

*Supporting Information for***Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to α,β -Unsaturated Lactams: Enantioselective Construction of All-Carbon Quaternary Stereocenters in Saturated Nitrogen-Containing Heterocycles***Tianyi Zhang, Yuji Nishiura, Alexander Q. Cusumano, Brian M. Stoltz**

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Materials and Methods

Unless otherwise stated, reactions were performed in clean, air-dried glassware under normal atmosphere using dry, deoxygenated solvents.¹ Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, or KMnO₄ staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 µm) was used for flash chromatography. ¹H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual CHCl₃ (δ 7.26 ppm). ¹³C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to CHCl₃ (δ 77.16 ppm). Data for ¹H 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. Data for ¹³C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of water (δ 1.56 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), acetone (δ 2.17 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. IR spectra were obtained by use of 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. Analytical SFC was performed with a Mettler SFC supercritical CO₂ 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. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source, or an Agilent 6230 TOF, in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Absolute stereochemistry of product **3f** is assigned via Vibrational Circular Dichroism (VCD) using a BioTools ChiralIR-2X VCD spectrometer in dual PEM mode, while the absolute stereochemistry of the remaining products are assigned by analogy to this result as well as previous results by our group and literature reports.^{2,4b} Reagents were

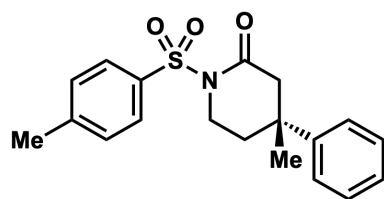
purchased from commercial sources and used as received unless otherwise stated. The ligand (*S*)-*t*-BuPyOx was prepared according to a literature procedure.³

List of Abbreviations

ee – enantiomeric excess, SFC – supercritical fluid chromatography, TLC – thin-layer chromatography, VCD – vibrational circular dichroism

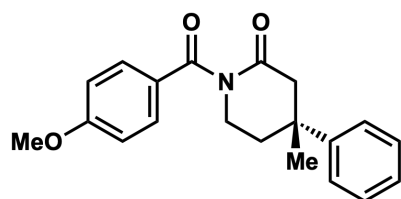
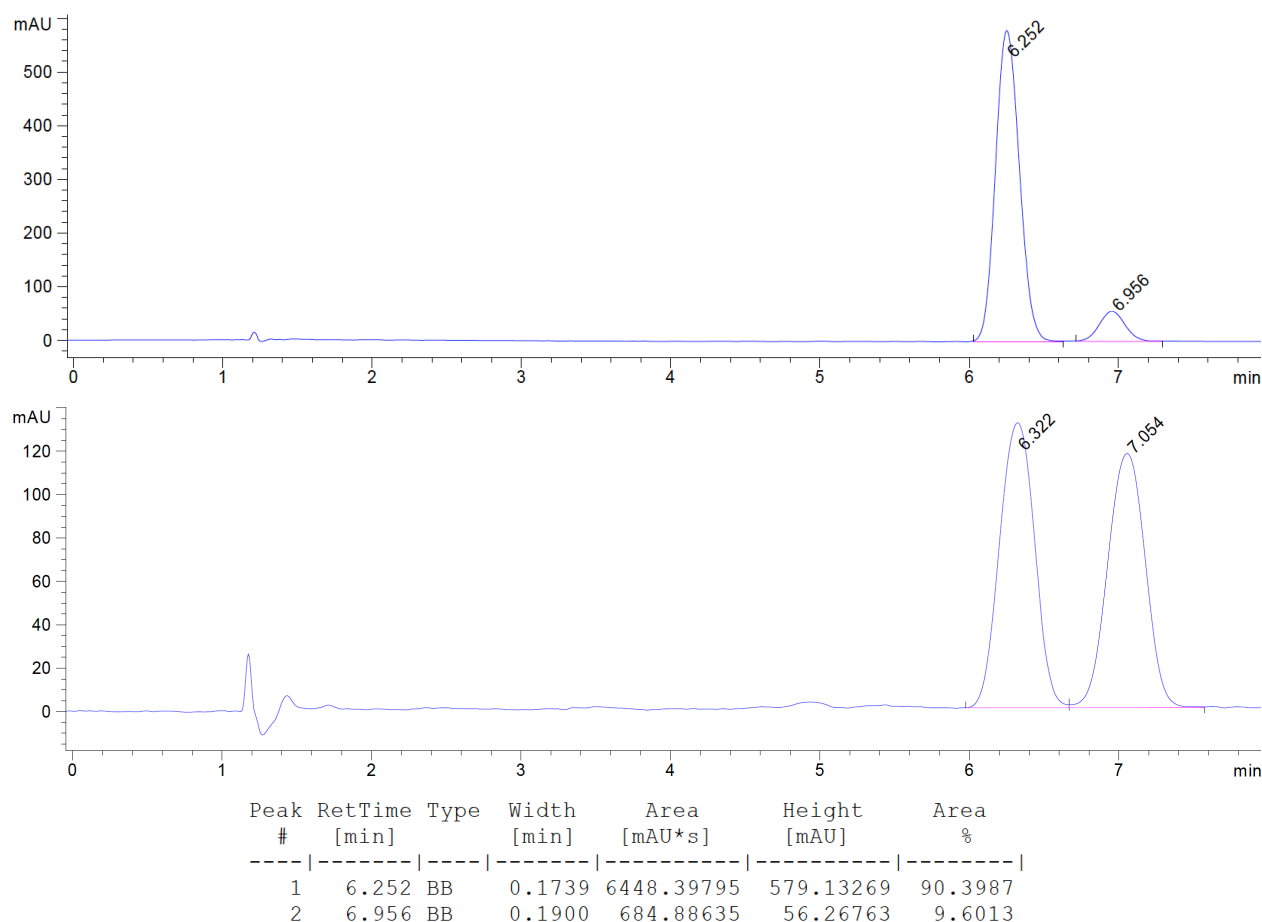
General Procedure for Pd-Catalyzed Asymmetric Conjugate Addition Reactions

A screw-top 1 dram vial was charged with a stir bar, Pd(OCOCF₃)₂ (10 mol%) and (*S*)-*t*-BuPyOx (12 mol%). The solids were dissolved in dichloromethane (substrate concentration 0.125 M) and stirred at room temperature for 15 min. A separate vial was charged with AgBF₄ (24 mol%) and added the homogeneous solution of Pd(OCOCF₃)₂ and (*S*)-*t*-BuPyOx in dichloromethane and stirred at room temperature for 10 min. A separate vial was charged with the appropriate α,β -unsaturated lactam (1.0 equiv.) and PhB(OH)₂ (2.0 equiv.) and added the pre-stirred solution of Pd(OCOCF₃)₂, (*S*)-*t*-BuPyOx, and AgBF₄ in dichloromethane, followed by water (5.0 mmol, 5 equiv.). The vial was then sealed and stirred at 30 °C for 16 h. The reaction mixture was filtered through a silica plug with ethyl acetate, and evaporated *in vacuo*. The crude reaction mixture was loaded directly onto a flash column and the product was isolated by silica gel flash chromatography (hexanes/EtOAc = 90:10 to 80:20).



(*R*)-4-methyl-4-phenyl-1-tosylpiperidin-2-one (**3a**)

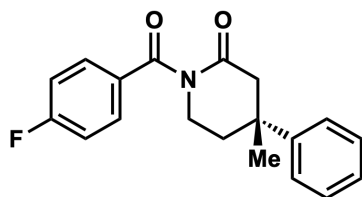
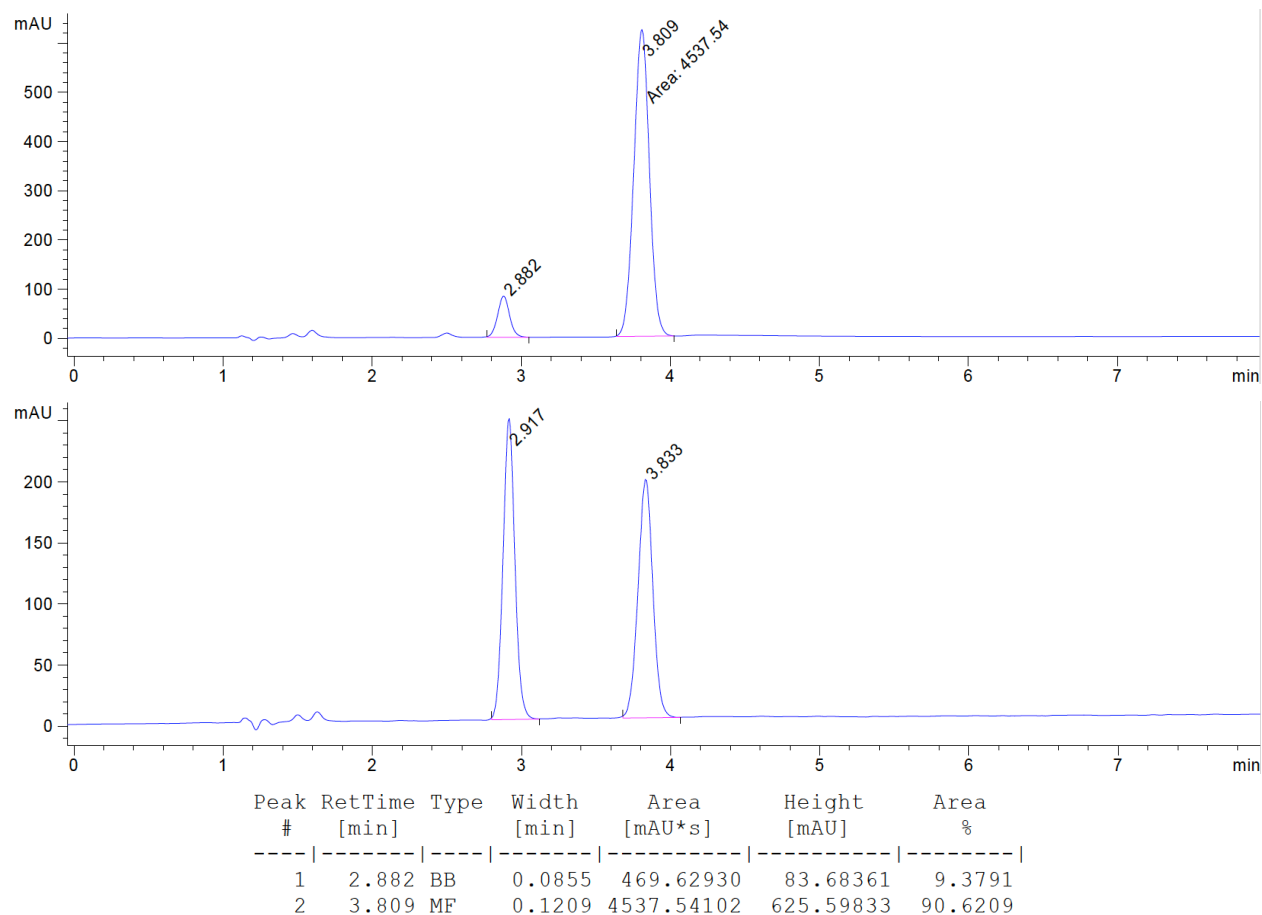
Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford (*R*)-4-methyl-4-phenyl-1-tosylpiperidin-2-one (**3a**) as a colorless oil (>99% yield by NMR internal standard; 82% ee). ¹H NMR (500 MHz, CDCl₃) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.21 (m, 5H), 7.07 (ddd, *J* = 6.7, 3.0, 1.2 Hz, 2H), 4.00 (dt, *J* = 12.2, 4.8 Hz, 1H), 3.31 (ddd, *J* = 12.4, 10.6, 4.7 Hz, 1H), 2.88 (dd, *J* = 17.4, 2.6 Hz, 1H), 2.50 (d, *J* = 17.4 Hz, 1H), 2.45 (s, 3H), 2.29 (dq, *J* = 11.8, 4.4 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.34 (s, 3H). ¹H NMR chemical shifts are consistent with reported values.⁴ SFC Conditions: 40% EtOH, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, *t*_R(time): major = 6.25, minor = 6.96.



(R)-1-(4-methoxybenzoyl)-4-methyl-4-phenylpiperidin-2-one (3b)

Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford (R)-1-(4-methoxybenzoyl)-4-methyl-4-phenylpiperidin-2-one (**3b**) as a colorless oil (90% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.49 (m, 2H), 7.41 – 7.23 (m, 5H), 6.89 – 6.84 (m, 2H), 3.84 (s, 3H), 3.79 (dt, *J* = 13.1, 5.6 Hz, 1H), 3.43 (ddd, *J* = 13.0, 9.4, 4.7 Hz, 1H), 3.05 (dd, *J* = 16.4, 2.1 Hz, 1H), 2.69 (d, *J* = 16.4 Hz, 1H), 2.37 (dddd, *J* = 13.7, 5.8, 4.7, 2.1 Hz, 1H), 2.16 (ddd, *J* = 14.1, 9.4, 5.0 Hz, 1H), 1.44 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 174.1, 172.8, 162.8, 145.7, 130.7, 129.0, 128.0, 127.0, 125.5, 113.6, 55.5, 46.9, 43.4, 38.8, 35.9, 29.9. IR (Neat Film, NaCl) 2962, 1674, 1604, 1510, 1393, 1274, 1255, 1173, 1027, 841, 766 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₂₀H₂₂NO₃⁺ [M+H]⁺: 324.1594, found 324.1596;

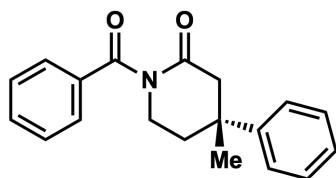
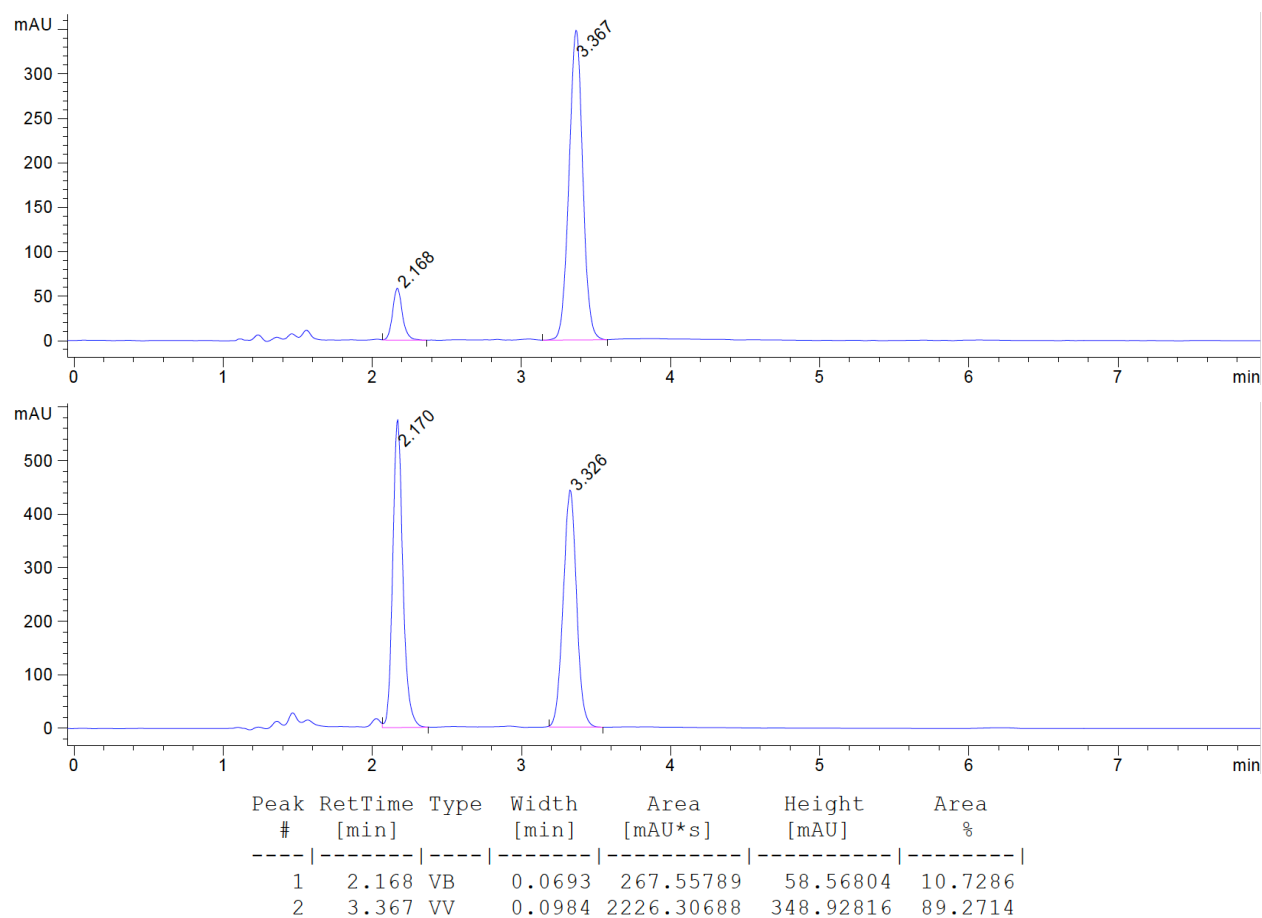
[α]_D²³ −85.7° (c 0.40, CHCl₃, 81% ee); SFC Conditions: 40% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R(time): major = 2.88, minor = 3.81.



(*R*)-1-(4-fluorobenzoyl)-4-methyl-4-phenylpiperidin-2-one (3c)

Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford (*R*)-1-(4-fluorobenzoyl)-4-methyl-4-phenylpiperidin-2-one (**3c**) as a colorless oil (65% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.47 (m, 2H), 7.41 – 7.30 (m, 5H), 7.08 – 7.01 (m, 2H), 3.82 (dt, *J* = 13.2, 5.3 Hz, 1H), 3.44 (ddd, *J* = 13.1, 9.5, 4.7 Hz, 1H), 3.06 (dd, *J* = 16.4, 2.2 Hz, 1H), 2.68 (dd, *J* = 16.5, 0.8 Hz, 1H), 2.39 (dddd, *J* = 13.9,

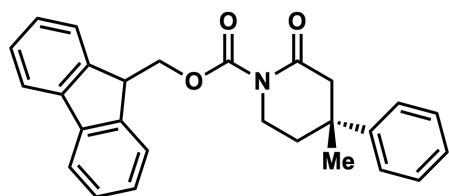
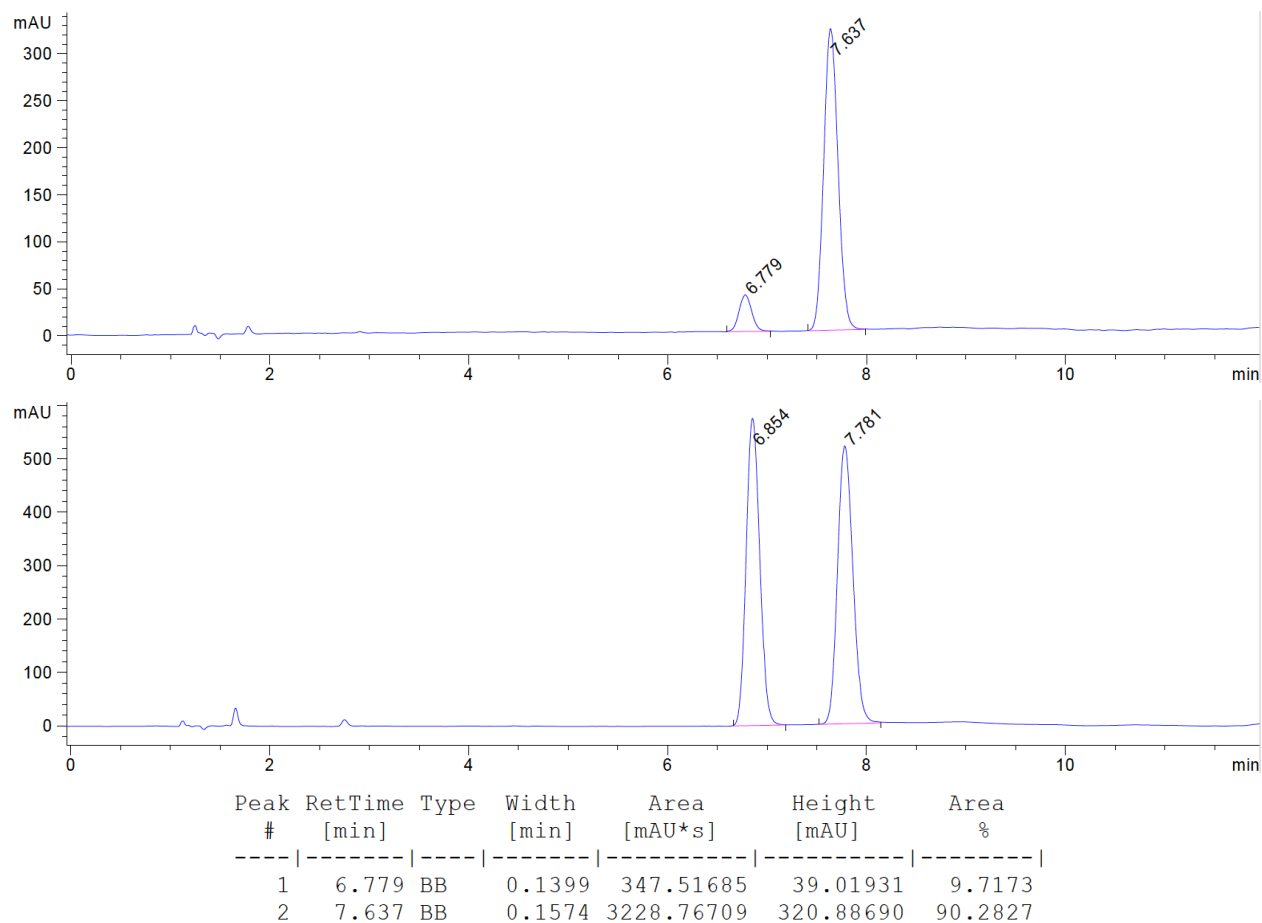
5.6, 4.8, 2.2 Hz, 1H), 2.16 (ddd, $J = 14.4, 9.7, 5.0$ Hz, 1H), 1.44 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.6, 169.2, 145.9, 132.8 (d, $J = 9.4$ Hz), 128.8, 126.7, 125.5, 115.7 (d, $J = 22.0$ Hz), 43.5, 39.4, 37.4, 35.1, 29.5. IR (Neat Film, NaCl) 2960, 1681, 1600, 1505, 1392, 1283, 1235, 1153, 845 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{19}\text{H}_{19}\text{FNO}_2^+$ $[\text{M}+\text{H}]^+$: 312.1394, found 312.1396; $[\alpha]^{23}_{\text{D}} - 61.0^\circ$ (c 0.20, CHCl_3 , 79% ee); SFC Conditions: 40% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, $t_{\text{R}}(\text{time})$: major = 3.37, minor = 2.17.



(*R*)-1-benzoyl-4-methyl-4-phenylpiperidin-2-one (3d)

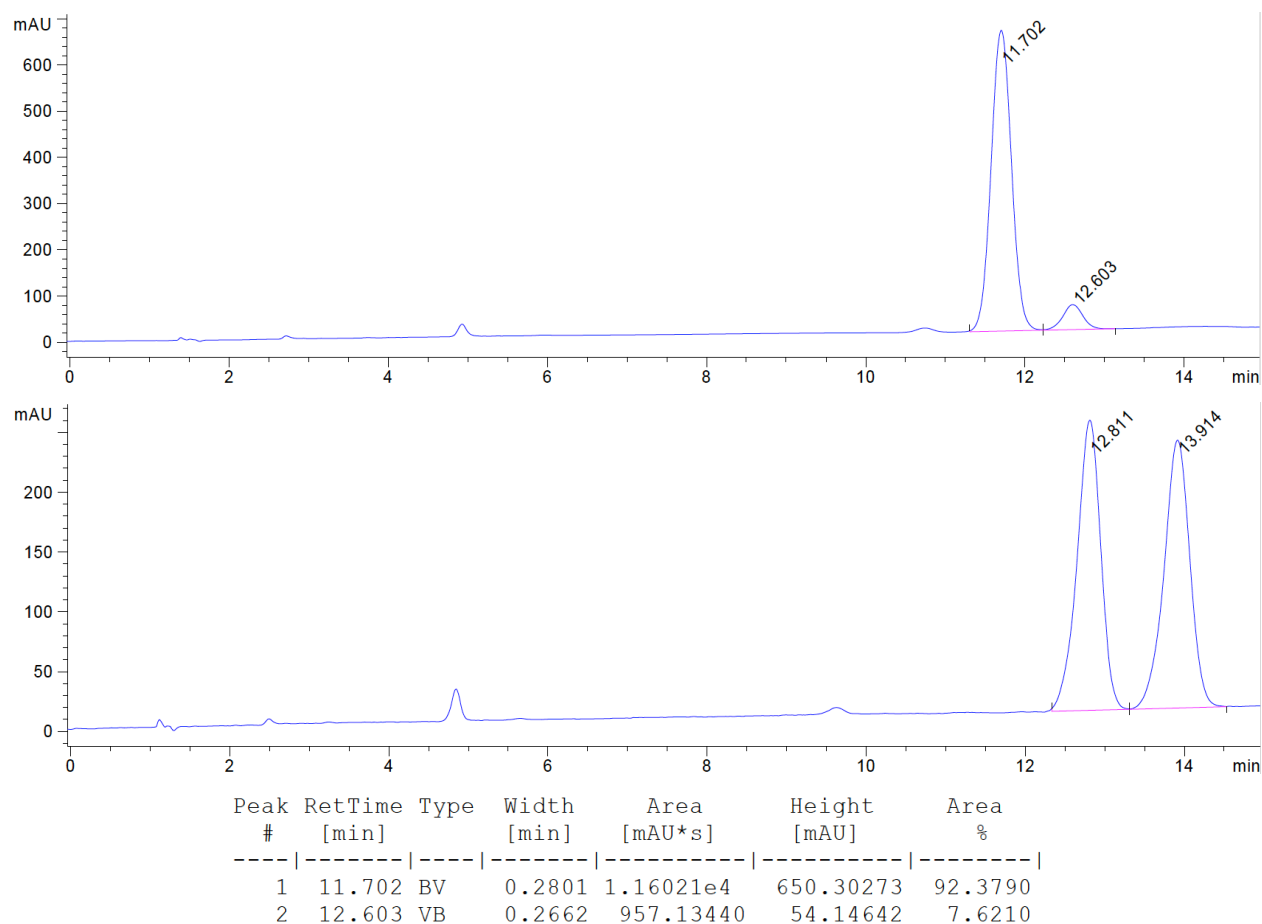
Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford (*R*)-1-benzoyl-4-methyl-4-phenylpiperidin-2-one (**3d**) as a colorless oil (77% yield by NMR internal standard). ^1H NMR (400 MHz, CDCl_3) δ 7.51 – 7.43 (m, 3H), 7.41 – 7.30

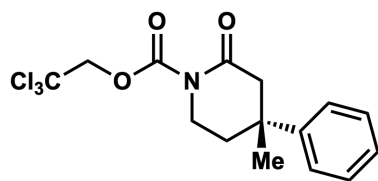
(m, 7H), 3.84 (ddd, $J = 13.1, 5.7, 5.1$ Hz, 1H), 3.45 (ddd, $J = 13.1, 9.5, 4.7$ Hz, 1H), 3.06 (dd, $J = 16.4, 2.1$ Hz, 1H), 2.69 (dd, $J = 16.4, 0.8$ Hz, 1H), 2.39 (dddd, $J = 13.8, 5.7, 4.7, 2.1$ Hz, 1H), 2.21 – 2.12 (m, 1H), 1.44 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.7, 172.8, 131.7, 129.1, 128.8, 128.5, 128.3, 128.0, 127.0, 125.5, 46.9, 43.3, 38.8, 35.9, 30.0. IR (Neat Film, NaCl) 2952, 1681, 1600, 1445, 1392, 1281, 1243, 1154, 703 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{19}\text{H}_{20}\text{NO}_2^+ [\text{M}+\text{H}]^+$: 294.1489, found 294.1488; $[\alpha]_{\text{D}}^{23} -71.3^\circ$ (c 0.26, CHCl_3 , 80% ee, consistent with reported value^{4b}); SFC Conditions: 15% EtOH, 2.5 mL/min, Chiralpak IC column, $\lambda = 210$ nm, $t_{\text{R}}(\text{time})$: major = 6.78, minor = 7.64.



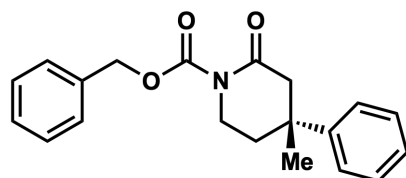
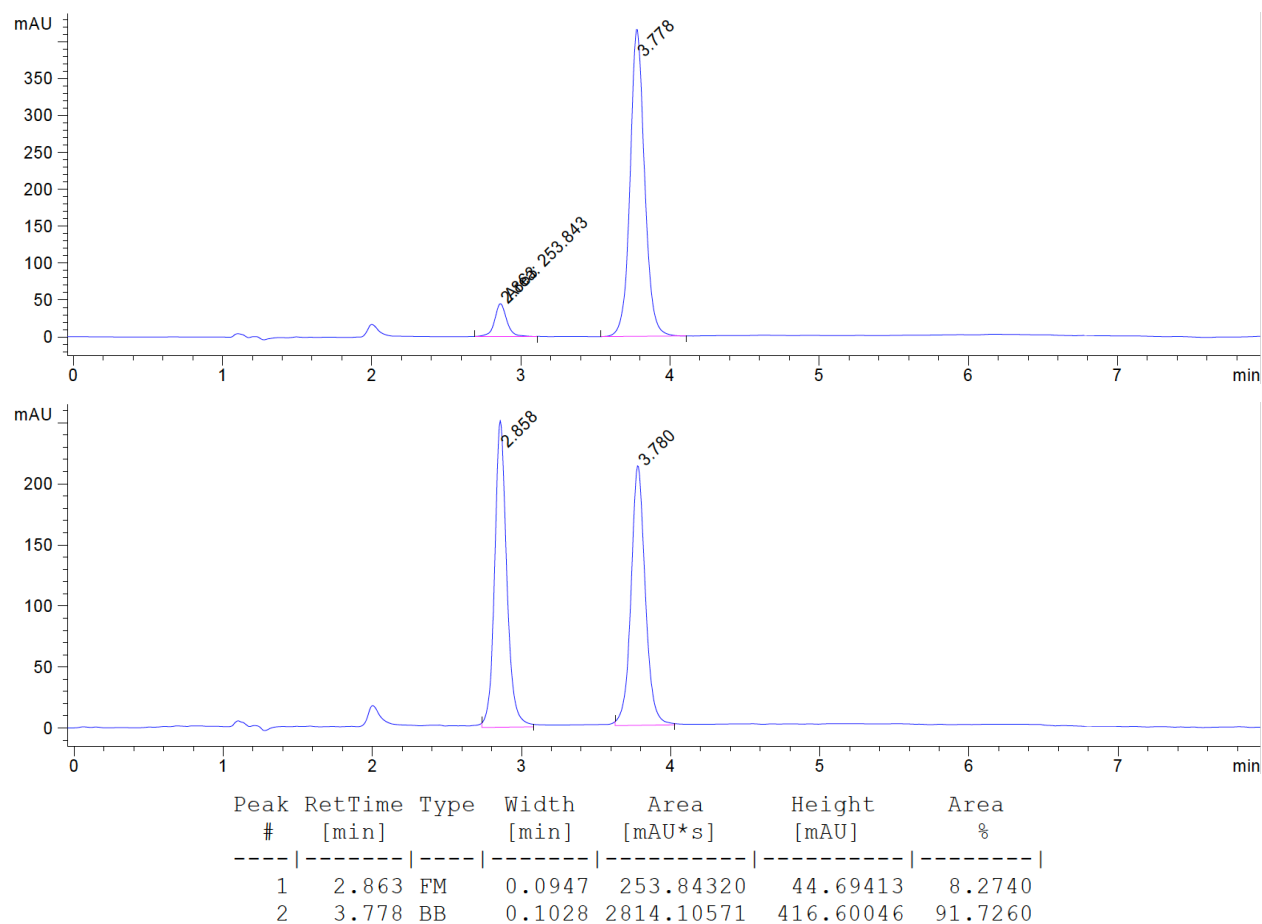
(9H-fluoren-9-yl)methyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (3e)

Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford (9*H*-fluoren-9-yl)methyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3e**) as a colorless oil (79% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.76 (ddt, *J* = 7.6, 1.9, 0.9 Hz, 2H), 7.74 – 7.63 (m, 3H), 7.43 – 7.28 (m, 10H), 4.47 (d, *J* = 1.4 Hz, 1H), 4.30 (t, *J* = 7.4 Hz, 1H), 3.76 (dt, *J* = 13.0, 5.3 Hz, 1H), 3.34 (ddd, *J* = 13.0, 9.8, 4.7 Hz, 1H), 3.11 (dd, *J* = 16.8, 2.2 Hz, 1H), 2.69 (dd, *J* = 16.8, 0.8 Hz, 1H), 1.42 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 154.4, 145.6, 143.7, 141.4, 129.0, 128.0, 127.3, 126.9, 125.5, 125.4, 120.1, 69.3, 47.4, 46.8, 44.0, 37.9, 36.2, 29.9. IR (Neat Film, NaCl) 2959, 1771, 1713, 1450, 1380, 1272, 1237, 758, 739 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₂₇H₂₅NNaO₃⁺ [M+Na]⁺: 434.1727, found 434.1728; [α]_D²³ −37.9° (c 0.43, CHCl₃, 85% ee, consistent with reported value^{4b}); SFC Conditions: 15% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, *t*_R(time): major = 11.70, minor = 12.60.



**2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3f**)**

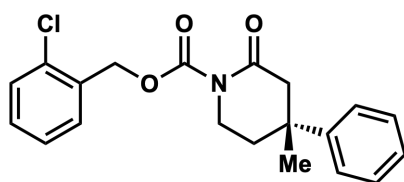
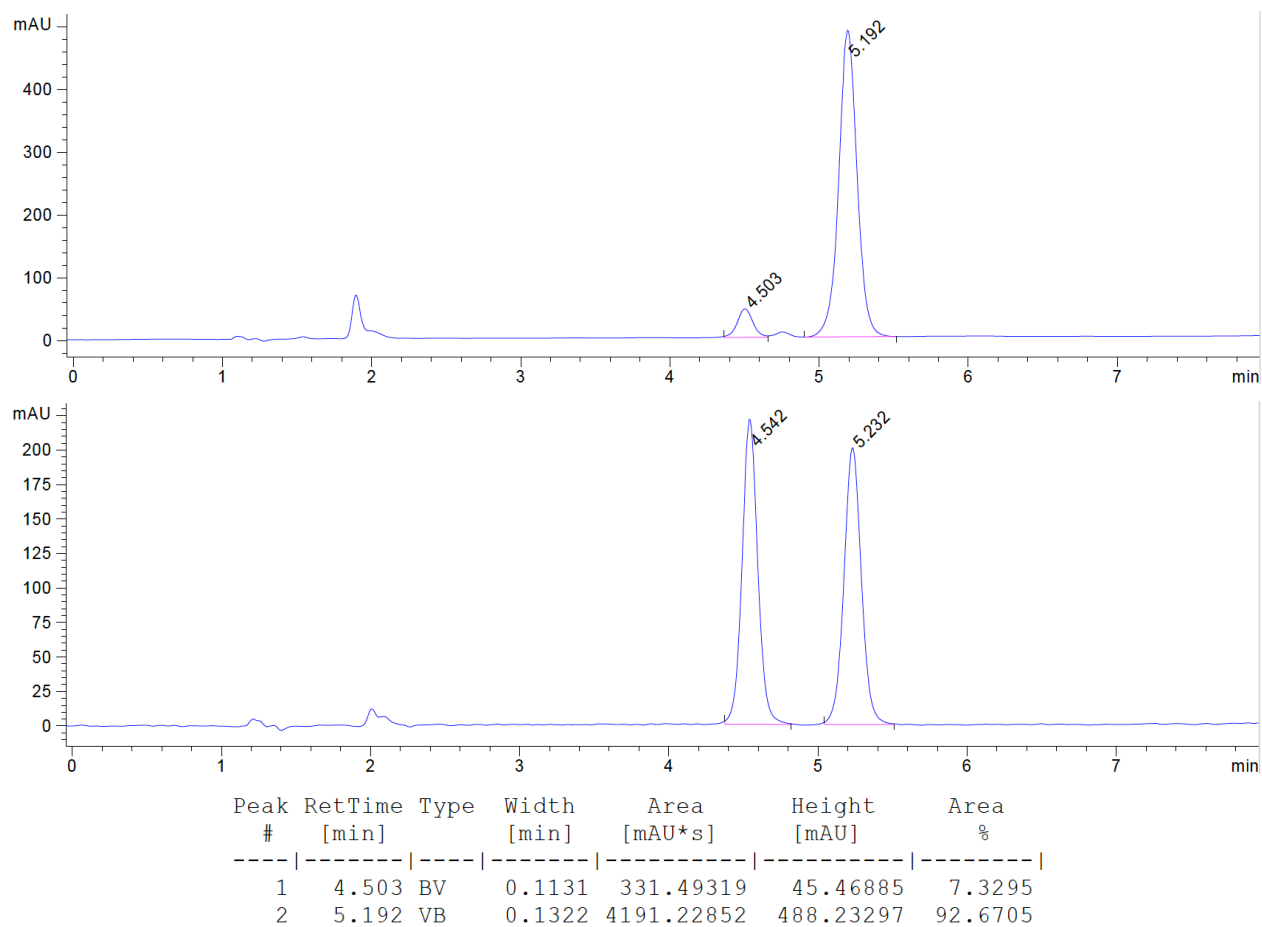
Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford 2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3f**) as a colorless oil (>99% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.23 (m, 5H), 4.87 (d, *J* = 11.9 Hz, 1H), 4.77 (d, *J* = 11.9 Hz, 1H), 3.86 (dt, *J* = 12.9, 5.2 Hz, 1H), 3.41 (ddd, *J* = 12.9, 9.9, 4.7 Hz, 1H), 3.11 (dd, *J* = 16.9, 2.2 Hz, 1H), 2.68 (d, *J* = 16.9 Hz, 1H), 2.29 (dtd, *J* = 13.9, 5.0, 2.2 Hz, 1H), 2.09 (ddd, *J* = 14.6, 10.0, 5.2 Hz, 1H), 1.41 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.9, 146.0, 128.8, 126.7, 125.5, 77.4, 43.7, 39.4, 37.5, 35.2, 29.9, 29.6. IR (Neat Film, NaCl) 2924, 1783, 1715, 1667, 1497, 1283, 1236, 1110, 784 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₅H₁₇Cl₃NO₃⁺ [M+H]⁺: 364.0269, found 364.0269; [α]_D²³ -52.8° (c 0.21, CHCl₃, 84% ee); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R(time): major = 3.78, minor = 2.86.



Benzyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3g**)

Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford benzyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3g**) as a colorless oil (76% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.22 (m, 10H), 5.32 – 5.18 (m, 2H), 3.77 (dt, *J* = 12.9, 5.3 Hz, 1H), 3.34 (ddd, *J* = 12.9, 9.7, 4.7 Hz, 1H), 3.04 (dd, *J* = 16.9, 2.1 Hz, 1H), 2.63 (d, *J* = 16.8 Hz, 1H), 2.22 (dtd, *J* = 13.6, 5.1, 2.1 Hz, 1H), 2.03 (ddd, *J* = 14.2, 9.7, 5.1 Hz, 1H), 1.38 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 154.1, 145.6, 135.5, 129.0, 128.7, 128.4, 128.2, 126.9, 125.5, 68.7, 47.3, 44.0, 38.0, 36.1, 29.8. IR (Neat Film, NaCl) 2961, 1771, 1714, 1452, 1380, 1281, 1236, 733 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₂₀H₂₂NO₃⁺ [M+H]⁺: 324.1594, found 324.1595; [α]_D²³ -57.0° (c 0.20, CHCl₃, 85% ee, consistent with

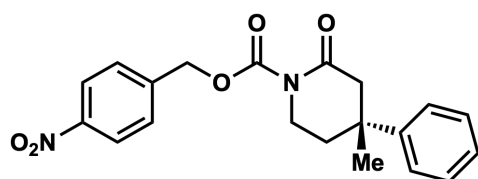
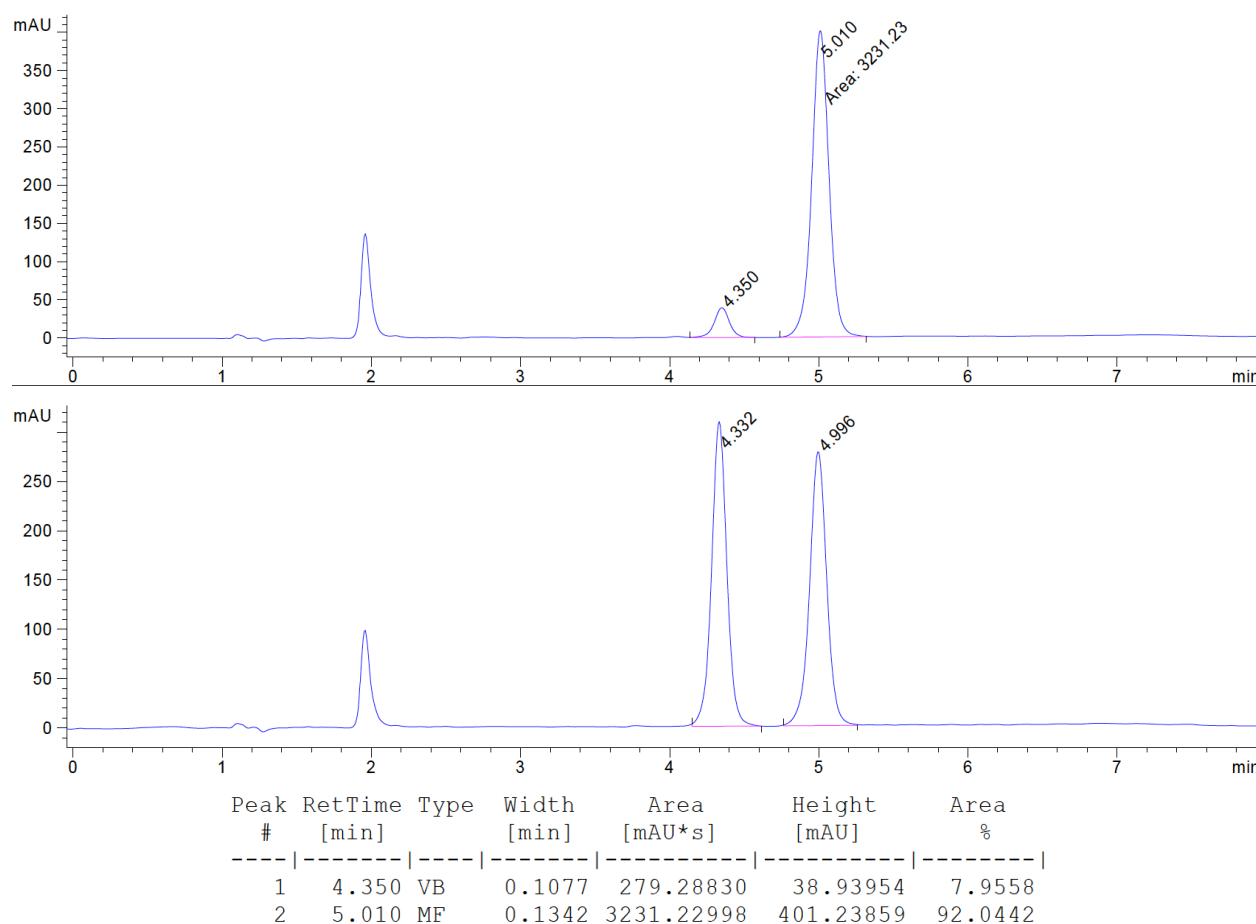
reported value^{4b}); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (time): major = 5.19, minor = 4.50.



2-chlorobenzyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3h**)

Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford 2-chlorobenzyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3h**) as a colorless oil (78% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.62 – 7.57 (m, 1H), 7.40 – 7.20 (m, 8H), 5.45 – 5.25 (m, 2H), 3.80 (dt, J = 13.0, 5.3 Hz, 1H), 3.36 (ddd, J = 13.0, 9.8, 4.7 Hz, 1H), 3.06 (dd, J = 16.9, 2.2 Hz, 1H), 2.65 (dd, J = 16.9, 0.8 Hz, 1H), 2.25 (dddd, J = 13.9, 5.6, 4.7, 2.2 Hz, 1H), 2.13 – 1.97 (m, 1H), 1.39 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.5,

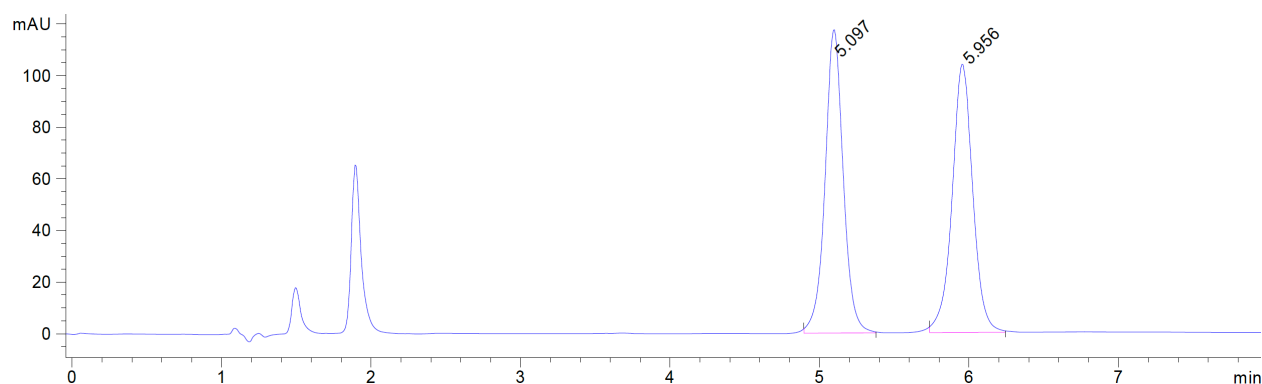
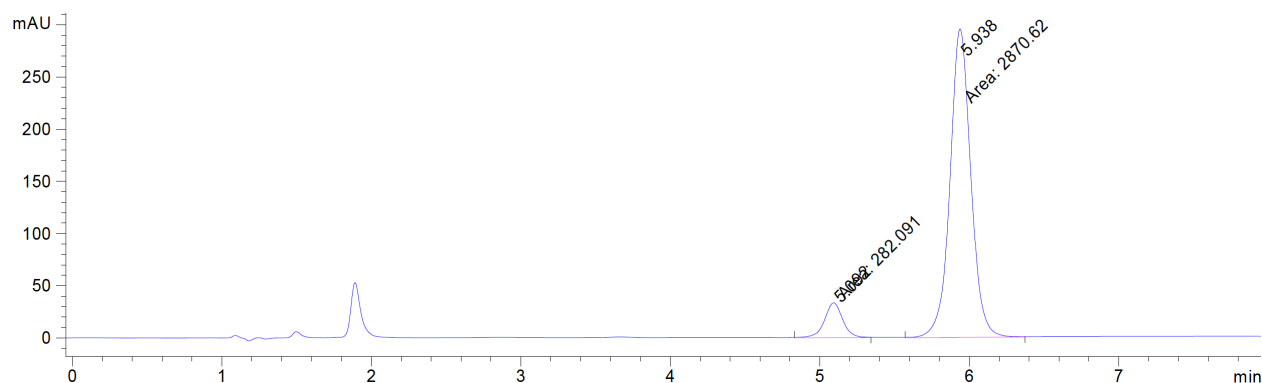
153.9, 145.5, 133.3, 133.2, 129.8, 129.6, 129.5, 129.0, 127.2, 126.9, 125.5, 66.0, 47.3, 44.0, 38.0, 36.1, 29.9. IR (Neat Film, NaCl) 2952, 1774, 1714, 1444, 1379, 1282, 1235, 1146, 1037, 757 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{20}\text{H}_{21}\text{ClNO}_3^+$ $[\text{M}+\text{H}]^+$: 358.1205, found 358.1214; $[\alpha]^{23}_{\text{D}} -62.2^\circ$ (c 0.16, CHCl_3 , 85% ee); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, $t_{\text{R}}(\text{time})$: major = 5.01, minor = 4.35.



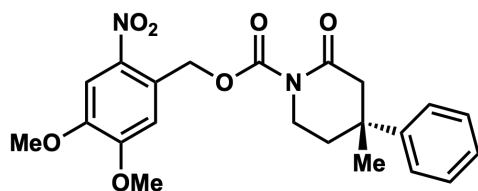
4-nitrobenzyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3i**)

Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford 4-nitrobenzyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3i**) as a colorless oil (95% yield by NMR internal standard). ^1H NMR (400 MHz, CDCl_3) δ 8.25 – 8.19 (m, 2H), 7.64 – 7.57 (m, 2H), 7.39 – 7.21 (m, 5H), 5.45 – 5.26 (m, 2H), 3.79 (dt, $J = 12.8, 5.2$ Hz, 1H),

3.35 (dddd, $J = 13.2, 9.9, 4.7, 0.8$ Hz, 1H), 3.08 (dd, $J = 16.8, 2.2$ Hz, 1H), 2.65 (d, $J = 16.9$ Hz, 1H), 2.27 (dtd, $J = 13.7, 5.1, 2.1$ Hz, 1H), 2.06 (ddd, $J = 14.3, 9.9, 5.1$ Hz, 1H), 1.40 (d, $J = 0.7$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.6, 154.2, 147.9, 145.3, 142.8, 129.1, 128.2, 127.0, 125.4, 124.0, 67.2, 47.3, 44.1, 38.1, 36.1, 30.0. IR (Neat Film, NaCl) 2953, 1773, 1713, 1604, 1559, 1521, 1496, 1345, 1317, 1282, 1237, 1110, 842 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_5^+$ $[\text{M}+\text{H}]^+$: 369.1445, found 369.1446; $[\alpha]^{23}_{\text{D}}$ -65.6° (c 0.21, CHCl_3 , 85% ee); consistent with reported values;^{4b} SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, $t_{\text{R}}(\text{time})$: major = 5.94, minor = 5.09.

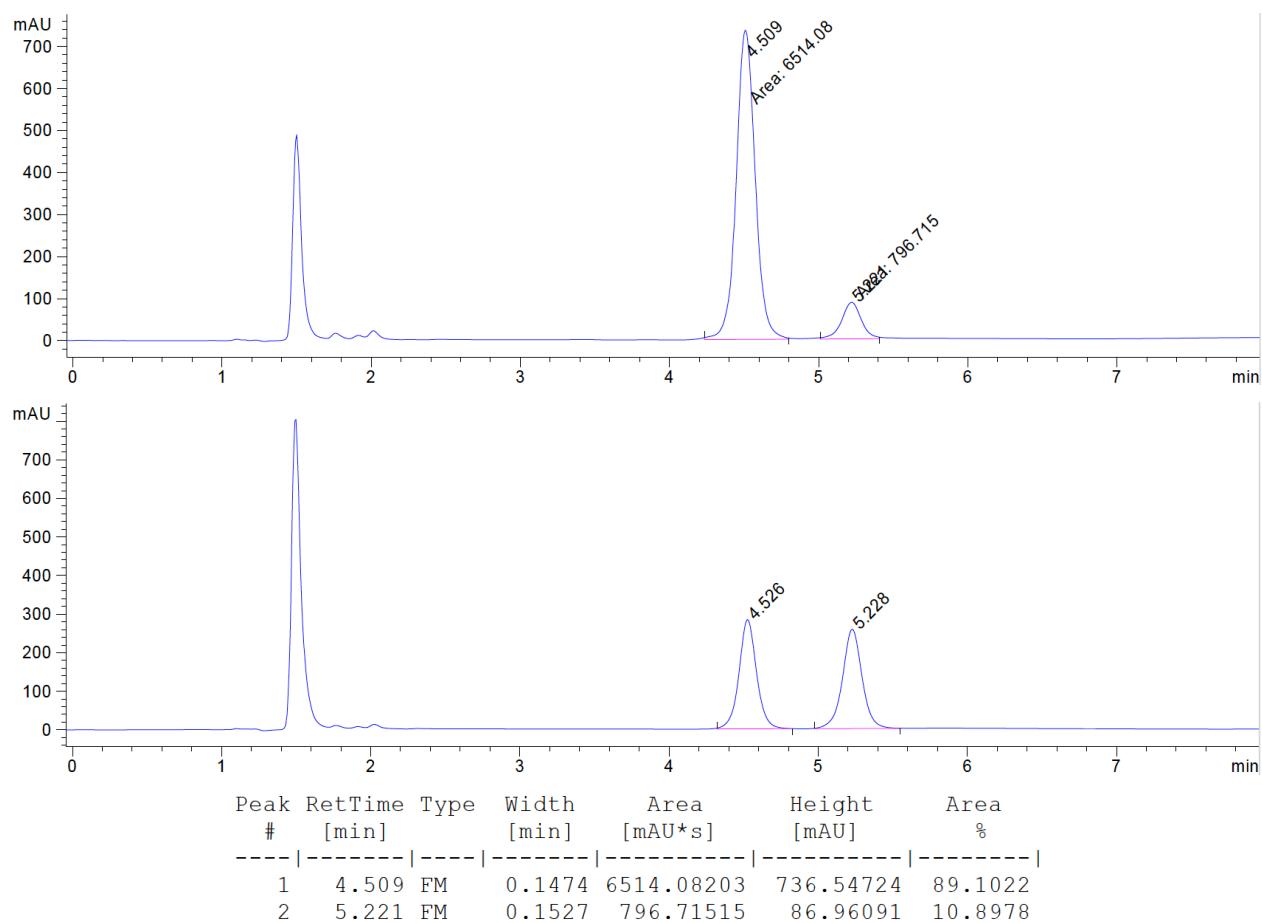


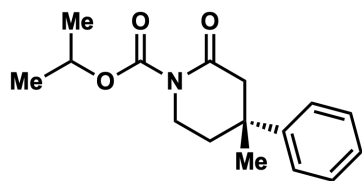
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.092	MM	0.1410	282.09128	33.33651	8.9476
2	5.938	MM	0.1618	2870.62476	295.73865	91.0524



4,5-Dimethoxy-2-nitrobenzyl (R)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (3j)

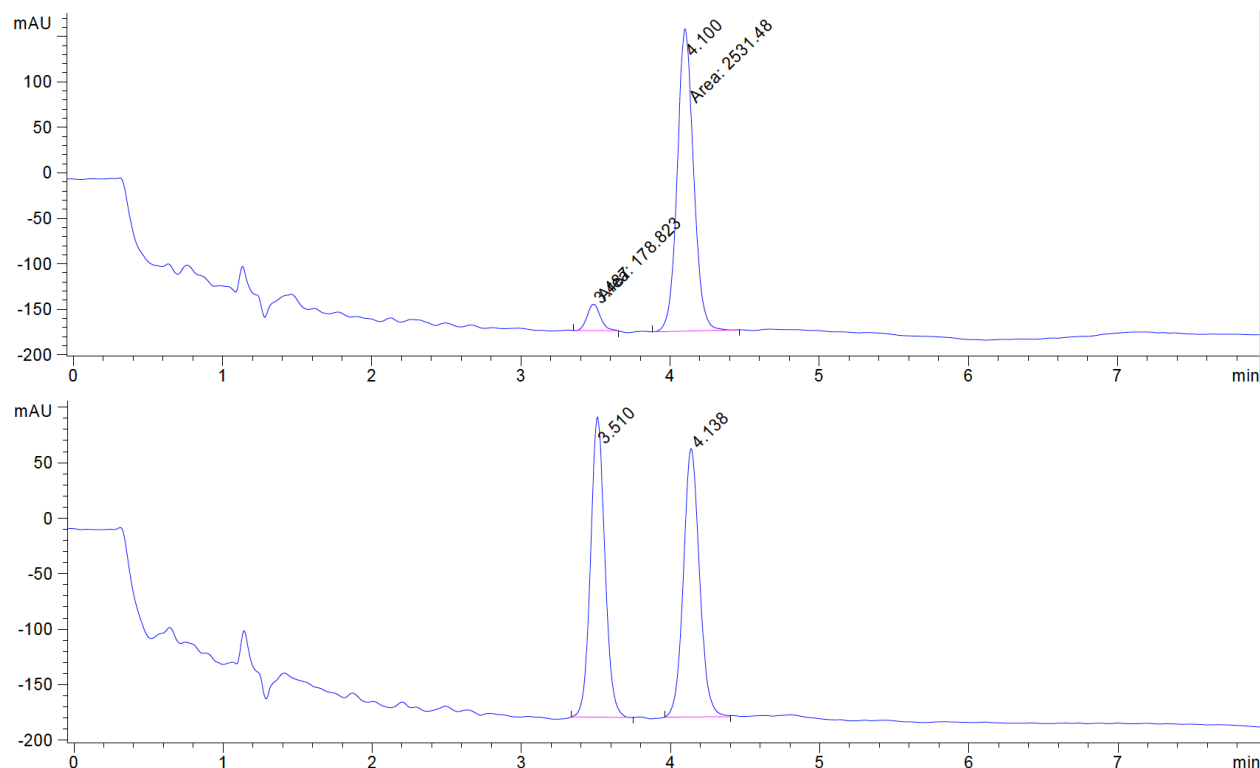
Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford 4,5-dimethoxy-2-nitrobenzyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3j**) as a colorless oil (94% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.75 (s, 1H), 7.43 – 7.22 (m, 5H), 5.73 (qd, *J* = 16.1, 0.8 Hz, 2H), 4.07 (s, 3H), 3.96 (s, 3H), 3.83 (dt, *J* = 13.2, 5.3 Hz, 1H), 3.40 (dddd, *J* = 13.1, 9.8, 4.7, 1.0 Hz, 1H), 3.07 (dd, *J* = 16.8, 2.1 Hz, 1H), 2.66 (d, *J* = 16.7 Hz, 1H), 2.29 (dtd, *J* = 14.0, 5.0, 2.1 Hz, 1H), 2.08 (ddd, *J* = 14.4, 9.8, 5.1 Hz, 1H), 1.41 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.7, 154.4, 148.0, 145.5, 135.8, 129.0, 128.1, 127.9, 127.0, 125.4, 110.8, 108.0, 66.3, 57.1, 56.5, 47.5, 44.2, 38.1, 36.1, 30.0. IR (Neat Film, NaCl) 2952, 1714, 1581, 1558, 1524, 1439, 1381, 1337, 1278, 1236, 1221, 1068, 1027, 722 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₂₂H₂₄N₂NaO₇⁺ [M+Na]⁺: 451.1476, found 451.1479; [α]_D²³ -18.6° (c 0.86, CHCl₃, 80% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, *t*_R(time): major = 4.51, minor = 5.23.



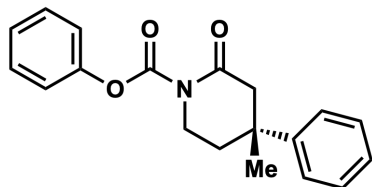


Isopropyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3k**)

Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford isopropyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3k**) as a colorless oil (84% yield by NMR internal standard). ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.20 (m, 5H), 5.03 (hept, J = 6.3 Hz, 1H), 3.72 (ddd, J = 13.1, 5.8, 5.0 Hz, 1H), 3.31 (ddd, J = 13.0, 9.6, 4.6 Hz, 1H), 3.01 (dd, J = 16.8, 2.1 Hz, 1H), 2.62 (dd, J = 16.7, 0.9 Hz, 1H), 2.21 (dddd, J = 13.8, 5.8, 4.7, 2.1 Hz, 1H), 2.03 (dddd, J = 13.7, 9.5, 5.1, 0.9 Hz, 1H), 1.38 (s, 3H), 1.30 (dd, J = 6.3, 4.8 Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.6, 153.7, 145.8, 129.0, 126.8, 125.5, 47.3, 43.8, 37.9, 36.1, 29.8, 21.9. IR (Neat Film, NaCl) 2977, 1771, 1714, 1283, 1236, 1144, 1104, 912, 772 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{16}\text{H}_{21}\text{NNaO}_3^+$ $[\text{M}+\text{Na}]^+$: 298.1414, found 298.1419; $[\alpha]^{23}_{\text{D}} -21.4^\circ$ (c 0.64, CHCl_3 , 86% ee); SFC Conditions: 5% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, $t_{\text{R}}(\text{time})$: major = 4.14, minor = 3.49.

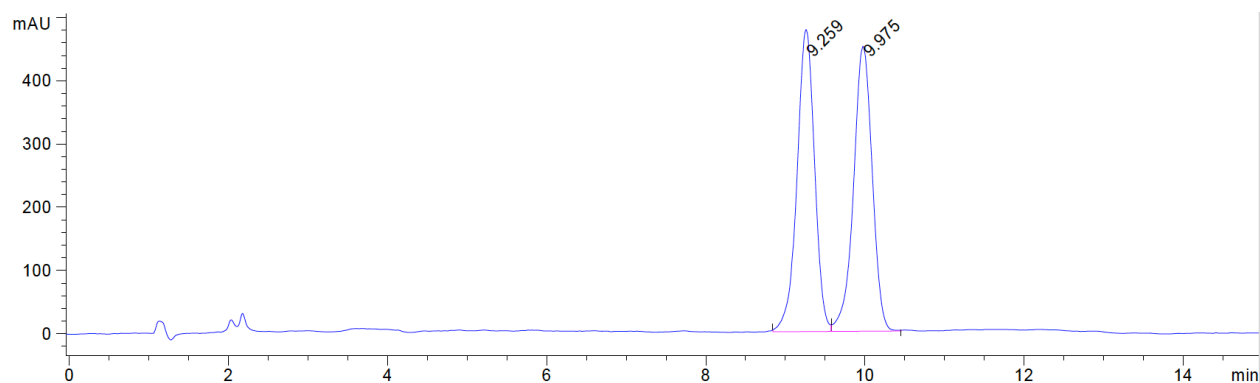


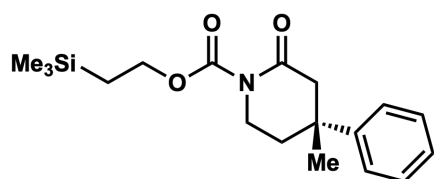
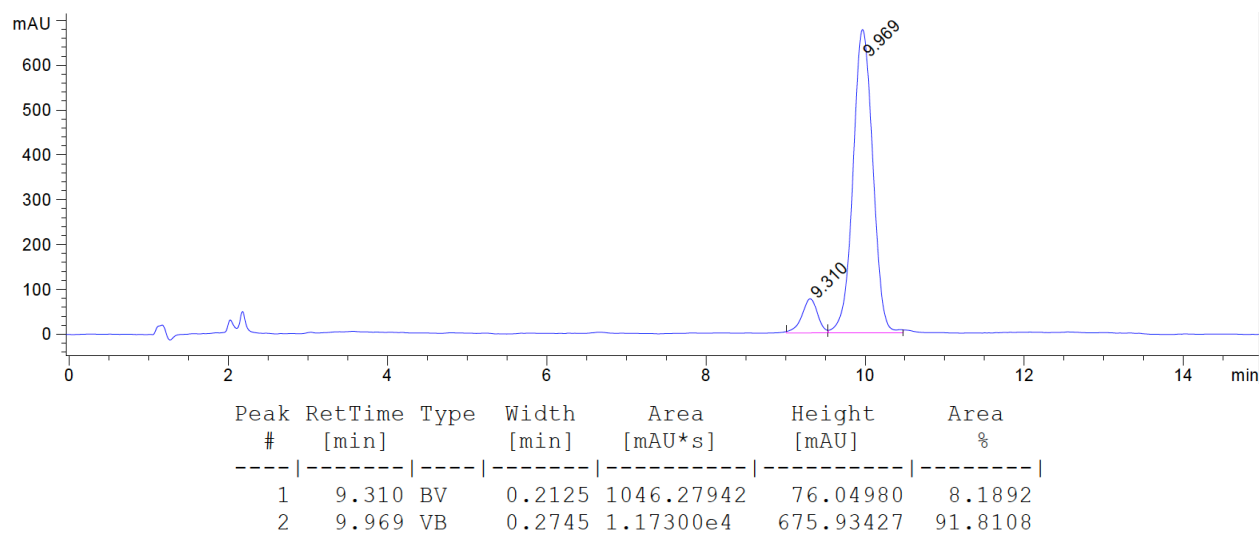
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.487	MM	0.1028	178.82283	29.00168	6.5979
2	4.100	MM	0.1268	2531.47852	332.85696	93.4021



Phenyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3I**)

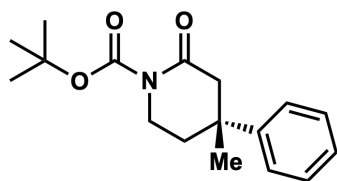
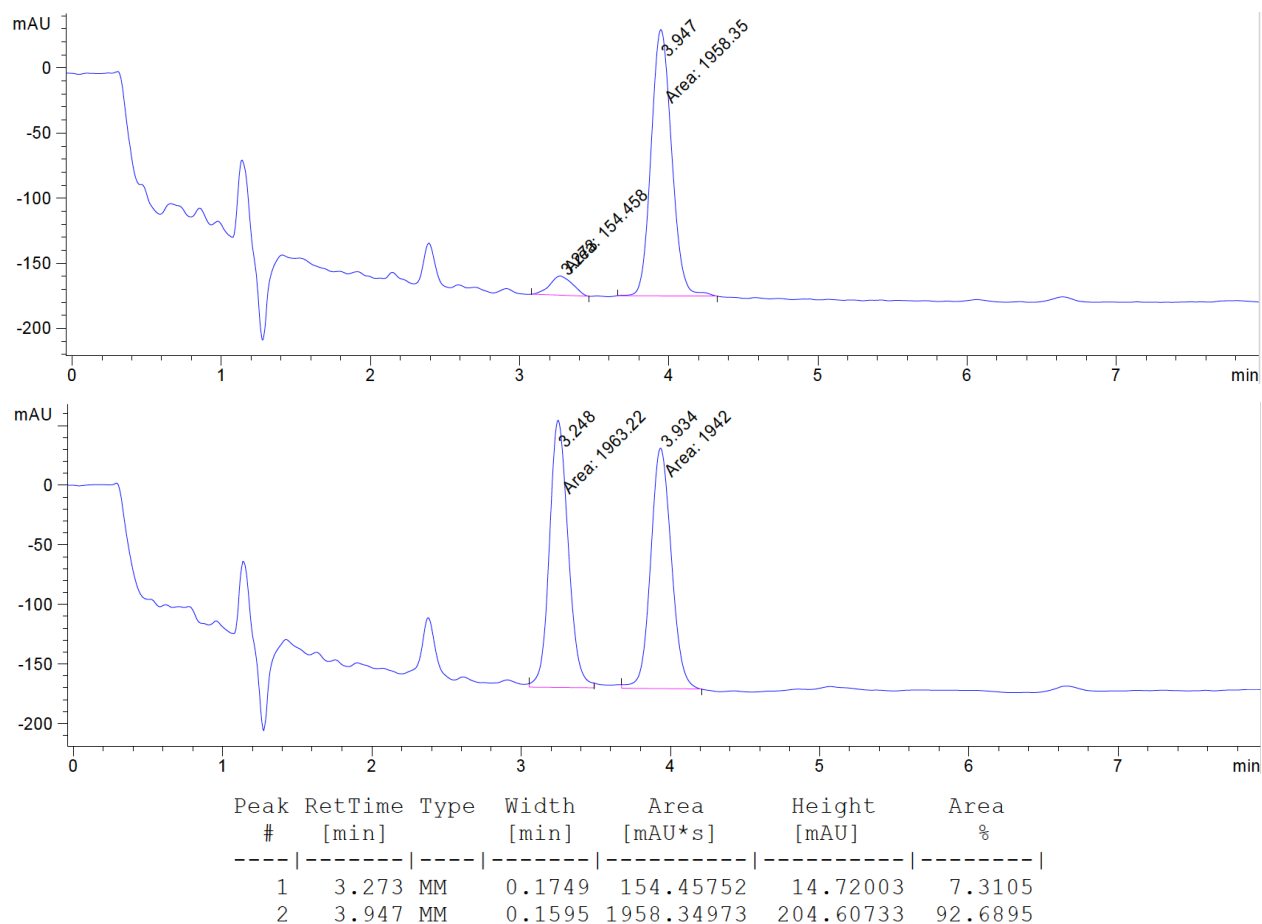
Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford phenyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3I**) as a colorless oil (95% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.31 (m, 6H), 7.30 – 7.21 (m, 2H), 7.18 – 7.13 (m, 2H), 3.90 (dt, *J* = 13.0, 5.3 Hz, 1H), 3.46 (ddd, *J* = 13.0, 9.8, 4.6 Hz, 1H), 3.13 (dd, *J* = 16.7, 2.2 Hz, 1H), 2.72 (dd, *J* = 16.7, 0.8 Hz, 1H), 2.32 (dddd, *J* = 13.9, 5.6, 4.6, 2.2 Hz, 1H), 2.13 (ddd, *J* = 14.6, 10.0, 5.2 Hz, 1H), 1.44 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.6, 150.8, 145.9, 129.5, 129.1, 128.8, 126.7, 126.2, 125.5, 121.6, 47.4, 43.7, 39.4, 35.1, 29.6. IR (Neat Film, NaCl) 2952, 1784, 1716, 1659, 1592, 1497, 1391, 1266, 1237, 1201, 842, 758 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₉H₂₀NO₃⁺ [*M*+*H*]⁺: 310.1438, found 310.1441; [*a*]_D²³ –44.6° (c 0.33, CHCl₃, 85% ee); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, *t*_R(time): major = 9.31, minor = 9.97.





2-(Trimethylsilyl)ethyl (*R*)-e4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3m**)

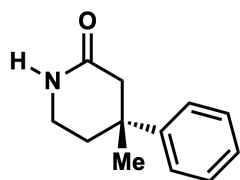
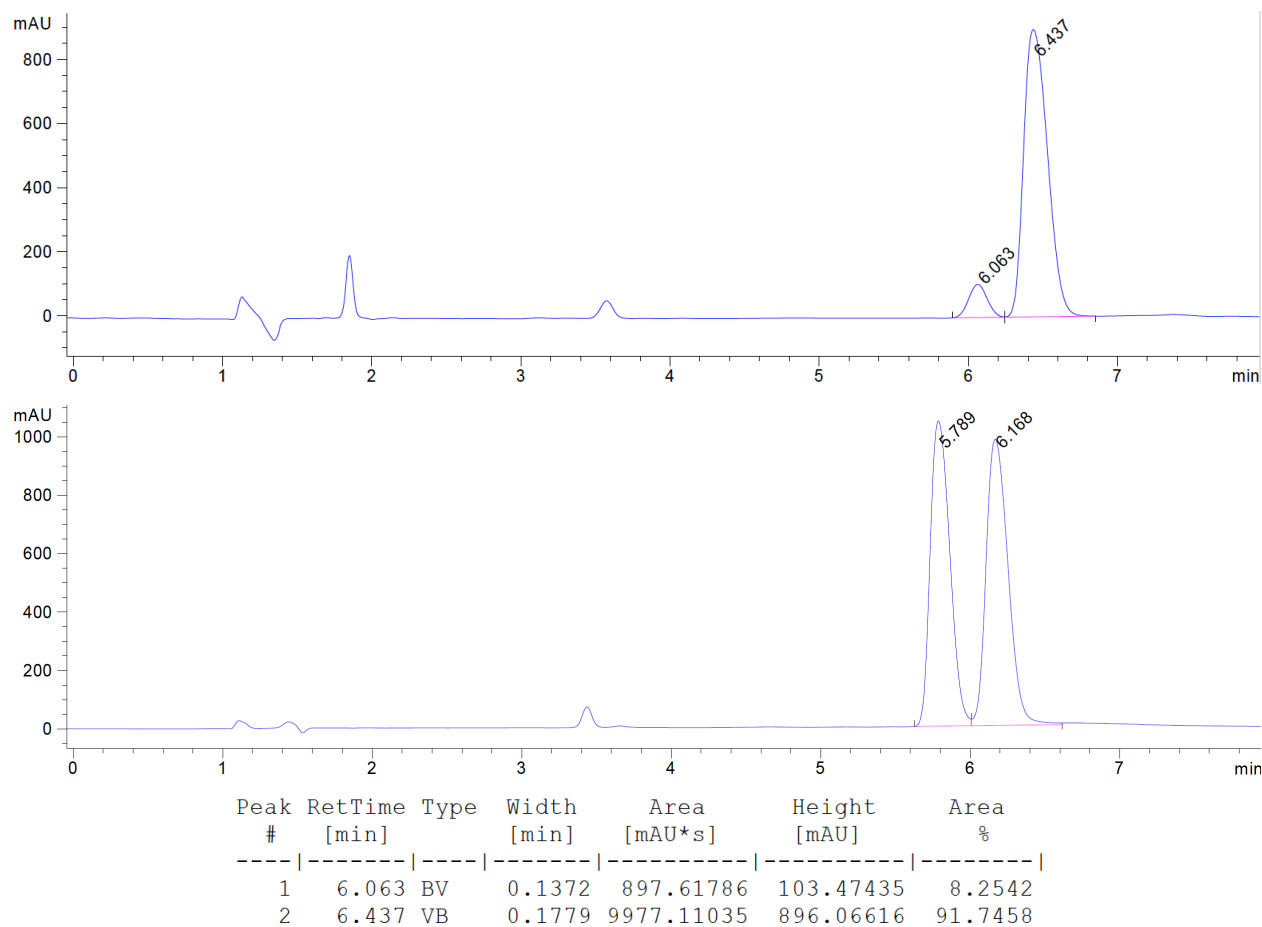
Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford 2-(trimethylsilyl)ethyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3m**) as a colorless oil (17% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.21 (m, 5H), 4.35 – 4.26 (m, 2H), 3.74 (dt, *J* = 13.0, 5.3 Hz, 1H), 3.31 (ddd, *J* = 13.0, 9.7, 4.6 Hz, 1H), 3.02 (dd, *J* = 16.8, 2.2 Hz, 1H), 2.62 (dd, *J* = 16.8, 0.8 Hz, 1H), 2.22 (dddd, *J* = 13.8, 5.6, 4.7, 2.1 Hz, 1H), 2.03 (ddd, *J* = 14.1, 9.6, 5.1 Hz, 1H), 1.38 (s, 3H), 1.14 – 1.04 (m, 2H), 0.03 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 154.4, 145.7, 129.0, 126.9, 125.5, 65.8, 47.3, 43.8, 37.9, 36.2, 29.8, 17.7, -1.4. IR (Neat Film, NaCl) 2952, 1715, 1236, 842 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₆H₂₄NO₃Si⁺ [M+H-C₂H₄]⁺: 306.1520, found 306.1522 (McLafferty rearrangement product); [α]_D²³ -39.5° (c 0.07, CHCl₃, 87% ee); SFC Conditions: 5% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R(time): major = 3.95, minor = 3.27.



***Tert*-butyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3n**)**

Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford *tert*-butyl (*R*)-4-methyl-2-oxo-4-phenylpiperidine-1-carboxylate (**3n**) as a colorless oil (21% yield by NMR internal standard). ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.18 (m, 5H), 3.69 (ddd, *J* = 13.0, 6.0, 4.9 Hz, 1H), 3.28 (ddd, *J* = 13.1, 9.4, 4.6 Hz, 1H), 3.00 (dd, *J* = 16.7, 2.0 Hz, 1H), 2.61 (dd, *J* = 16.7, 0.9 Hz, 1H), 2.25 – 2.16 (m, 1H), 2.03 (ddd, *J* = 14.0, 9.4, 5.0 Hz, 1H), 1.51 (s, 9H), 1.38 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.6, 128.9, 126.8, 125.5, 83.1, 47.4, 43.7, 36.2, 29.7, 28.2. IR (Neat Film, NaCl) 2923, 1713, 1284, 1154, 842 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₇H₂₃NNaO₃⁺ [*M*+Na]⁺: 312.1570, found 312.1573; [*a*]_D²³ –39.0° (c 0.06, CHCl₃,

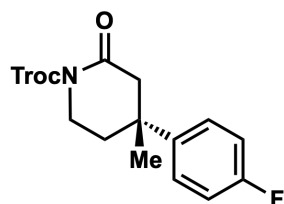
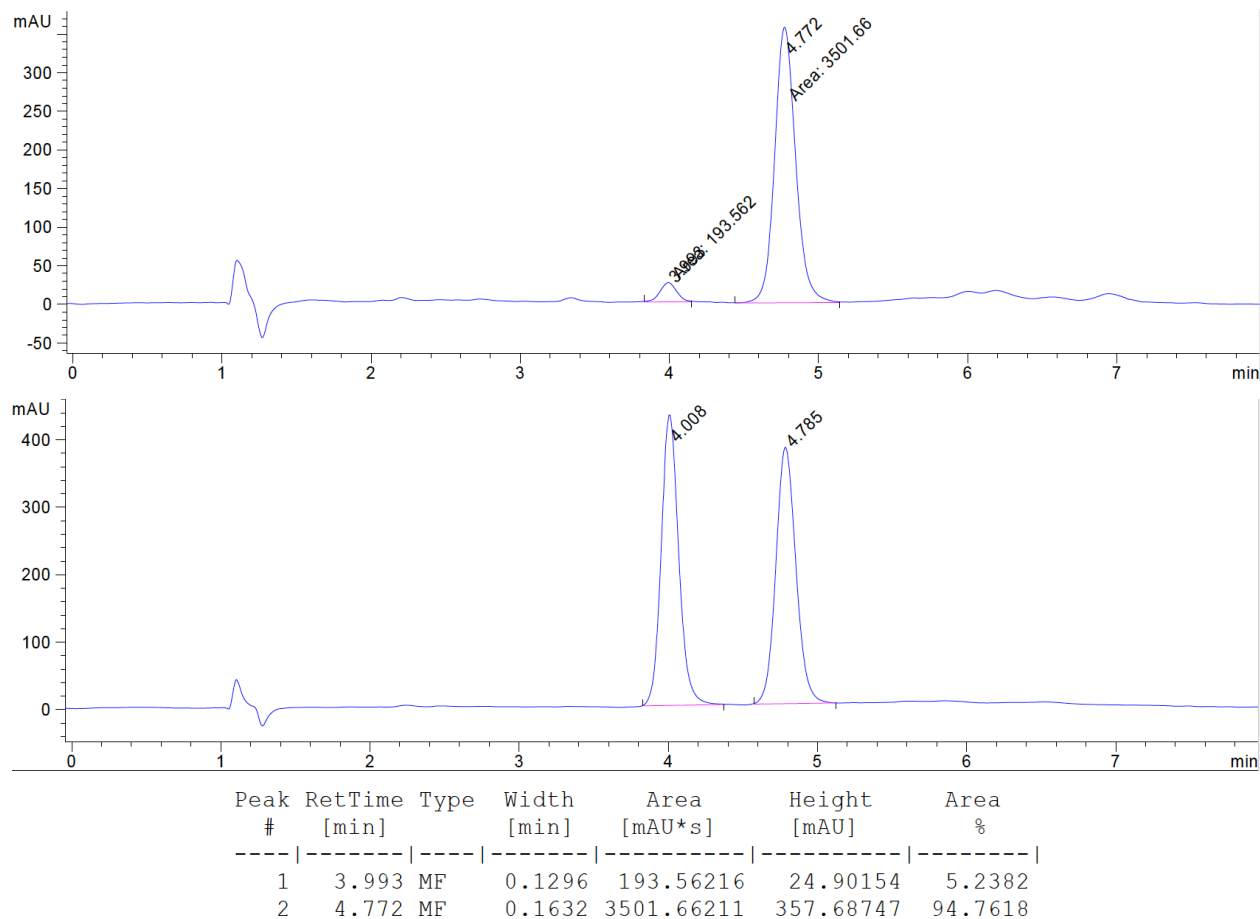
87% ee); SFC Conditions: 10% EtOH, 2.5 mL/min, Chiralpak IC column, $\lambda = 210$ nm, t_R (time): major = 6.44, minor = 6.06.



