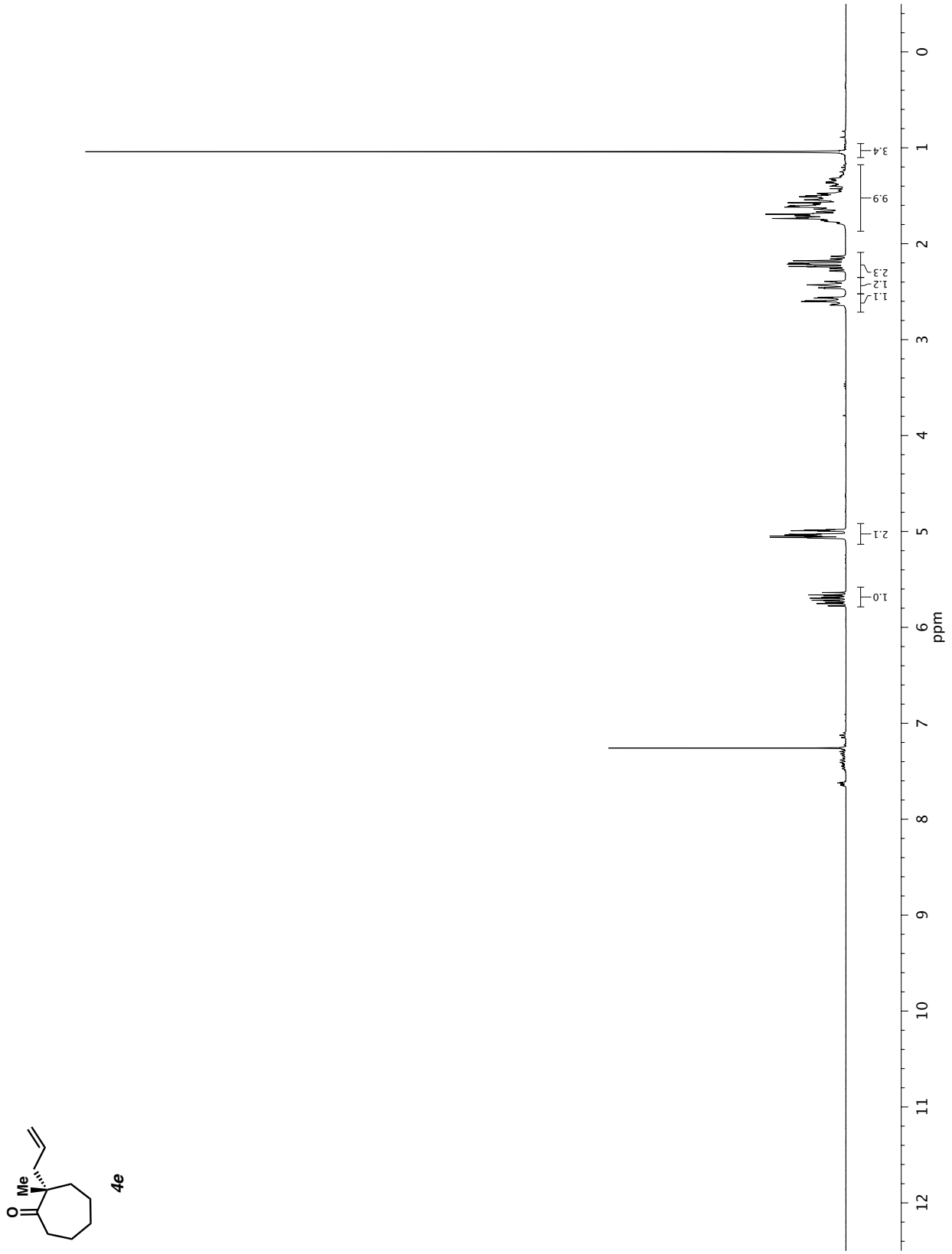
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4b**.