(*R*)-4-methyl-4-phenylpiperidin-2-one (**3o**)

Synthesized according to the general procedure and purified by preparatory TLC (hexanes/EtOAc = 60:40) to afford (*R*)-4-methyl-4-phenylpiperidin-2-one (**3o**) as a colorless oil (14% yield by NMR internal standard). ^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.22 (m, 5H), 5.76 (s, 1H), 3.33 – 3.23 (m, 1H), 3.04 – 2.93 (m, 1H), 2.86 (dd, $J = 17.4, 2.0$ Hz, 1H), 2.46 (d, $J = 17.4$ Hz, 1H), 2.19 – 2.06 (m, 1H), 1.96 (ddd, $J = 13.9, 9.1, 5.4$ Hz, 1H), 1.39 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 178.2, 128.8, 126.7, 126.2, 125.5, 43.7, 39.4, 35.1, 29.9, 29.6. IR (Neat Film, NaCl) 2926, 1657,

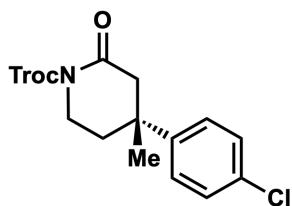
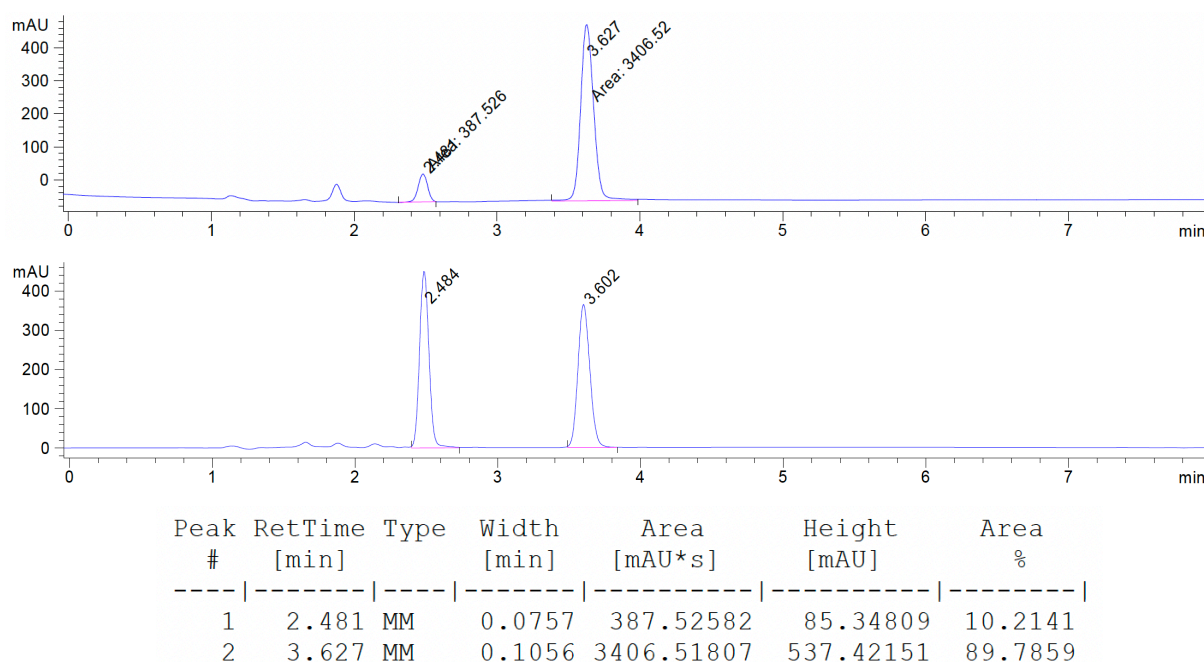
1507, 1341 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{12}\text{H}_{16}\text{NO}^+$ $[\text{M}+\text{H}]^+$: 190.1226, found 190.1226; $[\alpha]^{23}_{\text{D}} -48.0^\circ$ (c 0.02, CHCl_3 , 89% ee); SFC Conditions: 15% EtOH, 2.5 mL/min, Chiralcel OD-H column, $\lambda = 210$ nm, $t_{\text{R}}(\text{time})$: major = 4.77, minor = 3.99.



2,2,2-trichloroethyl (*R*)-4-(4-fluorophenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5a**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-(4-fluorophenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5a**) (34.2 mg, 0.089 mmol, 89%). ^1H NMR (500 MHz, CDCl_3) δ 7.28–7.25 (m, 2H), 7.06–7.02 (m, 2H), 4.87 (d, $J = 11.9$ Hz, 1H), 4.77 (d, $J = 11.9$ Hz, 1H), 3.86 (ddd, $J = 12.9, 5.3, 5.3$ Hz, 1H), 3.40 (ddd, $J = 12.9, 9.8, 4.7$ Hz, 1H), 3.05 (dd, $J = 16.9, 2.3$ Hz,

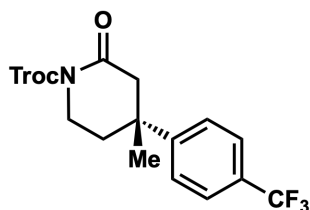
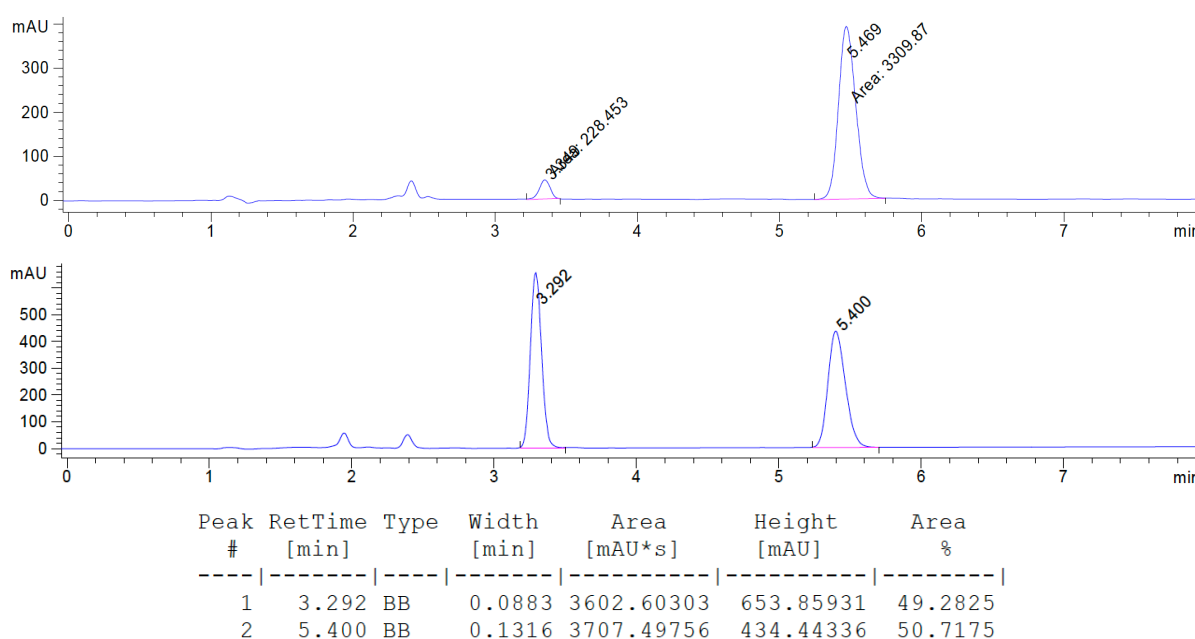
1H), 2.67 (d, $J = 16.9$ Hz, 1H), 2.28-2.23 (m, 1H), 2.12-2.12 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.1, 161.6 (d, $J = 245.9$ Hz), 152.0, 141.0 (d, $J = 3.3$ Hz), 127.1 (d, $J = 8.1$ Hz), 115.9 (d, $J = 21.1$ Hz), 94.5, 75.7, 47.4, 44.1, 37.6, 36.1, 30.0; IR (Neat Film, NaCl) 2960, 1778, 1731, 1513, 1373, 1292, 1048, 829, 771, 719 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{16}\text{Cl}_3\text{FNO}_3$ $[\text{M}+\text{H}]^+$: 382.0174, found 382.0181; $[\alpha]^{21}_{\text{D}} -53.5^\circ$ (c 1.00, CHCl_3 , 80% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, $t_{\text{R}}(\text{time})$: major = 3.63, minor = 2.48.



2,2,2-trichloroethyl (*R*)-4-(4-chlorophenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5b**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-(4-chlorophenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5b**) (38.0 mg, 0.095 mmol, 95%). ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.30 (m, 2H), 7.24–7.21 (m, 2H), 4.88 (d, $J = 11.9$ Hz, 1H), 4.77 (d, $J = 11.9$ Hz, 1H), 3.86 (ddd, $J = 13.0, 5.3, 5.3$ Hz, 1H), 3.40 (ddd, $J = 13.0, 9.9, 4.7$ Hz, 1H), 3.04 (dd, $J = 16.9, 2.2$ Hz, 1H), 2.66 (d, $J = 16.9$ Hz, 1H), 2.28-2.22 (m, 1H), 2.11-2.06 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 169.9, 151.9, 143.7, 132.9, 129.2, 126.9, 94.5, 75.7, 47.1, 44.1, 37.7, 35.9, 29.8;

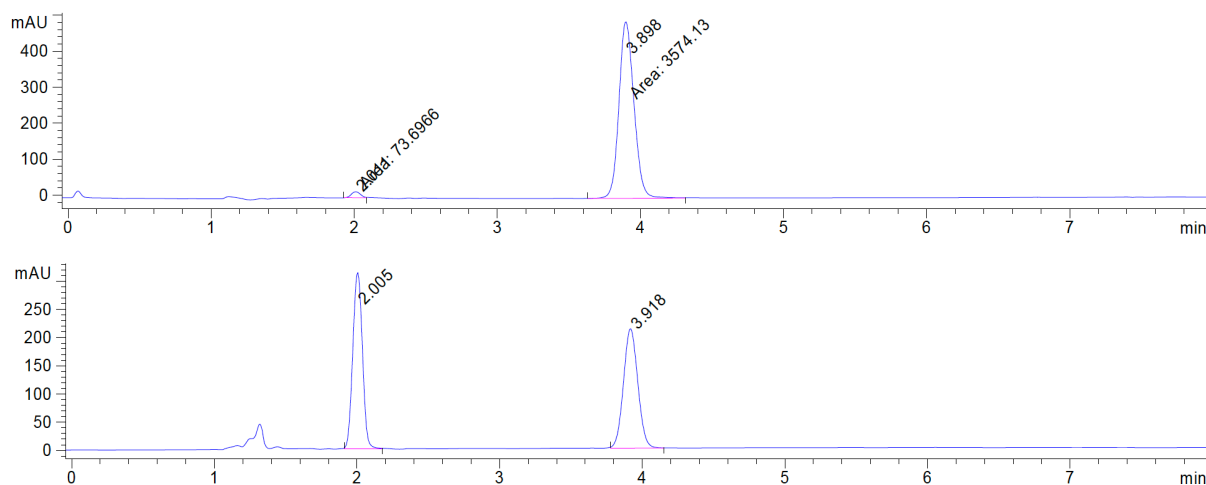
IR (Neat Film, NaCl) 2961, 1784, 1715, 1494, 1372, 1286, 1101, 827, 718 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{16}\text{Cl}_4\text{NO}_3$ $[\text{M}+\text{H}]^+$: 397.9879, found 397.9890; $[\alpha]_D^{22}$ -38.8° (c 1.00, CHCl_3 , 87% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, t_R (time): major = 5.40, minor = 3.29.



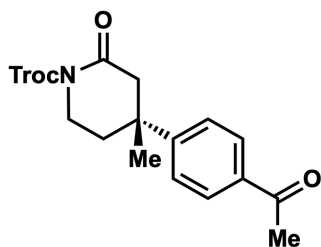
2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (5c**)**

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (**5c**) (31.6 mg, 0.073 mmol, 73%). ^1H NMR (500 MHz, CDCl_3) δ 7.63–7.61 (m, 2H), 7.44–7.42 (m, 2H), 4.88 (d, $J = 11.9$ Hz, 1H), 4.78 (d, $J = 11.9$ Hz, 1H), 3.88 (ddd, $J = 13.0, 5.4, 5.4$ Hz, 1H), 3.42 (ddd, $J = 13.0, 9.7, 4.7$ Hz, 1H), 3.09 (dd, $J = 16.9, 2.2$ Hz, 1H), 2.72 (dd, $J = 16.8, 0.8$ Hz, 1H), 2.34–2.28 (m, 1H), 2.18–2.11 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 169.7, 151.9, 149.4, 129.40 (q, $J = 32.6$ Hz), 126.06 (q, $J = 3.8$ Hz), 125.92, 124.07 (q, $J = 272.0$ Hz), 94.5, 75.7, 47.0, 44.0, 38.2, 35.8, 29.6; IR (Neat

Film, NaCl) 2963, 1782, 1721, 1454, 1327, 1236, 1119, 840, 717 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{16}\text{H}_{16}\text{Cl}_3\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 432.0142, found 432.0149; $[\alpha]^{21}_{\text{D}} -53.2^\circ$ (c 1.00, CHCl_3 , 96% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, $t_{\text{R}}(\text{time})$: major = 3.90, minor = 2.01.



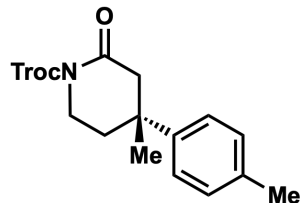
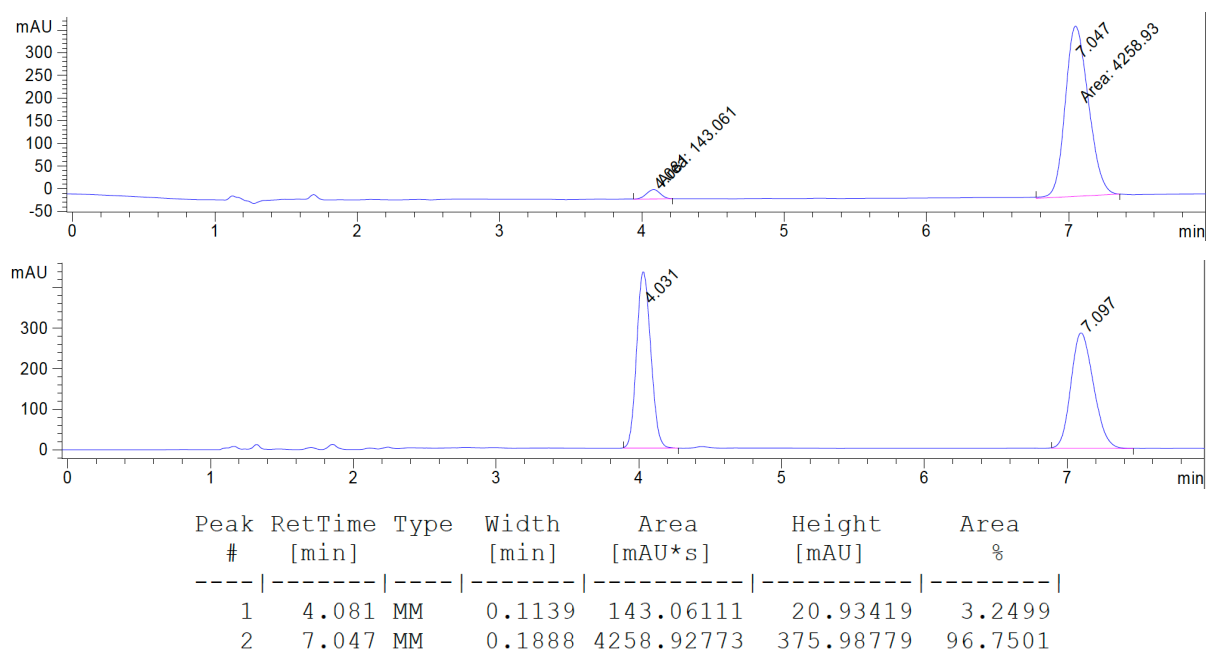
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.011	MM	0.0738	73.69660	16.64970	2.0203
2	3.898	MM	0.1213	3574.13184	490.97980	97.9797



2,2,2-trichloroethyl (*R*)-4-(4-acetylphenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5d**)

Synthesized according to the general procedure and purified by flash chromatography (Dichloromethane/EtOAc = 98:2 to 94:6) to afford 2,2,2-trichloroethyl (*R*)-4-(4-acetylphenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5d**) (24.7 mg, 0.061 mmol, 61%). ^1H NMR (500 MHz, CDCl_3) δ 7.95–7.93 (m, 2H), 7.42–7.39 (m, 2H), 4.87 (d, $J = 11.9$ Hz, 1H), 4.76 (d, $J = 11.9$ Hz, 1H), 3.87 (dd, $J = 13.0, 5.3, 5.3$ Hz, 1H), 3.40 (ddd, $J = 13.0, 9.8, 4.7$ Hz, 1H), 3.10 (dd, $J = 16.9, 2.2$ Hz, 1H), 2.71 (d, $J = 16.9$ Hz, 1H), 2.60 (s, 3H), 2.34–2.29 (m, 1H), 2.16–2.10 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 197.6, 169.8, 151.9, 150.7, 135.9, 129.1, 125.8, 94.5, 75.7, 47.0, 44.1, 38.3, 35.8, 29.6, 26.8; IR (Neat Film, NaCl) 2960, 1783, 1721, 1681, 1371, 1273, 1112,

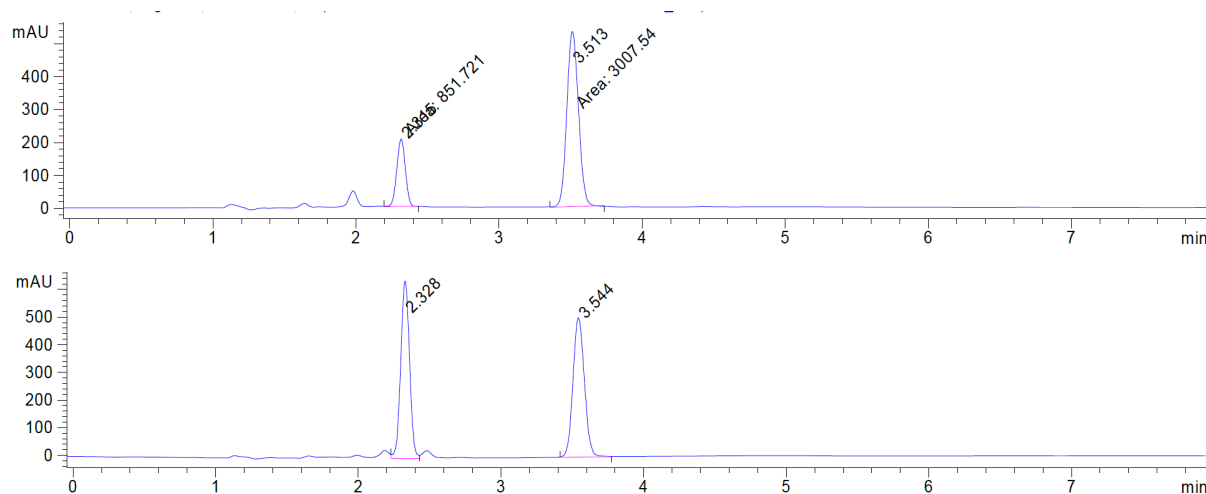
821, 717 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{17}\text{H}_{19}\text{Cl}_3\text{NO}_4$ $[\text{M}+\text{H}]^+$: 406.0374, found 406.0377; $[\alpha]_D^{21} -59.2^\circ$ (c 1.00, CHCl_3 , 94% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, $t_R(\text{time})$: major = 7.05, minor = 4.08.



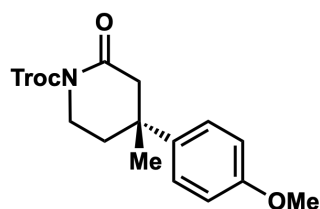
2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-(*p*-tolyl)piperidine-1-carboxylate (**5e**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-(*p*-tolyl)piperidine-1-carboxylate (**5e**) (32.3 mg, 0.079 mmol, 79%). ^1H NMR (500 MHz, CDCl_3) δ 7.19–7.15 (m, 4H), 4.88 (d, $J = 11.9$ Hz, 1H), 4.76 (d, $J = 11.9$ Hz, 1H), 3.85 (ddd, $J = 12.9, 5.2, 5.2$ Hz, 1H), 3.40 (ddd, $J = 12.9, 10.0, 4.7$ Hz, 1H), 3.08 (dd, $J = 16.9, 2.2$ Hz, 1H), 2.65 (d, $J = 16.9$ Hz, 1H), 2.34 (s, 3H), 2.29–2.24 (m, 1H), 2.10–2.04 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.4, 152.0, 142.2, 136.6, 129.7, 125.3, 94.6, 75.6, 47.3, 44.2, 37.6, 36.0, 30.0, 21.0; IR (Neat Film, NaCl) 2959, 1783, 1713, 1516, 1372, 1283, 1115, 819, 717 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{16}\text{H}_{19}\text{Cl}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 378.0425, found 378.0442; $[\alpha]_D^{21} -29.7^\circ$ (c 1.00, CHCl_3 ,

56% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, t_R (time): major = 3.51, minor = 2.32.

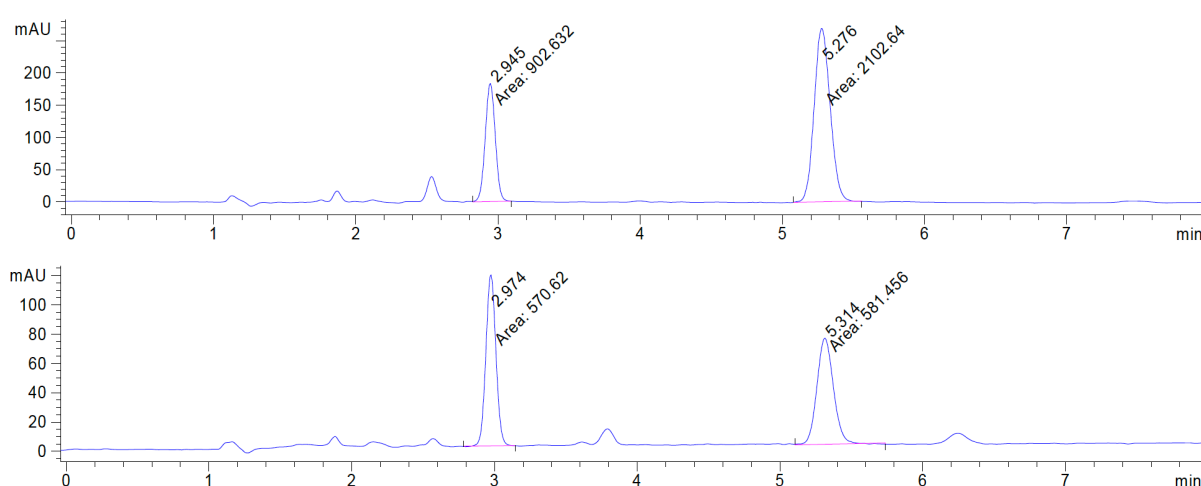


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.315	MM	0.0687	851.72107	206.53180	22.0696
2	3.513	MM	0.0935	3007.53613	536.26166	77.9304

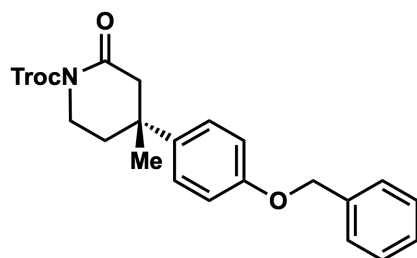


2,2,2-trichloroethyl (*R*)-4-(4-methoxyphenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5f**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-(4-methoxyphenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5f**) (8.8 mg 0.022 mmol, 22%). ^1H NMR (500 MHz, CDCl_3) δ 7.23 – 7.20 (m, 2H), 6.89 – 6.86 (m, 2H), 4.88 (d, $J = 11.9$ Hz, 1H), 4.76 (d, $J = 11.9$ Hz, 1H), 3.85 (ddd, $J = 12.8, 5.3, 5.3$ Hz, 1H), 3.80 (s, 3H), 3.39 (ddd, $J = 12.9, 10.1, 4.7$ Hz, 1H), 3.07 (dd, $J = 16.8, 2.3$ Hz, 1H), 2.65 (d, $J = 16.9$ Hz, 1H), 2.27-2.22 (m, 1H), 2.09-2.03 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.5, 158.4, 152.1, 137.1, 126.6, 114.3, 94.6, 75.6, 55.4, 47.5, 44.3, 37.4, 36.1, 30.1; IR (Neat Film, NaCl) 2958, 1782, 1717, 1515, 1284, 1113, 1034, 830, 717 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{16}\text{H}_{19}\text{Cl}_3\text{NO}_4$ $[\text{M}+\text{H}]^+$: 394.0374, found 394.0383; $[\alpha]_D^{21} -28.0^\circ$ (c 0.50, CHCl_3 , 40% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, t_R (time): major = 5.28, minor = 2.95.



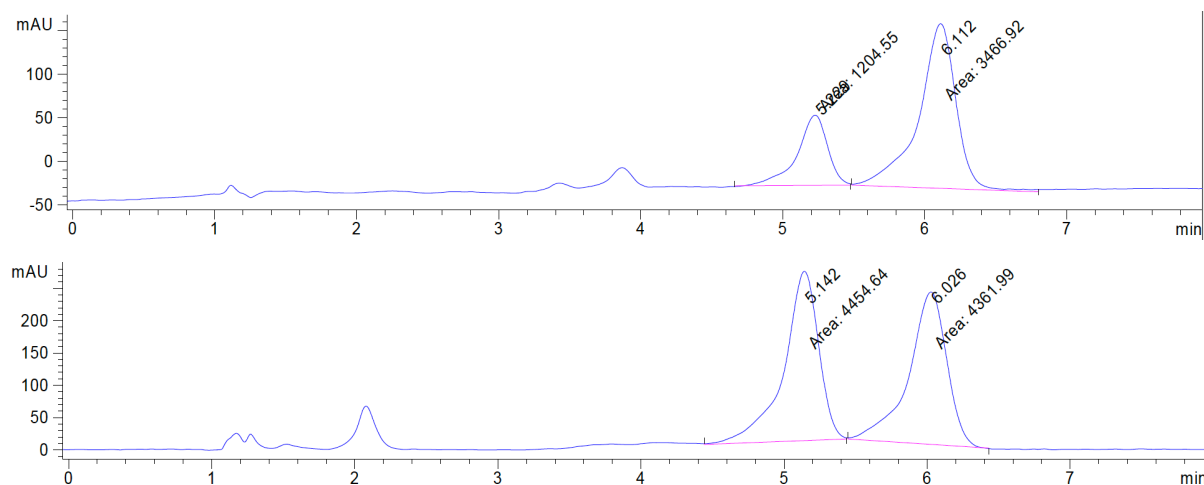
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.945	MM	0.0814	902.63177	184.77827	30.0349
2	5.276	MM	0.1298	2102.64478	269.90985	69.9651



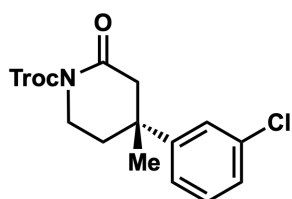
2,2,2-trichloroethyl (R)-4-(4-(benzyloxy)phenyl)-4-methyl-2-oxopiperidine-1-carboxylate (5g)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (R)-4-(4-(benzyloxy)phenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5g**) (20.1 mg, 0.043 mmol, 43%). ¹H NMR (500 MHz, CDCl₃) δ 7.44–7.32 (m, 5H), 7.23–7.20 (m, 2H), 6.97–6.94 (m, 2H), 5.05 (s, 2H), 4.88 (d, *J* = 11.9 Hz, 1H), 4.77 (d, *J* = 11.9 Hz, 1H), 3.85 (ddd, *J* = 12.8, 5.2, 5.2 Hz, 1H), 3.40 (ddd, *J* = 12.8, 10.0, 4.6 Hz, 1H), 3.06 (dd, *J* = 16.8, 2.3 Hz, 1H), 2.64 (d, *J* = 16.8 Hz, 1H), 2.27–2.22 (m, 1H), 2.09–2.03 (m, 1H), 1.38 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 170.5, 157.6, 152.1, 137.4, 137.0, 128.8, 128.2, 127.6, 126.6, 115.2, 94.6, 75.6, 70.2, 47.4, 44.3, 37.4, 36.1, 30.1; IR (Neat Film, NaCl) 2957, 1782, 1714, 1513, 1284, 1113, 1040, 823, 719 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₂₂H₂₃Cl₃NO₄ [M+H]⁺: 470.0687, found 470.0704; [α]_D²¹ –22.0° (c 0.50, CHCl₃, 48% ee);

SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralpak AS-H column, $\lambda = 210$ nm, t_R (time): major = 6.11, minor = 5.23.

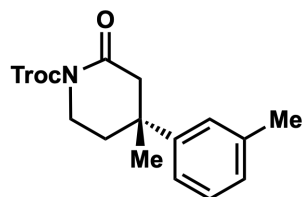
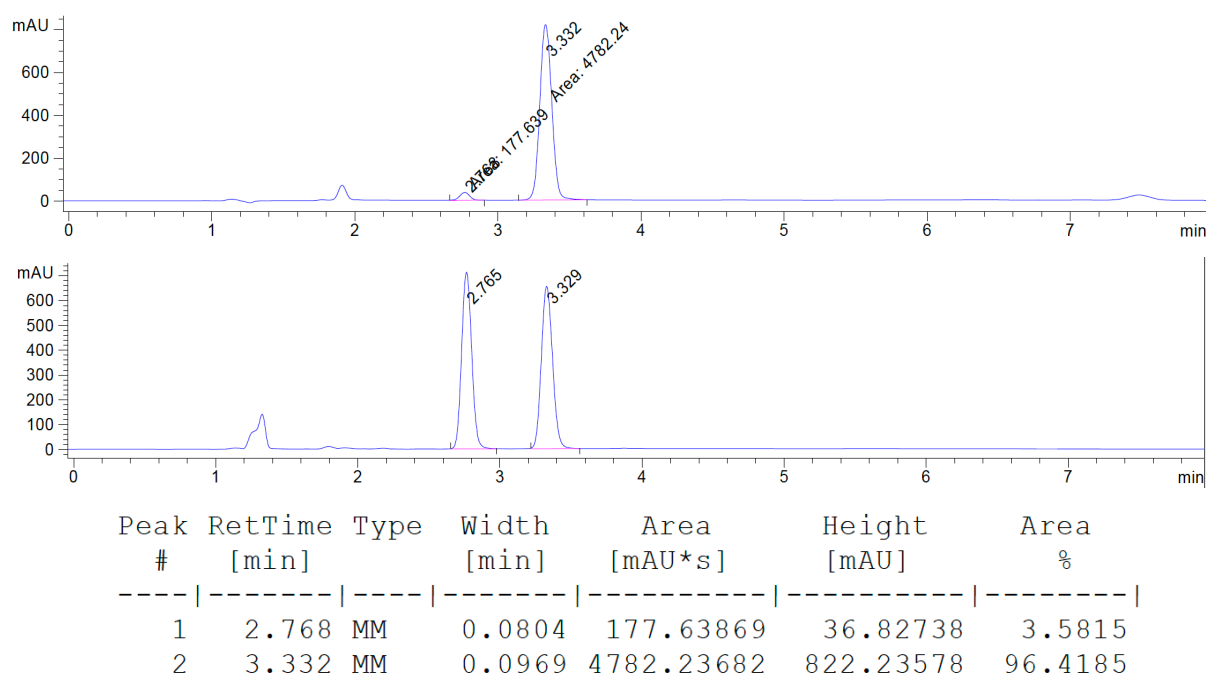


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.229	MM	0.2489	1204.54736	80.65742	25.7852
2	6.112	MM	0.3055	3466.92358	189.13077	74.2148



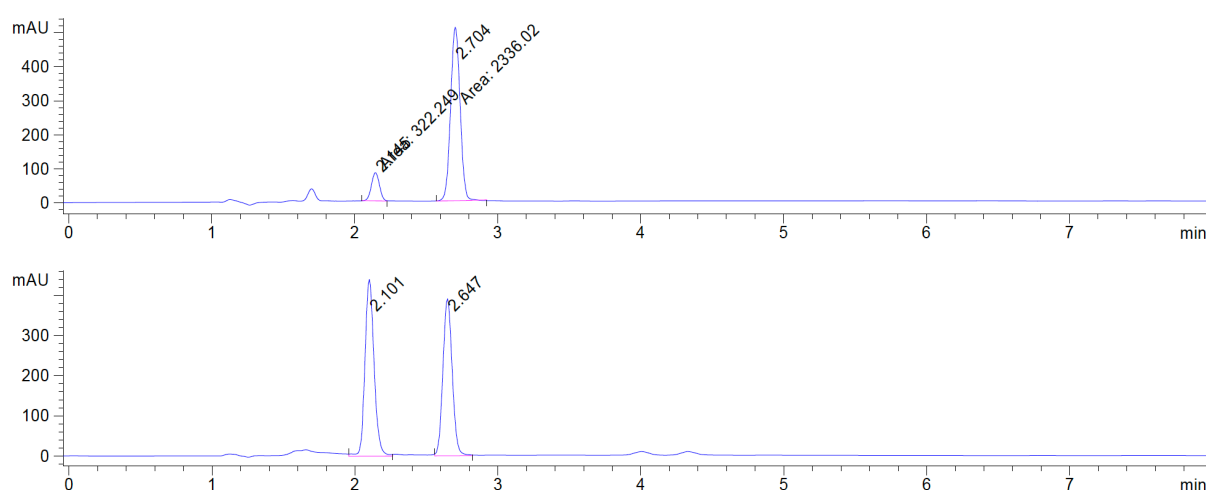
2,2,2-trichloroethyl (*R*)-4-(3-chlorophenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5i**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-(3-chlorophenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5i**) (37.4 mg 0.094 mmol, 94%). ^1H NMR (500 MHz, CDCl_3) δ 7.31–7.16 (m, 5H), 4.88 (d, $J = 11.9$ Hz, 1H), 4.79 (d, $J = 11.9$ Hz, 1H), 3.87 (ddd, $J = 12.9, 5.4, 5.4$ Hz, 1H), 3.50–3.41 (m, 1H), 3.05 (dd, $J = 16.9, 2.1$ Hz, 1H), 2.68 (d, $J = 16.9$ Hz, 1H), 2.29–2.24 (m, 1H), 2.13–2.07 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 169.8, 151.9, 147.5, 135.0, 130.3, 127.3, 125.9, 123.6, 94.5, 75.7, 47.0, 44.0, 38.0, 35.7, 29.6; IR (Neat Film, NaCl) 2960, 1785, 1715, 1476, 1285, 1237, 1103, 1050, 825, 717 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{16}\text{Cl}_4\text{NO}_3$ $[\text{M}+\text{H}]^+$: 397.9879, found 397.9888; $[\alpha]_D^{21}$ -61.9° (c 1.0, CHCl_3 , 93% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, t_R (time): major = 3.32, minor = 2.77.

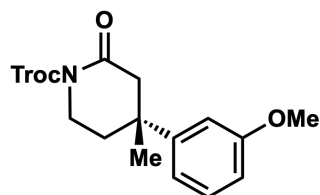


2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-(*m*-tolyl)piperidine-1-carboxylate (**5j**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-(*m*-tolyl)piperidine-1-carboxylate (**5j**) (34.7 mg 0.085 mmol, 85%). ¹H NMR (500 MHz, CDCl₃) δ 7.26–7.22 (m, 2H), 7.10–7.06 (m, 3H), 4.88 (d, *J* = 11.9 Hz, 1H), 4.77 (d, *J* = 11.9 Hz, 1H), 3.86 (ddd, *J* = 12.9, 5.2, 5.2 Hz, 1H), 3.42 (ddd, *J* = 12.9, 9.9, 4.7 Hz, 1H), 3.09 (dd, *J* = 16.9, 2.2 Hz, 1H), 2.66 (dd, *J* = 16.9, 0.7 Hz, 1H), 2.36 (s, 3H), 2.31–2.26 (m, 1H), 2.10–2.05 (m, 1H), 1.39 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 170.4, 152.0, 145.2, 138.6, 128.9, 127.7, 126.1, 122.5, 94.6, 75.6, 47.2, 44.2, 37.8, 36.0, 29.9, 21.8; IR (Neat Film, NaCl) 2959, 1788, 1713, 1452, 1372, 1283, 1226, 1118, 1049, 784, 715 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₆H₁₉Cl₃NO₃ [M+H]⁺: 378.0425, found 378.0440; [α]_D²⁵ –50.3° (c 1.0, CHCl₃, 76% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, *t*_R(time): major = 2.70, minor = 2.15.

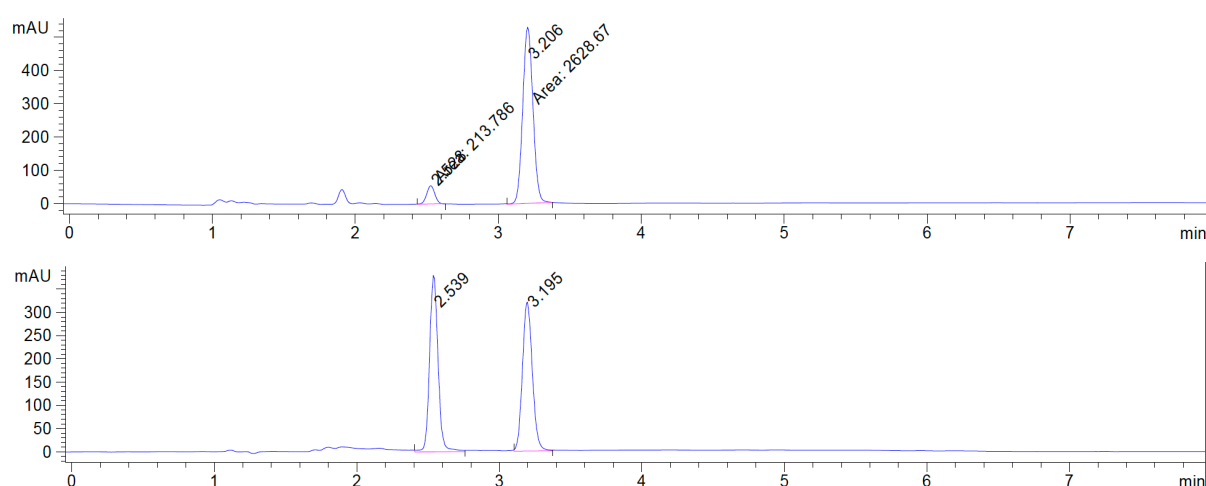


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.145	MM	0.0643	322.24866	83.55197	12.1225
2	2.704	MM	0.0760	2336.01978	511.99207	87.8775

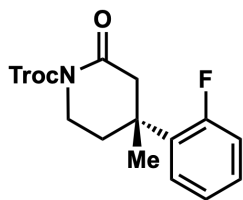


2,2,2-trichloroethyl (*R*)-4-(3-methoxyphenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5k**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-(3-methoxyphenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5k**) (27.0 mg, 0.068 mmol, 68%). ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.26 (m, 1H), 6.89–6.78 (m, 3H), 4.88 (d, *J* = 11.9 Hz, 1H), 4.77 (d, *J* = 11.9 Hz, 1H), 3.86 (ddd, *J* = 12.9, 5.3, 5.3 Hz, 1H), 3.81 (s, 3H), 3.43 (ddd, *J* = 12.9, 9.8, 4.7 Hz, 1H), 3.07 (dd, *J* = 16.9, 2.2 Hz, 1H), 2.66 (dd, *J* = 16.9, 0.8 Hz, 1H), 2.30–2.24 (m, 1H), 2.10–2.05 (m, 1H), 1.40 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 170.3, 160.1, 152.0, 147.0, 130.1, 117.8, 112.1, 111.6, 94.6, 75.6, 55.4, 47.3, 44.2, 38.0, 36.0, 29.8; IR (Neat Film, NaCl) 2959, 1783, 1714, 1582, 1372, 1283, 1048, 782, 718 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₆H₁₉Cl₃NO₄ [M+H]⁺: 394.0374, found 394.0382; [α]_D²¹ -47.7°(c 1.0, CHCl₃, 85% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R(time): major = 3.21, minor = 2.53.

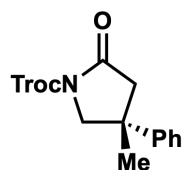
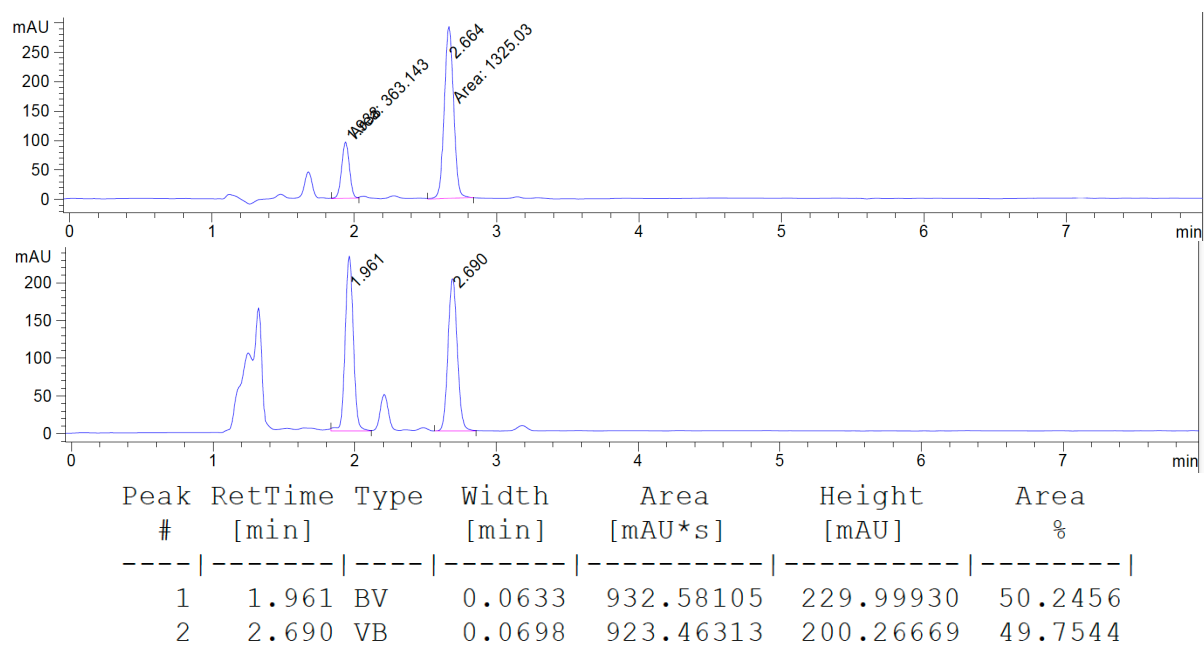


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.528	MM	0.0649	213.78555	54.88538	7.5211
2	3.206	MM	0.0825	2628.67480	531.11157	92.4789



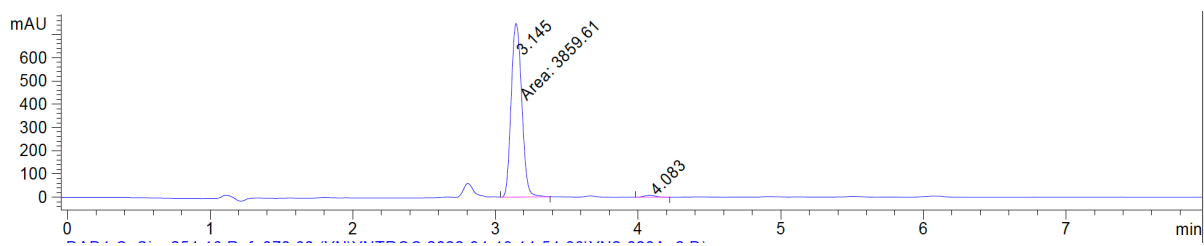
2,2,2-trichloroethyl (*R*)-4-(2-fluorophenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5I**)

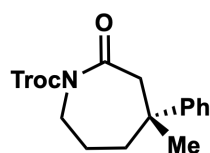
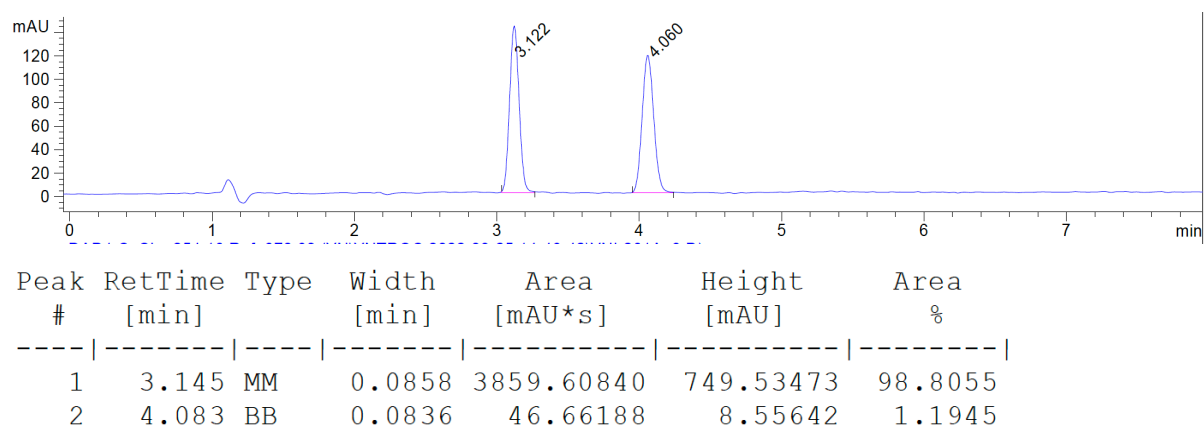
Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-(2-fluorophenyl)-4-methyl-2-oxopiperidine-1-carboxylate (**5I**) (11.5 mg, 0.030 mmol, 30%). ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.19 (m, 2H), 7.12–7.05 (m, 2H), 4.88 (d, *J* = 11.9 Hz, 1H), 4.78 (d, *J* = 11.9 Hz, 1H), 3.92 (ddd, *J* = 12.9, 5.1, 5.1 Hz, 1H), 3.43 (ddd, *J* = 12.9, 10.4, 4.5 Hz, 1H), 3.13 (dd, *J* = 16.9, 2.3 Hz, 1H), 2.68 (d, *J* = 16.9 Hz, 1H), 2.59–2.54 (m, 1H), 2.10–2.04 (m, 1H), 1.48 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 170.0, 161.25 (d, *J* = 247.6 Hz), 151.8, 131.57 (d, *J* = 11.2 Hz), 129.04 (d, *J* = 9.1 Hz), 127.29 (d, *J* = 5.1 Hz), 124.59 (d, *J* = 3.4 Hz), 116.87 (d, *J* = 24.0 Hz), 94.4, 75.5, 47.4, 44.2, 37.3, 34.0, 27.3; IR (Neat Film, NaCl) 2959, 1786, 1720, 1490, 1286, 1215, 1105, 830, 763, 717 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₅H₁₆Cl₃FNO₃ [M+H]⁺: 382.0174, found 382.0182; [α]_D²¹ – 28.3° (c 1.0, CHCl₃, 57% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R(time): major = 2.69, minor = 1.96.



2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-phenylpyrrolidine-1-carboxylate (**7a**)

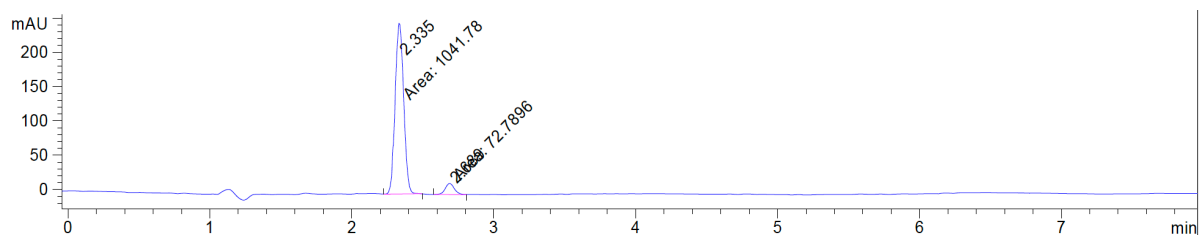
Synthesized according to the general procedure (Reaction time: 47h) and purified by flash chromatography (hexanes/EtOAc = 80:20 to 50:50) to afford 2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-phenylpyrrolidine-1-carboxylate (**7a**) (21.4 mg, 0.061 mmol, 61%). ¹H NMR (500 MHz, CDCl₃) δ 7.39 (t, *J* = 7.7 Hz, 2H), 7.33–7.20 (m, 3H), 4.92–4.86 (m, 2H), 4.09–4.05 (m, 2H), 3.02 (d, *J* = 16.8 Hz, 1H), 2.74 (d, *J* = 16.8 Hz, 1H), 1.53 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.7, 149.8, 145.1, 129.1, 127.3, 125.3, 94.6, 75.3, 58.0, 48.3, 39.7, 29.3; IR (Neat Film, NaCl) 2959, 1800, 1727, 1377, 1319, 1163, 1043, 763, 701 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₄H₁₅Cl₃NO₃ [M+H]⁺: 350.0112, found 350.0115; [α]_D²¹ +10.1° (c 0.5, CHCl₃, 97% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralpak AS-H column, λ = 210 nm, t_R(time): major = 3.15, minor = 4.08.

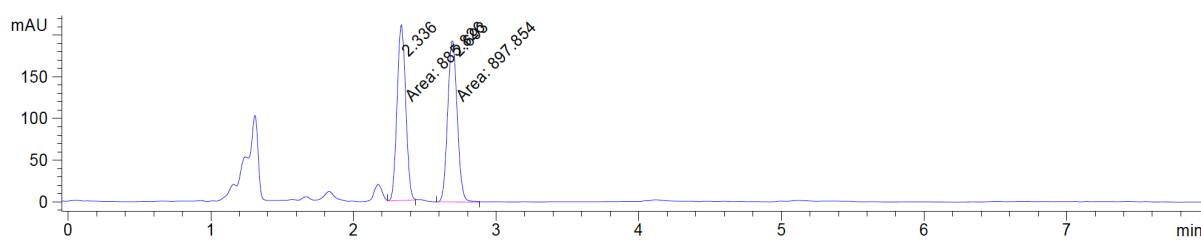




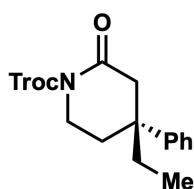
2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-phenylazepane-1-carboxylate (**7b**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-methyl-2-oxo-4-phenylazepane-1-carboxylate (**7b**) (35.8 mg, 0.095 mmol, 95%). ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.31 (m, 4H), 7.22–7.18 (m, 1H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.76 (d, *J* = 11.9 Hz, 1H), 4.02 (ddd, *J* = 15.3, 7.3, 2.9 Hz, 1H), 3.88 (ddd, *J* = 15.3, 7.7, 2.9 Hz, 1H), 3.33 (d, *J* = 14.6 Hz, 1H), 2.96 (d, *J* = 14.6 Hz, 1H), 2.32–2.27 (m, 1H), 1.97–1.91 (m, 2H), 1.87–1.81 (m, 1H), 1.39 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 173.1, 152.0, 147.3, 128.8, 126.5, 125.4, 94.7, 75.6, 50.9, 46.5, 41.5, 39.0, 29.4, 25.0; IR (Neat Film, NaCl) 2956, 1781, 1714, 1444, 1378, 1201, 1039, 811, 717 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₆H₁₉Cl₃NO₃ [M+H]⁺: 378.0425, found 378.0437; [α]_D²¹ -29.8° (c 1.0, CHCl₃, 87% ee); SFC Conditions: 25% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, *t_R*(time): major = 2.34, minor = 2.69.



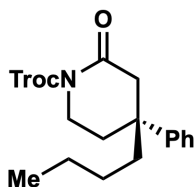


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.335	MM	0.0693	1041.78174	250.65233	93.4693
2	2.689	MM	0.0751	72.78957	16.15755	6.5307



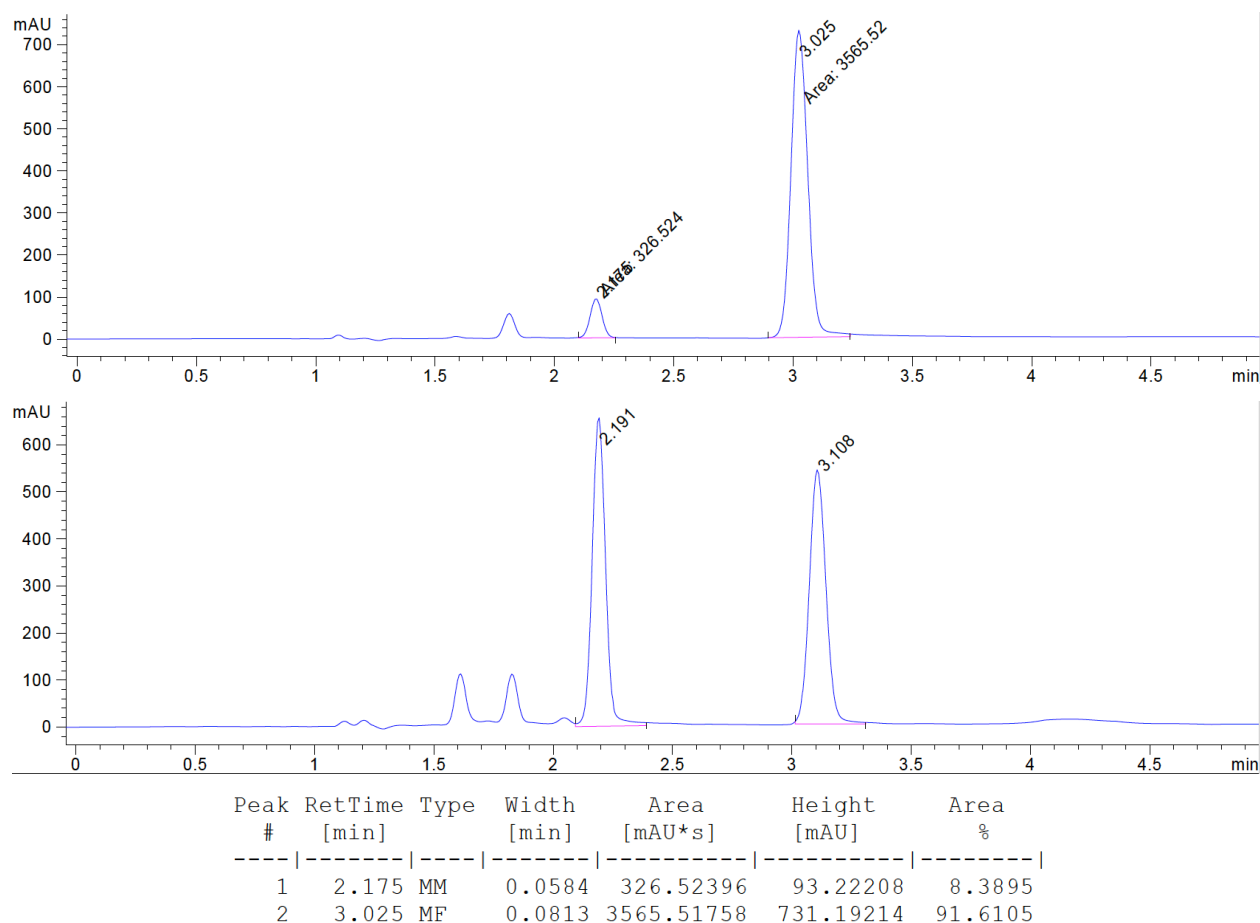
2,2,2-trichloroethyl (*R*)-4-ethyl-2-oxo-4-phenylpiperidine-1-carboxylate

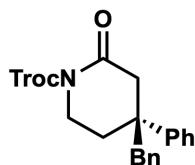
Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 80:20 to 75:25) to afford 2,2,2-trichloroethyl (*R*)-4-ethyl-2-oxo-4-phenylpiperidine-1-carboxylate (28.3 mg, 0.075 mmol, 75%). ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.21 (m, 5H), 4.86 (d, *J* = 11.9 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 3.83 (dt, *J* = 12.8, 4.9 Hz, 1H), 3.33 (ddd, *J* = 12.8, 10.7, 4.6 Hz, 1H), 3.15 (dd, *J* = 17.0, 2.5 Hz, 1H), 2.60 (d, *J* = 17.0 Hz, 1H), 2.26 (dtd, *J* = 14.0, 4.6, 2.6 Hz, 1H), 2.10 (ddd, *J* = 14.0, 10.8, 5.2 Hz, 1H), 1.91 – 1.80 (m, 1H), 1.71 – 1.60 (m, 1H), 0.65 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 152.0, 142.9, 129.0, 126.9, 126.3, 94.6, 75.6, 44.8, 44.0, 41.5, 35.8, 34.8, 8.1. IR (Neat Film, NaCl) 2961, 2924, 1782, 1718, 1460, 1446, 1373, 1286, 1227, 1143, 1107, 1047, 821, 760, 717, 702 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₆H₁₉Cl₃NO₃ [M+H]⁺: 378.0425, found 378.0427; [α]_D²² –49.8° (c 0.14, CHCl₃, 84% ee).



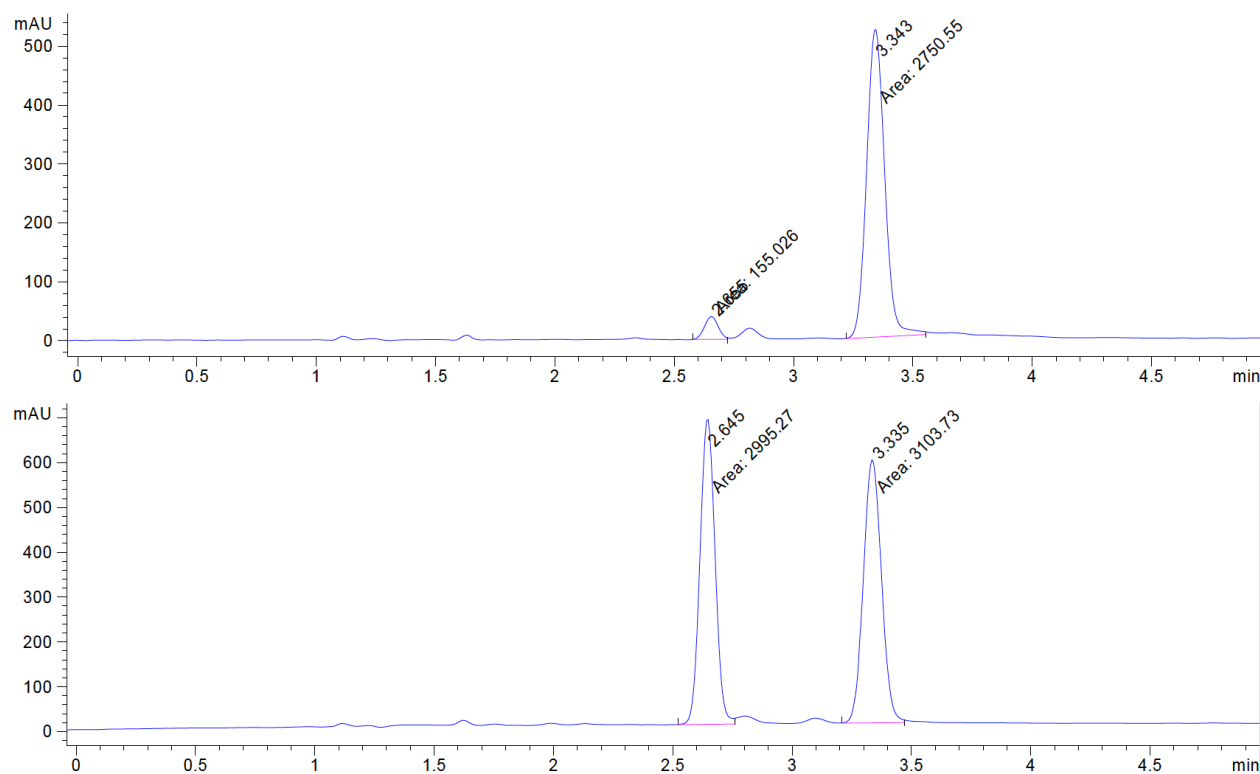
2,2,2-trichloroethyl (*R*)-4-butyl-2-oxo-4-phenylpiperidine-1-carboxylate (7c)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 75:25) to afford 2,2,2-trichloroethyl (*R*)-4-butyl-2-oxo-4-phenylpiperidine-1-carboxylate (**7c**) (34.9 mg, 0.086 mmol, 86%). ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.29 (m, 2H), 7.24 (ddd, *J* = 7.1, 3.6, 2.0 Hz, 3H), 4.86 (d, *J* = 11.9 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 3.82 (dt, *J* = 12.9, 4.9 Hz, 1H), 3.32 (ddd, *J* = 12.8, 10.7, 4.6 Hz, 1H), 3.15 (dd, *J* = 17.0, 2.5 Hz, 1H), 2.62 (d, *J* = 17.0 Hz, 1H), 2.25 (dtd, *J* = 14.0, 4.6, 2.5 Hz, 1H), 2.10 (ddd, *J* = 13.9, 10.7, 5.2 Hz, 1H), 1.79 (ddd, *J* = 13.6, 12.2, 4.4 Hz, 1H), 1.59 (ddd, *J* = 13.4, 12.3, 4.4 Hz, 1H), 1.23 – 1.13 (m, 2H), 1.13 – 1.01 (m, 1H), 0.91 – 0.82 (m, 1H), 0.79 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 152.0, 143.3, 129.0, 126.9, 126.1, 94.6, 75.6, 45.3, 43.9, 43.0, 41.2, 35.1, 25.8, 23.1, 14.0. IR (Neat Film, NaCl) 2956, 2927, 2857, 1785, 1719, 1463, 1447, 1395, 1373, 1287, 1224, 1106, 1042, 825, 763, 719, 701 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₈H₂₃Cl₃NO₃ [M+H]⁺: 406.0738, found 406.0748; [α]_D²³ –46.1° (c 0.10, CHCl₃, 83% ee); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R(time): major = 3.03, minor = 2.18.

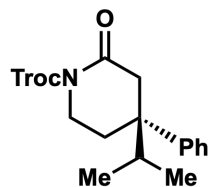


**2,2,2-trichloroethyl (*R*)-4-benzyl-2-oxo-4-phenylpiperidine-1-carboxylate (**7d**)**

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 95:5 to 80:20) to afford 2,2,2-trichloroethyl (*R*)-4-benzyl-2-oxo-4-phenylpiperidine-1-carboxylate (**7d**) (33.9 mg, 0.077 mmol, 76%). ^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.30 (m, 2H), 7.30 – 7.23 (m, 1H), 7.22 – 7.12 (m, 5H), 6.80 – 6.73 (m, 2H), 4.85 (d, J = 12.0 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 3.87 (ddd, J = 12.8, 5.4, 3.3 Hz, 1H), 3.26 (ddd, J = 12.8, 12.0, 4.4 Hz, 1H), 3.07 – 2.98 (m, 2H), 2.90 (d, J = 13.4 Hz, 1H), 2.67 (d, J = 17.0 Hz, 1H), 2.44 (ddt, J = 13.9, 4.4, 3.2 Hz, 1H), 2.16 – 2.07 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.4, 151.9, 142.3, 136.0, 130.5, 129.1, 128.1, 127.2, 126.9, 126.6, 94.6, 75.6, 50.0, 44.4, 43.9, 42.4, 34.2. IR (Neat Film, NaCl) 2926, 1782, 1719, 1495, 1474, 1453, 1396, 1372, 1287, 1222, 1167, 1103, 1044, 821, 768, 703 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{21}\text{H}_{21}\text{Cl}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 440.0582, found 440.0593; $[\alpha]^{23}_{\text{D}}$ -25.2° (c 1.0, CHCl_3 , 90% ee); SFC Conditions: 30% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, $t_{\text{R}}(\text{time})$: major = 3.34, minor = 2.66.

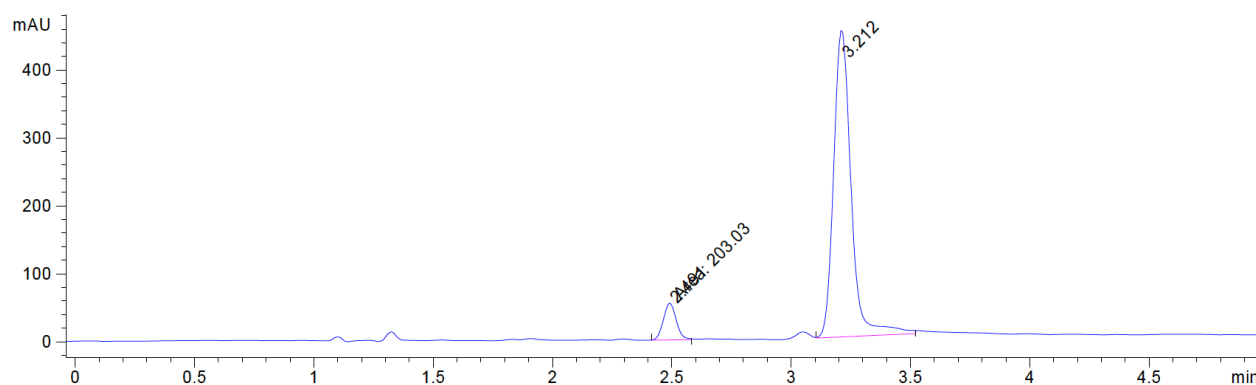


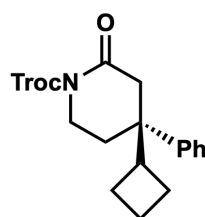
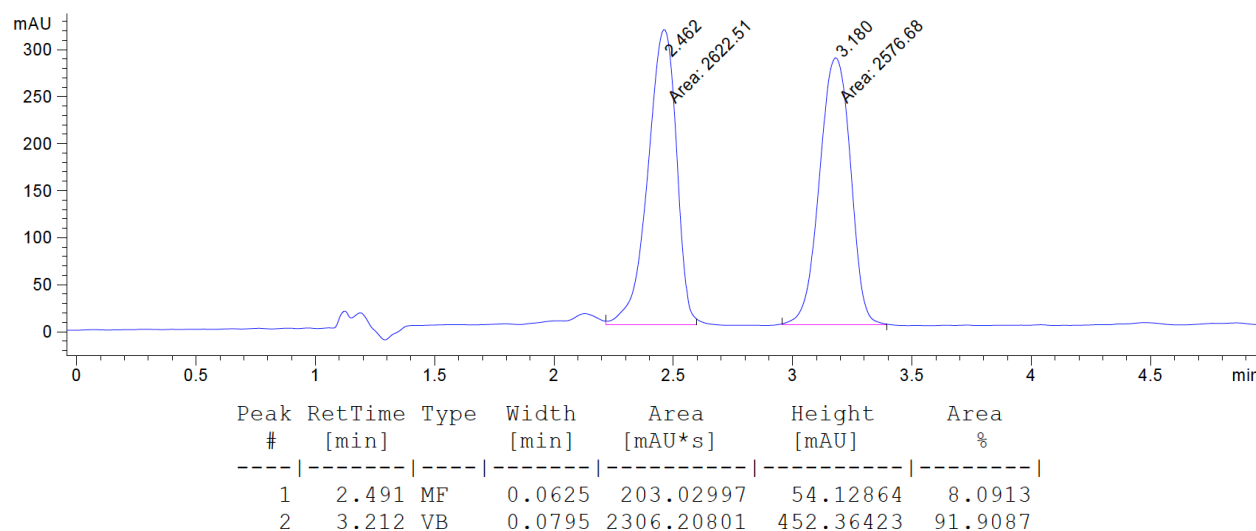
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.655	MF	0.0665	155.02623	38.83154	5.3355
2	3.343	MF	0.0874	2750.54517	524.36719	94.6645



2,2,2-trichloroethyl (*R*)-4-isopropyl-2-oxo-4-phenylpiperidine-1-carboxylate (**7e**)

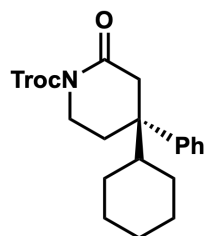
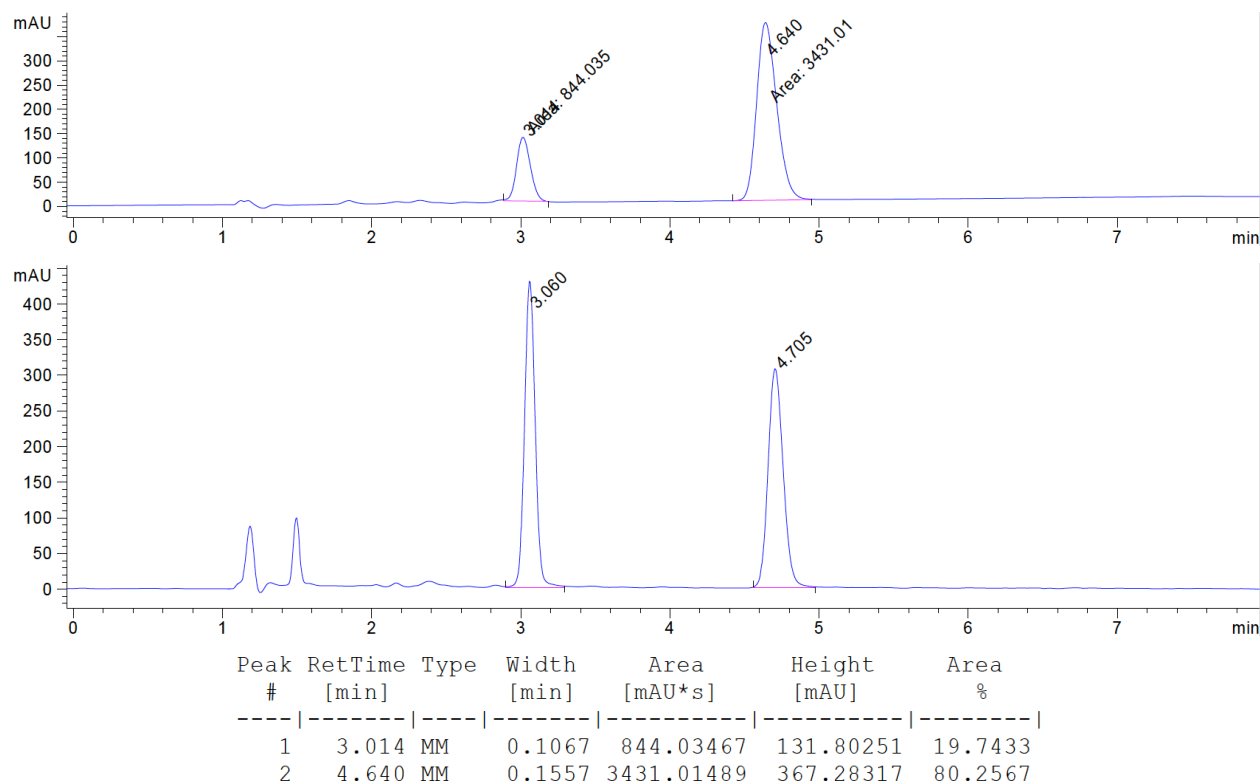
Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-isopropyl-2-oxo-4-phenylpiperidine-1-carboxylate (**7e**) (31.8 mg, 0.081 mmol, 81%). ^1H NMR (400 MHz, CDCl_3) δ 7.34 (ddd, J = 9.4, 5.8, 1.8 Hz, 2H), 7.29 – 7.20 (m, 3H), 4.85 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 11.9 Hz, 1H), 3.84 (ddd, J = 12.7, 5.4, 3.1 Hz, 1H), 3.23 – 3.11 (m, 2H), 2.63 (d, J = 17.0 Hz, 1H), 2.30 (ddt, J = 14.0, 4.3, 3.1 Hz, 1H), 2.15 (ddd, J = 14.0, 12.2, 5.4 Hz, 1H), 1.96 (hept, J = 6.8 Hz, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.0, 151.8, 141.9, 128.8, 126.9, 94.6, 75.5, 44.3, 44.2, 40.9, 37.9, 32.4, 17.6, 17.2. IR (Neat Film, NaCl) 2961 1784, 1719, 1467, 1446, 1372, 1286, 1226, 1141, 1102, 1055, 820, 785, 762, 720, 703 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{17}\text{H}_{20}\text{Cl}_3\text{NNaO}_3$ $[\text{M}+\text{Na}]^+$: 414.0401, found 414.0409; $[\alpha]_D^{23}$ -40.3° (c 1.0, CHCl_3 , 84% ee); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (time): major = 3.21, minor = 2.49.





2,2,2-trichloroethyl (*R*)-4-cyclobutyl-2-oxo-4-phenylpiperidine-1-carboxylate (**7f**)

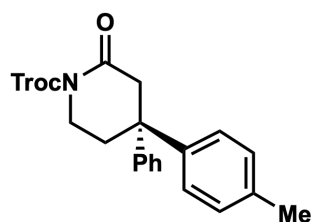
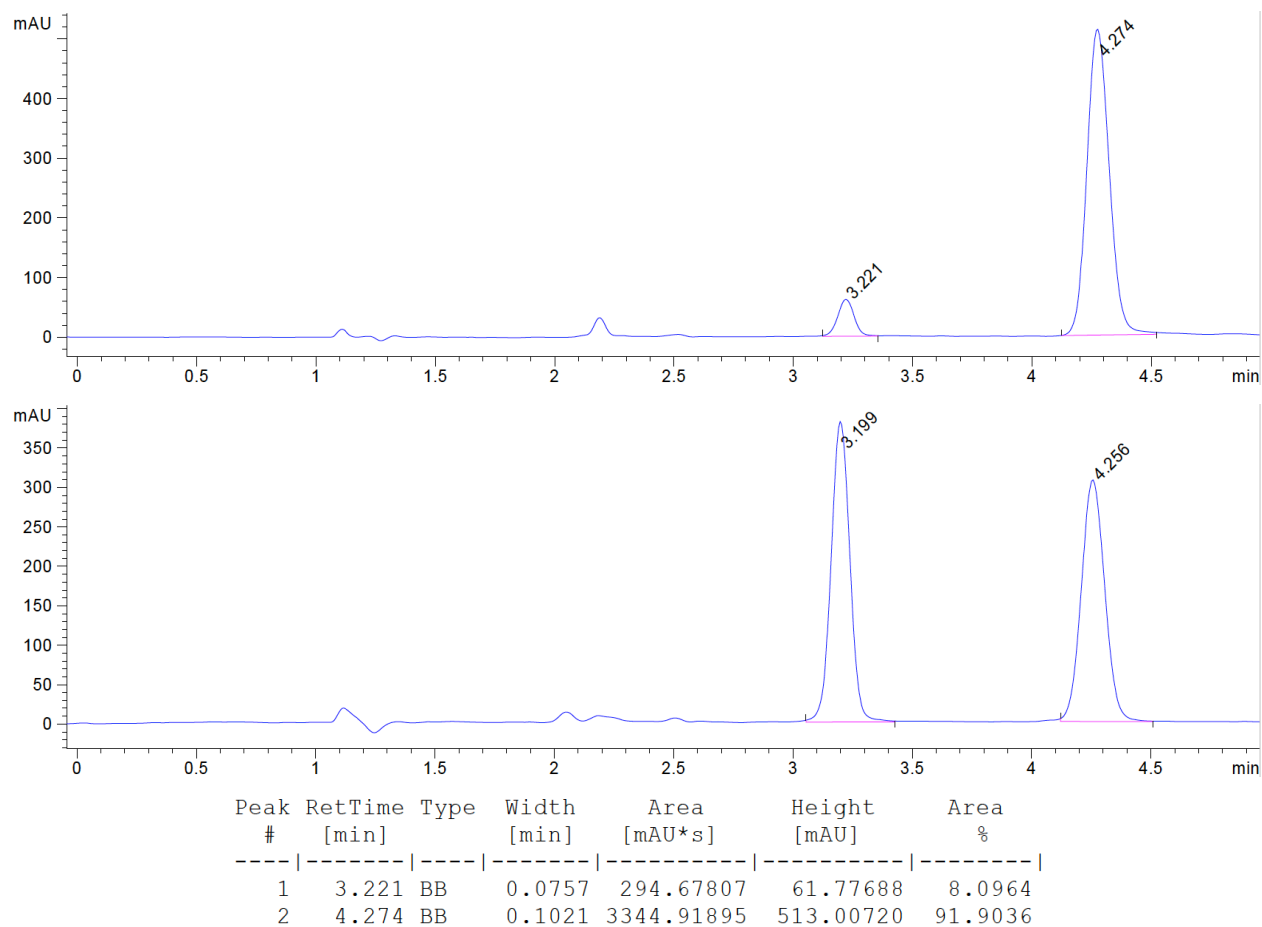
Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 70:30) to afford 2,2,2-trichloroethyl (*R*)-4-cyclobutyl-2-oxo-4-phenylpiperidine-1-carboxylate (**7f**) (36.1 mg, 0.064 mmol, 91%). ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.32 (m, 2H), 7.27 – 7.22 (m, 3H), 4.86 (d, *J* = 11.9 Hz, 1H), 4.70 (d, *J* = 11.9 Hz, 1H), 3.88 (ddd, *J* = 12.8, 5.4, 3.4 Hz, 1H), 3.38 – 3.27 (m, 1H), 3.09 (dd, *J* = 16.8, 3.0 Hz, 1H), 2.71 (d, *J* = 16.8 Hz, 1H), 2.63 – 2.50 (m, 1H), 2.31 – 2.22 (m, 1H), 2.07 (ddd, *J* = 14.0, 11.9, 5.5 Hz, 1H), 1.90 – 1.76 (m, 2H), 1.76 – 1.52 (m, 4H). ¹³C NMR (126 MHz, cdcl₃) δ 170.9, 151.9, 141.7, 128.9, 126.9, 126.4, 94.6, 75.5, 46.5, 44.0, 42.6, 41.9, 30.6, 23.7, 23.1, 17.1. IR (Neat Film, NaCl) 2958, 1784, 1716, 1445, 1398, 1372, 1311, 1283, 1227, 1095, 1049, 824, 721 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₈H₂₁Cl₃NO₃ [M+H]⁺: 404.0582, found 404.0595; [α]_D²³ –33.2° (c 1.0, CHCl₃, 61% ee); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, *t_R*(time): major = 3.01, minor = 4.64.



2,2,2-trichloroethyl (*R*)-4-cyclohexyl-2-oxo-4-phenylpiperidine-1-carboxylate (**7g**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 75:25) to afford 2,2,2-trichloroethyl (*R*)-4-cyclohexyl-2-oxo-4-phenylpiperidine-1-carboxylate (**7g**) (25.0 mg, 0.058 mmol, 58%). ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.31 (m, 2H), 7.26 – 7.21 (m, 3H), 4.85 (d, *J* = 11.9 Hz, 1H), 4.68 (d, *J* = 11.9 Hz, 1H), 3.83 (ddd, *J* = 12.7, 5.3, 3.1 Hz, 1H), 3.24 – 3.13 (m, 2H), 2.68 (d, *J* = 16.9 Hz, 1H), 2.29 (ddt, *J* = 14.0, 4.4, 3.2 Hz, 1H), 2.18 (ddd, *J* = 14.0, 12.1, 5.4 Hz, 1H), 1.91 – 1.76 (m, 2H), 1.65 (ddd, *J* = 18.5, 12.1, 6.5 Hz, 2H), 1.55 (tt, *J* = 12.0, 3.0 Hz, 1H), 1.36 (dd, *J* = 10.9, 5.6 Hz, 1H), 1.29 – 1.18 (m, 1H), 1.13 – 0.97 (m, 2H), 0.86 (dq, *J* = 22.1, 12.4, 3.6 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 171.1, 151.8, 142.3, 128.8, 126.9, 94.6, 75.5, 48.5, 44.4, 44.0, 41.7, 32.0, 27.5, 27.4, 26.9, 26.9, 26.5. IR (Neat Film, NaCl) 2929, 2853, 1784, 1715, 1495, 1474, 1446, 1395, 1372, 1285, 1222, 1103, 1045, 823, 761, 705 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₂₀H₂₅Cl₃NO₃ [M+H]⁺:

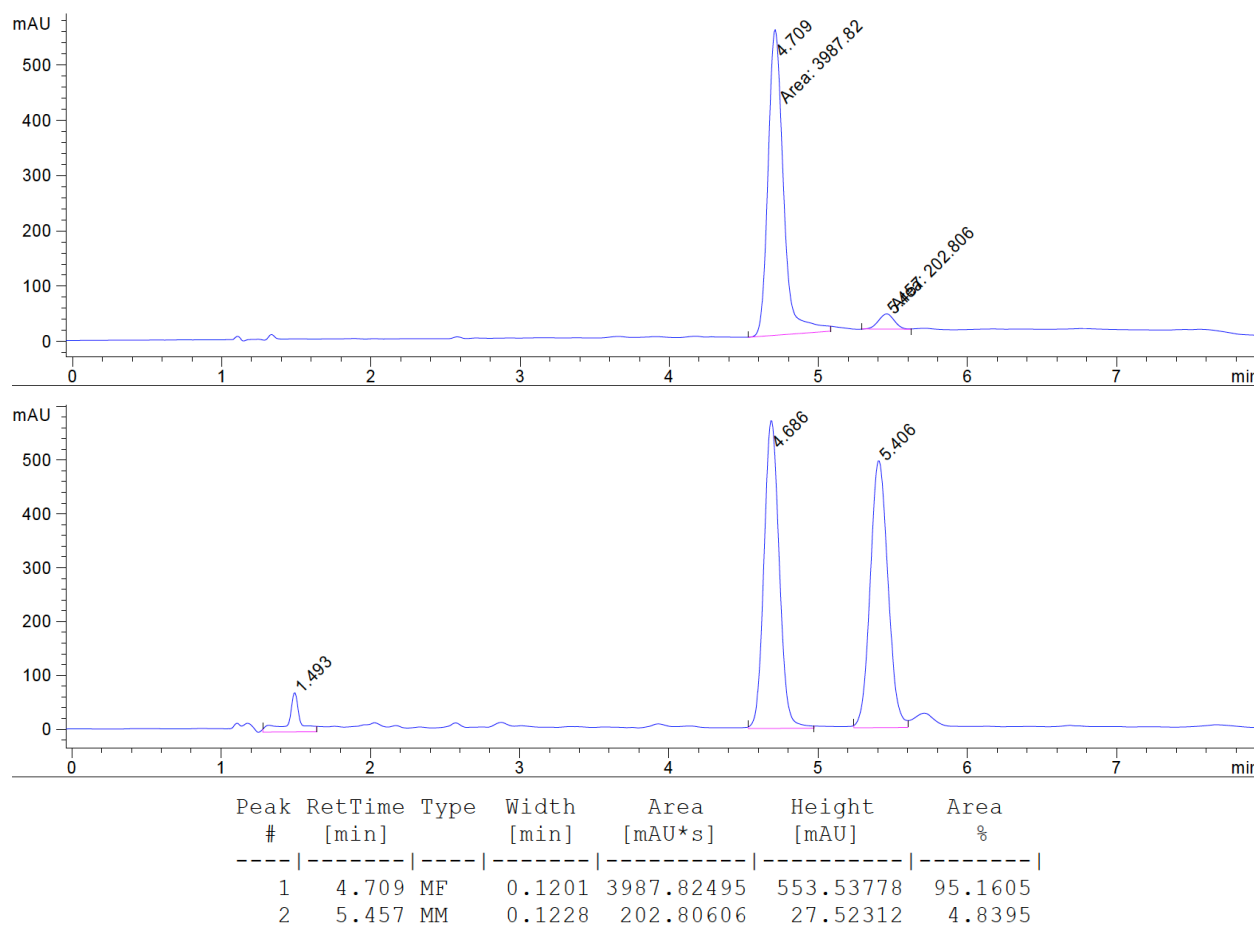
432.0895, found 432.0904; $[\alpha]_D^{23} -44.9^\circ$ (c 1.0, CHCl_3 , 84% ee); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, t_R (time): major = 4.27, minor = 3.22.