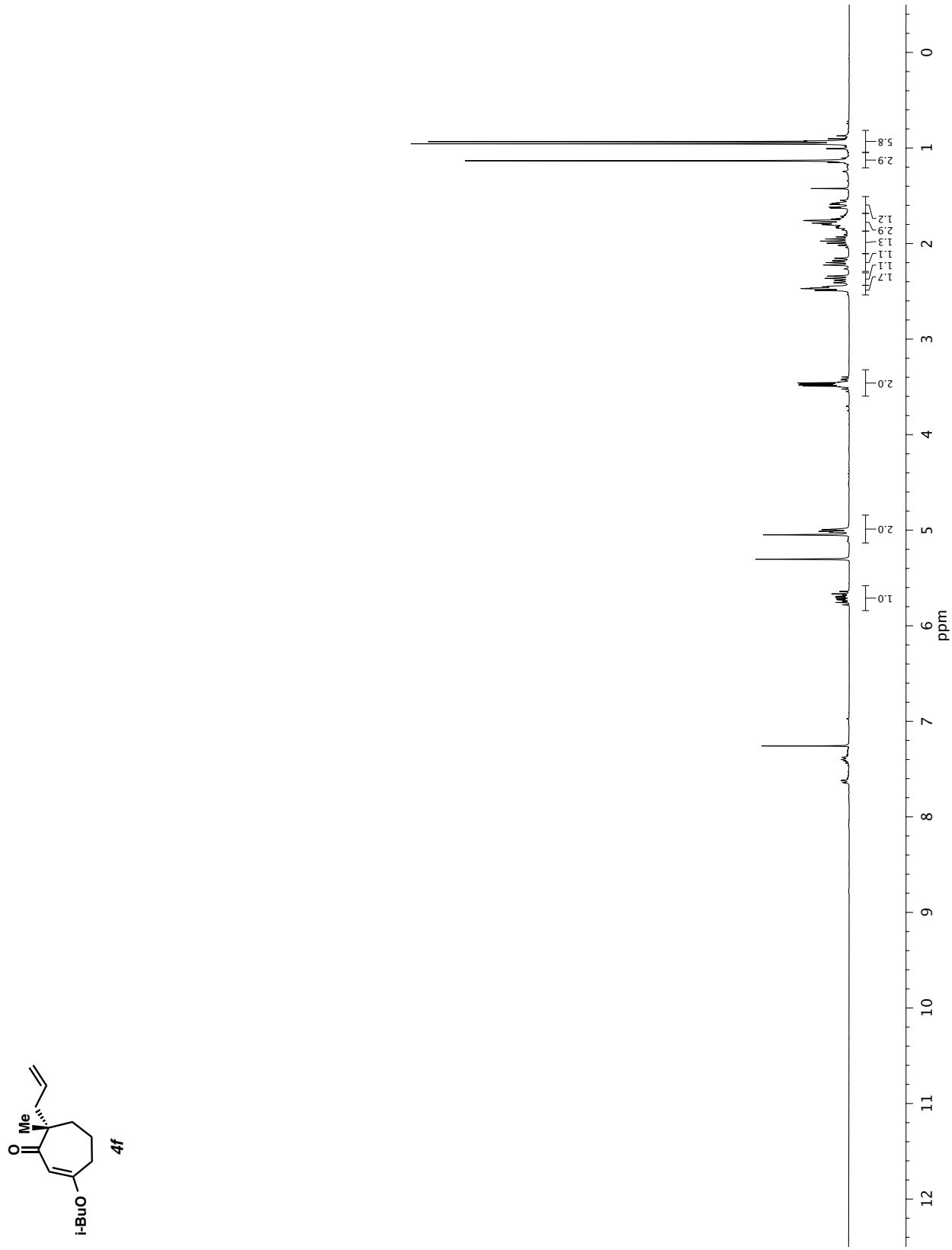
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4c**.