2,2,2-trichloroethyl (*S*)-2-oxo-4-phenyl-4-(*p*-tolyl)piperidine-1-carboxylate (**7h**)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 90:10 to 75:25) to afford 2,2,2-trichloroethyl (*S*)-2-oxo-4-phenyl-4-(*p*-tolyl)piperidine-1-carboxylate (**7h**) (26.5 mg, 0.058 mmol, 58%). ^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.26 (m, 2H), 7.25 – 7.15 (m, 3H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.08 – 7.03 (m, 2H), 4.82 (d, $J = 1.0$ Hz, 2H), 3.57 (td, $J = 5.7, 1.1$ Hz, 2H), 3.13 (d, $J = 1.3$ Hz, 2H), 2.68 – 2.60 (m, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.9, 151.9, 145.8, 142.5, 136.7, 129.6, 128.9, 126.96,

126.58, 126.52, 94.6, 75.6, 47.78, 45.48, 43.88, 33.7, 21.1. IR (Neat Film, NaCl) 2917, 2849, 1783, 1714, 1446, 1396, 1372, 1313, 1279, 1226, 1097, 1053, 813, 763, 718, 700 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{21}\text{H}_{21}\text{Cl}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 440.0582, found 440.0589; $[\alpha]^{23}_{\text{D}} +1.21^\circ$ (c 1.0, CHCl_3 , 90% ee); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, $t_{\text{R}}(\text{time})$: major = 4.71, minor = 5.46.



General Procedure for the Synthesis of Racemic Products

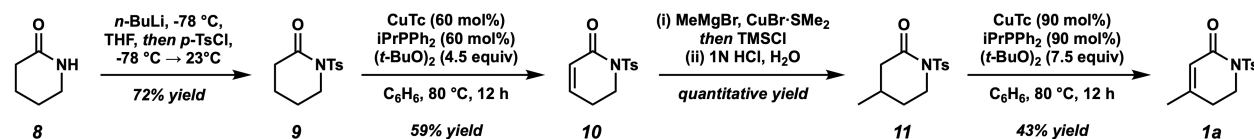
Racemic products were synthesized in a manner analogous to the general procedure using 2,2'-bipyridine (12 mol%) as an achiral ligand.

Synthesis of Conjugate Addition Substrates

Substrate Synthesis for Reaction Condition Optimization

Utilizing previously reported protocols,⁵ we synthesized substrate **1a** (β -methyl- α,β -unsaturated-*N*-tosyl-lactam, i.e., $\text{R}^1 = \text{Ts}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$, and $n = 1$ in **Error! Reference source not found.**) f

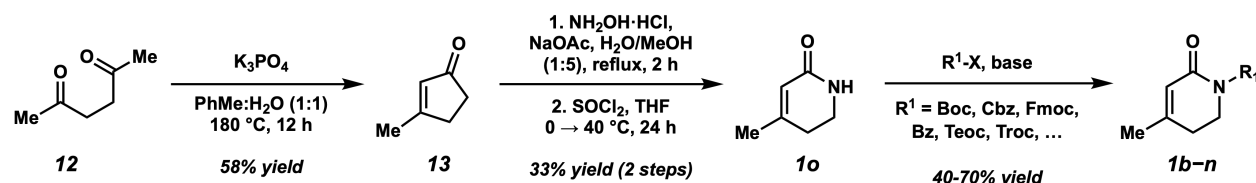
from a readily available and economical substrate (δ -valerolactam), affording an overall 17% yield through a four-step route (Scheme S1).



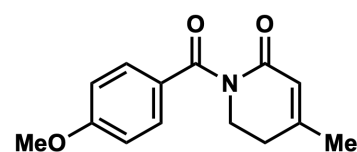
Scheme S1. Synthesis of substrate **1a**.

Substrate Synthesis for Investigations of Protecting Group Scope

For investigating the protecting group scope, a more divergent synthetic route was developed to synthesize lactams **3a–o** with different *N*-protecting groups instead (Scheme S2). Following an intramolecular Knoevenagel condensation,⁶ a Beckman rearrangement⁷ furnished the precursor NH-lactam that can then be masked by a variety of *N*-protecting groups.⁸ This was achieved within three steps, requiring merely two flash-column purifications. We have managed to obtain the α,β -unsaturated lactams **3a–o** with a range of carbamate, sulfonamide and amide groups to evaluate the scope of *N*-protecting groups compatible with the catalytic system developed.



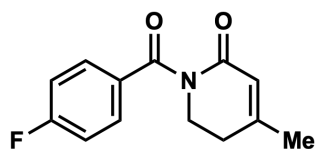
Scheme S2. Synthesis of α,β -unsaturated lactams **3a–o** with different *N*-protecting groups R^1 . Base = *n*-BuLi, DMAP/triethylamine, or Na_2CO_3 . X = Cl or Succinimidyl.



1-(4-methoxybenzoyl)-4-methyl-5,6-dihydropyridin-2(1H)-one (**1b**)

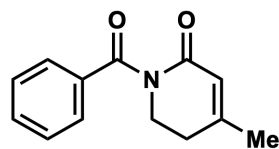
Prepared according to literature protocols.^{8c} To a cooled (0 °C) solution of lactam **1o** (33.3 mg, 0.29 mmol, 1.00 equiv), triethylamine (120 μ L, 0.88 mmol, 3.00 equiv), and DMAP (3.6 mg, 29 μ mol, 0.102 equiv) in THF (1.17 mL) was added benzoyl chloride (80 μ L, 0.58 mmol, 2.00 equiv) dropwise over 5 min. The reaction mixture was allowed to warm to ambient temperature and stirred for 14 h. The reaction mixture was then diluted with brine (2 mL) and EtOAc (2 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 3 mL), and the combined organic phases were washed with brine (2 x 6 mL), dried over Na_2SO_4 , filtered, and concentrated

under reduced pressure. The resulting oil was purified by flash chromatography (1.7 x 20 cm SiO₂, 10 to 50% EtOAc in hexanes) to afford lactam **1b** as a yellow solid (25.3 mg, 35% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.62 – 7.56 (m, 2H), 6.90 – 6.84 (m, 2H), 5.78 (d, *J* = 1.7 Hz, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 3.84 (s, 3H), 2.50 (t, *J* = 6.5 Hz, 2H), 2.05 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.5, 166.1, 162.6, 157.5, 131.0, 128.3, 121.1, 113.4, 55.5, 43.7, 30.2, 23.2. IR (Neat Film, NaCl) 2934, 1681, 1605, 1512, 1470, 1418, 1385, 1316, 1256, 1225, 1174, 1027, 992, 842, 770 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₄H₁₆NO₃⁺ [*M*+H]⁺: 246.1125, found 246.1125.



1-(4-fluorobenzoyl)-4-methyl-5,6-dihydropyridin-2(1*H*)-one (**1c**)

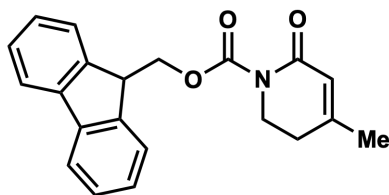
Prepared according to a similar procedure for substrate **1b**, with lactam **1o** (32.5 mg, 0.28 mmol, 1.00 equiv), triethylamine (240 μL, 1.76 mmol, 6.28 equiv), DMAP (3.4 mg, 29 μmol, 0.099 equiv) and benzoyl chloride (140 μL, 1.16 mmol, 4.00 equiv) in THF (1.2 mL), warming from 0 °C to room temperature for 28 h. Purified by flash chromatography (1.5 x 22 cm SiO₂, 0% to 50% EtOAc in hexanes) to afford lactam **1c** as a yellow solid (19.8 mg, 29% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 8.7, 5.1 Hz, 2H), 7.05 (t, *J* = 8.3 Hz, 2H), 5.78 (p, *J* = 1.4 Hz, 1H), 4.01 – 3.94 (m, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.06 (d, 1.7 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 172.9, 165.9, 163.6, 158.1, 132.94 (d, *J* = 9.5 Hz), 130.97 (d, *J* = 9.0 Hz), 120.9, 115.3 (d, *J* = 22.1 Hz), 43.4, 30.2, 23.3. IR (Neat Film, NaCl) 2926, 1693, 1682, 1602, 1506, 1471, 1386, 1317, 1292, 1226, 1155, 1095, 1012, 846, 767 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₃H₁₂FNO₂⁺ [*M*]⁺: 233.0847, found 233.0859.



1-benzoyl-4-methyl-5,6-dihydropyridin-2(1*H*)-one (**1d**)

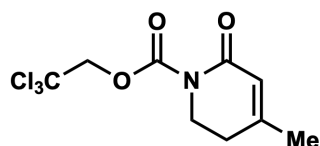
Prepared according to a similar procedure for substrate **1b**, with lactam **1o** (33.5 mg, 0.29 mmol, 1.00 equiv), triethylamine (120 μL, 0.88 mmol, 3.00 equiv), DMAP (3.6 mg, 29 μmol, 0.102 equiv) and benzoyl chloride (70 μL, 0.58 mmol, 2.00 equiv) in THF (1.2 mL), warming from 0 °C to room temperature for 14 h. Purified by flash chromatography (1.5 x 20 cm SiO₂, wet loading with

toluene, 10% to 30% EtOAc in hexanes) to afford lactam **1d** as an orange solid (25.3 mg, 42% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.59 – 7.32 (m, 5H), 5.78 (h, J = 1.5 Hz, 1H), 3.99 (t, J = 6.5 Hz, 2H), 2.55 – 2.49 (m, 2H), 2.06 (dd, J = 1.5, 0.8 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.0, 165.8, 158.0, 136.3, 131.6, 128.29, 128.09, 120.9, 43.3, 30.1, 23.2. IR (Neat Film, NaCl) 3059, 2933, 1681, 1601, 1471, 1448, 1385, 1317, 1222, 1167, 1013, 991, 793, 732 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{13}\text{H}_{14}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 216.1019, found 216.1020.



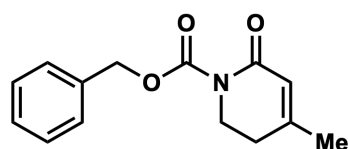
(9H-fluoren-9-yl)methyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (1e**)**

Prepared according to literature protocols.^{8b} In a flame-dried dram vial, a solution of *N*-H lactam **1o** (35.0 mg, 0.31 mmol, 1.00 equiv.) in dioxane (0.610 ml) was stirred with 10% Na_2CO_3 solution (0.610 ml) and cooled at 0°C . 9-Fluorenylmethyl chloroformate (111 mg, 0.43 mmol, 1.40 equiv.) was added portionwise and the resulting mixture was stirred at 0°C for 2 h and kept at room temperature overnight. Reaction mixture was diluted with H_2O (1.5 mL) and extracted with EtOAc (3 \times 2 ml). The organic layer was washed with NaHCO_3 solution and acidified with 10% HCl, then extracted with EtOAc (3 \times 5 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2 x 24 cm SiO_2 , 10% to 100% EtOAc in hexanes followed by 1% to 10% MeOH in EtOAc) to afford *N*-Fmoc lactam **1e** as an off-white solid (18.8 mg, 26% yield brsm; 9.9 mg substrate **1o** recovered). ^1H NMR (400 MHz, CDCl_3) δ 7.80 – 7.74 (m, 4H), 7.43 – 7.38 (m, 2H), 7.33 (td, J = 7.5, 1.1 Hz, 2H), 5.87 (q, J = 1.4 Hz, 1H), 4.50 (d, J = 7.5 Hz, 2H), 4.34 (t, J = 7.5 Hz, 1H), 3.95 (t, J = 6.4 Hz, 2H), 2.39 (t, J = 6.4 Hz, 2H), 2.01 (q, J = 1.0 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.8, 156.5, 154.5, 143.81, 141.37, 127.91, 127.33, 125.6, 121.69, 120.03, 69.2, 60.5, 46.9, 43.7, 30.0, 23.1, 21.2, 14.3. IR (Neat Film, NaCl) 2921, 1703, 1451, 1382, 1323, 1295, 1222, 1153, 1085, 758, 738 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{21}\text{H}_{20}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$: 334.1438, found 334.1435.



2,2,2-Trichloroethyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**1f**)

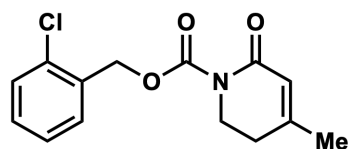
Prepared according to literature protocols.^{8a} To a solution of *N*-H lactam **1o** (40.0 mg, 0.35 mmol, 1.00 equiv.) in dry THF (1.6 mL) was added dropwise a solution of *n*BuLi (145 μ L, 0.36 mmol, 2.5 M in hexane, 1.02 equiv.) at -78°C under inert N_2 atmosphere. The reaction was stirred for 30 min at this temperature. Then a solution of TrocCl (50 μ L, 0.37 mmol, 1.05 equiv.) in dry THF (0.6 mL) was added dropwise and the reaction mixture was stirred for 4 h at -78°C . The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the aqueous layer was extracted with Et_2O (3 x 3 mL). The combined organic phases were washed with saturated aqueous NaCl, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by flash chromatography (2 x 20 cm SiO_2 , 20% to 40% EtOAc in hexanes, wet loading in toluene) to afford *N*-Troc lactam **1f** as a brown gel-like amorphous solid (56.9 mg, 57% yield). ^1H NMR (400 MHz, CDCl_3) δ 5.84 (q, J = 1.5 Hz, 1H), 4.88 (s, 2H), 4.01 (t, J = 6.4 Hz, 2H), 2.42 (t, J = 6.4 Hz, 2H), 2.00 (d, J = 1.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.4, 156.8, 152.2, 121.4, 94.7, 75.7, 44.0, 29.9, 23.2. IR (Neat Film, NaCl) 2935, 1715, 1540, 1394, 1213, 1101, 834 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_9\text{H}_{11}\text{NO}_3^+$ [$\text{M}+\text{H}$] $^+$: 285.9799, found 285.9800.



Benzyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**1g**)

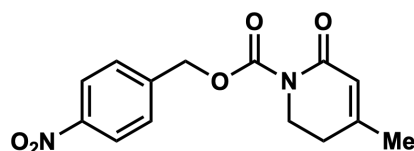
Prepared according to a similar procedure for substrate **1f**, with *N*-H lactam **1o** (26.0 mg, 0.22 mmol, 1.00 equiv.), *n*BuLi (90 μ L, 0.22 mmol, 2.5 M in hexane, 1.00 equiv.), and CbzCl (106 μ L, 30-35% v/v in toluene, 0.22 mmol, 1.00 equiv.) in 230 μ L THF, at -78°C for 3.5 hours. Purified by flash chromatography (2.0 x 15 cm SiO_2 , wet loading in CHCl_3 /toluene, 30% to 50% EtOAc in hexanes) to afford *N*-Cbz lactam **1g** as a yellowish-white solid (21.7 mg, 39% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.48 – 7.42 (m, 2H), 7.40 – 7.28 (m, 3H), 5.80 (q, J = 1.4 Hz, 1H), 5.31 (s, 2H), 3.93 (t, J = 6.5 Hz, 2H), 2.35 (t, J = 6.5 Hz, 2H), 1.97 (d, J = 1.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.9, 156.3, 135.7, 129.9, 128.69, 128.35, 128.14, 121.7, 68.6, 43.8, 29.9, 23.1.

IR (Neat Film, NaCl) 2929, 1762, 1704, 1456, 1382, 1323, 1296, 1209, 1167, 1086, 1027, 861, 732 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{14}\text{H}_{15}\text{NNaO}_3^+$ $[\text{M}+\text{Na}]^+$: 268.0944, found 268.0948;



2-chlorobenzyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**1h**)

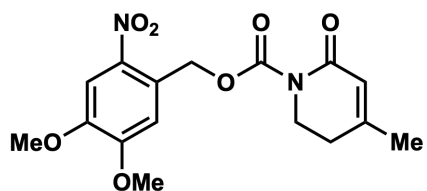
Prepared according to a similar procedure for substrate **1f**, with *N*-H lactam **1o** (40.0 mg, 0.35 mmol, 1.00 equiv.), *n*BuLi (150 μL , 0.35 mmol, 2.5 M in hexane, 1.01 equiv.), and (2-Cl)CbzCl (60 μL , 0.39 mmol, 1.11 equiv.) in 400 μL THF, at -78°C for 3.5 hours. Purified by flash chromatography (2.2 x 23 cm SiO_2 , wet loading in CH_2Cl_2 /toluene, 20% to 33% EtOAc in hexanes) to afford *N*-2-ClCbz lactam **1h** as a pale-yellow solid (64.8 mg, 66% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.67 (dd, $J = 7.4, 1.8$ Hz, 1H), 7.37 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.33 – 7.21 (m, 3H), 5.81 (q, $J = 1.5$ Hz, 1H), 5.41 (s, 2H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.38 (t, $J = 6.5$ Hz, 2H), 1.99 (d, $J = 1.4$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.8, 156.5, 154.1, 133.5, 132.9, 129.6, 129.4, 129.4, 127.2, 121.6, 65.9, 43.8, 29.9, 23.1. IR (Neat Film, NaCl) 2066, 2927, 1767, 1713, 1697, 1651, 1471, 1445, 1383, 1323, 1296, 1224, 1153, 1088, 1051, 1039, 968, 947, 862, 757, 730 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{14}\text{H}_{15}\text{ClNO}_3^+$ $[\text{M}+\text{H}]^+$: 280.0735, found 280.0737;



4-nitrobenzyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**1i**)

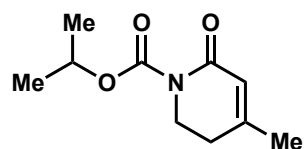
Prepared according to a similar procedure for substrate **1f**, with *N*-H lactam **1o** (40.0 mg, 0.35 mmol, 1.00 equiv.), *n*BuLi (145 μL , 0.36 mmol, 2.5 M in hexane, 1.02 equiv.), and (4- NO_2)CbzCl (90.5 mg, 0.37 mmol, 1.05 equiv.) in 1.8 mL THF, at -78°C for 3.5 hours. Purified by flash chromatography (2 x 20 cm SiO_2 , wet loading in toluene, 20% to 50% EtOAc in hexanes) to afford *N*-(4- NO_2)Cbz lactam **1i** as an off-white solid (68.6 mg, 68% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.22 (dd, $J = 9.0, 2.3$ Hz, 3H), 7.67 – 7.63 (m, 2H), 5.82 (h, $J = 1.4$ Hz, 1H), 5.40 (s, 2H), 3.96 (t, $J = 6.4$ Hz, 2H), 2.43 – 2.36 (m, 2H), 2.00 (dd, $J = 1.5, 0.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.7, 157.0, 154.4, 147.8, 143.1, 128.1, 123.9, 121.5, 67.1, 43.8, 29.9, 23.1. IR (Neat Film, NaCl) 2933, 1765, 1697, 1646, 1606, 1558, 1520, 1471, 1435, 1384, 1347, 1323, 1295, 1223,

1212, 1153, 1109, 1088, 1034, 1015, 852, 772, 758, 738 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_5^+$ $[\text{M}+\text{H}]^+$: 291.0976, found 291.0978;



4,5-dimethoxy-2-nitrobenzyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**1j**)

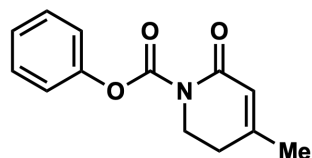
Prepared according to a similar procedure for substrate **1f**, with *N*-H lactam **1o** (40.0 mg, 0.35 mmol, 1.00 equiv.), *n*BuLi (145 μL , 0.36 mmol, 2.5 M in hexane, 1.02 equiv.), and NvocCl (101.0 mg, 0.37 mmol, 1.05 equiv.) in 4.0 mL THF, at -78°C for 4.5 hours. Purified by flash chromatography (2.0 x 18 cm SiO_2 , wet loading in CHCl_3 /toluene, 20% to 50% EtOAc in hexanes) to afford *N*-Nvoc lactam **1j** as an off-white solid (80.6 mg, 67% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.92 (s, 1H), 7.76 (s, 1H), 5.82 (q, $J = 1.5$ Hz, 1H), 5.77 (d, $J = 0.9$ Hz, 2H), 4.08 (s, 3H), 4.00 (t, $J = 6.5$ Hz, 2H), 3.97 (s, 4H), 2.42 (t, $J = 6.4$ Hz, 2H), 2.02 (d, $J = 1.4$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.9, 157.1, 154.4, 154.3, 147.9, 138.7, 128.2, 121.5, 110.7, 107.9, 66.2, 57.1, 56.5, 43.9, 29.9, 23.1. IR (Neat Film, NaCl) 2944, 1715, 1694, 1579, 1524, 1465, 1439, 1384, 1323, 1280, 1221, 1090, 1067, 795 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{NaO}_7^+$ $[\text{M}+\text{Na}]^+$: 373.1006, found 373.1012;



Isopropyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**1k**)

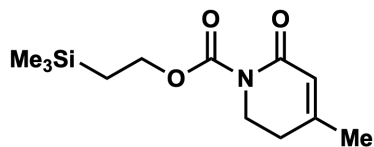
Prepared according to a similar procedure for substrate **1f**, with *N*-H lactam **1o** (30.0 mg, 0.26 mmol, 1.00 equiv.), *n*BuLi (105 μL , 0.26 mmol, 2.5 M in hexane, 1.00 equiv.), and isopropyl chloroformate (265 μL , 1M in toluene, 0.26 mmol, 1.00 equiv.) in 1.4 mL THF, at -78°C for 3.5 hours. Purified by flash chromatography (12 g SiO_2 , wet loading in toluene, 25% to 50% EtOAc in hexanes) to afford *N*-*i*PrOC lactam **1k** as a pale-yellow oil (29.9 mg, 59% yield). ^1H NMR (400 MHz, CDCl_3) δ 5.77 (h, $J = 1.4$ Hz, 1H), 5.07 (hept, $J = 6.3$ Hz, 1H), 3.88 (dd, $J = 6.8, 6.2$ Hz, 2H), 2.38 – 2.28 (m, 2H), 1.95 (dt, $J = 1.7, 0.9$ Hz, 3H), 1.33 (d, $J = 6.3$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.0, 155.8, 153.8, 121.8, 71.1, 43.6, 29.9, 23.0, 21.0. IR (Neat Film, NaCl) 2981,

1762, 1705, 1472, 1387, 1318, 1295, 1221, 1167, 1108, 1084, 1027, 915, 863 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{10}\text{H}_{15}\text{NNaO}_3^+$ $[\text{M}+\text{Na}]^+$: 220.0944, found 220.0945;



Phenyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (1l)

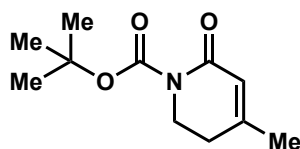
Prepared according to a similar procedure for substrate **1f**, with *N*-H lactam **1o** (30.0 mg, 0.26 mmol, 1.00 equiv.), *n*BuLi (105 μL , 0.26 mmol, 2.5 M in hexane, 1.00 equiv.), and phenyl chloroformate (40 μL , 0.26 mmol, 1.00 equiv.) in 1.8 mL THF, at -78°C for 3.5 hours. Purified by flash chromatography (12 g SiO_2 , wet loading in toluene, 25% to 50% EtOAc in hexanes) to afford *N*-PhOC lactam **1l** as a brownish-white solid (36.7 mg, 59% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.34 (m, 2H), 7.26 – 7.17 (m, 3H), 5.87 (h, $J = 1.4$ Hz, 1H), 4.04 (t, $J = 6.4$ Hz, 2H), 2.45 (ddt, $J = 7.3, 6.3, 1.1$ Hz, 2H), 2.03 (dd, $J = 1.5, 0.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.7, 156.9, 153.2, 150.9, 129.5, 126.1, 121.7, 121.6, 44.1, 30.0, 23.2. IR (Neat Film, NaCl) 2932, 1774, 1728, 1700, 1495, 1386, 1325, 1297, 1278, 1227, 1191, 1163, 1074, 1026, 855, 747 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{13}\text{H}_{14}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$: 232.0968, found 232.0969;



2-(trimethylsilyl)ethyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (1m)

Prepared according to a similar procedure for substrate **1f**, with *N*-H lactam **1o** (40.0 mg, 0.35 mmol, 1.00 equiv.), *n*BuLi (145 μL , 0.36 mmol, 2.5 M in hexane, 1.02 equiv.), and *N*-[2-(Trimethylsilyl)ethoxycarbonyloxy]succinimide (Teoc-OSu, 95.1 mg, 0.37 mmol, 1.05 equiv.) in 2.0 mL THF, at -78°C for 3.5 hours. Purified by flash chromatography (2 x 20 cm SiO_2 , wet loading in toluene, 25% to 50% Et_2O in hexanes) to afford *N*-Teoc lactam **1m** as a colorless oil (47.3 mg, 53% yield). ^1H NMR (400 MHz, CDCl_3) δ 5.78 (h, $J = 1.4$ Hz, 1H), 4.37 – 4.32 (m, 2H), 3.91 (t, $J = 6.5$ Hz, 2H), 2.37 – 2.32 (m, 2H), 1.97 (dd, $J = 1.5, 0.8$ Hz, 3H), 1.15 – 1.10 (m, 2H), 0.05 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.9, 156.0, 154.5, 121.7, 65.6, 43.6, 29.9, 25.6, 23.0, 17.7, -1.5. IR (Neat Film, NaCl) 2953, 2899, 1809, 1789, 1745, 1712, 1651, 1471, 1455,

1429, 1384, 1323, 1295, 1250, 1213, 1172, 1150, 1084, 1061, 935, 861, 839, 773 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{12}\text{H}_{21}\text{NNaO}_3\text{Si}^+$ $[\text{M}+\text{Na}]^+$: 278.1183, found 278.1191;

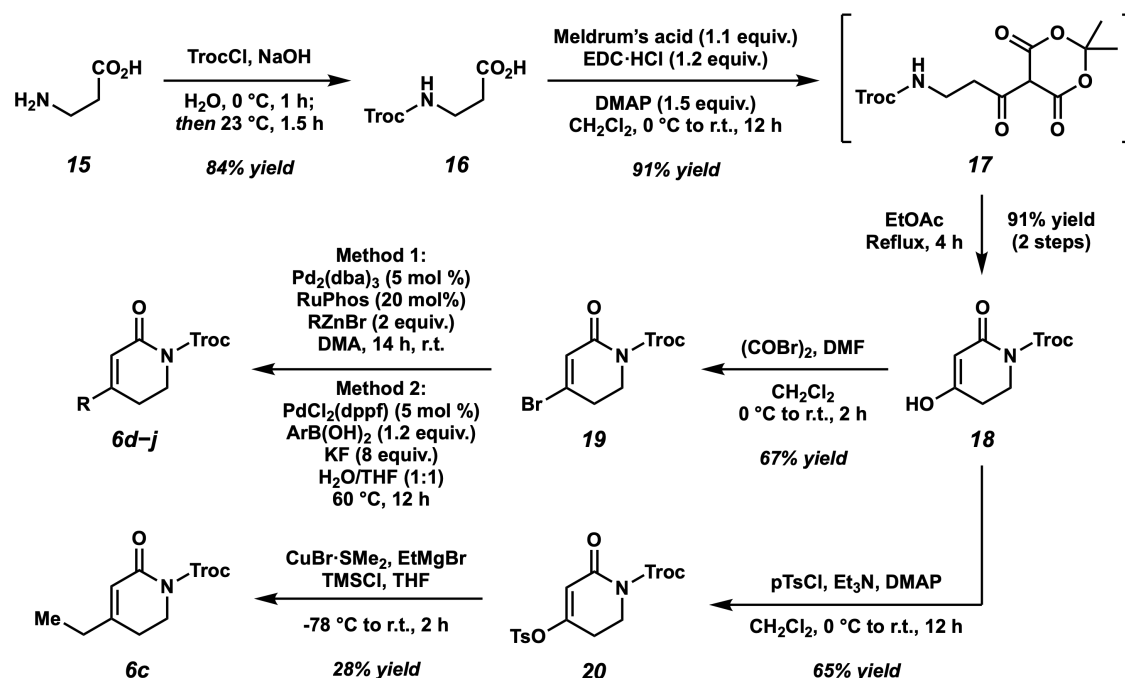


tert-butyl 4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (1n)

Prepared according to a similar procedure for substrate **1f**, with *N*-H lactam **1o** (30.0 mg, 0.26 mmol, 1.00 equiv.), *n*BuLi (105 μL , 0.26 mmol, 2.5 M in hexane, 1.00 equiv.), and $(\text{Boc})_2\text{O}$ (57 μL , 0.26 mmol, 1.00 equiv.) in 1.4 mL THF, at $-78\text{ }^\circ\text{C}$ for 3.5 hours. Purified by flash chromatography (12 g SiO_2 , wet loading in toluene, 20% to 40% EtOAc in hexanes) to afford *N*-Boc lactam **1n** as a yellow gel (27.1 mg, 49% yield). ^1H NMR (400 MHz, CDCl_3) δ 5.76 (dd, $J = 2.5, 1.3$ Hz, 1H), 3.84 (t, $J = 6.5$ Hz, 2H), 2.33 (t, $J = 6.5$ Hz, 2H), 1.96 (d, $J = 1.7$ Hz, 3H), 1.55 (d, $J = 1.0$ Hz, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.2, 155.5, 152.9, 121.9, 82.9, 43.5, 30.0, 28.2, 27.5, 23.0. IR (Neat Film, NaCl) 2930, 1759, 1714, 1471, 1455, 1392, 1368, 1307, 1245, 1218, 1174, 1151, 1191, 1072, 1028, 853, 843, 791 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{11}\text{H}_{17}\text{NNaO}_3^+$ $[\text{M}+\text{Na}]^+$: 234.1102, found 234.1101;

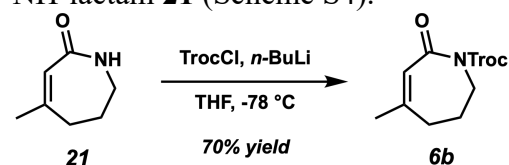
Substrate Synthesis for Investigations of Substrate Scope

To investigate the β -substituent scope, we synthesized lactams **6c–j** from the commercially available β -alanine (**15**) as the starting material (Scheme S3). Following a Troc protection of the primary amine,⁹ an EDC-mediated condensation of the carboxylic acid with Meldrum's acid followed by decarboxylative pericyclic ring opening under reflux conditions afforded the β -hydroxy- α,β -unsaturated-lactam **18**.¹⁰ In one route, **18** was converted to the β -brominated congener **19** using Vilsmeier's reagent,¹¹ followed by a $\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^3)$ Negishi coupling,^{10, 12} or a $\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^2)$ Suzuki-Miyaura coupling¹³ to afford α,β -unsaturated lactams **6d–j**. Alternatively, β -hydroxy- α,β -unsaturated-lactam **18** could undergo a tosylation,¹⁴ followed by a tandem 1,4-Grignard addition and elimination reaction¹⁵ to afford the β -ethyl substrate **6c**.



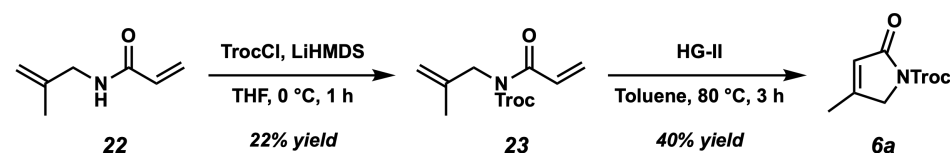
Scheme S3. Synthesis of α,β -unsaturated lactams **6d–j** with different β -substituents R^2 .

The seven-membered lactam substrate **6b** was prepared by Troc protection of the corresponding NH-lactam **21** (Scheme S4).^{6a}

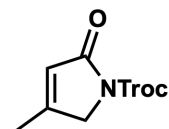


Scheme S4. Synthesis of seven-membered α,β -unsaturated lactams **6b**.

The five-membered lactam substrate **6a** was prepared via an *N*-H Troc protection of a linear amide **22** followed by an olefin metathesis catalyzed by Grubbs' catalyst (Scheme S5).¹⁶



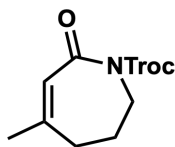
Scheme S5. Synthesis of the five-membered α,β -unsaturated lactam substrate **6a**.



2,2,2-trichloroethyl 4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**6a**)

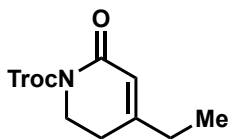
To a stirred solution of 2,2,2-trichloroethyl acryloyl(2-methylallyl)carbamate (**23**) (242 mg, 0.805 mmol, 1.00 equiv.) in toluene (8.0 mL) was added Grubbs 2nd generation catalyst (68.0 mg, 0.081

mmol, 0.10 eq.) at room temperature under N₂. After being stirred at 80 °C for 3 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc = 70:30 to 50:50) to afford 2,2,2-trichloroethyl 4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**6a**) (88.8 mg, 0.326 mmol, 40%). ¹H NMR (500 MHz, CDCl₃) δ 5.93 (d, *J* = 1.5 Hz, 1H), 4.89 (s, 2H), 4.36 (s, 2H), 2.16 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 169.1, 159.5, 148.7, 122.6, 94.7, 74.9, 54.1, 15.8; R (Neat Film, NaCl) 1788, 1383, 1281, 1102, 832, 733 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₈H₉Cl₃NO₃ [M+H]⁺: 271.9643, found 271.9655.



2,2,2-trichloroethyl 5-methyl-7-oxo-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (**6b**)

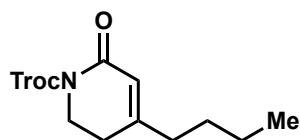
To a stirred solution of 4-methyl-1,5,6,7-tetrahydro-2*H*-azepin-2-one (**21**) (100 mg, 0.799 mmol, 1.00 eq.) in THF (2.0 mL) was added 2.5 M *n*-BuLi in hexane (0.383 mL, 0.959 mmol, 1.20 eq.) at -78 °C under N₂. After being stirred at the same temperature for 15 min, TrocCl (0.129 mL, 0.959 mmol, 1.20 eq.) was added to reaction mixture at -78 °C. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with NH₄Cl aq. and poured into water. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc = 80:20 to 60:40) to afford 2,2,2-trichloroethyl 5-methyl-7-oxo-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (**6b**) (169 mg, 0.562 mmol, 70%). ¹H NMR (500 MHz, CDCl₃) δ 5.89 (d, *J* = 1.5 Hz, 1H), 4.88 (s, 2H), 3.86 (t, *J* = 6.4 Hz, 3H), 2.38 (t, *J* = 7.3 Hz, 2H), 2.04–1.98 (m, 5H). ¹³C NMR (126 MHz, CDCl₃) δ 169.6, 153.8, 151.7, 122.9, 94.9, 75.4, 44.4, 30.0, 26.4, 25.4; IR (Neat Film, NaCl) 2953, 1771, 1700, 1378, 1282, 1178, 1100, 851, 715 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₀H₁₃Cl₃NO₃ [M+H]⁺: 299.9956, found 299.9967.



2,2,2-trichloroethyl 4-ethyl-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate

Prepared according to literature protocols.^{5c} To a solution of 37.2 mg (0.181 mmol) of copper(I) bromide-dimethyl sulfide complex in 4.4 mL of THF at -78 °C was added 145 μL of a solution of ethylmagnesium bromide (380 μL, 0.381 mmol, 1M in THF, 2.10 equiv.). The mixture was stirred

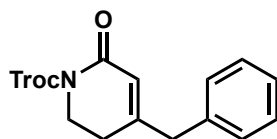
for 10 min, warmed to $-40\text{ }^{\circ}\text{C}$, stirred for 10 min, cooled to $-78\text{ }^{\circ}\text{C}$ and stirred for another 10 min. Sequential addition of freshly distilled chlorotrimethylsilane ($80\text{ }\mu\text{L}$, 0.636 mmol , 3.5 equiv.) followed by a solution of 2,2,2-trichloroethyl 6-oxo-4-(tosyloxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (**20**) (80.0 mg , 0.181 mmol , 1.00 equiv.) in 4.4 mL of THF produced a reaction mixture that was warmed to $-40\text{ }^{\circ}\text{C}$ and stirred for 1 h. After warming to rt and stirring for 15 min, 1*N* aqueous HCl (1 mL) was added and the mixture was stirred at rt for 15 min. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by flash column chromatography ($1\text{ x }20\text{ cm SiO}_2$, 0% to 3% EtOAc in CH_2Cl_2) afforded 2,2,2-trichloroethyl 4-ethyl-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate as a pale-yellow gel (15.4 mg , 28% yield). ^1H NMR (400 MHz , CDCl_3) δ 5.83 (t, $J = 1.4\text{ Hz}$, 1H), 4.88 (s, 2H), 4.00 (t, $J = 6.5\text{ Hz}$, 2H), 2.41 (t, $J = 6.4\text{ Hz}$, 2H), 2.28 (qt, $J = 7.5, 1.5\text{ Hz}$, 2H), 1.12 (t, $J = 7.4\text{ Hz}$, 3H). ^{13}C NMR (101 MHz , CDCl_3) δ 163.7, 161.9, 152.1, 119.5, 94.8, 75.7, 44.1, 29.8, 28.7, 11.1. IR (Neat Film, NaCl) 2925, 1771, 1704, 1652, 1540, 1456, 1379, 1318, 1223, 1206, 1169, 1091, 874 cm^{-1} .



2,2,2-trichloroethyl 4-butyl-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (**6c**)

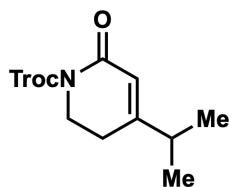
Prepared according to literature protocols.¹¹ To a solution of $\text{Pd}_2(\text{dba})_3$ (4.3 mg , $4.6\text{ }\mu\text{mol}$, 0.054 equiv.) and RuPhos (8.0 mg , $17.1\text{ }\mu\text{mol}$, 0.200 equiv.) in dry dimethylacetamide (DMA, 0.430 mL), 2,2,2-trichloroethyl 4-bromo-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (**19**, 30.0 mg , 0.085 mmol , 1.00 equiv.) was added at r.t. After stirring for 10 min, a solution of the *n*BuZnBr ($170\text{ }\mu\text{L}$, 0.903 mmol , 1*M* in dry DMA, 2.00 equiv.) prepared according to procedure in ref. 12 was added at once. After the reaction mixture was stirred at r.t. for 14 h, the solvent was removed under reduced pressure. Purification by flash chromatography ($1.2\text{ cm x }20\text{ cm SiO}_2$, wet loading in toluene, 5% to 20% EtOAc in hexanes) afforded 2,2,2-trichloroethyl 4-butyl-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (**6c**) as a pale brown gel (18.7 mg , 67% yield). ^1H NMR (400 MHz , CDCl_3) δ 5.72 (p, $J = 1.4\text{ Hz}$, 1H), 4.77 (s, 2H), 3.89 (t, $J = 6.4\text{ Hz}$, 2H), 2.34 – 2.27 (m, 2H), 2.18 – 2.10 (m, 2H), 1.44 – 1.34 (m, 2H), 1.30 – 1.19 (m, 2H), 0.82 (t, $J = 7.3\text{ Hz}$, 3H). ^{13}C NMR (101 MHz , CDCl_3) δ 163.6, 160.8, 152.1, 120.4, 94.8, 75.7, 44.1, 36.5, 28.8, 28.6, 22.4, 13.9. IR (Neat Film, NaCl) 2954, 2929, 1777, 1710, 1679, 1378, 1325, 1303, 1284, 1223, 1149, 1105,

1058, 783, 717 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{12}\text{H}_{17}\text{Cl}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 328.0269, found 328.0271;



2,2,2-trichloroethyl 4-benzyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (6d)

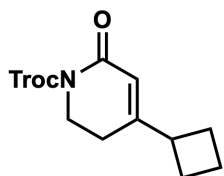
Prepared according to a similar procedure for substrate **6c**, with $\text{Pd}_2(\text{dba})_3$ (16.9 mg, 18.5 μmol , 0.050 equiv.), RuPhos (34.5 mg, 74.0 μmol , 0.200 equiv.), 2,2,2-trichloroethyl 4-bromo-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**19**, 130.0 mg, 0.370 mmol, 1.00 equiv.), and freshly prepared benzyl zinc bromide solution (1.50 mL, 1.0 M in DMA, 4.00 equiv.). Purified by flash chromatography (1 x 20 cm SiO_2 , wet loading in toluene, 15% to 25% EtOAc in hexanes) to afford 2,2,2-trichloroethyl 4-benzyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**6d**) as a white amorphous solid (87.7 mg, 67% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.21 (m, 3H), 7.18 – 7.14 (m, 2H), 5.84 (p, J = 1.4 Hz, 1H), 4.86 (s, 2H), 3.96 (dd, J = 6.7, 6.2 Hz, 2H), 3.55 (t, J = 0.9 Hz, 2H), 2.37 (dddd, J = 6.8, 6.1, 1.5, 0.8 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.5, 158.9, 152.0, 136.2, 129.2, 129.0, 127.4, 121.7, 94.7, 75.7, 44.2, 43.2, 28.0. IR (Neat Film, NaCl) 2921, 1772, 1704, 1684, 1540, 1456, 1418, 1374, 1311, 1284, 1208, 1171, 1099, 1054, 749, 719 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{15}\text{Cl}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 362.0112, found 362.0118;



2,2,2-trichloroethyl 4-isopropyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (6e)

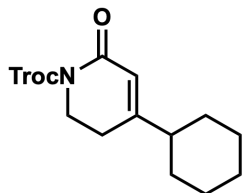
Prepared according to a similar procedure for substrate **6c**, with $\text{Pd}_2(\text{dba})_3$ (26.9 mg, 28.5 μmol , 0.050 equiv.), RuPhos (53.2 mg, 113.8 μmol , 0.200 equiv.), 2,2,2-trichloroethyl 4-bromo-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**19**, 200.0 mg, 0.569 mmol, 1.00 equiv.), and freshly prepared isopropyl zinc bromide solution (2.2 mL, 1.0 M in DMA, 4.00 equiv.). Purified by flash chromatography (1.5 x 21 cm SiO_2 , wet loading in toluene, 5% to 25% EtOAc in hexanes) to afford 2,2,2-trichloroethyl 4-isopropyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**6e**) as a yellowish-white solid (72.5 mg, 41% yield). ^1H NMR (400 MHz, CDCl_3) δ 5.83 (q, J = 1.3 Hz,

1H), 4.88 (s, 2H), 3.99 (dd, $J = 6.8, 6.1$ Hz, 2H), 2.51 – 2.45 (m, 1H), 2.43 (td, $J = 6.4, 1.2$ Hz, 2H), 1.12 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 165.8, 163.9, 152.1, 118.6, 94.8, 75.7, 44.3, 34.8, 26.8, 20.4. IR (Neat Film, NaCl) 2926, 1774, 1712, 1375, 1317, 1284, 1206, 1105, 1059, 722, 682 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{11}\text{H}_{15}\text{Cl}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 314.0112, found 314.0115;



2,2,2-trichloroethyl 4-cyclobutyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (6f)

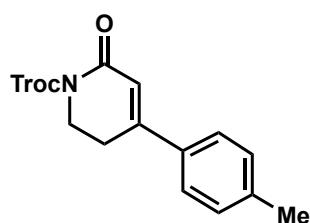
Prepared according to a similar procedure for substrate **6c**, with $\text{Pd}_2(\text{dba})_3$ (26.1 mg, 28.5 μmol , 0.050 equiv.), RuPhos (53.1 mg, 113.8 μmol , 0.200 equiv.), 2,2,2-trichloroethyl 4-bromo-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**19**, 200.0 mg, 0.569 mmol, 1.00 equiv.), and freshly prepared cyclobutyl zinc bromide solution (2.2 mL, 1.0 M in DMA, 4.00 equiv.). Purified by flash chromatography (2 cm x 21 cm SiO_2 , wet loading in toluene, 15% to 25% EtOAc in hexanes) to afford 2,2,2-trichloroethyl 4-cyclobutyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**6f**) as a pale-yellow gel (29.7 mg, 16% yield). ^1H NMR (400 MHz, CDCl_3) δ 5.79 (q, $J = 1.4$ Hz, 1H), 4.88 (s, 2H), 3.99 (t, $J = 6.4$ Hz, 2H), 3.17 – 3.04 (m, 1H), 2.38 – 2.31 (m, 2H), 2.20 (dt, $J = 9.3, 7.3, 2.2$ Hz, 2H), 2.07 – 1.94 (m, 3H), 1.90 – 1.75 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.8, 163.1, 152.0, 118.1, 94.6, 75.6, 44.0, 40.6, 26.8, 26.2, 18.0. IR (Neat Film, NaCl) 2931, 1772, 1702, 1316, 1205, 1106, 683 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{12}\text{H}_{15}\text{Cl}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 326.0112, found 326.0115;



2,2,2-trichloroethyl 4-cyclohexyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (6g)

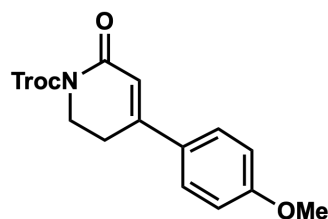
Prepared according to a similar procedure for substrate **6c**, with $\text{Pd}_2(\text{dba})_3$ (16.9 mg, 18.5 μmol , 0.050 equiv.), RuPhos (34.5 mg, 74.0 μmol , 0.200 equiv.), 2,2,2-trichloroethyl 4-bromo-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**19**, 130.0 mg, 0.370 mmol, 1.00 equiv.), and freshly prepared cyclohexyl zinc bromide solution (2.22 mL, 1.0 M in DMA, 6.00 equiv.). Purified by

flash chromatography (1 cm x 20 cm SiO₂, wet loading in toluene, 10% to 25% EtOAc in hexanes) to afford 2,2,2-trichloroethyl 4-cyclohexyl-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (**6g**) as a yellowish-white solid (64.2 mg, 49% yield). ¹H NMR (500 MHz, CDCl₃) δ 5.80 (d, *J* = 1.3 Hz, 1H), 4.88 (s, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.10 (t, *J* = 11.7 Hz, 1H), 1.86 – 1.77 (m, 4H), 1.38 – 1.14 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 165.0, 164.0, 152.1, 118.8, 94.8, 75.7, 44.91, 44.26, 30.9, 27.2, 26.17, 26.03. IR (Neat Film, NaCl) 2928, 2853, 1772, 1706, 1684, 1456, 1416, 1375, 1320, 1286, 1206, 1167, 1149, 1103, 1059, 862, 834, 812, 785, 718 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₄H₁₈Cl₃NNaO₃ [M+Na]⁺: 376.0244, found 376.0256;



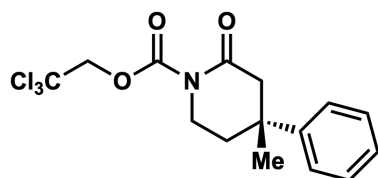
2,2,2-trichloroethyl 6-oxo-4-(*p*-tolyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (6h**)**

Prepared according to literature protocols.¹³ To a solution of 2,2,2-trichloroethyl 6-oxo-4-(tosyloxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (**20**) (0.200 g, 0.452 mmol, 1.00 equiv.), *p*-toluenylboronic acid (73.8 mg, 0.543 mmol, 1.20 equiv.), and PdCl₂(PPh₃)₂ (16.1 mg, 0.0229 mmol) in THF (1.6 mL) was added a solution of KF (210.2 mg, 3.62 mmol, 8.00 equiv.) in H₂O (1.6 mL), and the mixture was stirred at 60 °C overnight. Upon cooling, the reaction mixture was extracted with Et₂O, and the extracts were shaken with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash chromatography (1.5 cm x 21 cm SiO₂, wet loading in toluene, 10% to 25% EtOAc in hexanes) afforded 2,2,2-trichloroethyl 6-oxo-4-(*p*-tolyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**6h**) as a yellowish white solid (29.2 mg, 18% yield). ¹H NMR (500 MHz, cdcl₃) δ 7.46 – 7.43 (m, 2H), 7.25 (d, *J* = 7.7 Hz, 2H), 6.38 (t, *J* = 1.3 Hz, 1H), 4.92 (s, 2H), 4.16 (dd, *J* = 6.7, 6.0 Hz, 2H), 2.90 (td, *J* = 6.4, 1.3 Hz, 2H), 2.40 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 163.9, 154.3, 152.1, 141.3, 133.5, 129.9, 126.1, 119.0, 94.8, 75.8, 44.1, 26.9, 21.5. IR (Neat Film, NaCl) 2976, 1771, 1697, 1372, 1323, 1205, 1111, 817 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₅H₁₅Cl₃NO₃ [M+H]⁺: 362.0112, found 362.0118.



2,2,2-trichloroethyl 4-(4-methoxyphenyl)-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (6h)

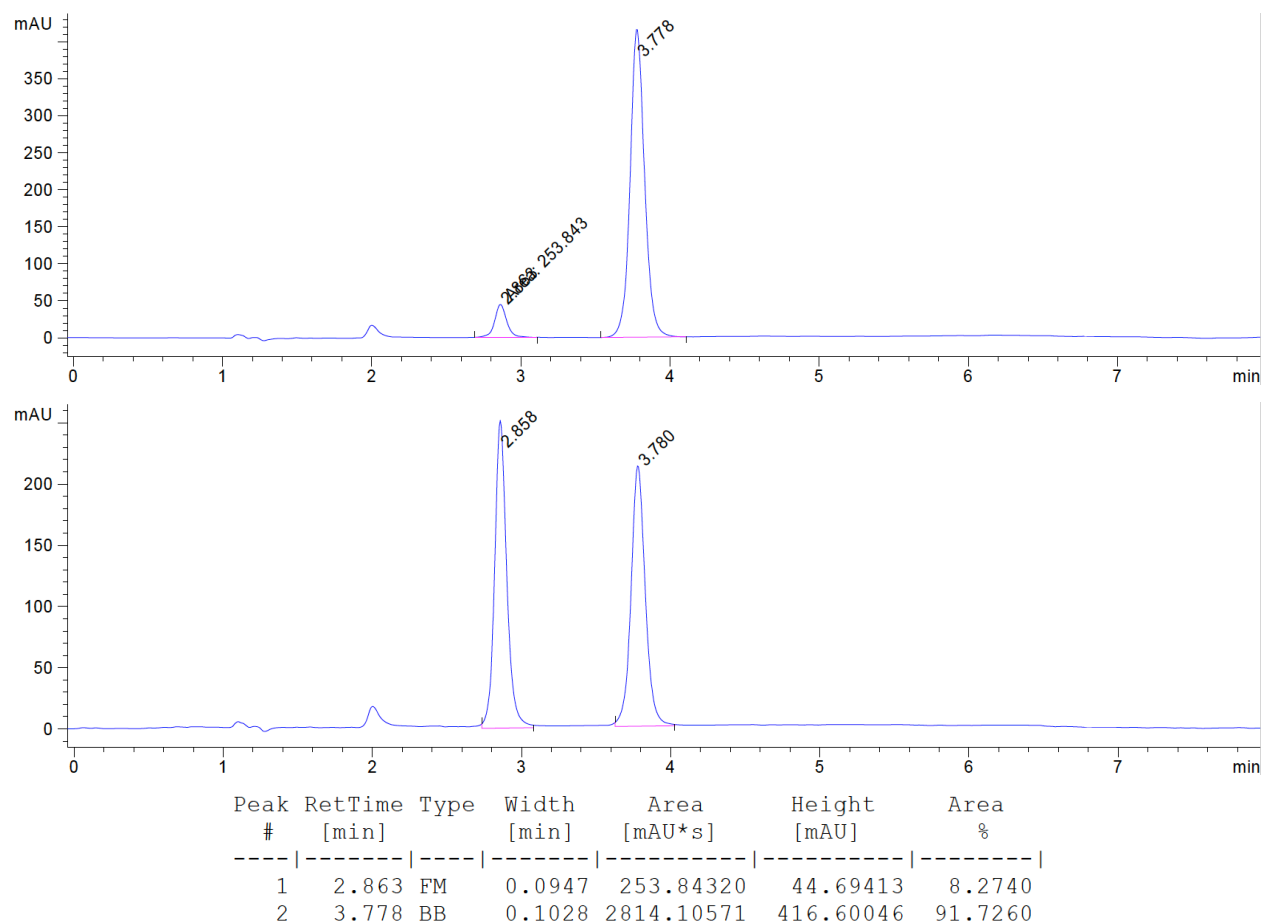
Prepared according to a similar procedure for substrate **6h**, with 2,2,2-trichloroethyl 6-oxo-4-(tosyloxy)-3,6-dihydropyridine-1(2H)-carboxylate (**20**) (0.300 g, 0.678 mmol, 1.00 equiv.), *p*-methoxybenzeneboronic acid (123.7 mg, 0.814 mmol, 1.20 equiv.), PdCl₂(PPh₃)₂ (24.1 mg, 0.0343 mmol) and KF (315.4 mg, 5.43 mmol, 8.00 equiv.). Purified by flash chromatography (24 gram SiO₂, dry loading in celite, 0% to 5% EtOAc in CH₂Cl₂) to afford 2,2,2-trichloroethyl 4-(4-methoxyphenyl)-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**6i**) as a light-yellow gel (50.0 mg, 20% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.49 (m, 2H), 6.98 – 6.92 (m, 2H), 6.34 (t, *J* = 1.2 Hz, 1H), 4.91 (s, 2H), 4.14 (dd, *J* = 6.8, 6.0 Hz, 2H), 3.86 (s, 3H), 2.88 (ddd, *J* = 7.2, 6.0, 1.3 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.0, 161.8, 153.8, 152.1, 128.5, 127.8, 117.9, 114.5, 94.8, 75.7, 55.6, 44.0, 26.9. IR (Neat Film, NaCl) 2916, 1771, 1721, 1697, 1602, 1514, 1464, 1422, 1374, 1329, 1280, 1206, 1183, 1166, 1112, 1030, 873, 831, 791, 760, 719 cm⁻¹; HRMS (ESI) *m/z* calc'd for C₁₅H₁₄Cl₃NNaO₄ [M+Na]⁺: 399.9881, found 399.9882.



Procedure for the large-scale preparation of compound 3f

A screw-top 20 mL scintillating vial was charged with a stir bar, Pd(OCOCF₃)₂ (33 mg, 0.10 mmol, 10 mol%) and (*S*)-*t*-BuPyOx (25 mg, 0.12 mmol, 12 mol%). The solids were dissolved in dichloromethane (8.0 mL) and stirred at room temperature for 15 min. A separate 20 mL scintillating vial was charged with AgBF₄ (47 mg, 0.24 mmol, 24 mol%), followed by the clear yellow homogeneous solution of Pd(OCOCF₃)₂ and (*S*)-*t*-BuPyOx in dichloromethane, and stirred at room temperature for 10 min. A separate 20 mL scintillating vial was charged with α,β-unsaturated lactam **1f** (285 mg, 1.0 mmol, 1.0 equiv.) and PhB(OH)₂ (246 mg, 0.20 mmol, 2.0 equiv.) and added the pre-stirred dichloromethane solution of Pd(OCOCF₃)₂, (*S*)-*t*-BuPyOx, and

AgBF₄, followed by water (0.090 mL, 5.0 mmol, 5 equiv.). The vial was then sealed and stirred at 30 °C for 16 h. The reaction mixture was filtered through a silica plug with ethyl acetate and evaporated *in vacuo*. The crude reaction mixture was loaded directly onto a flash column and the product was isolated by silica gel column chromatography (hexanes/EtOAc = 60:40) to provide **3f** as a colorless oil (326 mg, 0.89 mmol, 90% yield, 84% ee). All characterization data matched those reported above for compound **3f**; [α]²³_D −52.8° (*c* 0.21, CHCl₃); SFC Conditions: 20% EtOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R(time): major = 3.78, minor = 2.86.



Ligand Screening

We tested various types of chiral privileged ligands, including sparteine, pyridine-oxazolines (PyOx), pyridine-bisoxazolines (PyBOX), bisoxazolines (BOX), bioxazolines (BiOX), phosphinoxazolines (PHOX), and quinoline-oxazolines (QUINOX) (Table S1). The results revealed that except for PyOx ligands, all other ligands containing a similar tert-butyl group at the chiral center resulted in much more diminished yield and enantioinduction than the (*S*)-*t*-BuPyOx

ligand in our default conditions. In ligand evaluations conducted by Stoltz and co-workers on a similar cyclohexenone system,² analogous results on the chemical competency of different classes of ligands were reported. As a result, we continue to use PyOx ligands as the default chiral ligand for the catalysis. To account for this observation, we reasoned that the conversion and enantioinduction of the catalytic reaction could be further improved through modulating the steric and electronic features on the PyOx ligand. The testing of various PyOx ligands showed the necessity of including the *tert*-butyl steric bulk on the oxazoline ring in order to retain high enantioselectivity, as reducing the steric bulk (phenyl, cyclohexyl, isopropyl and Inda) lowers yield and asymmetric induction (Table S1). At the same time, our investigation has revealed that electron-withdrawing groups such as -CF₃ on the ligand backbone seemed to help in the turnover of the active catalyst and maintain a moderate level of asymmetric induction (40% ee, Table S1).

Table S1. Screening of chiral ligands shows (S)-*t*-BuPyOx ligand to be most favored

<p style="text-align: center;"> $\text{Pd}(\text{OCOCF}_3)_2$ (5 mol%) Ligand (6 mol%) $\text{PhB}(\text{OH})_2$ (2 equiv) NH_4PF_6 (30 mol%), H_2O (5 equiv), O_2 $\text{ClCH}_2\text{CH}_2\text{Cl}$, 60 °C, 16 h </p>			
<p style="text-align: center;">1a 2a</p>			
<p style="text-align: center;">(-)-Sparteine 0% yield</p>	<p style="text-align: center;"><i>t</i>-Bu-PyBox 0% yield</p>	<p style="text-align: center;"><i>t</i>-Bu-(diMe)Box 0% yield</p>	<p style="text-align: center;"><i>t</i>-Bu-(diMe)Box 0% yield</p>
<p style="text-align: center;"><i>t</i>-Bu-BiOX 0% yield</p>	<p style="text-align: center;"><i>t</i>-Bu-cyano-BOX 0% yield</p>	<p style="text-align: center;"><i>t</i>-Bu-QUINOX 8% yield, 2% ee</p>	<p style="text-align: center;"><i>t</i>-Bu-PHOX 0% yield</p>
<p style="text-align: center;">(<i>S</i>)-<i>t</i>-BuPyOx[#] Trial 1: 49% yield, 41% ee Trial 2: 15% yield, 51% ee*</p>	<p style="text-align: center;">(<i>S</i>)-<i>t</i>-Bu-CF₃PyOX Trial 2: 32% yield, 40% ee</p>	<p style="text-align: center;">(<i>S</i>)-CyPyOX Trial 2: 12% yield, 19% ee</p>	<p style="text-align: center;">IndaPyOX Trial 2: 12% yield, -13% ee</p>
<p style="text-align: center;">(<i>S</i>)-<i>i</i>-PrPyOX Trial 2: 6% yield, 15% ee</p>	<p style="text-align: center;">(<i>S</i>)-PhPyOX Trial 2: 4% yield, x% ee</p>		

[#] Inconsistent result, seems related to whether $\text{PhB}(\text{OH})_2$ stock solution was added hot (due to solubility issues)

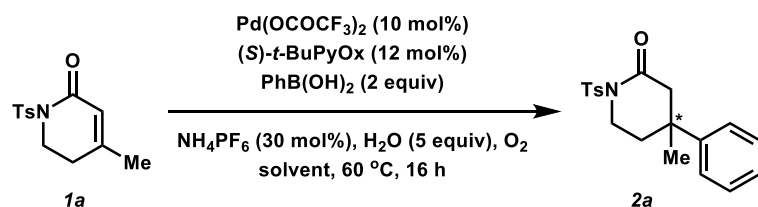
* All NMR yields calculated with a 1,3,5-trimethoxybenzene internal standard (0.333 equiv) added to crude reaction mixture prior to work-up; ee's calculated through SFC (40% EtOH, Column 1 - IC)

One challenge is the reproducibility of results for the DCE solvent. For instance, for the default (*S*)-*t*-BuPyOx ligand condition, we discovered a diminished yield but a slightly improved

enantioinduction upon repetition (Table S1). Empirically, we tried a higher catalyst (10 mol%) and ligand (12 mol%) loading, which did correlate with a moderate increase in the yield and enantioselectivity of the reaction. Our rationalization is that because the system is more prone to random errors at the 0.02 mmol scale used, using a higher amount of catalyst and ligand may improve replicability by reducing random errors, while increasing the concentration and lifetime of the cationic Pd(II) active catalyst (before significant catalyst deactivation) would elevate conversion and yield. This precatalyst and ligand loading was then included as part of our default catalytic conditions for all following screens.

Solvent Screening

Starting with the 1,2-DCE solvent, we investigated the effect of solvents on the reaction (**Table S2**). We propose that the purported cationic Pd active catalyst can be better stabilized in more Lewis basic solvents, before it coordinates to the ene-lactam moiety in substrate **1a**. This helps to diminish the likelihood for another equivalence of PhB(OH)₂ to bind and undergo reductive elimination to afford biphenyl and palladium black as an off-cycle pathway that depletes our catalytic system of available catalysts. Echoing this hypothesis, our results showed that ethereal solvents like tetrahydrofuran (THF, entry 3) and 1,4-dioxane (entry 4) increased the yield and enantioinduction in comparison to DCE (entry 2). In particular, the 1,4-dioxane solvent afforded 92% conversion and 82% yield, with a moderate elevation in asymmetric induction (55% ee). Furthermore, we found a substantial increase in enantioselectivity of reaction for chloroform, toluene and dichloromethane (entries 7-9) upon cooling of the reaction mixture (40 °C). Dichloromethane (DCM, entry 9) was set as the default solvent for subsequent screening based on yield and conversion. Subsequent reaction condition screening in DCM allowed us to set 30 °C and 4 equivalence to be the default temperature and phenylboronic acid loading, respectively.

Table S2. Screening of selected solvents.

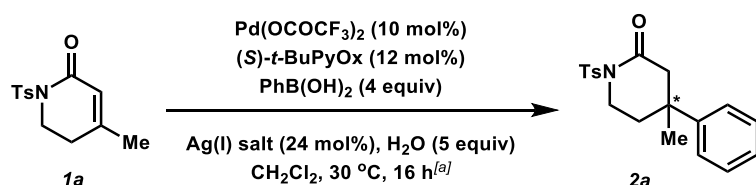
Entry	Solvent	Conversion (%)	Yield (%)	ee (%)
1	NaTFA(aq)*	32	32	21
2	Dichloroethane	37	35	34
3	Tetrahydrofuran	63	56	47
4	Dioxane	92	82	55
5	Chloroform	39	25	61
6	Toluene	62	43	62
7	Chloroform ^[a]	36	25	73
8	Toluene ^[a]	73	55	72
9	Dichloromethane ^[a]	84	68	72

^[a] 40 °C instead of 60 °C

Silver(I) additive screening

Investigation of silver(I) additives (Table S3) revealed a moderate counterion effect. Silver tetrafluoroborate, AgBF_4 , provided the highest reaction yield and excellent enantioselectivity and was used in subsequent reaction optimization efforts. Despite providing a marginally higher enantioselectivity, trifluoroacetate (AgOCOCF_3), lactate and acetate (AgOAc) salts were not selected as they provided significantly lower reaction yields than AgBF_4 .

Table S3. Screening of different silver(I) additives

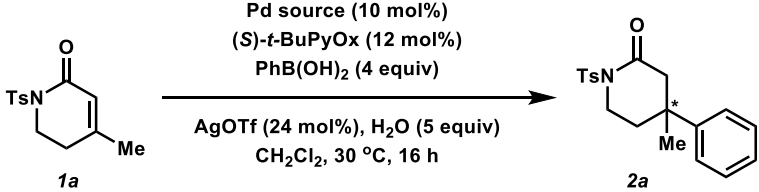
				
Ag(I) salt	Conversion (%)	Yield (%)	ee (%)	Counterion pK _a
AgSbF ₆	100	100	73	N/A
AgPF ₆	100	100	78	-20
AgOTf	97	97	80	-15
AgBF ₄	100	100	82	-4.9
AgOTs	89	93	82	-2.8
Ag(OCOCF ₃)	61	58	85	0.0
Ag(lactate)	67	75	84	3.86
AgOAc	48	47	86	4.75

^[a] Default condition: 0.02 mmol **1a**, 10 mol% Pd(OCOCF₃)₂, 12 mol% (S)-*t*-BuPyOx, 24 mol% Ag(I) salt, H₂O (5 equiv), CH₂Cl₂ (250 mM), 30 °C, 16 h

Precatalyst screening

A range of palladium (II) precatalysts were investigated with respect to their effect on reaction yield and enantioselectivity (Table S4). Monomeric palladium (II) precatalysts containing alkene ligands (i.e., COD and NBD) provided no significant conversion or yield. We speculate that the more electron-rich olefin ligands (COD and NBD) coordinate more strongly to the Lewis-acidic and cationic palladium (II) center, and inhibits the coordination of the more electron-deficient olefin motif in our lactam, thus inhibiting catalytic turnover (Figure 2). In comparison, Pd(OCOCF₃)₂ remains the optimal precatalyst and is used for subsequent reaction optimization and substrate-scope exploration.

Table S4. Investigation of varying Pd(II) precatalysts in the presence of AgOTf additive. nbd \equiv norbornadiene; cod \equiv 1,5-cyclooctadiene.

			
Pd(II) Source	Conversion (%)	Yield (%)	ee (%)
Pd(OCOCF₃)₂	100	100	80
Pd(OAc) ₂	93	92	64
PdBr ₂	7	5	64
PdCl ₂	8	6	73
Pd(NCMe) ₂ Cl ₂	47	45	71
Pd(NCPh) ₂ Cl ₂	36	32	72
Pd(nbd) ₂ Cl ₂	0	0	-
Pd(cod) ₂ Cl ₂	0	0	-

Determination of Absolute Configuration of 3f by Vibrational Circular Dichroism (VCD)

Experimental Protocol. A solution of **3f** (50 mg/mL) in CDCl₃ was loaded into a front-loading SL-4 cell (International Crystal Laboratories) possessing BaF₂ windows and a 100 mm path length. Infrared (IR) and VCD spectra were acquired on a BioTools ChiralIR-2X VCD spectrometer as a set of 24 one-hour blocks (24 blocks, 3120 scans per block) in dual PEM mode. A 15-minute acquisition of neat (+)- α -pinene control yielded a VCD spectrum in agreement with literature spectra. IR and VCD spectra were background corrected using a 30-minute block IR acquisition of the empty instrument chamber under gentle N₂ purge, and were solvent corrected using a 16-hour (16 blocks, 3120 scans per block) IR/VCD acquisition of CDCl₃ in the same 100 μ m BaF₂ cell. The reported spectra represent the result of block averaging.

Computational Protocol. The arbitrarily chosen (*R*) enantiomer of compound **3f** was subjected to an exhaustive initial molecular mechanics-based conformational search (OPLS_2005 force field, CHCl₃ solvent, 10.0 kcal/mol cutoff, “Enhanced” torsional sampling) as implemented in MacroModel program.¹⁷ The resulting ensemble containing 43 conformers were subsequently optimized using the B3PW91 functional, cc-pVTZ(-f) basis, and implicit PBF solvation model for chloroform using the Jaguar program.¹⁸ Harmonic frequencies computed at the B3PW91/cc-pVTZ(-f)/PBF(chloroform) level were scaled by 0.98. The resultant 43 structurally unique

conformers possessing all positive Hessian eigenvalues were Boltzmann weighted by relative free energy at 298.15 K. The predicted IR and VCD frequencies and intensities of the retained conformers were convolved using Lorentzian line shapes ($\gamma = 4 \text{ cm}^{-1}$) and summed using the respective Boltzmann weights to yield the final predicted IR and VCD spectra of the (*R*) enantiomer of **3f**. The predicted VCD of the corresponding (*S*) enantiomer was generated by inversion of sign. From the good agreement between the predicted and measured IR and VCD spectra in the useful range (1000–1400 cm^{-1} , see below), the absolute configuration of **3f** was assigned as (*R*).

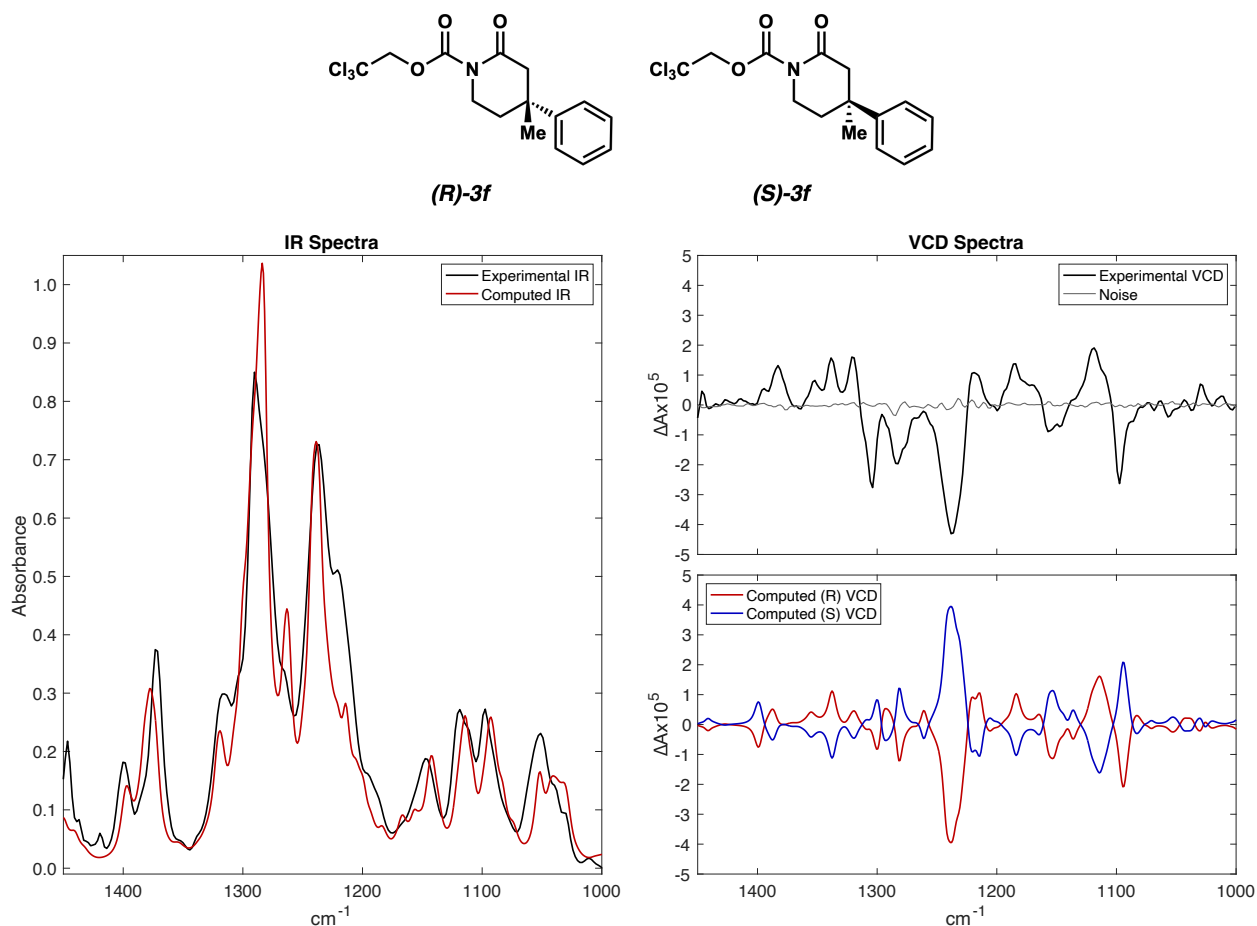


Figure S1. Comparison of experimental VCD and IR spectra for product **3f** to computed spectra for (*R*)-**3f**. Experimental IR spectrum in good agreement with computed spectrum. Experimental VCD spectrum for **3f** is in excellent agreement with computed spectrum for (*R*)-**3f**.

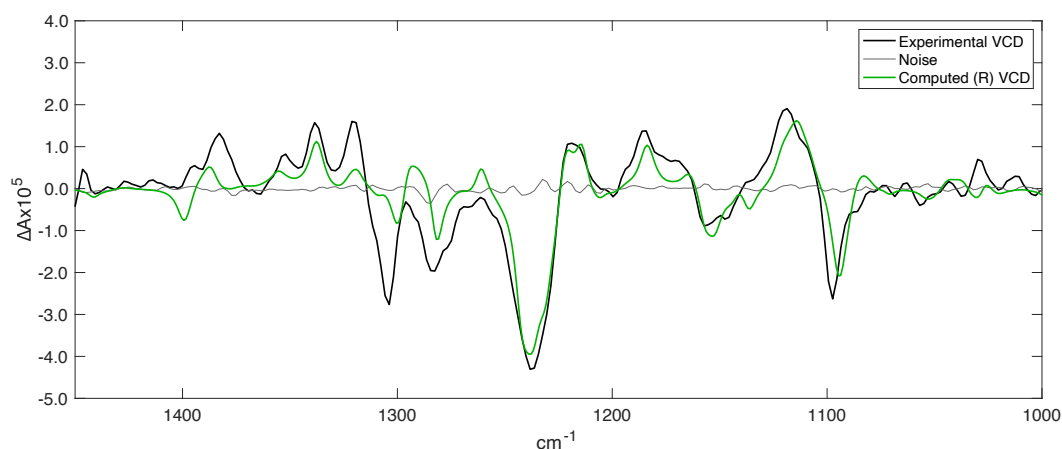


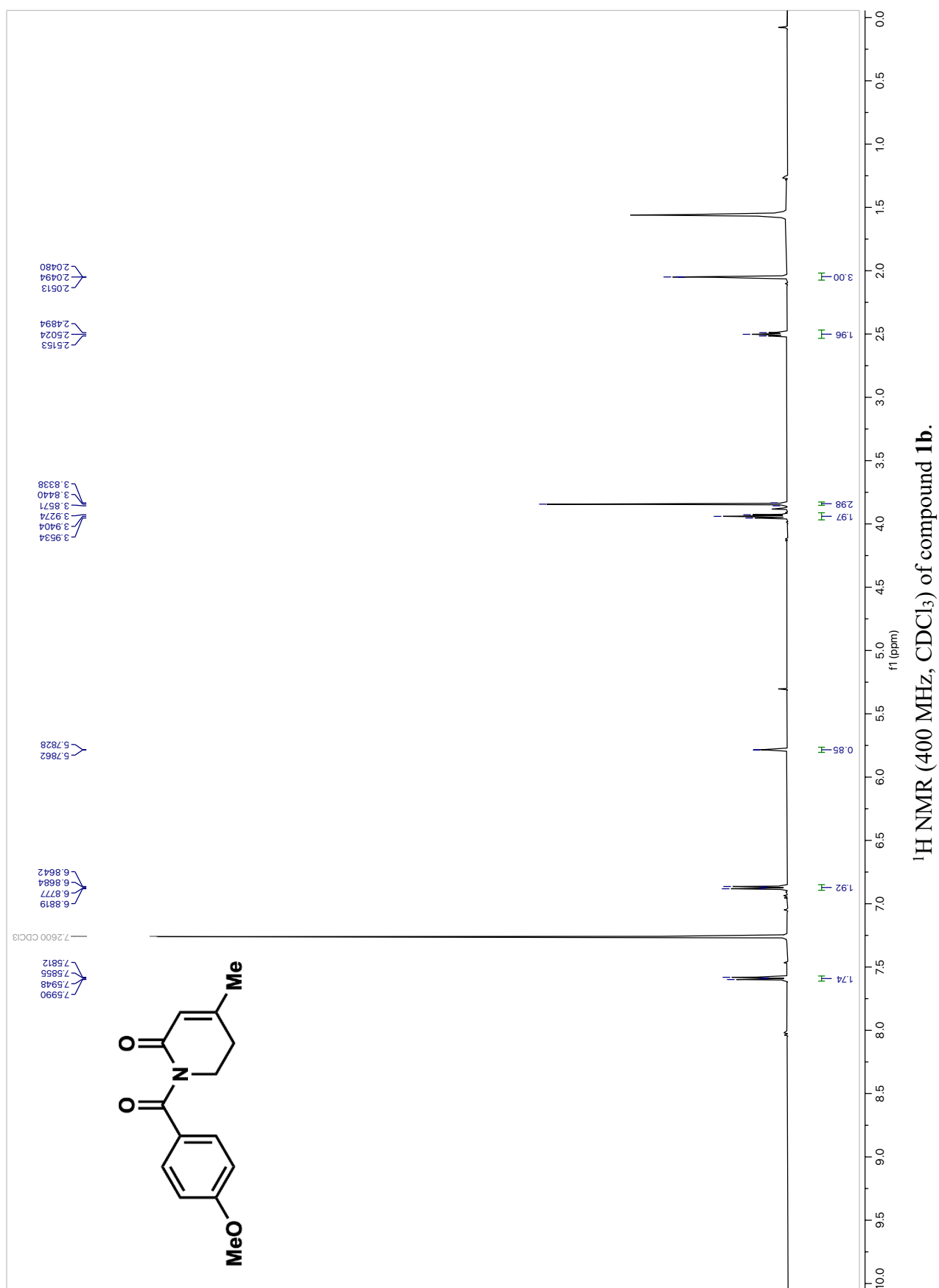
Figure S2. Overlay of experimental VCD spectrum of **3f** with computed spectra for (*R*)-**3f**.

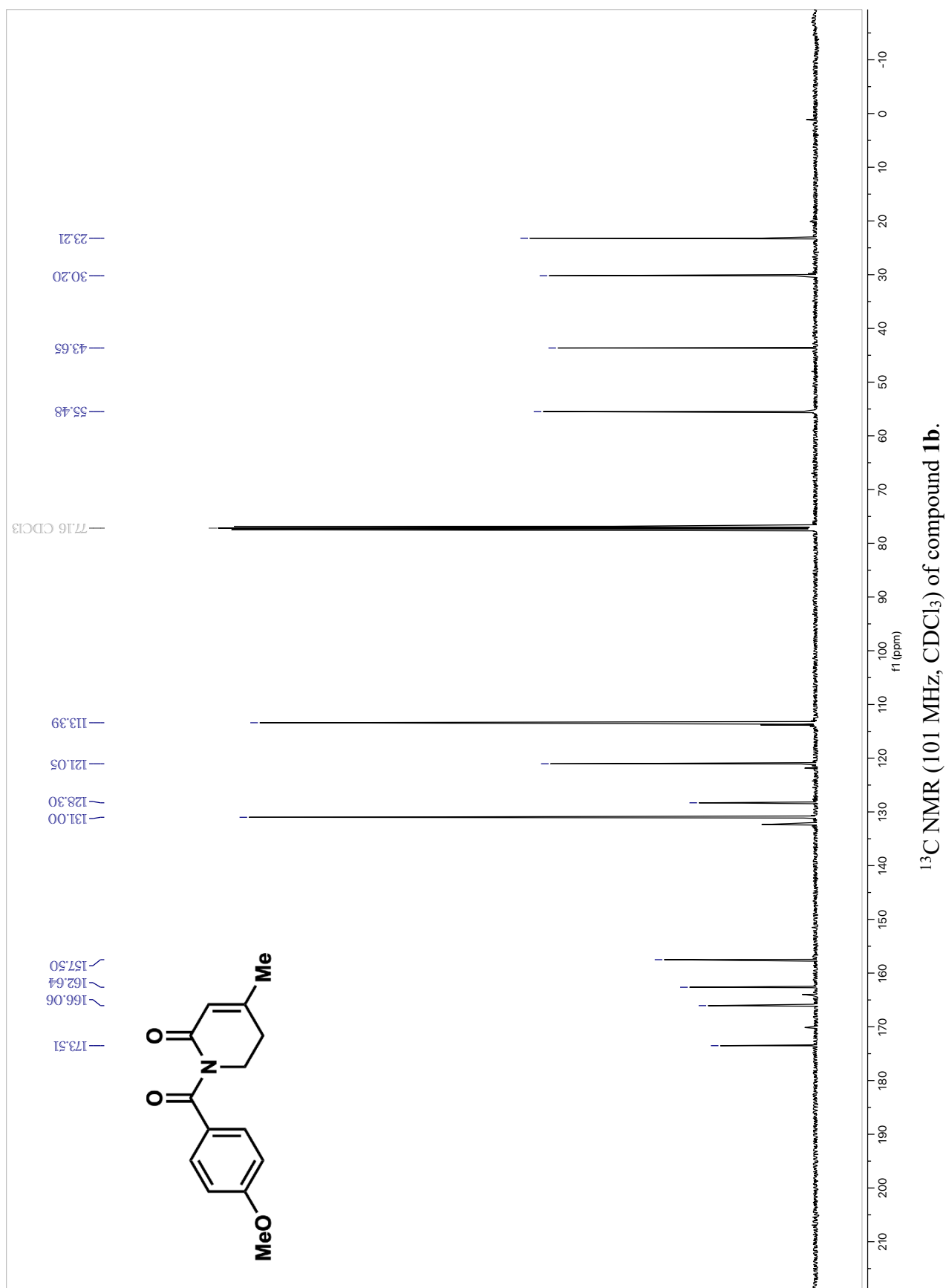
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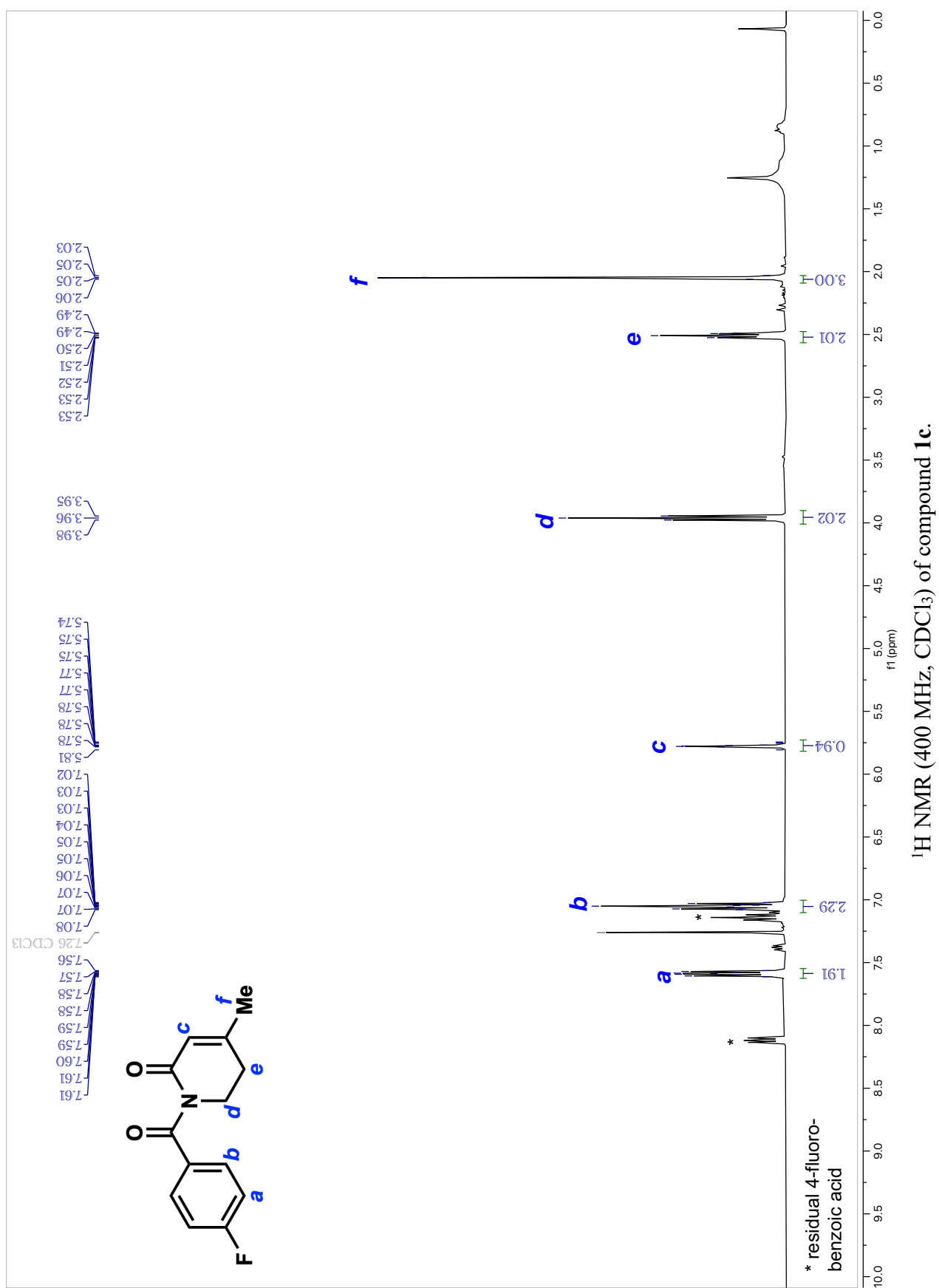
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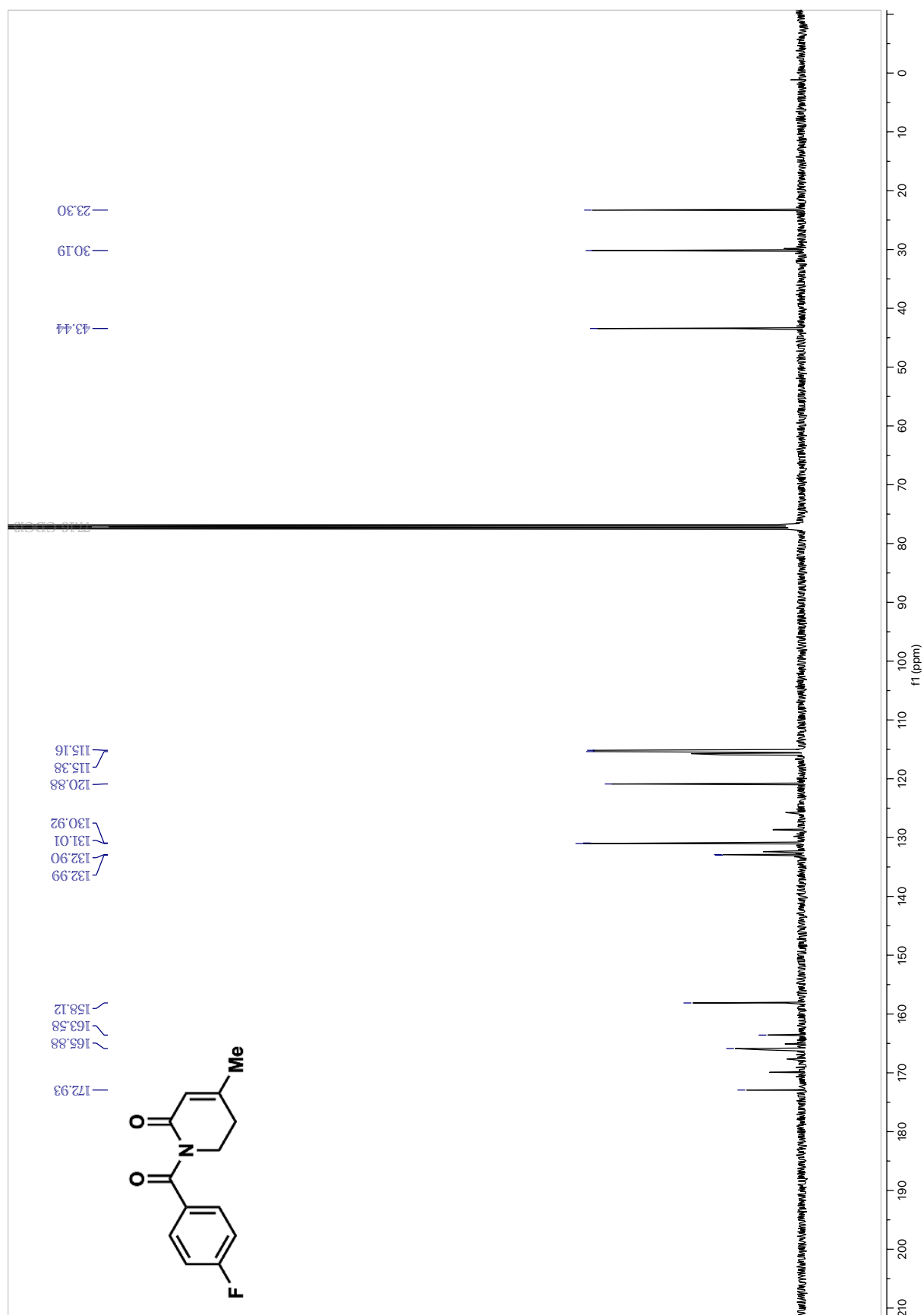
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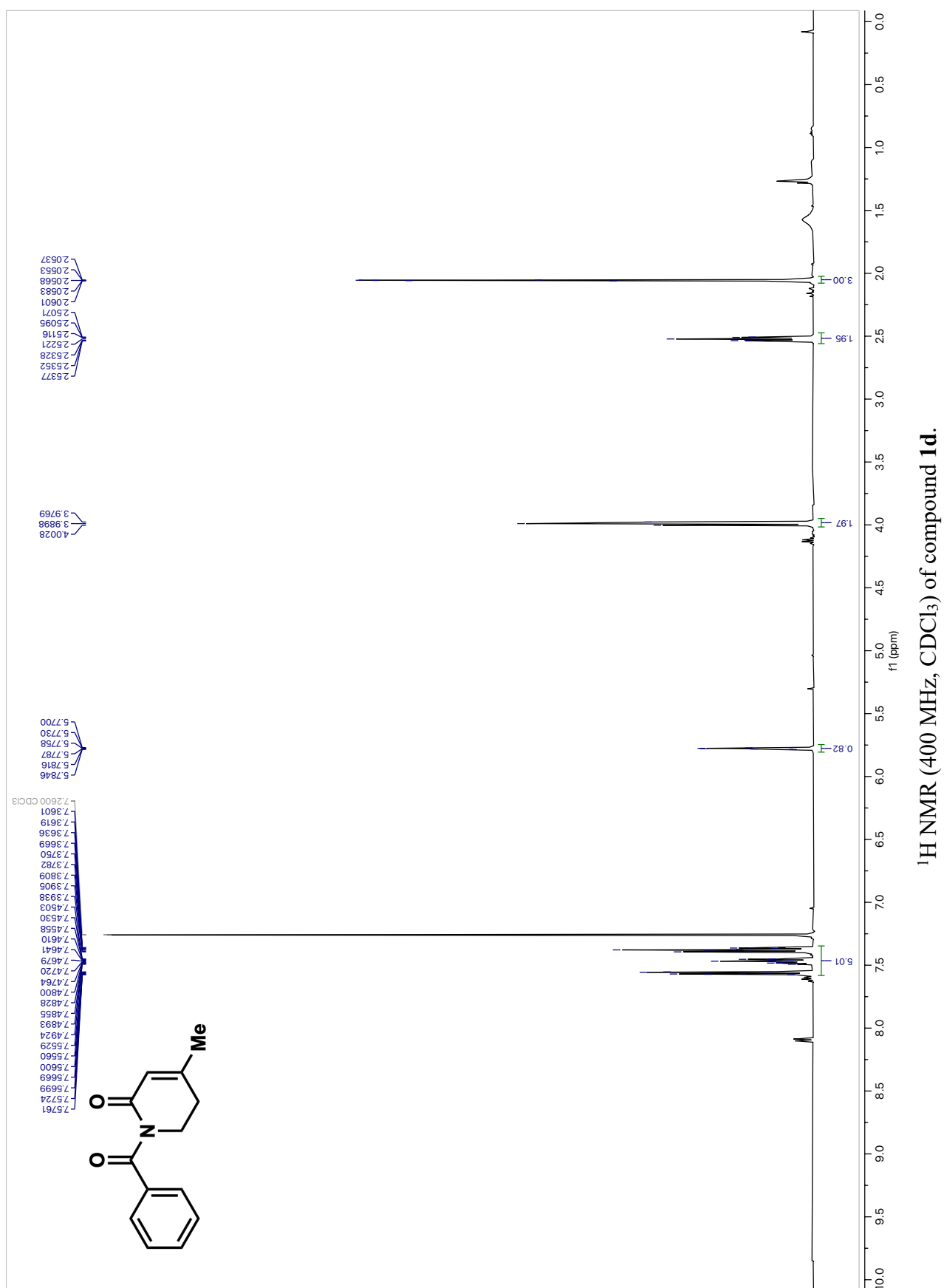
NMR Spectra of New Compounds