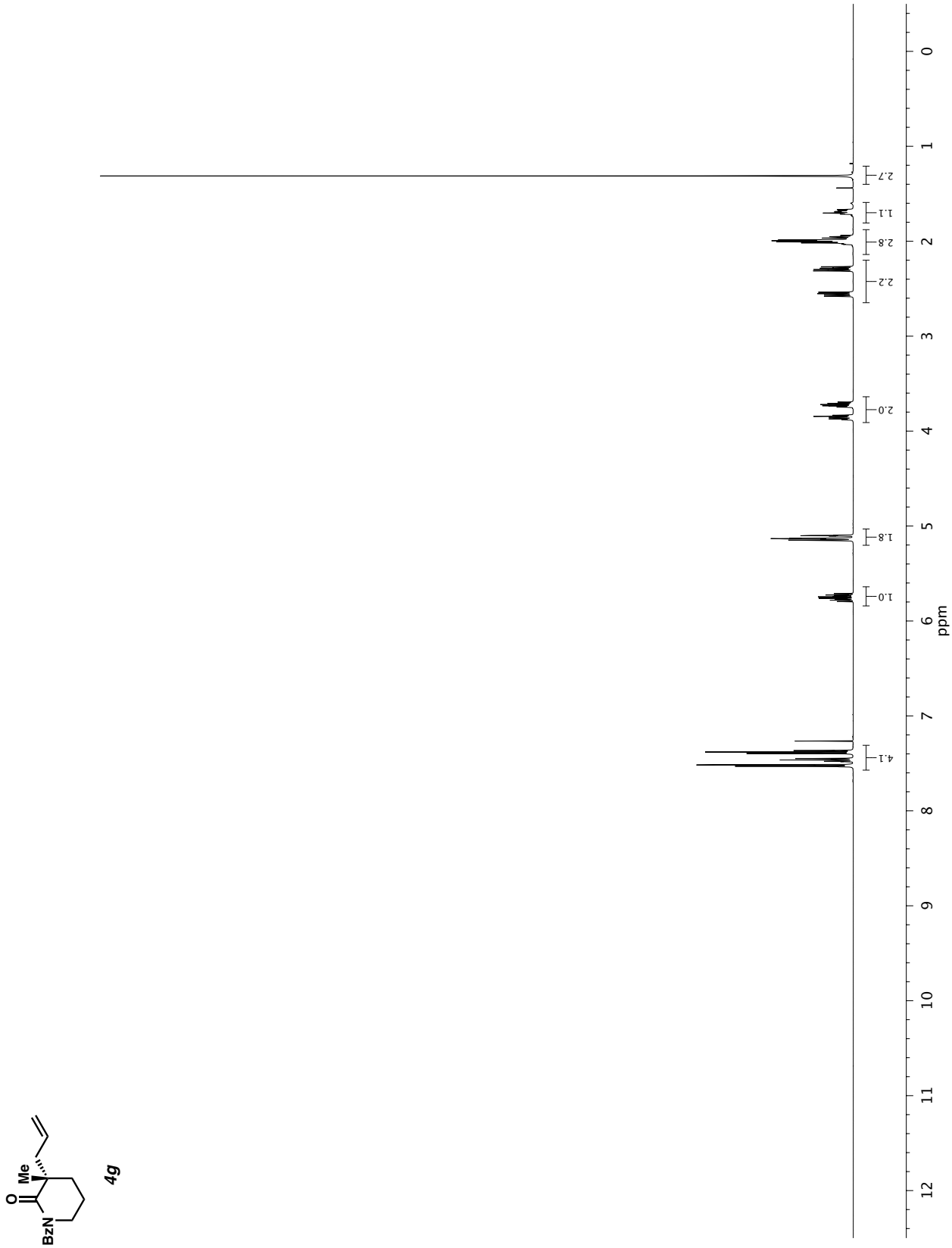
^{1}H NMR (300 MHz, $CDCl_3$) of compound **4d**.