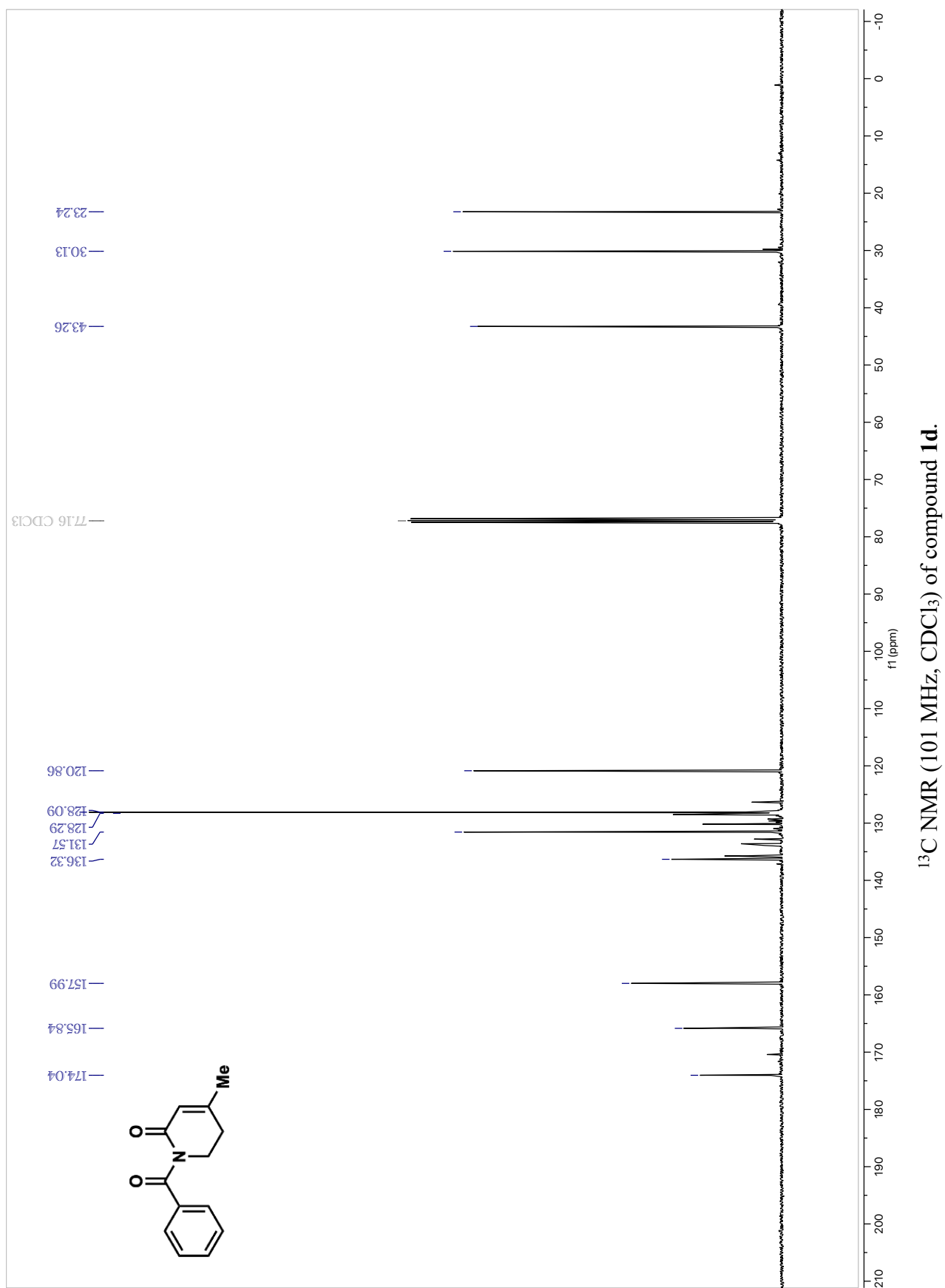


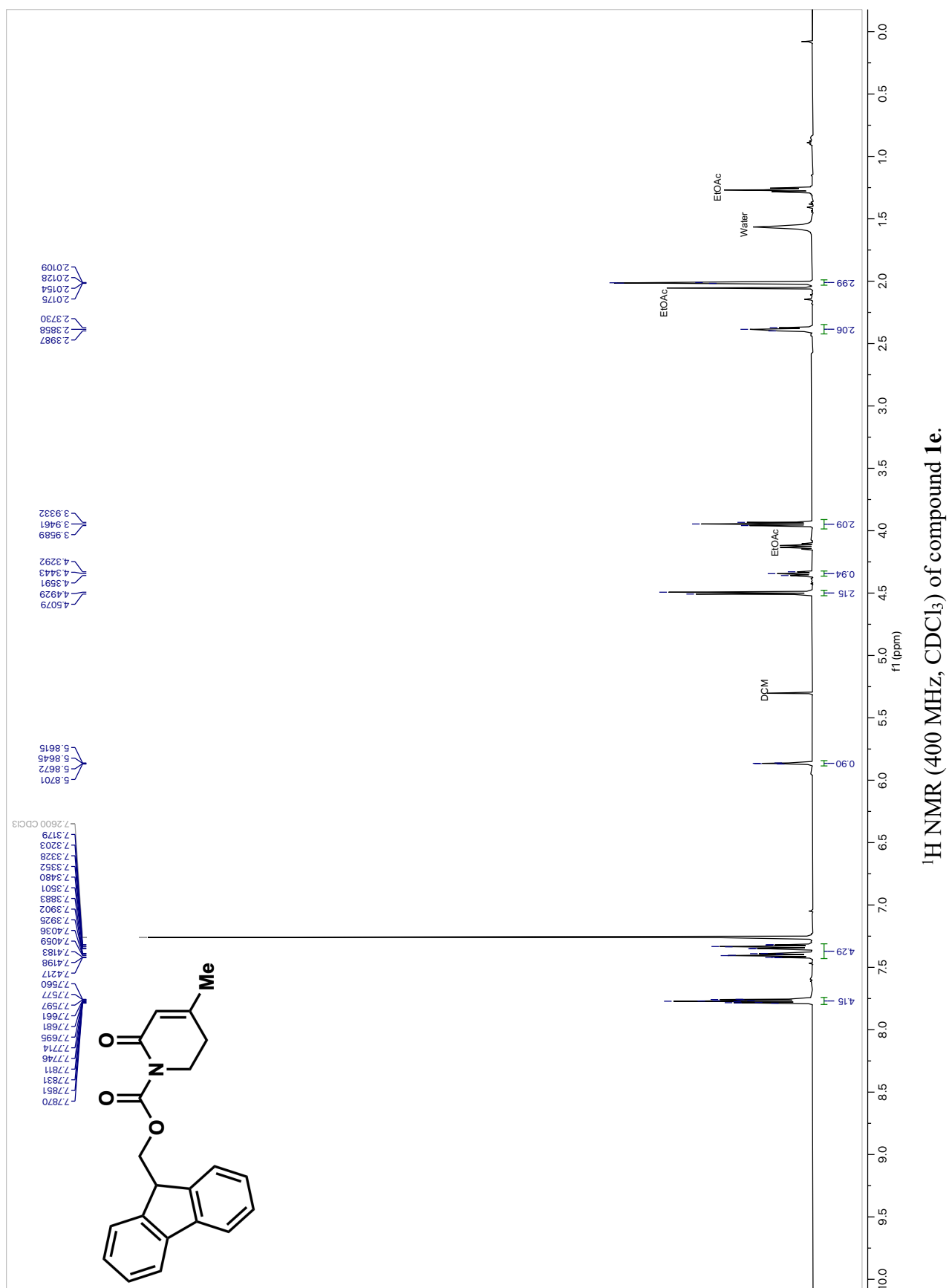


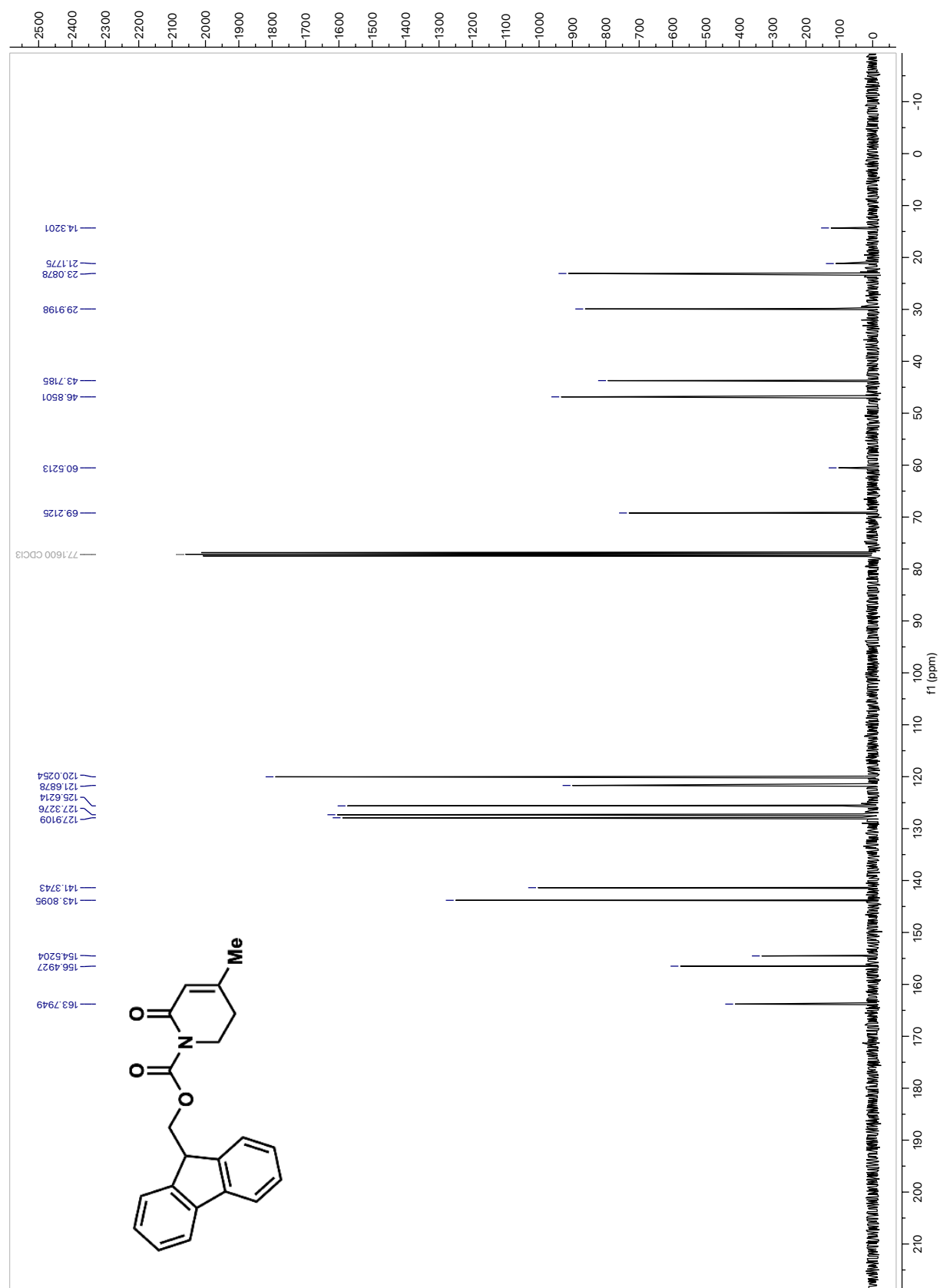


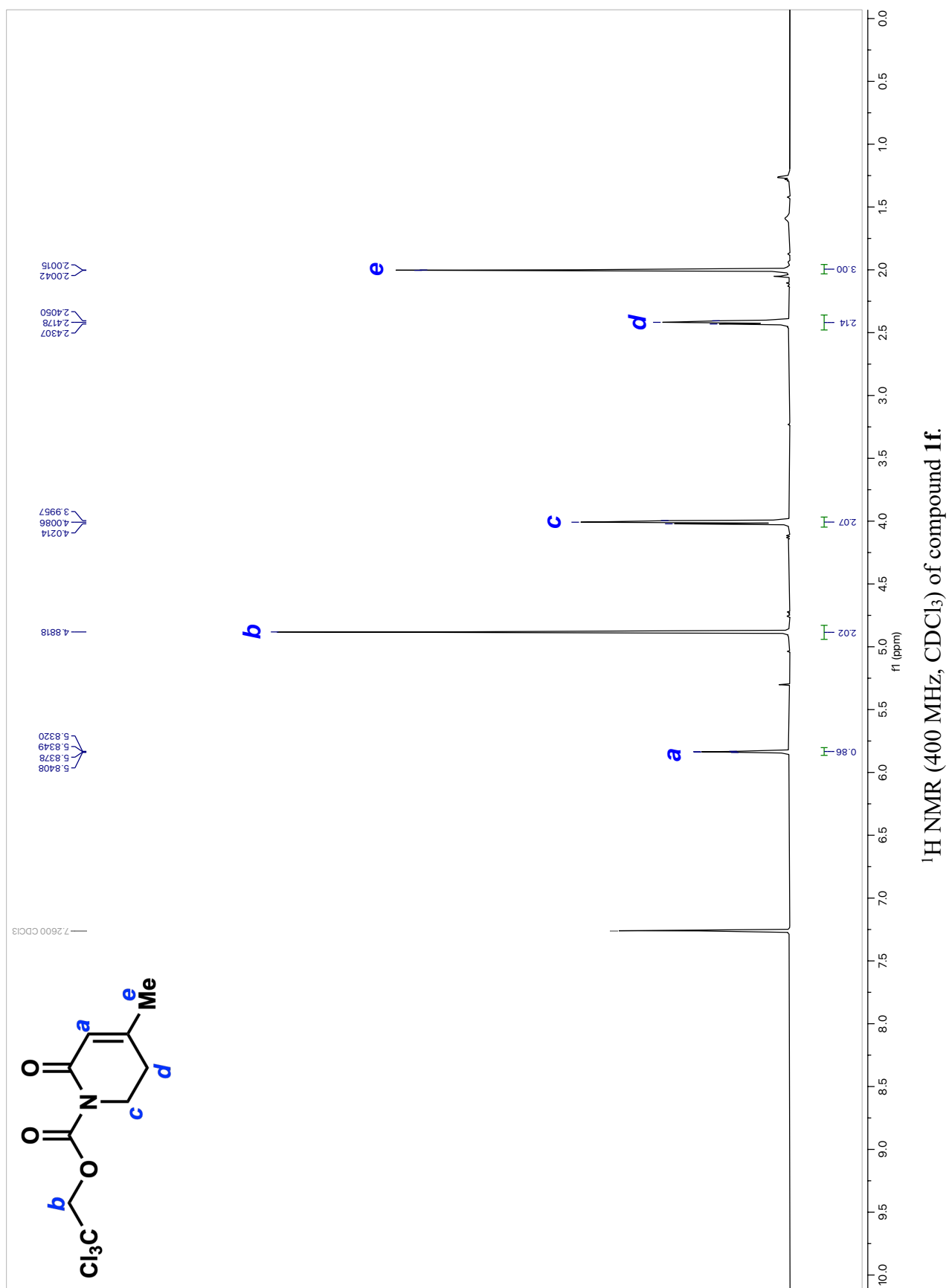


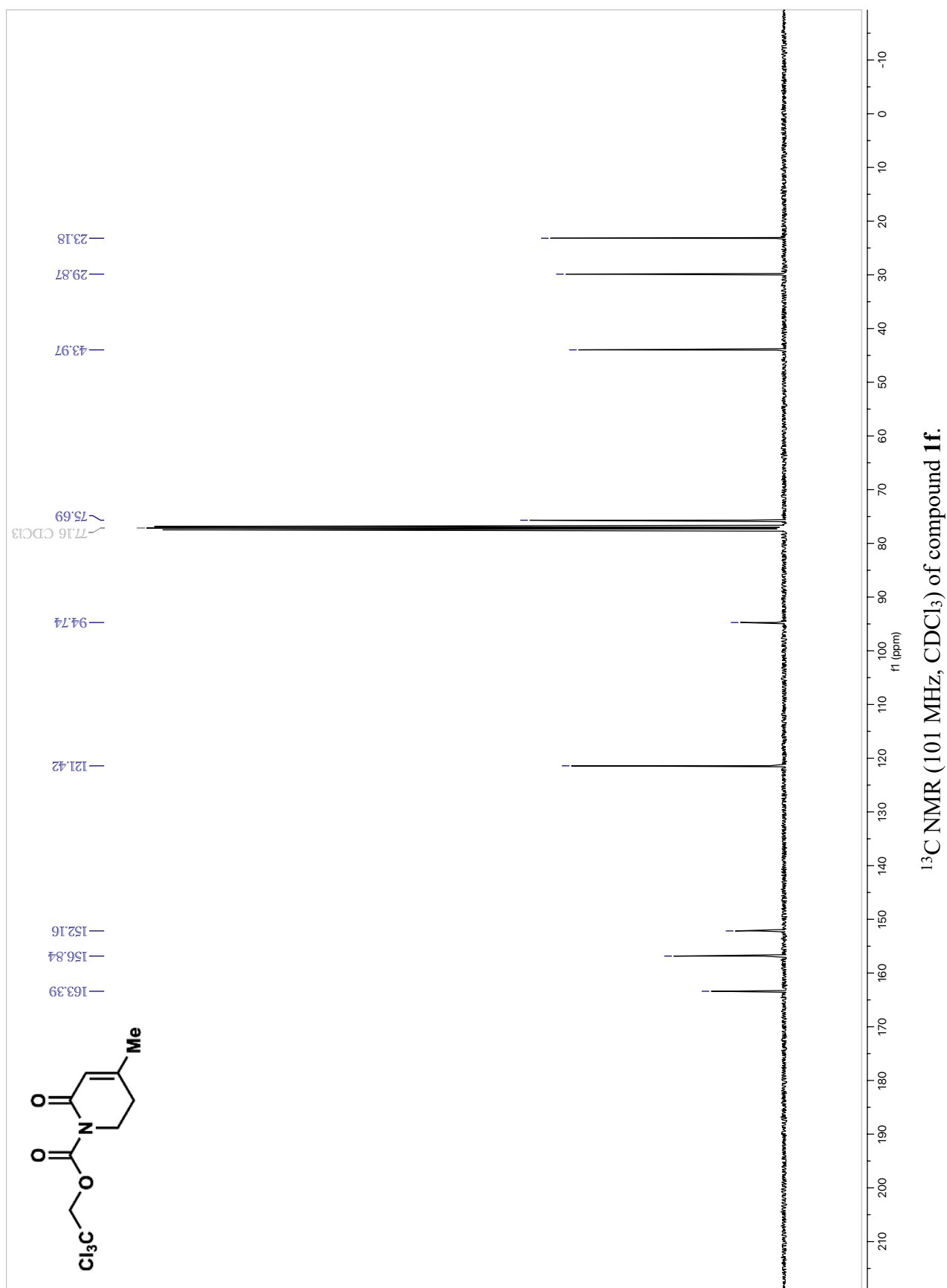


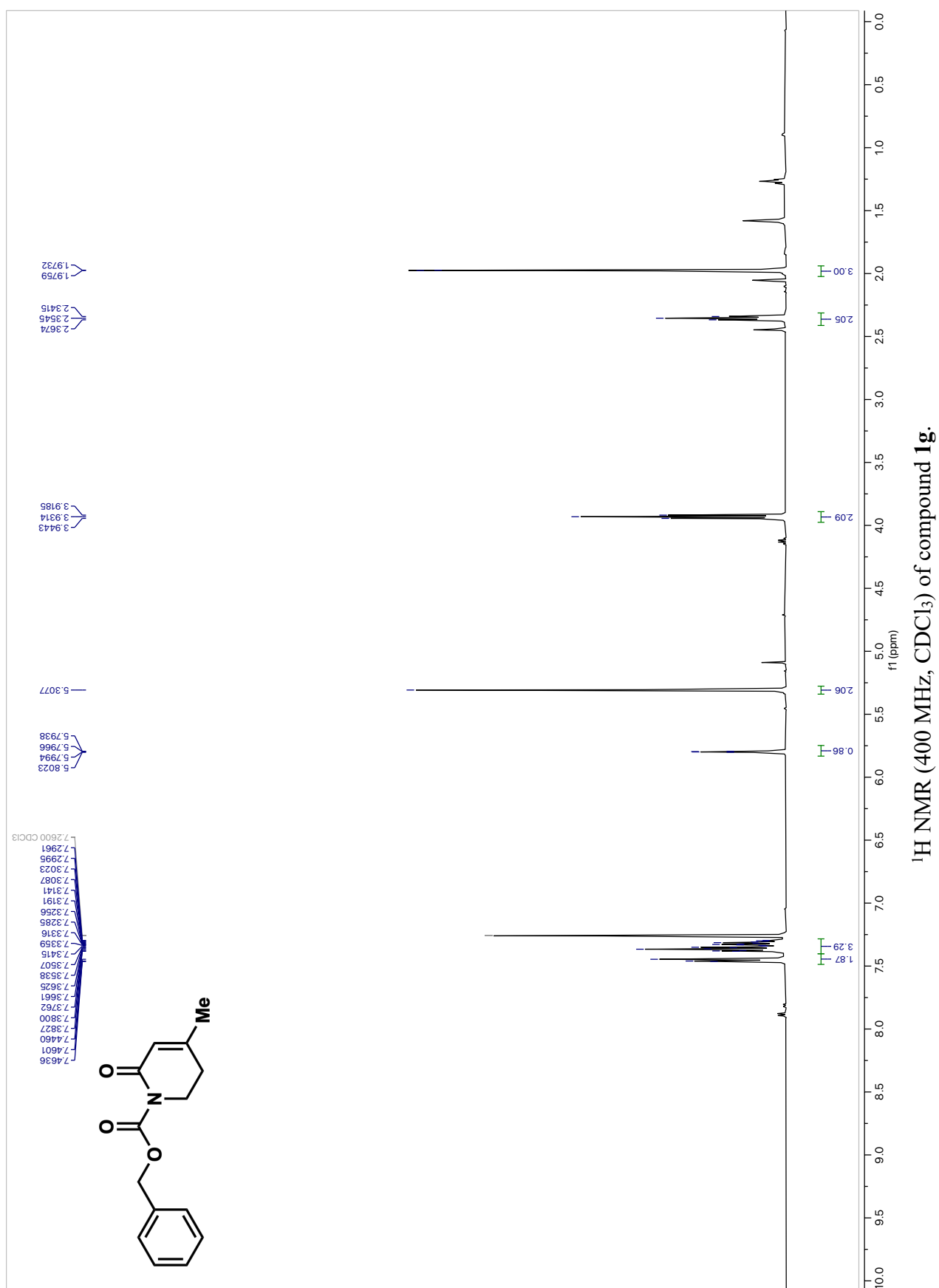


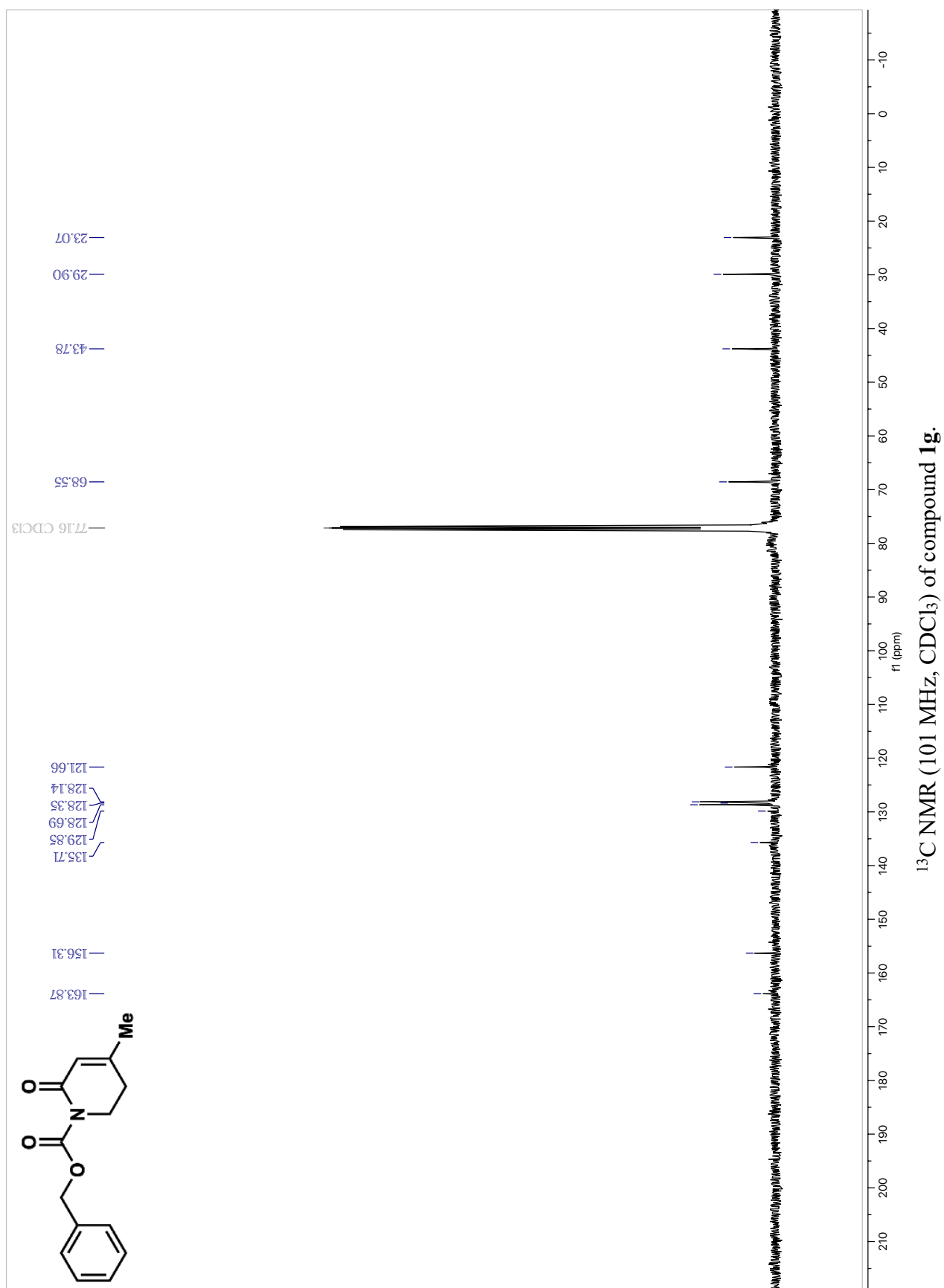


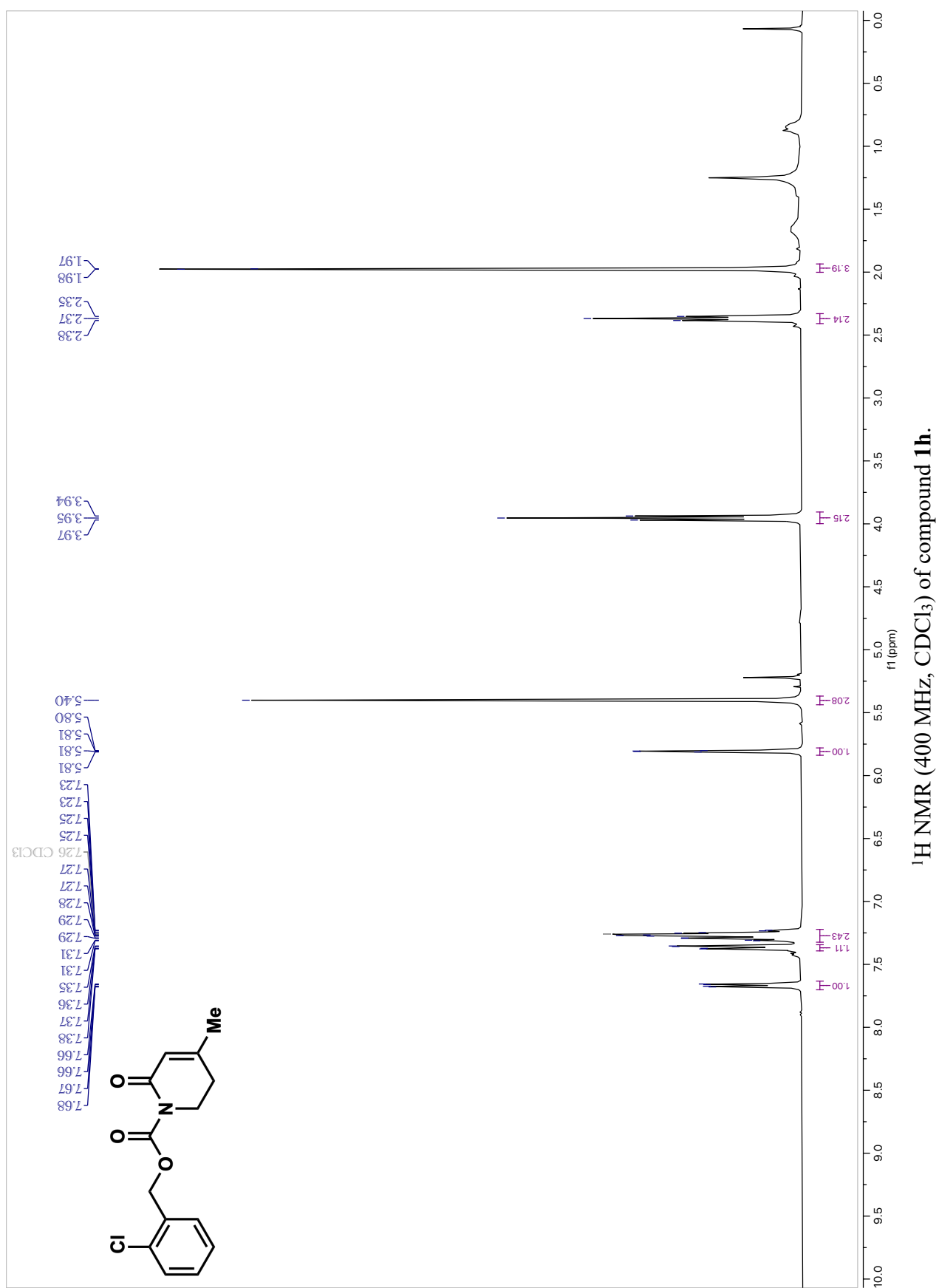


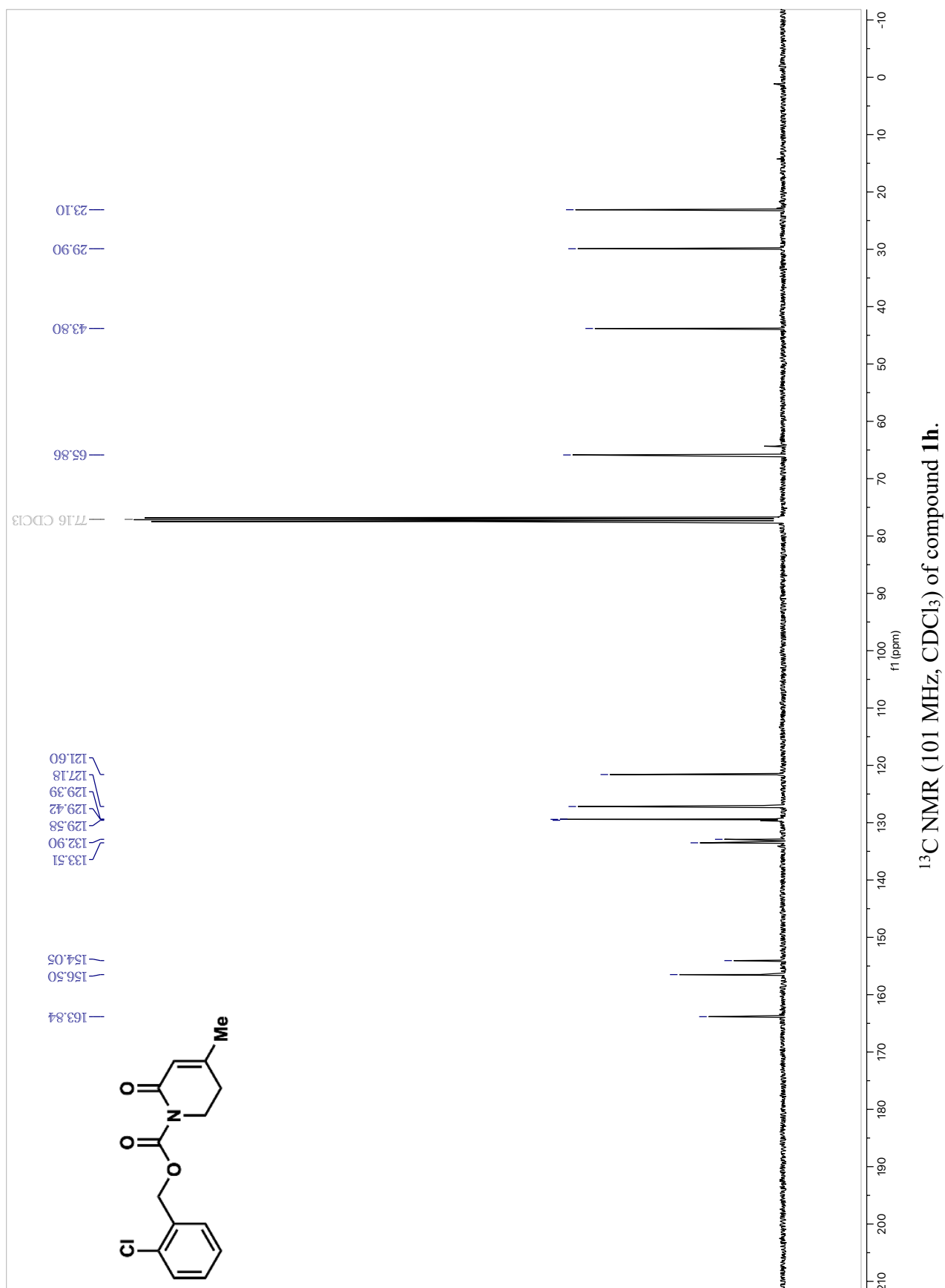


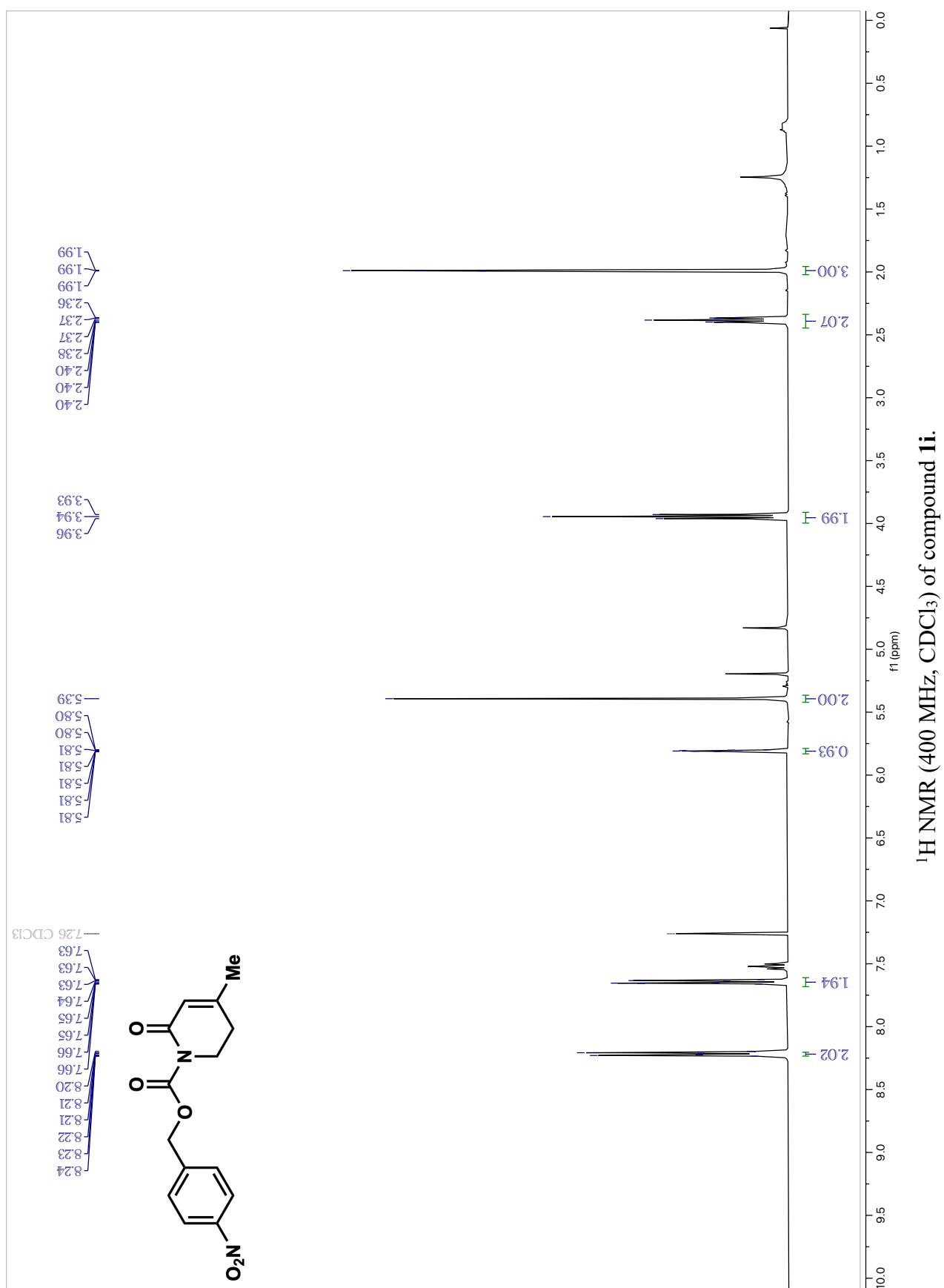


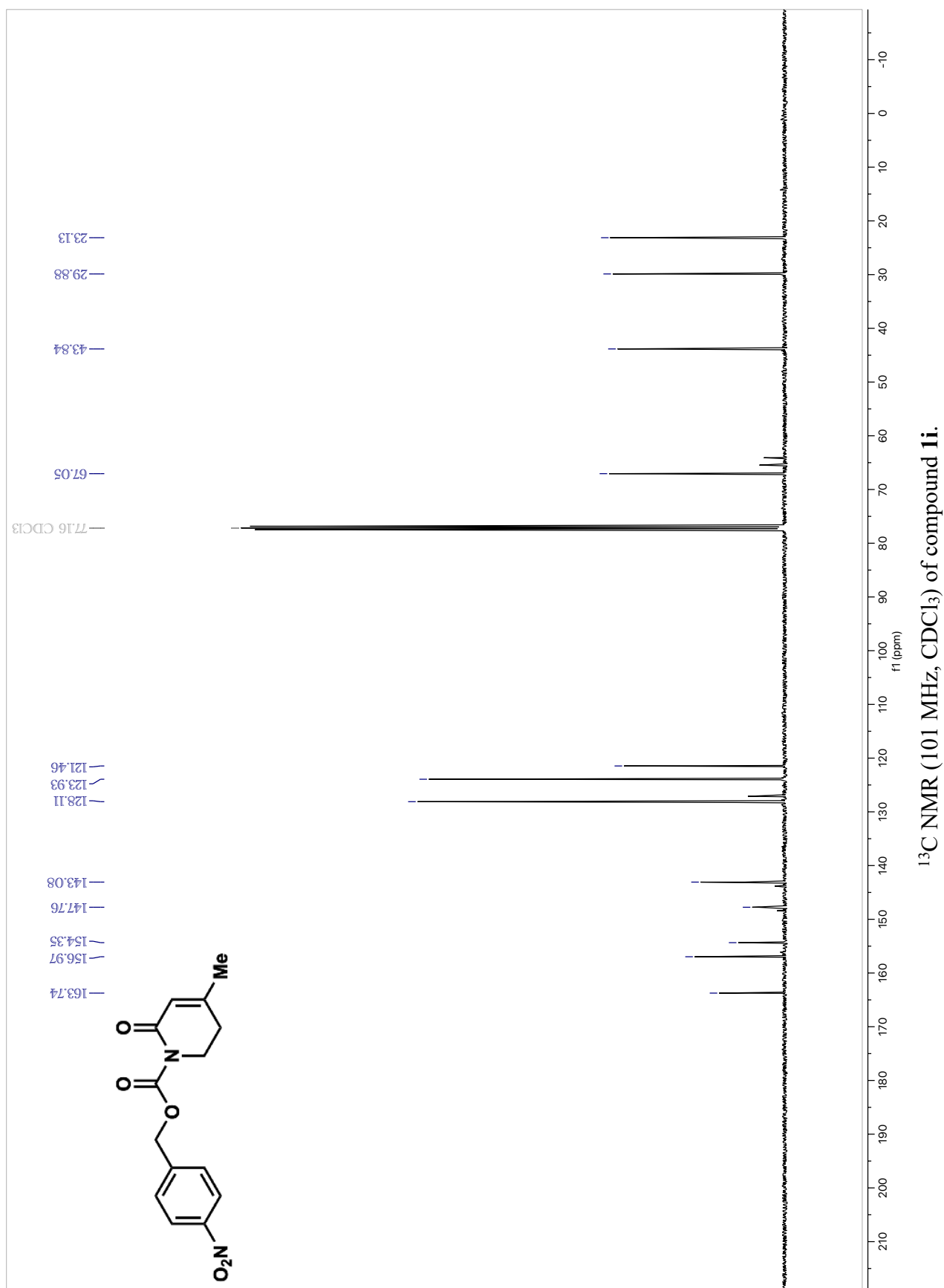


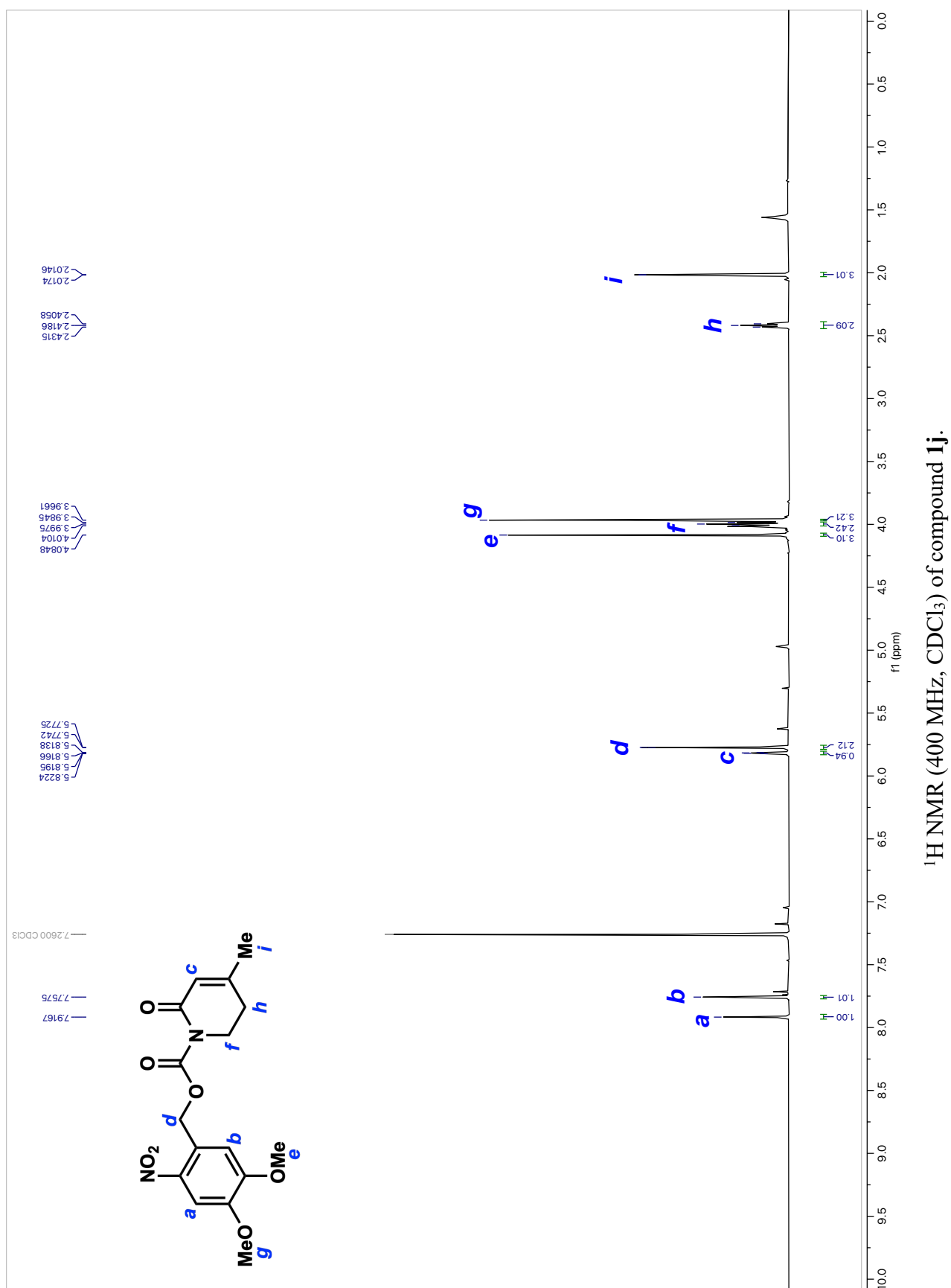


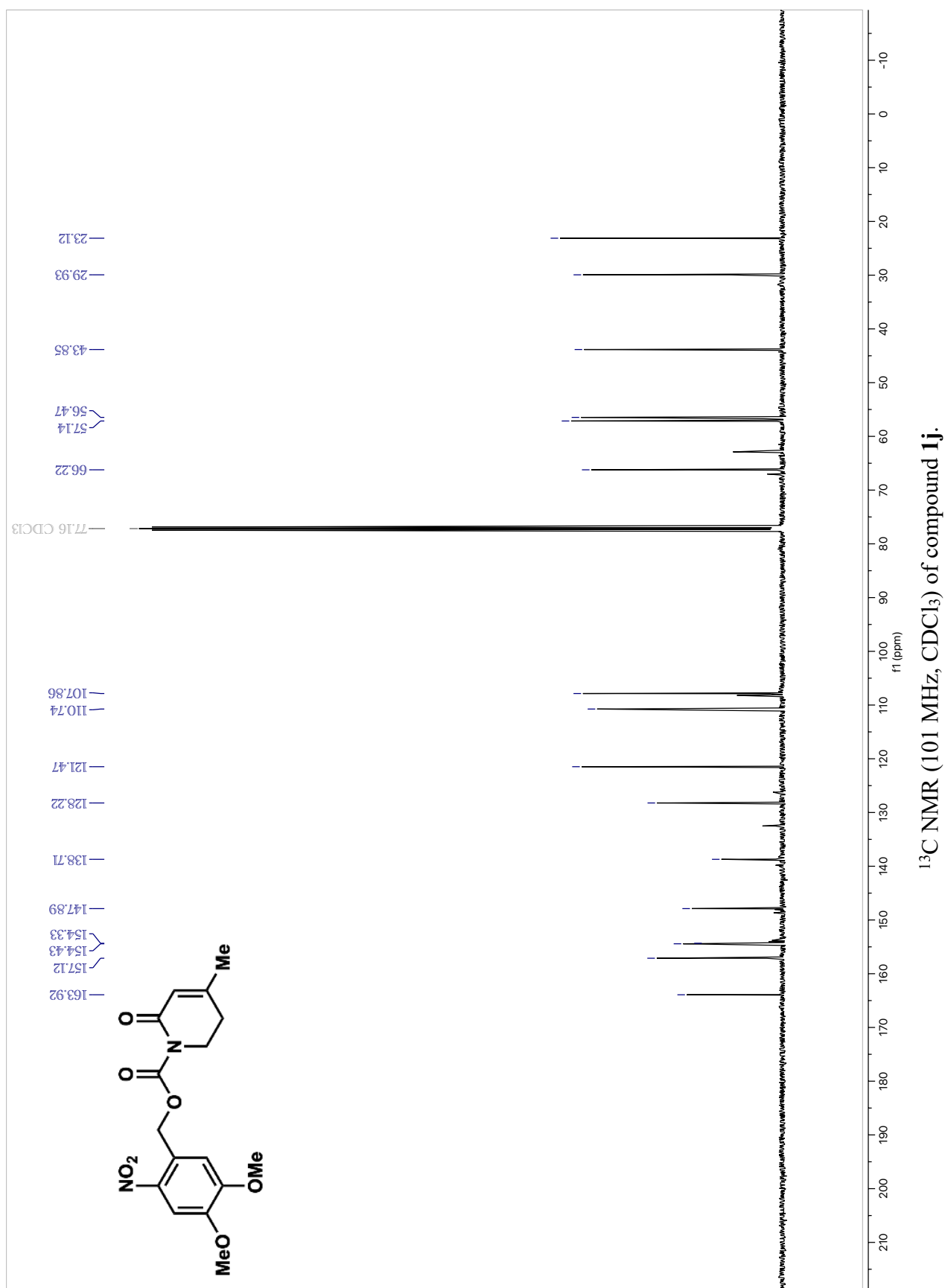


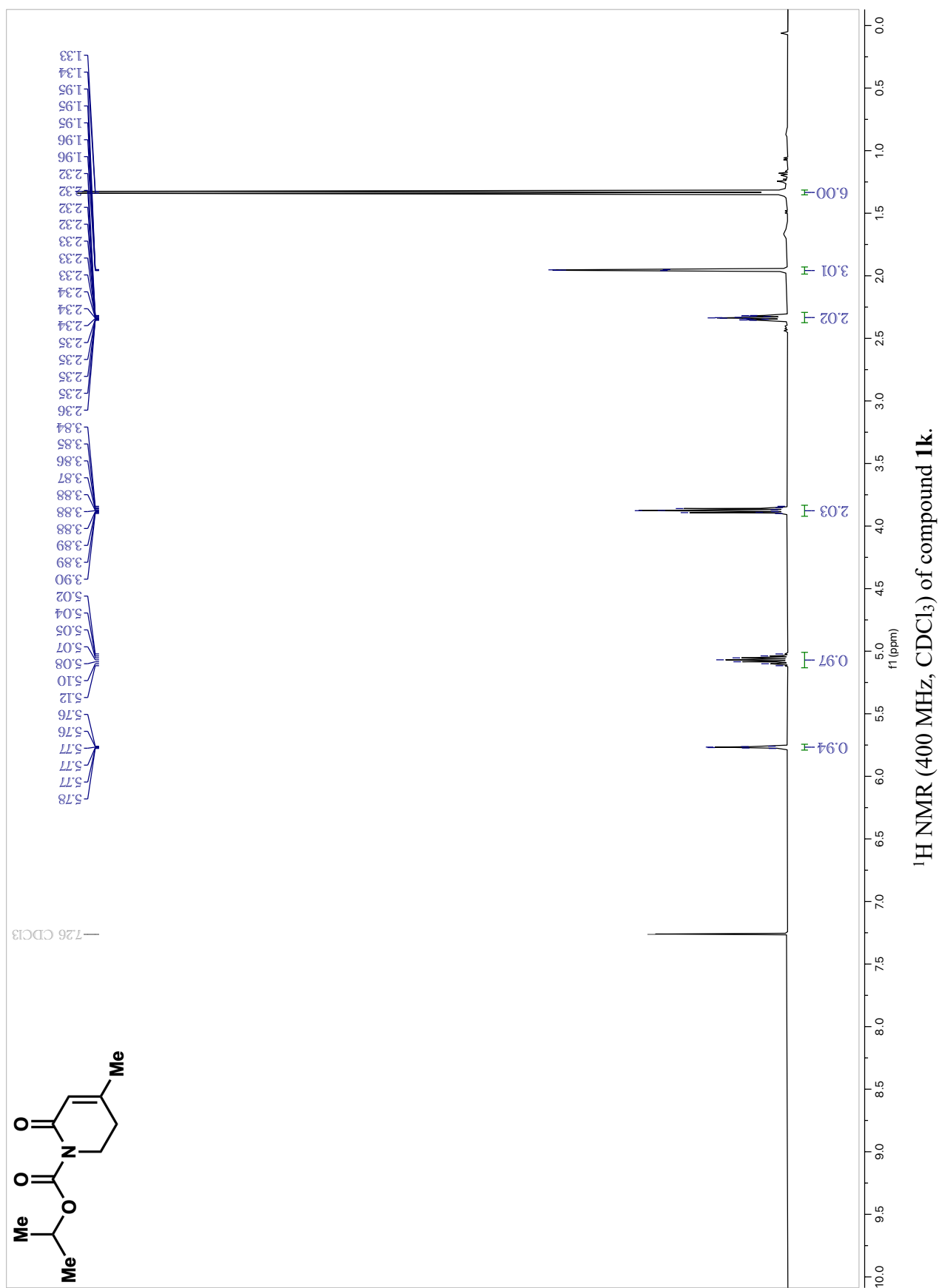


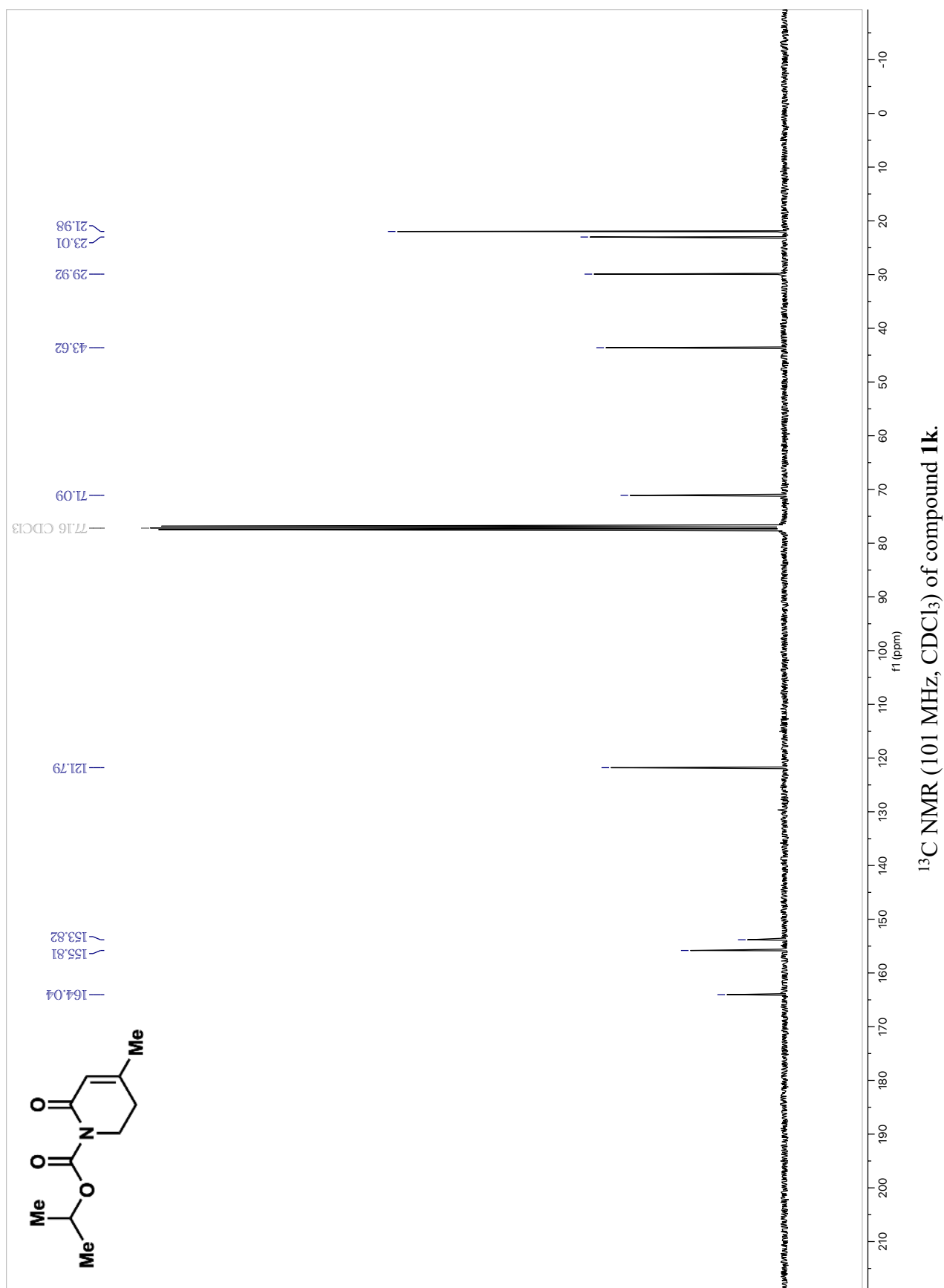


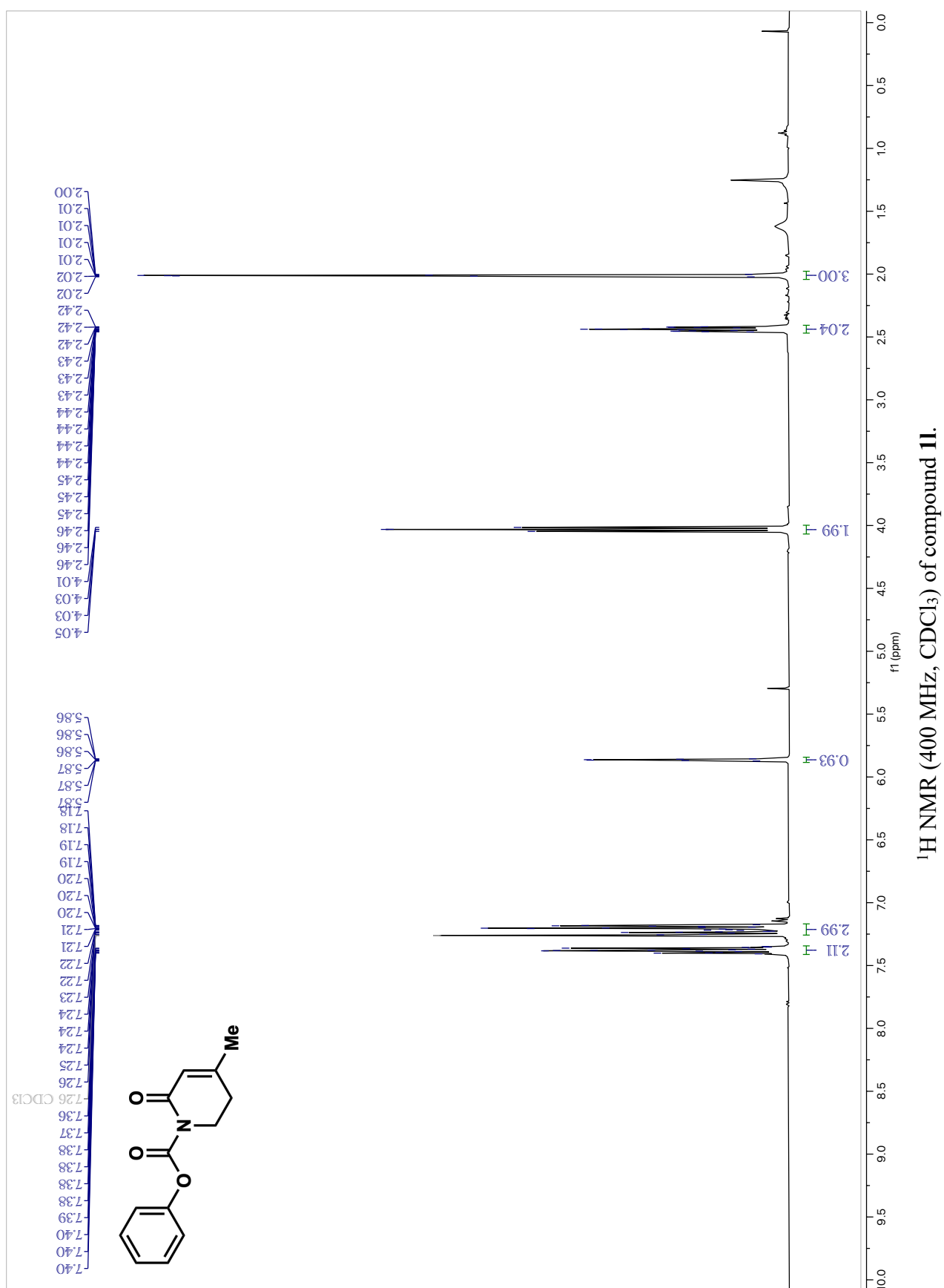


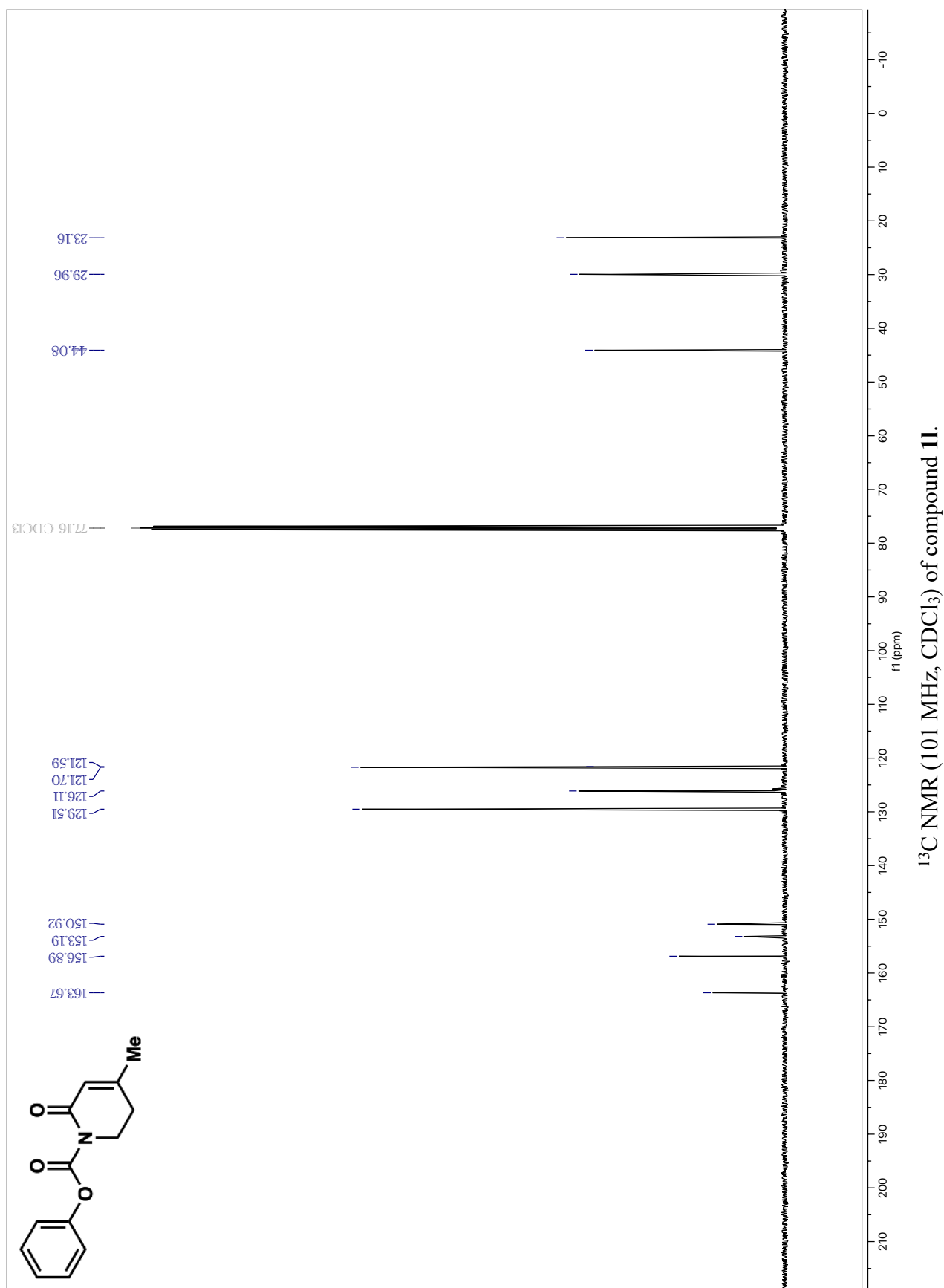


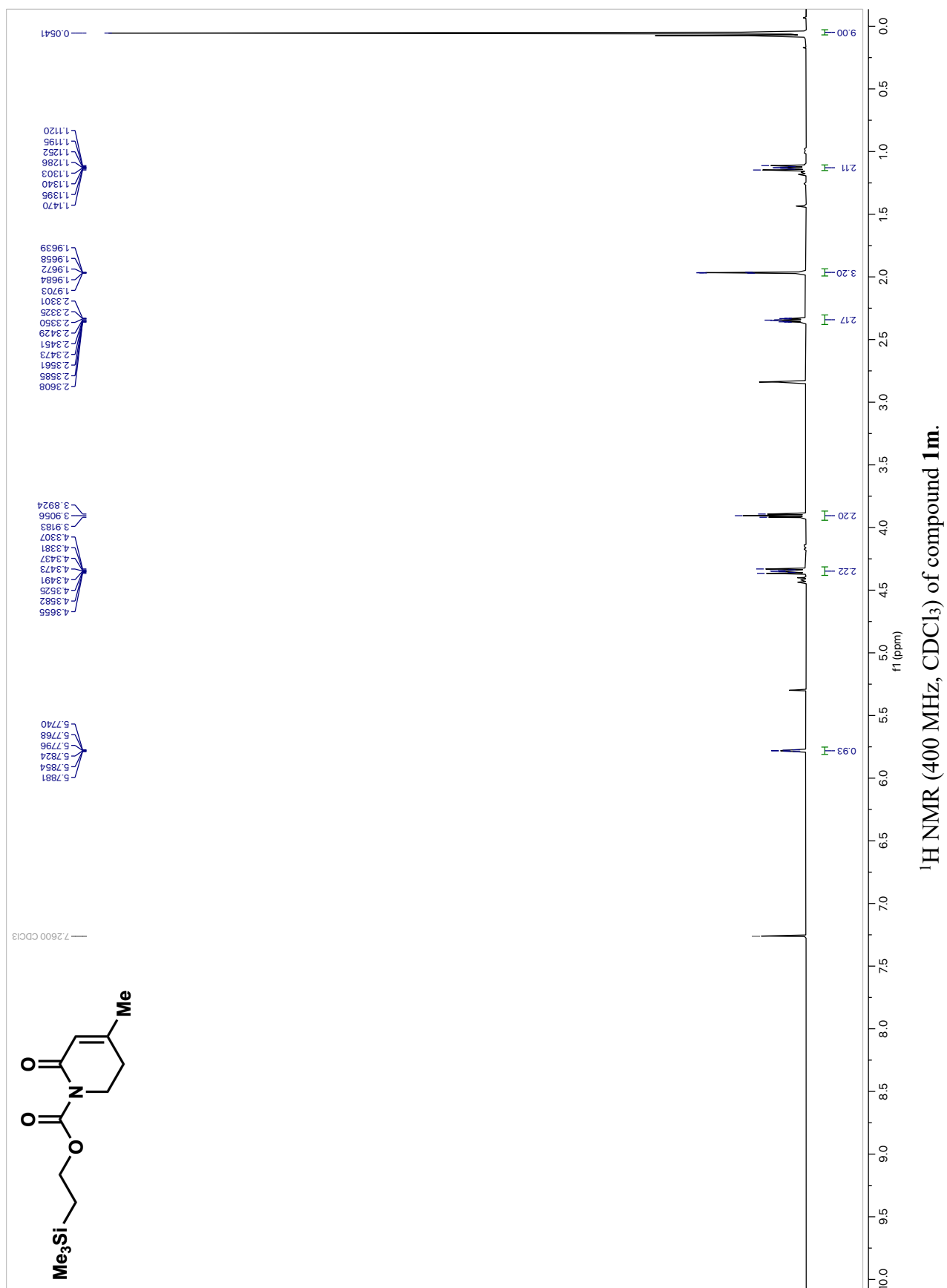


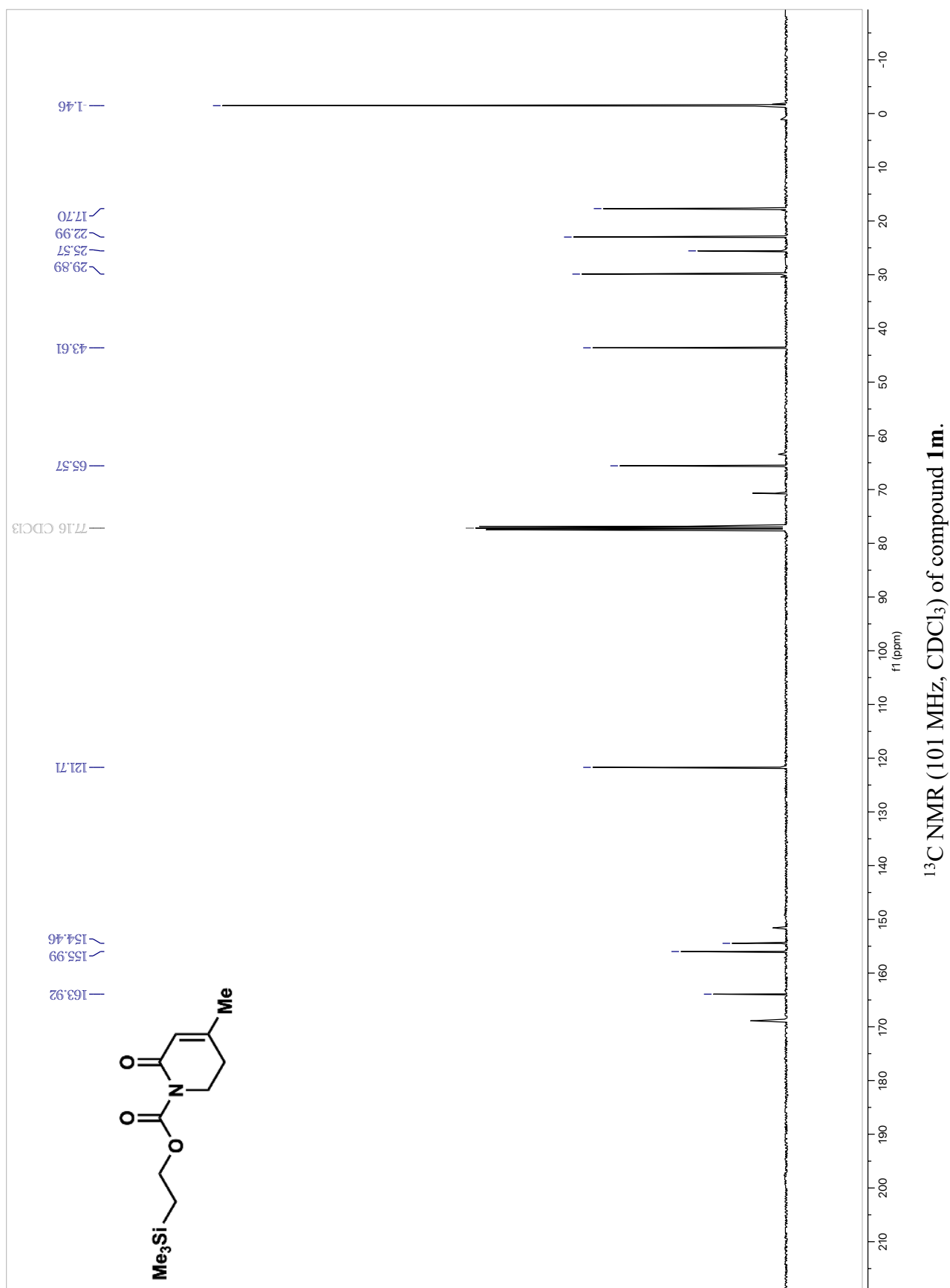


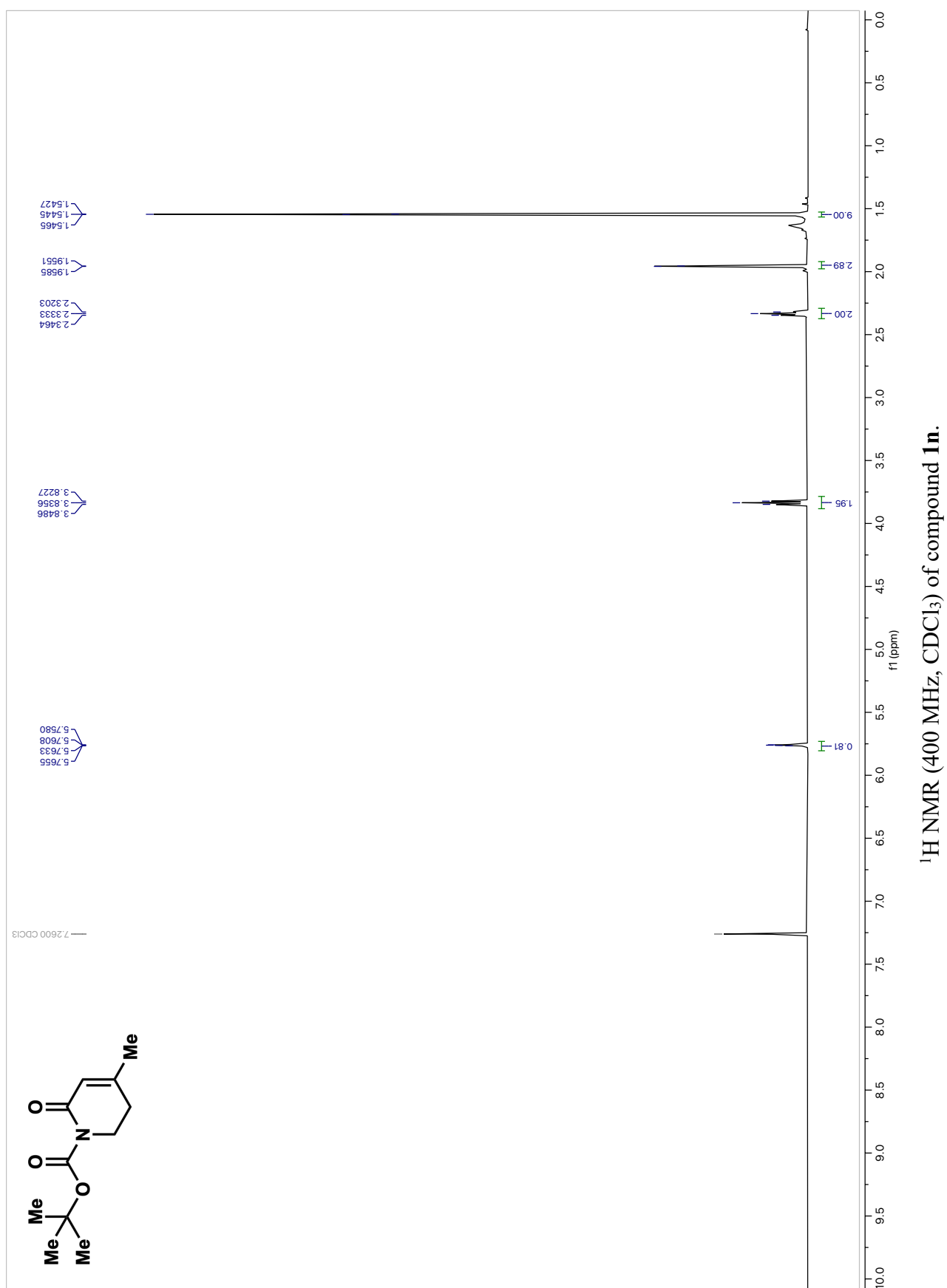


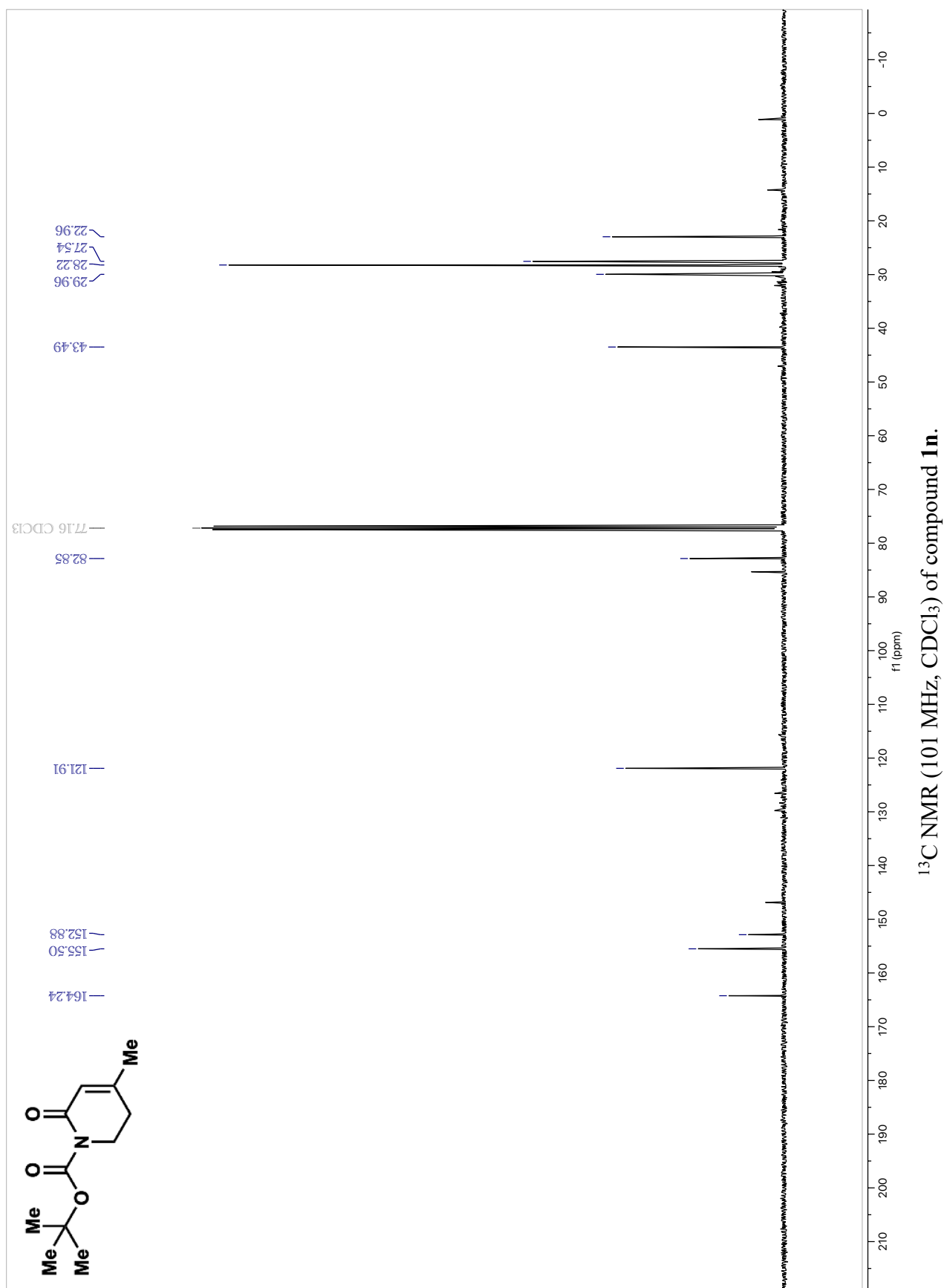


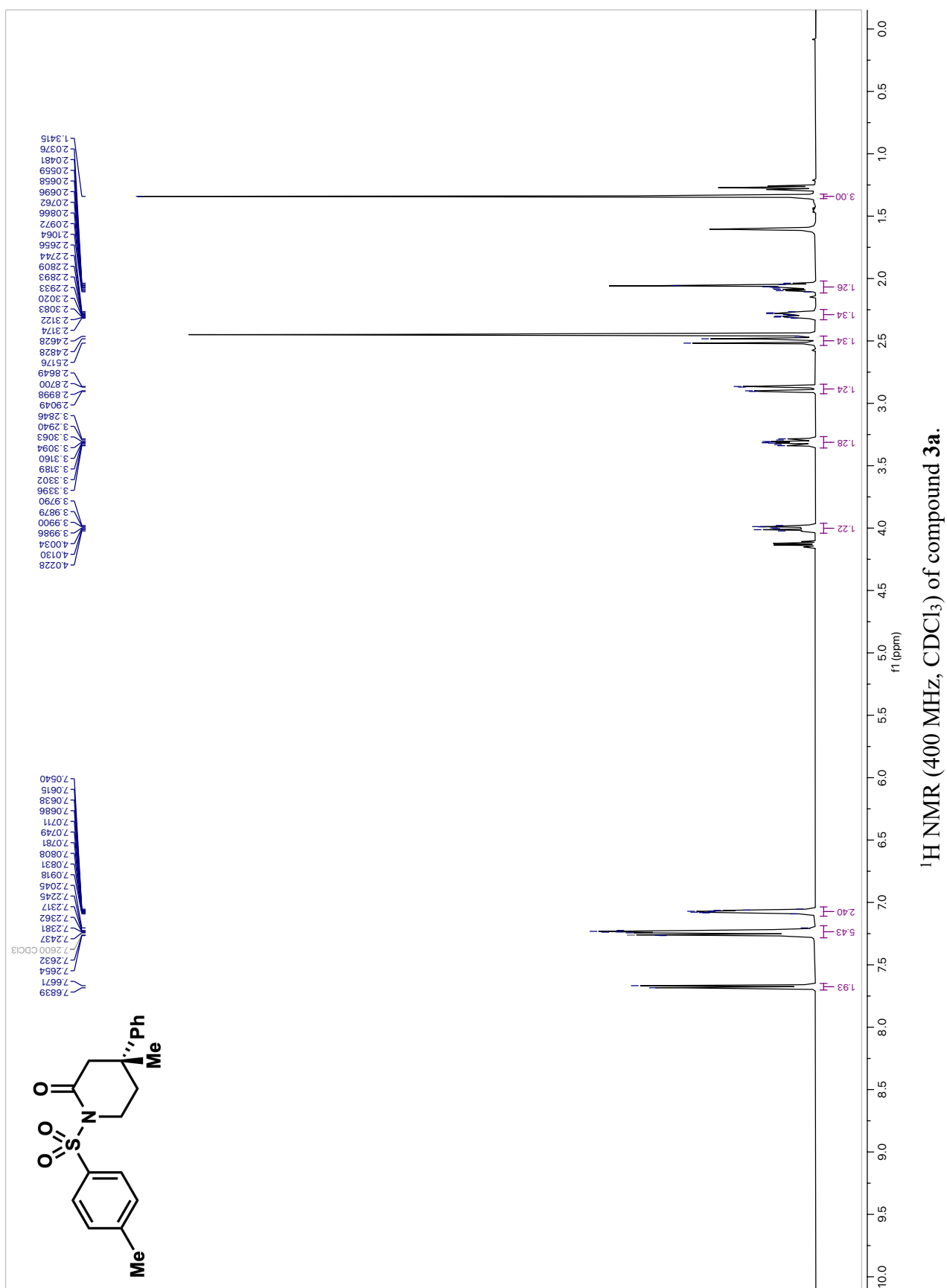


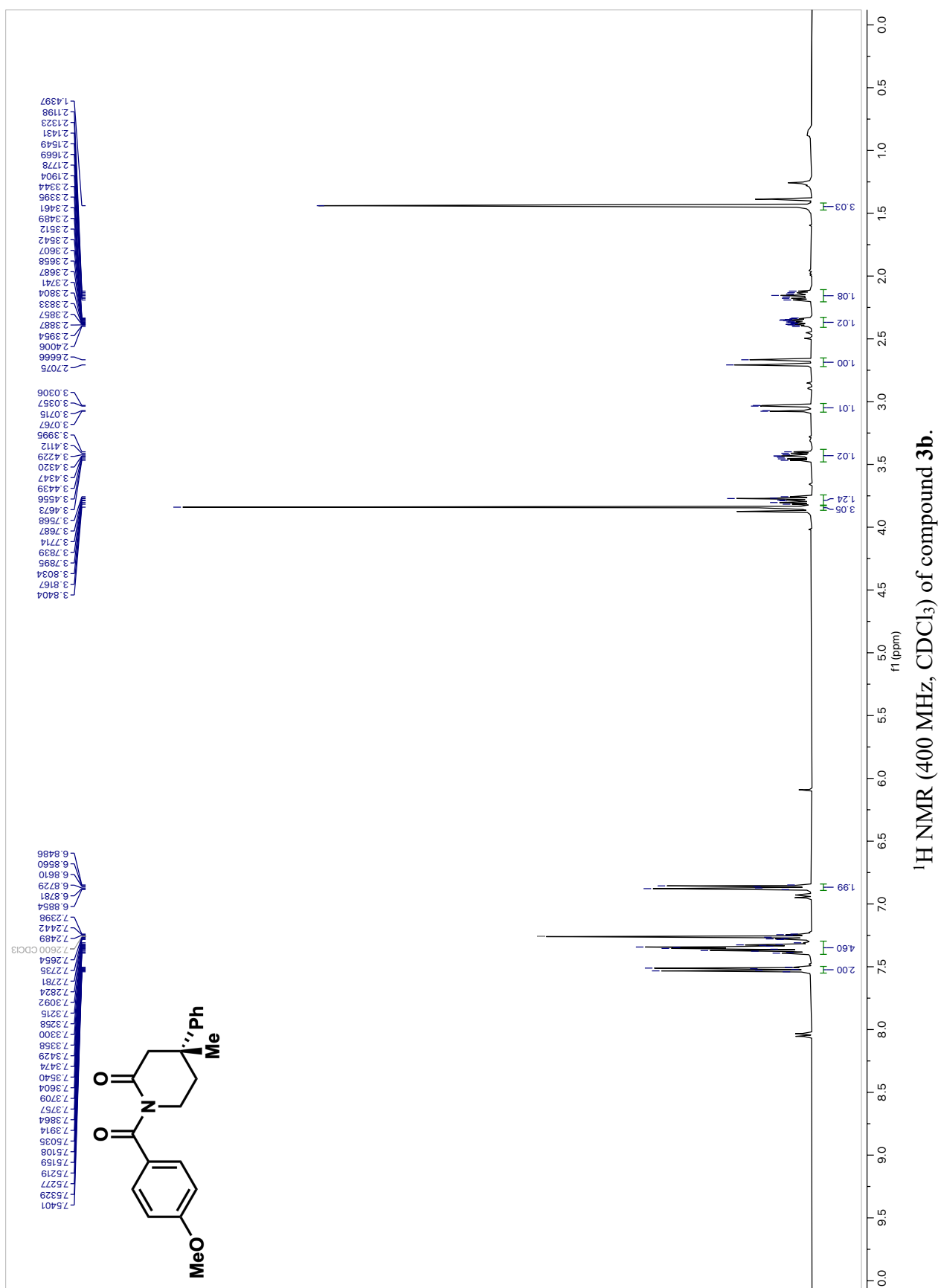


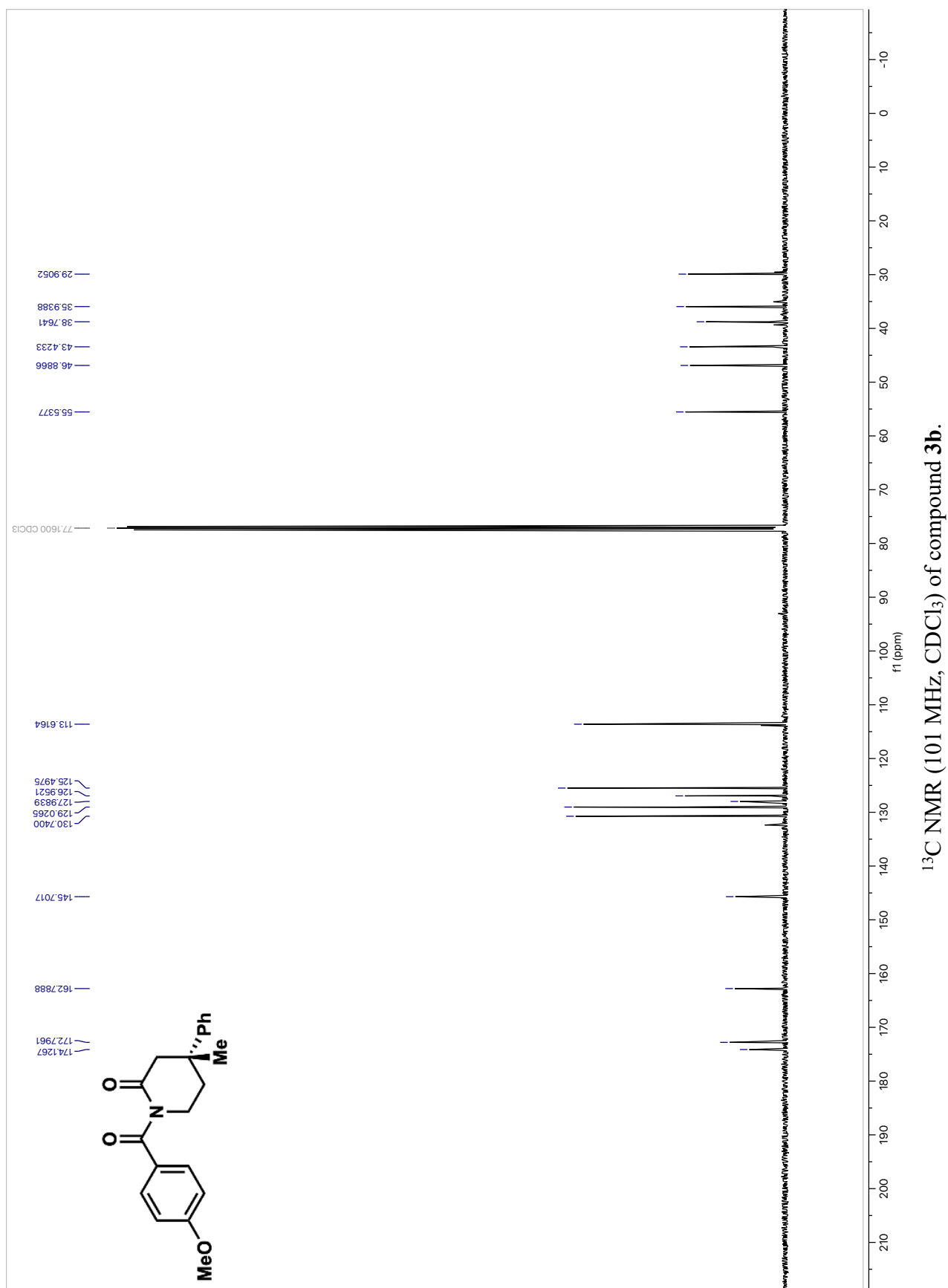


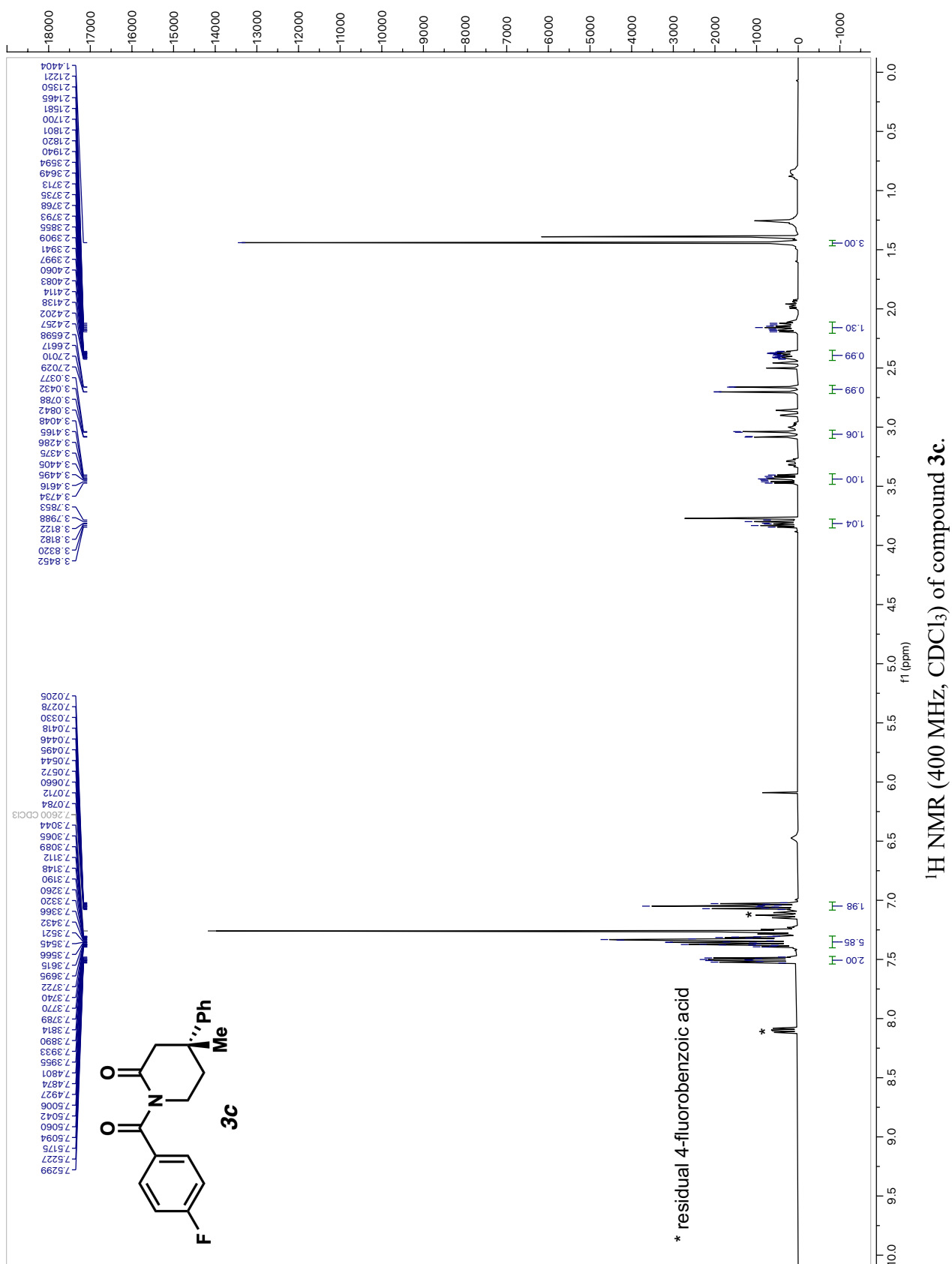


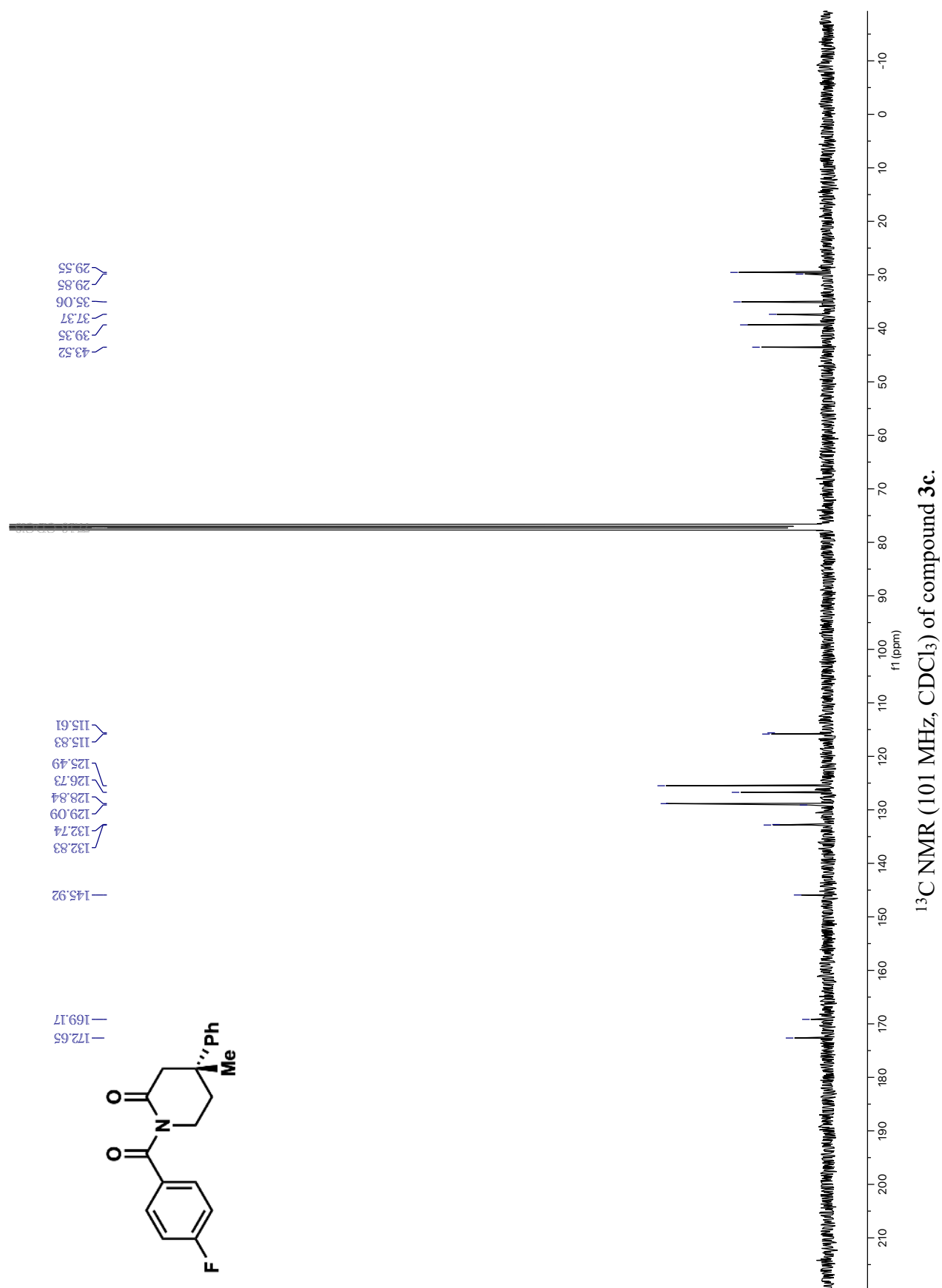


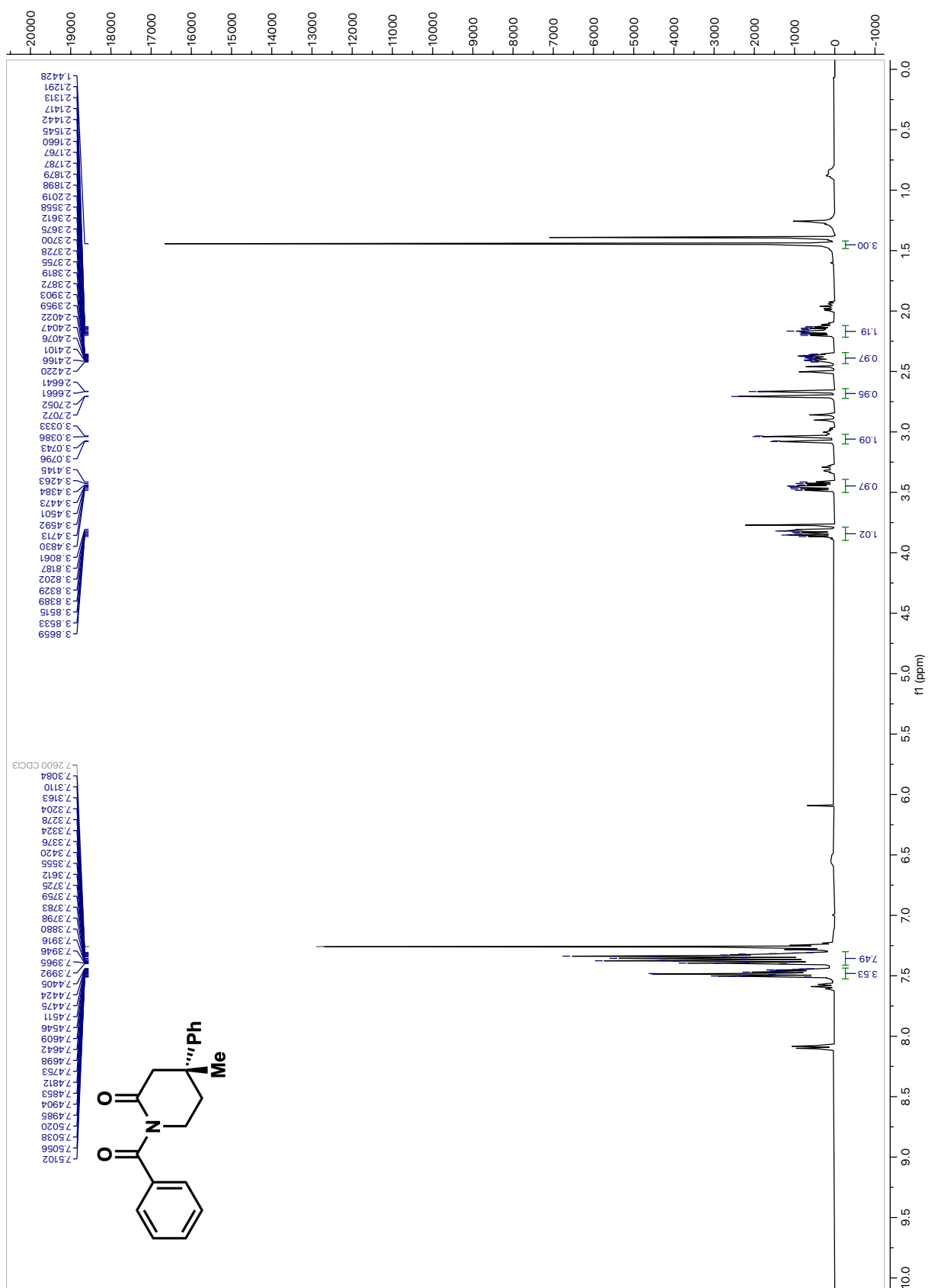


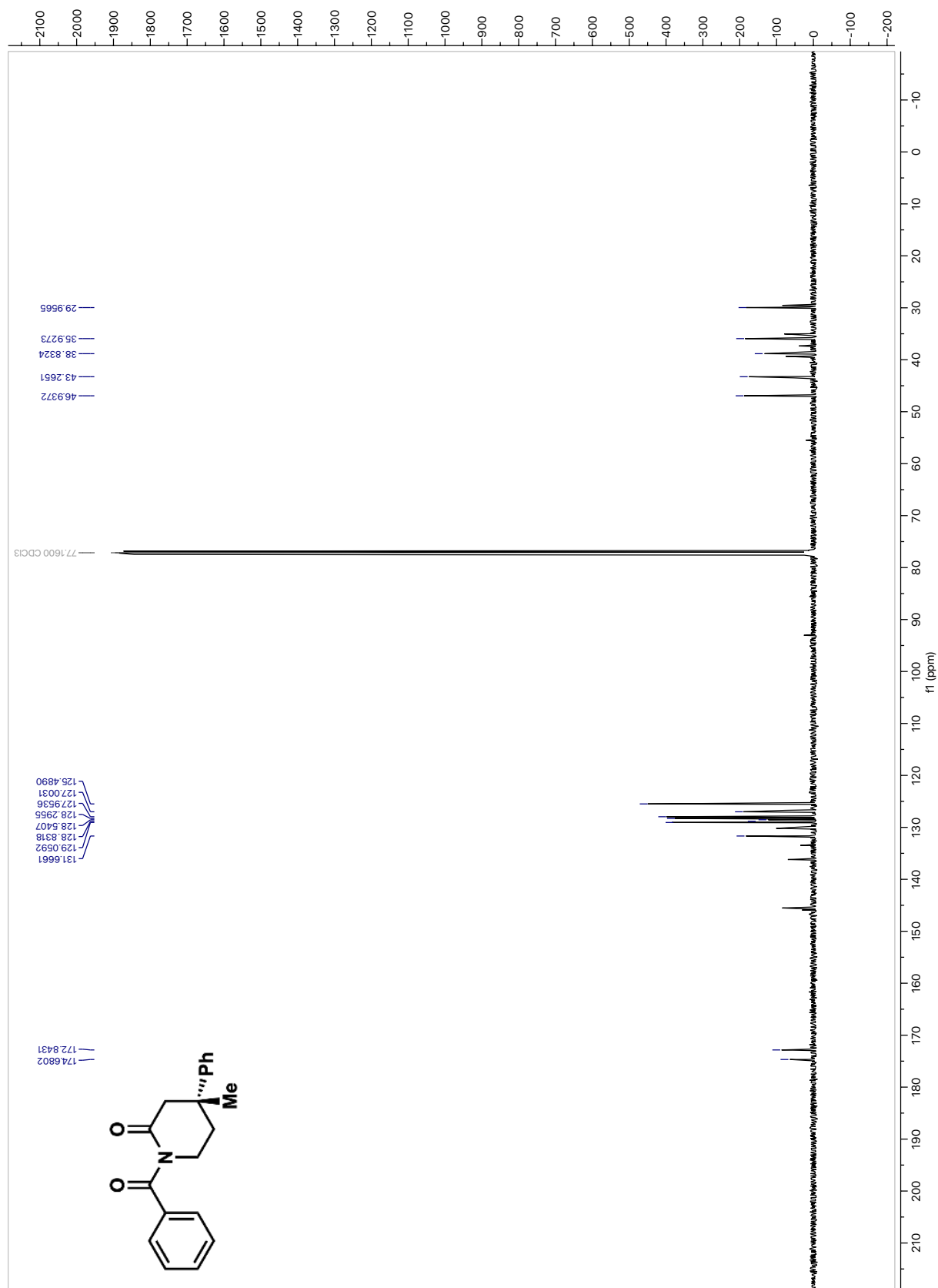


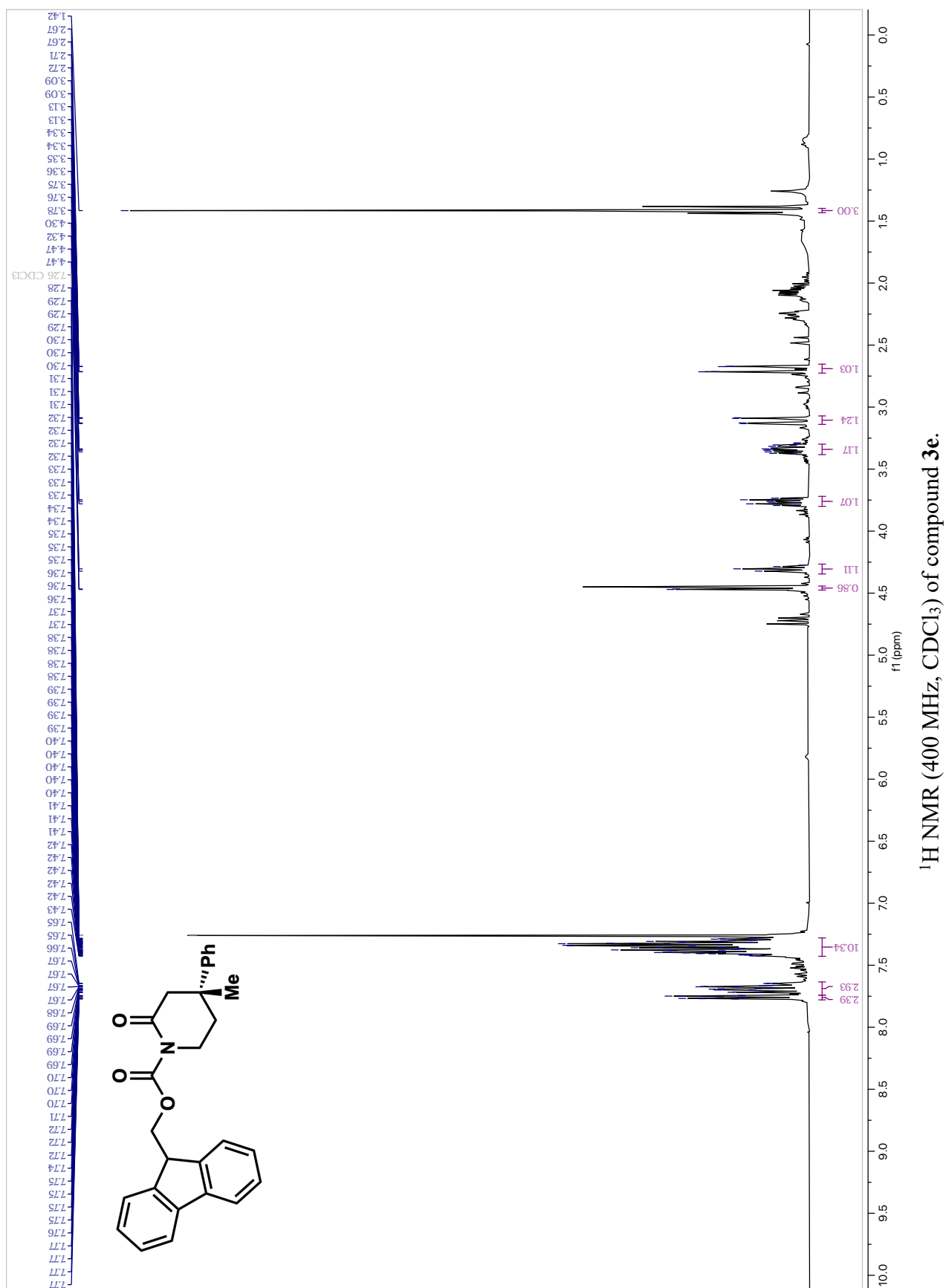


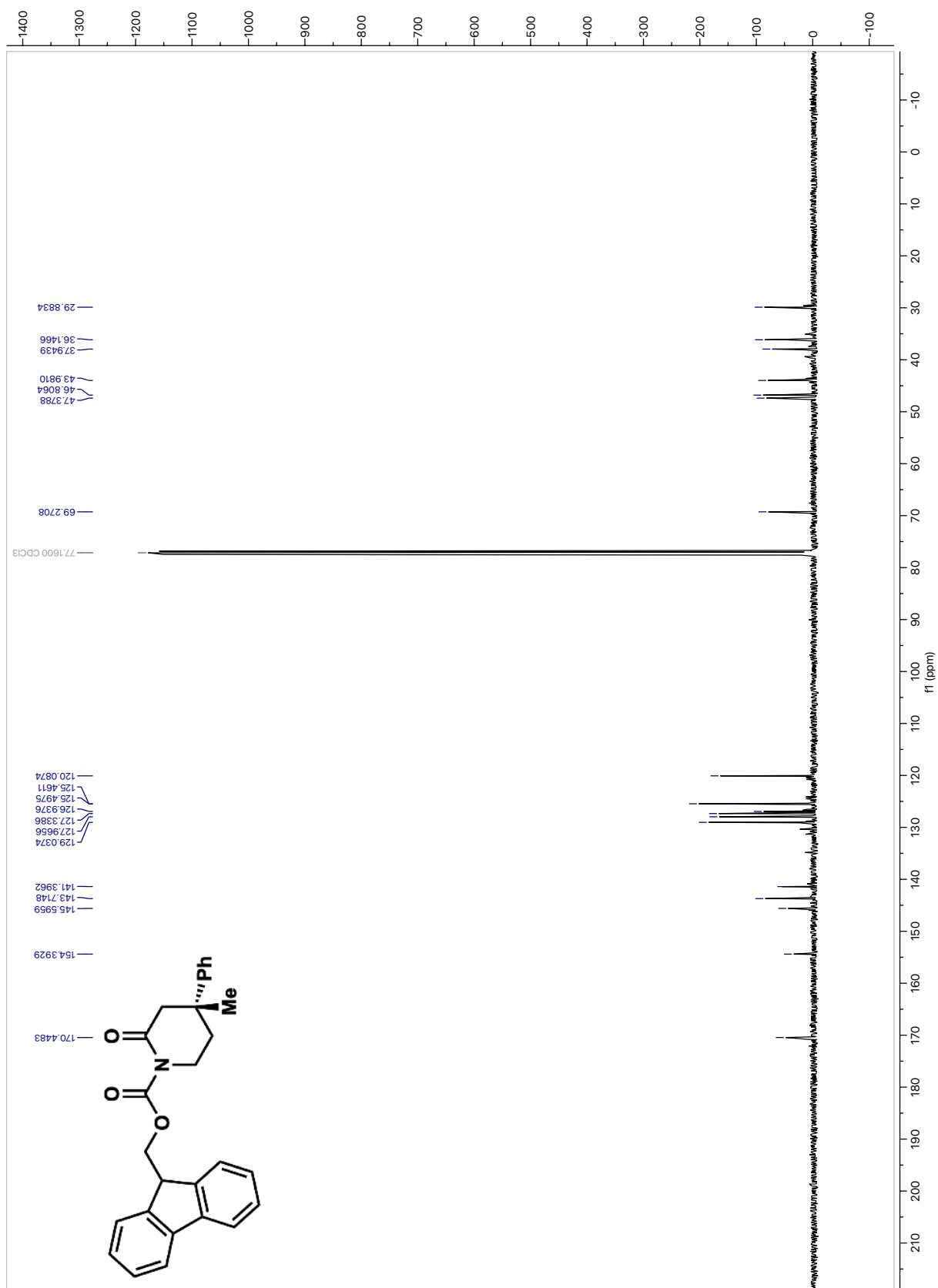


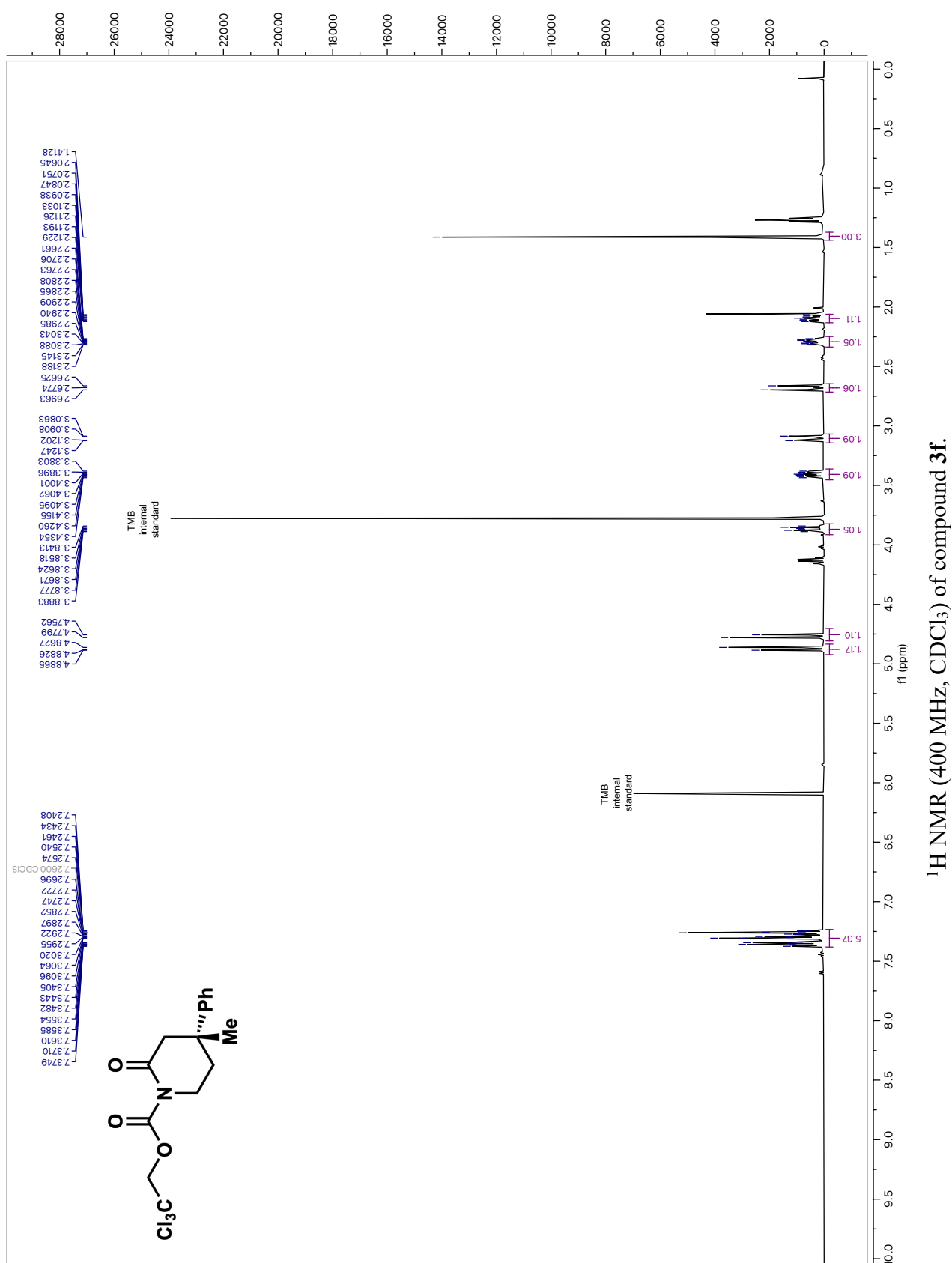


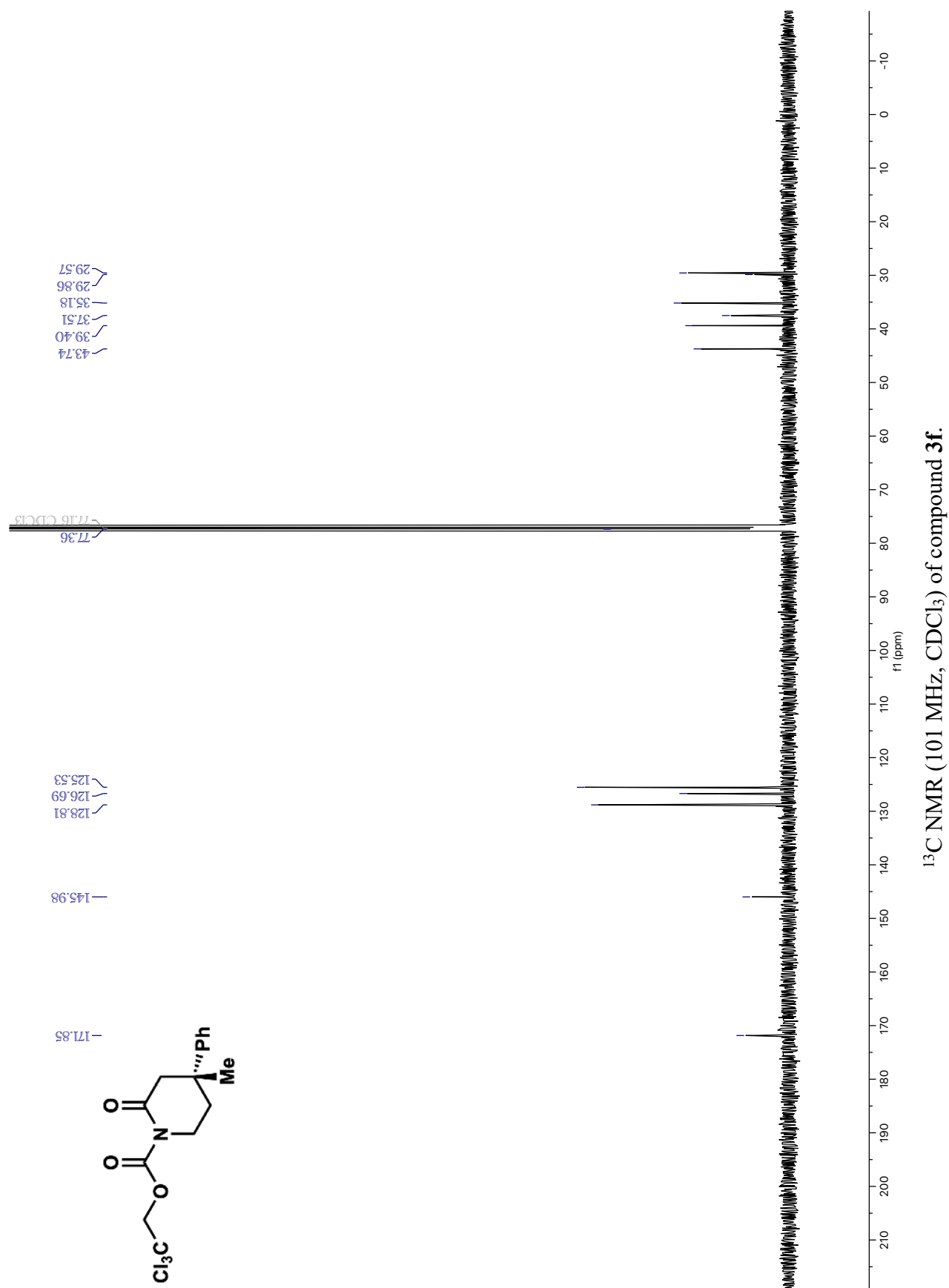


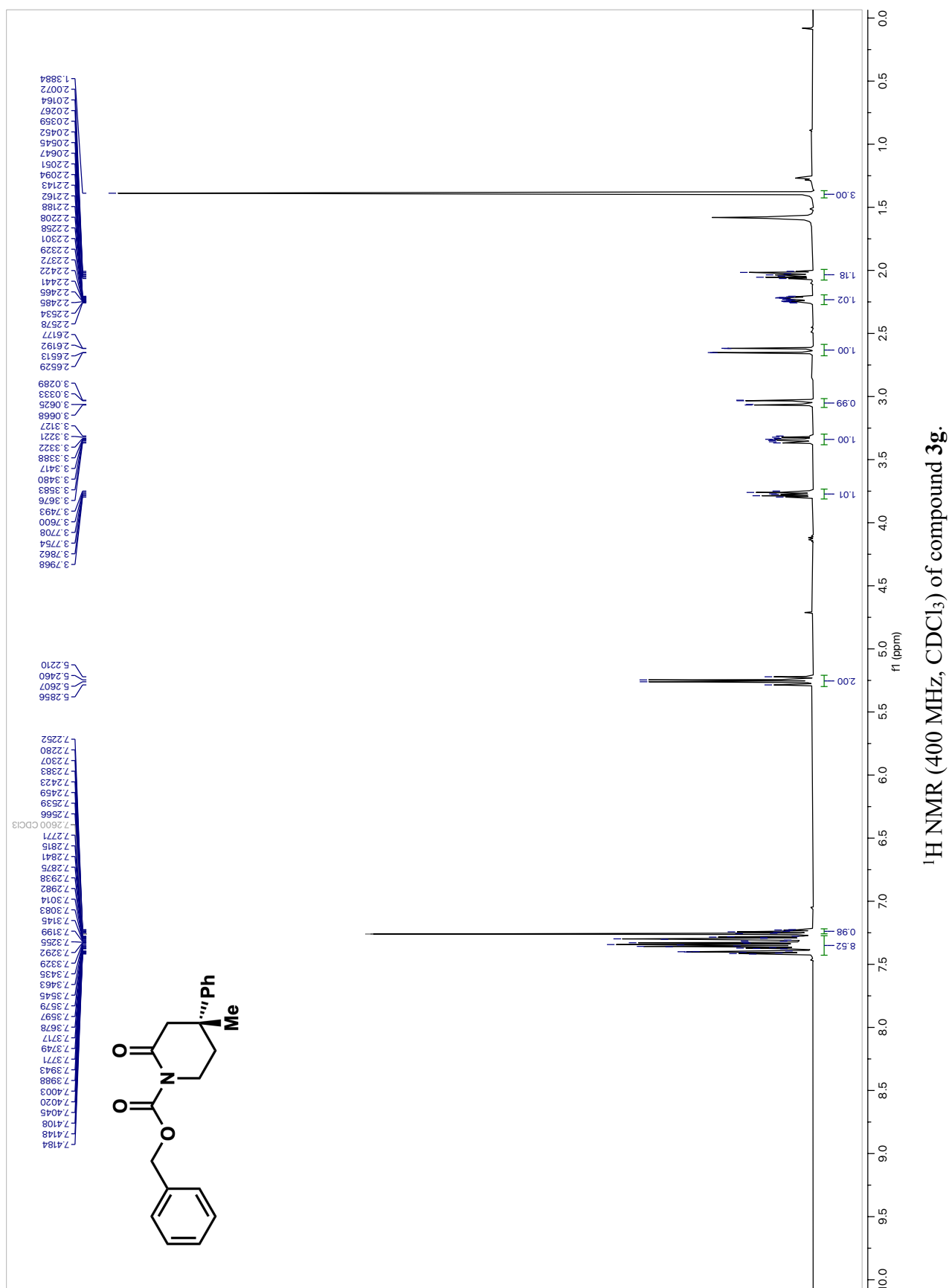


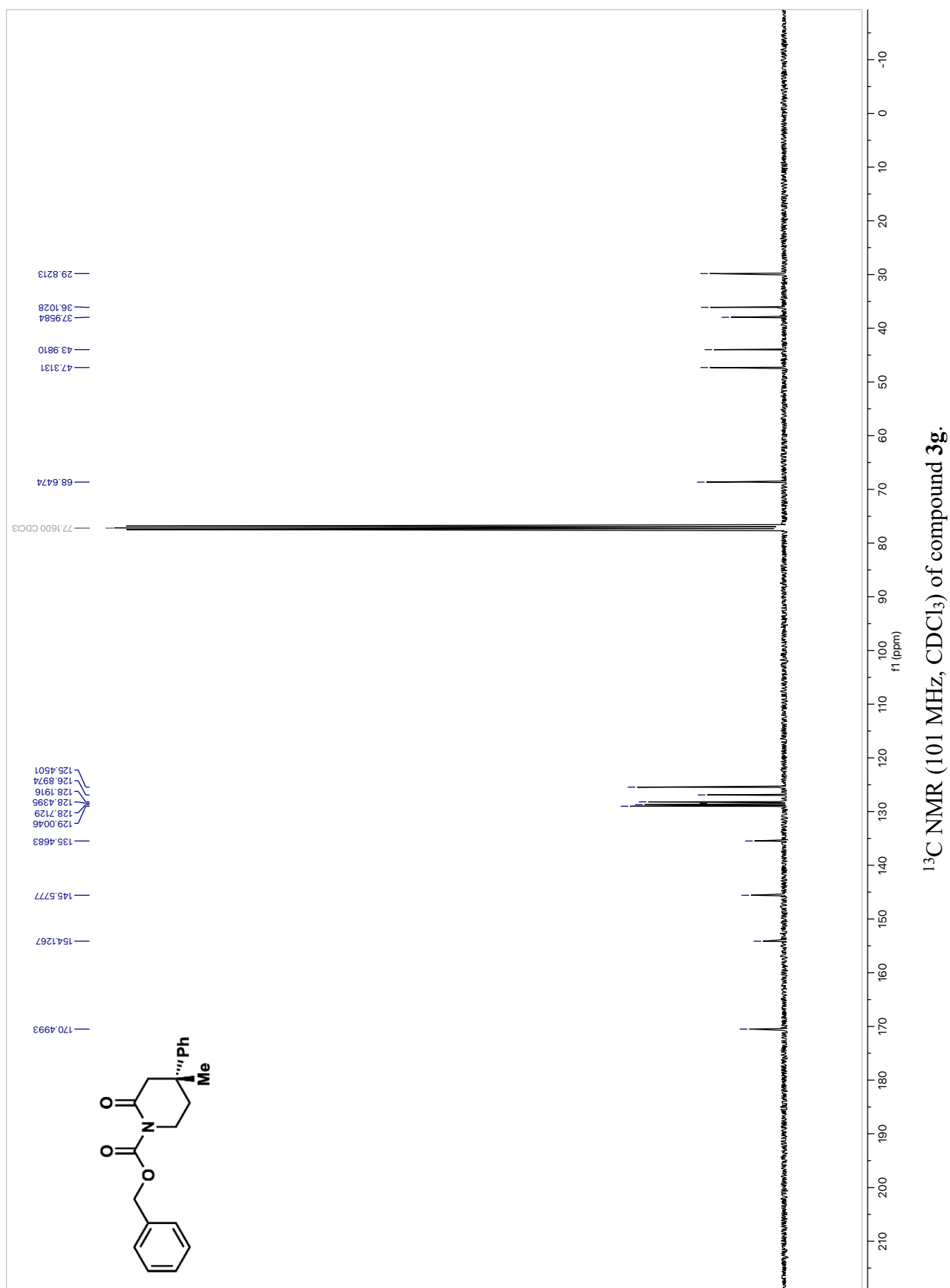


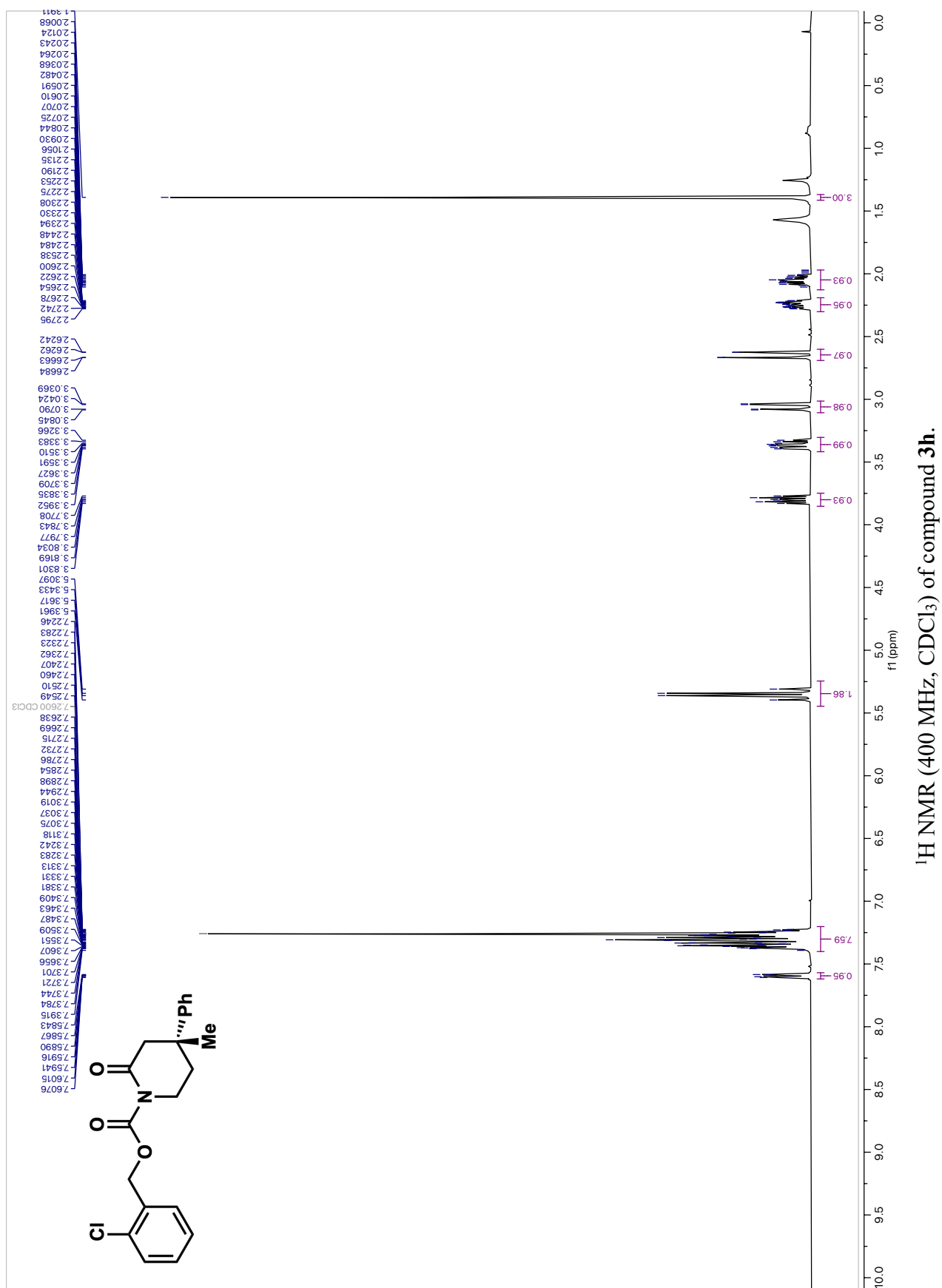


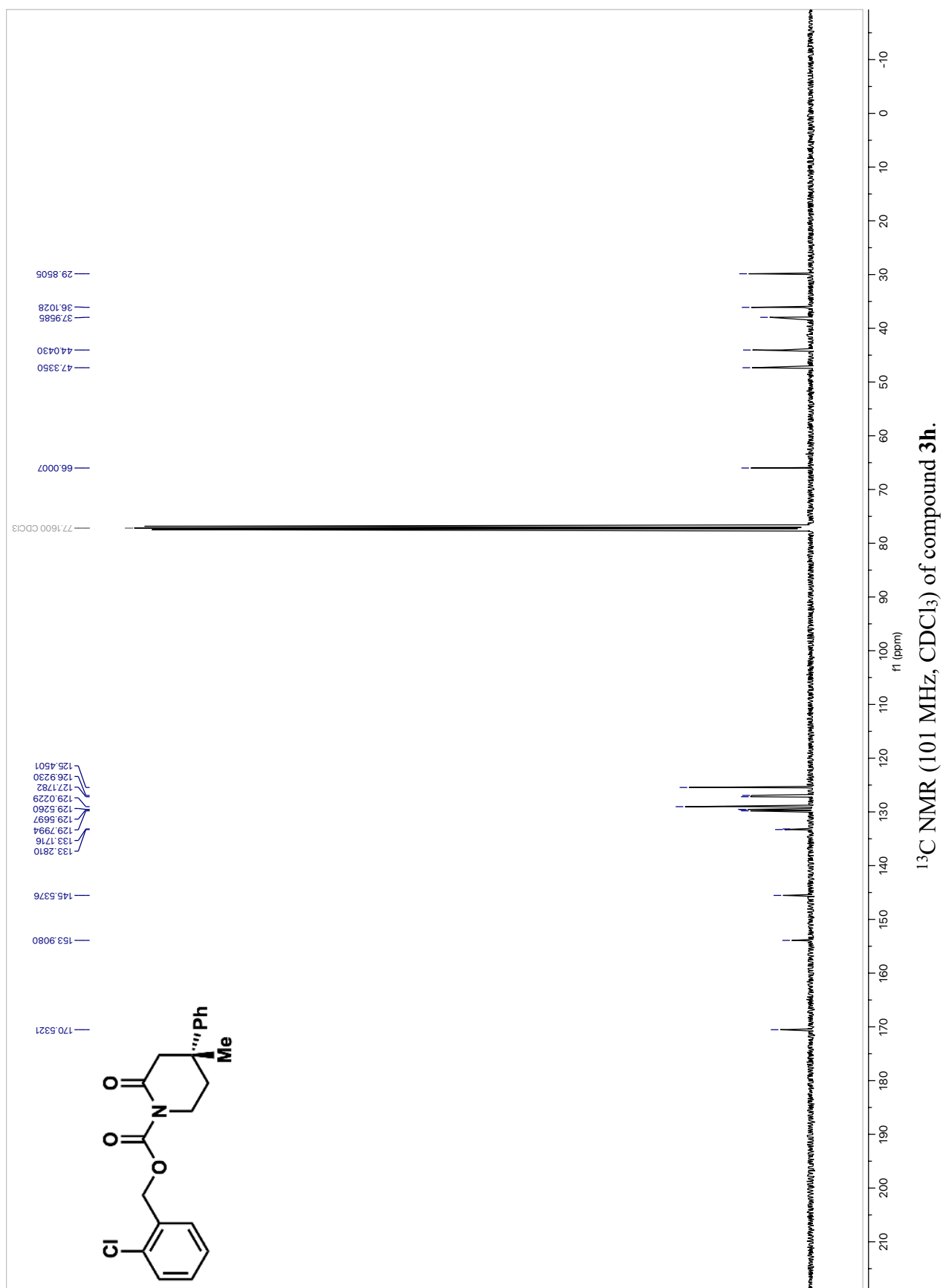


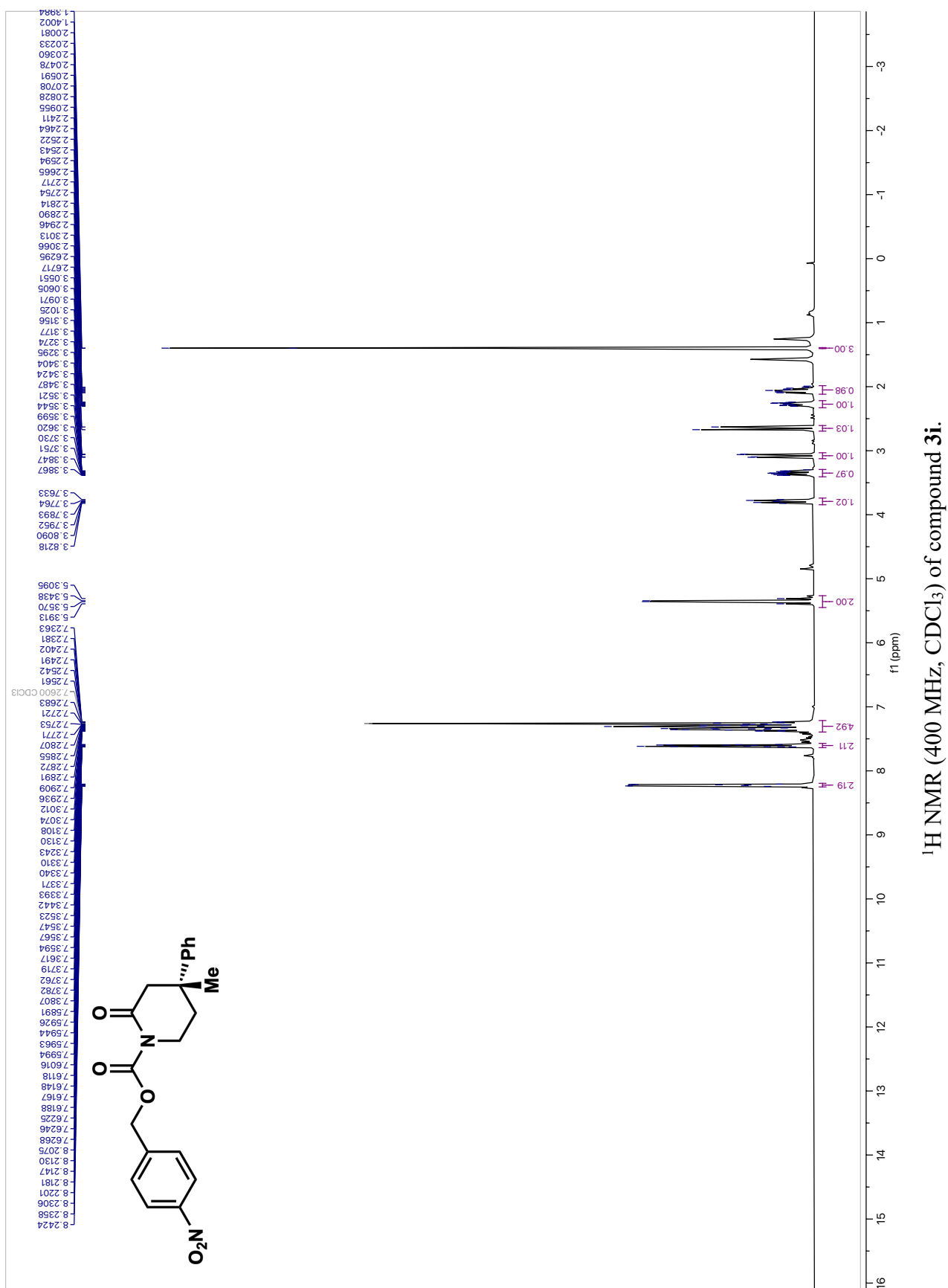


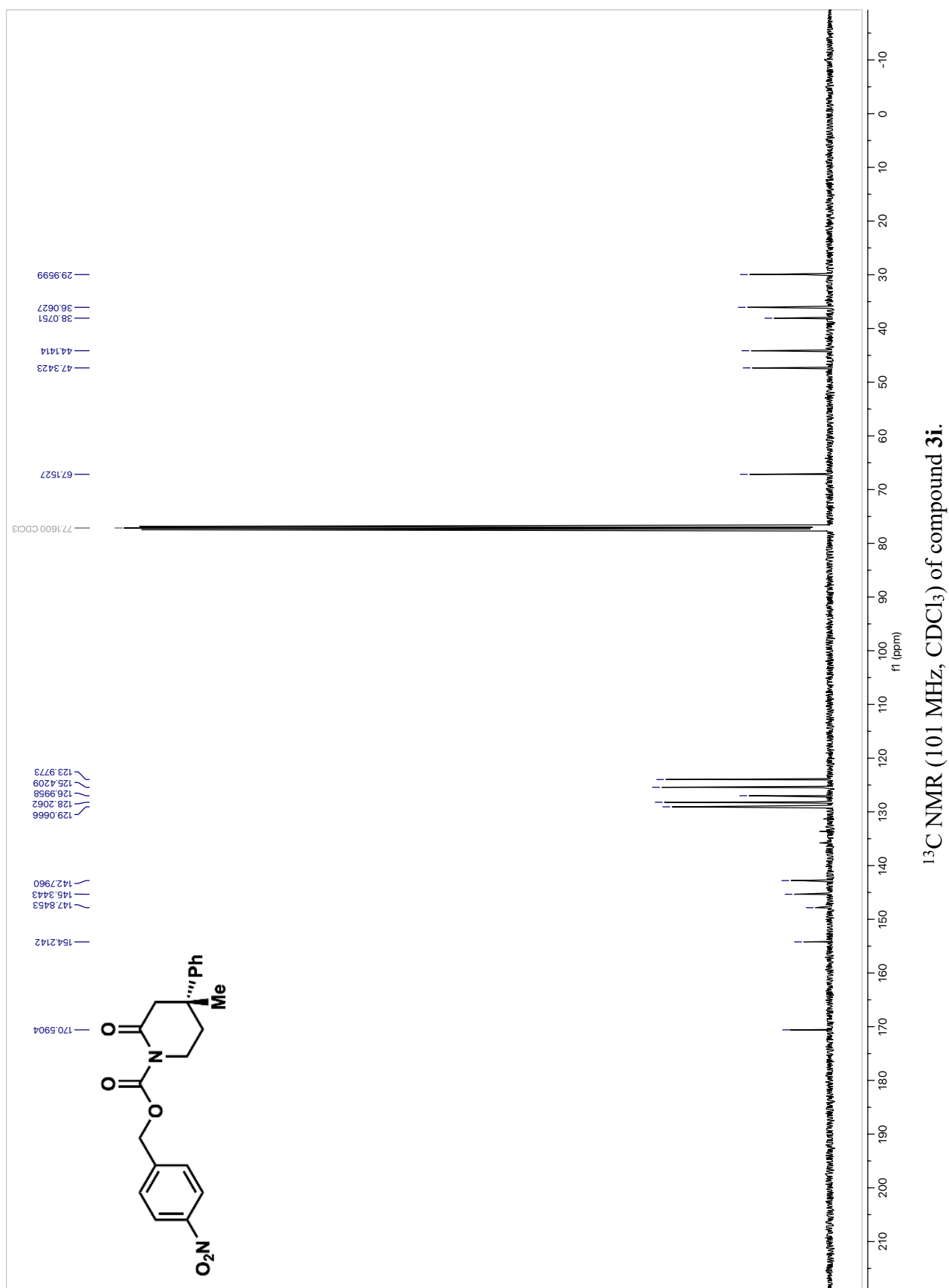


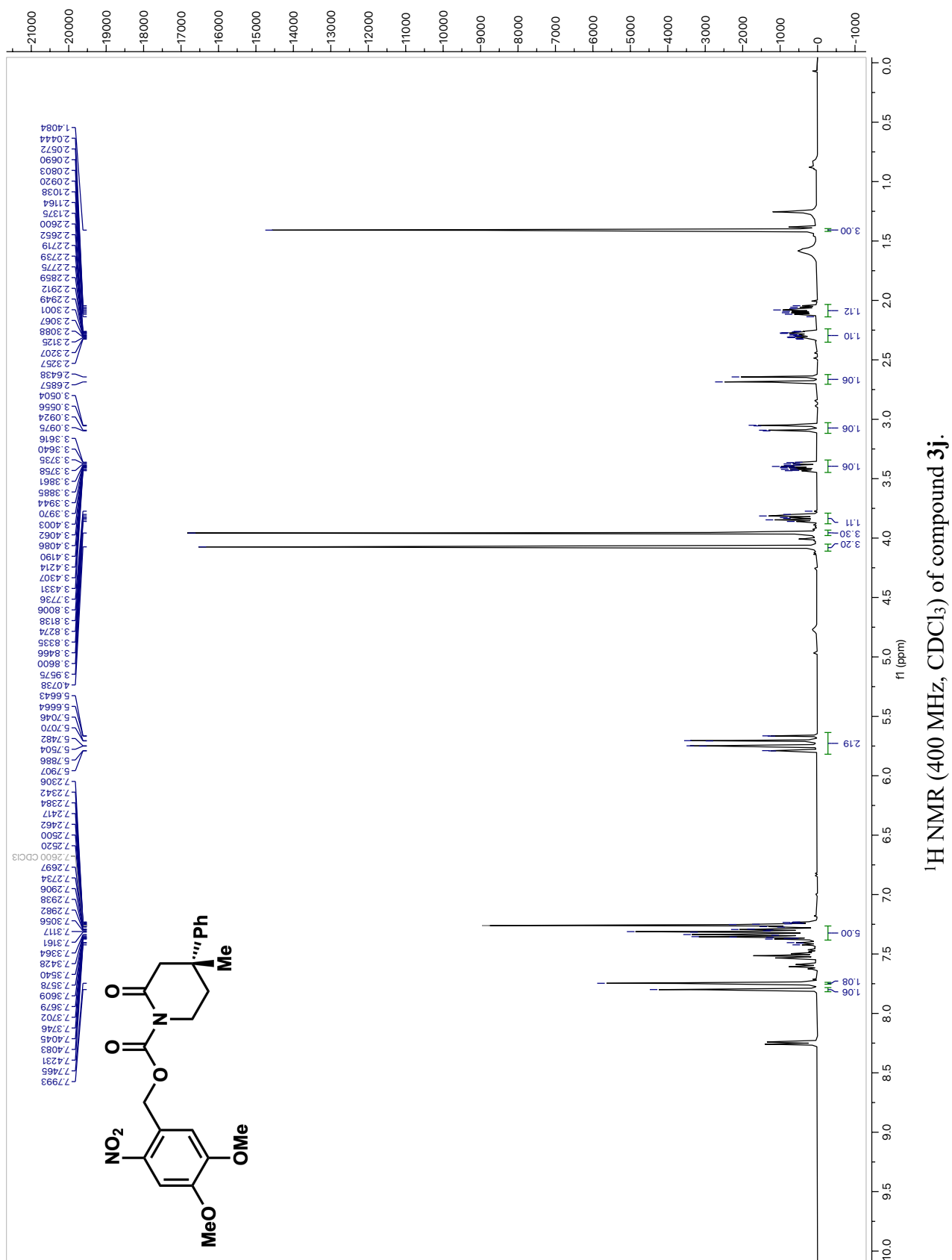


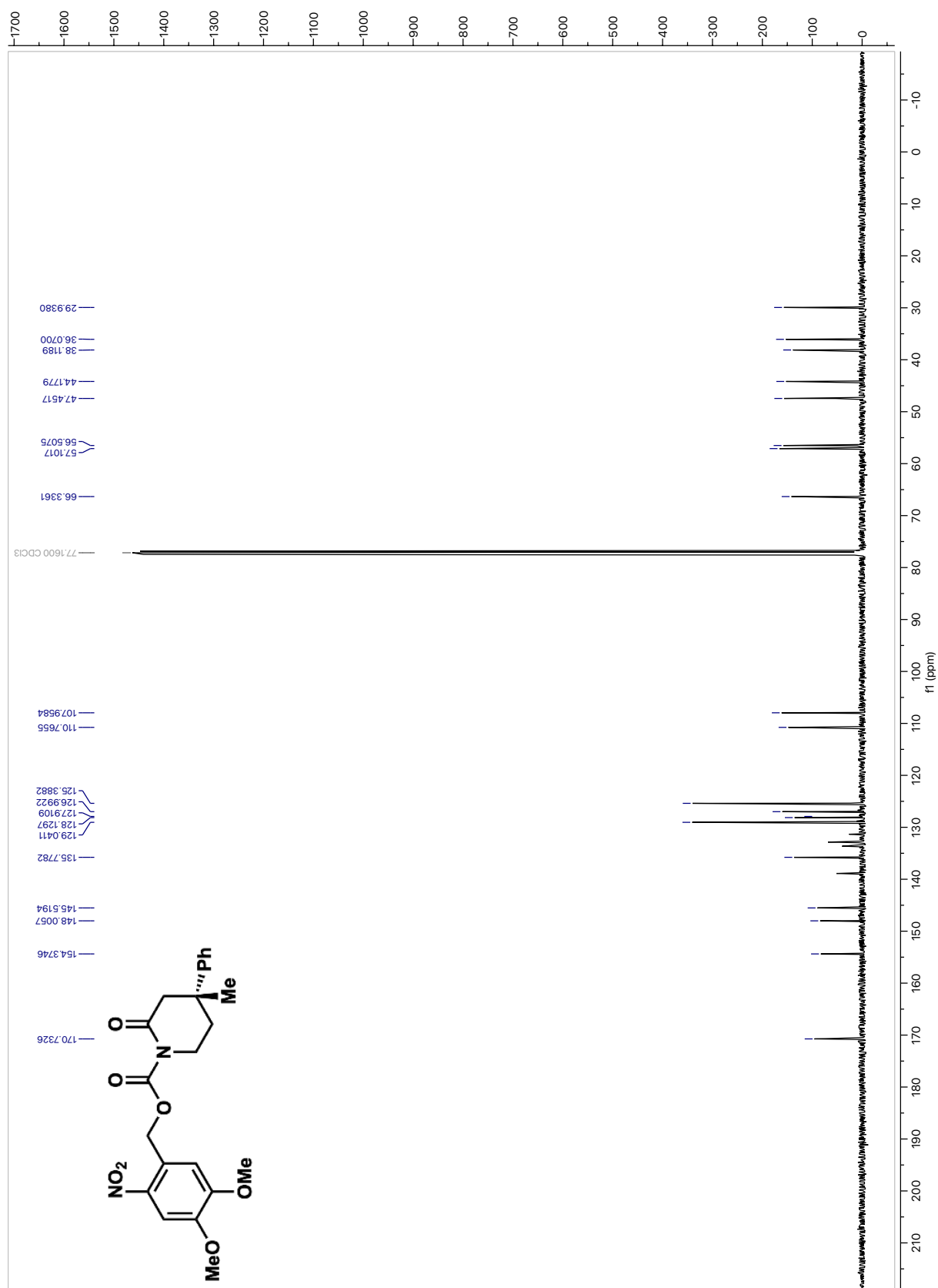


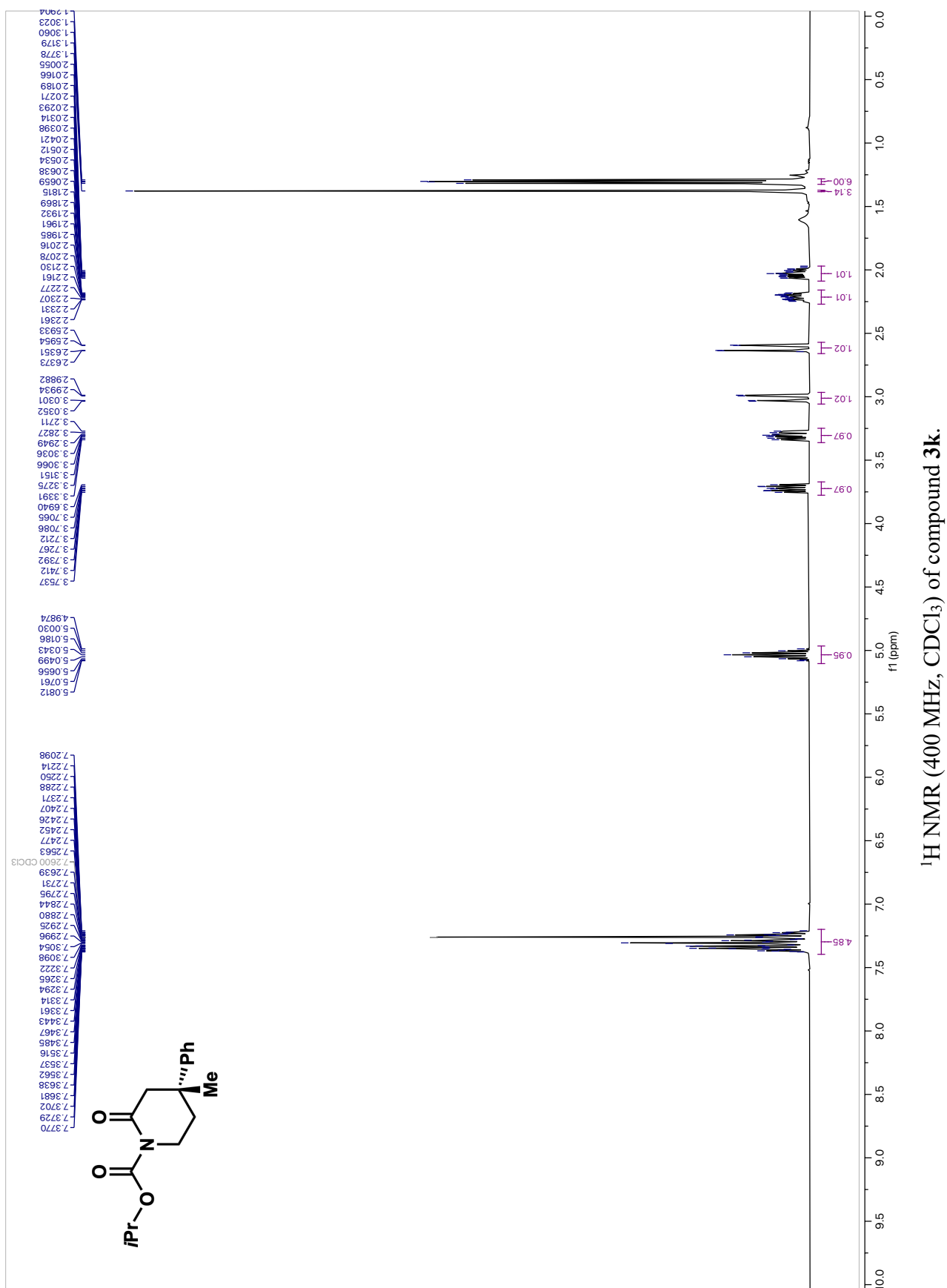


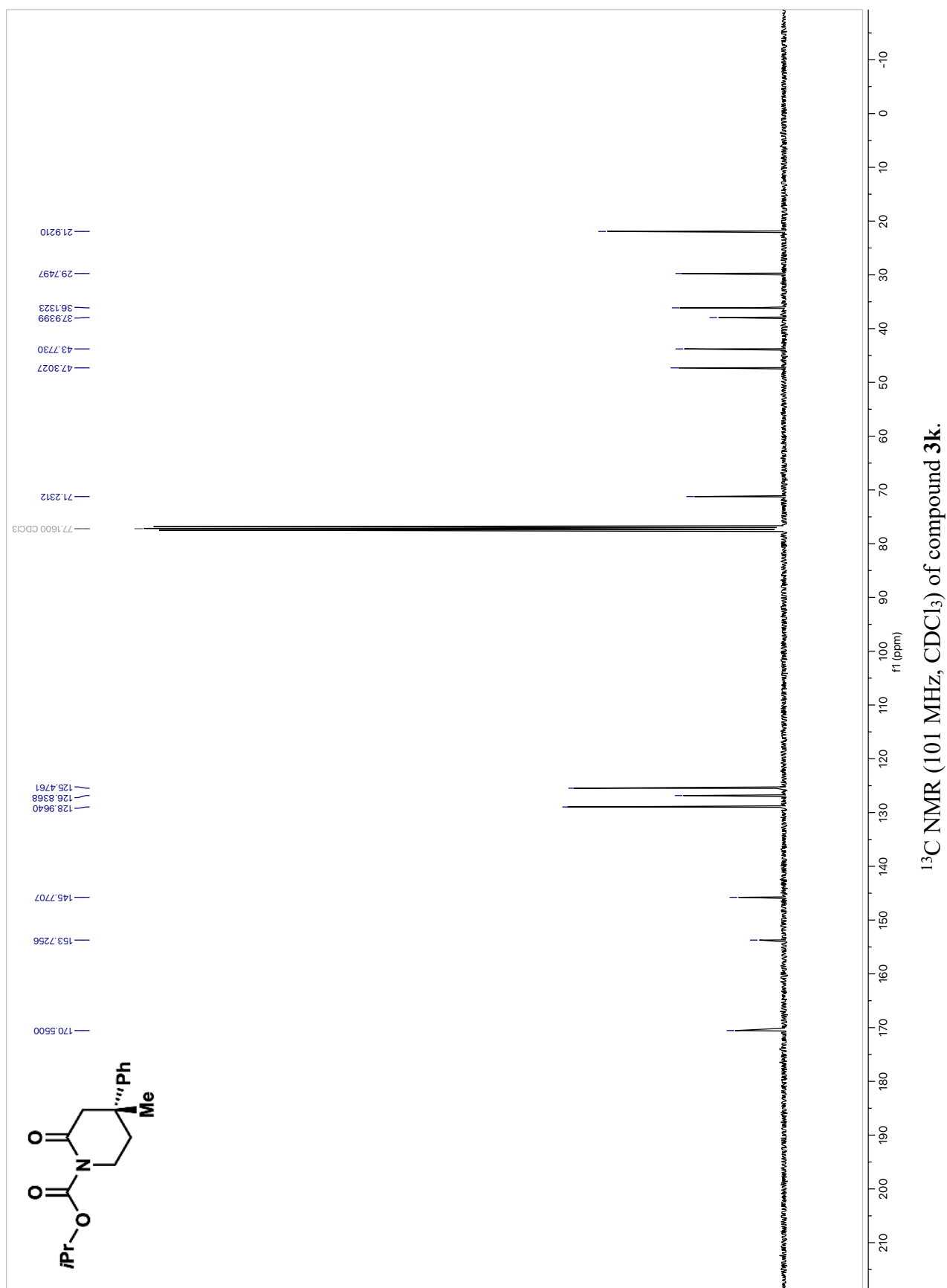


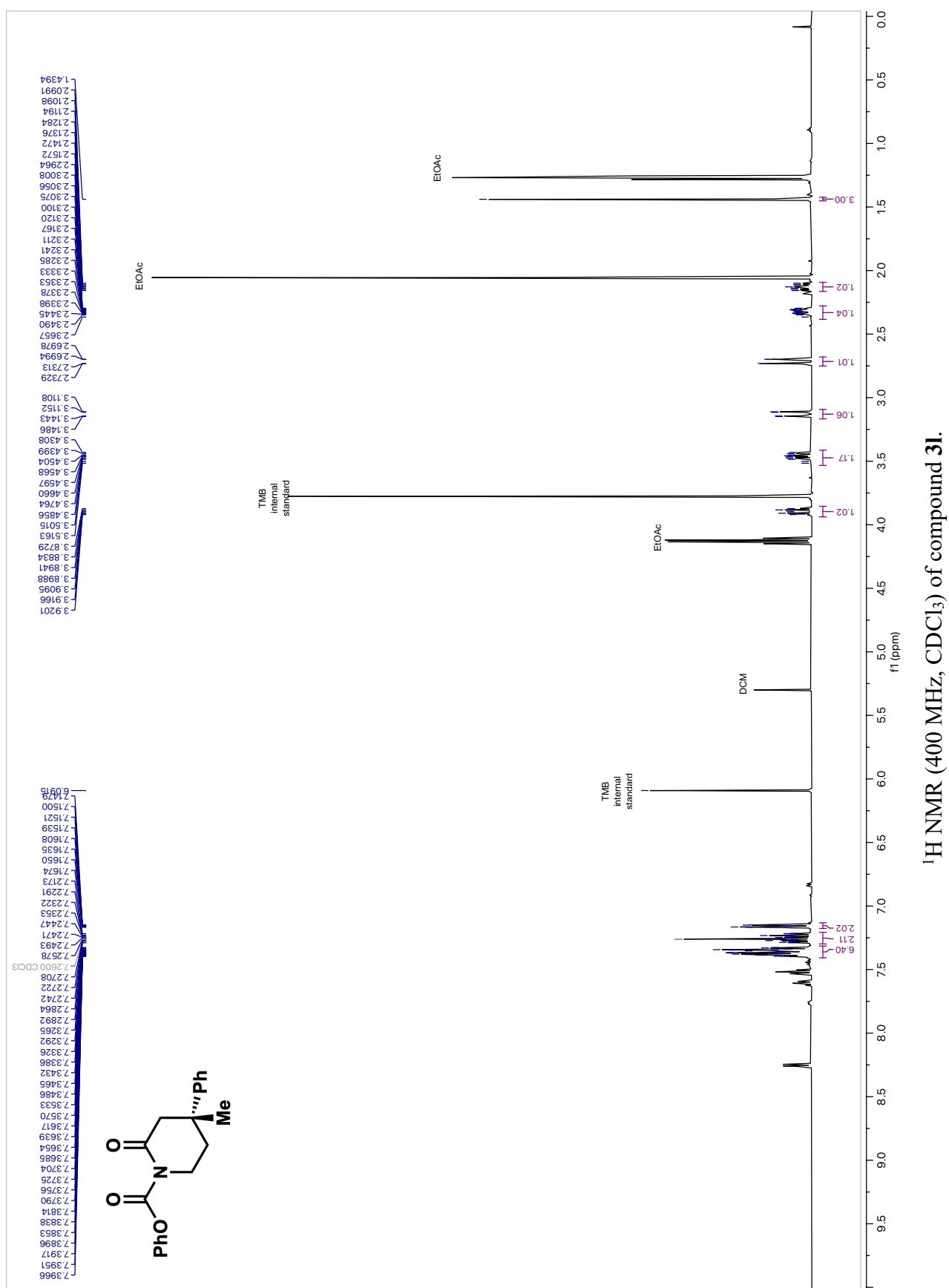


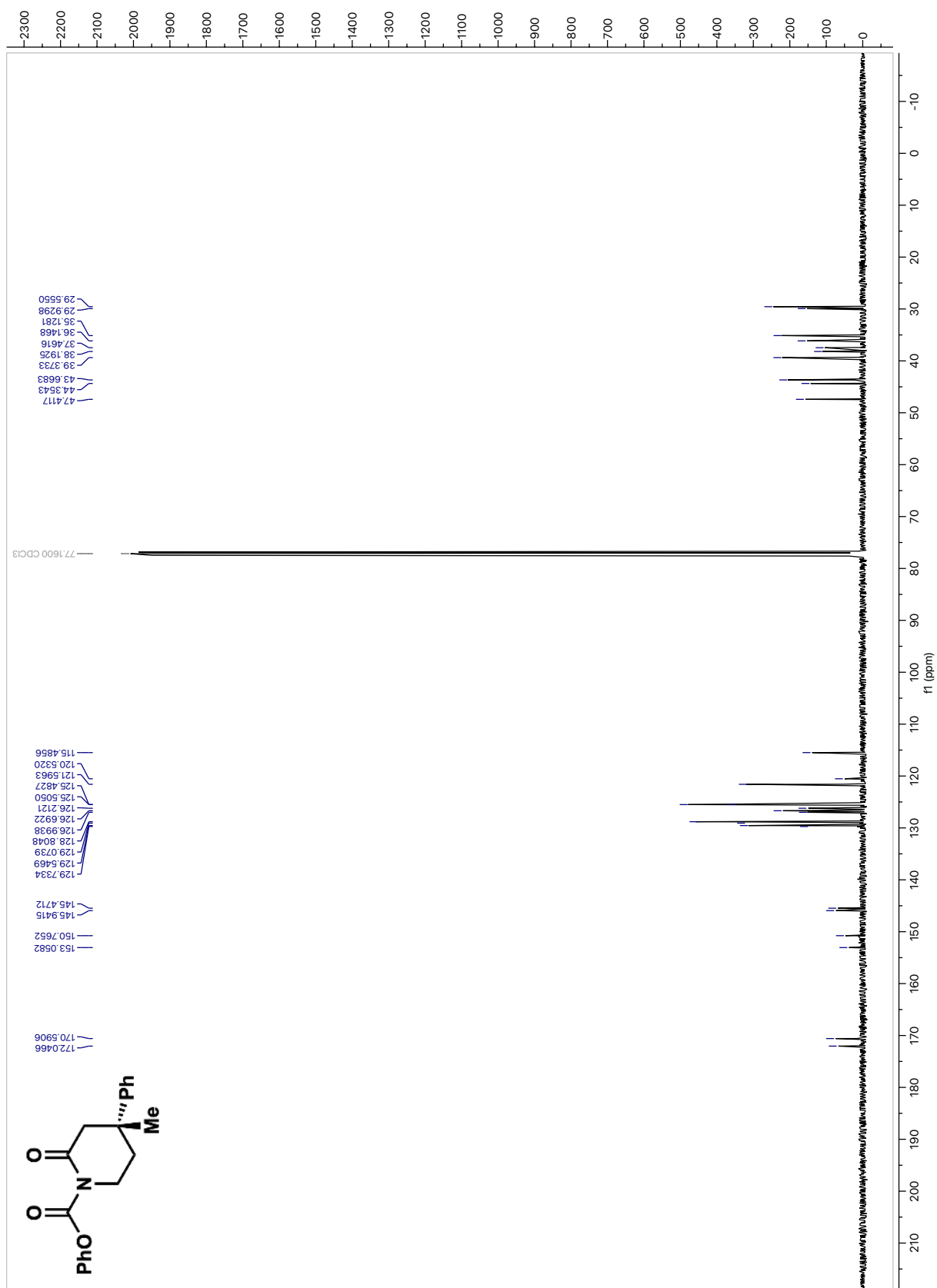


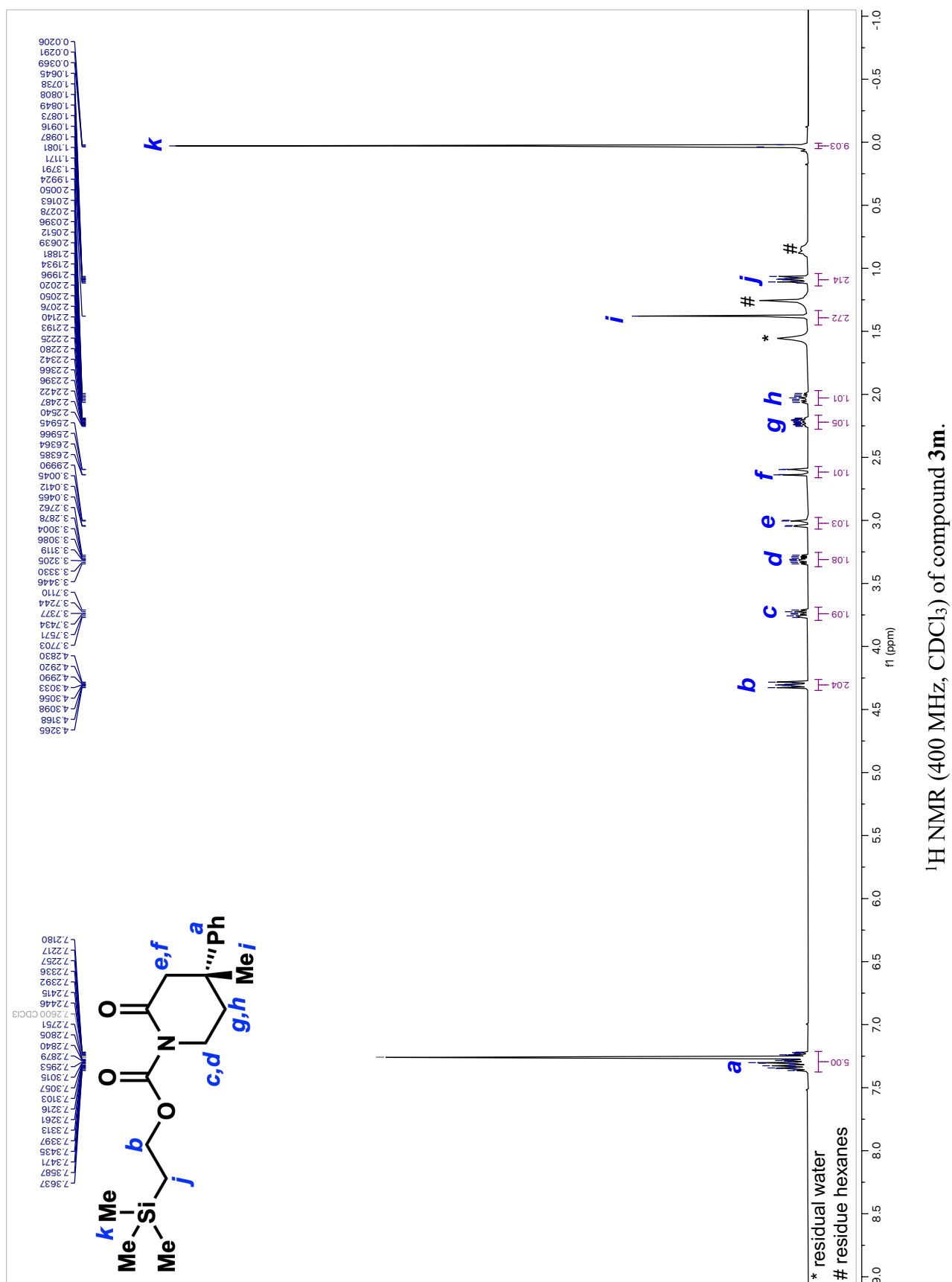


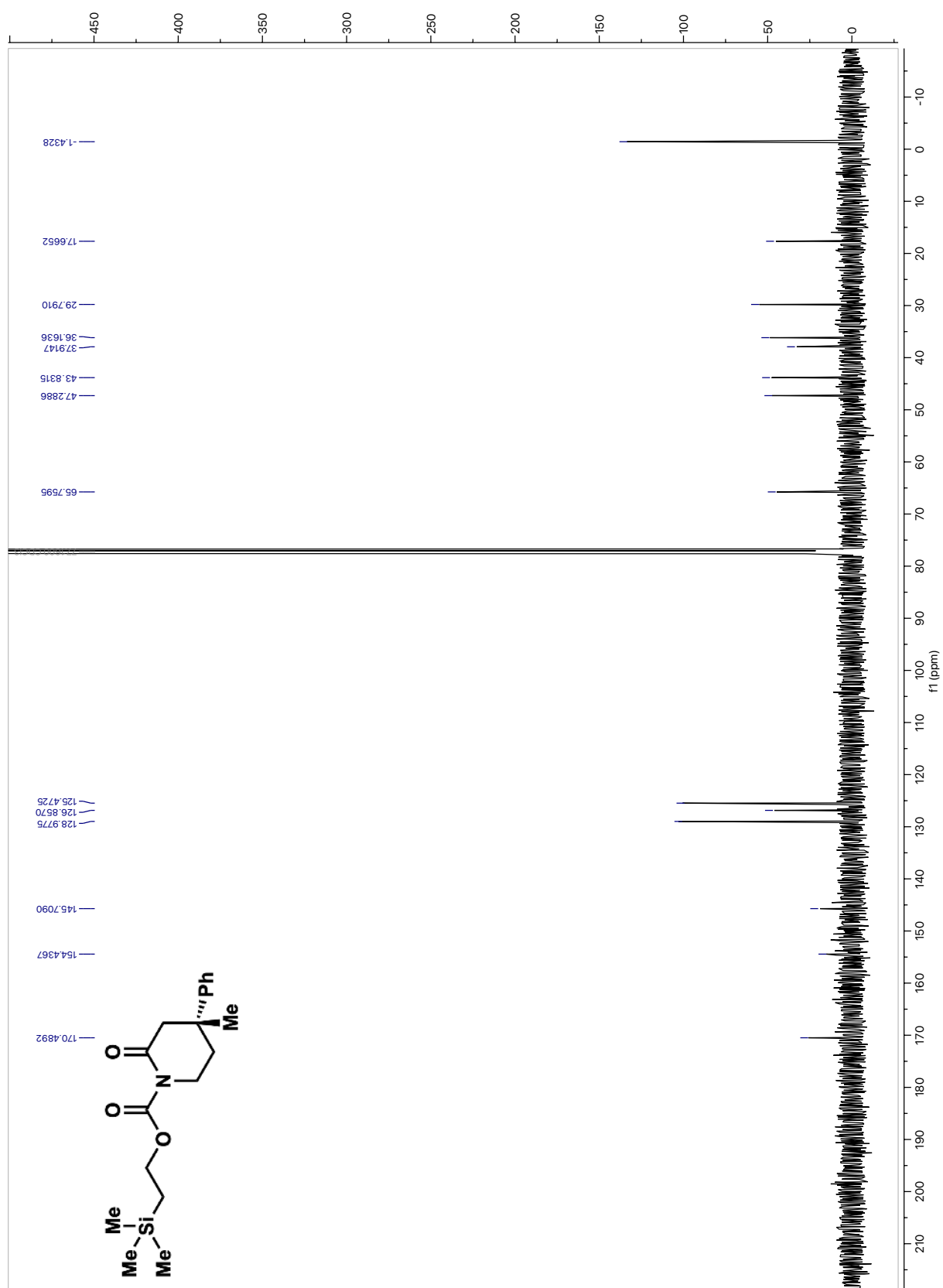


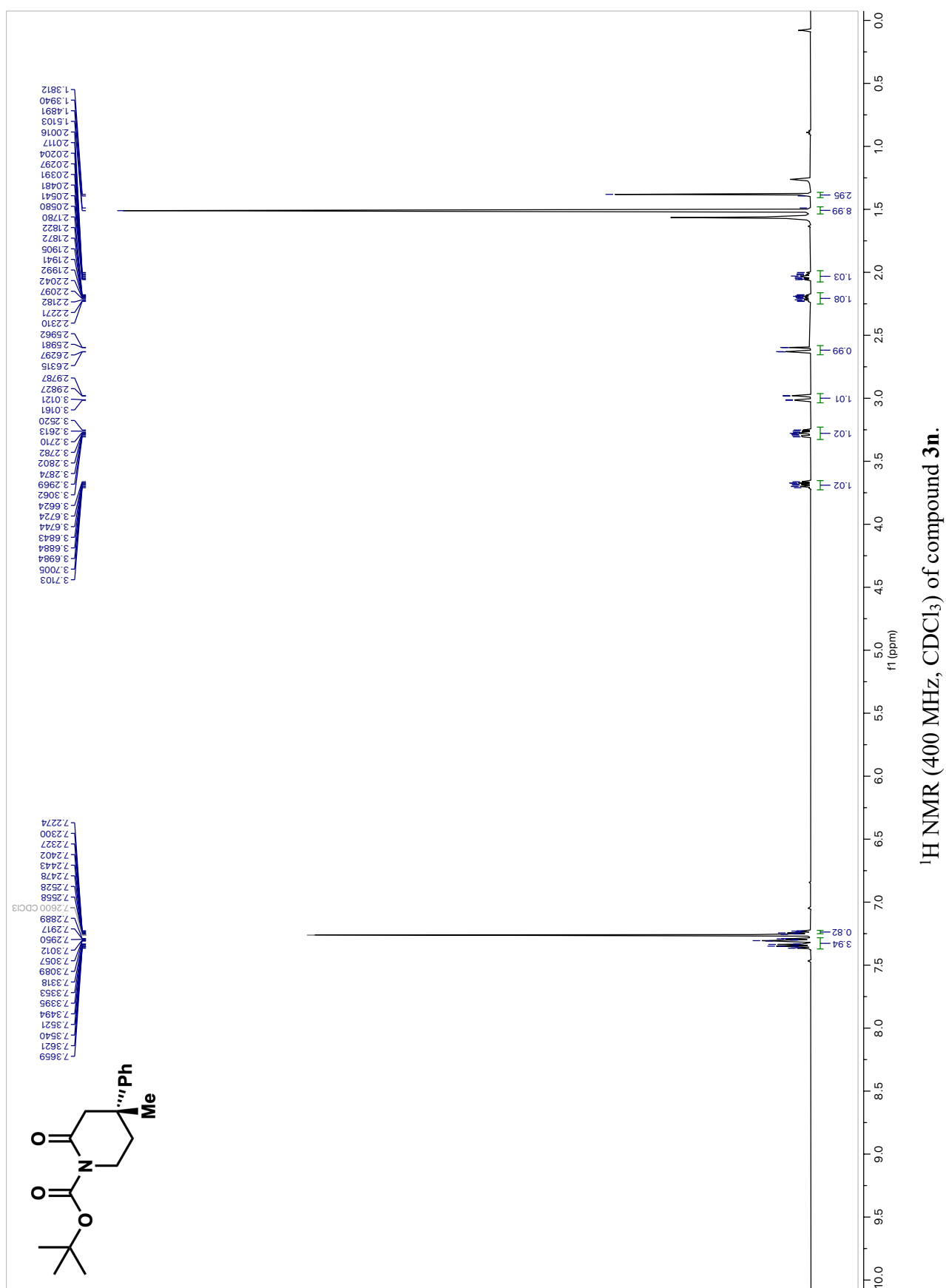


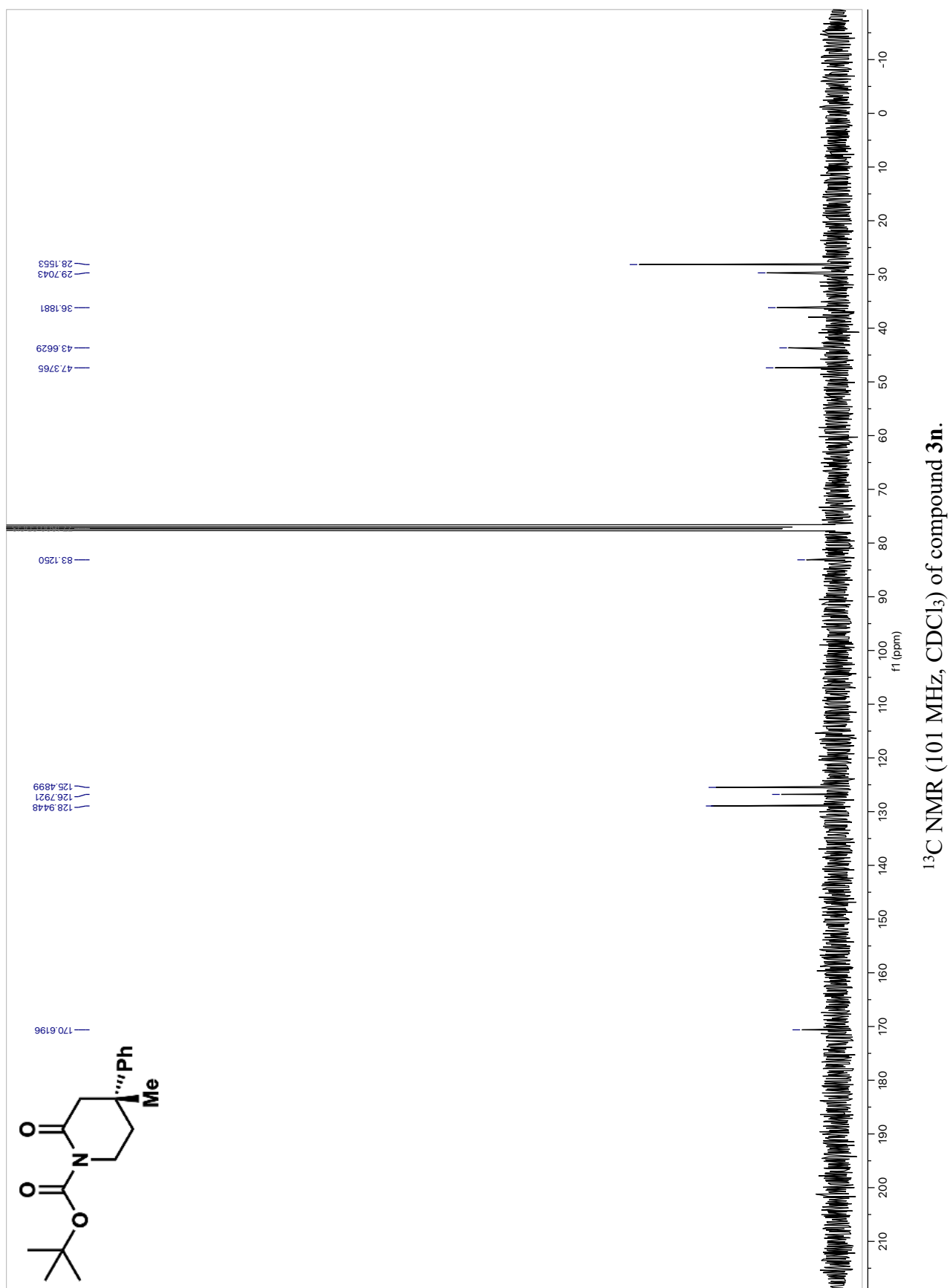


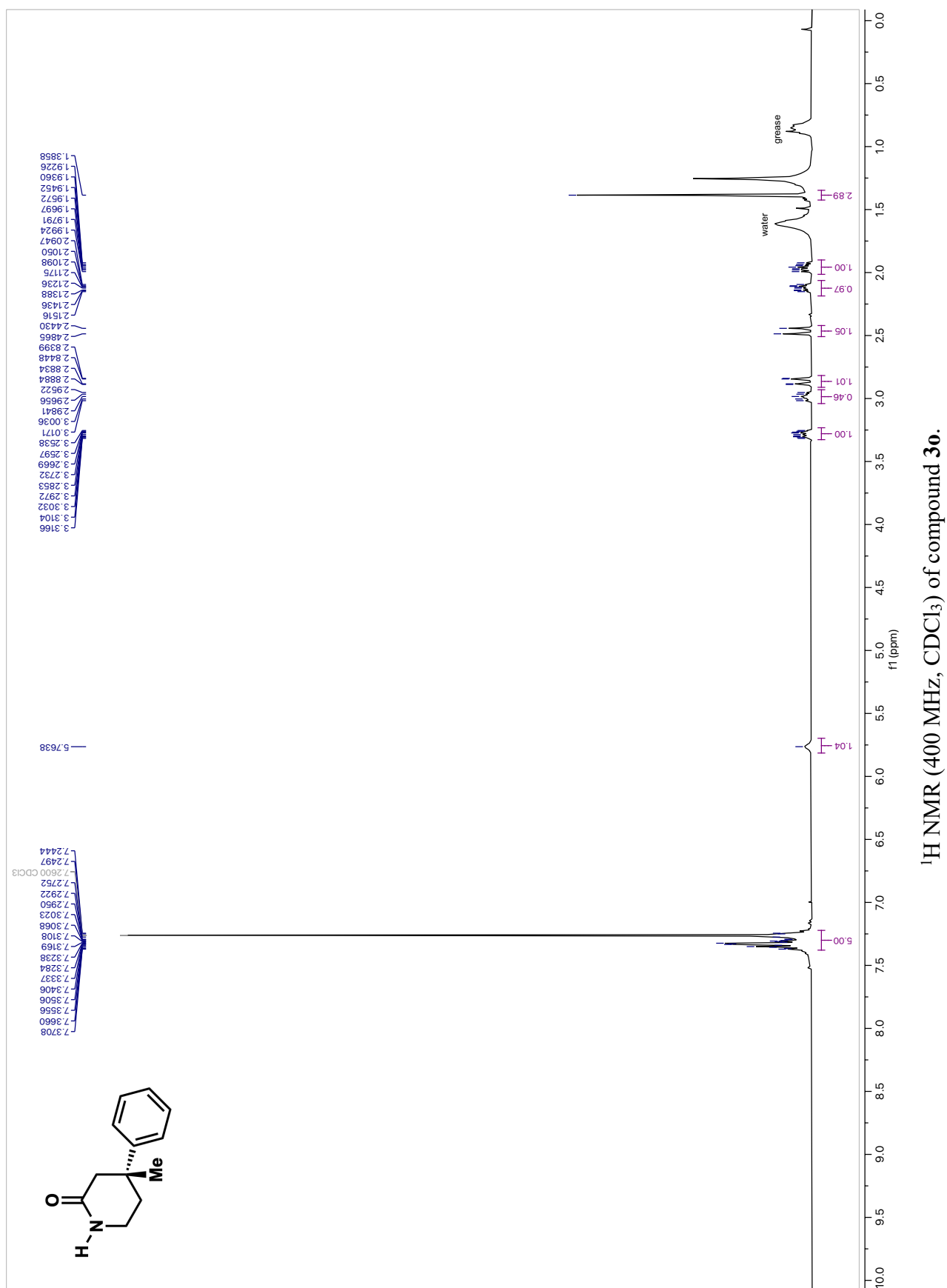


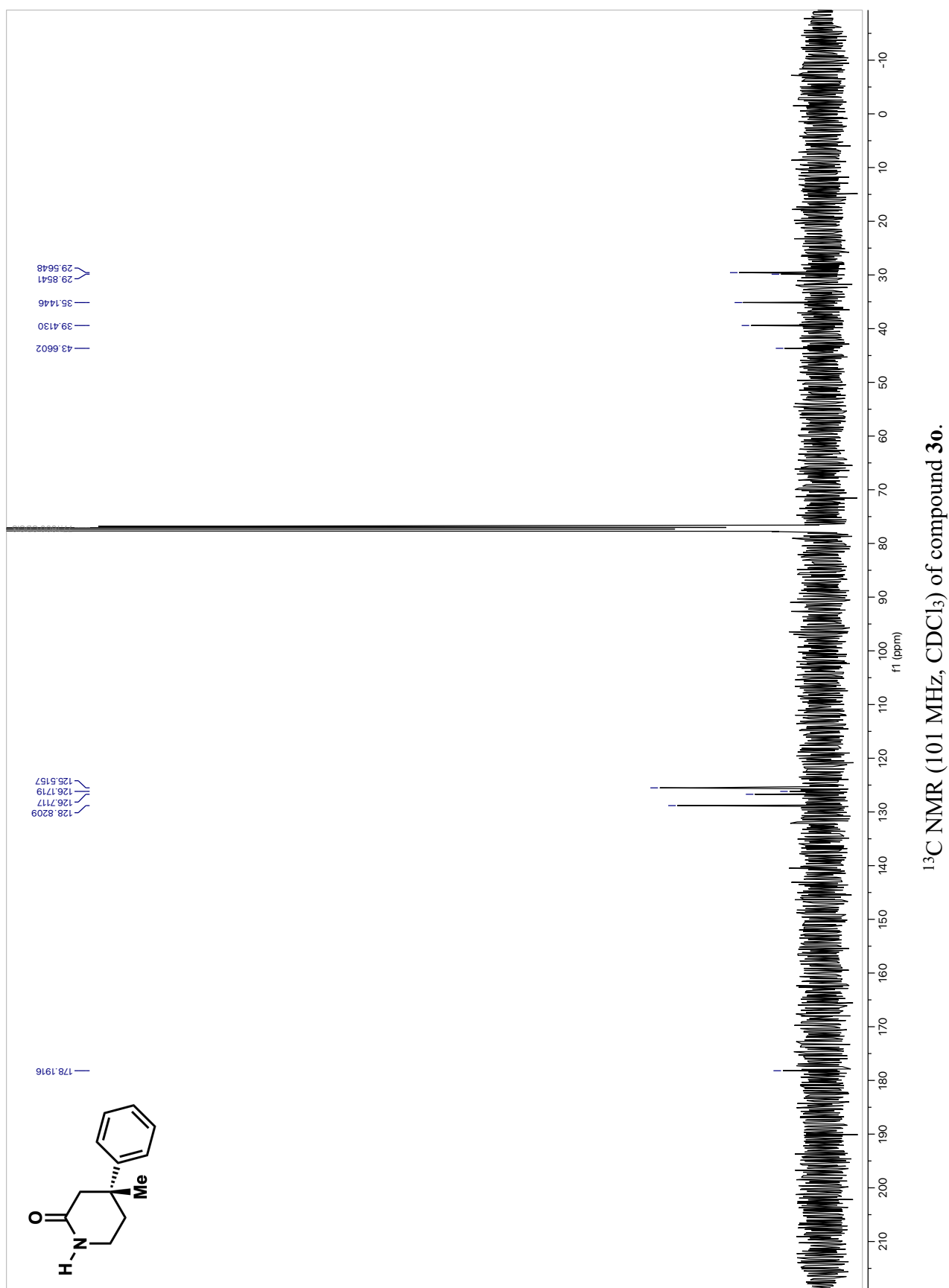


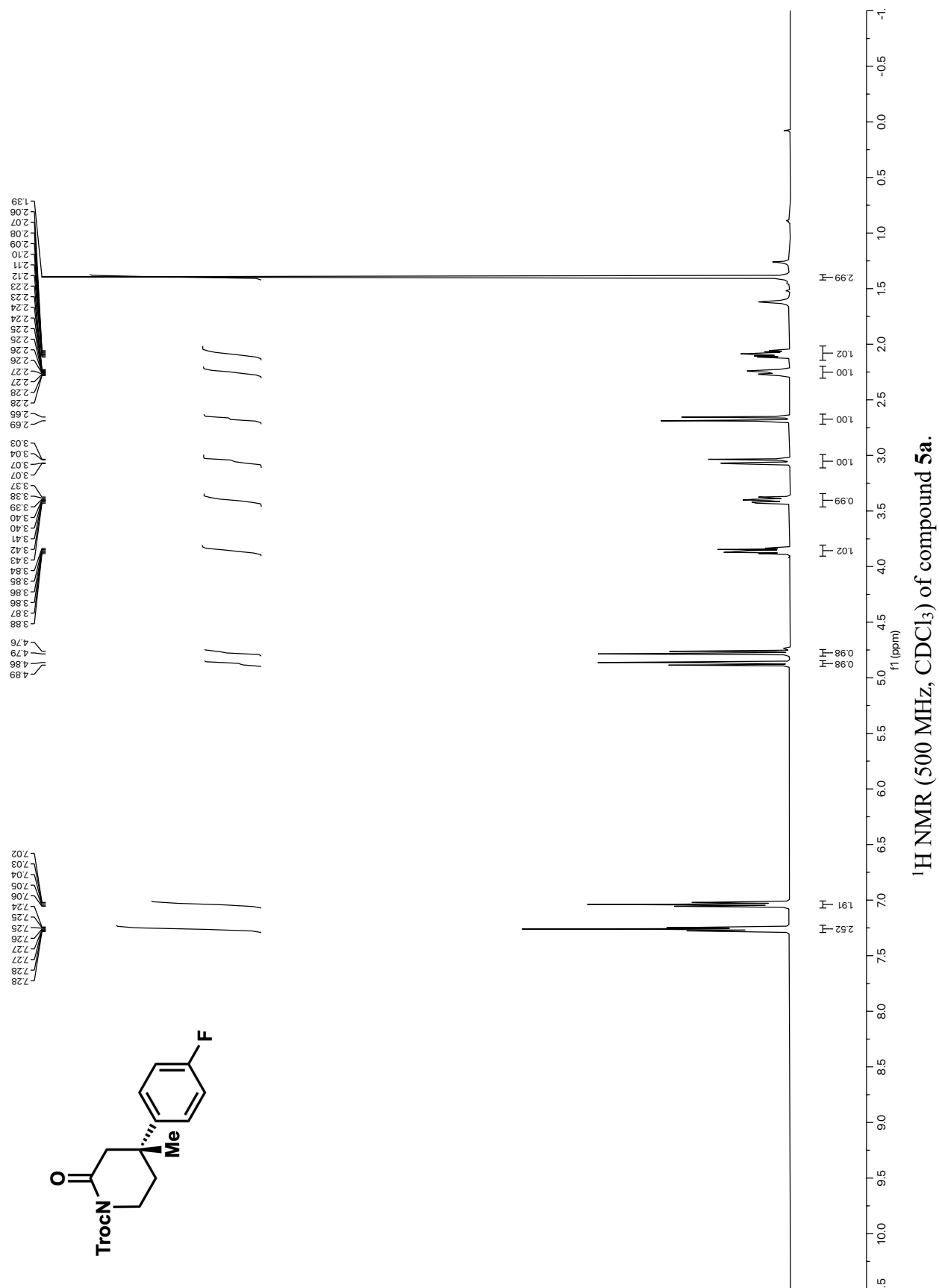


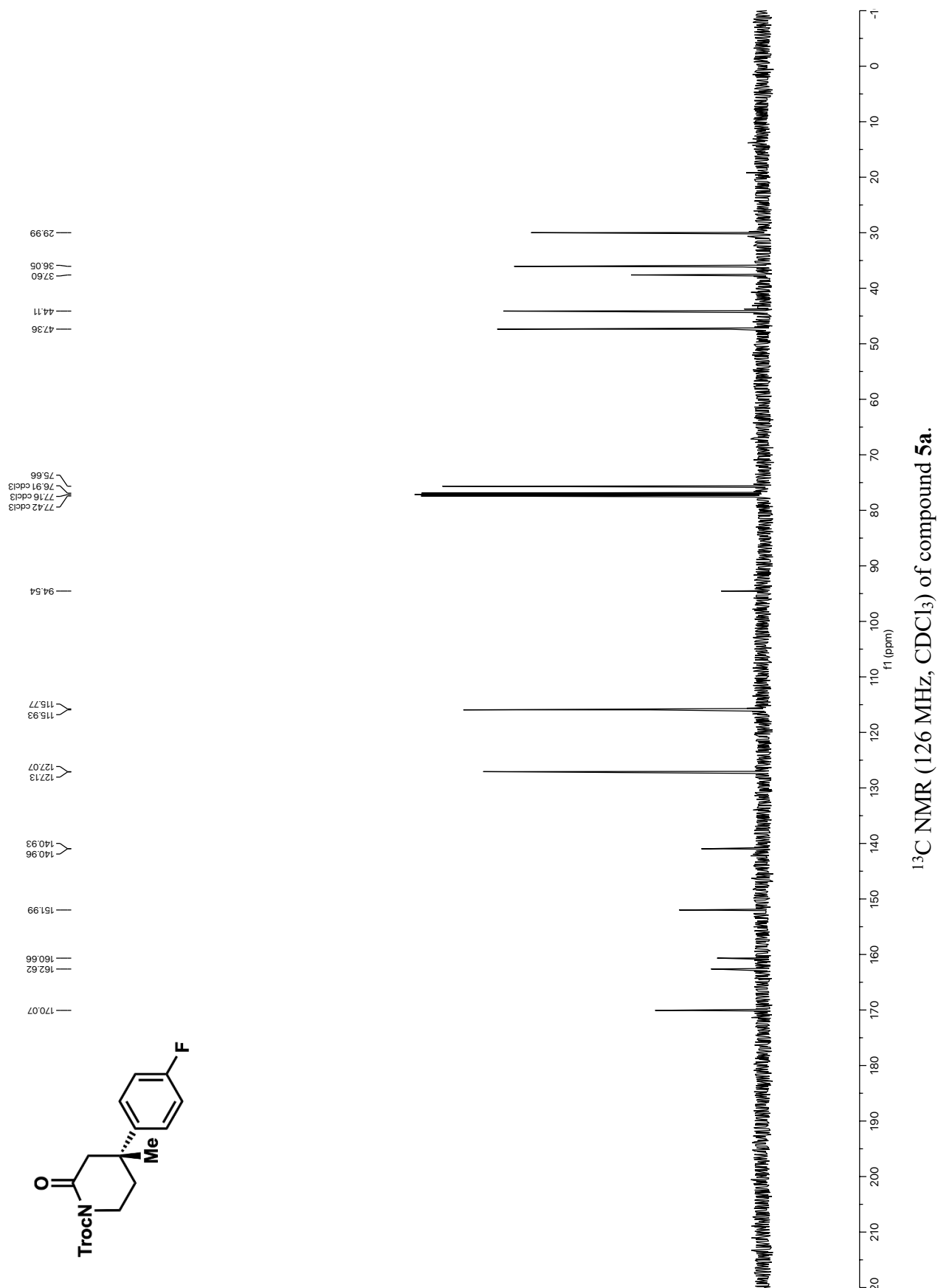


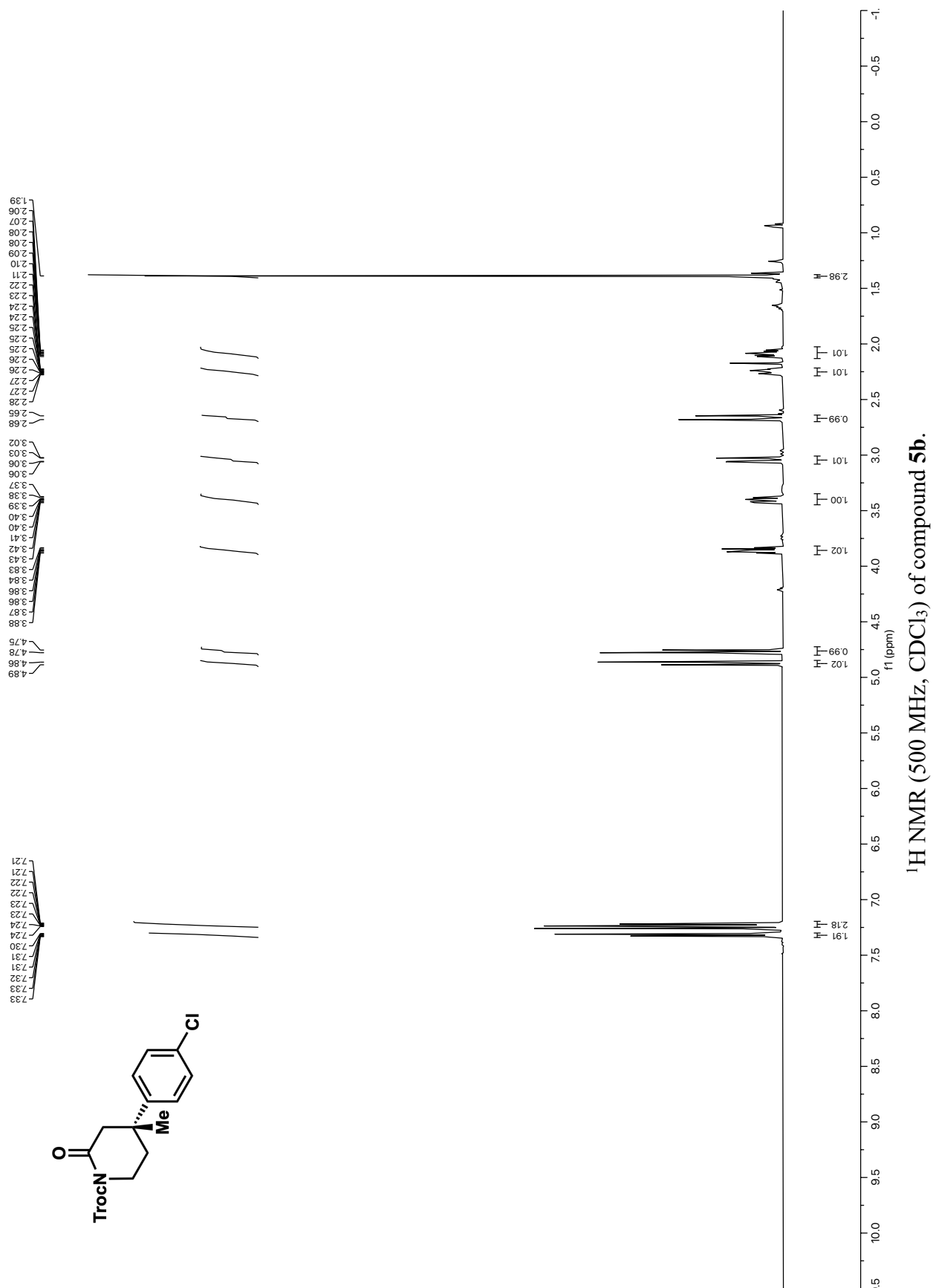