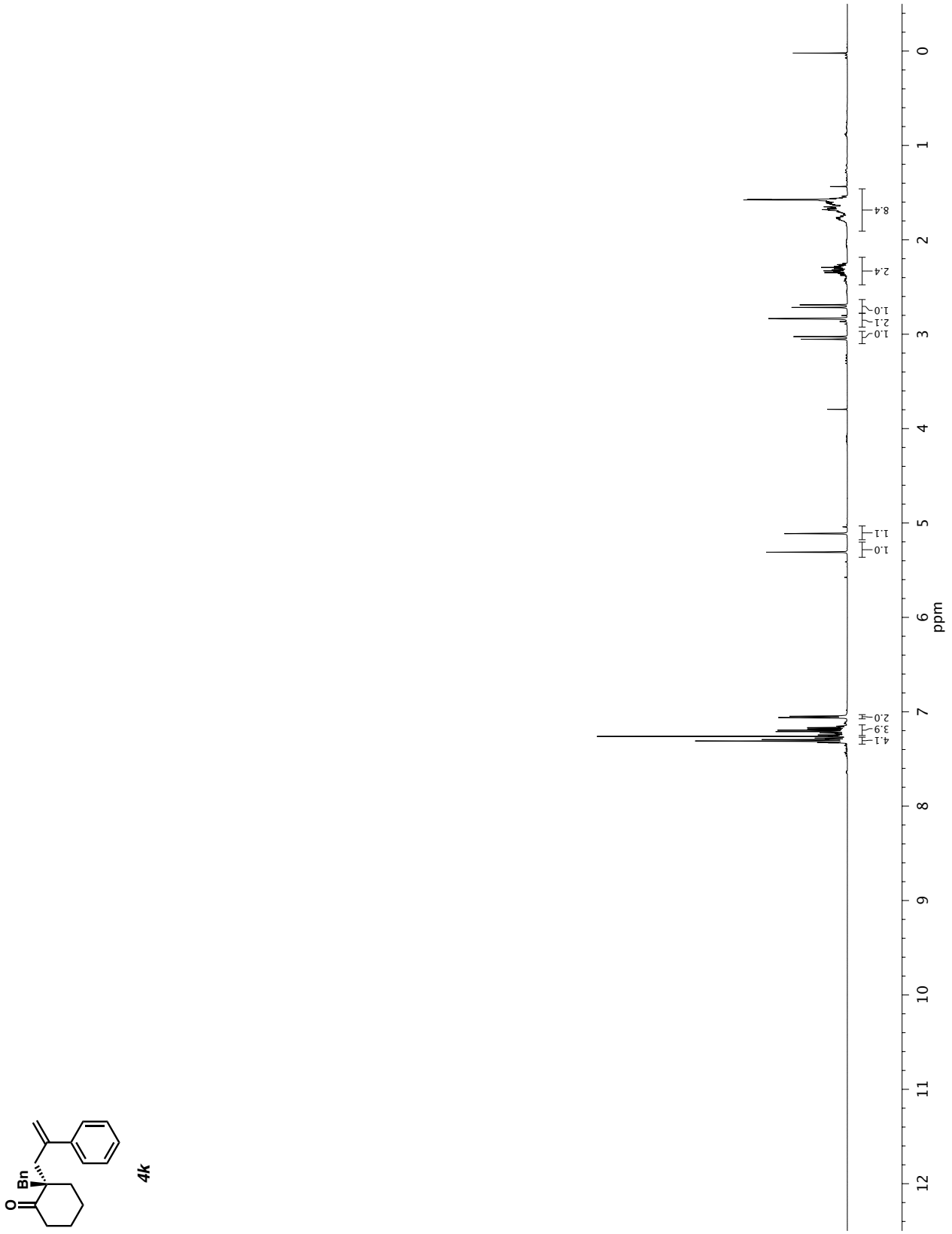
^{1}H NMR (300 MHz, $CDCl_3$) of compound **4e**.



^{1}H NMR (300 MHz, $CDCl_3$) of compound **4f**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **4g**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **4k**.