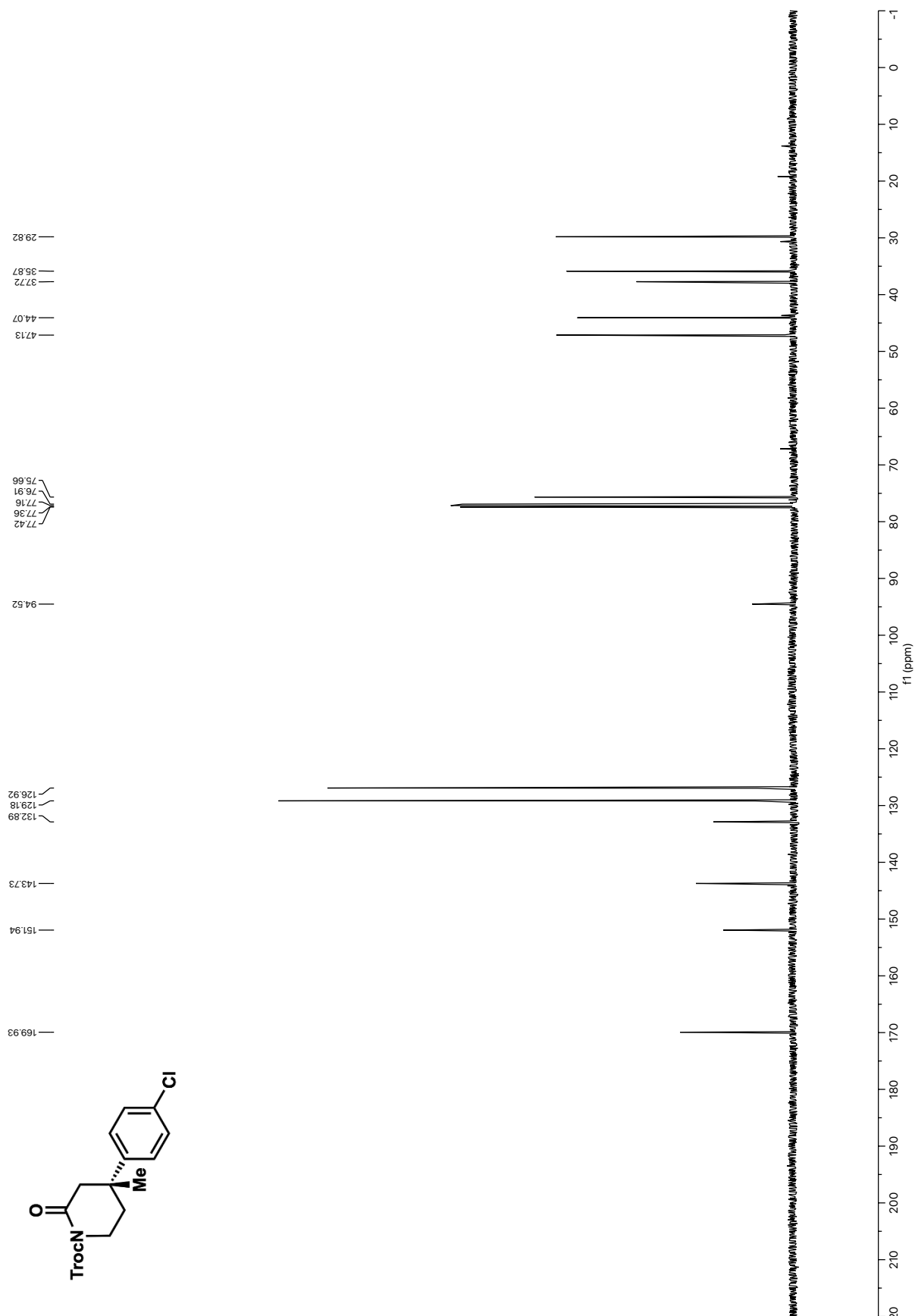


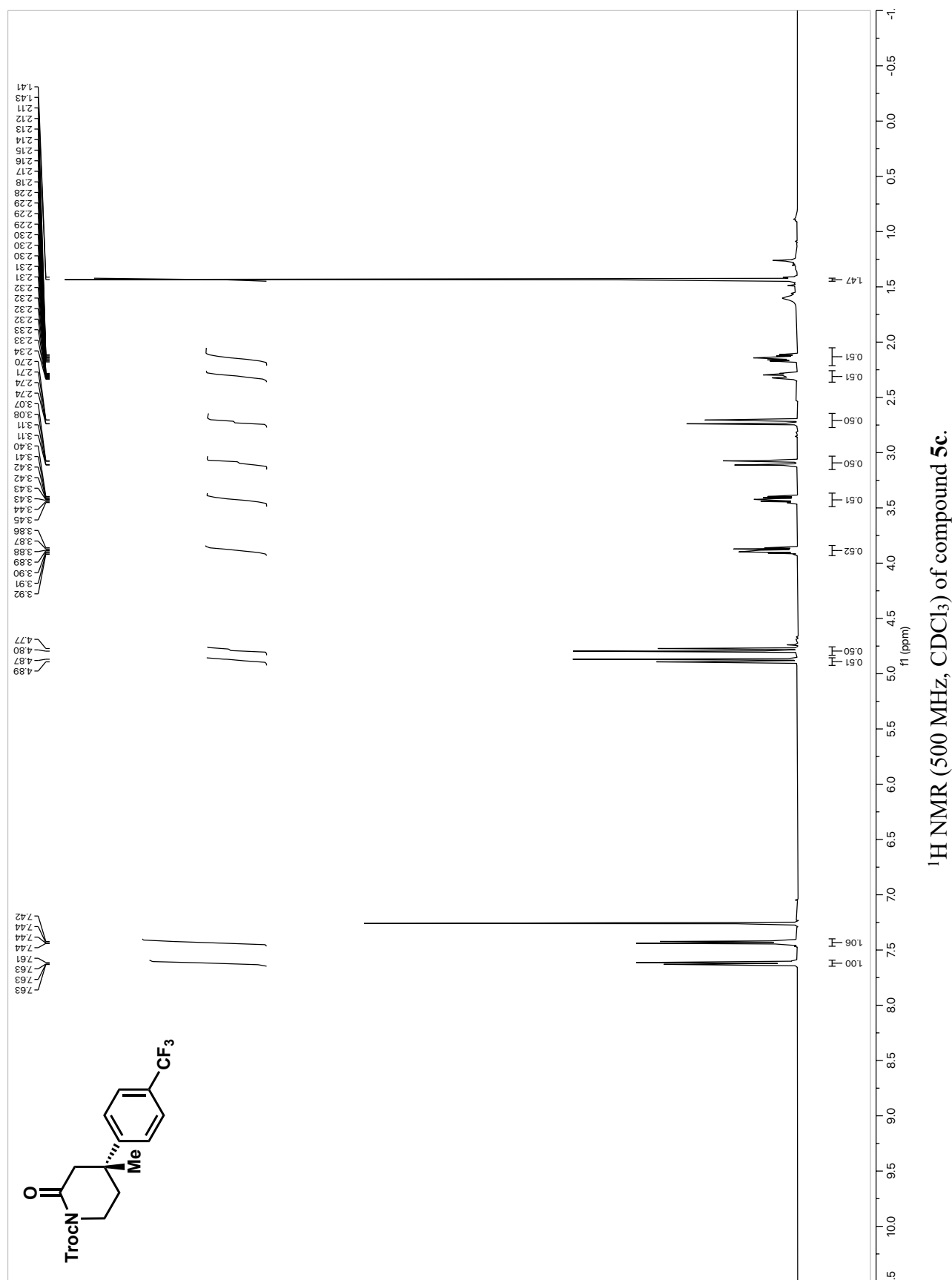


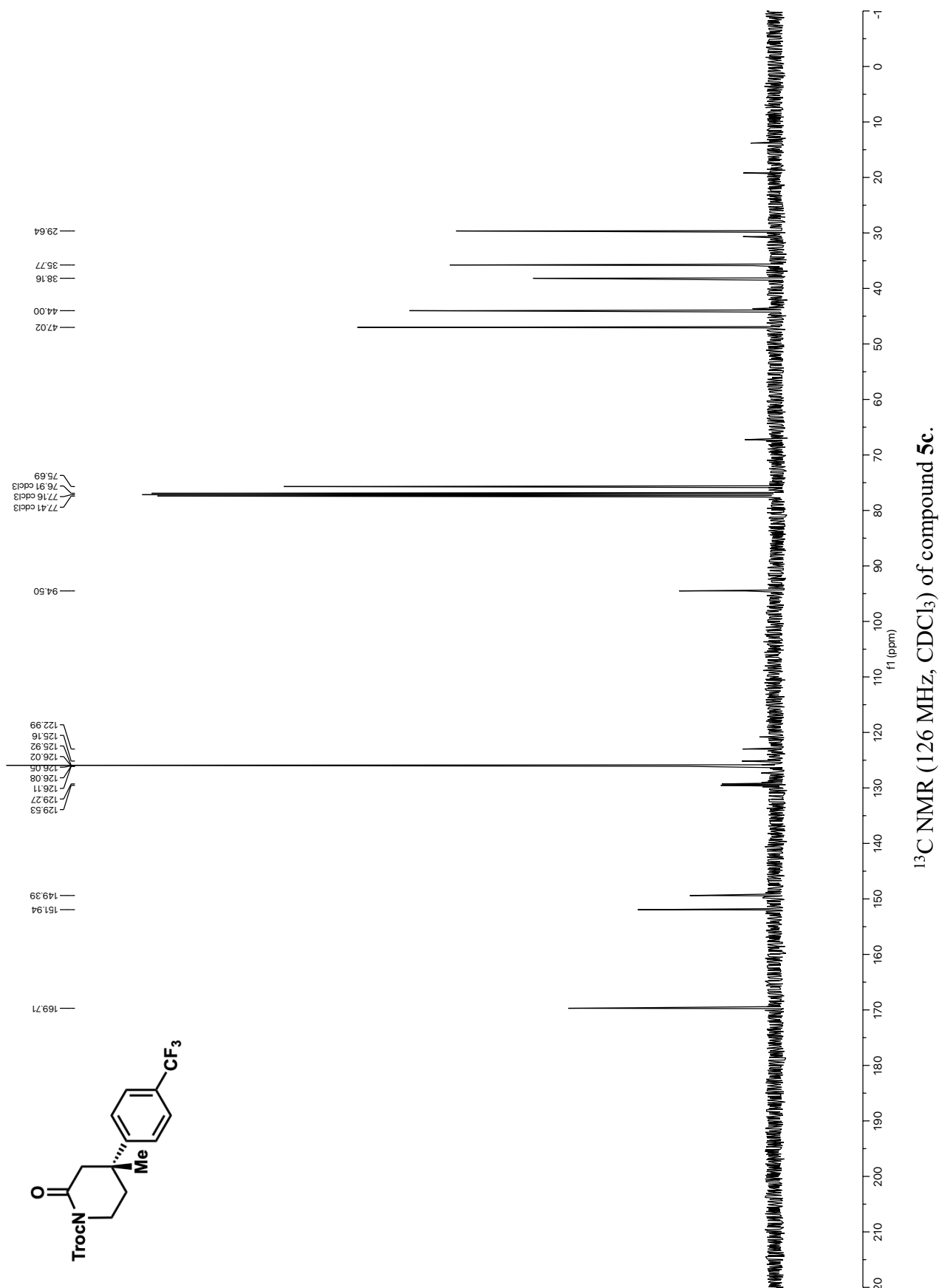


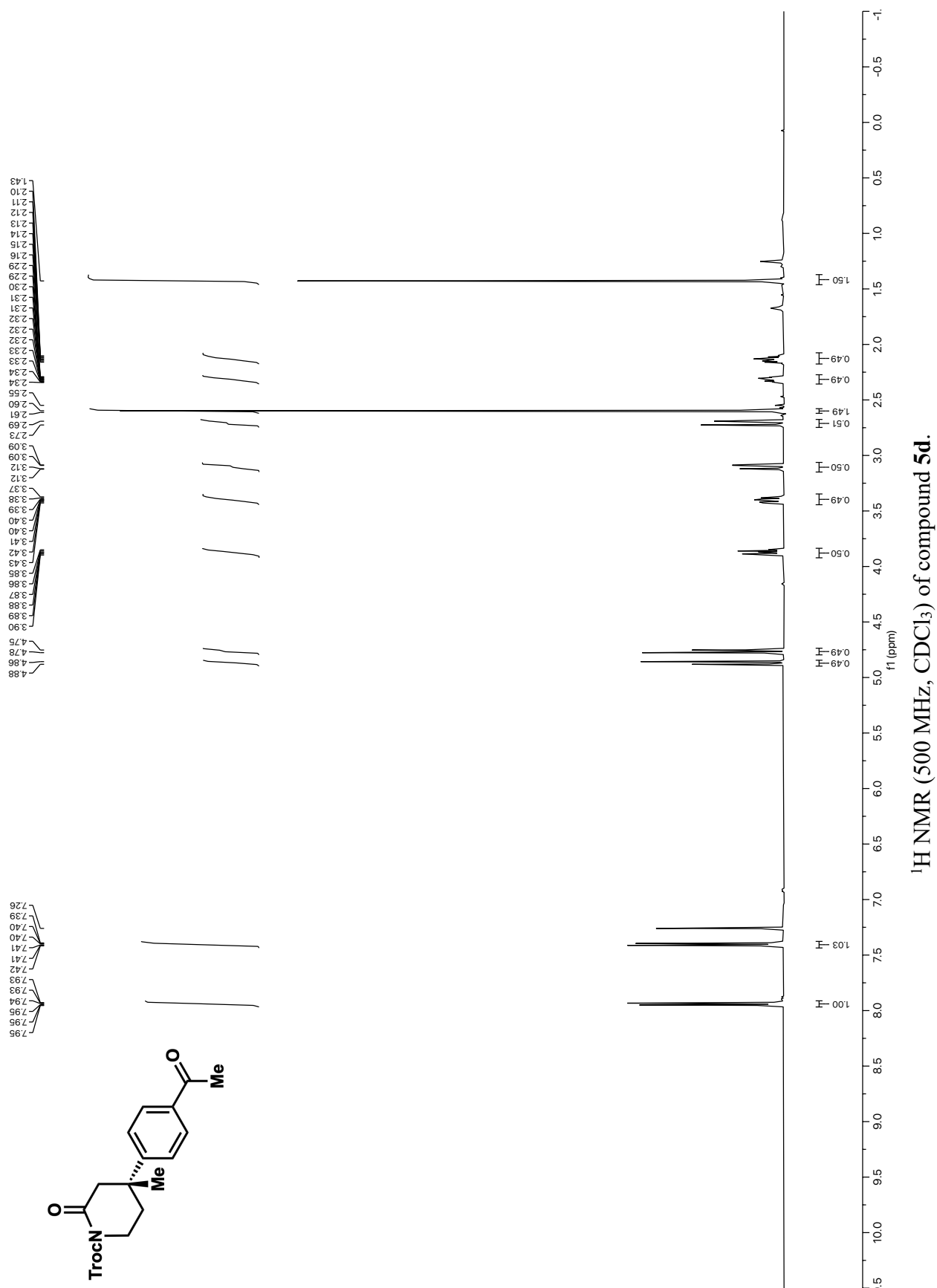


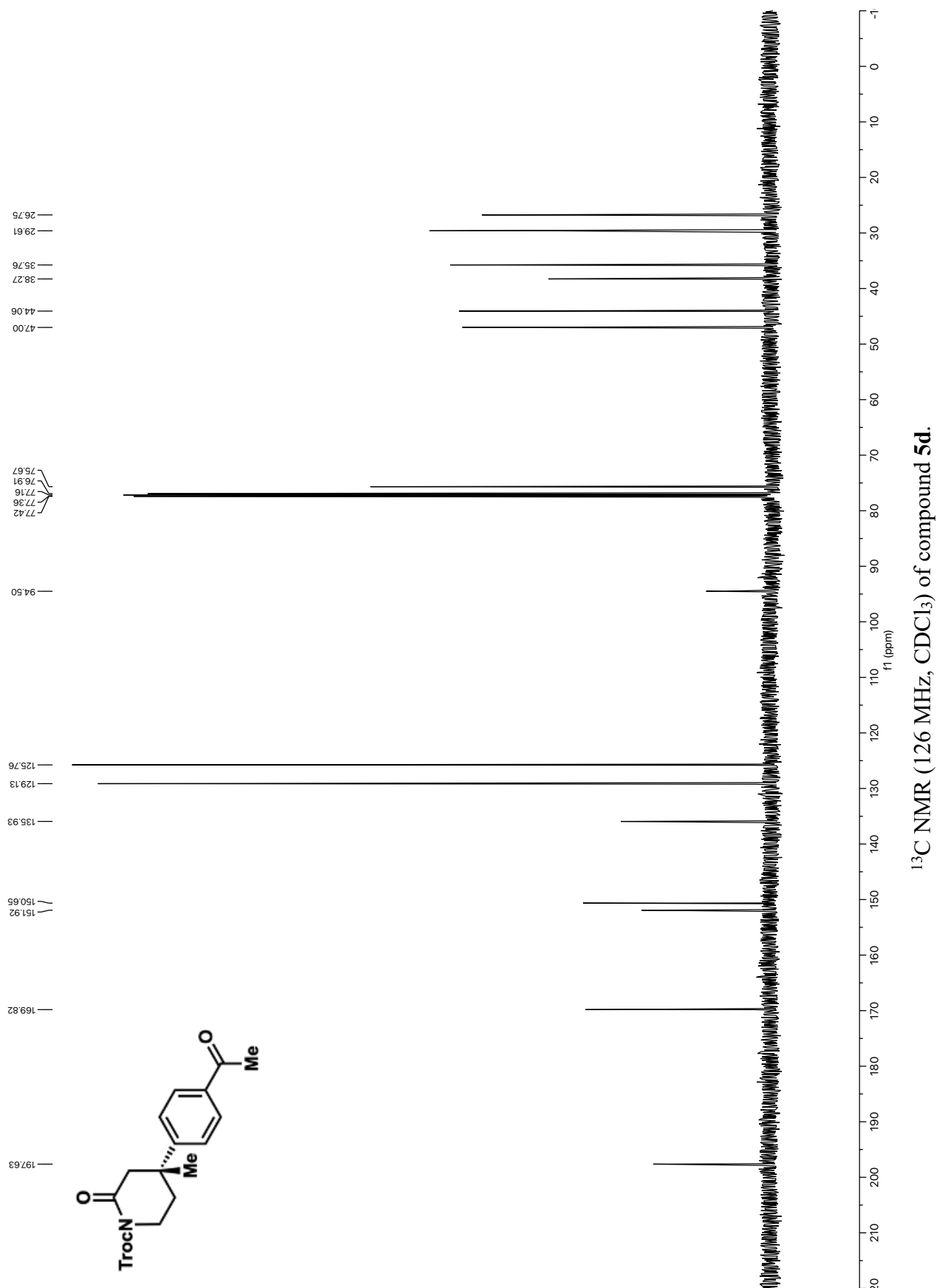


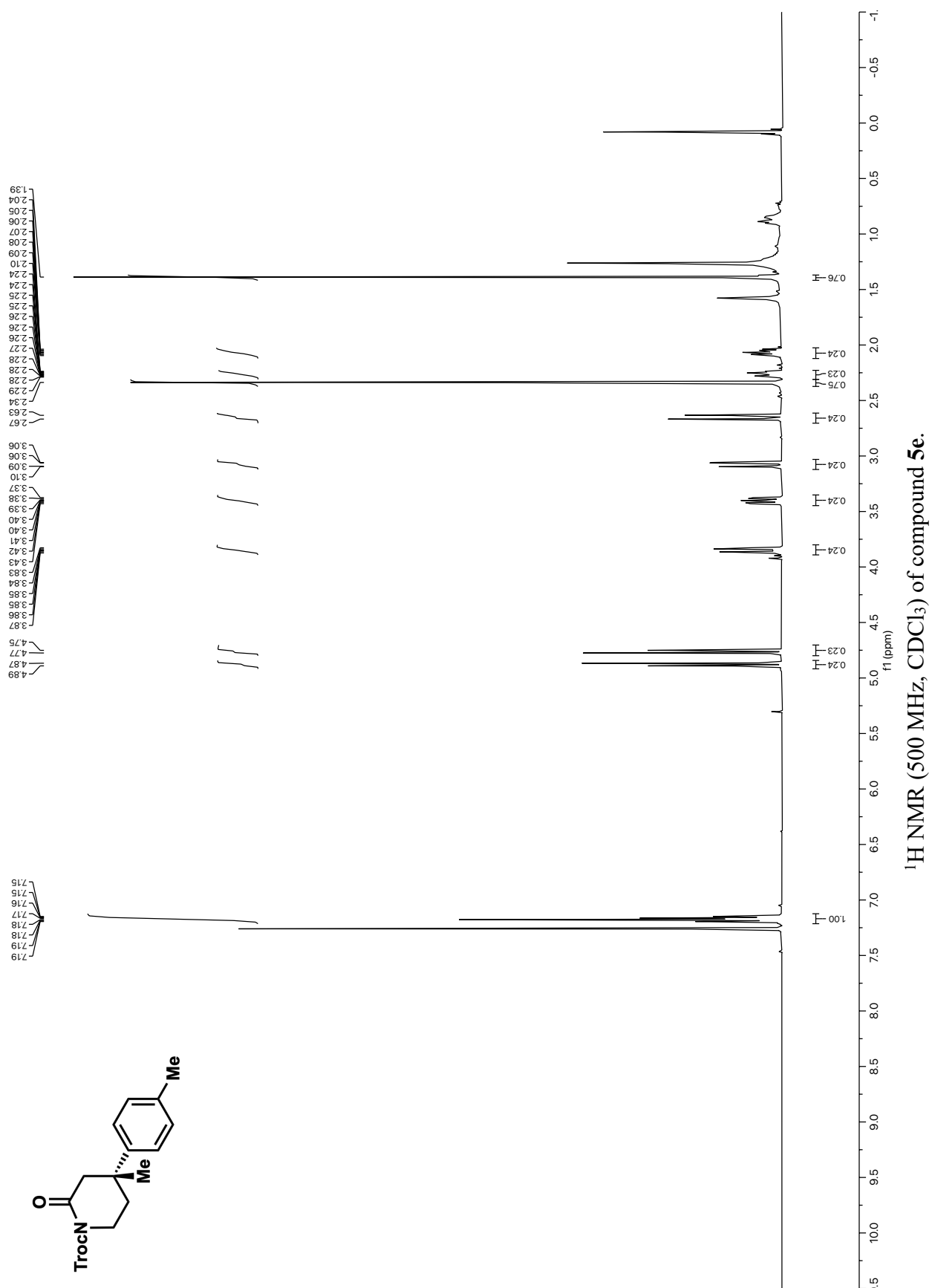


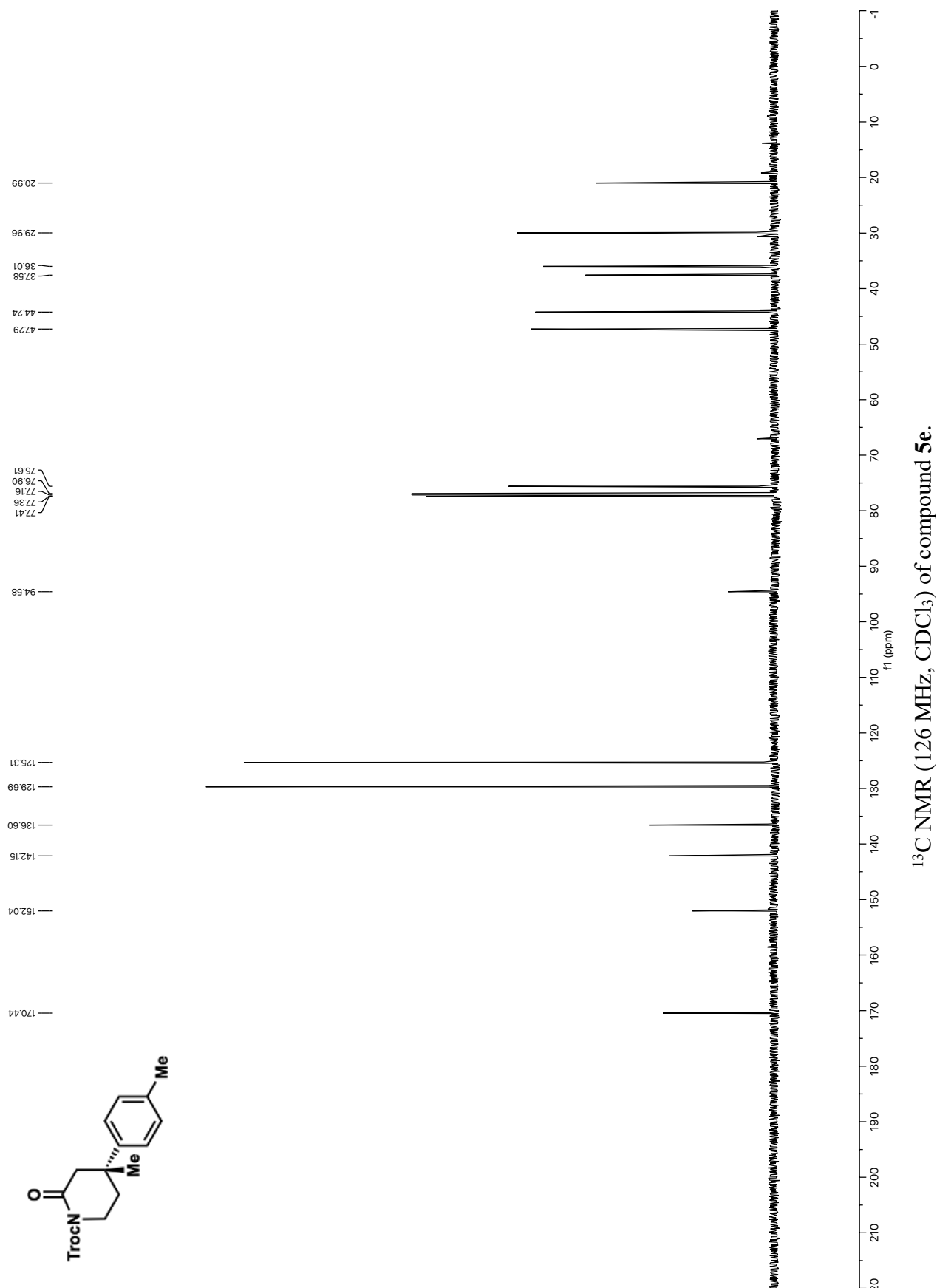


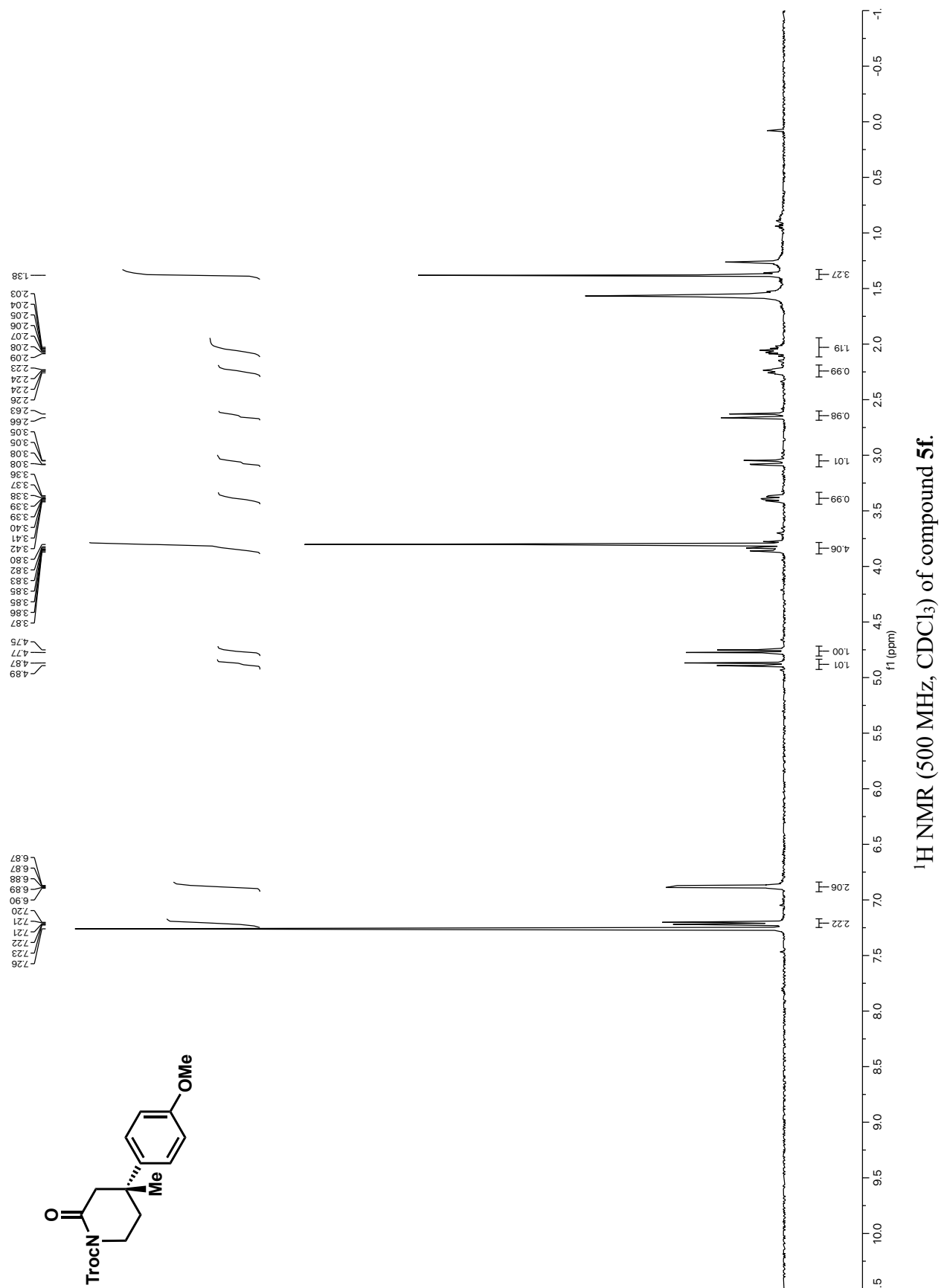


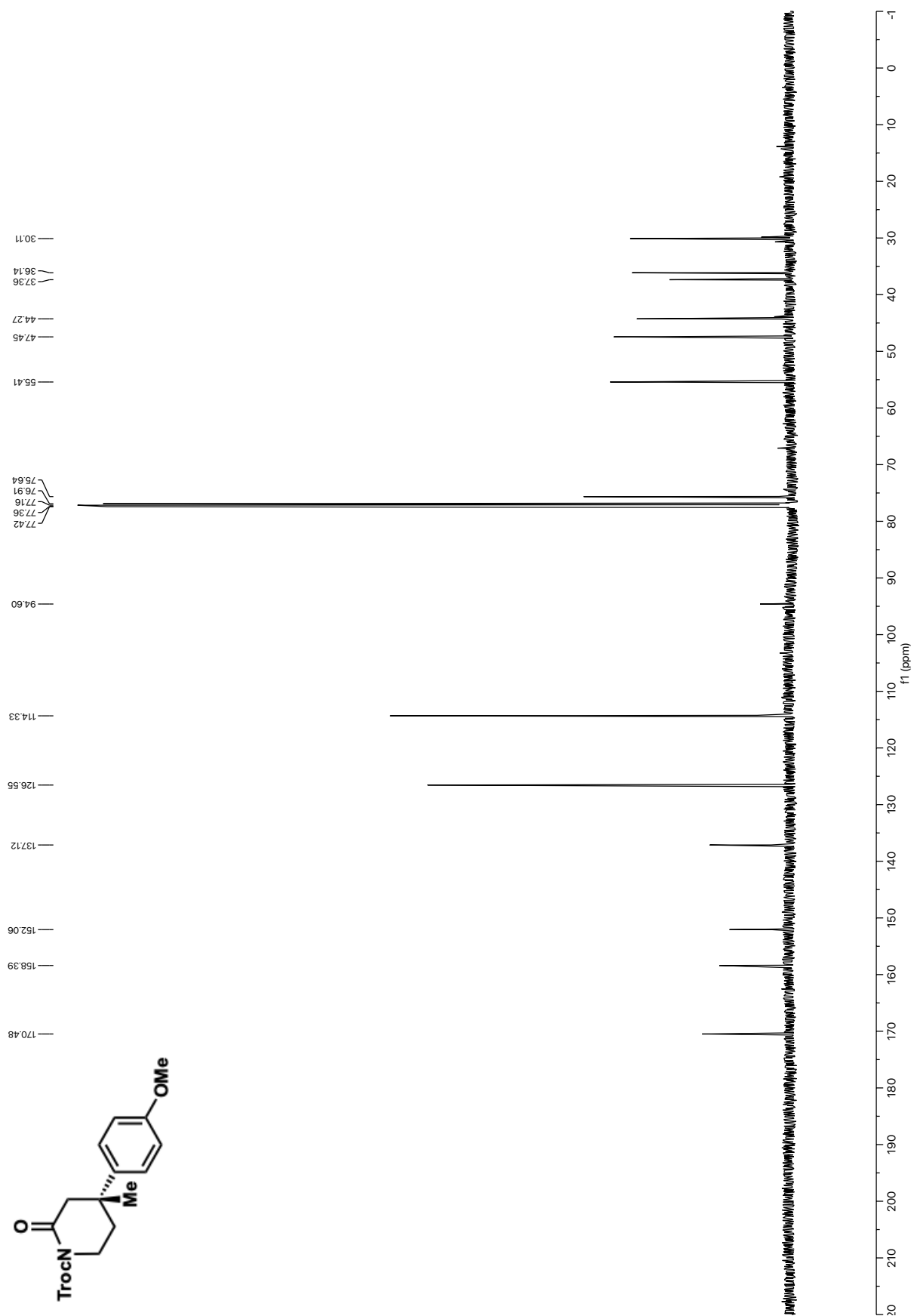


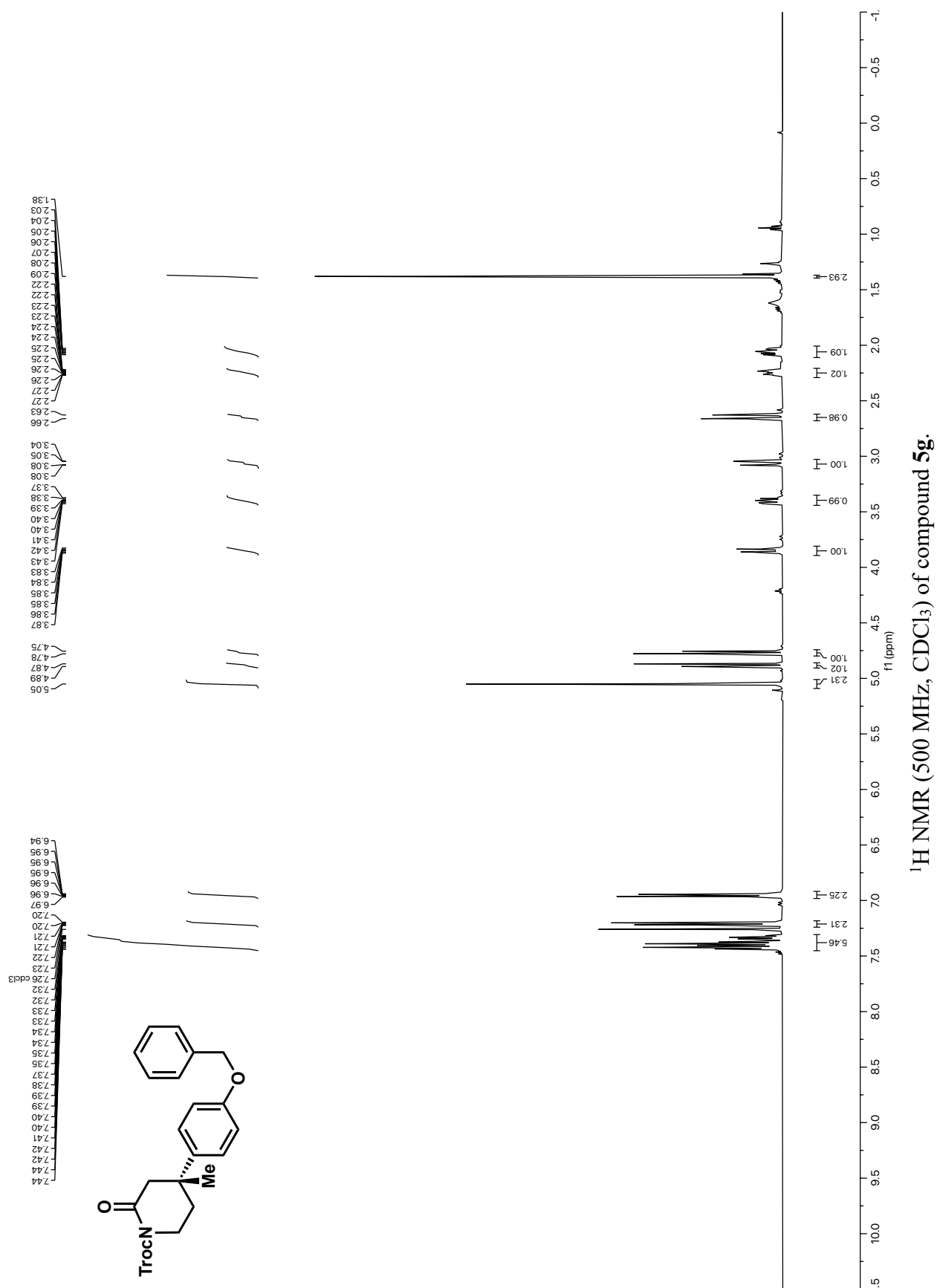


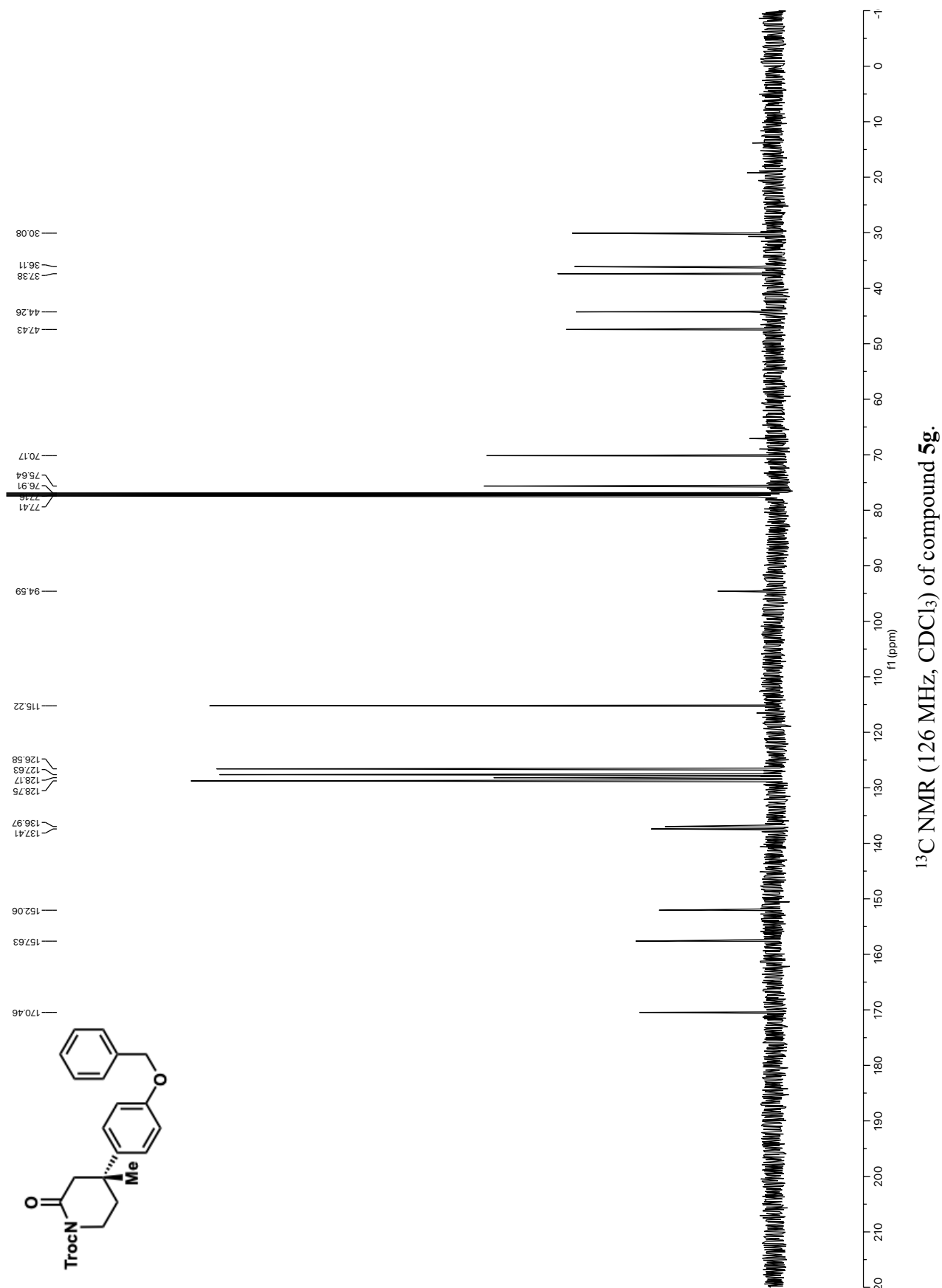


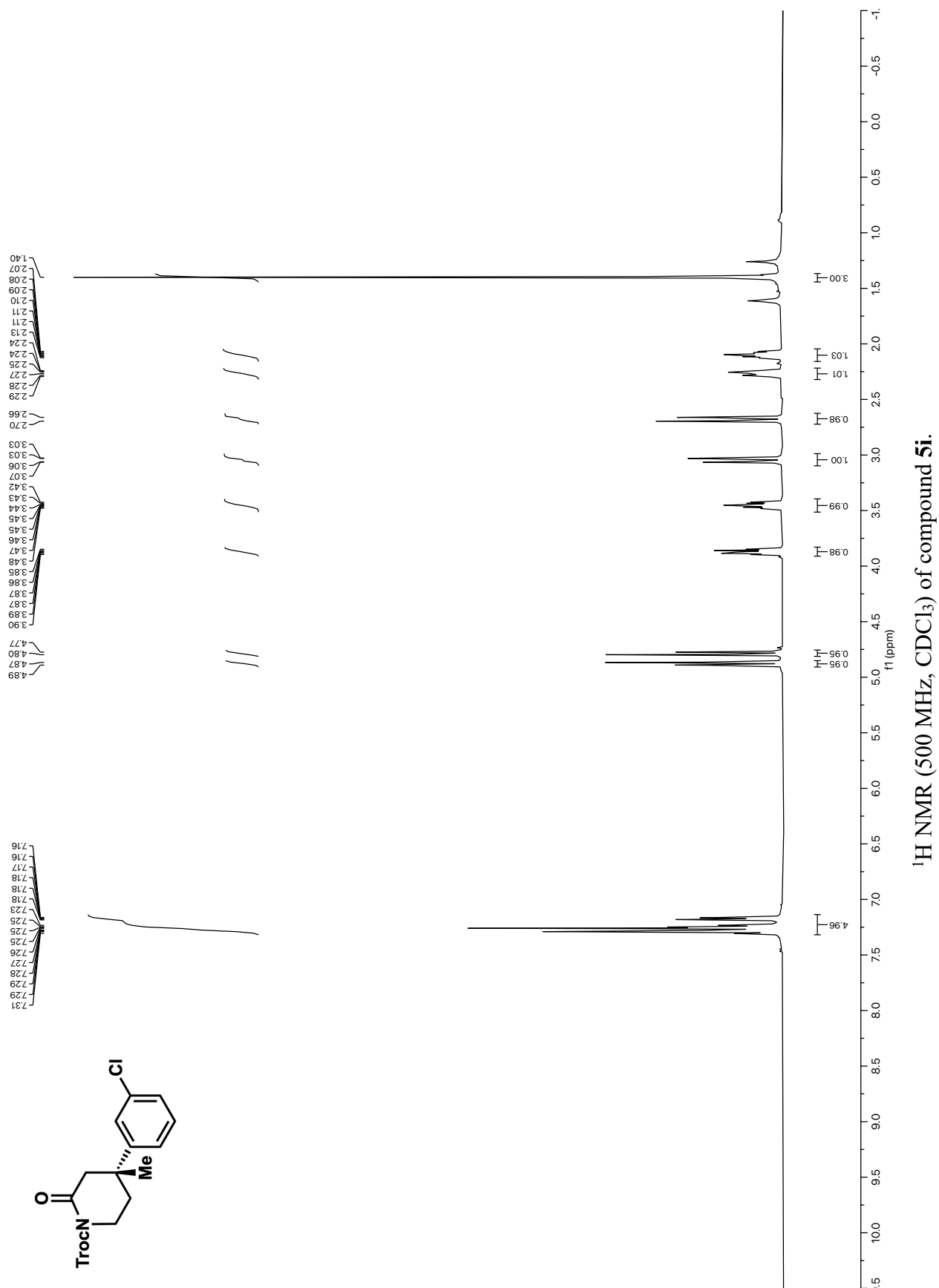


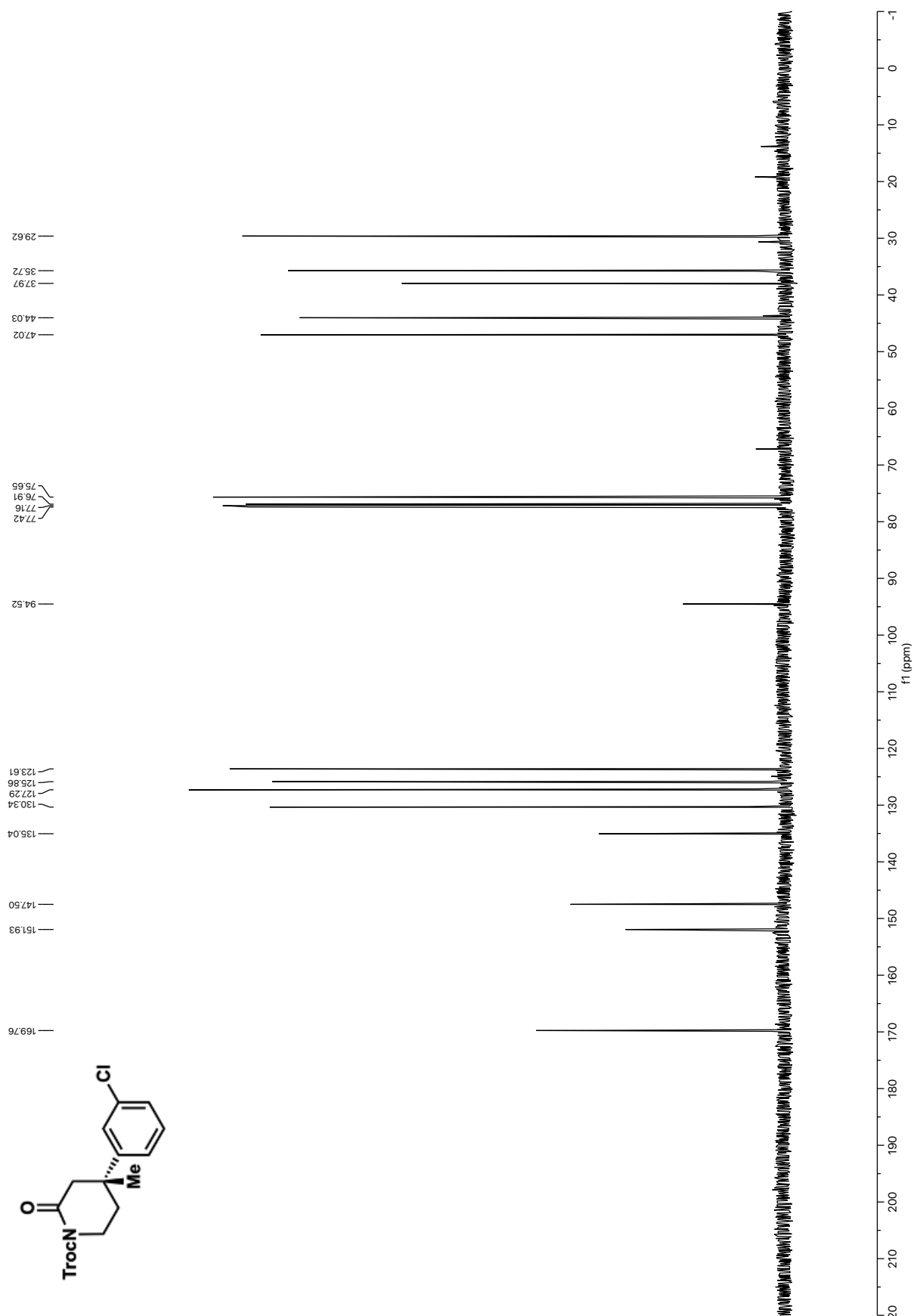


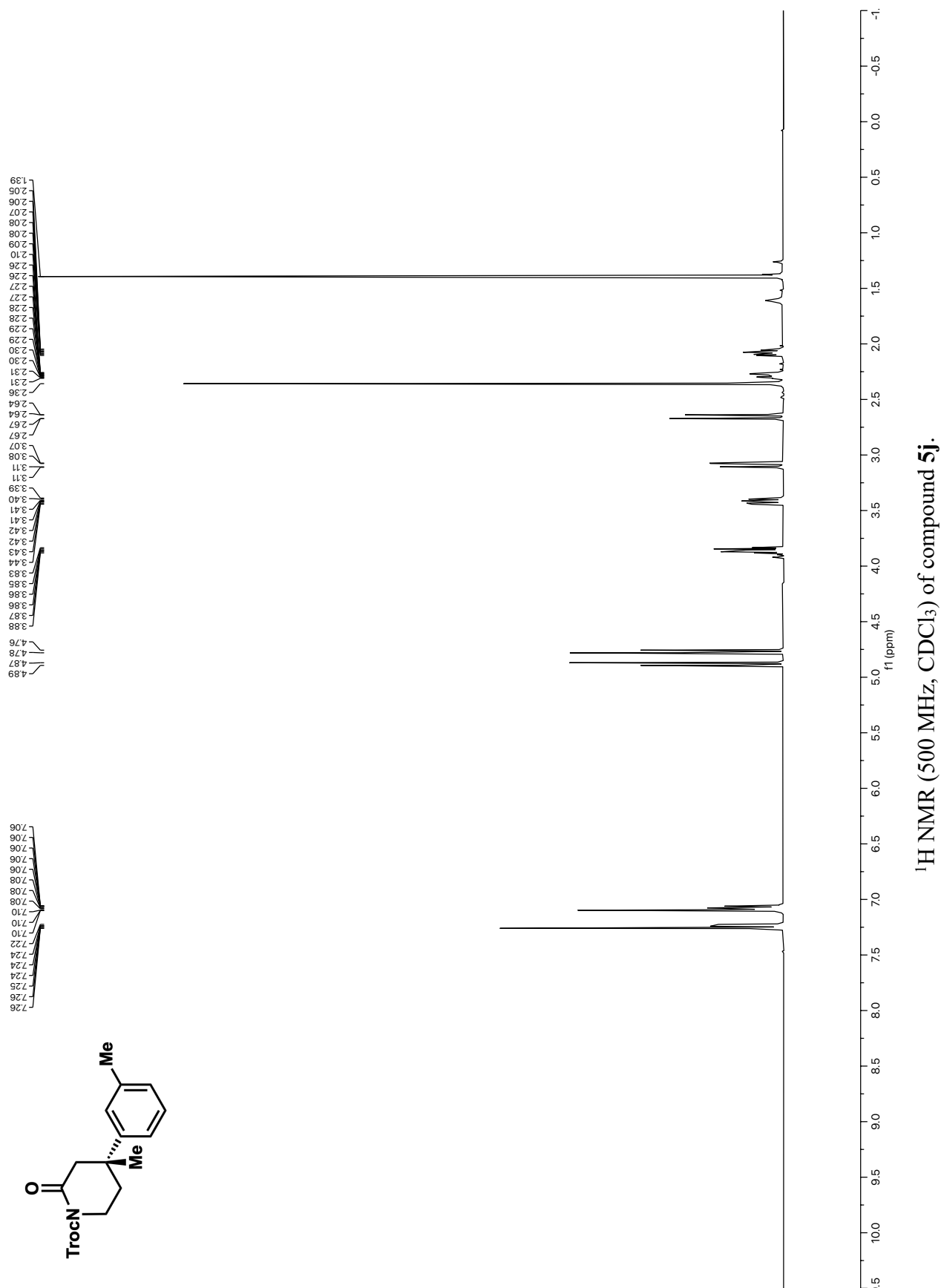


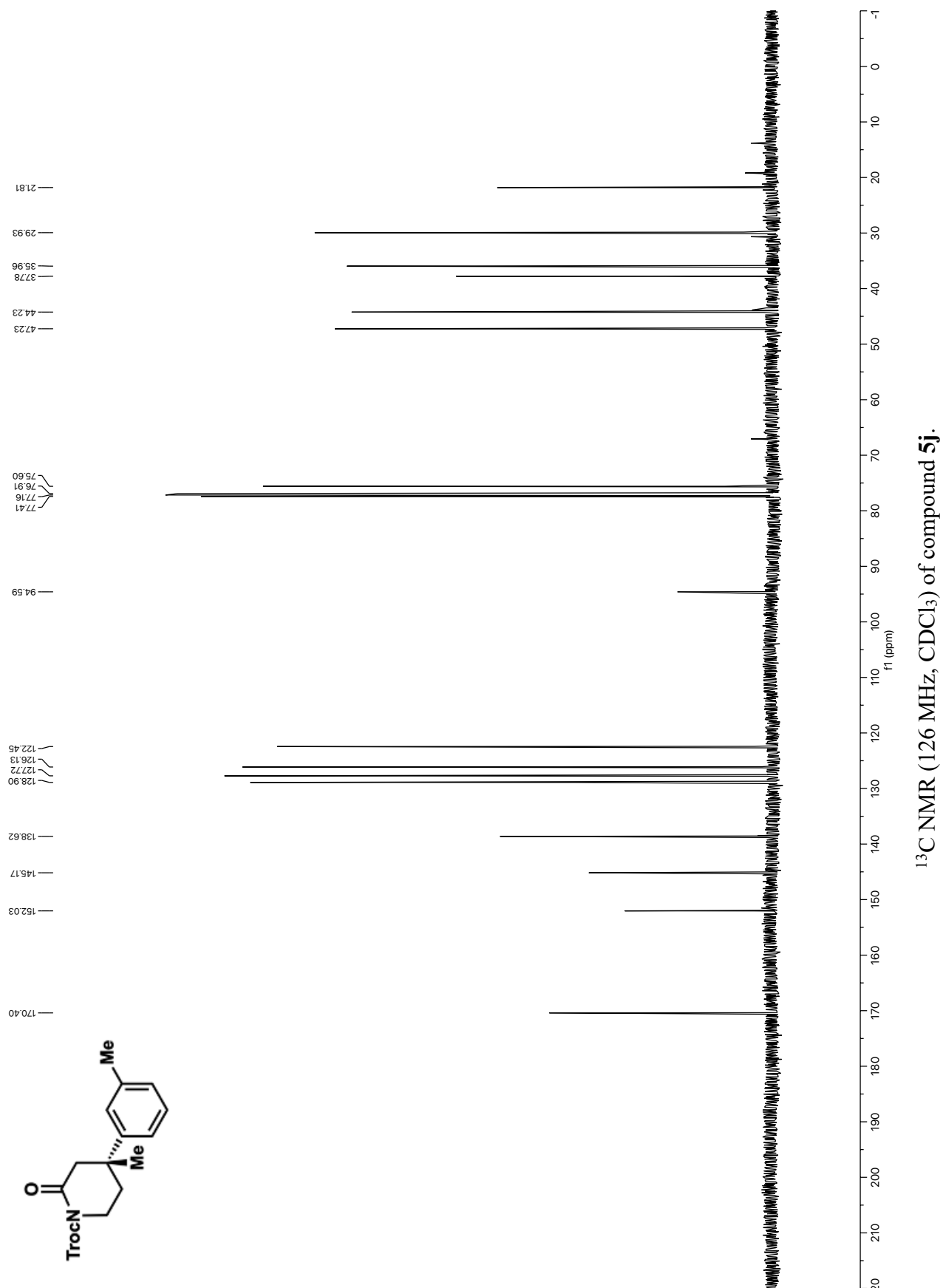


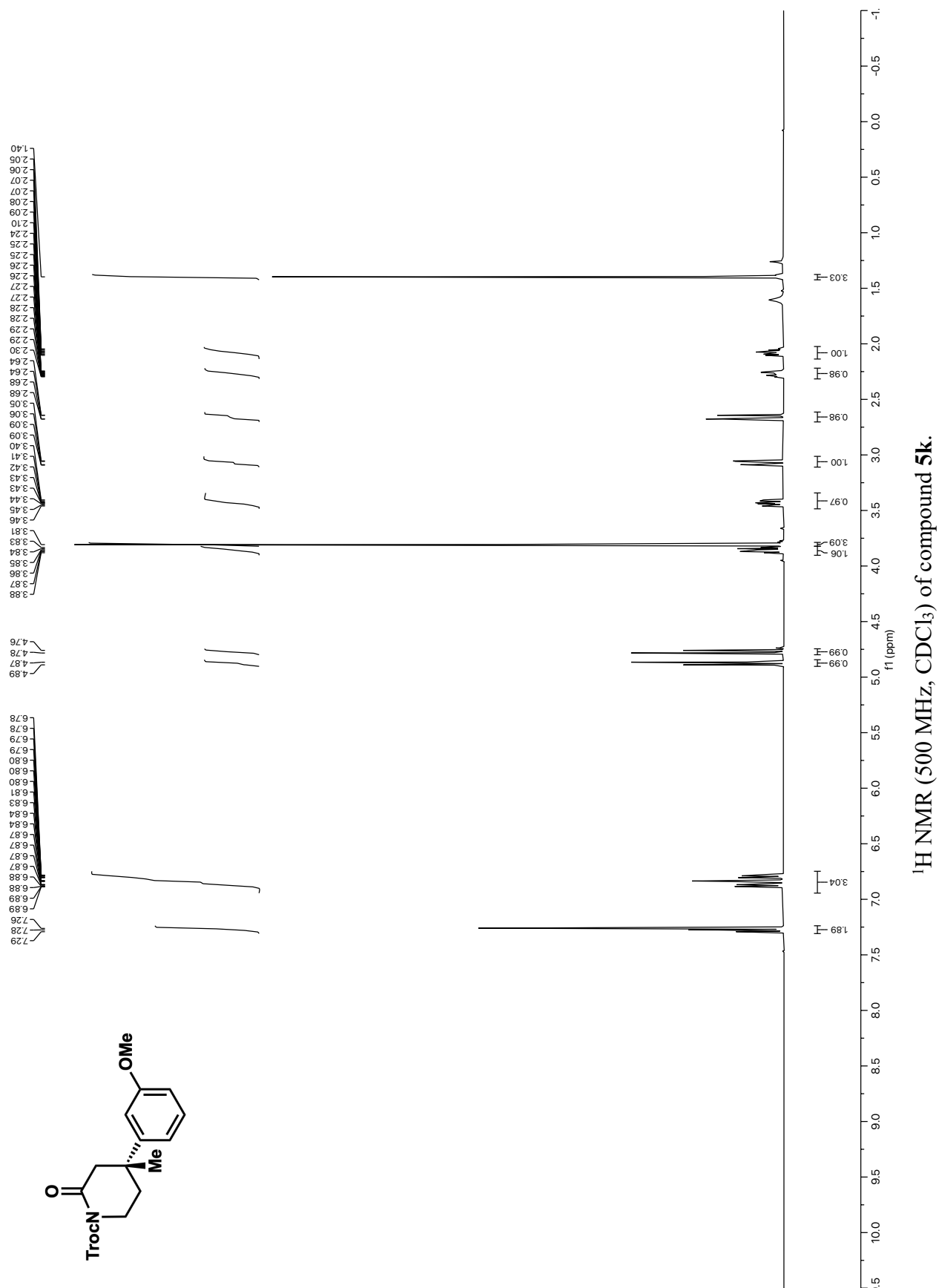


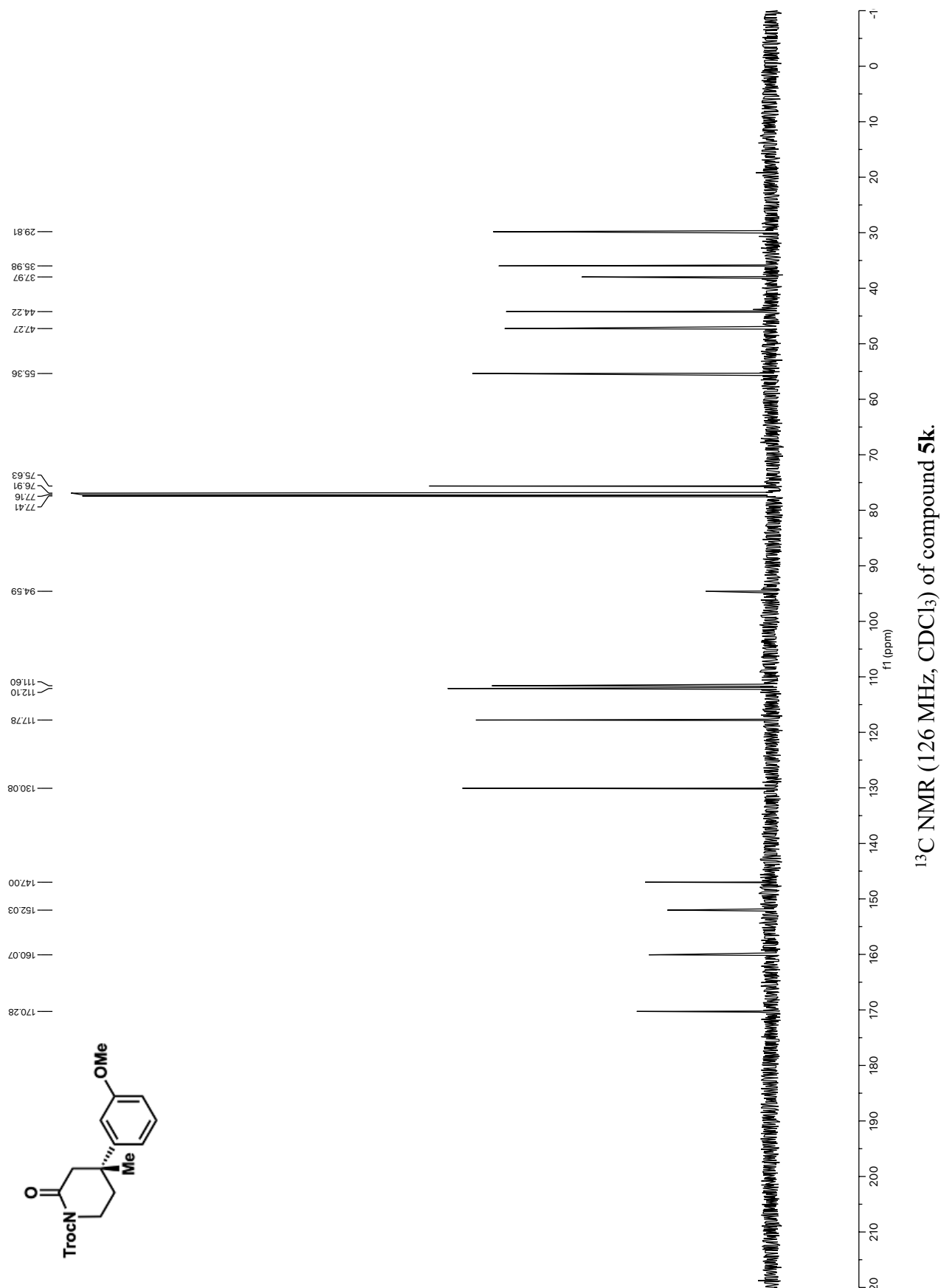


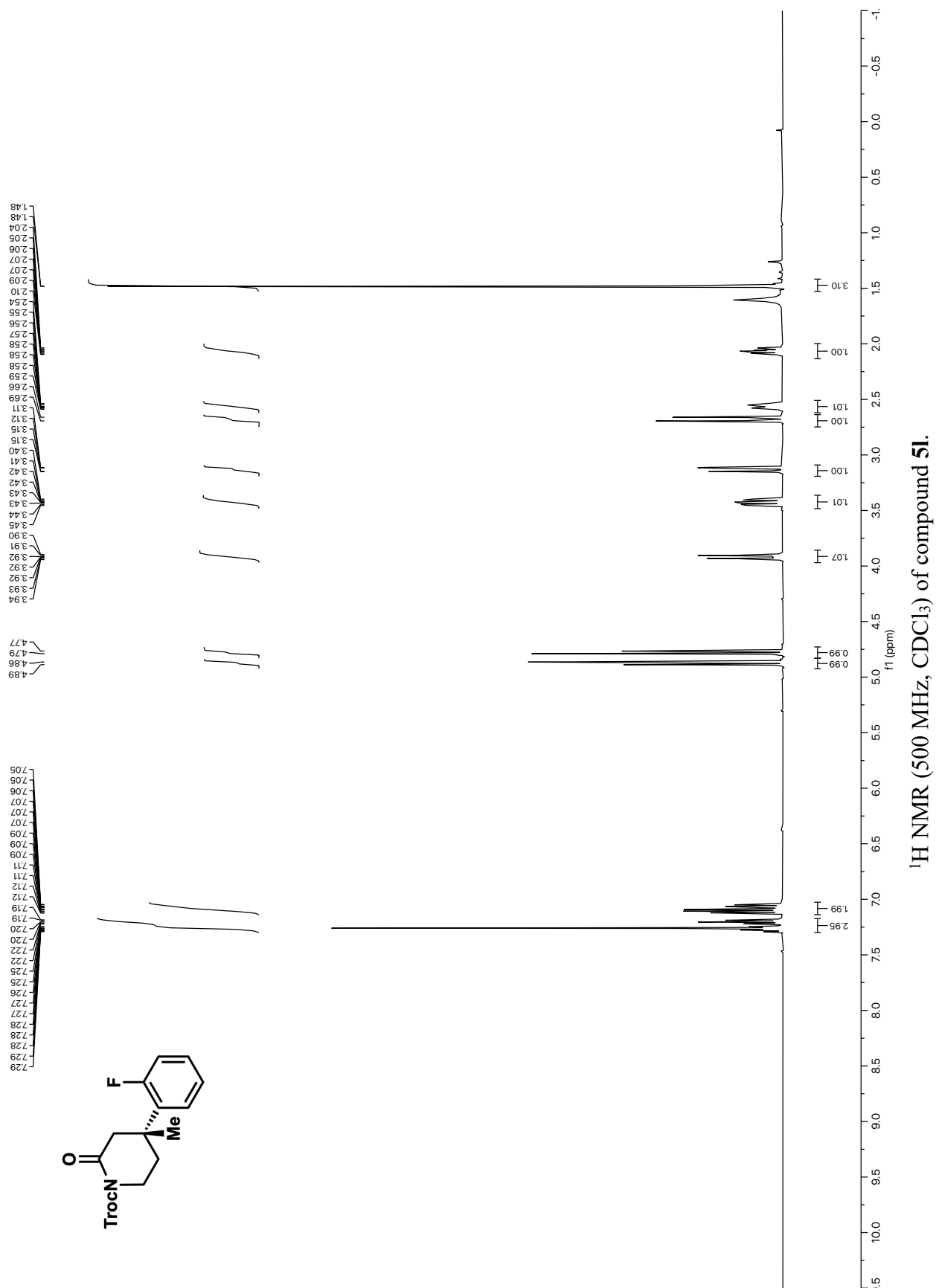


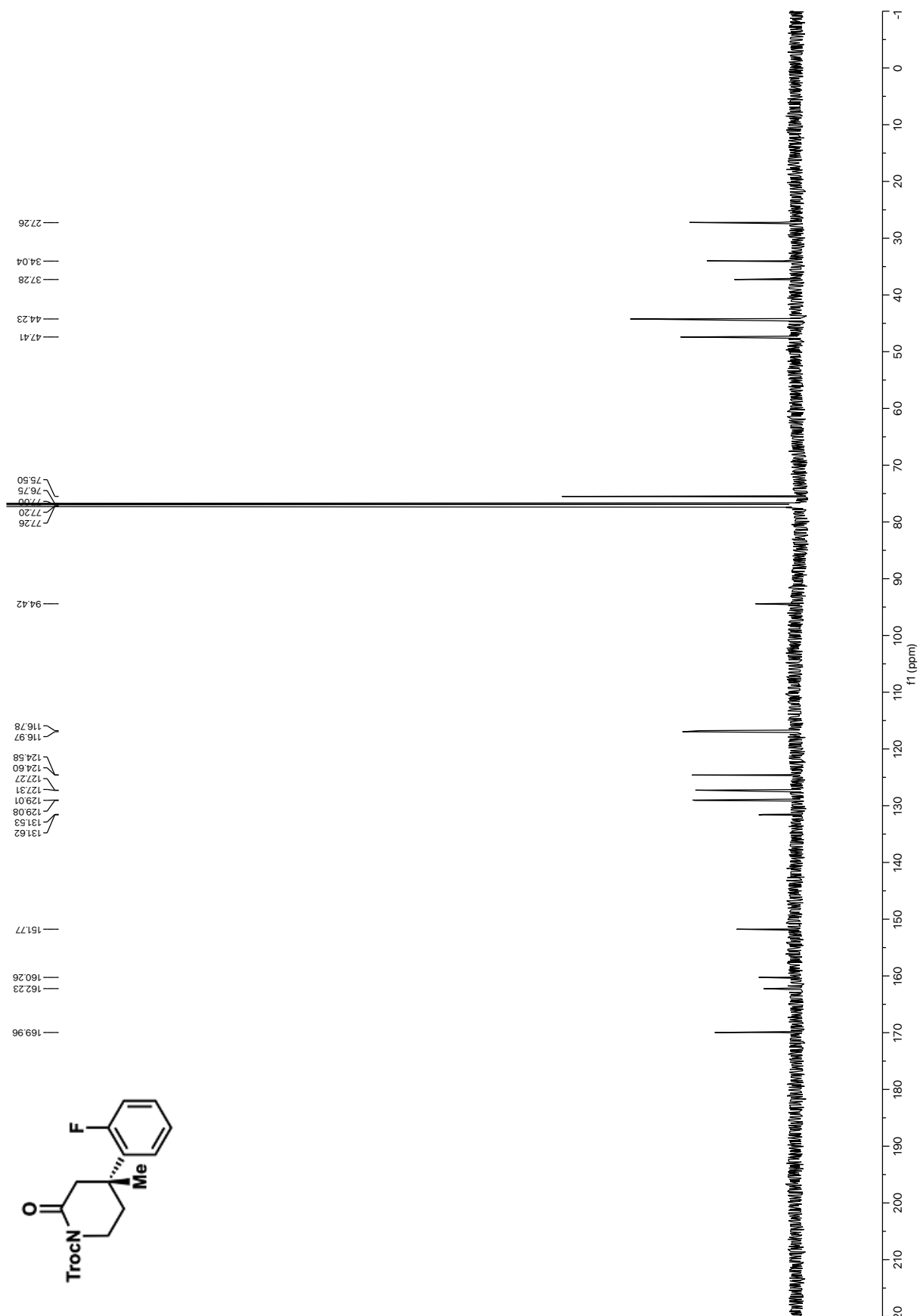


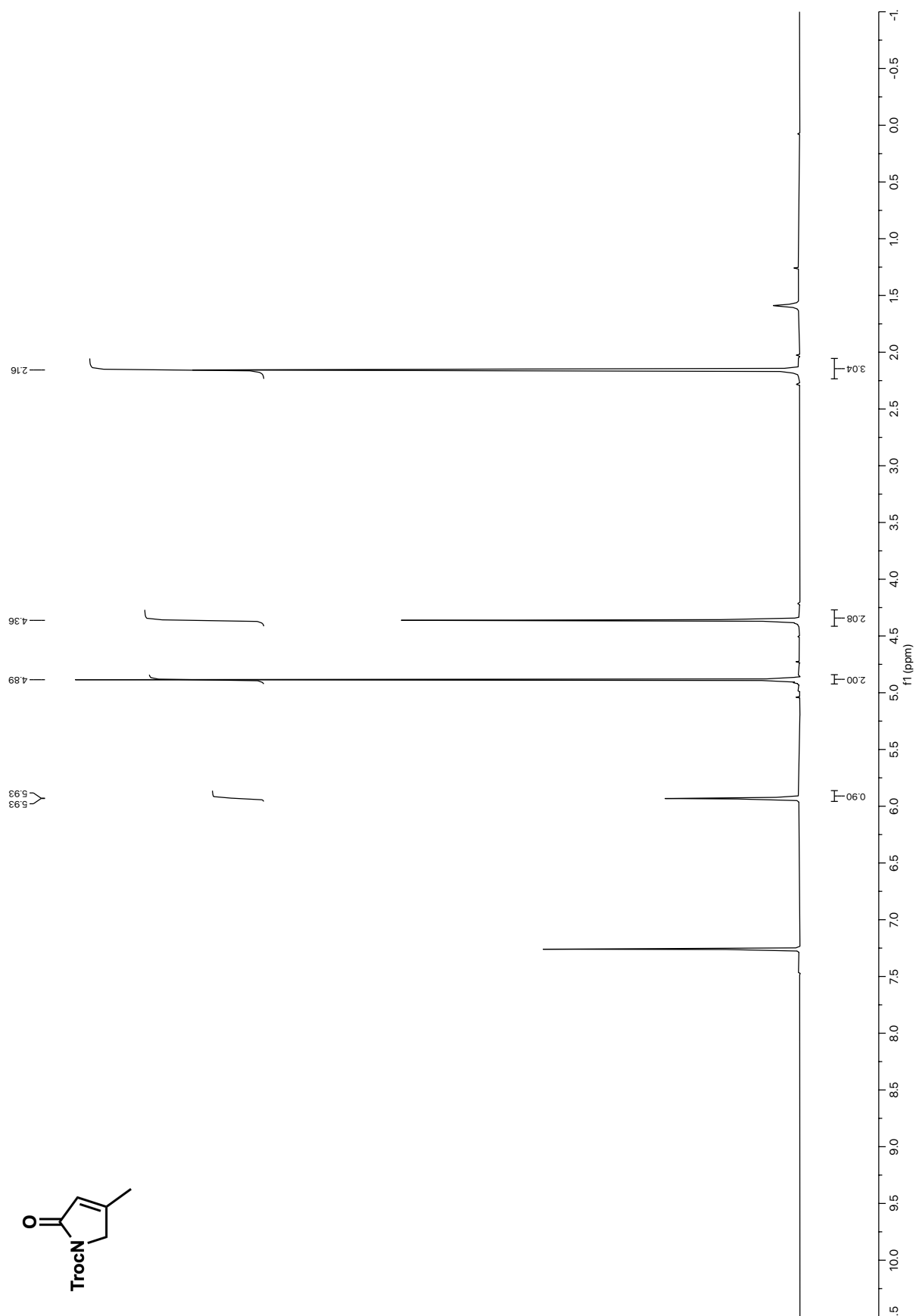


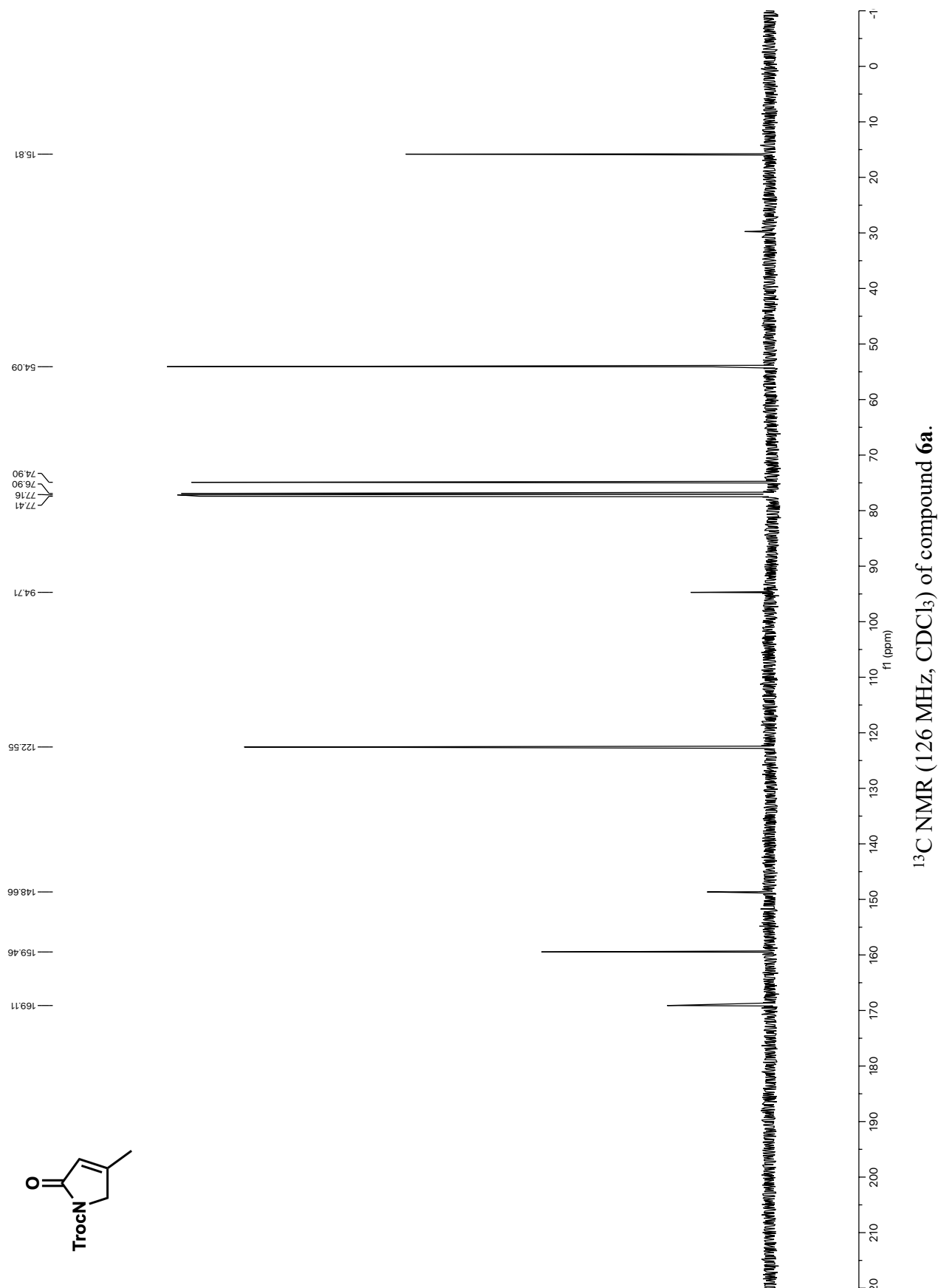


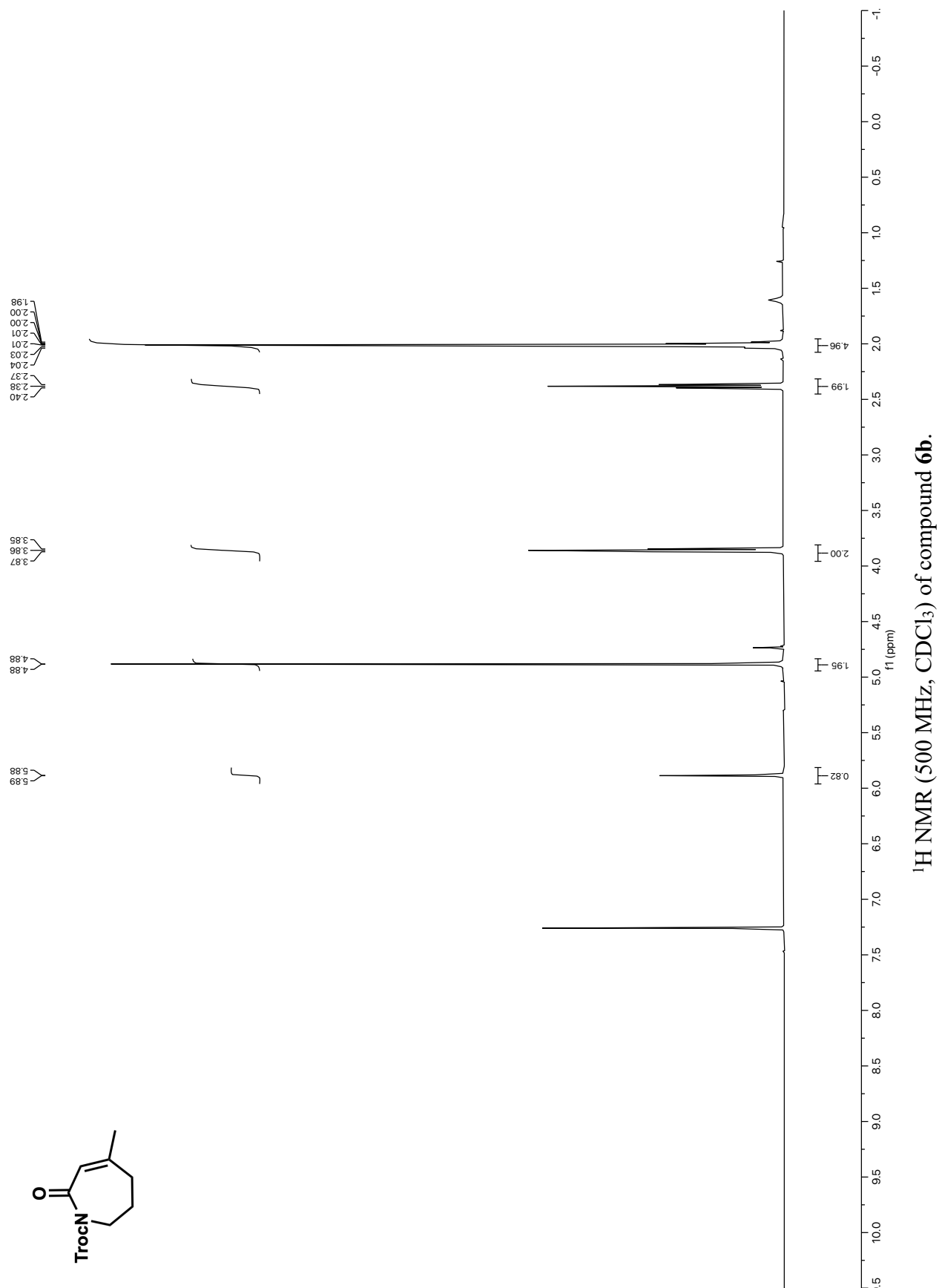


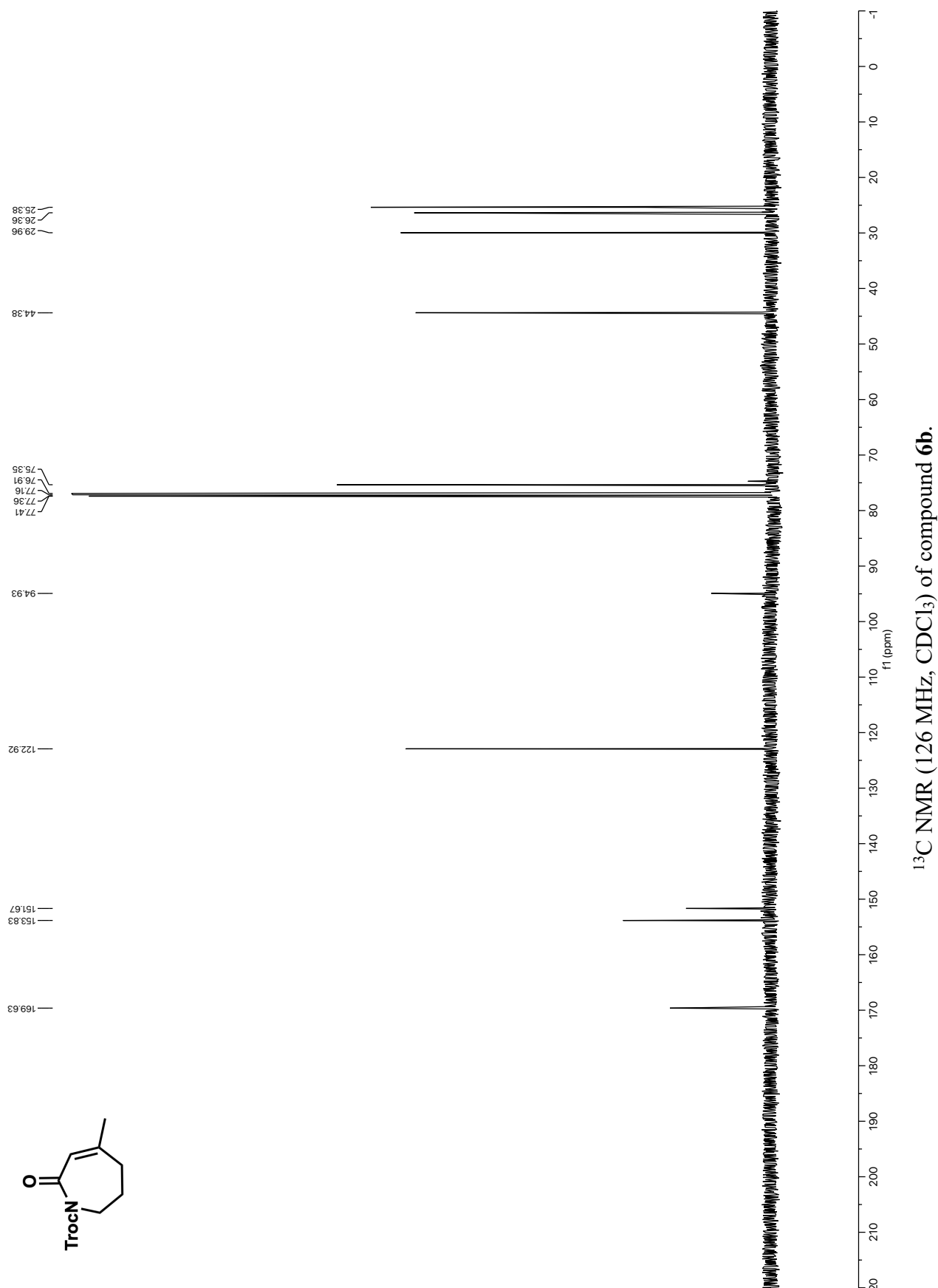


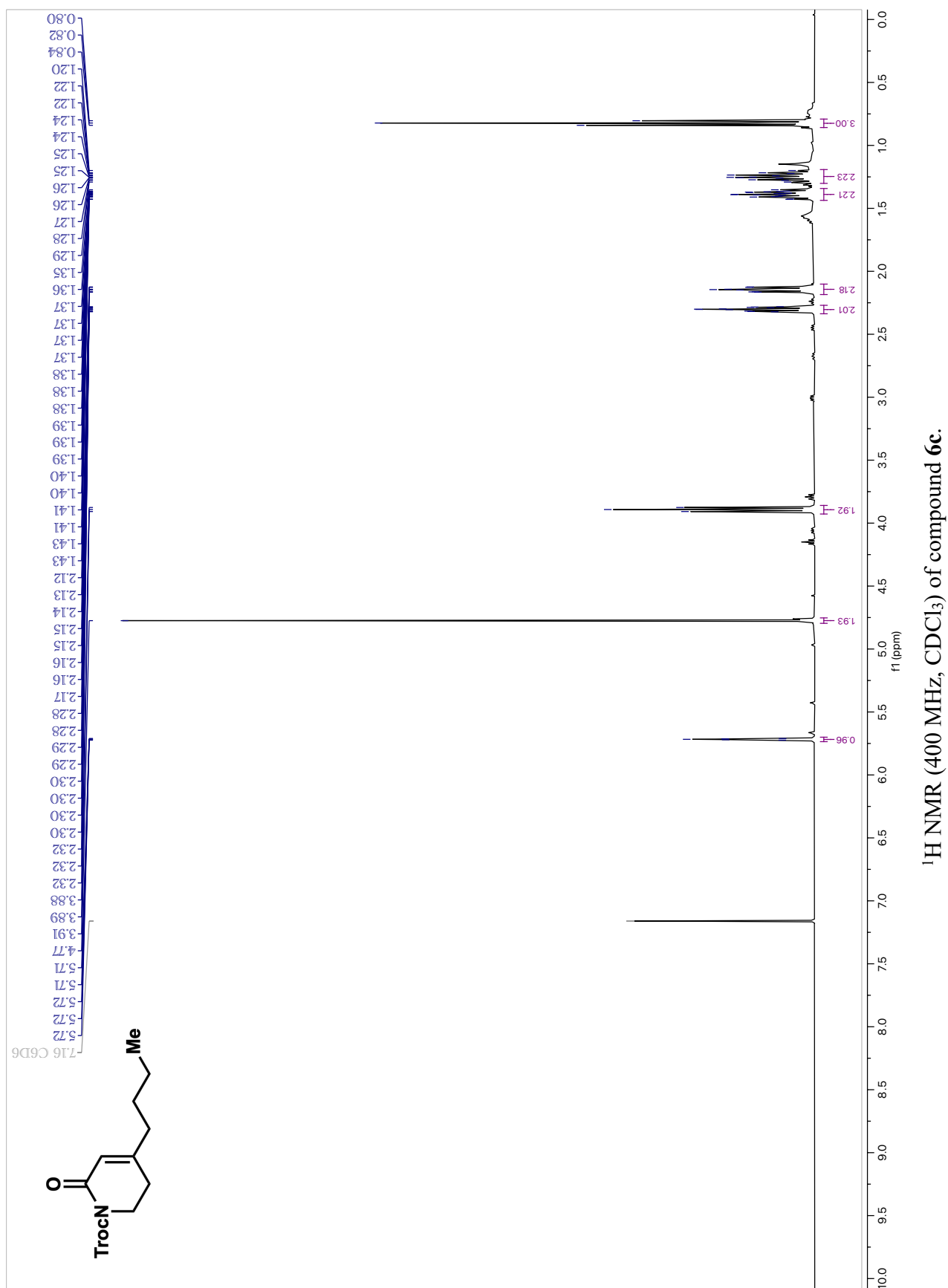


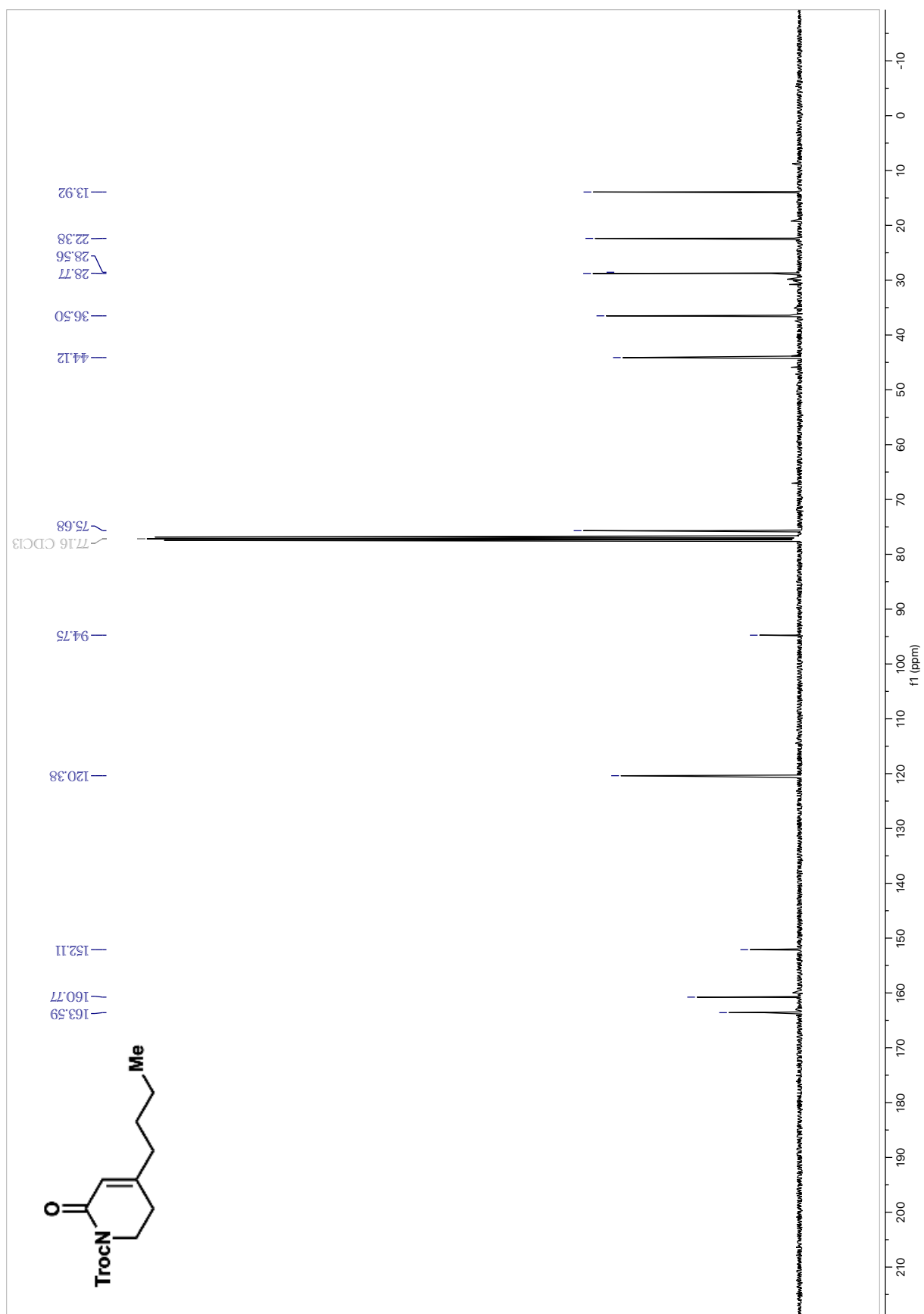


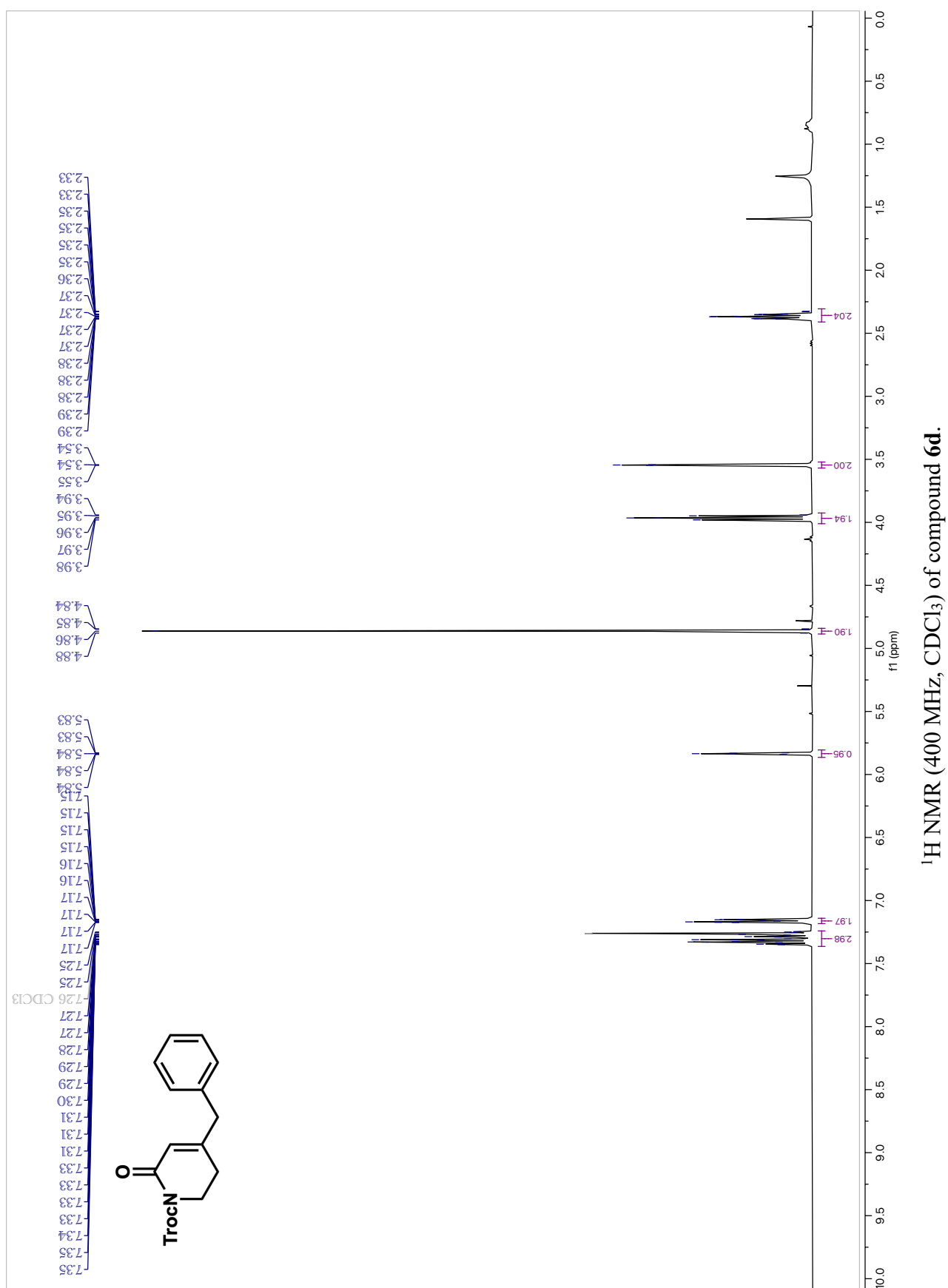


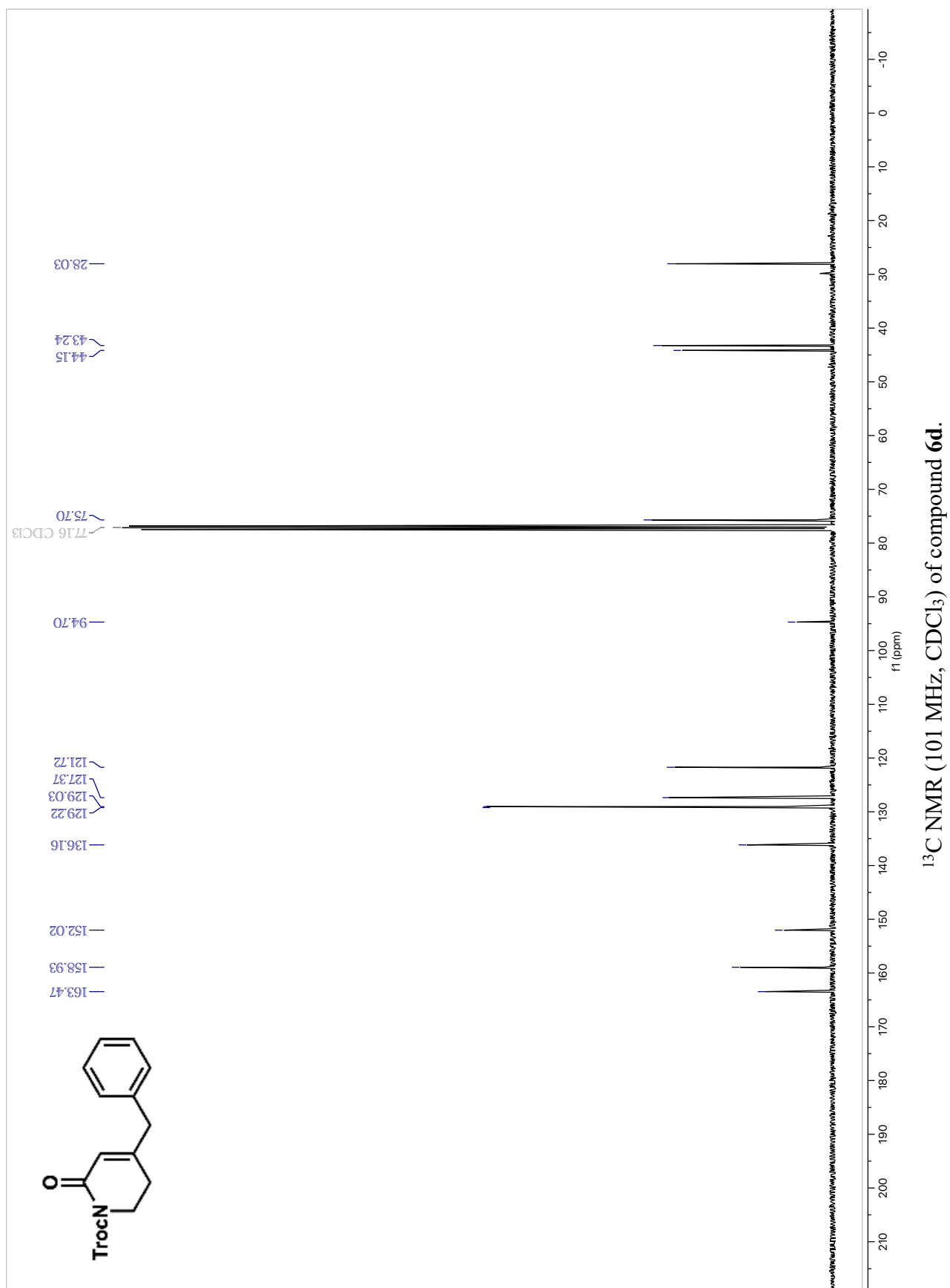


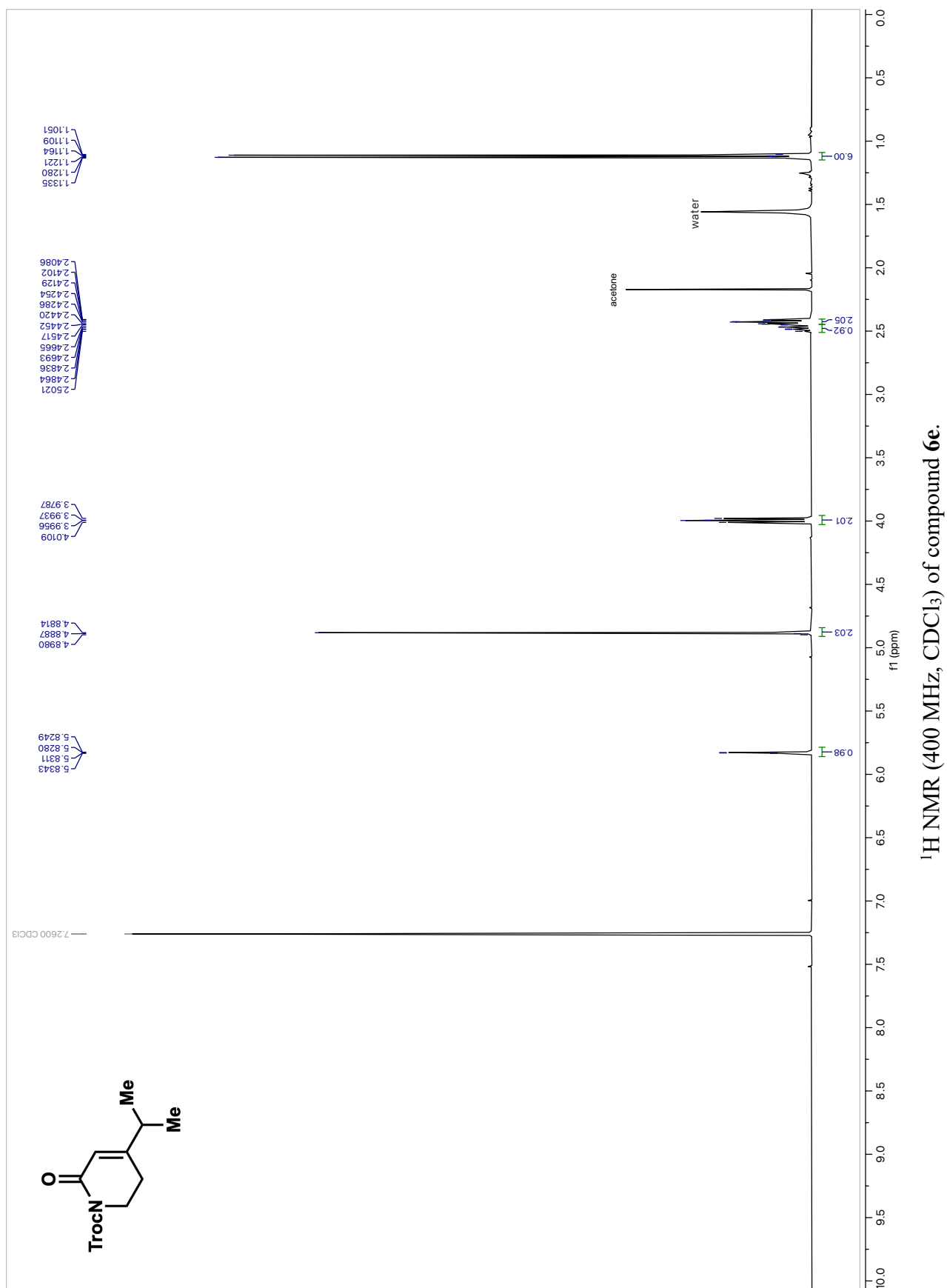


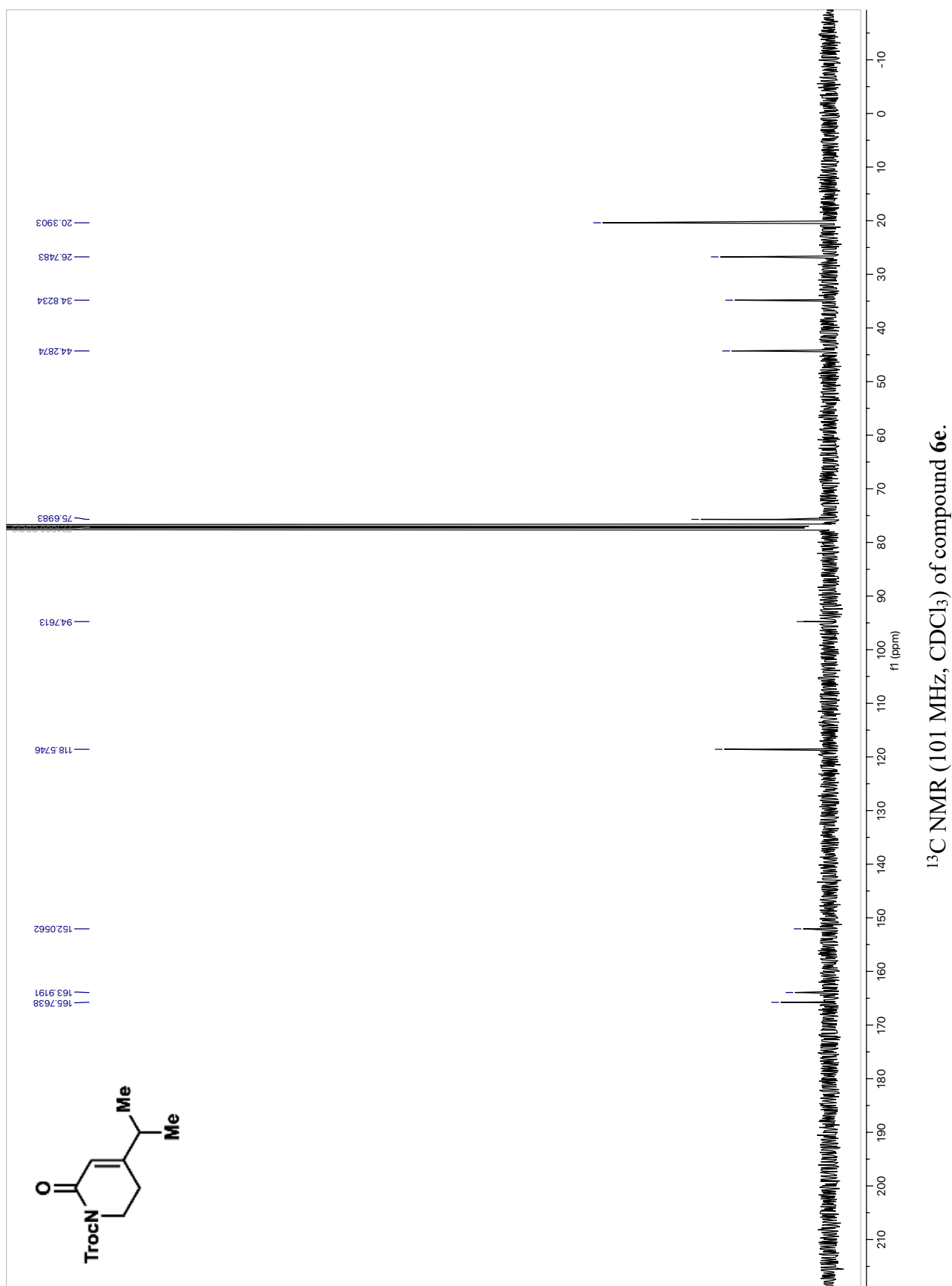


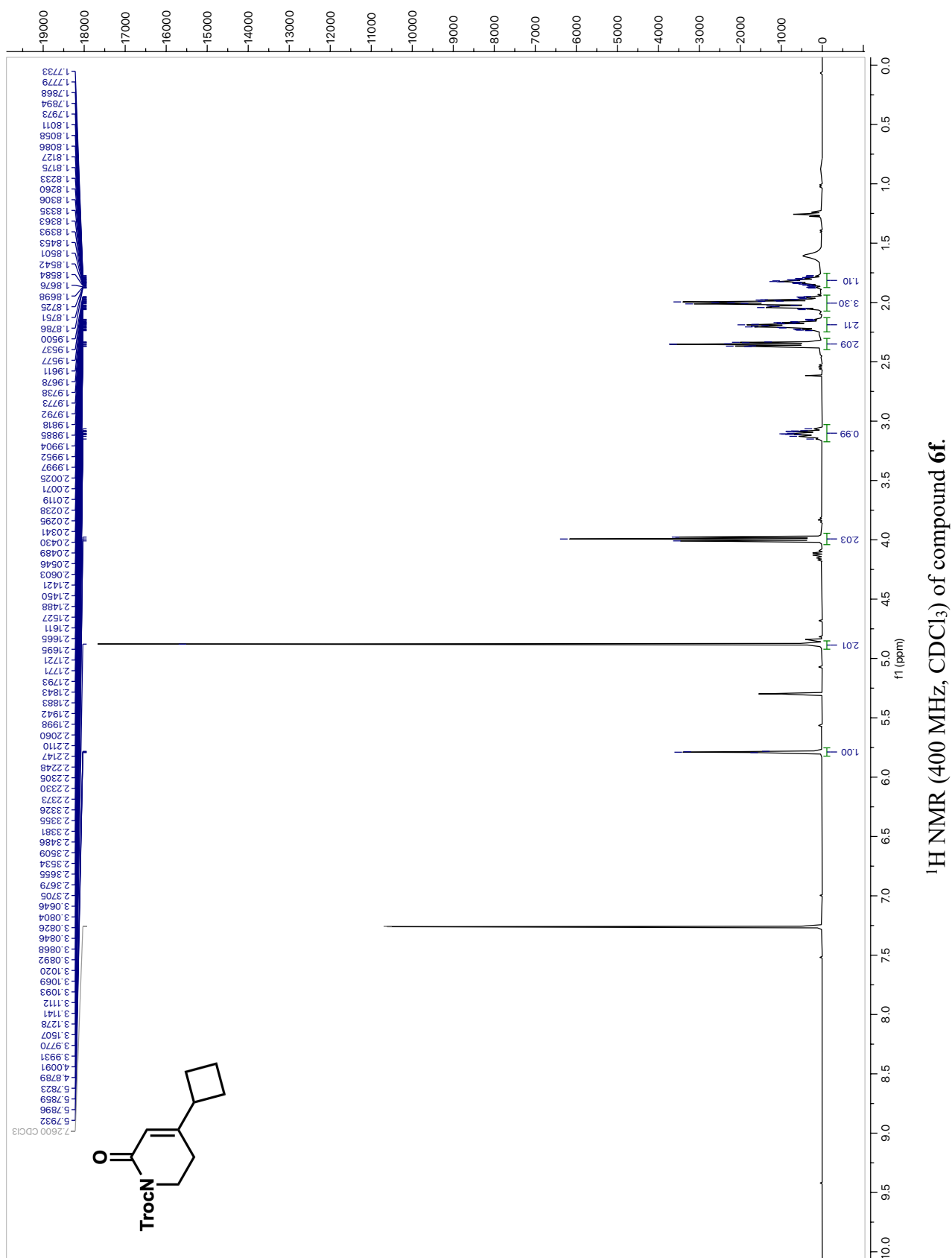


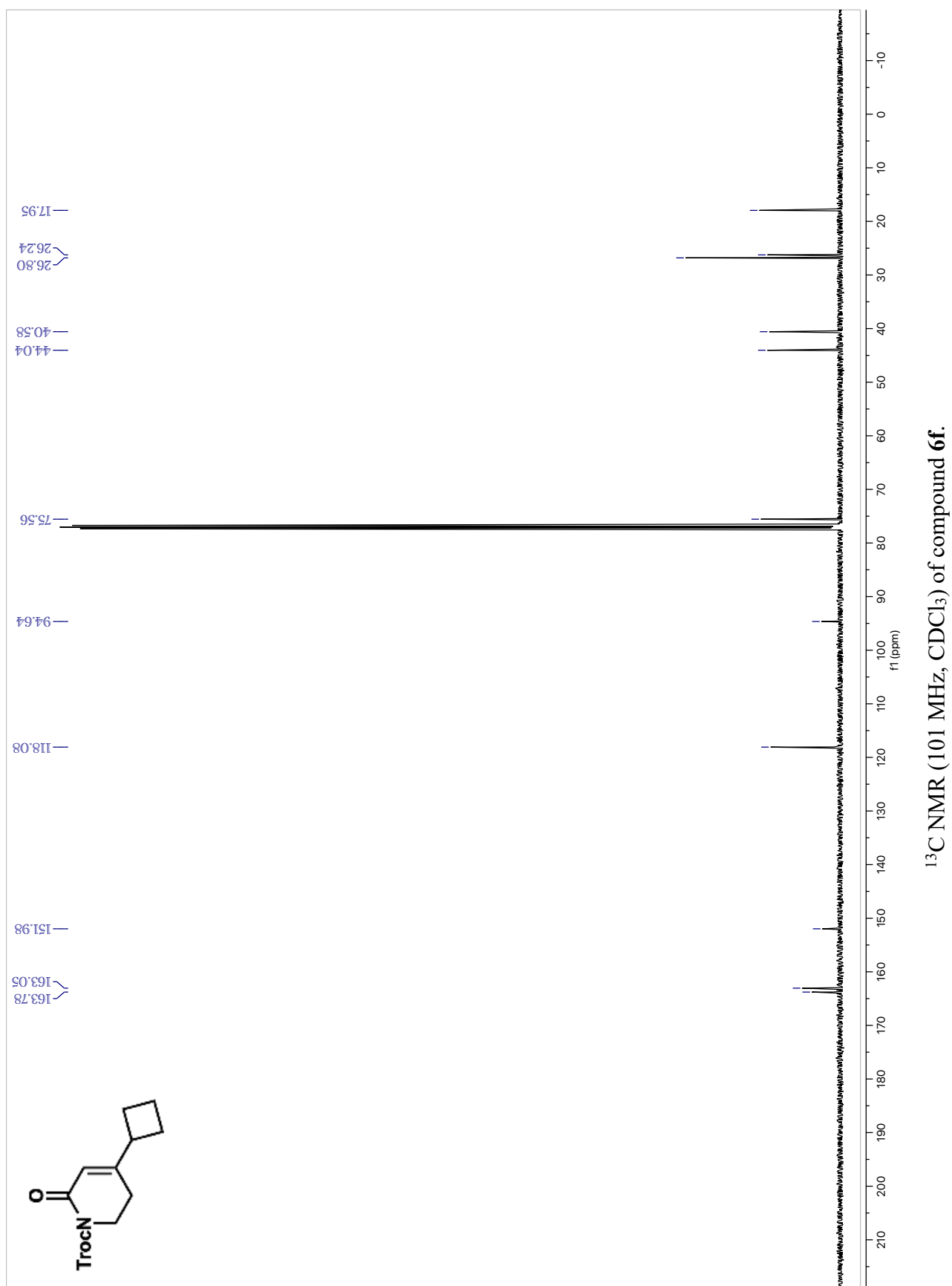


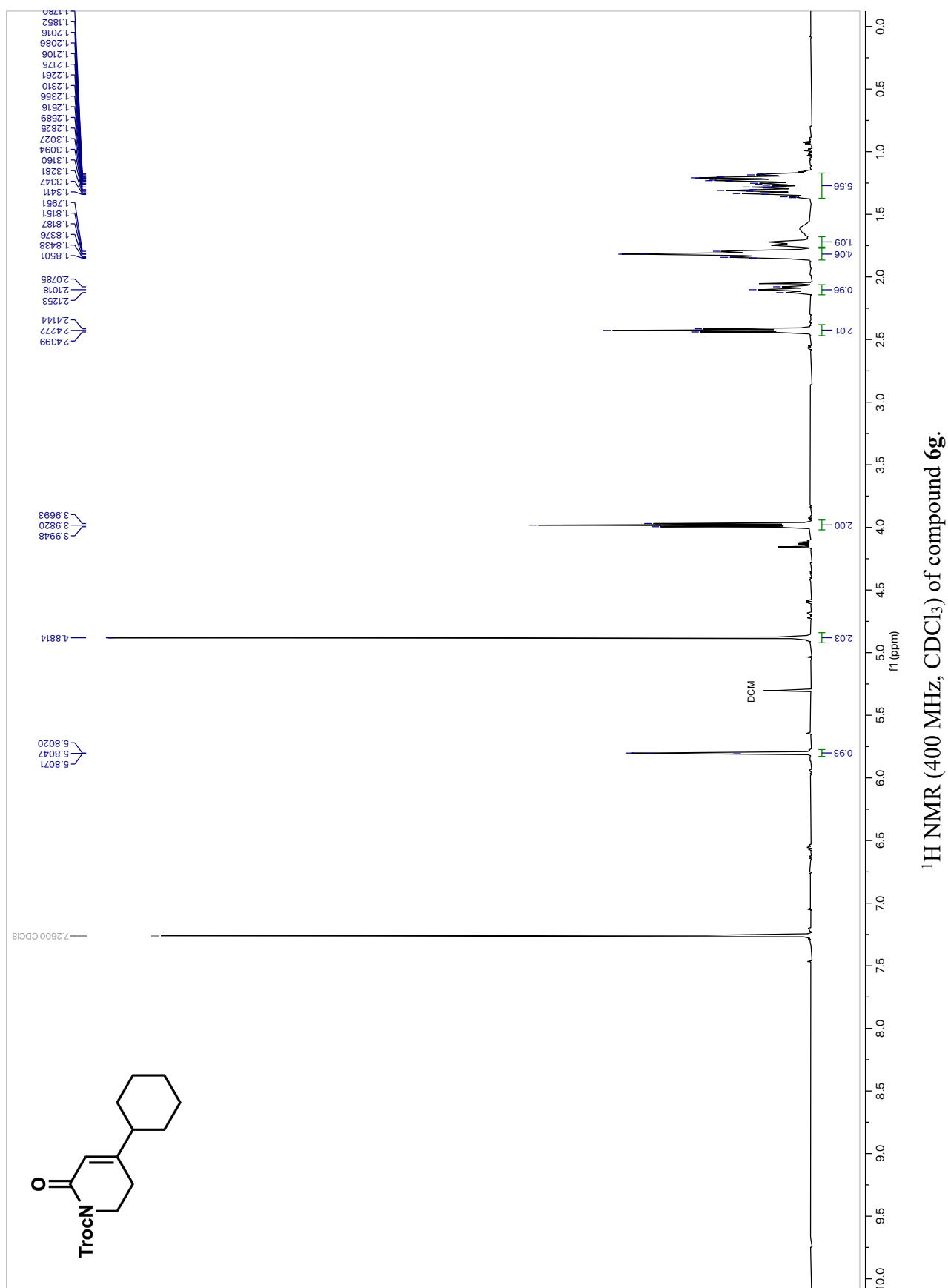


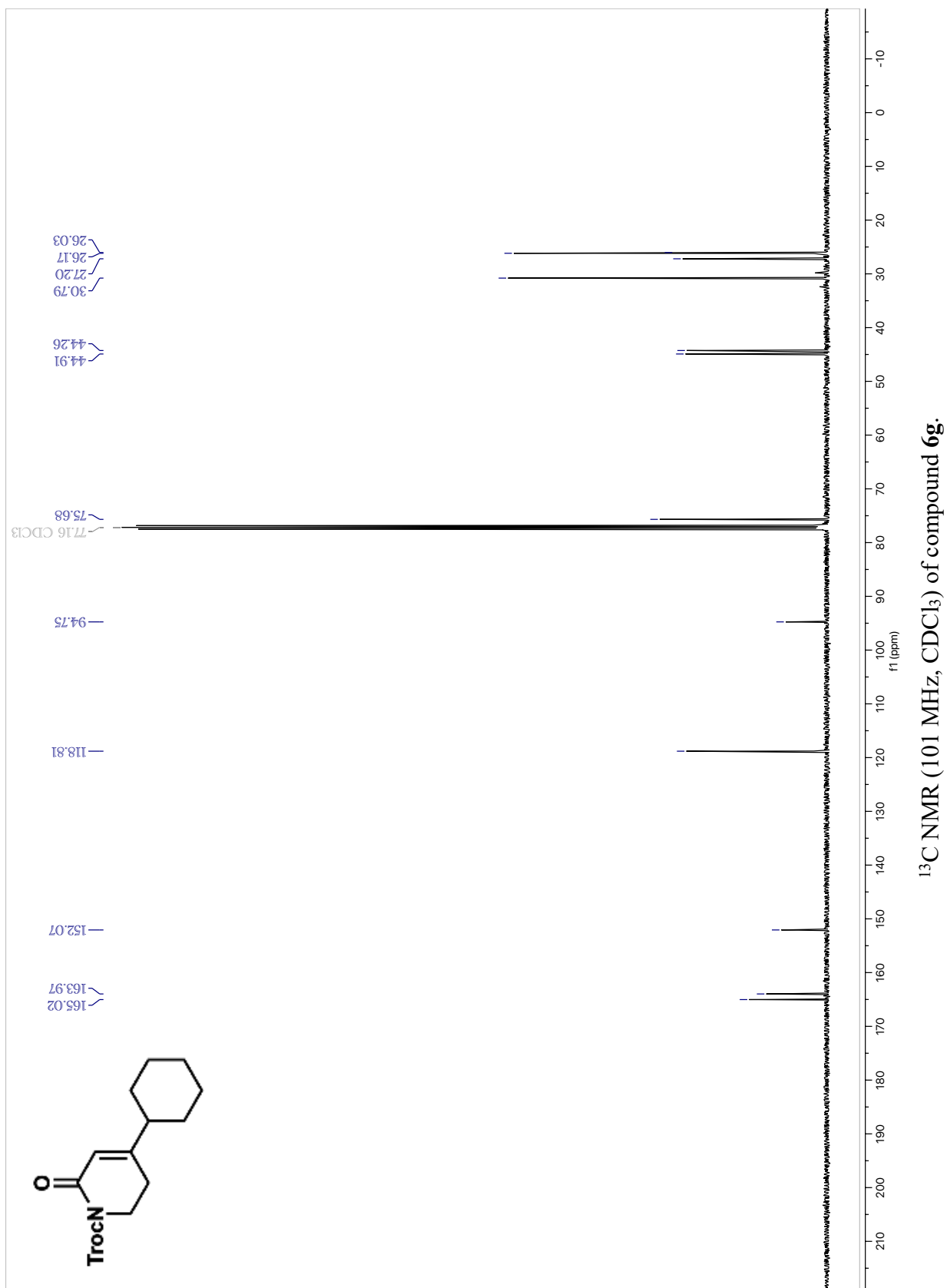


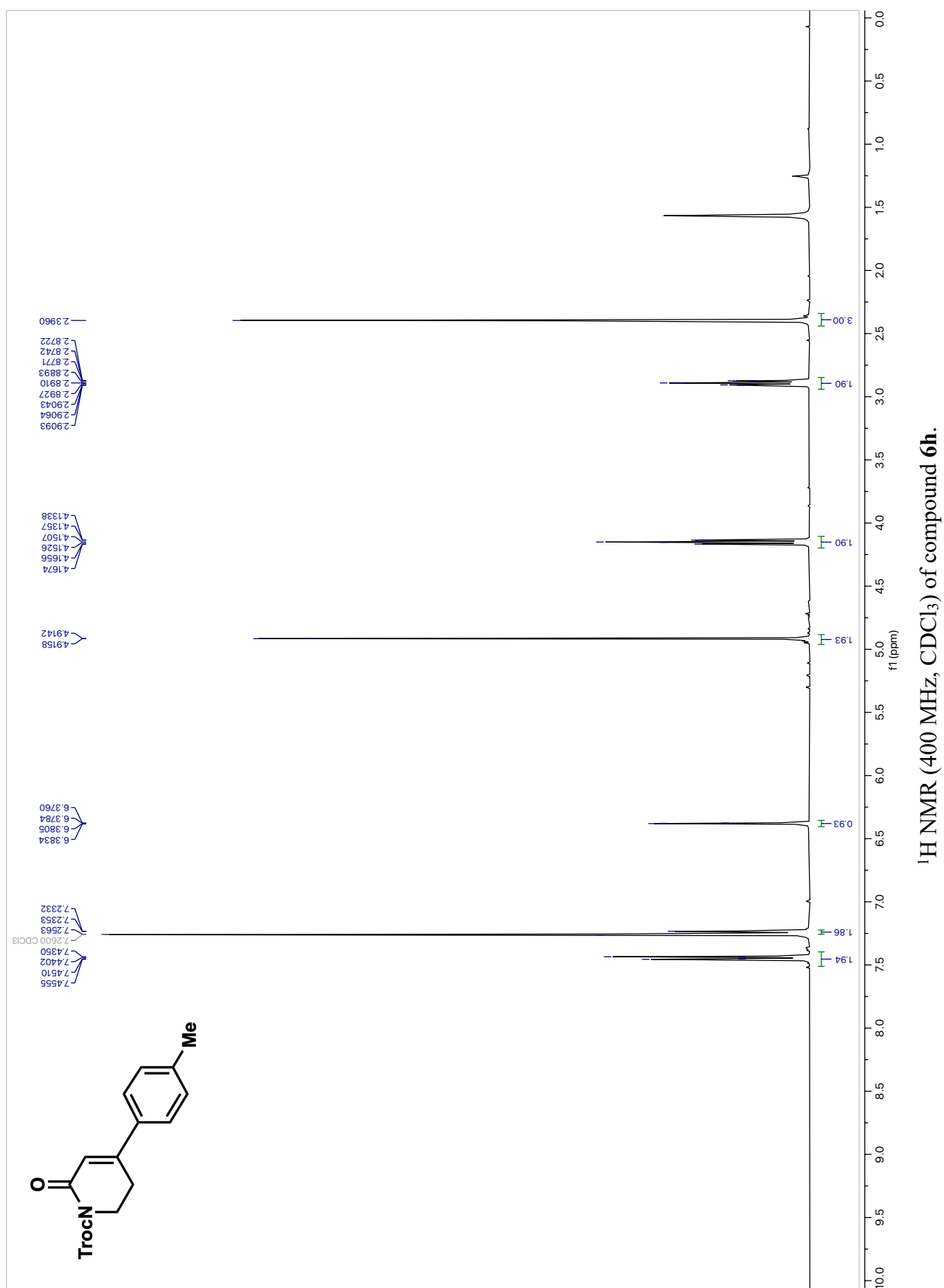


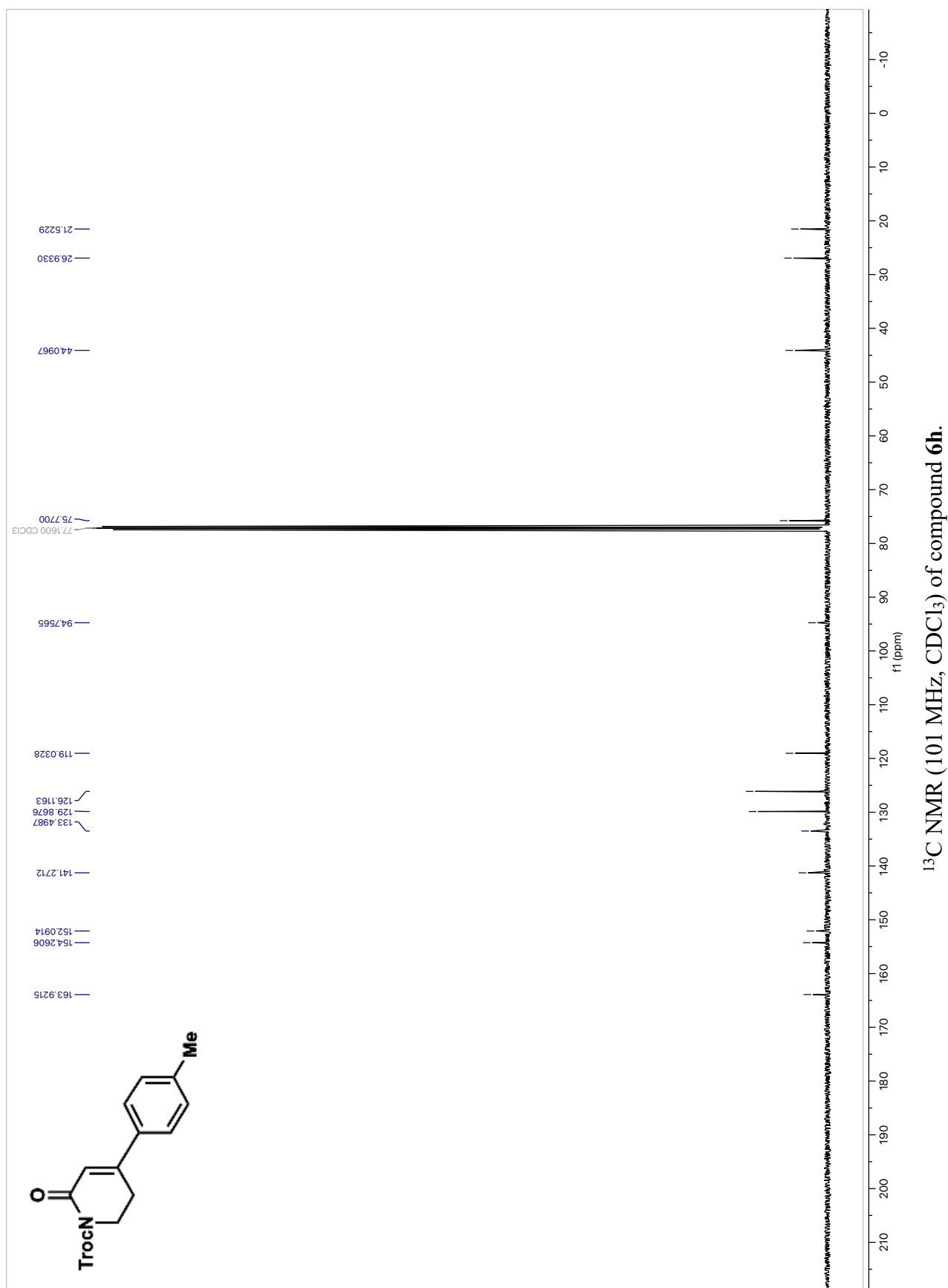


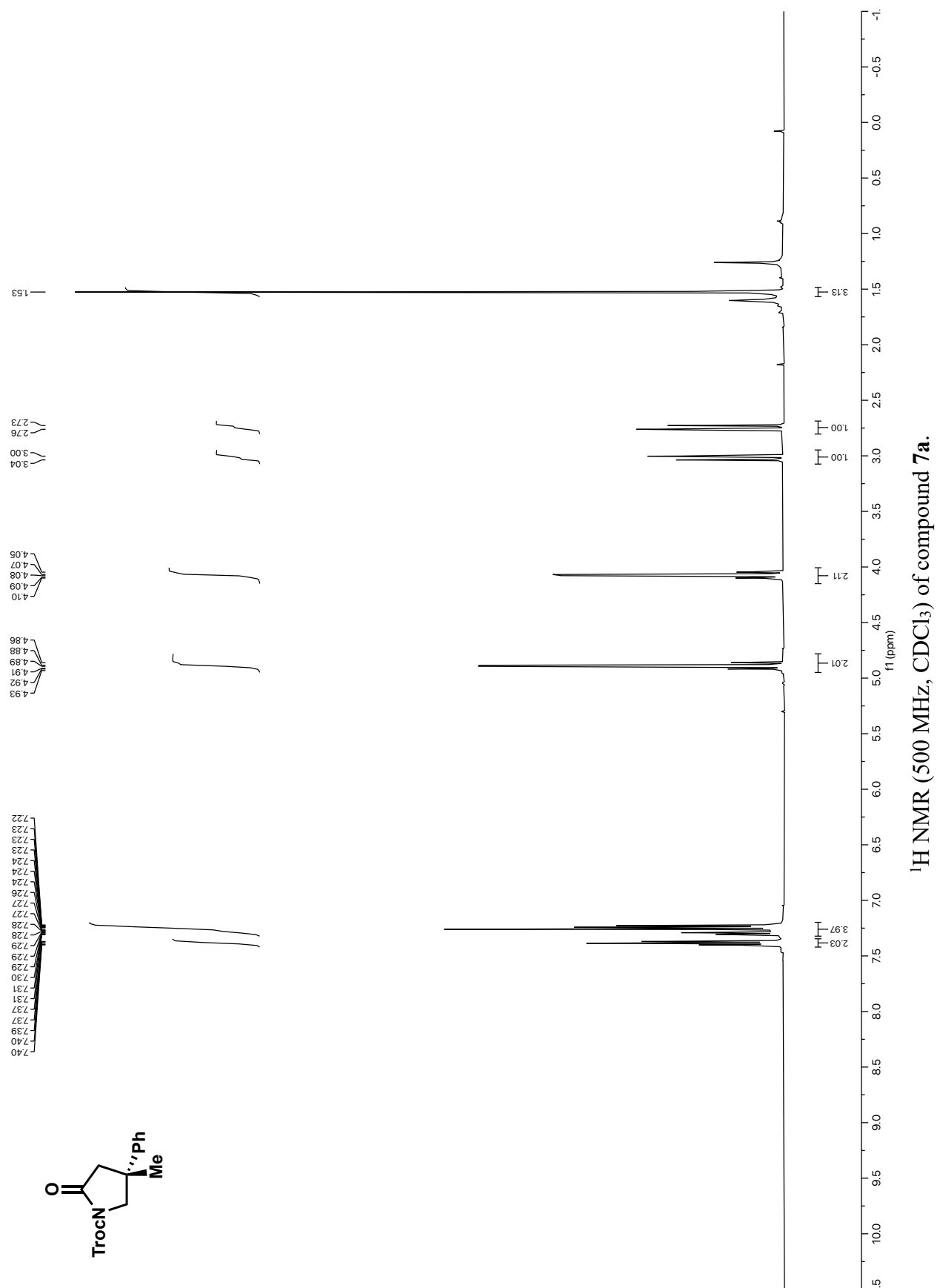


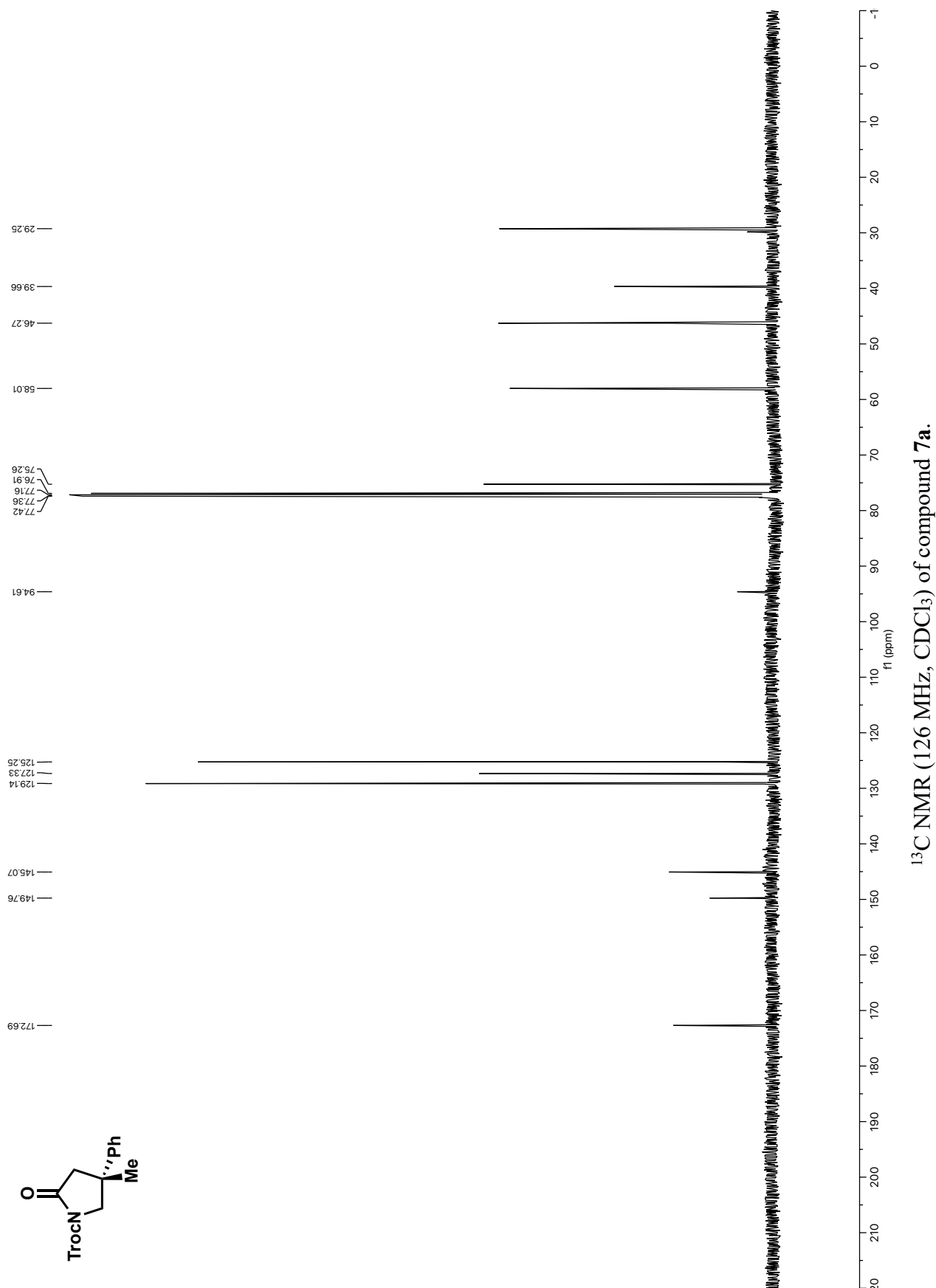


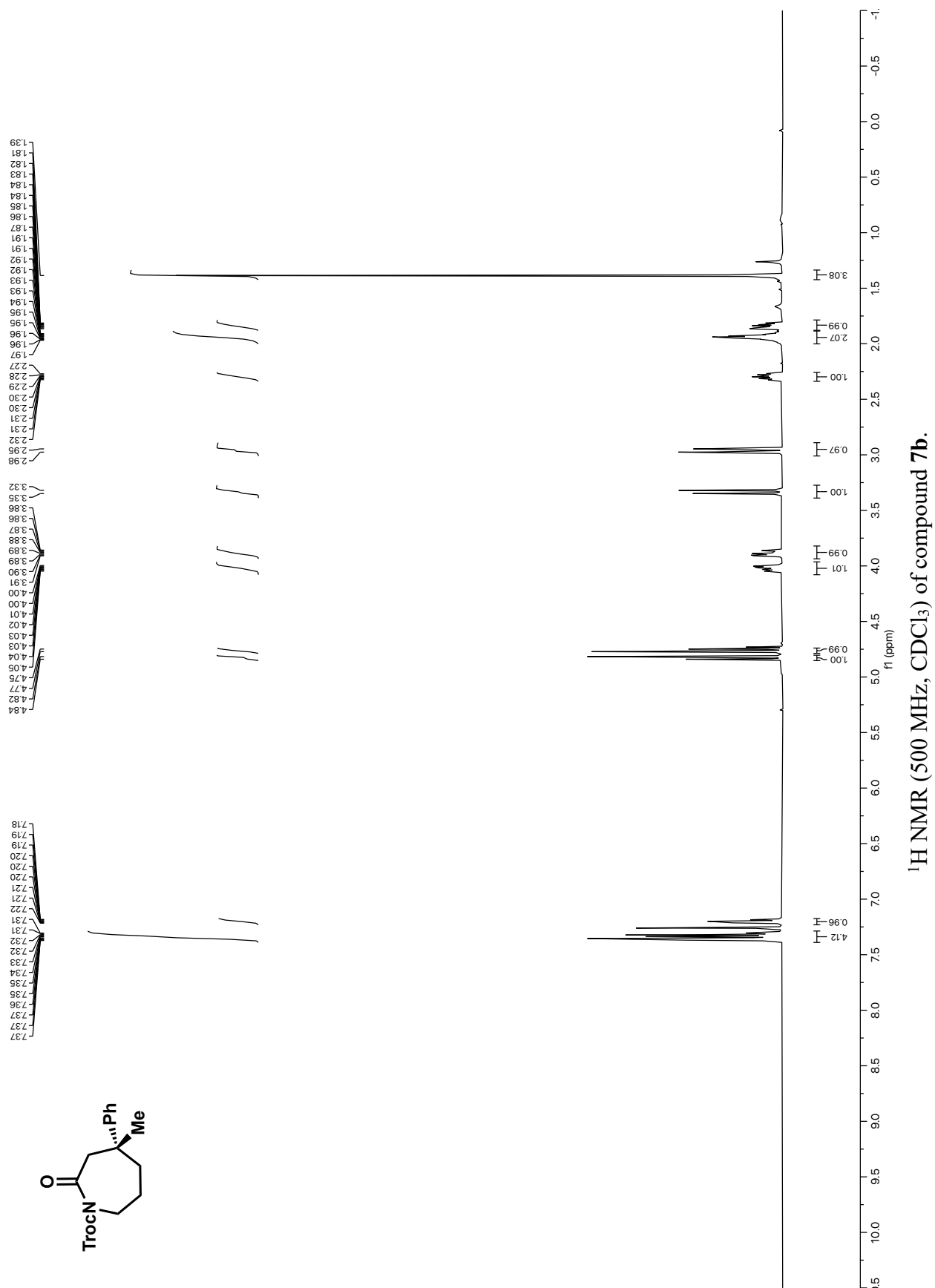


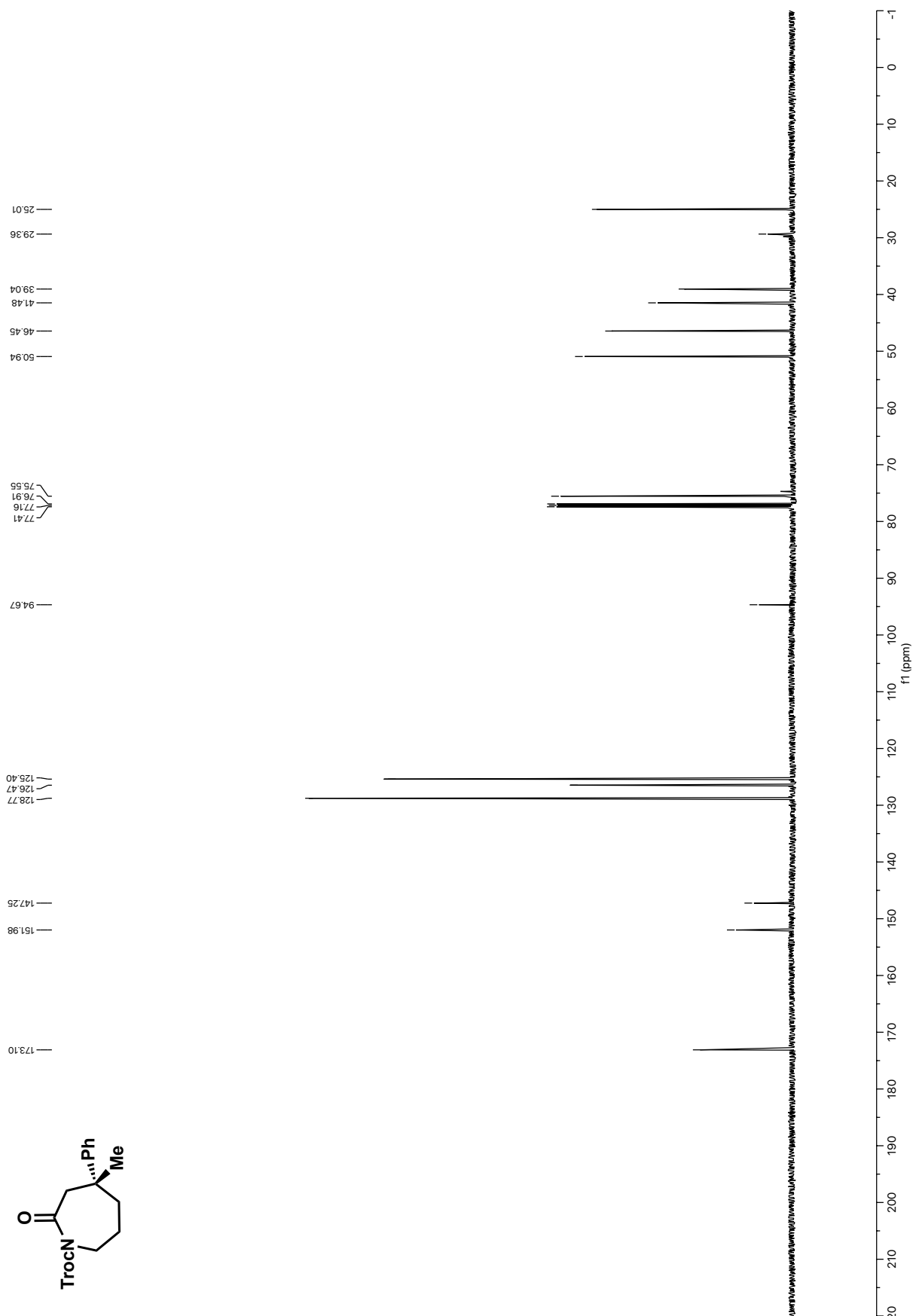
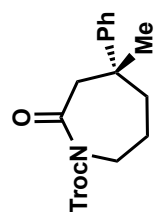


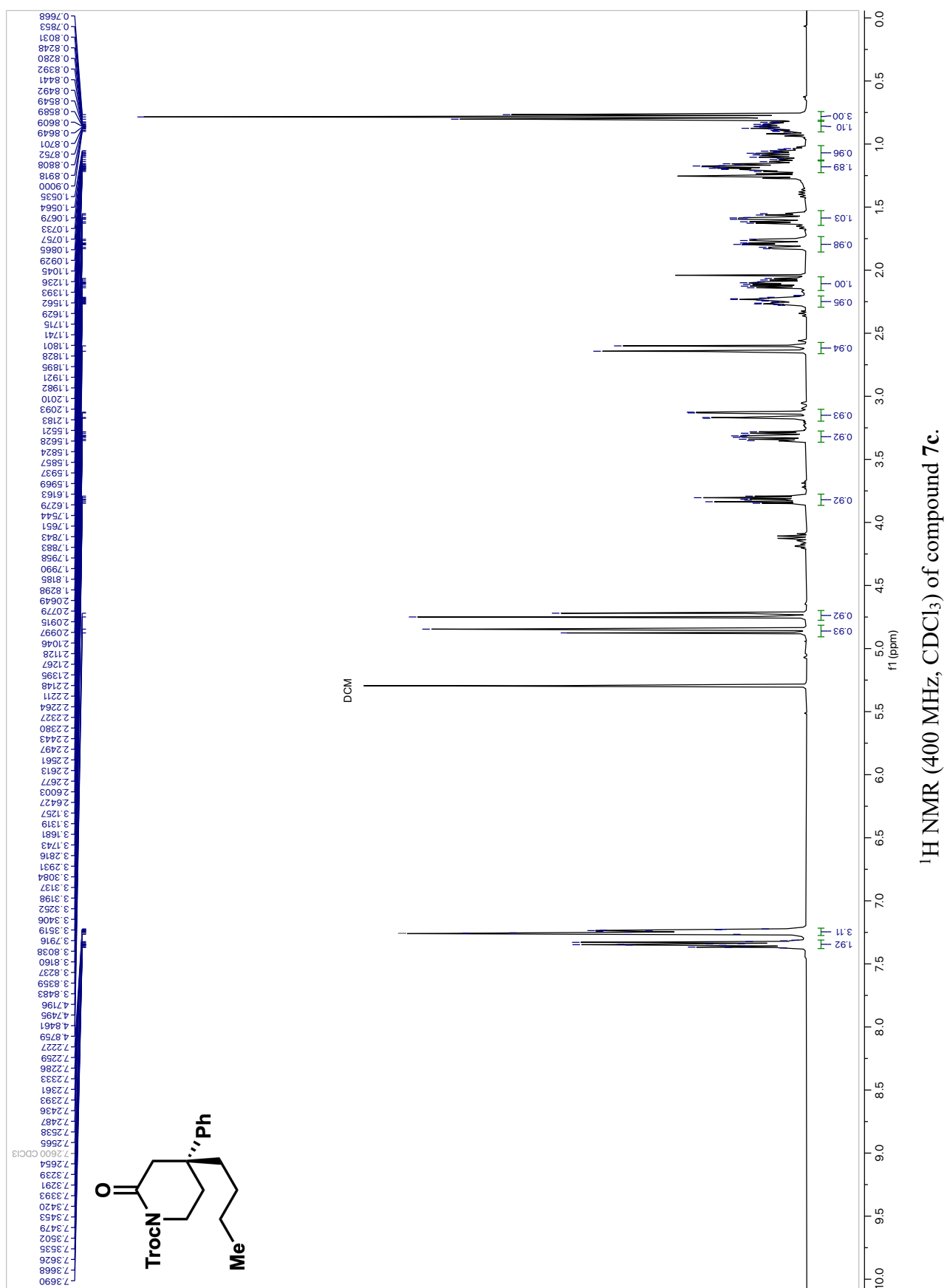


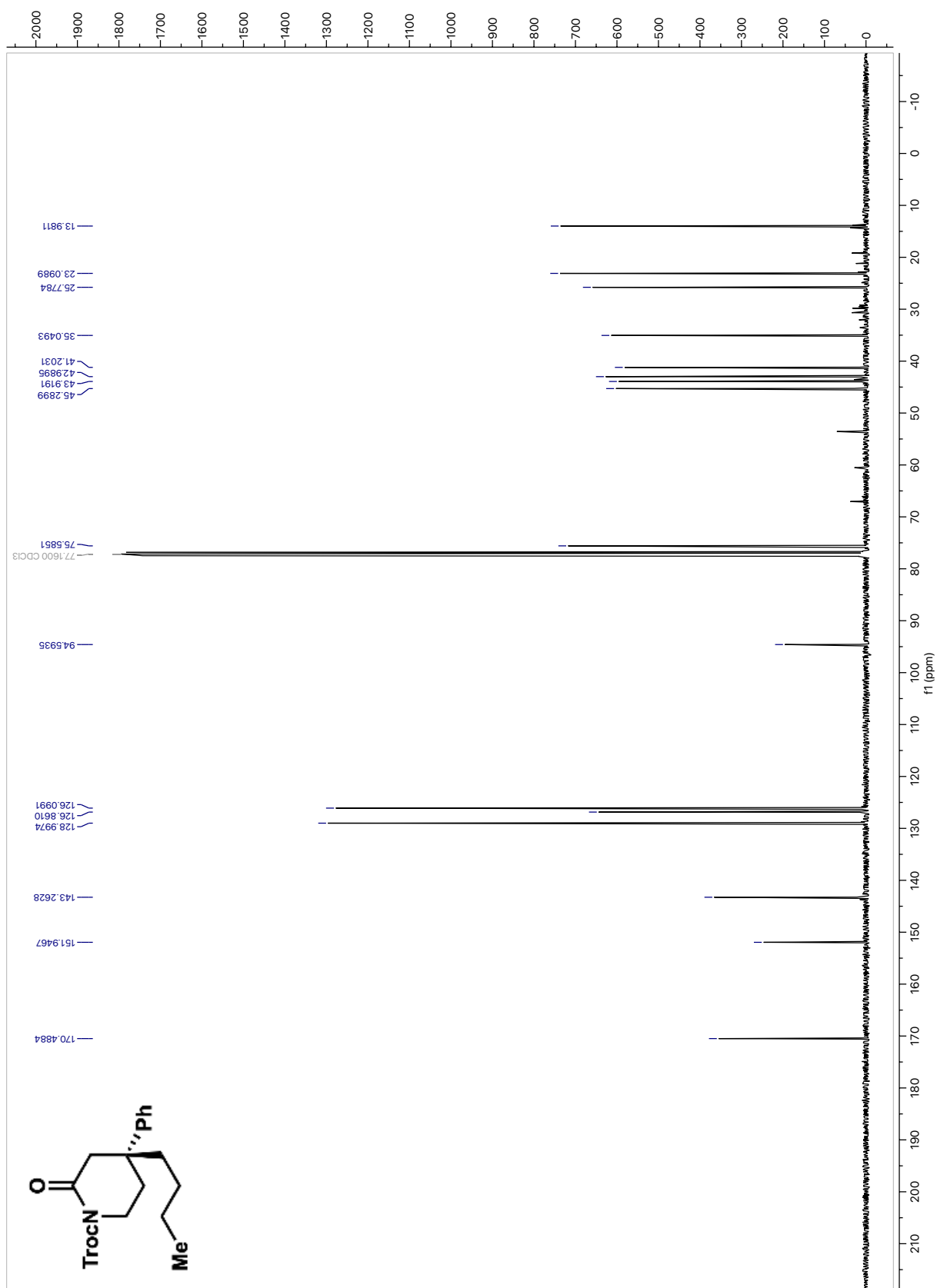


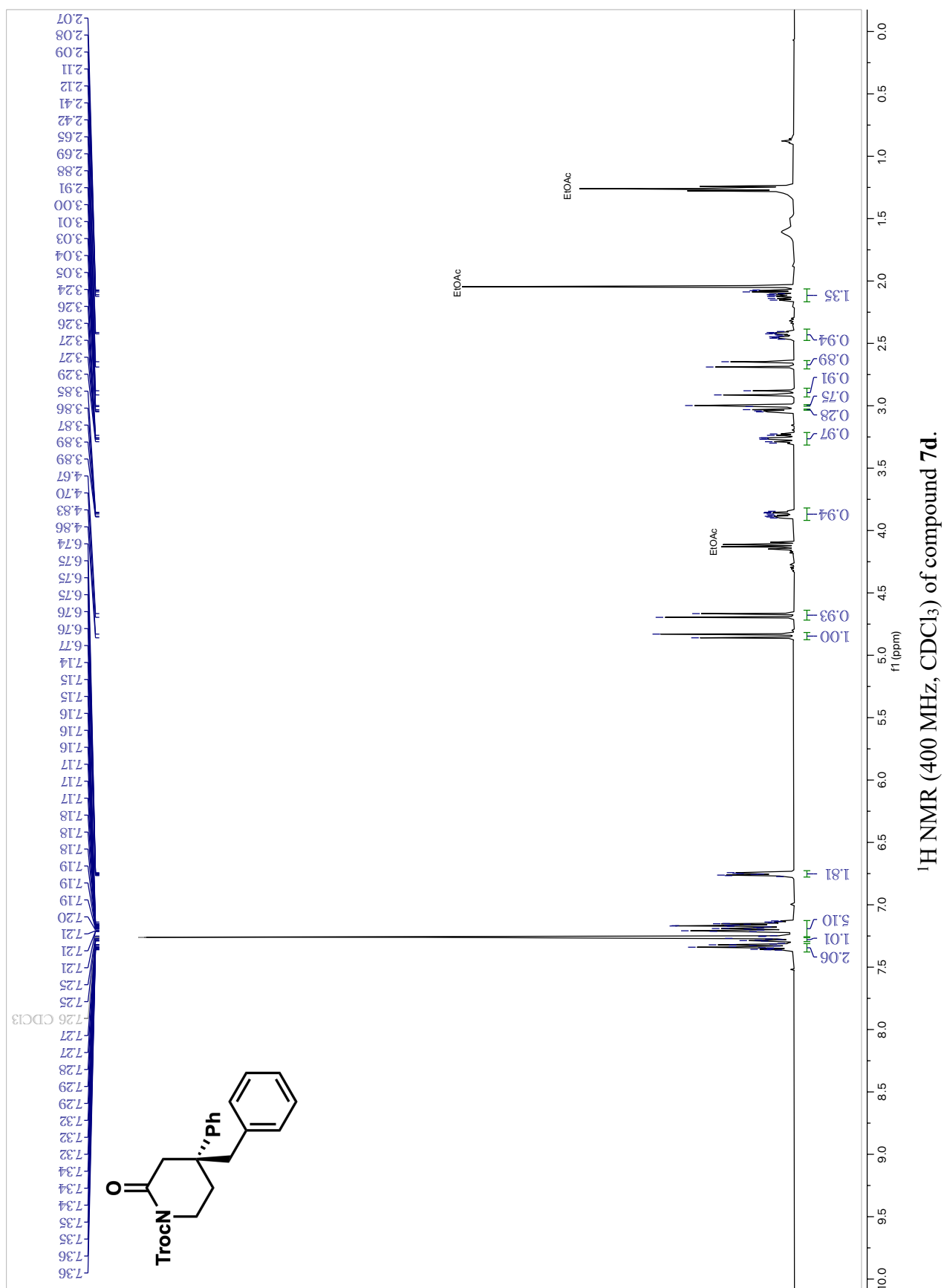


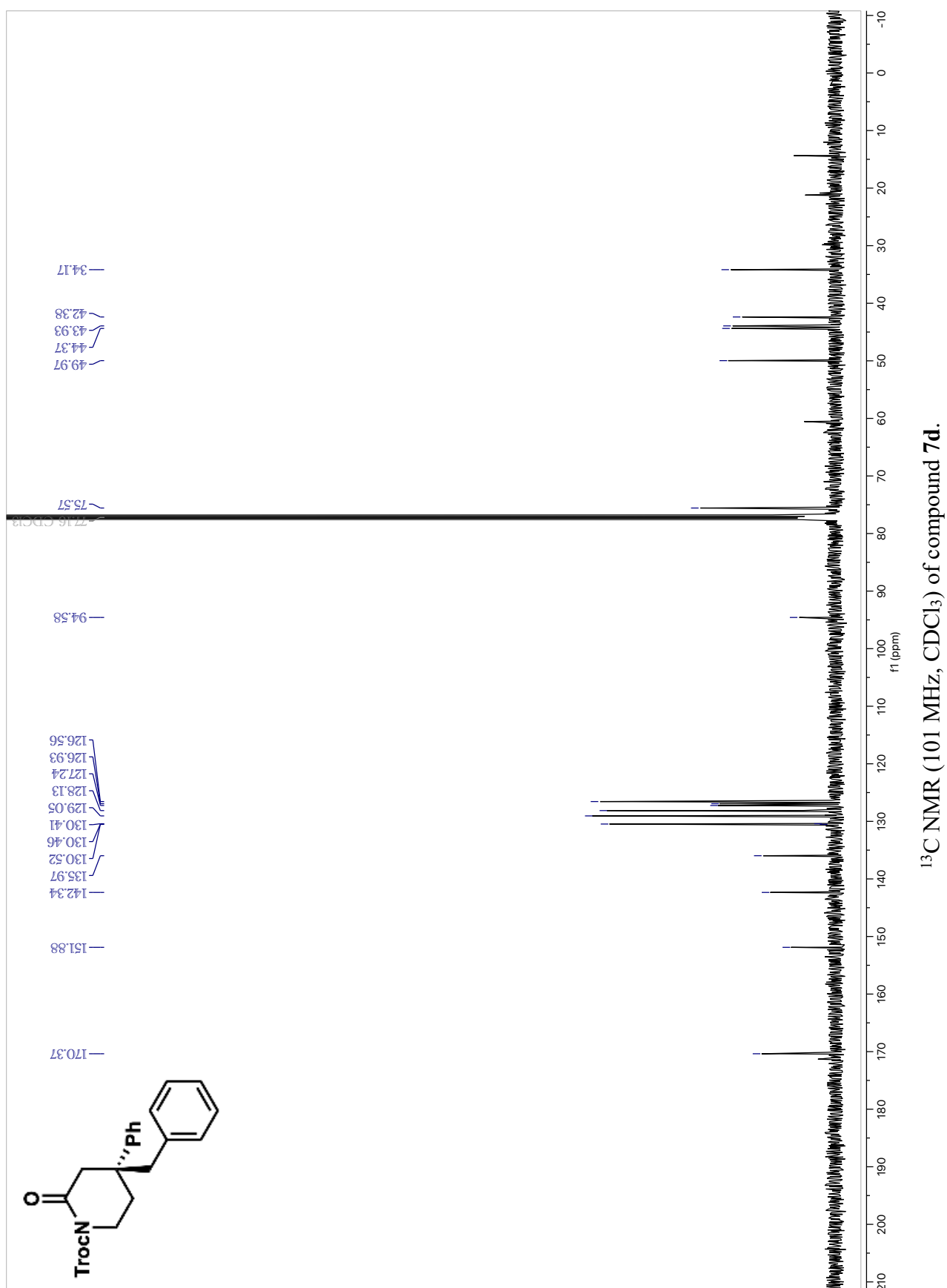


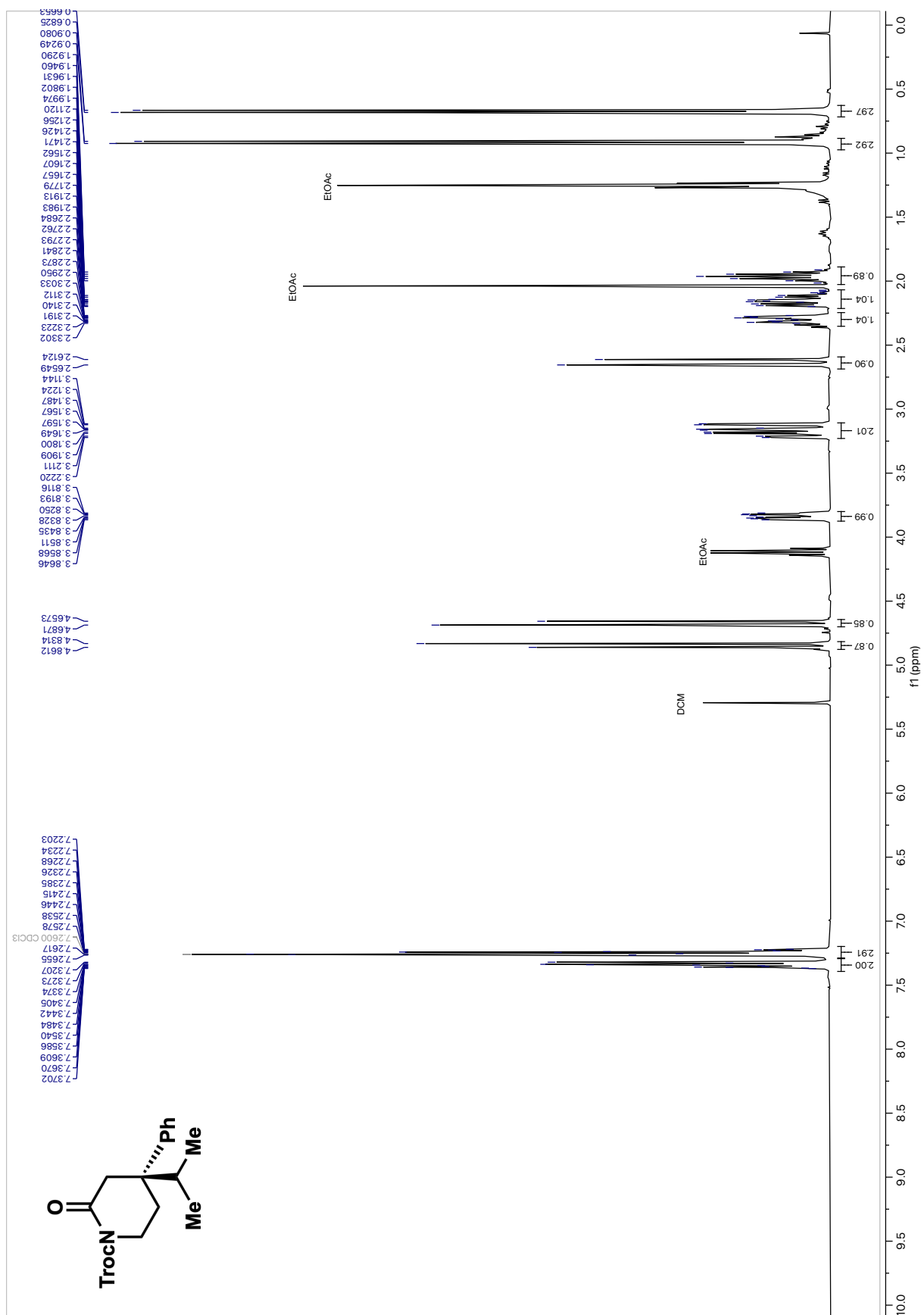


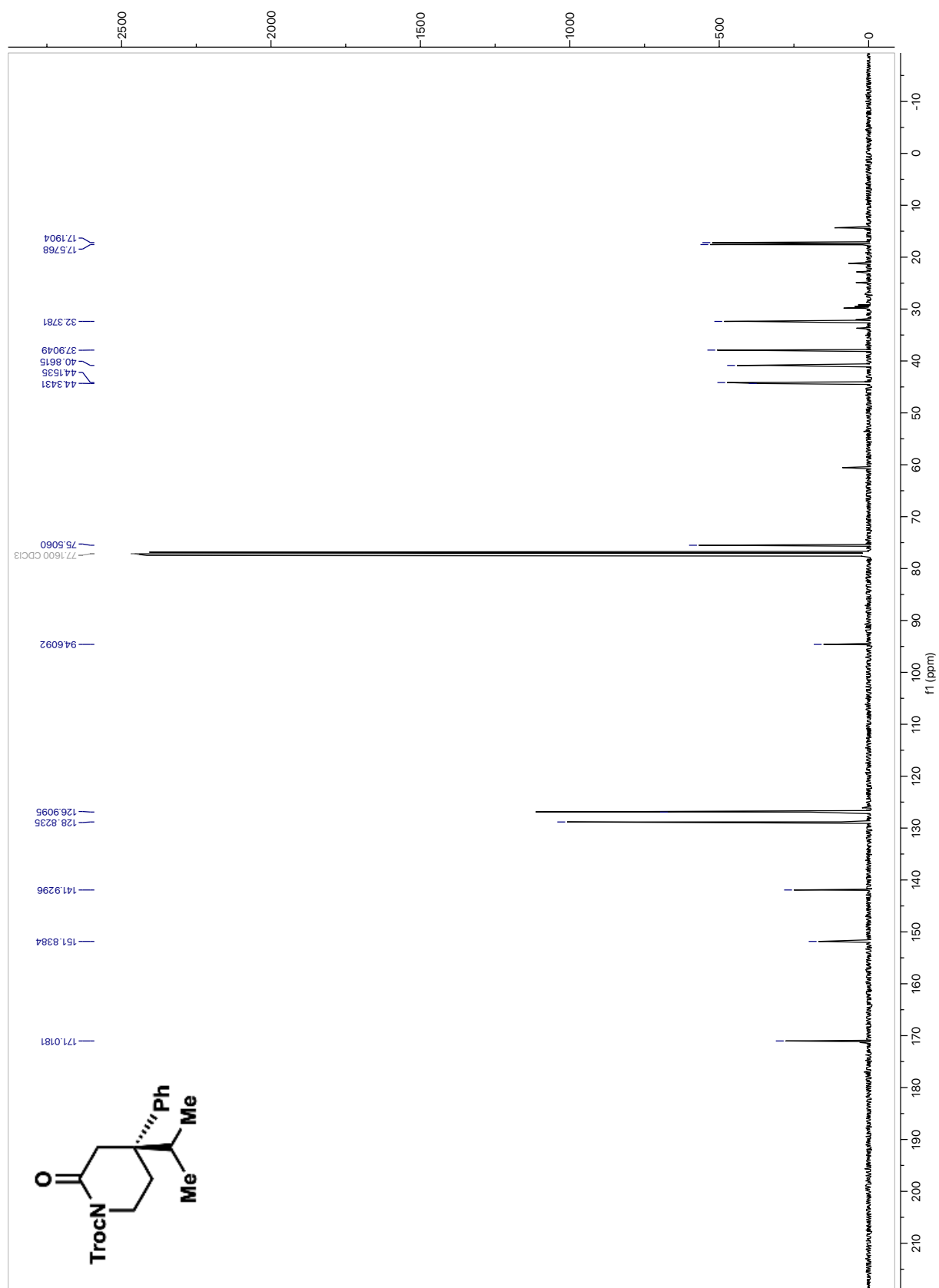


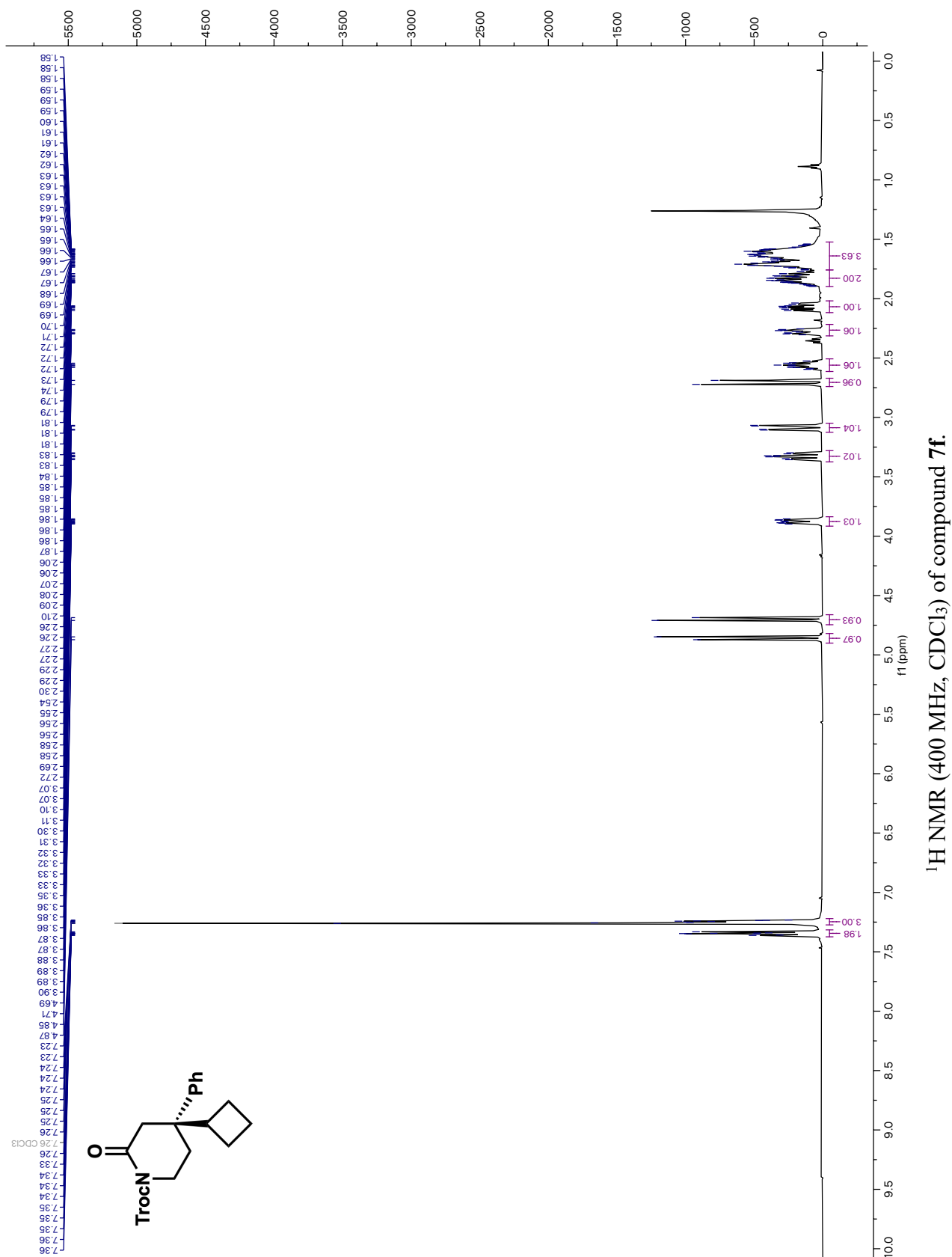


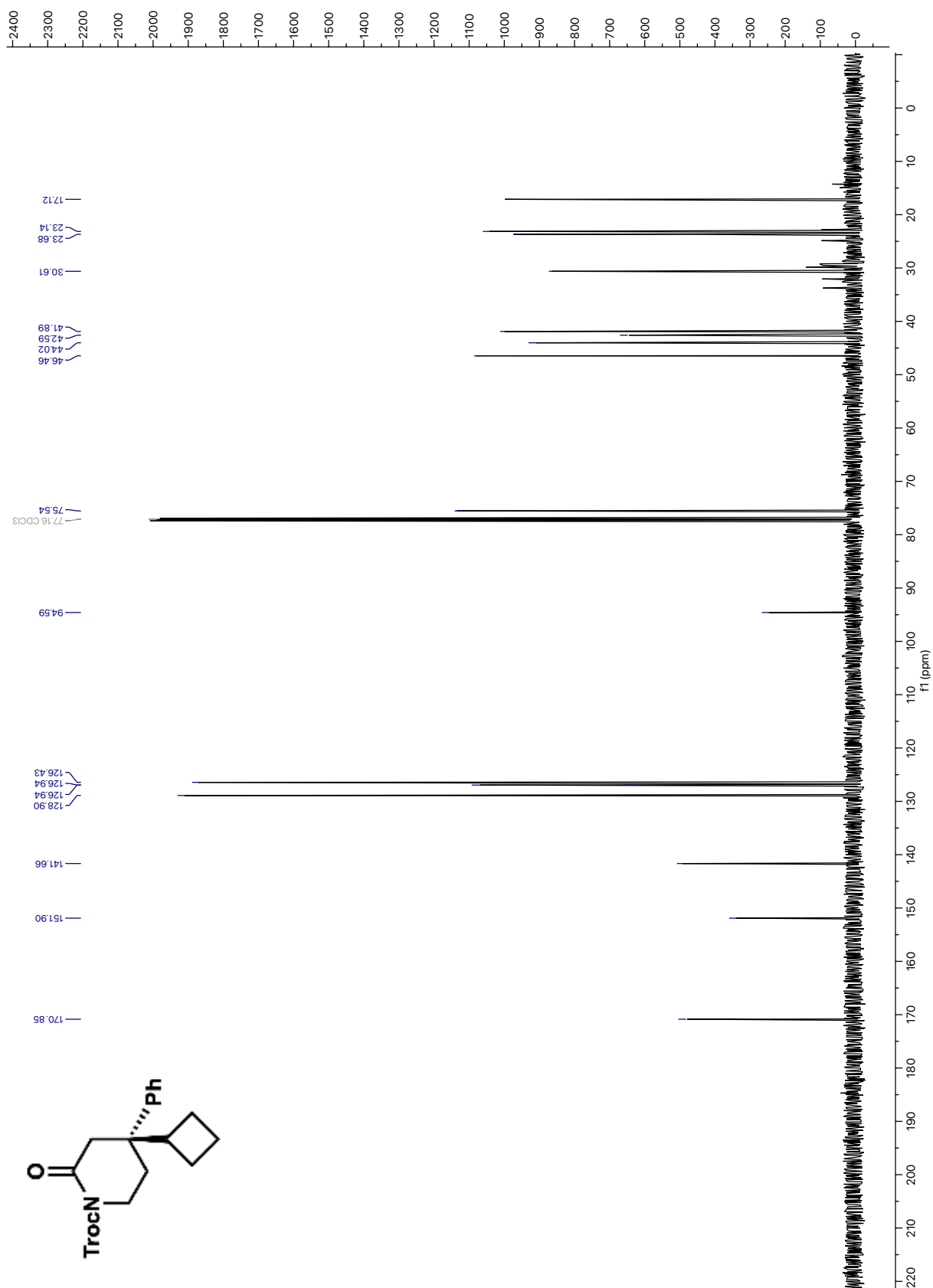


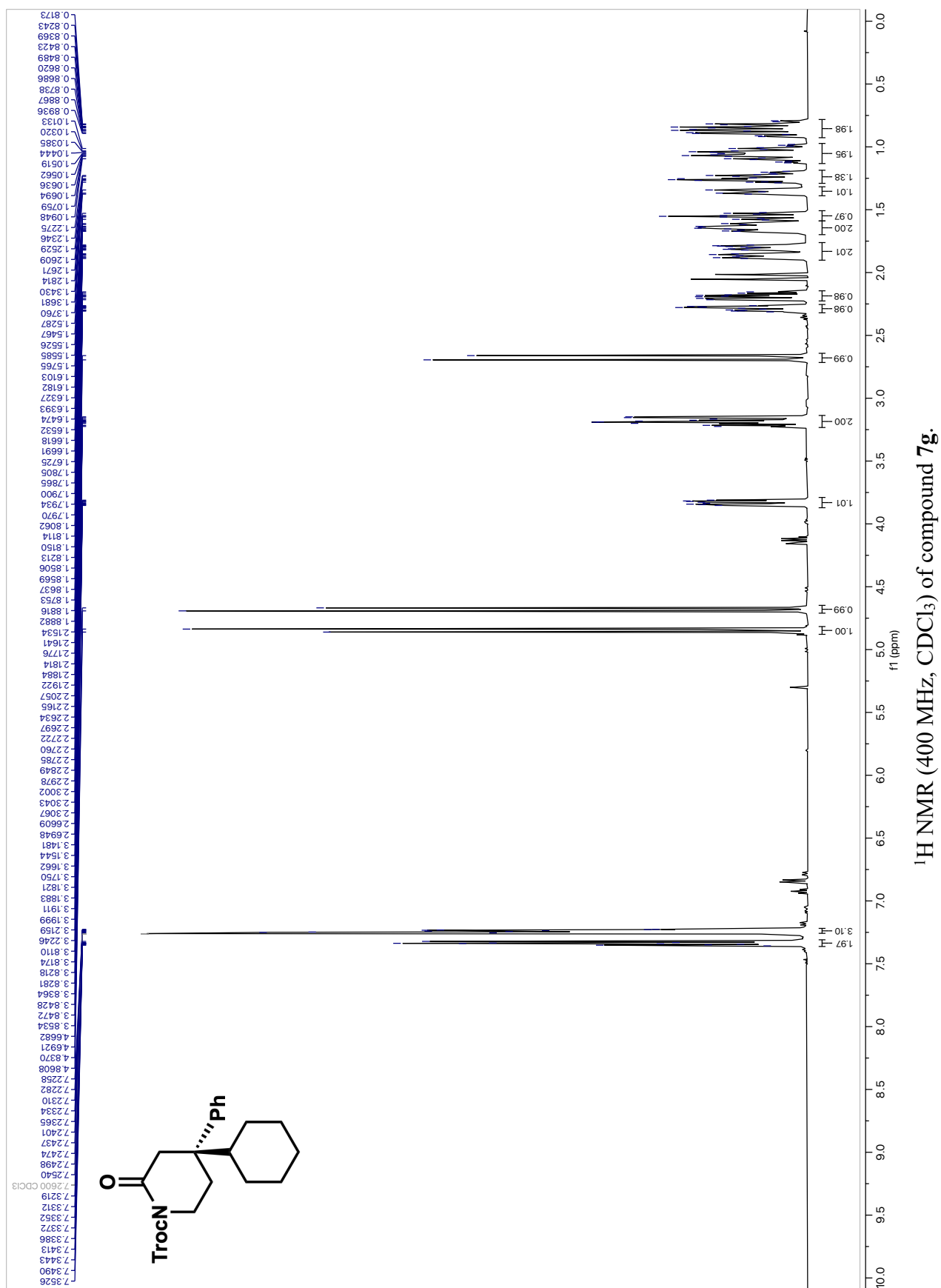


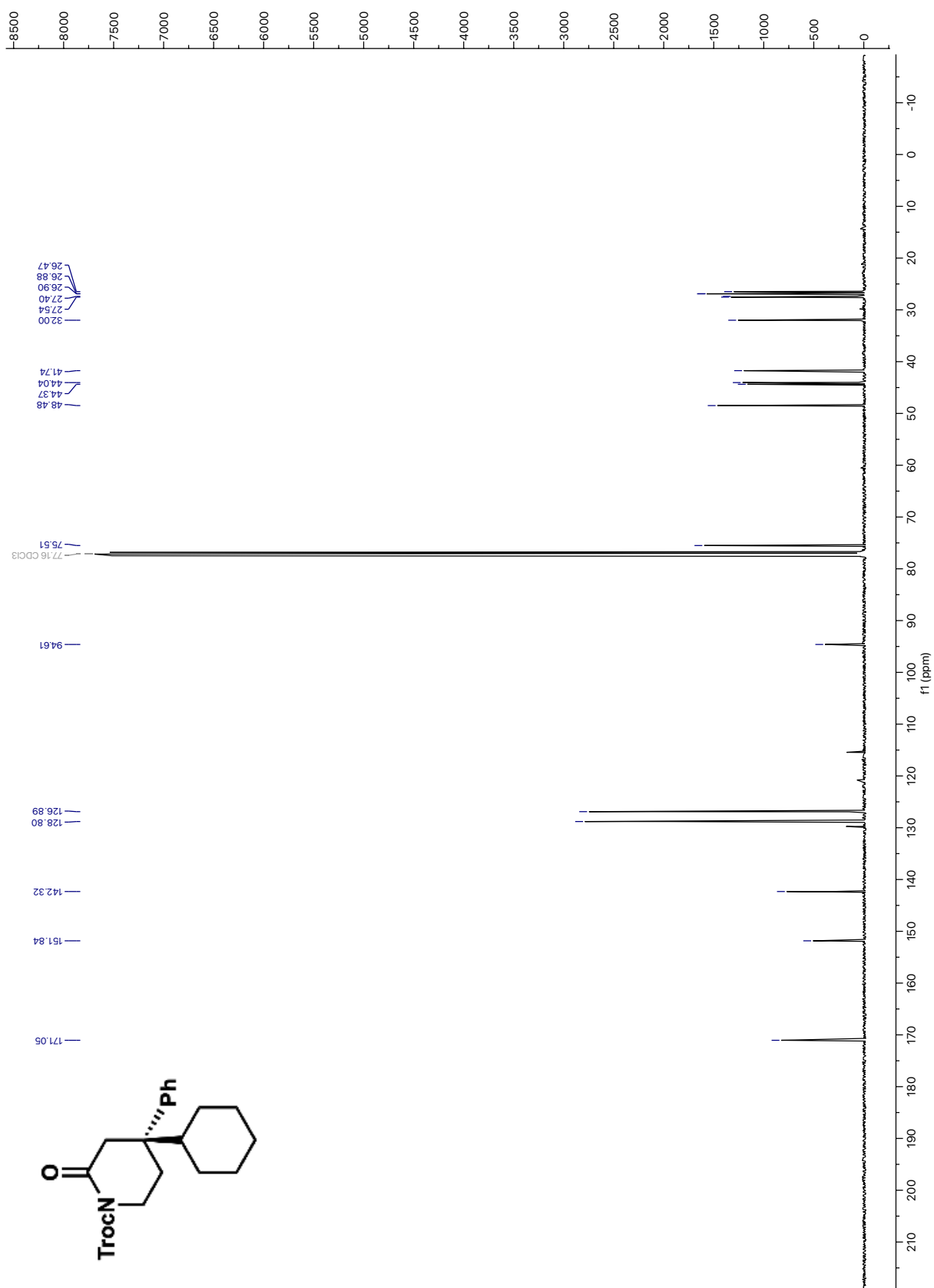


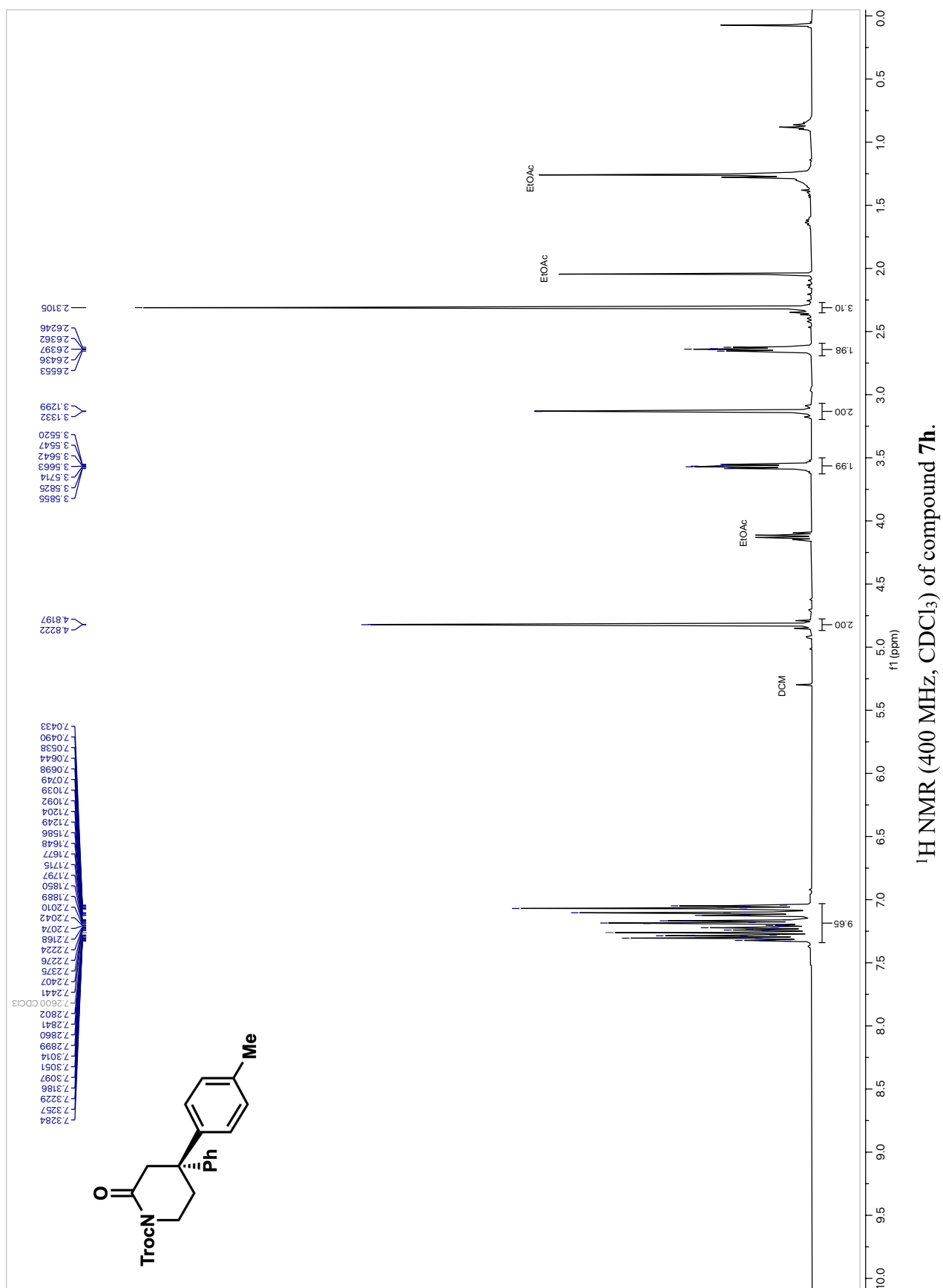


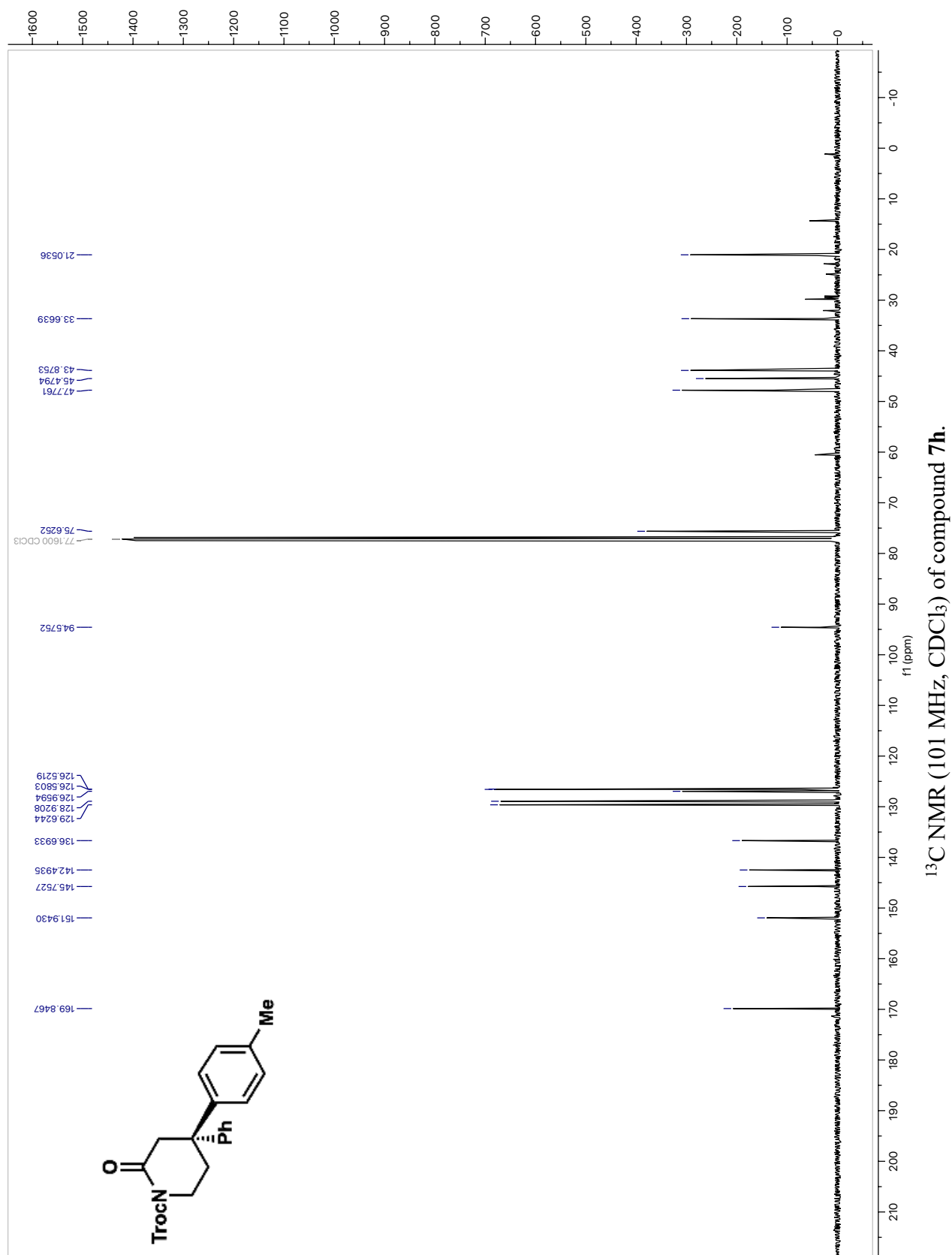












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